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COMPARATIVE IN-SILICO PROFILING OF ADME, DRUG LIKENESS, AND TARGET PREDICTION OF SPISULOSINE AND SELECTED ANALOGUES

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ABSTRACT

Spisulosine, also known as ES-285, is an anticancer compound isolated from a marine organism, Spisula polynyma, and has shown significant preclinical potential, but its clinical trial was discontinued in 2008 due to dose-limiting neurotoxicity. This study implements an in-silico approach to effectively evaluate the pharmacokinetic, ADME (Absorption, Distribution, Metabolism, Excretion) profiles, integrated with molecular target prediction, for ES-285 and three of its analogues: Xestoaminol C, 3-epi-Xestoaminol C, and 1-Deoxysphingosine, using SwissADME and SwissTargetPrediction web tools, for pharmacokinetic and target predictions. All compounds demonstrated high predicted gastrointestinal absorption and blood-brain barrier (BBB) permeation, consistent with the neurotoxic effect. A significant difference in metabolic profiles was observed, with Spisulosine and 1-Deoxysphingosine predicted to inhibit multiple cytochrome P450 (CYP) isoforms, suggesting a high risk for drug-drug interactions, while Xestoaminol C and 3-epi-Xestoaminol C showed a limited inhibition profile, affecting only CYP2D6, although none of the compounds inhibited CYP3A4. The predicted primary molecular target of Spisulosine and its analogues was sphingosine kinase 1 (SPHK1), validating their anticancer property. These findings highlight the potential of Xestoaminol C and 3-epi-Xestoaminol C as promising leads for further chemical optimization, particularly for reducing BBB penetration and improving the overall therapeutic window of this class of compounds.

KEYWORDS: In-silico, Spisulosine, Xestoaminol C, 3-epi-Xestoaminol C, 1-Deoxysphingosine.

1. INTRODUCTION

The drug discovery and development are a complex and time-intensive process, often encountering significant challenges related to unfavourable pharmacokinetic profiles and unforeseen toxicities. Many potential drugs fail during clinical trials and drug approval due to inadequate pharmacokinetic behaviour, in terms of Absorption, Distribution, Metabolism, and Excretion (ADME) profiles.[1] In response to these challenges, Artificial intelligence (AI) has evolved as a modern approach in drug discovery, helping to overcome the major limitations associated with traditional methods, such as low success rates, extended development duration, and financial burden[2]. AI can push up the drug discovery process by machine learning (ML) and deep learning (DL).[2] In silico methods have emerged as essential tools in modern drug discovery, by predicting various pharmacokinetic and targets, directly from a chemical structure of compound.[3]

Spisulosine (known as ES-285) is a marine derived compound with reported anticancer activity, obtained from a marine organism *spisula polynyma*. it restricts cell proliferation by disruption of actin cytoskeleton dynamics in cell.[4]

Spisulosine's clinical trial was discontinued in Phase I trial in 2008 due to severe neurotoxicity, a dose-limiting adverse effect.[5,6] Xestoaminol C is a marine derived sphingoid isolated from Fijian sponge Xestospongia sponges.[7] 3-epi-Xestoaminol C was isolated from brown algae Xiphophora chondrophylla, it exhibits bioactivity against mycobacteria.[7]

The present study performs a comparative in silico evaluation of Spisulosine and three of its analogues: Xestoaminol C, 3-epi-Xestoaminol C, and 1-Deoxysphingosine. The objectives include: first, to predict their key pharmacokinetic properties using SwissADME; second, to identify their probable molecular targets using SwissTargetPrediction. By integrating these computational results, we seek to illustrate the structural features that contribute to both safety and efficacy thereby guiding future rational drug design efforts to develop Spisulosine analogues with an improved therapeutic window.

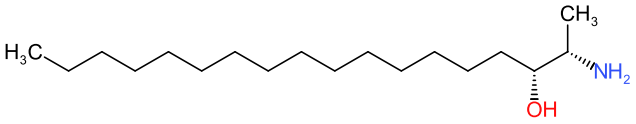
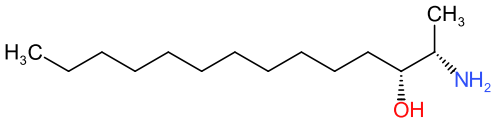
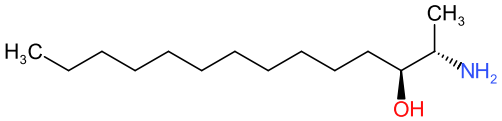
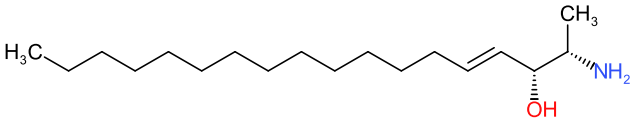
2. MATERIALS AND METHODS

