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CADD-DRIVEN DESIGN OF MERIDIANIN ANALOGUES AS DUAL GSK-3B AND DYRK1A INHIBITORS FOR NEUROPROTECTION AND COGNITIVE ENHANCEMENT

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ABSTRACT

In the competitive field of neurodegenerative diseases, such as Alzheimer's and Parkinson's, this research offers a new family of dual-targeted directed ligands, all centered on a unique 2-aminopyrimidine-indole scaffold, derived from marine meridianins. The study employed a structure-based design and synthesis of inhibitors for GSK-3β and DYRK1A kinases, assembling a logical family of 40 ligands via computer screening for drug-likeness according to Lipinski's Rule of Five (Molinspiration) and prediction of kinase inhibition potential with PASS prediction methods. The study's validity is further evidenced by molecular docking tests, where two kinases were employed to make predictions, and 80 docking runs were conducted with AutoDock to confirm the predictions. The study's results reveal that the new family of ligands has shown higher activity than that of the standard compound, indirubicin-3-monoxime. Out of the family, M16 and M32 emerged as the best dual inhibitors, providing the best docking scores, where -10.05 and -10.20 kcal/mol are for GSK-3β, and -8.62 and -9.37 kcal/mol are for DYRK1A kinases, respectively. ADME and toxicity prediction, carried out with ADMETlab 2.0, revealed excellent blood-brain barrier permeability and positive pharmacokinetics with acceptable toxicity, providing a rationale for further research into more potent neuroprotective agents in

the field of neurodegenerative diseases research.

KEYWORDS: 2-Aminopyrimidine–indole; dual-target directed ligands; Neurodegenerative diseases; Kinase inhibitors; Molecular docking; Computer-aided drug design; Neuroprotection; GSK-3β; DYRK1A.

INTRODUCTION

Drug Design and Discovery

Drug design and discovery involves designing new drug compounds by modifying their structures. In neuropharmacology, this involves enhancing neuroprotective properties and minimizing side effects.[15] The primary concept of drug design and discovery involves designing a drug that can target specific areas in the body.[8,9]

PRINCIPLES GUIDING CNS DRUG DEVELOPMENT

Development of CNS drugs involves more than just applying the simple rules of drug design. Lipinski's Rule of Five acts as a guiding principle, and for neurodegenerative diseases, crossing the blood-brain barrier is essential. The BOILED-Egg model helps in predicting this, and the drug should not be a substrate for P-glycoprotein. ADMET helps in predicting this and nervous system toxicity.[17,18]

COMPUTER-AIDED DRUG DESIGN (CADD) IN NEUROSCIENCE

CADD has significantly changed the way we deal with the development of drugs for neuroscience by introducing computer-based thinking into the design of drug molecules. It combines computer chemistry, modeling, and bioinformatics to identify molecules that can target neurological diseases precisely. This reduces costs significantly, which is essential for the development of neurodegenerative diseases.[8,18]

MOLECULAR DOCKING: VISUALIZING MOLECULAR INTERACTIONS

Molecular docking is one of the key pillars of computer-aided drug design, which predicts where the ligand will bind to the receptor and how it will interact with the receptor's active site. This is especially important for neurodegenerative diseases. Molecular docking can be performed with different levels of flexibility: rigid docking, semi-flexible docking, and completely flexible docking.

THE PRIVILEGED SCAFFOLD: 2-AMINOPYRIMIDINE, INDOLE

Marine-derived alkaloids, such as Meridianins, have a special structure known as the 2-aminopyrimidine, indole scaffold. This structure shows promise for developing neurotherapeutic agents, as it can be modified to improve its pharmacokinetic and pharmacodynamic properties.[5,1]

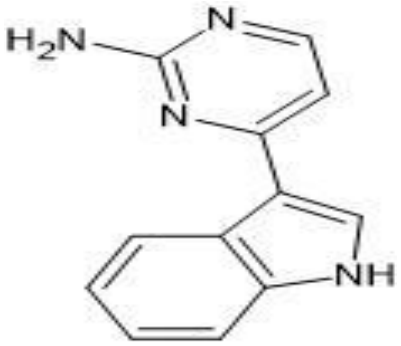


Fig. 1: Core structure of the 2-Aminopyrimidine, Indole Scaffold.

SCHEME FOR SYNTHESIS

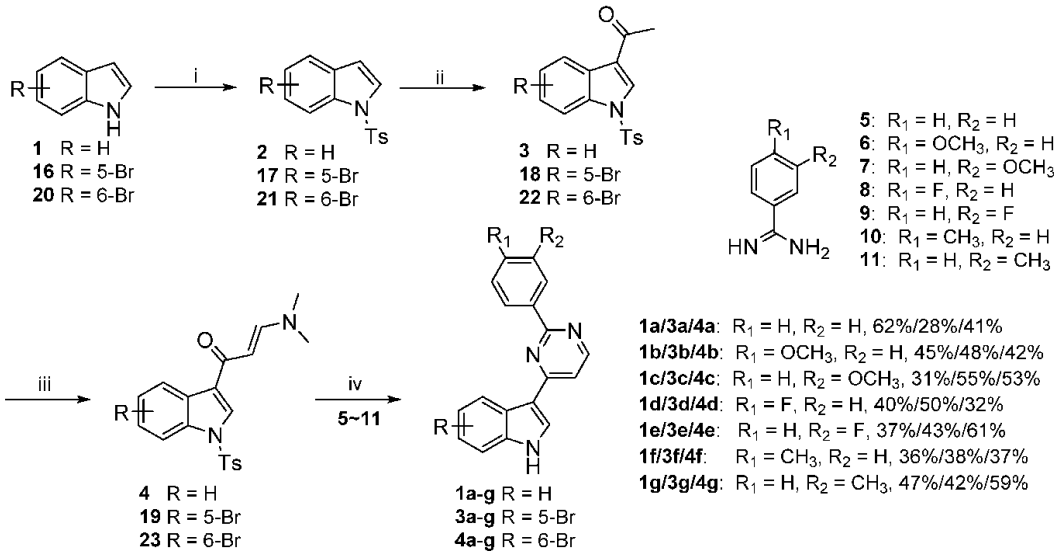
The concise multistep routes toward the synthesis of meridianin natural products and their analogues have used commercially available indole scaffolds. Taken as a whole, the reported strategies have used indolic N-protection, C-3 functionalization, enaminone formation, and final heterocyclic or side-chain elaboration to afford access to a very wide range of structurally diverse derivatives.[6,14,20]

Following the representative approach described in Schemes 1 and 2,(Fig :2 and Fig :3)the indole nitrogen is first protected with tosyl chloride under basic conditions to give N-tosylated intermediates, which then undergo Friedel-Crafts acylation at the C-3 position with acetic anhydride and aluminum chloride to introduce the acetyl functionality. Further transformation of such intermediates into their corresponding enaminone derivatives via reaction with DMF-DMA provides key precursors for further diversification. Final meridianin analogues were formed by either cyclocondensation or nucleophilic substitution with appropriate heterocyclic or substituted amine partners in the presence of potassium carbonate:

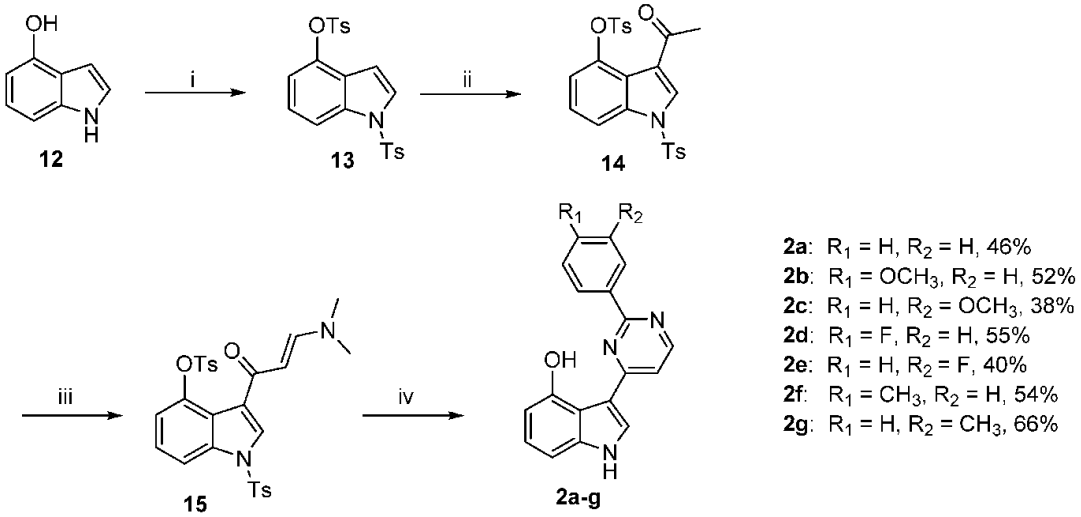
A second approach entails the contemporaneous protection of the indolic nitrogen and the phenolic hydroxyl group, followed by a similar process of C-3 acylation, enaminone formation, and final couplings, and provides other derivatives of meridianin with another pattern of substitution.

Correspondingly, the alkylated isothiouronium derivatives were prepared by the attachment of dibromoalkyl or bromoalkyl chains to appropriate starting materials under basic conditions followed by cyclization with thiourea according to Schemes 3 and 4 (Fig:4 and Fig :5). This thus afforded entry into sulfurcontaining analogues at variable alkyl chain lengths, increasing the chemical diversity of the meridianin scaffold.

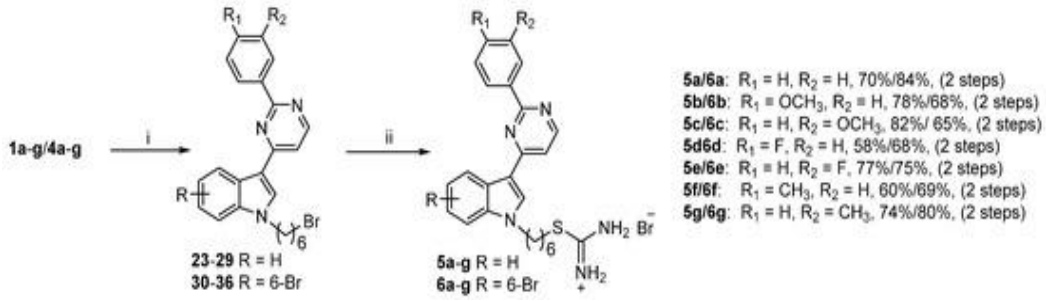
Such synthetic methodologies also provide modular and flexible routes to prepare natural meridianins and their structurally modified analogues for further studies into their structure-activity relationships and optimization into pharmacologically active candidates.



