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STRUCTURE BASED DRUG DESIGN AND MOLECULAR DOCKING STUDIES OF ADENINE DERIVATIVES FOR SKIN CANCER THERAPY

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- ## Abstract :

Skin cancer represents one of the most prevalent and rapidly increasing malignancies worldwide, with melanoma being the most aggressive and life-threatening subtype due to its high metastatic potential. Recent advances in cancer biology have highlighted the critical role of the tumor microenvironment (TME) in promoting tumor progression and immune evasion. Among various molecular targets, the Adenosine A2A receptor (A2AR), a G-protein coupled receptor, has emerged as a key regulator of immunosuppression in cancer.

The present study focuses on the design, development, and evaluation of adenine-based derivatives as potential inhibitors of the A2A receptor using structure-based molecular docking approaches. A total of 50 novel compounds were designed by modifying the adenine scaffold, particularly at the C2 position, to enhance binding affinity and pharmacological activity. Molecular docking was performed using SwissDock to predict ligand–receptor interactions, binding conformations, and energy profiles.

The results revealed that several compounds exhibited strong binding affinity toward the A2A receptor, with compounds ADS14, ADS50, ADS39, ADS48, and ADS35 demonstrating the most favorable docking scores. The study also highlighted the importance of hydrogen bonding, hydrophobic interactions, and π–π stacking in stabilizing ligand–receptor complexes.

Overall, the findings suggest that adenine derivatives represent promising candidates for the development of novel anticancer agents targeting A2AR-mediated immunosuppressive pathways. However, further experimental validation through in vitro and in vivo studies is required.

- **Keywords:** Skin cancer, Adenosine A2A receptor, Molecular docking, Adenine derivatives, Structure-based drug design, Swiss Dock

1.Introduction

Cancer is a complex group of diseases characterized by uncontrolled cell proliferation, invasion of surrounding tissues, and metastasis to distant organs. It remains one of the leading causes of morbidity and mortality worldwide. Among various cancer types, skin cancer is the most commonly diagnosed malignancy, primarily caused by prolonged exposure to ultraviolet (UV) radiation.

Skin cancer is broadly classified into:

- Basal Cell Carcinoma (BCC)
- Squamous Cell Carcinoma (SCC)
- Melanoma

Figure 1: Skin Cancer

Among these, melanoma is the most aggressive form and is responsible for the majority of skin cancer-related deaths. The pathogenesis of skin cancer involves genetic mutations, particularly in tumor suppressor genes such as p53 and oncogenes like BRAF, leading to uncontrolled cellular proliferation.

In recent years, the role of the tumor microenvironment (TME) has gained significant attention. Tumor cells create an immunosuppressive environment that allows them to evade immune surveillance. One of the key mechanisms involves the accumulation of extracellular adenosine, which interacts with the Adenosine A2A receptor (A2AR) present on immune cells.

Activation of A2AR leads to increased intracellular cyclic AMP (cAMP) levels, which suppress immune responses by inhibiting T-cell activation and cytokine production. This process enables tumor cells to escape immune detection and promotes cancer progression.

Therefore, targeting the A2A receptor has emerged as a promising strategy for cancer therapy. Blocking this receptor can restore immune function and enhance anti-tumor activity.

2. Literature Review

Previous studies have extensively explored the role of molecular pathways and computational techniques in cancer therapy.

- Harish Chandra Pal et al. (2016) reported that melanoma progression is closely associated with dysregulation of the ERK signaling pathway and highlighted the potential of phytochemicals as anticancer agents.
- Meng et al. (2011) provided a comprehensive overview of molecular docking techniques, emphasizing their importance in drug discovery and identifying receptor flexibility as a major challenge.
- Dahlén et al. (2026) demonstrated the use of artificial intelligence and multimodal learning models to predict metastatic risk in melanoma, showing improved accuracy compared to traditional methods.
- Jacobson (2009) discussed the therapeutic importance of adenosine receptors, particularly A2AR, in various diseases including cancer.
- Rodríguez et al. (2015) used structure-based docking to identify ligands for A2AR, although challenges remained in identifying effective agonists due to limited understanding of receptor activation mechanisms.

