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Original Article

In silico ADMET Study, Synthesis and Anticholinesterase Activity of 1,8-Naphthyridine Derivatives

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ABSTRACT

Background: This study aimed to synthesize 1,8-naphthyridine derivatives, conduct an *in silico* ADMET analysis, and evaluate the compounds' anti-cholinesterase activity *in vitro*. **Materials and Methods:** The Conrad-Limpach method employed ethylacetoacetate and 2-aminopyridine to synthesize 1,8-naphthyridine derivatives. A modified Ellman's methodology was employed to assess the anti-cholinesterase activity of our synthesized compounds and to determine the percent inhibition and IC_{50} values. **Results:** The compounds exhibit a yield ranging from 65% to 72%. All compounds satisfy Lipinski's five criteria; hence, they adhere to the rule. **Conclusion:** The synthesized compounds inhibited AChE activity in a dose-dependent manner, ranging from 3.54% to 64.06%. The IC_{50} values, derived from the inhibition percentage, were determined to be 9.99 µM, 10.87 µM, 7.64 µM, 17.01 µM, and 12.74 µM for HSN_1 through HSN_5, respectively. The suppression of cholinesterase enzyme obstructs the degradation of acetylcholine into its constituents, choline and acetyl-CoA. The chemicals inhibited the cholinesterase enzyme in a dose-dependent manner. The findings prompted us to determine that 1,8-naphthyridine derivatives may be refined to yield prospective AChE inhibitors.

Keywords: Acetylcholinesterase, Alzheimer, Conrad-Limpach, Lipinski rule, Naphthyridine.

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INTRODUCTION

Memory impairment, cognitive difficulties, and/or neuronal degeneration in the brain are manifestations of Alzheimer's Disease (AD), a multifactorial neurodegenerative disorder that progresses with aging.[1] Approximately, 5-20% of the global population across all age demographics experiences serious symptoms. The precise etiology of Alzheimer's Disease (AD) remains ambiguous, possibly resulting from a confluence of many neurodegenerative elements. This encompasses diminished synaptic Acetylcholine (ACh) levels associated with neuronal malfunction; the development of senile plaques or neurofibrillary tangles; elevated concentrations of neurotoxic amyloid beta peptides; oxidative stress; and additional factors.[2-4] Cholinesterase enzymes catalyze the hydrolysis of Acetylcholine (ACh) into choline and acetic acid, a crucial mechanism for cholinergic neurons to return to their resting state after stimulation. AChE inhibitors or anti-cholinesterases obstruct the cholinesterase enzyme, hence enhancing the quantity and duration of the neurotransmitter effect by preventing the breakdown of ACh.[5] The fast breakdown of the neurotransmitter acetylcholine by Acetylcholinesterase (AChE) impedes impulse transmission in numerous cholinergic routes within the central and peripheral nervous systems. Enzyme inactivation, caused by various inhibitors, results in the accumulation of acetylcholine, excessive stimulation of nicotinic and muscarinic receptors, and disruption of neurotransmission. The most relevant drugs and toxins are acetylcholinesterase inhibitors, which function by interfering with the enzyme.[6]

Naphthyridine is the bioisostere of quinoline in which N replaces one C-H.[7] It is known to be resistant to attack by electrophilic reagents undergo quaternization and on oxidation with peracids yield N-oxides.[8] Due to structural resemblance to quinoline, the naphthyridine derivatives have been extensively studied for exploring their diverse biological activities. 1,8-naphthyridines have been widely investigated for various pharmacological actions including cardiovascular effects, antihistaminic, antibacterial etc.[9-11] Previous studies have also related 1,8-naphthyridine nucleus to be isosteric to the azelastine. The basic amino group of this nucleus paves its role in majority of its actions. In the present investigation we planned to design and synthesize novel 1,8-naphthyridine derivatives for anti-cholinesterase activity.