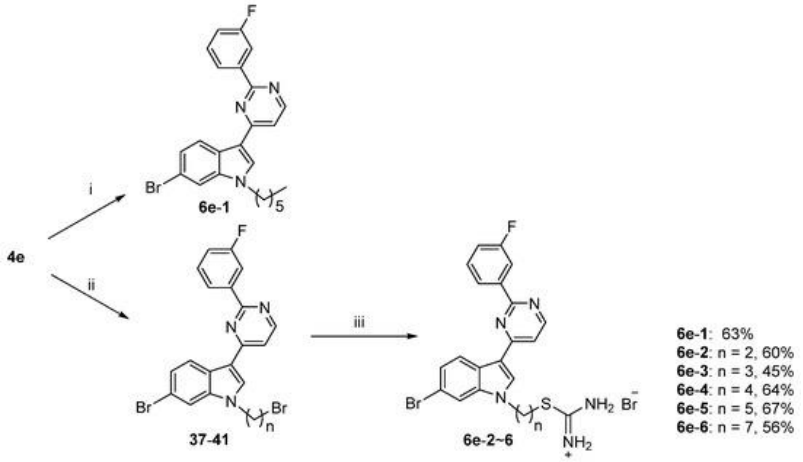
Scheme 1. (Figure:2).



Scheme 2. (Figure:3).



Scheme 3. (Figure:4).



Scheme 4. (Figure:5).

CHEMICAL AND PHARMACOLOGICAL PROFILE

The 2-aminopyrimidine-indole core (Figure:6) is a fused heterocyclic system. Its biological activity mainly relies on the electronic properties of its nitrogen atoms. The indole part typically contributes to hydrophobic interactions and π-stacking in enzyme pockets. The 2-aminopyrimidine group serves as a classic pharmacophore, forming significant hydrogen bonds with kinase hinge regions. This dual functionality increases its chances of targeting multiple sites, including inhibiting kinases associated with neurodegeneration. [2,5]

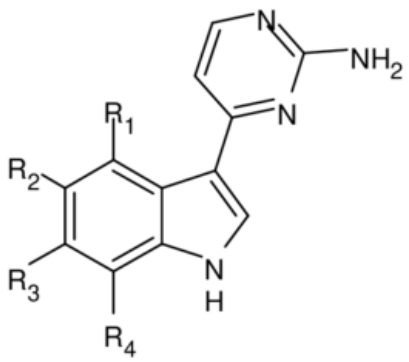


Figure 6.

NEURODEGENERATIVE DISEASES: A THERAPEUTIC CHALLENGE

Neurodegenerative diseases such as Alzheimer's disease (AD) and Parkinson's disease (PD) involve the gradual and irreversible loss of neuronal structure and function.[11] Unlike cancer, which features uncontrolled cell growth, neurodegeneration involves complex processes such as protein misfolding and aggregation—for example, amyloid-β, tau, and α-synuclein—neuroinflammation, oxidative stress, and disrupted cell signaling pathways. This complexity often makes single-target therapies ineffective, emphasizing the need for dual-target directed ligands (DTDLs).[4,11]

COMMON PATHOLOGICAL HALLMARKS

Key processes driving neurodegeneration include:

- Synaptic Dysfunction and Loss: This is the initial event that leads to cognitive and motor decline.
- Proteinopathy: This refers to the buildup of harmful protein aggregates.
- Chronic Neuroinflammation: Continual activation of microglia and astrocytes contributes to the condition.
- Mitochondrial Dysfunction and Oxidative Stress: These issues lead to neuronal energy failure and damage.
- Aberrant Kinase Signaling: Overactivity of kinases like GSK-3β and DYRK1A causes tau phosphorylation, neuroinflammation, and neuronal death.

CLASSIFICATION OF NEUROPROTECTIVE AGENTS

Neurotherapeutic strategies can be grouped by their main target or mechanism:

- Symptomatic Agents: Cholinesterase inhibitors (Donepezil), NMDA receptor antagonists (Memantine).
- Disease-Modifying Agents (Under Investigation):
- Anti-Amyloid & Anti-Tau Therapies: Monoclonal antibodies, tau aggregation inhibitors.
- Kinase Inhibitors: Targeting GSK-3β, CDK5, DYRK1A.
- Anti-inflammatories & Immunomodulators.
- Neurotrophic Factor Enhancers.
- Multi-Target Directed Ligands (MTDLs): These are designed to tackle multiple pathways simultaneously, which is the focus of this project.[16,19,10]

PROJECT RATIONALE

Considering the limitations of current therapies and the complex causes of conditions like AD and PD, this project aims to systematically design new 2-aminopyrimidine-indole derivatives as dual-target kinase inhibitors using in silico methods. By utilizing CADD tools, including molecular docking against GSK-3β andDYRK1A virtual screening, and in silico ADMET profiling, we aim to identify optimized lead compounds that display better neuroprotective properties, balanced dual-target activity, and favorable CNS drug-like characteristics for further development.[4,11,13]

AIM

To design and assess new 2-aminopyrimidine-indole derivatives as dual-target kinase inhibitors for treating neurodegenerative diseases using in silico methods.

OBJECTIVES

- Lead Identification and Scaffold Analysis: To select the 2-aminopyrimidine-indole scaffold and determine its reactive sites for designing analogues.
- Rational Analogue Design: To make targeted chemical modifications and include functional groups to improve dual-target affinity and central nervous system (CNS) drug-like properties.
- Computational Modeling and Virtual Screening: To create 3D structures of the designed ligands, predict their drug-like properties (Lipinski's Rule, bioavailability), and evaluate their potential biological activities.
- Dual-Target Molecular Docking: To assess the binding affinity and interactions of the designed derivatives with key neurodegenerative targets (GSK-3β, DYRK1A) using molecular docking simulations.
- In Silico ADMET Profiling: To predict the pharmacokinetic properties, blood-brain barrier (BBB) permeability, and toxicity profiles of promising candidates using computational tools.[9]

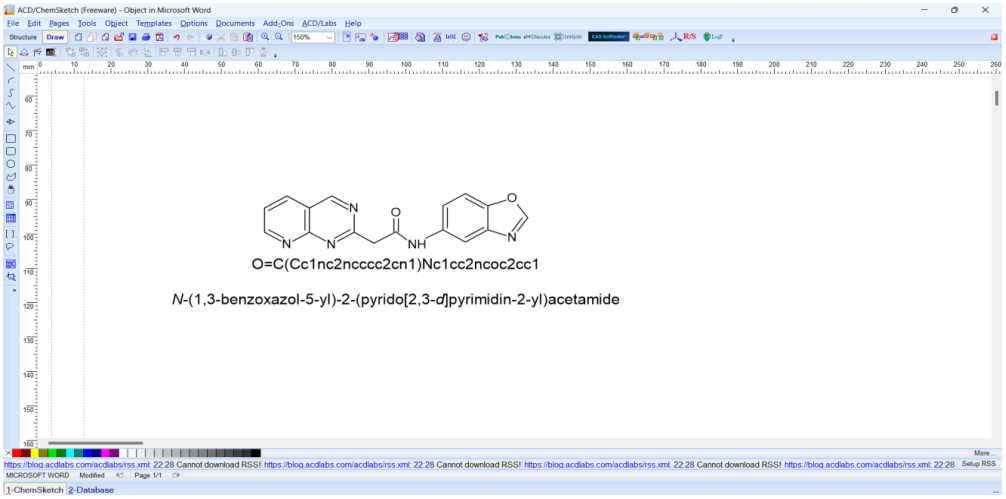
MATERIALS AND METHODS

An integrated in silico pipeline was used to design and evaluate novel 2-aminopyrimidine-indole derivatives. The workflow involved various computational chemistry and cheminformatics software tools, as summarized in the table below.[4,5]`

SOFTWARE TOOLS	PRIMARY APPLICATION IN THIS WORK
ACD/Chemsketch	Drawing chemical structures and generating initial 2D/3D models.
Molinspiration	Calculating molecular properties and screening with Lipinski's Rule of Five.
PASS Online	Predicting possible biological activity spectra.
AutoDock	Conducting molecular docking simulations to find binding affinity.
ADMETlab 2.0	Performing detailed In silico toxicity and ADMET profiling.

CHEMICAL STRUCTURE ELABORATION: ACD/CHEMSKETCH

ACD/ChemSketch (Advanced Chemistry Development) is a program for drawing and visualizing chemical structures. It was used to create the 2D structures of the lead scaffold and all proposed derivatives. The software allowed precise adjustments of the indole and pyrimidine rings, systematic substitutions, and initial geometry optimization. This provided the foundational files for further computational analyses.

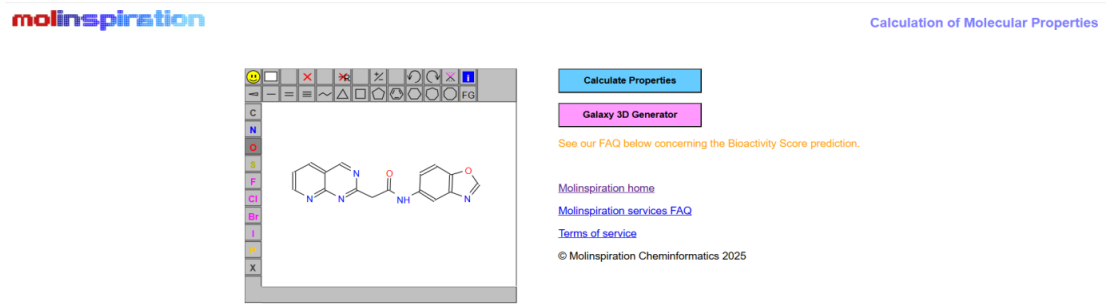


DRUG-LIKENESS PREDICTION: MOLINSPIRATION

Molinspiration tools calculated key physicochemical descriptors for early drug discovery. All designed compounds were checked against Lipinski's Rule of Five. This guideline assesses the likelihood of oral bioavailability. The rule checks:

* Molecular weight (< 500 Da)
* Octanol-water partition coefficient (Log P < 5)
* Number of hydrogen bond donors (< 5)
* Number of hydrogen bond acceptors (< 10)

Compounds that meet these criteria have a better chance of success as orally administered drugs.



BIOLOGICAL ACTIVITY PREDICTION: PASS (PREDICTION OF ACTIVITY SPECTRA FOR SUBSTANCES)

PASS Online predicts various biological activities from a compound's structure. By entering the SMILES notation of each designed derivative, the software provides two probability values: Pa (Probability to be Active) and Pi (Probability to be Inactive) for numerous activities. This helps create a preliminary in silico activity profile focusing on predictions for kinase inhibition, neuroprotection, and anti-inflammatory effects.