The computational analyses were performed on four compounds: Spisulosine, Xestoaminol C, 3-epi-Xestoaminol C, and 1-Deoxysphingosine. The canonical SMILES (Simplified Molecular Input Line Entry System) notation for each compound was obtained and used as the input for all further in silico analyses [Table 1]. The molecular formulas, chemical structures and PubChem CIDs for each compound were also collected for reference [Table 2].

Table 1: Canonical Smiles of Spisulosine, Xestoaminol C, 3-Epi-Xestoaminol C, And 1-Deoxysphingosine.

Compound	Canonical Smiles
Spisulosine	CCCCCCCCCCCCCCC[C@H]([C@H](C)N)O
Xestoaminol C	CCCCCCCCCCC[C@H]([C@H](C)N)O
3-epi-Xestoaminol C	CCCCCCCCCCC[C@@H]([C@H](C)N)O
1-Deoxysphingosine	CCCCCCCCCCCCC/C=C/[C@H]([C@H](C)N)O

Table 2: Molecular Formula, Pubchem Cids, & Chemical Structure of Spisulosine and Its Analogues.

Molecule Name	Molecular Formula	PubChem CIDs	Chemical Structure
Spisulosine[8]	C18H39NO	9925886	
Xestoaminol C[9]	C14H31NO	14756407	
3-epi-XestoaminolC[10]	C14H31NO	90683233	
1-Deoxy-sphingosine[11]	C18H37NO	15928896	

2.1 ADME and physicochemical property prediction

The SwissADME web tool, a freely accessible and user-friendly tool was used for predicting a wide range of ADME and physicochemical properties.[12] The key parameters of evaluation included the following:

2.1.1 **Physicochemical description** Molecular weight (MW), the number of heavy atoms, the number of rotatable bonds, the number of hydrogen bond acceptors and donors, Molar Refractivity, and Topological Polar Surface Area (TPSA).

2.1.2 **Lipophilicity** The lipophilicity of each compound was predicted using five different computational models: (iLOGP, XLOGP3, WLOGP, MLOGP, SILICOS-IT), iLOGP is a simple in-house physics-based method to predict a compound's partition coefficient (LogP).[13]

2.1.3 **Pharmacokinetics:** Prediction of Gastrointestinal (GI) absorption, Blood-Brain Barrier (BBB) permeation (using the BOILED-Egg model),[14] P-glycoprotein (P-gp) substrate activity, inhibition of major Cytochrome P450 (CYP) isoforms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), and log Kp (skin permeation).

2.1.4 **Water solubility:** The water solubility of each compound was predicted using the ESOL model, water soluble molecule assists many drug development activities, for drug discovery oral administration is one important property affecting absorption.[15]

2.2 Molecular target prediction

SwissTargetPrediction web tool was used to perform ligand-based target prediction for each small bioactive molecule.[16] This tool functions by comparing the query compound's chemical structure to a vast database of known bioactive molecules and their protein targets[16]. The tool provides a probability score for each predicted target and categorizes the target class (e.g., Enzyme, G Protein-Coupled Receptor, Kinase).

3. RESULT AND DISCUSSION

The Comparative in silico evaluation of Spisulosine (ES-285) and its three analogues (Xestoaminol C, 3-epi-Xestoaminol C, and 1-Deoxysphingosine) provided detailed insights into their pharmacokinetic (ADME), and target prediction profiles.

3.1 ADME and pharmacochemical properties

The predicted physicochemical parameters of Spisulosine and its analogues are summarized in [Table 3]. The data indicates that Spisulosine and 1-Deoxysphingosine are larger molecules, characterized by higher molecular weights (285.51 and 283.49, respectively), compared to Xestoaminol C and 3-epi-Xestoaminol C (both with MW: 229.4), and all four compounds were found to have an identical Topological Polar Surface Area (TPSA) of 46.25.

Table 3: Predicted Physiochemical Properties of Spisulosine, Xestoaminol C, 3-Epi-Xestoaminol C, And 1-Deoxysphingosine.