These studies collectively highlight the importance of computational approaches and A2AR as a therapeutic target in cancer research.

3. Materials and Methods

3.1 Drug Design Strategy

The present study employed a structure-based drug design approach to develop novel adenine derivatives targeting the A2A receptor. Adenine was selected as the core scaffold due to its biological relevance and ability to form strong interactions with protein targets.

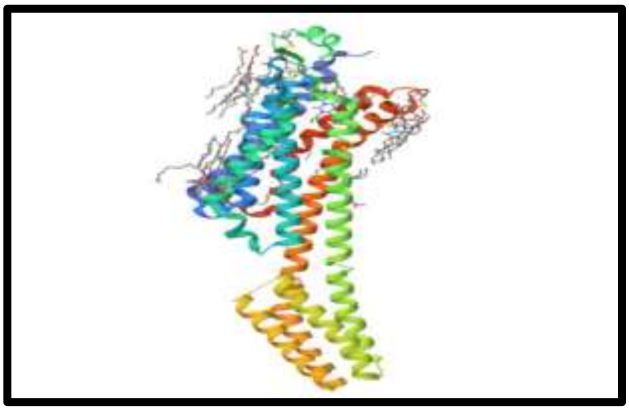
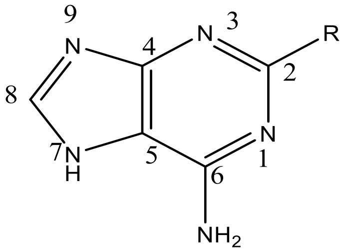


Fig.3.1.Crystallographic structure of Adenosine A2

3.2 Ligand Design and Optimization

A library of 50 compounds was designed by introducing various substituents at different positions of the adenine nucleus, particularly the C2 position. These modifications were aimed at improving:



- Binding affinity
- Selectivity
- Metabolic stability

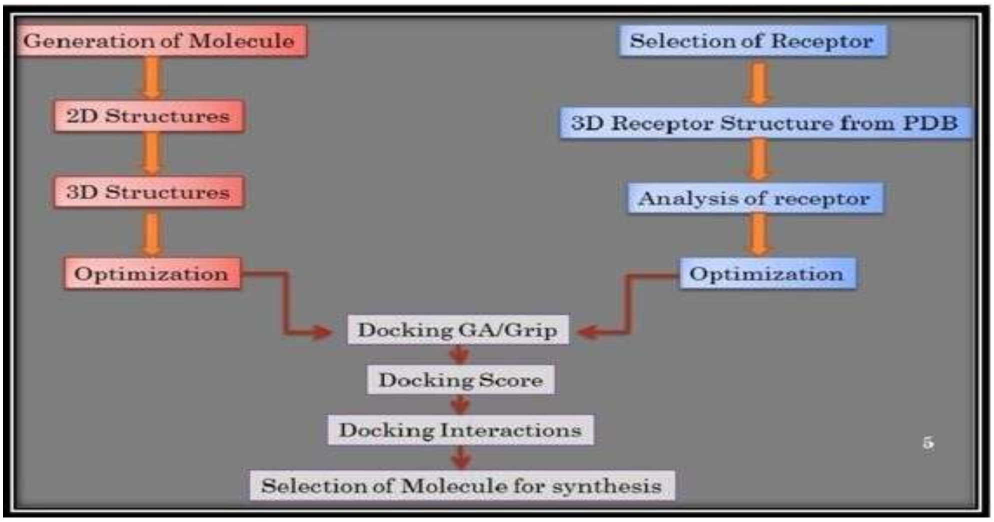
3.3 Molecular Docking

Molecular docking studies were carried out using SwissDock, a web-based docking platform that predicts ligand–protein interactions based on energy minimization and scoring functions.