TARGET IDENTIFICATION AND PROTEIN PREPARATION

Key protein targets involved in neurodegenerative pathways were selected:

- Glycogen Synthase Kinase-3 Beta (GSK-3β): PDB ID: 1Q41
- Dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A):PDB ID: 5B30

Their 3D crystal structures were retrieved from the Protein Data Bank (PDB), a global source for macromolecular structure data. Using AutoDock Tools, these PDB files were prepared for docking by removing water molecules, adding polar hydrogens, assigning Kollman charges, and defining the rigid receptor structure.

LIGAND PREPARATION AND DOCKING PROTOCOL: AUTODOCK

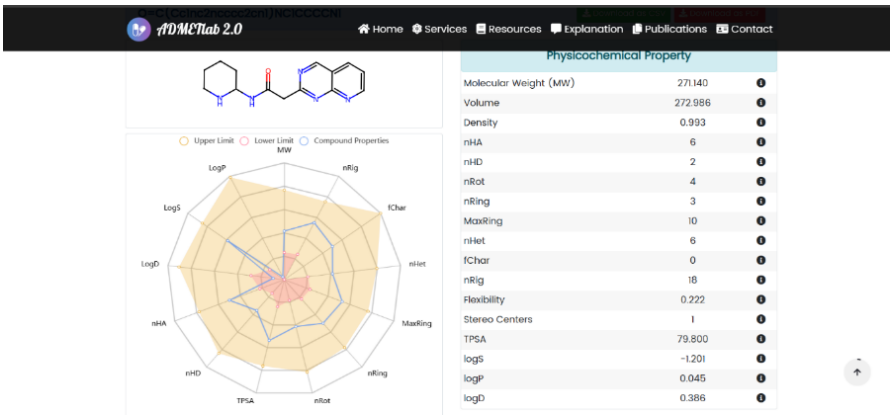
The 3D structures of the designed ligands were energy-minimized and converted to the required PDBQT format. AutoDock, a widely used program for molecular docking, was employed. A docking grid box covered the ATP-binding site of each kinase target. Each of the 40 designed derivatives was docked against two protein targets, resulting in a total of 80 individual docking simulations. The binding affinity (measured in kcal/mol) and the best binding pose for each ligand-protein pair were analyzed.

PHARMACOKINETIC AND TOXICITY PROFILING

a) ADMETlab 2.0: This platform offered a more detailed in silico toxicity assessment. Key predictions included:

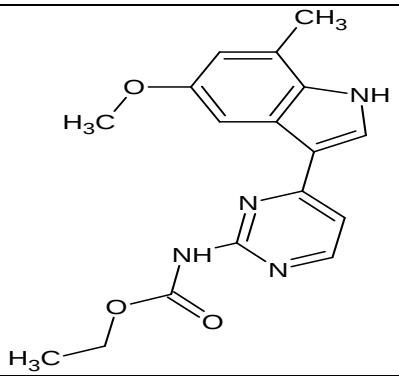
- Human Hepatotoxicity
- AMES Mutagenicity
- hERG Channel Inhibition (risk of cardiotoxicity)
- Drug-Induced Liver Injury (DILI)
- Carcinogenicity

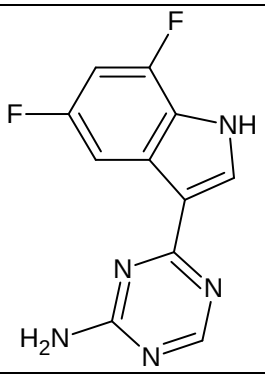
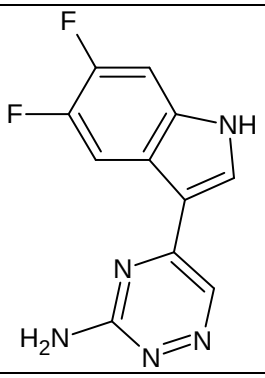
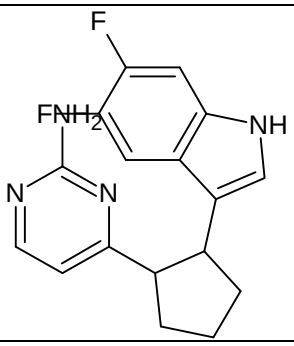
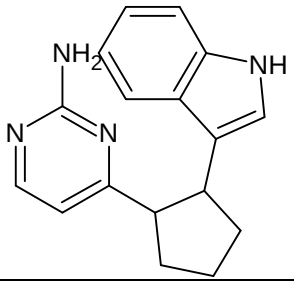
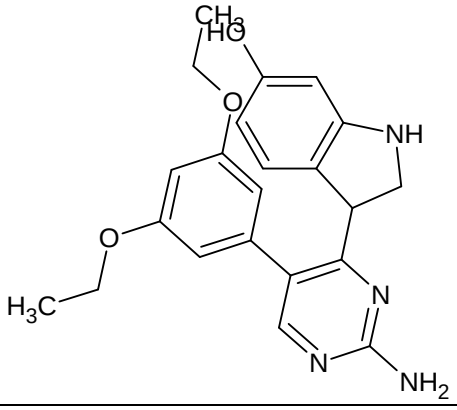
These predictions helped eliminate compounds with high potential toxicity risks early in the design process.[7]

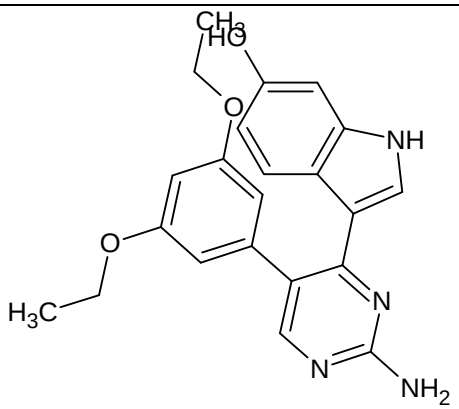
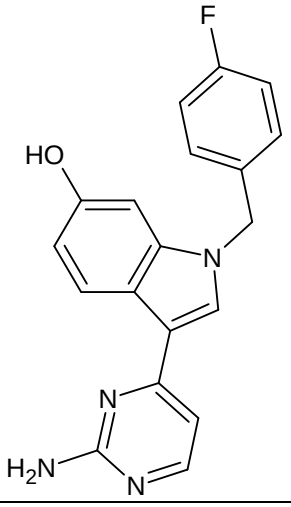
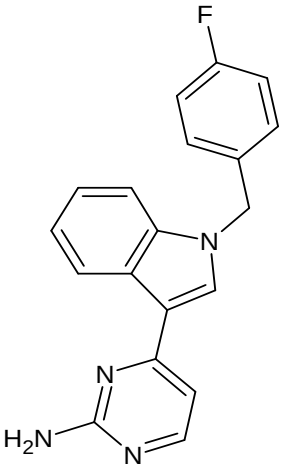
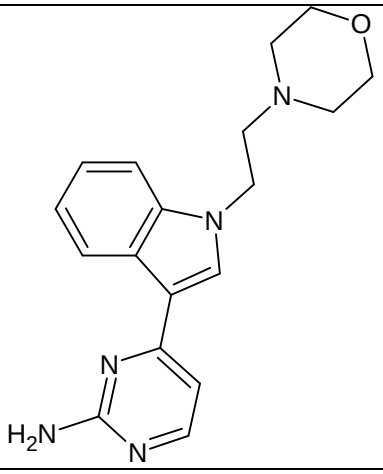


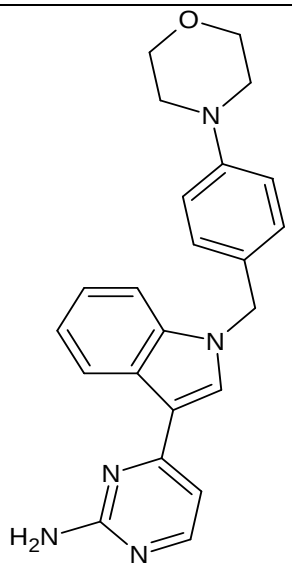
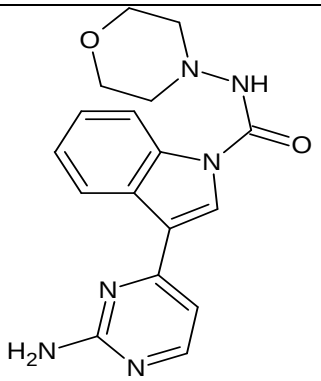
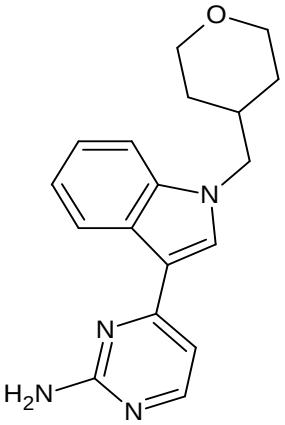
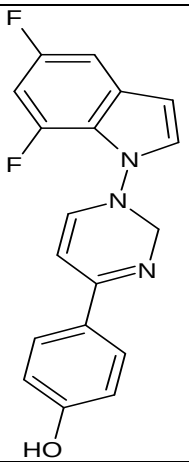
DESIGNED ANALOGUES

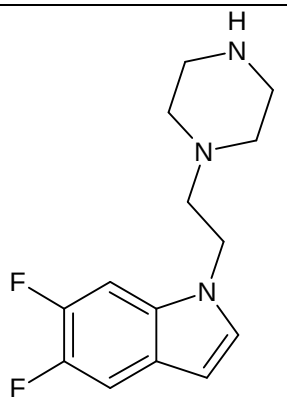
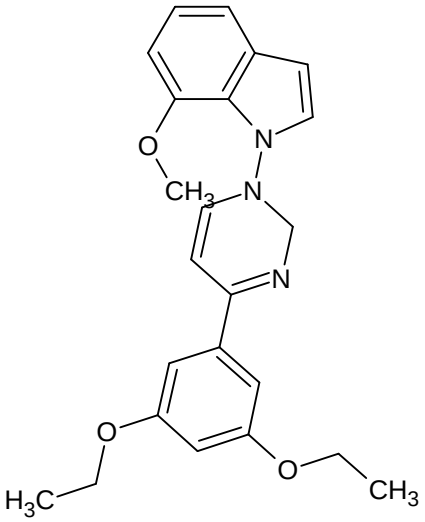
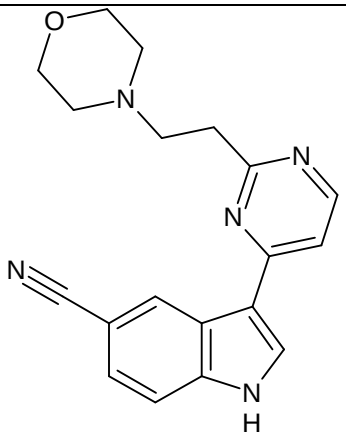
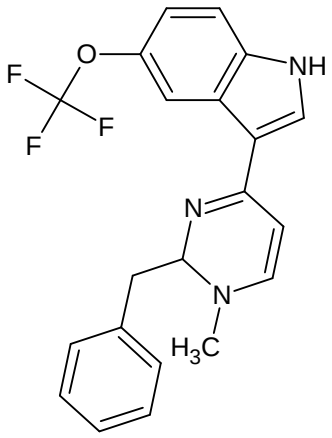
The structures of the derivatives were drawn using ACD/Chemsketch and their drug-likeness properties were calculated using Molinspiration, followed by activity prediction through PASS. They were then docked using AutoDock software. The designed 2-aminopyrimidine–indole analogues are presented in Table