Physicochemical Property	Spisulosine	Xestoaminol C	3-epi-Xestoaminol C	1-deoxysphingosine
Molecular weight	285.51	229.4	229.4	283.49
Heavy atoms	20	16	16	20
Rotatable bonds	15	11	11	14
Molar Refractivity	92.51	73.28	73.28	92.04
TPSA	46.25	46.25	46.25	46.25

[Figure 1] presents the lipophilicity values. The LogP values show that Spisulosine (5.2) and 1-Deoxysphingosine (4.99) were significantly more lipophilic than Xestoaminol C (3.71) and 3-epi-Xestoaminol C (3.75). This higher lipophilicity of the C18 analogues (Spisulosine and 1-Deoxysphingosine) suggest stronger membrane permeability, which is a key factor in distribution. The water solubility of the compounds, as predicted by the ESOL (Estimated SOLubility) model, is presented in [figure 2], showing that the C14 analogues are more soluble than C18 compounds.

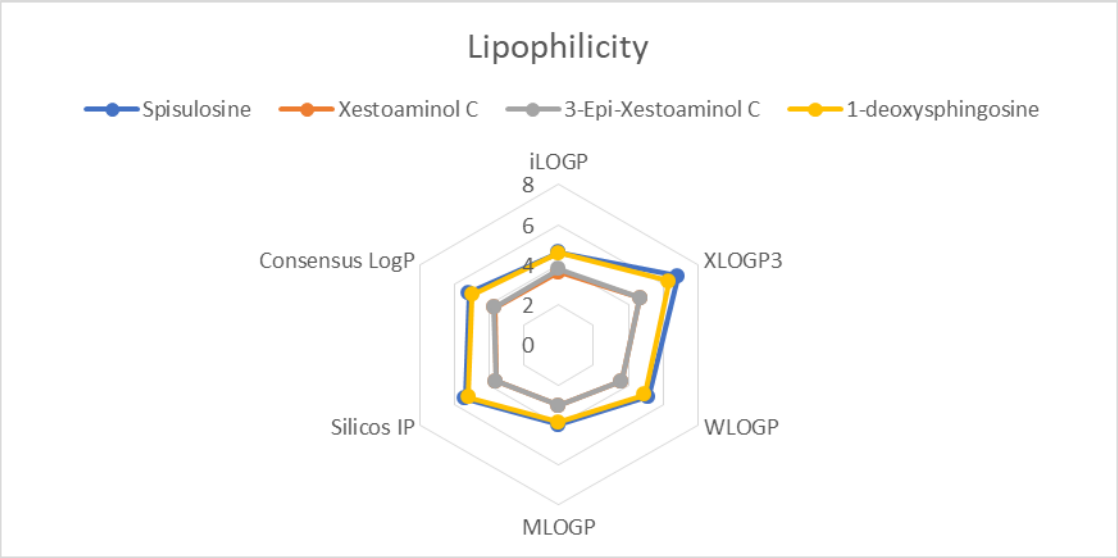


Figure 1: lipophilicity of Spisulosine and selected analogues.

Log S scale: Insoluble < -10, Poorly soluble < -6, Moderately soluble < -4, Soluble < -2, Very soluble < 0, > highly soluble.