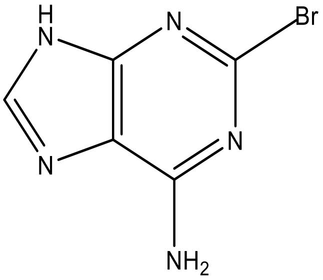
3.4 Docking Procedure

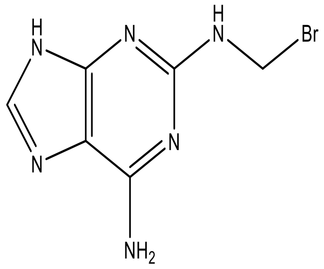
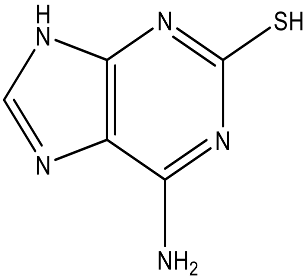
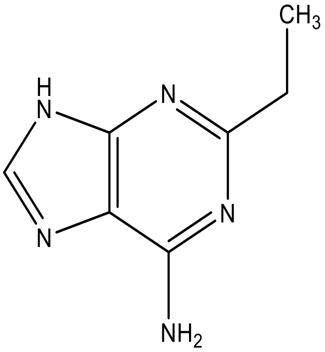
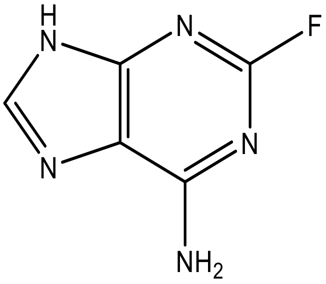
The docking process involved the following steps:

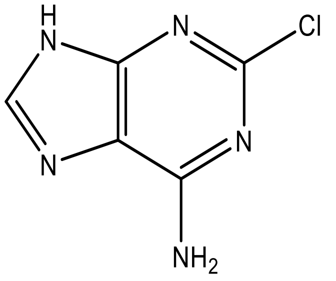
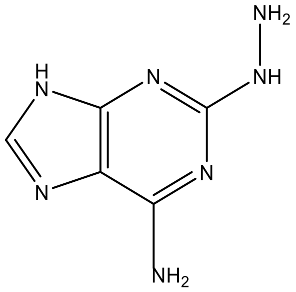
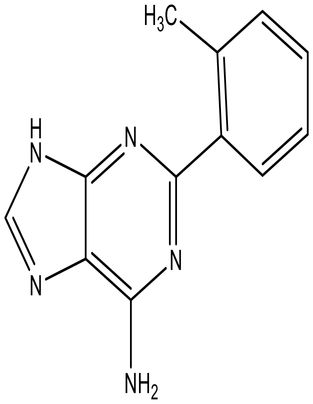
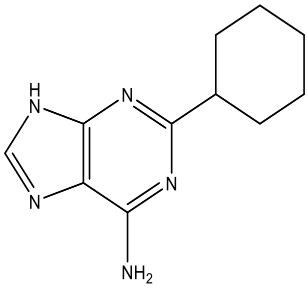
- Preparation of ligand structures and energy minimization
- Retrieval and preparation of protein structure (A2A receptor)
- Removal of water molecules and addition of hydrogen atoms
- Docking simulation using EADock DSS algorithm
- Scoring and ranking based on binding energy
- Visualization of interactions

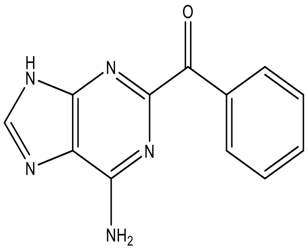
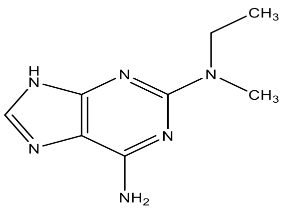
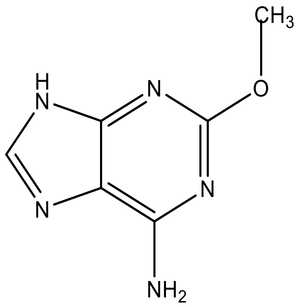
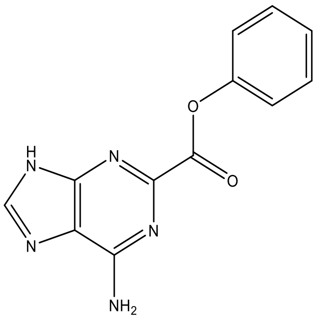