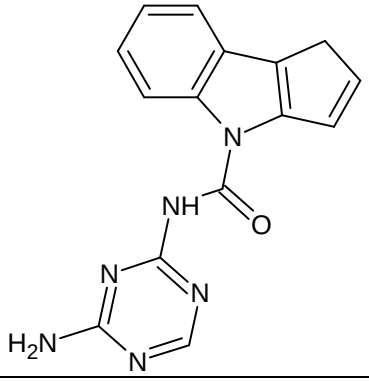
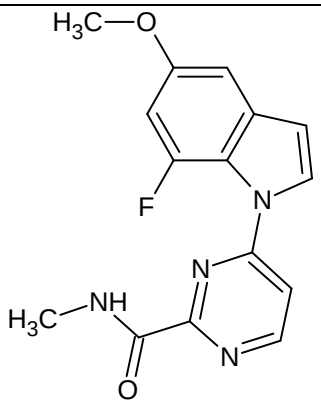
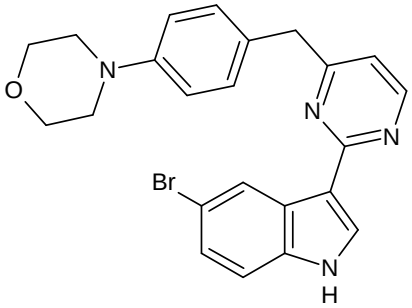
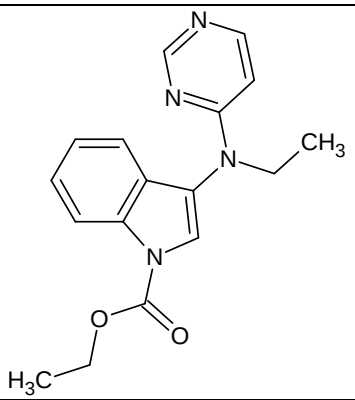
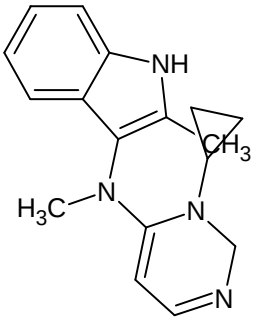
COMPOUND CODE	LIGANDS
M1	

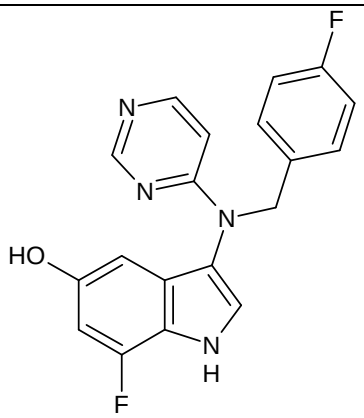
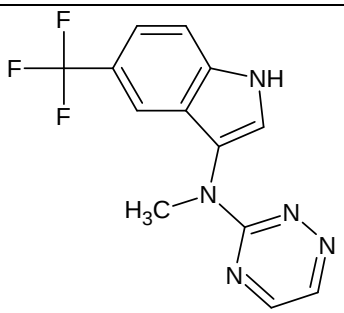
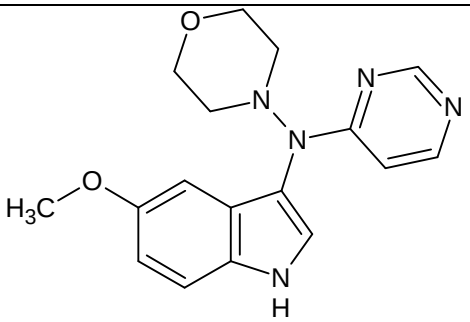
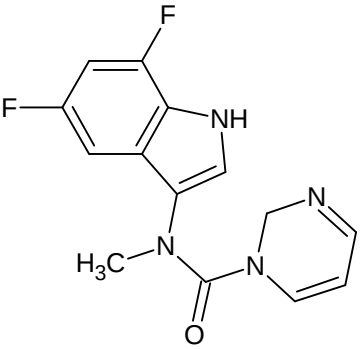
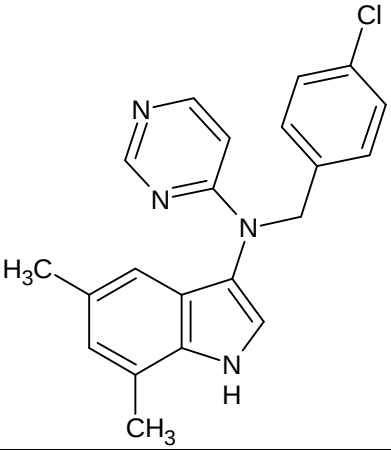
M2	
M3	
M4	
M5	
M6	

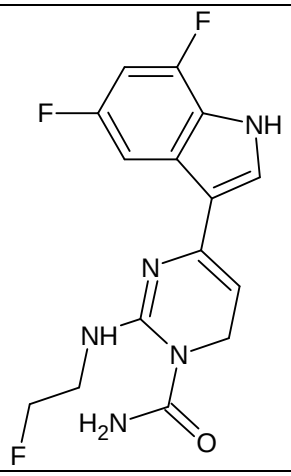
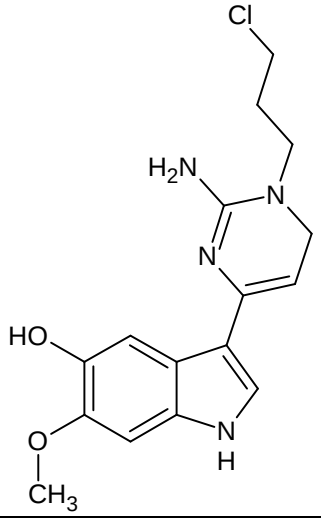
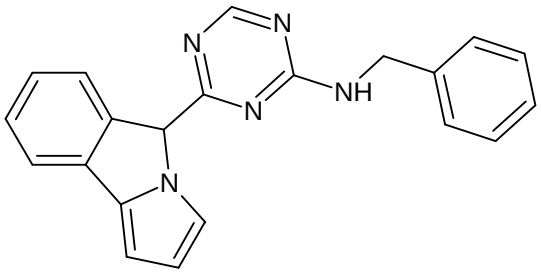
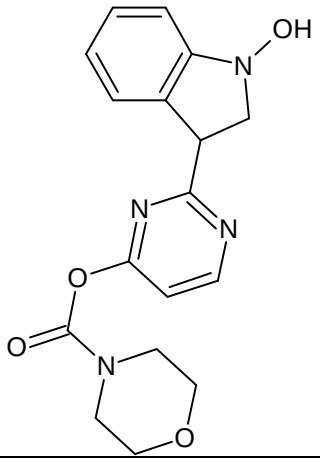
M7	
M8	
M9	
M10	

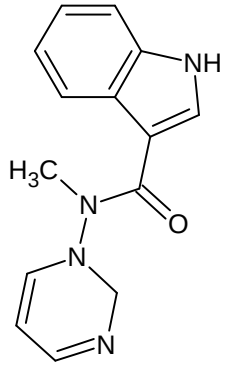
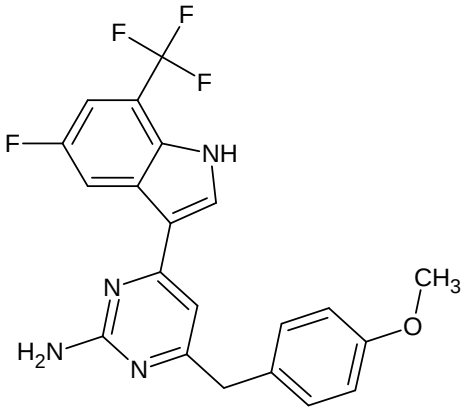
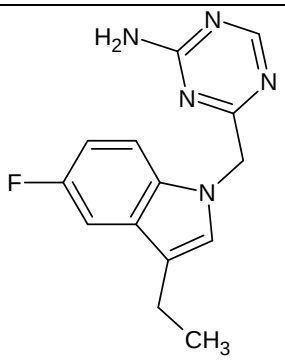
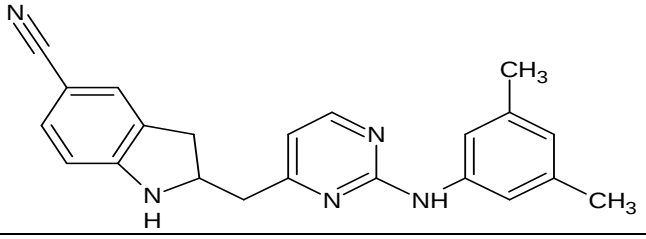
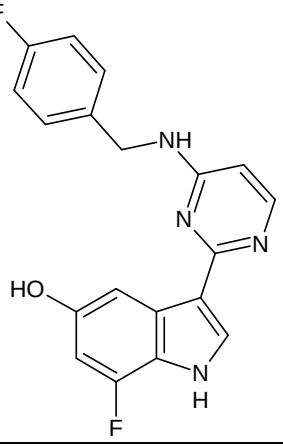
M11	
M12	
M13	
M14	

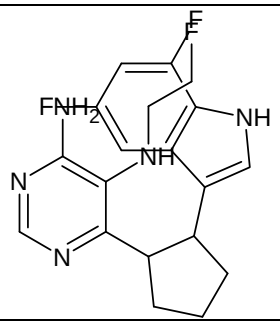
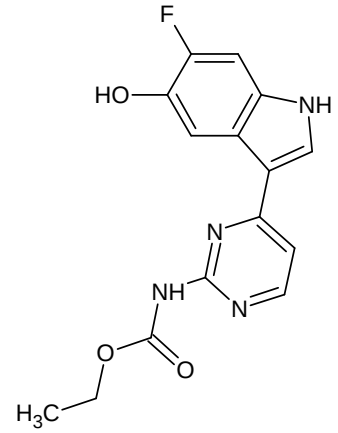
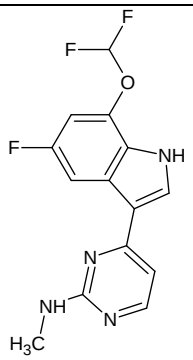
M15	
M16	
M17	
M18	