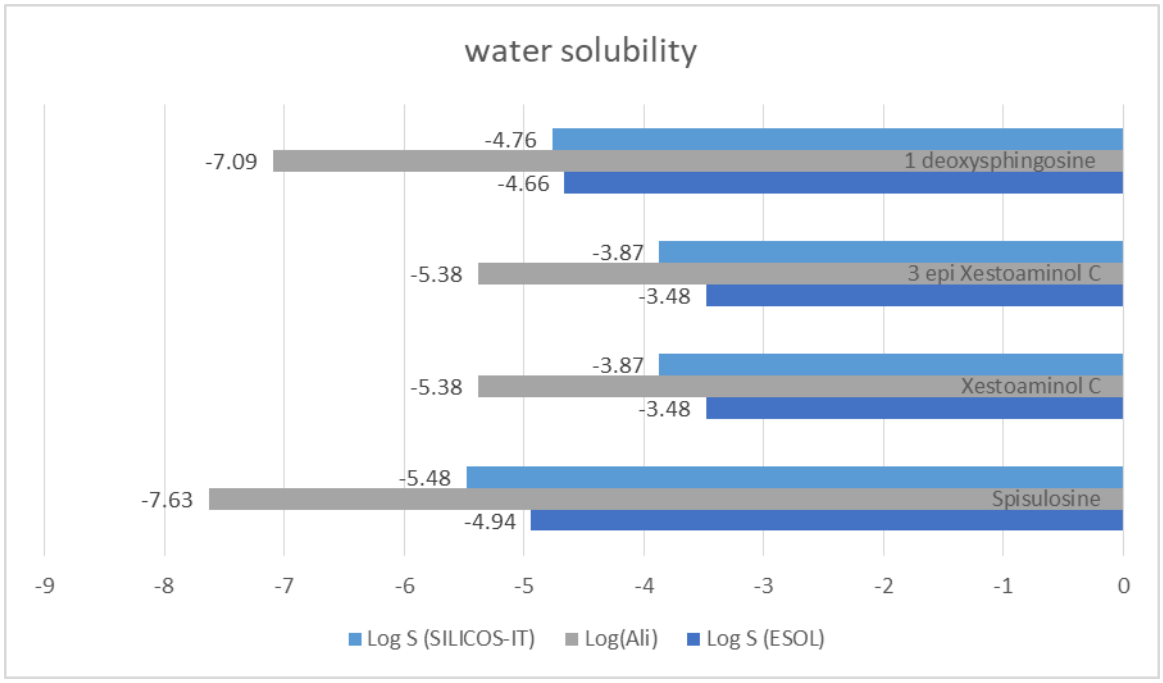


Figure 2: Water Solubility of Spisulosine and It's Three Analogues.

The pharmacokinetic properties, including absorption, permeation, and metabolic inhibition, predicted by SwissADME is provided in [Table 4]. All four compounds were predicted to have high gastrointestinal (GI) absorption, indicating a high potential for oral bioavailability. Furthermore, all four compounds were predicted to be blood-brain barrier (BBB) permeants, these findings are visually supported by the BOILED-Egg (Brain or IntestinaL EstimateD) permeation predictive model of SwissADME [figure 3] and [figure 4]. The yellow region (the yolk) indicates chance of penetrating to the brain, while the white region reflects the space filled by molecules that absorb more by the GI tract[17]. This prediction is highly relevant to the neurotoxicity concerns associated with Spisulosine. This property also supports potential activity against brain tumors.

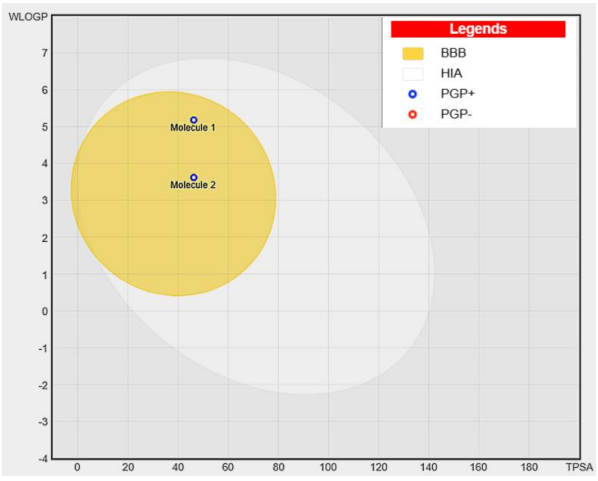


Figure 3: Boiled-Egg Plot of Spisulosine (Molecule 1) And Xestoaminol C (Molecule 2) (BBB- Blood Brain Barrier, HIA – Human Intestinal Absorption, PGP+ (P-Glycoprotein Substrate), PGP- (P-Glycoprotein Non-Substrate))

(BBB- blood brain barrier, HIA – human intestinal absorption, PGP+ (P-glycoprotein substrate), PGP- (P-glycoprotein non-substrate))

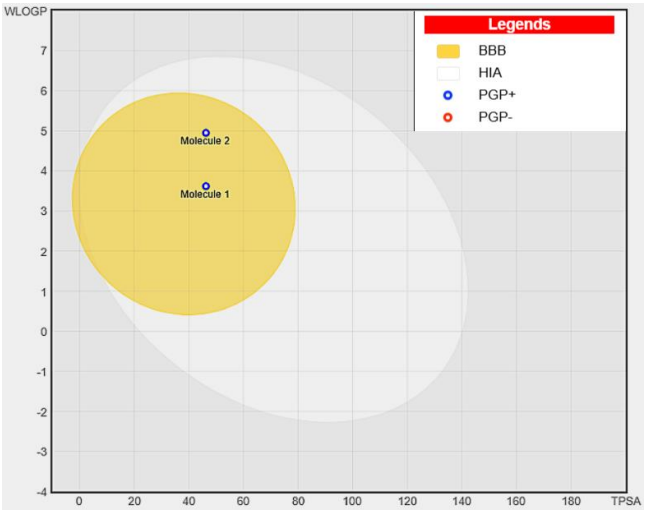


Figure 4: Bolied-Egg Plot Of 3-Epi-Xestoaminlo C (Molecule 1) And 1-Deoxysphingosine (Molecule 2).