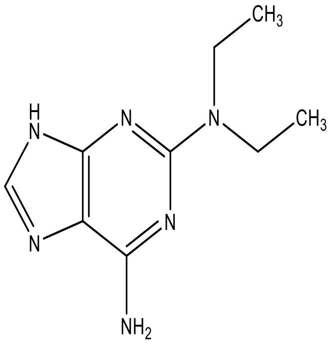
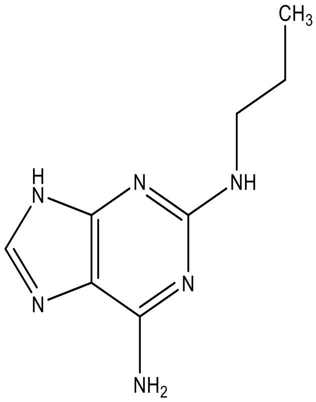
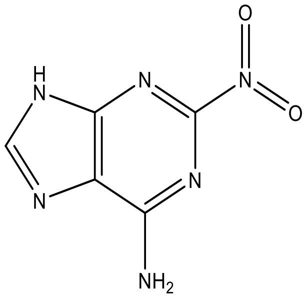
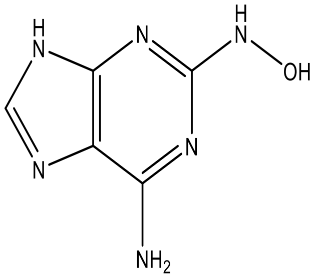
04.Physicochemical Characteristic and Docking Score of Compounds:

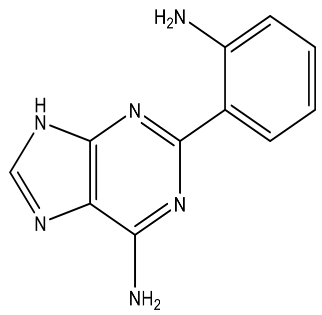
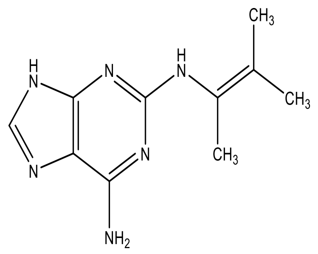
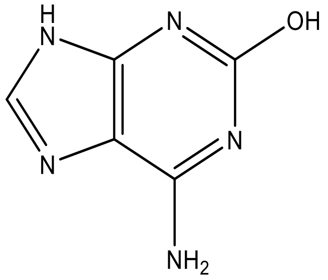
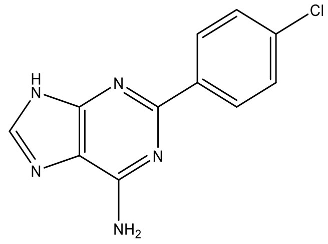
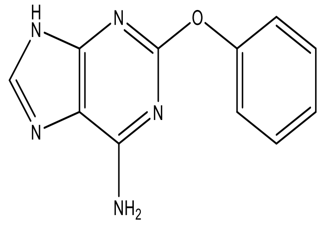
Molecular code	Molecular Structure	IUPAC Name	Molecular Formula	Molecular Weight	AC Score	Swissparam Score
ADS1		2-bromo-9H-purine-6-amine	$C_5H_4BrN_5$	214.03	-21.9602	-4.734