M19	
M20	
M21	
M22	
M23	

M24	
M25	
M26	
M27	
M28	

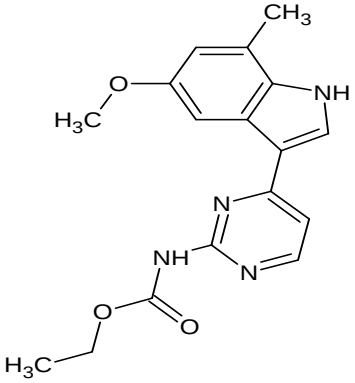
M29	
M30	
M31	
M32	

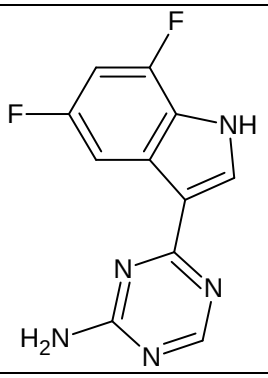
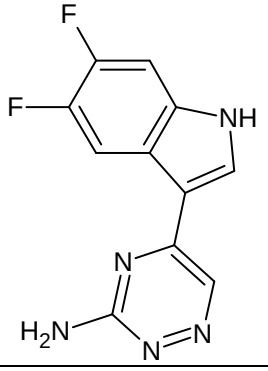
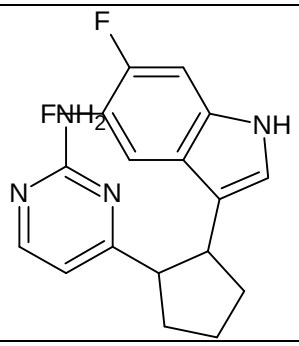
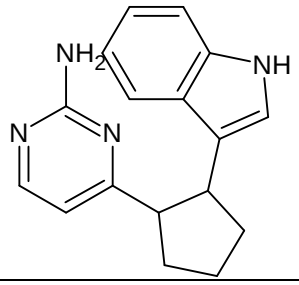
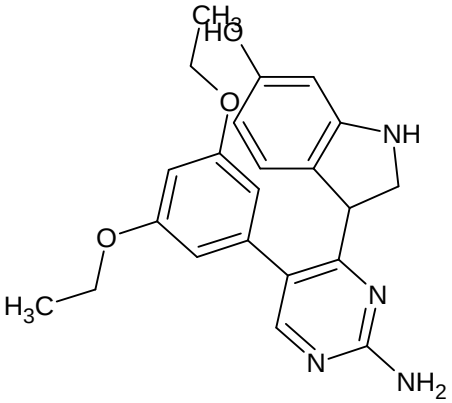
M33	
M34	
M35	
M36	
M37	

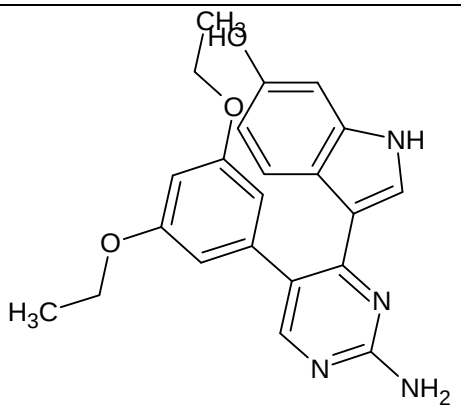
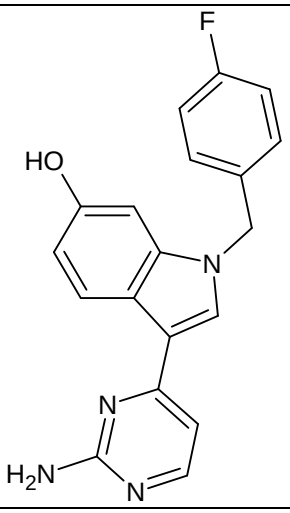
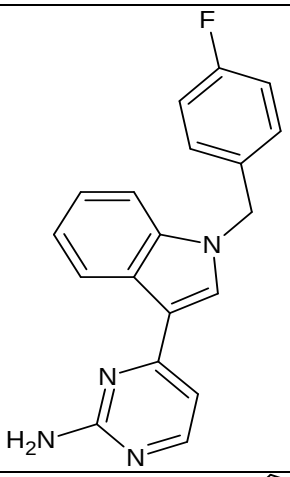
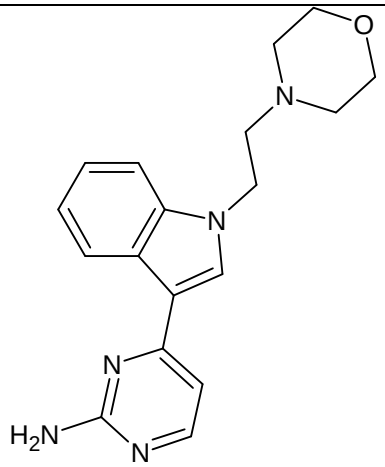
M38	
M39	
M40	  M

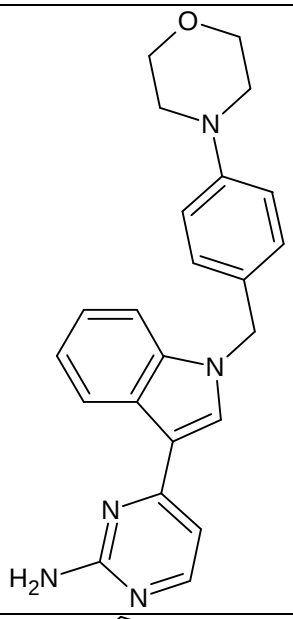
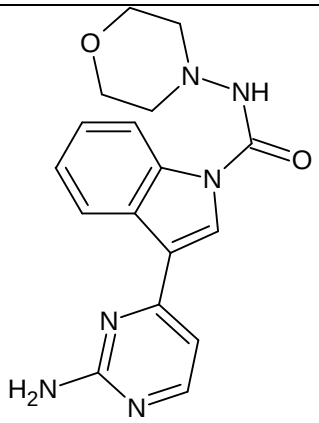
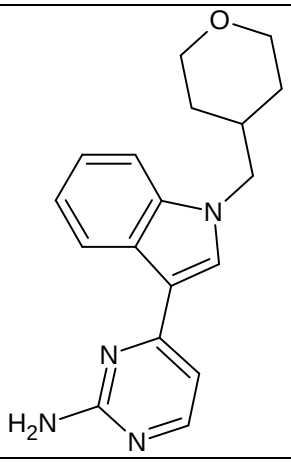
RESULTS AND DISCUSSION

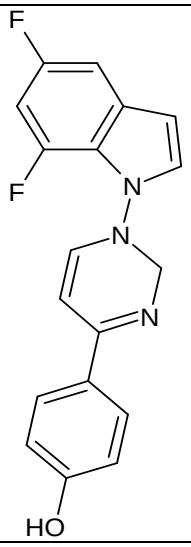
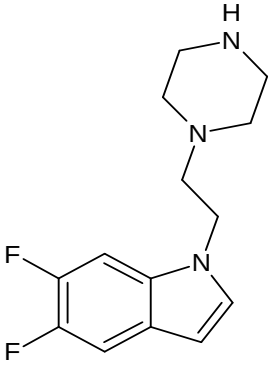
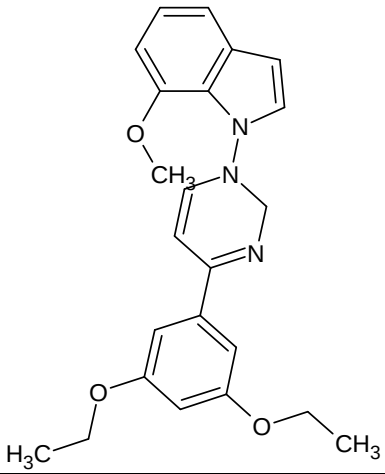
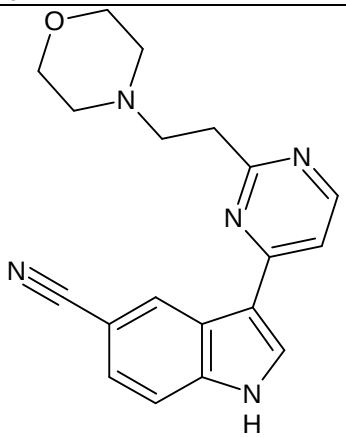
The structures of the 2-aminopyrimidine–indole analogues were generated using ACD/Chemsketch, and their SMILES and IUPAC names are provided in Table 2.1.

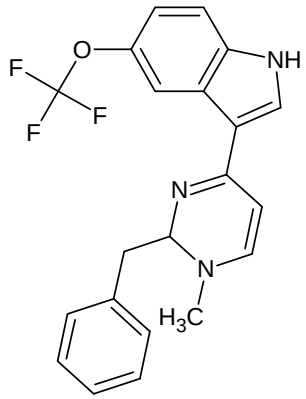
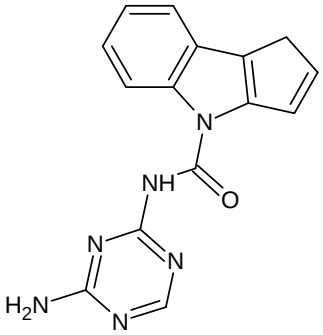
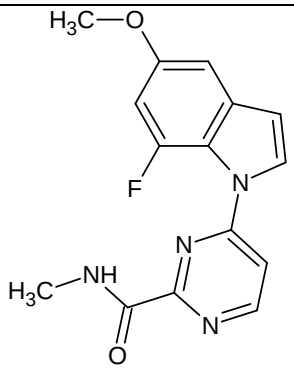
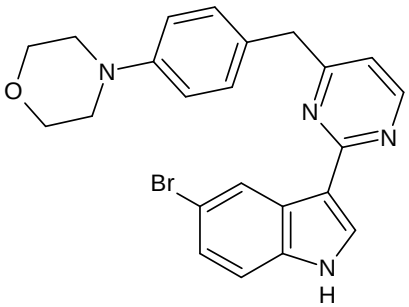
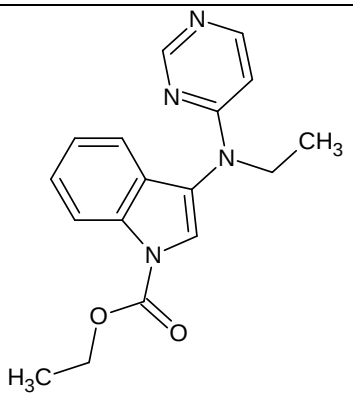
COMPOUND CODE	LIGANDS	SMILES	IUPAC
M1		CCOC(=O)Nc3nccc(c1c[nH]c2c(C)cc(OC)cc12)n3	5-Methoxy-7-methyl-1H-indol-3-yl-5-(carbamoylamino)pyrimidine