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MATERIALS AND METHODS

All chemicals, reagents, and solvents were utilized without purification were procured from Sigma, CDH, and Loba. The melting temperature was ascertained using the open capillary method, solubility was qualitatively assessed, and the retention factor was established by Thin Layer Chromatography (TLC) employing pre-coated silica gel G plates.[12,13] The Conrad-Limpach technique for synthesizing quinolines employed ethyl acetoacetate and 2-aminopyridine to produce 1,8-naphthyridine derivatives. The methodologies employed to synthesize the 1,8-naphthyridine derivatives (Scheme 1) are illustrated in the subsequent scheme, which is derived from the research conducted by Mishra.[14] and Sulistyowaty *et al.*[15]

Synthesis of 2-hydroxy-4-methyl-1, 8-naphthyridine

0.1 mole of ethyl acetoacetate was combined with 0.1 mole of amino pyridine. 5 mL of strong sulfuric acid were added to the mixture. A white solid precipitate began to form in the reaction vessel. The mixture was further heated to 135°C and subjected to reflux. The white powder gradually begun to dissipate. Thin-layer chromatography was employed to monitor the reaction during the reflux of the combination. The product was synthesized by chilling the reaction mixture overnight. Ethanol was subsequently employed for filtration, drying, and recrystallization.

General method for synthesis of 4-methyl-1,8-naphthyridin-2-yl benzoate derivatives (HSN_{1-5})

The subsequent procedures involved dissolving 0.1 mole of 2-hydroxy-4-methyl-1,8-naphthyridine in ethanol, introducing 0.12 mole of benzoyl chloride derivatives, and maintaining agitation at 0°C for 2 hr. To inhibit the generation of CO_2 gas bubbles, the resultant mixture was treated with a 10% $NaHCO_3$ solution. Subsequent to the filtration of the solid, the mixture was washed with cold water. The substance was recrystallized from ethanol to extract the active constituents.

In silico ADMET study

The ligands' 2D structures were sketched on ChemDraw Ultra 12.0 and imported into Chem 3D to generate the three-dimensional structures. After creating the official SMILES (simplified molecular-input line-entry system) in ChemDraw, SwissADME and pkCSM's online tools performed ADMET analysis, physicochemical parameter prediction, and Lipinski rule of five drug-likeness. The Lipinski Rule-of-five linked physicochemical and pharmacokinetic factors.[16,17]

Evaluation of Anti-cholinesterase Activity

Preparation of test solutions

To achieve the final concentration of -10 µM, the synthesized compounds were dissolved in appropriate amount of DMOS and mixed with phosphate buffer solution (PBS, pH 7.8).

Test procedure

Ellman's reagent, a prevalent chromogenic agent, was employed in the AChE-catalyzed hydrolysis reaction.[18,19] Forty microliters of 50 mM Tris-HCl buffer at pH 8.0, twenty microliters of the test sample solution, and one hundred microliters of Ellman's reagent-prepared by dissolving 18.5 mg of reagent in 10 mL of water-were combined with twenty microliters of AChE solution (comprising 0.26 U/mL of enzyme mixed with 15 mL of buffer) and placed in each well of a 96-well microplate. The assembly was placed in an incubator for 15 min at 25°C. The absorbance was measured at 412 nm. Subsequently, 20 µL of a substrate, consisting of Acetyl Thiocholine (ACTh) mixed with water, was added to the wells. The microplate was thereafter placed in a room at 37°C for a duration of 20 min to ensue develop. The whole AChE activity was measured by conducting a blank test. The absorbance at 412 nm was quantified and inhibition was calculated by the formula:

$$\%\text{AChE inhibition} = (A_{blank} - A_{sample}) / A_{blank} \times 100$$

RESULTS AND DISCUSSION

Chemistry

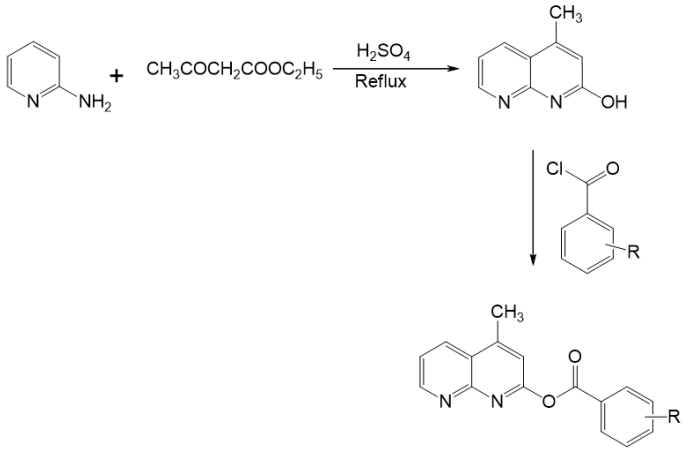
Five 1,8-napthyridine derivatives (HSN_{1-5}) were synthesized and the physical and chemical characterization was done (Table 1).