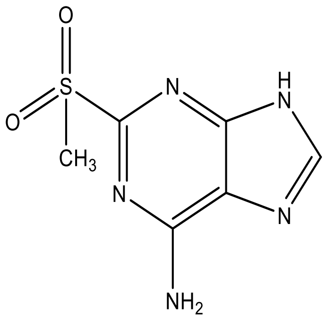
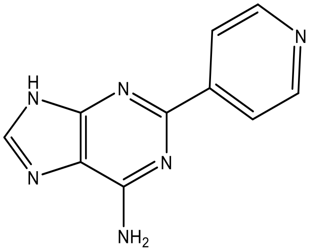
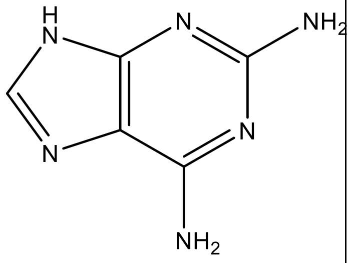
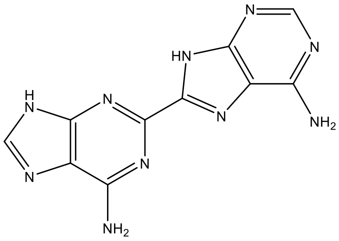
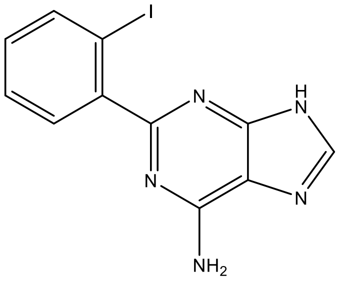
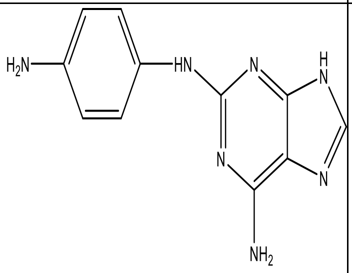
ADS2		N2-(bromomethyl)-9H-purine-2,6-diamine	C6H7BrN6	243.6	-0.12	-3.431
ADS3		6-amino-9H-purine-2-thiol	C5H5N5S	167.19	-23.4172	-5.9367
ADS4		2-ethyl-9H-purine-6-amine	C7H9N5	163.18	-20.2780	-6.6211
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS5		2-fluoro-9H-purine-6-amine	C5H4FN5	153.12	-23.1764	-6.4361

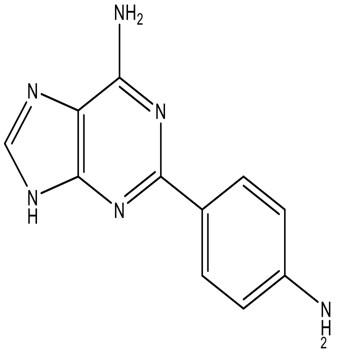
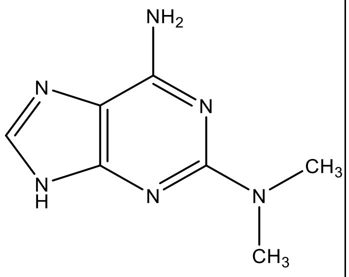
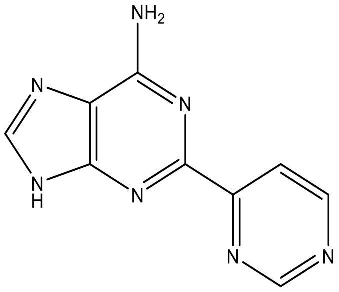
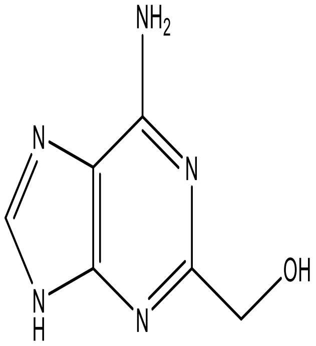
ADS6		2-chloro-9H-purine-6-amine	C5H4ClN5	169.57	-23.0241	-6.5118
ADS7		2-hydrazineyil-9H-purine-6-amine	C6H8N7	165.08	0.595369	-6.7180
ADS8		2-(o-tolyl)-9H-purine-6-amine	C12H11N5	225.26	5.646027	-7.4334
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS9		2-cyclohexyl-9H-purine-6-amine	C11H15N5	217.2	-27.1289	-6.9873