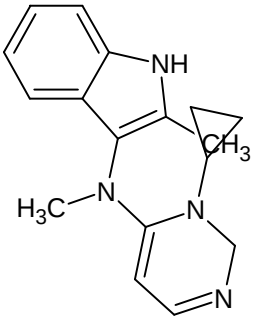
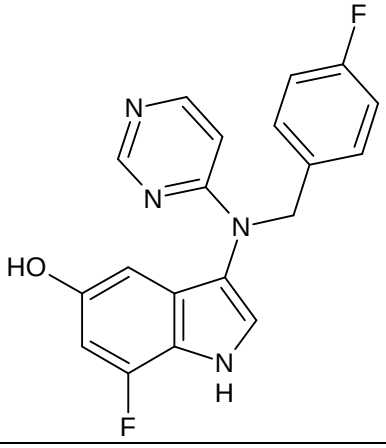
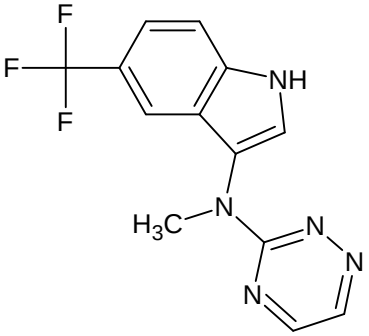
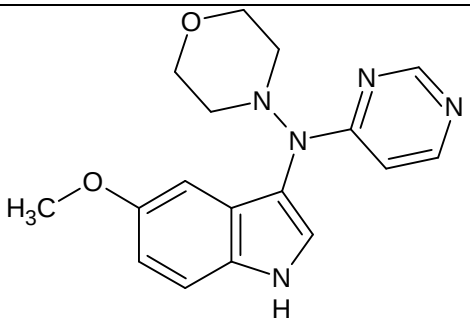
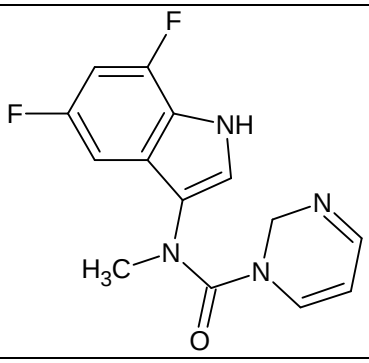
M2		Nc3ncnc(c1c[nH]c2c(F)cc(F)cc12)n3	2-Amino-4-(5,7-difluoro-1H-indol-3-yl)-1,3,5-triazine
M3		Nc3nncc(c1c[nH]c2cc(F)c(F)cc12)n3	2-Amino-4-(5,6-difluoro-1H-indol-3-yl)-1,3,5-triazine
M4		Nc4nccc(C1CCCC1c2c[nH]c3cc(F)c(F)cc23)n4	5,7-Difluoro-1H-pyrrolo[2,3-b]indolo[3,2-d]pyrimidine
M5		Nc4nccc(C1CCCC1c2c[nH]c3ccccc23)n4	Pyrrolo[2,3-b]indolo[3,2-d]pyrimidine
M6		Oc2ccc(NCc1ccc(F)cc1)c3NCCNc23	N¹-(4-Fluorobenzyl)-5-hydroxy-6,7,8,9-tetrahydro-1H-pyrido[3,4-b]pyrazine

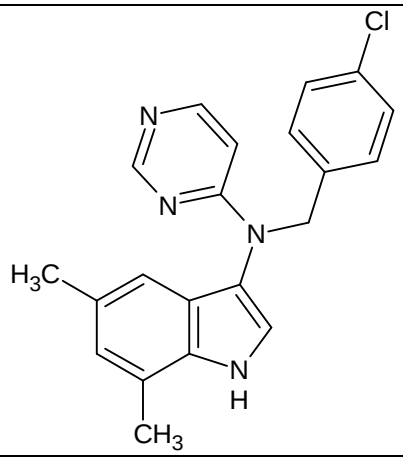
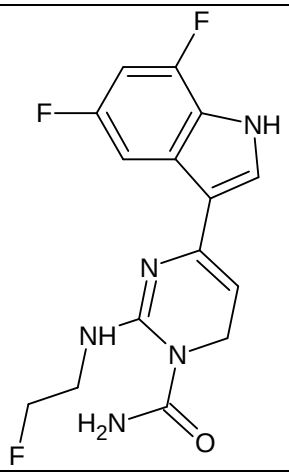
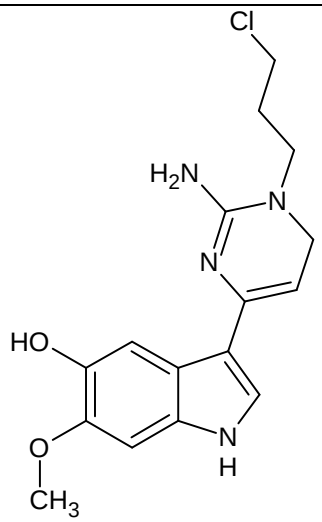
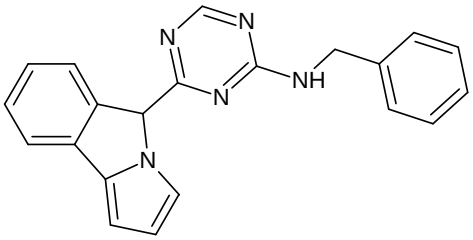
M7		CCOc4cc(OCC)cc(c1cnc(N)nc1c2c[nH]c3cc(O)ccc23)c4	4-(3,5-diethoxyphenyl)-4-(5-hydroxy-1H-indol-3-yl)-4,5-dihydropyrimidin-2-amine
M8		Nc4nccc(c2cn(Cc1ccc(F)cc1)c3cc(O)ccc23)n4	N¹-(4-fluorobenzyl)-5-hydroxy-6,7,8,9-tetrahydro-1H-pyrido[3,4-b]pyrazine
M9		Nc4nccc(c2cn(Cc1ccc(F)cc1)c3ccccc23)n4	4-Amino-7-(1-(4-fluorobenzyl)-1H-indol-3-yl)pyrido[2,3-b]pyridine
M10		Nc4nccc(c2cn(CCN1CCOCC1)c3ccccc23)n4	1-(2-morpholinoethyl)-1H-indole

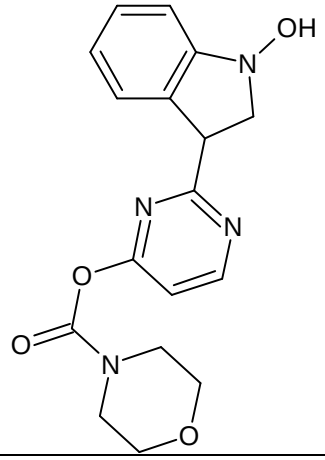
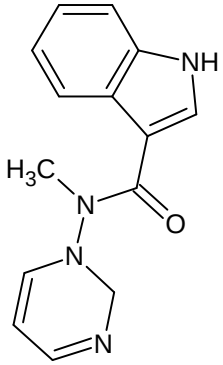
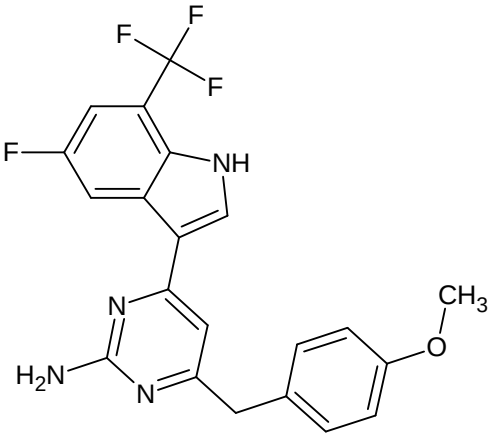
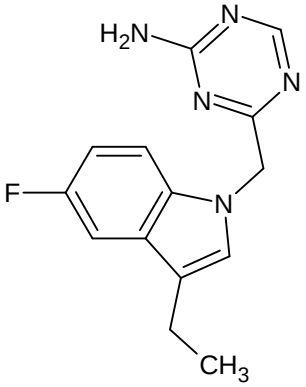
M11		Nc5nccc(c3cn(Cc2ccc(N1CCOCC1)cc2)c4ccccc34)n5	(4-(Morpholin-4-yl)phenyl)methyl
M12		Nc4nccc(c2cn(C(=O)NN1CCOCC1)c3ccccc23)n4	4-(1-(morpholin-4-ylcarbamoyl)-1H-indol-3-yl)pyrimidin-2-amine
M13		Nc4nccc(c2cn(CC1CCOCC1)c3ccccc23)n4	4-(1-((morpholin-4-yl)methyl)-1H-indol-3-yl)pyrimidin-2-amine

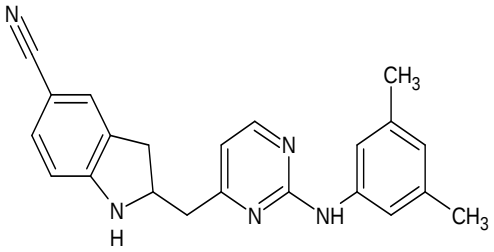
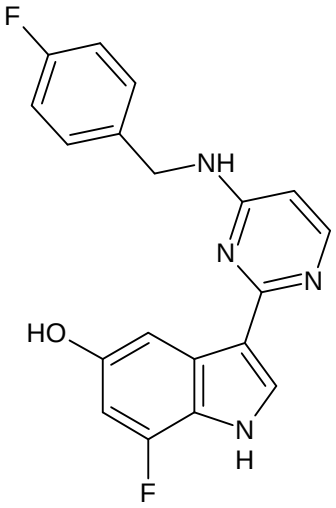
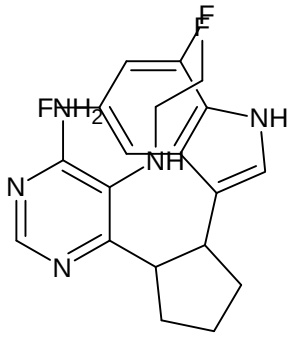
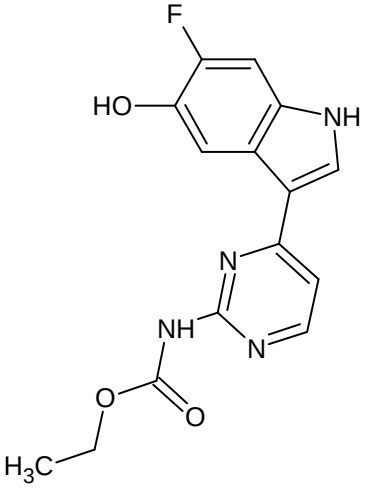
M14		Oc4ccc(C3=NCN(n2ccc1cc(F)cc(F)c12)C=C3)cc4	4-(5,7-difluoro-1H-indol-3-yl)-6-(4-hydroxyphenyl)pyrimidine)
M15		Fc3cc2ccn(CCN1CCNCC1)c2cc3F	1-Methyl-5,6-difluoro-3-[2-(piperazin-1-yl)ethyl]-1H-indole
M16		CCOc4cc(OCC)cc(C3=NCN(n2ccc1cccc(OC)c12)C=C3)c4	4-(7-methoxy-1H-indol-3-yl)-6-(3,5-diethoxyphenyl)pyrimidine
M17		N#Cc4ccc3[nH]cc(c2ccnc(CCN1CCOCC1)n2)c3c4	1-[2-(morpholin-4-yl)ethyl]-4-(5-cyano-1H-indol-3-yl)pyrimidin-2-amine