4-methyl-1,8-naphthyridin-2-yl benzoate (HSN_1)

^{1}H-NMR (δ ppm): 6.85-8.70 (aromatic protons), 2.57 (methyl protons); FTIR (cm^{-1}): 3050.55 (C-H), 1327.08-1225.82 (C-C, aromatic), 850.64 (C-N).

4-methyl-1,8-naphthyridin-2-yl 2-chlorobenzoate (HSN_2)

^{1}H-NMR (δ ppm): 6.88-8.70 (aromatic protons), 2.57 (methyl protons); FTIR (cm^{-1}): 3050.55 (C-H), 1327.08-1225.82 (C-C, aromatic), 850.64 (C-N).



Scheme 1: Synthesis of 1,8-naphthyridine derivatives.

4-methyl-1,8-naphthyridin-2-yl 3-methoxybenzoate (HSN_3)

^{1}H-NMR (δ ppm): 6.85-8.70 (aromatic protons), 2.57 (methyl protons); FTIR (cm^{-1}): 3017.39 (C-H), 1399.26-1253.77 (C-C, aromatic), 821.51 (C-N).

4-methyl-1,8-naphthyridin-2-yl 3-fluorobenzoate (HSN_4)

^{1}H-NMR (δ ppm): 6.88-8.70 (aromatic protons), 2.57 (methyl protons); FTIR (cm^{-1}): 3029.11 (C-H), 1325.36-1221.91 (C-C, aromatic), 867.04 (C-N).

4-methyl-1,8-naphthyridin-2-yl 2,6-dichlorobenzoate (HSN_5)

^{1}H-NMR (δ ppm): 6.85-8.70 (aromatic protons), 2.57 (methyl protons); FTIR (cm^{-1}): 2972.32 (C-H), 1412.08-1296.02 (C-C, aromatic), 851.13 (C-N).

Anticholinesterase activity

The anticholinesterase activity was evaluated by Ellman's method and the results of inhibition of cholinesterase activity was calculated from the absorbance of blank and the test solutions (Table 2).

The synthesized derivatives were able to inhibit AChE activity dose dependently form 3.54 to 64.06%. The IC_{50} was calculated from inhibition percentage and was found to be 9.99 µM, 10.87 µM, 7.64 µM, 17.01 µM and 12.74 µM for HSN_1 to HSN_5 respectively.

In silico ADMET properties of synthesized naphthyridine derivatives

The SMILES of the synthesized naphthyridine derivatives was generated using chemdraw ultra 12.0 software. SwissADME made predictions about the physicochemical properties of the substances *in silico* are presented in Table 3, and the ADMET properties predicted by pkCSM are presented in Table 4 and Figure 1.

DISCUSSION

Chemistry

The synthesis of naphthyridine from β-keto esters adheres to the principles of the Conrad-Limpach synthesis of quinolines. The condensation of 2-aminopyridine with ethyl acetoacetate produced 4-methyl-1,8-naphthyridine. The mechanism underlying the cyclization is contingent upon temperature. An anil is generated when the amine and ester at the keto group undergo condensation at low temperatures; subsequent heating of this anil facilitates its transformation into naphthyridine-4-one. The condensation of the amine at the ester functional group produces the anilide as an initial product at elevated temperatures. Heat or acidity induces the anilide to cyclize, followed by oxidation that yields 2-hydroxy-4-methyl-1,8-naphthyridine. The nucleophilic attack of the hydroxyl group of naphthyridine on the electron-deficient chloride of benzoyl chloride leads to nucleophilic substitution, facilitating the esterification process and yielding the desired molecules. The spectral analysis of the synthesized derivatives indicated the presence of aromatic protons and methyl protons in all molecules. The protons of methoxy were detected in HSN_3. The FTIR spectrum displayed stretching vibrations attributed to C-H, C-C, C=C, C-O, and C-N in the compounds.