All compounds were predicted to be P-glycoprotein (P-gp) substrates, P-gp is a member of the ATP-binding cassette (ABC) transporter family. P-gp is a molecular gatekeeper, actively pumps xenobiotics out of the brain parenchyma. This phenomenon keeps the intracellular drug concentration in tumor cells below a therapeutic threshold that can lead to cytotoxic effect of anti-tumor drugs[18]. The C14 analogues (Xestoaminol C and 3-epi-Xestoaminol C), with their lower lipophilicity, likely have a lower passive influx rate. This would allow the P-gp efflux pump to operate more effectively, actively removing the compounds from the brain parenchyma at a rate that prevents the threshold for neurotoxicity from being reached. This differential interaction with the P-gp system, mediated by their physicochemical differences, provides the superior safety profile of the C14 analogues and should be a primary focus for future experimental validation.

Table 4: Pharmacokinetic Properties of Spisulosine, Xestoaminol C, 3-Epi-Xestoaminol C, And 1-Deoxysphingosine.

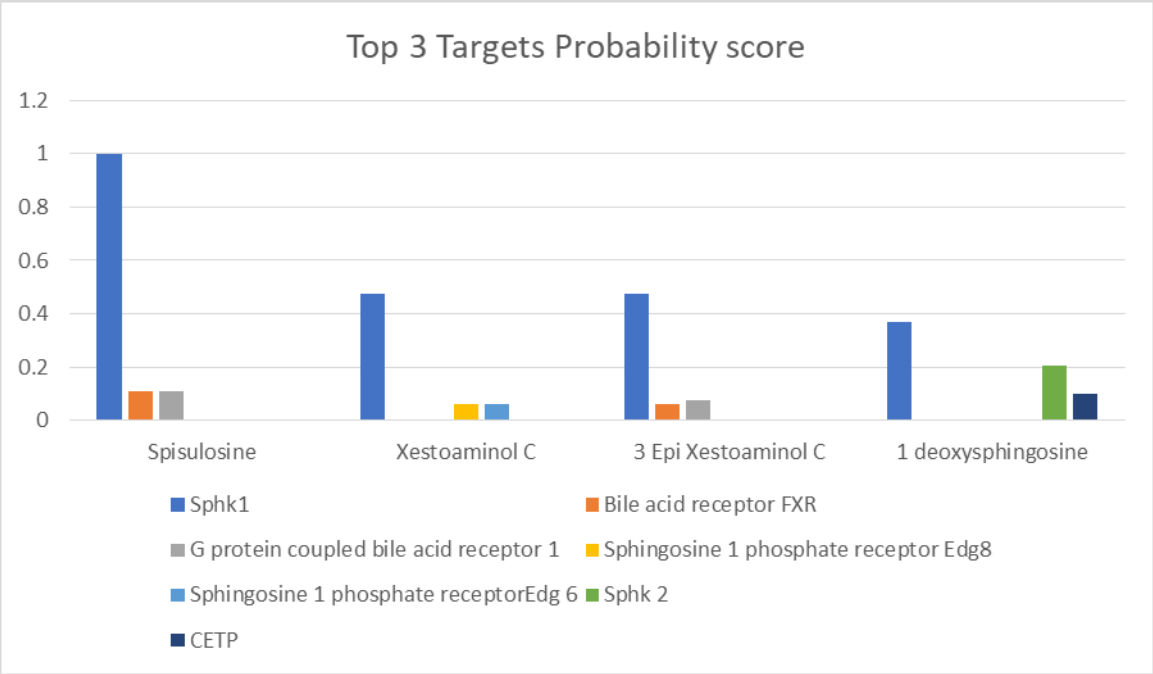
Pharmacokinetic Property	Compounds			
	Spisulosine	Xestoaminol- C	3-epi-Xestoaminol C	1-Deoxysphingosine
GI Absorption	High	High	High	High
BBB Permeant	Yes	Yes	Yes	Yes
P-gp Substrate	Yes	Yes	Yes	Yes
CYP1A2 Inhibitor	No	No	No	No
CYP2C19 Inhibitor	No	No	No	No
CYP2C9 Inhibitor	Yes	No	No	Yes
CYP2D6 Inhibitor	Yes	Yes	Yes	Yes
CYP3A4 Inhibitor	No	No	No	No
Log Kp (skin permeation)	-3.18 cm/s	-4.38 cm/s	-4.38 cm/s	-3.54 cm/s