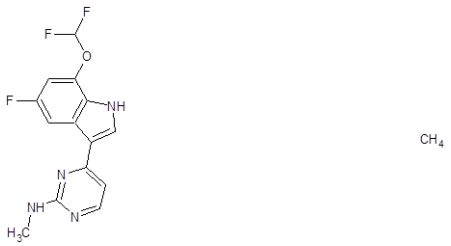
M18		CN3C=CC(c1c[nH]c2ccc(OC(F)(F)F)cc12)=NC3Cc4ccccc4	4-(benzyl)-1-methyl-4-(5-(trifluoromethoxy)-1H-indol-3-yl)pyrimidine
M19		Nc4ncnc(NC(=O)n3c1C=CCc1c2ccccc23)n4	N-(1,3,5-triazin-2-yl)carbamoyl-1,2,3,3a,4,5-hexahydroindolo[2,3-b]cyclopenta
M20		CNC(=O)c3nccc(n2ccc1cc(OC)cc(F)c12)n3	N-[2-(N-methylcarbamoyl)pyrimidin-4-yl]-5-methoxy-7-fluoroindole
M21		Brc5ccc4[nH]cc(c3nccc(Cc2ccc(N1CCOCC1)cc2)n3)c4c5	2-(5-bromo-1H-indol-3-yl)-4-[(4-morpholin-4-yl)benzyl]pyrimidine
M22		CCOC(=O)n3cc(N(CC)c1ccncn1)c2ccccc23	N-[(ethoxycarbonyl)-1H-indol-3-yl]-N-ethylpyrimidin-4-amine

M23		Cc2[nH]c1ccccc1c2N(C)C3=CC=NCN3C4CC4	N-(2-methyl-1H-indol-3-yl)-N-methyl-3-cyclopropylpyrimidin-4-amine
M24		Oc4cc(F)c3[nH]cc(N(Cc1ccc(F)cc1)c2ccncn2)c3c4	N-(4-fluorobenzyl)-N-(5-hydroxy-7-fluoro-1H-indol-3-yl)pyrimidin-4-amine
M25		CN(c1nccnn1)c2c[nH]c3ccc(C(F)(F)F)cc23	N-(5-(trifluoromethyl)-1H-indol-3-yl)-N-methyl-1,2,4-triazin-3-amine
M26		COc4ccc3[nH]cc(N(c1ccncn1)N2CCOCC2)c3c4	N-(5-methoxy-1H-indol-3-yl)-N-morpholin-4-ylpyrimidin-4-amine
M27		CN(C(=O)N1C=CC=NC1)c2c[nH]c3c(F)cc(F)cc23	N-(5,7-difluoro-1H-indol-3-yl)-N-methylpyrimidine-3-carboxamide

M28		Cc4cc(C)c3[nH]cc(N(Cc1ccc(Cl)cc1)c2ccncn2)c3c4	N-(4-chlorobenzyl)-N-(5,7-dimethyl-1H-indol-3-yl)pyrimidin-4-amine
M29		NC(=O)N3CC=C(c1c[nH]c2c(F)cc(F)cc12)N=C3NCCF	N-[2-(2-fluoroethylcarbamoyl)-pyrimidin-4-yl]-5,7-difluoro-1H-indole
M30		COc3cc2[nH]cc(C1=CCN(CCCCl)C(N)=N1)c2cc3O	N-(3-chloropropyl)-4-(5-hydroxy-6-methoxy-1H-indol-3-yl)pyrimidin-2-amine
M31		c5ccc(CNc4ncnc(C3c1ccccc1c2cccn23)n4)cc5	N-benzyl-N-(4-(indolizino[1,2-b]triazin-3-yl)amino)-1,3,5-triazine

M32		O=C(Oc3ccnc(C2CN(O)c1ccccc12)n3)N4CCOCC4	N-[4-(1-oxide-1H-indol-3-yl)pyrimidin-2-yl]carbamoyl morpholine
M33		CN(C(=O)c1c[nH]c2ccccc12)N3C=CC=NC3	N-Methyl-N-(pyrimidin-3-yl)-1H-indole-3-carboxamide
M34		COc4ccc(Cc3cc(c1c[nH]c2c(C(F)(F)F)cc(F)cc12)nc(N)n3)cc4	N-(4-methoxybenzyl)-4-(5-(trifluoromethyl)-7-fluoro-1H-indol-3-yl)pyrimidin-2-amine
M35		CCc2cn(Cc1ncnc(N)n1)c3ccc(F)cc23	2-Amino-4-[(5-fluoro-3-ethyl-1H-indol-1-yl)methyl]-1,3,5-triazine

M36		Cc4cc(C)cc(Nc3nccc(CC2Cc1cc(C#N)ccc1N2)n3)c4	N-(3,5-dimethylphenyl)-4-(5-cyano-2-methyl-1H-indol-3-yl)pyrimidin-2-amine
M37		Oc4cc(F)c3[nH]cc(c2nccc(NCc1ccc(F)cc1)n2)c3c4	N-(4-Fluorobenzyl)-4-(5-hydroxy-7-fluoro-1H-indol-3-yl)pyrimidin-2-amine
M38		Nc4ncnc(C1CCCC1c2c[nH]c3c(F)cc(F)cc23)c4NCCF	N-[2-(2-fluoroethylcarbamoyl)-4-(5,7-difluoro-1,2,3,3a,4,5-hexahydroindolo[2,3-b]cyclopenta-3-yl)pyrimidin-4-yl]carbamate
M39		CCOC(=O)Nc3nccc(c1c[nH]c2cc(F)c(O)cc12)n3	N-ethylcarbamoyl-4-(5-hydroxy-6-fluoro-1H-indol-3-yl)pyrimidin-2-amine

M40		CNc3nccc(c1c[nH]c2c(OC(F)F)cc(F)cc12)n3	4-(5-fluoro-7-(difluoromethoxy)-1H-indol-3-yl)-N-methylpyrimidin-2-amine

MOLINSPIRATION VALUES

The MOLINSPIRATION values depicts whether the molecule follows Lipinski Rule of Five. The drug likeness properties of proposed ligands were shown in table2.2.

SL NO.	Mol.Wt <500	TPSA	nHAcc <10	nHDon <5	Log P <5	Nrotb <5	nViolations
1	326.36	89.14	7	2	3.29	5	0
2	247.21	80.49	5	3	0.63	1	0
3	247.21	80.49	5	3	0.17	1	0
4	314.34	67.60	4	3	1.94	2	0
5	278.36	67.60	4	3	2.68	2	0
6	273.31	56.31	4	4	2.57	3	0
7	390.44	106.29	7	4	3.87	6	0
8	334.35	76.97	5	3	2.96	3	0
9	318.36	56.74	4	2	3.46	3	0
10	323.40	69.21	6	2	1.58	4	0
11	385.47	69.21	6	2	3.25	4	0
12	338.37	98.31	8	3	1.21	2	0
13	308.38	65.97	5	2	2.46	3	0
14	325.32	40.76	4	1	2.57	2	0
15	265.31	20.20	3	1	0.81	3	0
16	391.47	48.24	6	0	4.59	7	0
17	333.39	77.84	6	1	1.73	4	0
18	385.39	40.63	4	1	4.79	5	0
19	292.30	98.73	7	3	2.24	1	0
20	300.29	69.05	6	1	1.55	3	0
21	449.35	54.05	5	1	5.21	4	0
22	310.36	60.26	6	0	2.75	5	0
23	280.38	34.63	4	1	2.11	3	0
24	352.34	65.04	5	2	3.24	4	0
25	293.25	57.70	5	1	2.24	3	0
26	325.37	66.52	7	1	1.97	4	0
27	290.27	51.70	5	1	1.24	1	0
28	362.86	44.81	4	1	4.96	4	0
29	337.31	86.51	6	4	0.72	4	0
30	334.81	86.88	6	4	1.71	5	0
31	355.44	73.63	5	2	4.76	4	0
32	342.36	88.03	8	1	1.20	3	0
33	254.29	51.70	5	1	1.42	2	0

34	416.38	76.38	5	3	4.10	5	0
35	271.30	69.63	5	2	1.11	3	0
36	339.40	55.64	5	1	3.43	4	0
37	352.34	73.83	5	3	3.41	4	0
38	375.40	79.62	5	4	2.04	5	0
39	316.29	100.14	7	3	2.73	4	0
40	308.26	62.84	5	2	2.14	4	0

PASS VALUES

The significance of PASS value is to predict the probability to be active or probability to be inactive. It also enables us to evaluate the contribution of each atom in the structure to its biological activity. The PASS value of proposed derivatives was shown in the table 2.3.