Each derivative (HSN_1-HSN_5) carries a benzoyl substituent at the 2-hydroxy position of the naphthyridine. The novelty arises from varying the substituents on the benzoyl ring (e.g., chloro, methoxy, fluoro, dichloro), which modulates electronic effects and steric hindrance. The combination of the heteroaromatic naphthyridine ring (electron-deficient due to nitrogen atoms) with electron-donating or electron-withdrawing substituents on the benzoyl moiety creates a tunable system. This directly influences acetylcholinesterase binding affinity, as seen in the activity differences (HSN_3 with methoxy being most potent, HSN_4 with fluoro being least). The ester linkage introduces conformational flexibility while maintaining planarity of the aromatic system. This balance between rigidity (heteroaromatic core) and adaptability (benzoyl ester substituents) is a structural innovation compared to previously reported naphthyridines.[20-23]

The physicochemical profiling of compounds HSN_1-HSN_5 revealed consistent compliance with Lipinski's Rule of Five, suggesting favorable drug-likeness across the series. All compounds exhibited molecular weights below 500 g/mol, hydrogen bond donor counts of zero, and hydrogen bond acceptor counts between four and five, aligning with established oral bioavailability criteria. Lipophilicity (Log P) values ranged from 3.53 to 4.82, indicating moderate to high hydrophobicity. While HSN_1-HSN_4 maintained Log P values within the optimal range (≤4), HSN_5 approached the upper threshold, suggesting potential challenges in balancing permeability with aqueous solubility. This observation was corroborated by Log S values, where HSN_5 demonstrated the lowest predicted solubility (-5.52), in contrast to the relatively moderate solubility of HSN_1-HSN_4 (approximately -4.1 to -4.7). Polar Surface Area (PSA) values remained consistently low (52-61 Å²), well below the 140 Å² threshold, supporting the likelihood of efficient passive diffusion across biological membranes. Similarly, the Number of Rotatable Bonds (NRB) was restricted to three or four, suggesting limited conformational flexibility, which is generally advantageous for oral bioavailability. Among the series, HSN_1 and HSN_4 emerged as the most balanced candidates, combining moderate lipophilicity (Log P ~3.5-3.7), acceptable solubility, and low PSA. HSN_3, with a slightly higher PSA (61.31 Å²), may exhibit improved polarity-driven interactions but remains within the favorable permeability range. Conversely, HSN_5, despite its higher

molecular refractivity (85.92), displayed excessive lipophilicity and poor solubility, potentially limiting its pharmacokinetic performance.[24]

The ADMET profiling of compounds HSN_1-HSN_5 provides a comprehensive view of their pharmacokinetic and toxicological behavior, complementing the physicochemical analysis. All compounds demonstrated high intestinal absorption, with values exceeding 96%, indicating strong potential for oral bioavailability. The loading capacity in water (log mol/L) ranged from -3.43 to -4.41, consistent with moderate to low aqueous solubility. Notably, HSN_5 exhibited the poorest solubility (-4.412), in line with its higher lipophilicity. Porosity (log Papp) values were favorable across the series (1.33-1.43), suggesting efficient permeability. Transdermal permeability (log Kp) values were consistently negative (~ -2.4 to -2.6), indicating limited suitability for transdermal delivery. The volume of distribution (VDss) values were relatively low (log L/kg between -0.075 and -0.264), suggesting restricted tissue distribution and a tendency toward plasma confinement. Central Nervous System (CNS) permeability values (log PS) revealed limited brain penetration, with HSN_2 (-1.973) showing the highest potential, while HSN_3 and HSN_4 (-2.842 and -2.826, respectively) were least permeable. This suggests that the series is more suited for peripheral rather than CNS-targeted applications. Toxicological predictions revealed consistent hepatotoxicity across all compounds, warranting caution in further development. The AMES mutagenicity test was positive for HSN_1-HSN_4, but negative for HSN_5, suggesting that HSN_5 may have a comparatively safer genotoxic profile despite its solubility limitations. Acute oral toxicity (LD_{50}) values ranged from 2.50 to 2.70 mol/kg, indicating moderate toxicity across the series. these findings suggest that HSN_1-HSN_4 are strong candidates for further optimization, particularly with structural modifications to mitigate toxicity.

Anticholinesterase activity

The inhibition of cholinesterase enzyme prevents the breakdown of acetylcholine into its component's choline and acetyl CoA. The compounds were able to inhibit cholinesterase enzyme in a dose dependent manner. The results show that the presence of electron donating group in the compound was beneficial for anticholinesterase action (HSN_3). Presence of strong electron withdrawing group in compound was detrimental for anticholinesterase action (HSN_4). Non-substituted compound (HSN_1) was more effective in inhibition of cholinesterase action than a di-substituted compound (HSN_5).

Table 1: Physical and chemical features of HSN_{1-5}.