A prominent difference was observed in the Cytochrome P450 (CYP) enzyme inhibition profiles of Spisulosine and its analogues. Both Spisulosine and 1-deoxysphingosine were predicted to inhibit CYP2C9 and CYP2D6, indicating a higher potential for (DDIs) drug-drug interactions.[19] While, Xestoaminol C and 3-epi-Xestoaminol C showed limited inhibition profile, affecting only CYP2D6. The smaller C14 analogues (Xestoaminol C and 3-epi-Xestoaminol C) exhibit a more favourable CYP inhibition profile than the larger C18 compounds (Spisulosine and 1-

deoxysphingosine). This difference is an important factor in evaluating their potential as safe drug candidates. Although none of the compound inhibited CYP3A4, which is the single most important enzyme in human drug metabolism, responsible for the biotransformation of a vast number of clinically used drugs[20]. Avoiding the inhibition of this specific isoform significantly reduces the risk of common DDIs and ADR. This indicates that C14 analogues, which inhibit only a single CYP isoform and not the highly relevant CYP3A4, have comparatively safer metabolic profiles and favourable candidates for further development.

Predicted skin permeability values shows that Spisulosine had the highest predicted skin permeation (-3.18 cm/s), followed by 1-deoxysphingosine (-3.54 cm/s). In contrast, Xestoaminol C and 3-epi-Xestoaminol C show lower skin permeation (both -4.38 cm/s).

Figure 5: Top 3 Targets Predictions of Compound Spisulosine, Xestoaminol C, 3 Epi Xestoaminol C, And 1 Deoxysphingosine.



Molecular target prediction

Molecular target prediction shows that all four compounds share a common primary molecular target: sphingosine kinase 1 (Sphk1) in [figure 5] with target class enzyme. This finding provides validation for their shared mechanism of action and supports the anticancer potential of the analogues. Sphingosine kinase 1 (SphK1) is a lipid kinase plays a vital role in the sphingolipid signaling pathway by catalyzing the phosphorylation of sphingosine to sphingosine-1-phosphate (S1P).[21] Elevated levels of S1P are known to promote cell proliferation and survival are frequently observed in various cancer types. Targeting SphK1, and SphK2 by using inhibitors to produce low levels of S1P can be an effective approach for cancer therapy.[22] The predicted affinity of Spisulosine and its analogues for Sphk1 provides a direct link to their anticancer properties.

While the primary target is consistent across the compound, there is a notable difference in the probability scores assigned by the SwissTargetPrediction tool. Spisulosine received a perfect probability score of 1.0, while Xestoaminol C and 3-epi-Xestoaminol C scored 0.4768 and 1-deoxysphingosine scored 0.3708. The lower scores for the analogues

may indicate a potential reduction in binding affinity or selectivity, a direct consequence of their structural differences, particularly the shorter C14 carbon chain. While the C14 analogues are predicted to have significantly more favourable ADME and metabolic profiles, they may also be less potent than the parent compound. This requires a careful consideration of the dose-response relationship in future studies.

CONCLUSION

In conclusion, this in-silico comparative analysis provides a comprehensive profile of Spisulosine and its three analogues, successfully identifying a plausible computational basis for the parent compound's clinical failure and, more importantly, locating a promising lead compound for future drug development. The study's findings demonstrate that while all four compounds share high predicted gastrointestinal absorption and blood-brain barrier permeation, the smaller C14 analogues, Xestoaminol C and 3-epi-Xestoaminol C, exhibit a significantly more favourable safety profile. This improved profile is attributed to their lower lipophilicity and a cleaner metabolic action, characterized by a limited CYP inhibition profile compared to the C18 analogues.

By retaining the primary therapeutic target, Sphingosine Kinase 1, the C14 compounds represent an ideal drug discovery outcome: a structural modification that reduces major risks —specifically, neurotoxicity and the risk of drug-drug interactions—while preserving the expected anticancer mechanism of action. This work underlines the value of modern in silico methods in accelerating the drug discovery process, enabling the rapid evaluation of a compound's toxicity and guiding rational drug design efforts. The C14 analogues identified in this study are suggested as better options for future experimental validation and lead optimization, representing a new and safer generation of Spisulosine-derived anticancer agents.

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