COMPOUNDS	PASS VALUES gsk3b		PASS VALUES dyrk1a	
	Pa	Pi	Pa	Pi
1	0.342	0.044	0.169	0.008
2	0.118	0.030	0.165	0.009
3	0.341	0.104	0.341	0.104
4	0.152	0.017	0.171	0.008
5	0.325	0.303	0.185	0.005
6	0.376	0.058	0.108	0.014
7	0.147	0.018	0.208	0.044
8	0.376	0.028	0.208	0.005
9	0.290	0.180	0.250	0.110
10	0.204	0.008	0.276	0.004
11	0.172	0.012	0.227	0.004
12	0.127	0.024	0.199	0.005
13	0.145	0.018	0.259	0.004
14	0.134	0.008	0.241	0.147
15	0.042	0.041	0.094	0.074
16	0.104	0.038	0.169	0.008
17	0.118	0.030	0.165	0.009
18	0.271	0.177	0.171	0.008
19	0.329	0.096	0.155	0.012
20	0.156	0.015	0.185	0.005
21	0.140	0.026	0.115	0.043
22	0.119	0.029	0.230	0.004
23	0.147	0.018	0.208	0.005
24	0.173	0.011	0.250	0.004
25	0.204	0.008	0.204	0.008
26	0.172	0.012	0.338	0.003
27	0.127	0.024	0.287	0.004
28	0.145	0.018	0.259	0.004
29	0.083	0.051	0.`109	0.052
30	0.086	0.049	0.139	0.021
31	0.608	0.004	0.123	0.034
32	0.321	0.141	0.259	0.043

33	0.140	0.020	0.120	0.026
34	0.102	0.040	0.161	0.010
35	0.326	0.099	0.100	0.065
36	0.093	0.045	0.099	0.080
37	0.107	0.036	0.122	0.036
38	0.087	0.033	0.098	0.067
39	0.092	0.046	0.159	0.011
40	0.111	0.033	0.188	0.005

MOLECULAR DOCKING

The 40 analogues were docked on 3 different receptors GSK-3B and DYRK1A with a total of 80 docking runs.[3,5]

- **Table below shows the docking score on the receptor 7FHS.**

SL.NO	COMPOUND CODE	RECEPTOR (DYRK1A)	DOCKING SCORE
1	M1	DYRK1A	-6.36
2	M2	DYRK1A	-5.03
3	M3	DYRK1A	-5.72
4	M4	DYRK1A	-6.58
5	M5	DYRK1A	-6.67
6	M6	DYRK1A	-6.78
7	**M7**	DYRK1A	**-9.44**
8	M8	DYRK1A	-6.71
9	M9	DYRK1A	-6.32
10	M10	DYRK1A	-7.39
11	M11	DYRK1A	-7.47
12	M12	DYRK1A	-6.68
13	M13	DYRK1A	-6.45
14	M14	DYRK1A	-7.24
15	M15	DYRK1A	-6.33
16	**M16**	DYRK1A	**-8.62**
17	M17	DYRK1A	-7.02
18	M18	DYRK1A	-7.51
19	M19	DYRK1A	-6.26
20	M20	DYRK1A	-6.69
21	M21	DYRK1A	-7.86
22	M22	DYRK1A	-6.67
23	M23	DYRK1A	-7.03
24	**M24**	DYRK1A	**-8.07**
25	M25	DYRK1A	-5.85
26	M26	DYRK1A	-6.99
27	M27	DYRK1A	-6.39
28	**M28**	DYRK1A	**-8.86**
29	M29	DYRK1A	-6.82
30	M30	DYRK1A	-6.52

31	M31	DYRK1A	-7.65
32	**M32**	DYRK1A	**-9.37**
33	M33	DYRK1A	-6.68
34	M34	DYRK1A	-6.94
35	M35	DYRK1A	-5.03
36	M36	DYRK1A	-7.59
37	M37	DYRK1A	-7.53
38	M38	DYRK1A	-5.44
39	M39	DYRK1A	-6.50
40	M40	DYRK1A	4.94
	STANDARD (indirubicin-3- monoxime)	DYRK1A	**6.29**

- Table below shows the docking score on the receptor GSK-3B.

SL.NO	COMPOUND CODE	RECEPTOR GSK3 -B	DOCKING SCORE
1	M1	GSK-3B	-6.47
2	M2	GSK-3B	-6.78
3	M3	GSK-3B	-5.01
4	M4	GSK-3B	-5.19
5	M5	GSK-3B	-6.68
6	M6	GSK-3B	-7.02
7	M7	GSK-3B	-6.96
8	**M8**	GSK-3B	**-8.06**
9	M9	GSK-3B	-7.82
10	M10	GSK-3B	-5.50
11	**M11**	GSK-3B	**-9.10**
12	M12	GSK-3B	-7.55
13	M13	GSK-3B	-7.48
14	M14	GSK-3B	-7.99
15	M15	GSK-3B	-6.88
16	**M16**	GSK-3B	**-10.05**
17	M17	GSK-3B	-7.96
18	M18	GSK-3B	-7.20
19	M19	GSK-3B	-6.77
20	M20	GSK-3B	-7.48
21	M21	GSK-3B	-7.23
22	M22	GSK-3B	-7.35
23	M23	GSK-3B	-7.20
24	**M24**	GSK-3B	**-8.43**
25	M25	GSK-3B	-5.96
26	M26	GSK-3B	-6.58
27	M27	GSK-3B	-6.47
28	**M28**	GSK-3B	**-8.66**
29	M29	GSK-3B	-6.79
30	M30	GSK-3B	-7.04
31	M31	GSK-3B	-7.73
32	**M32**	GSK-3B	**-10.20**

33	M33	GSK-3B	-7.57
34	M34	GSK-3B	-7.10
35	M35	GSK-3B	-6.12
36	**M36**	GSK-3B	**-9.83**
37	M37	GSK-3B	-6.16
38	M38	GSK-3B	-5.75
39	M39	GSK-3B	-6.75
40	M40	GSK-3B	-5.50
	STANDARD (Indirubicin-3-monoxime)		**-8.02**

PHARMACOKINETIC EVALUATION USING ADMET2.0

Pharmacokinetics and Toxicity evaluation was evaluated by using ADMETlab 2.0.

COMPOUND CODE	ABSORPTION	DISTRIBUTION	METABOLISM		EXCRETION		TOXICITY	
	CACO-2 PERMEABILITY	VDss	CYP1A2 inhibitor	HLM STABILITY	Cl plasma	T1/2	DILI	CARCINOGENICITY
M1	-4.716	1.875	+++	+++	4.603	0.802	0.991	0.815
M2	-4.817	1.633	++	+++	5.889	1.077	0.959	0.709
M3	-5.141	1.568	+++	+++	7.006	1.083	0.964	0.752
M4	-5.285	0.988	++	+++	7.373	1.164	0.926	0.747
M5	-5.202	1.242	++	++	8.398	1.517	0.792	0.719
M6	-4.866	1.068	+++	+++	8.089	0.399	0.959	0.423
M7	-4.983	1.542	+++	+++	7.659	1.173	0.976	0.811
M8	-5.163	2.612	+++	++	6.145	0.745	0.967	0.898
M9	-5.035	2.299	+++	+	6.769	0.539	0.98	0.893
M10	-4.804	2.954	+++	+++	7.926	0.438	0.957	0.911
M11	-4.734	1.256	+++	++	6.0	0.349	0.999	0.975
M12	-4.68	2.007	+	++	6.56	1.033	0.989	0.837
M13	-4.806	4.796	++	+++	8.963	1.066	0.94	0.912
M14	-4.759	1.149	+++	++	6.019	0.784	0.862	0.542
M15	-5.086	40142	+++	++	7.018	0.524	0.881	0.6
M16	-4.537	1.274	+++	++	6.297	0.395	0.986	0.79
M17	-4.976	1.811	++	+	6.16	1.186	0.63	0.572
M18	-4.814	3.634	++	+++	8.306	1.572	0.82	0.084
M19	-4.636	1.566	+++	++	4.414	0.973	0.977	0.931
M20	-4.743	0.992	+	+++	5.545	1.192	0.964	0.767
M21	-5.013	1.459	+++	+	5.352	0.375	0.981	0.856
M22	-4.663	0.877	+++	+++	4.998	0.653	0.893	0.747
M23	-4.803	2.51	+++	++	6.545	0.4	0.791	0.715
M24	-4.87	1.246	+++	+++	5.271	0.755	0.676	0.48
M25	-4.718	1.026	+++	+++	7.215	0.974	0.83	0.226
M26	-4.629	1.151	+++	++	7.096	0.754	0.858	0.867
M27	-4.541	1.046	+++	+++	5.262	1.011	0.857	0.627
M28	-4.722	1.361	+++	+++	5.912	0.526	0.84	0.285
M29	-4.927	0.074	+++	+++	5.667	0.74	0.904	0.85
M30	-5.305	1.637			5.527	1.683	0.761	0.68

M31	-4.798	0.621	+++	+++	4.802	0.526	0.858	0.77
M32	-5.164	1.028	+++	++	2.942	1.305	0.886	0.929
M33	-4.657	1.554	+++	++	7.621	1.377	0.617	0.678
M34	-5.089	5.02	++	+++	8.755	0.525	0.911	0.305
M35	-5.01	1.621	++	++	8.794	0.843	0.934	0.78
M36	-5.095	5.068	+++	+++	5.829	0.643	0.875	0.262
M37	-4.947	0.899	+++	++	5.404	0.691	0.757	0.779
M38	-4.994	1.892	+++	+++	6.24	0.871	0.979	0.574
M39	-5.118	2.383	+++	++	5.682	0.801	0.994	0.617
M40	-4.928	0.901	+++	++	3.79	0.765	0.902	0.566

SUMMARY AND CONCLUSION

In this study, we proposed and tested a new series of 40 compounds of the 2-aminopyrimidine-indole family, which target both GSK-3β and DYRK1A kinases, with the aim of neuroprotection and cognitive improvement. This has been achieved by employing an integrated approach of in silico research.

Inspiration for the design of the new compounds came from the natural product meridianin. The new compounds possess good drug-likeness properties. To be specific, all of the new compounds of this series obey Lipinski's rule of five, which makes them good candidates for oral bioavailability. The new compounds also possess good kinase inhibitory potential, as predicted by the PASS program.[12]

The new compounds exhibited strong affinities for the target kinases, as predicted by the docking study. For the target kinase GSK-3β, M16 (-10.05 kcal/mol) and M32 (-10.20 kcal/mol) exhibited stronger affinities than the positive control, indirubicin-3-monoxime, which exhibited an affinity of -8.02 kcal/mol. For the target kinase DYRK1A, M7 (-9.44 kcal/mol) and M32 (-9.37 kcal/mol) exhibited the highest affinities among the new derivatives, making them the most potent compounds for the target kinase DYRK1A. More importantly, M16 and M32 possess the highest affinity for the target kinase GSK-3β.[4,12]

ADMET predictions, which employed ADMETlab 2.0, revealed that the new derivatives possess good pharmacokinetic properties, including good Caco-2 permeability, suitable volume of distribution, and good metabolic stability. The new derivatives also possess good toxicity profiles, with only moderate risks of drug-induced liver injury and carcinogenicity.

In conclusion, the CADD approach employed in this study has led to the design of new 2-aminopyrimidine-indole derivatives as potential dual-target agents for the treatment of

neurodegenerative diseases, with M16 and M32 being the most promising dual inhibitors of both GSK-3β and DYRK1A kinases, as they possess the highest affinity for the target kinase GSK-3β, as well as good pharmacokinetic properties.[16,19]

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