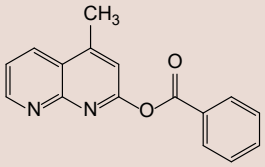
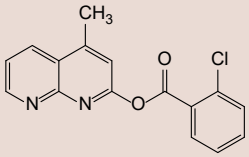
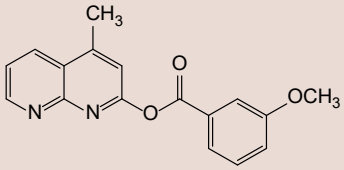
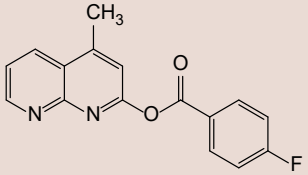
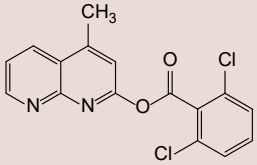
Code	Structural Formula	Yield	Melting point	Solubility
HSN_1		68	120-121°C	DMSO
HSN_2		72	117-119°C	DMSO
HSN_3		67	166-168°C	DMSO
HSN_4		65	140-142°C	DMSO
HSN_5		69	146-148°C	DMSO

Table 2: %Inhibition of cholinesterase action.

Code	% AChE inhibition				
	2 µM	4 µM	6 µM	8 µM	10 µM
HSN_1	12.76	25.05	33.09	40.42	49.64
HSN_2	11.58	19.85	28.84	36.64	46.80
HSN_3	15.83	29.78	38.06	52.95	64.06
HSN_4	3.54	9.45	15.60	21.51	28.60
HSN_5	7.56	14.42	22.45	31.20	39.24

Table 3: Physicochemical properties of HSN_{1-5}.

Compound Code	MW	HBD	HBA	Log P	NRB	PSA	MR	Log S
HSN_1	264.28	0	4	3.56	3	52.08	75.9	-4.12
HSN_2	298.72	0	4	4.19	3	52.08	80.91	-4.7
HSN_3	294.3	0	5	3.53	4	61.31	82.4	-4.16
HSN_4	282.27	0	5	3.66	3	52.08	75.86	-4.26
HSN_5	333.17	0	4	4.82	3	52.08	85.92	-5.52

Table 4: ADMET of HSN_{1-5}.

ADMET Parameters	HSN_1	HSN_2	HSN_3	HSN_4	HSN_5
Absorption					
Loading capacity in water (log mol/L)	-3.512	-3.731	-3.432	-3.446	-4.412
Porosity of $CaCO_2$ (log Papp in 10-6 cm/s)	1.358	1.399	1.334	1.338	1.425
Percentage of Human Intestinal Absorption	98.568	97.011	99.392	98.236	96.183
Transdermal Permeability (log Kp)	-2.448	-2.499	-2.642	-2.633	-2.605
Distribution					
(log L/kg) of VDss in humans	-0.189	-0.172	-0.228	-0.264	-0.075
Central nervous system permeability (log PS)	-2.094	-1.973	-2.842	-2.826	-2.779
Metabolism					
CYP2D6 enzyme product	No	No	No	No	No
Substrate for cytochrome P_{450} 3A4	Yes	Yes	Yes	Yes	Yes
Excretion					
Complete Elimination Rate (log mL/min/kg)	0.771	0.005	0.743	0.648	0.052
Sustaining renal OCT2	No	No	No	No	No
Toxicity					
Exposure to AMES	Yes	Yes	Yes	Yes	No
Hepatotoxicity	Yes	Yes	Yes	Yes	Yes
Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	2.503	2.618	2.662	2.541	2.706

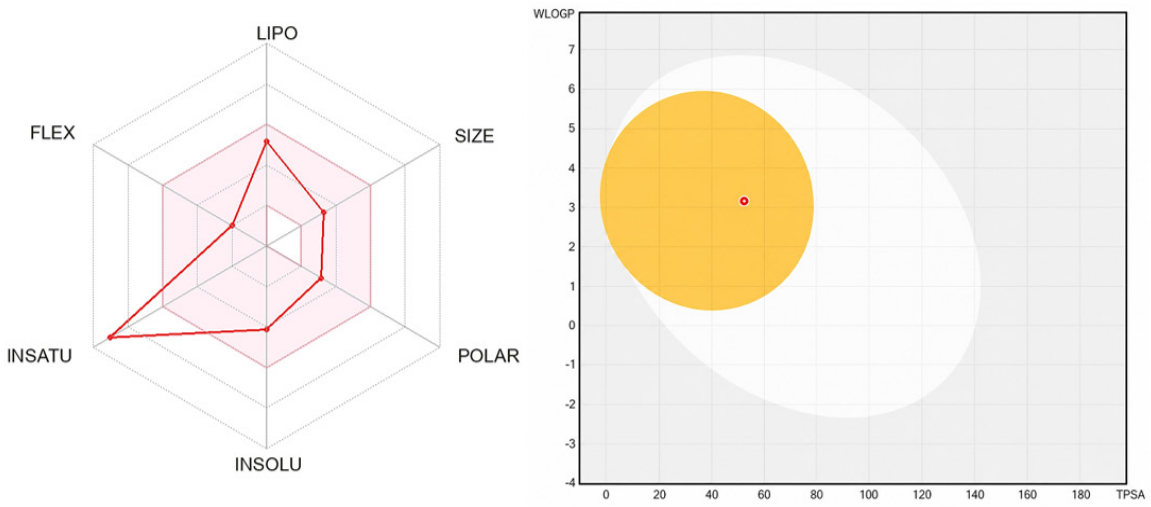


Figure 1: Physicochemical properties and Boiled Egg diagram of HSN_1.

CONCLUSION

The present study successfully synthesized five novel 1,8-naphthyridine derivatives (HSN_1-HSN_5) via the Conrad-Limpach method and evaluated the *in silico* ADMET properties alongside *in vitro* anticholinesterase activity. All compounds adhered to Lipinski's Rule of Five, confirming their drug-likeness and potential for oral bioavailability. The ADMET analysis revealed consistently high intestinal absorption (>96%), moderate aqueous solubility, and limited CNS penetration, suggesting that these molecules are more suitable for peripheral cholinergic modulation rather than central nervous system targeting. Toxicity profiling indicated hepatotoxicity across the series, while AMES mutagenicity was observed in HSN_1-HSN_4 but absent in HSN_5, highlighting a safety trade-off between efficacy and genotoxic risk. Biological evaluation demonstrated dose-dependent inhibition of acetylcholinesterase, with IC_{50} values ranging from 7.64 µM to 17.01 µM. Among the derivatives, HSN_3 (bearing an electron-donating methoxy group) exhibited the strongest inhibitory activity, whereas HSN_4 (fluoro-substituted) showed the weakest, underscoring the influence of electronic substituents on enzyme inhibition. The unsubstituted HSN_1 also performed better than the di-substituted HSN_5, suggesting steric and electronic effects play a critical role in activity modulation.

Overall, the findings establish that 1,8-naphthyridine derivatives represent promising scaffolds for acetylcholinesterase inhibition, with HSN_3 emerging as the most potent candidate. However, the observed hepatotoxicity and mutagenicity necessitate further structural optimization and safety evaluation. Future work should focus on derivative refinement, substitution pattern optimization, and formulation strategies to enhance solubility and reduce toxicity, thereby advancing these molecules toward potential therapeutic applications in Alzheimer's disease.

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ABBREVIATIONS

ACh: Acetylcholine; **AChE:** Acetylcholinesterase; **AD:** Alzheimer's Disease; **ADMET:** Absorption, Distribution, Metabolism, Excretion and Toxicity; **CNS:** Central Nervous System; **DMSO:** Dimethyl Sulfoxide; **FTIR:** Fourier Transform Infrared Spectroscopy; **HBA:** Hydrogen Bond Acceptors; **HBD:** Hydrogen Bond Donors; **HSN:** Hydroxy Substituted Naphthyridine; **IC50:** Half Maximal Inhibitory Concentration; **LD50:** Median Lethal Dose; **Log P:** Partition Coefficient; **Log S:** Solubility Coefficient; **MR:** Molar Refractivity; **MW:** Molecular Weight; **NRB:** Number of Rotatable Bonds; **PBS:** Phosphate Buffer Solution; **pkCSM:** Pharmacokinetic Properties Prediction using Graph-Based Signatures; **PSA:** Polar Surface Area; **SMILES:** Simplified Molecular Input Line Entry System; **TLC:** Thin Layer Chromatography; **Tris-HCl:** Tris Hydrochloride; **VDss:** Volume of Distribution at Steady State.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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