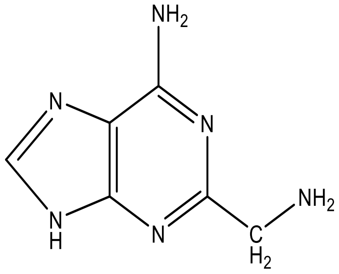
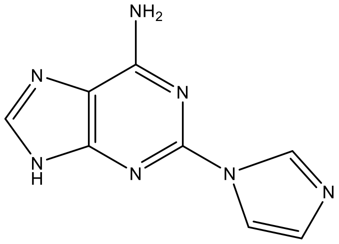
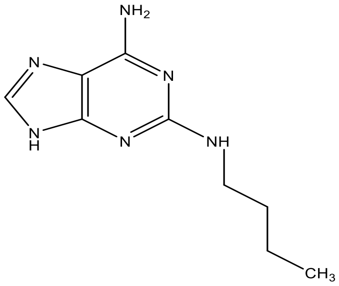
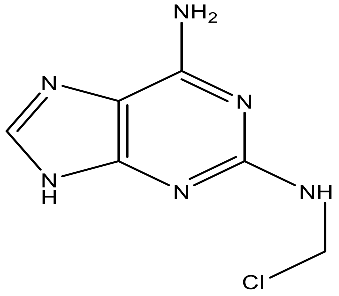
ADS10		(6-amino-9H-purine-2-yl)(phenyl)methanone	C12H9N5O	239.2	25.9966	-7.6608
ADS11		N2-ethyl-N2-methyl-9H-purine-2,6-diamine	C8H12N6	192.2	-64.1777	-7.0597
ADS12		2-methoxy-9H-purine-6-amine	C6H7N5O	165.16	-33.0890	-6.4520
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS13		phenyl 6-amino-9H-purine-2-carboxylate	C12H9N5O2	255.24	37.782756	-7.6632

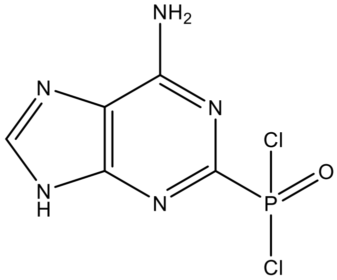
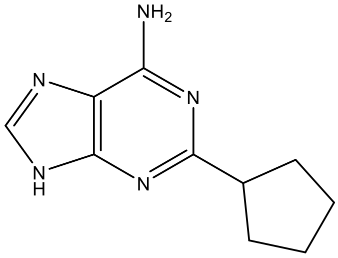
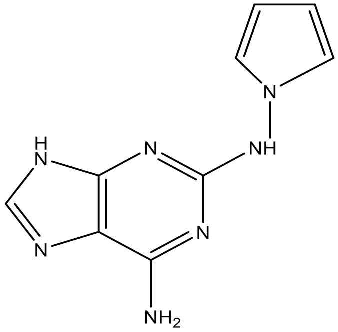
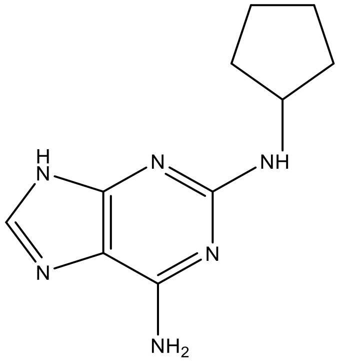
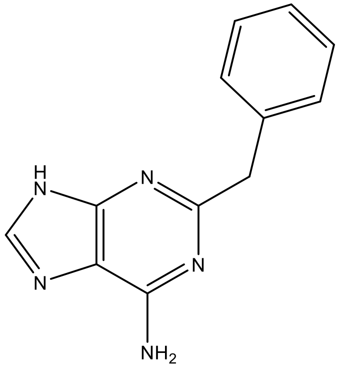
ADS14		N2,N2-diethyl-9H-purine-2,6-diamine	C9H14N6	206.13	-105.138251	-7.167.7
ADS15		N2-propyl-9H-purine-2,6-diamine	C8H12N6	192.23	-75.291493	-7.0483
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS16		2-nitro-9H-purin-6-amine	C5H4N6O2	180.13	42.227617	-6.5328
ADS17		2-(hydroxyamino)-9H-purin-6-amine	C5H6N6O	166.14	-20.652226	-6.6113

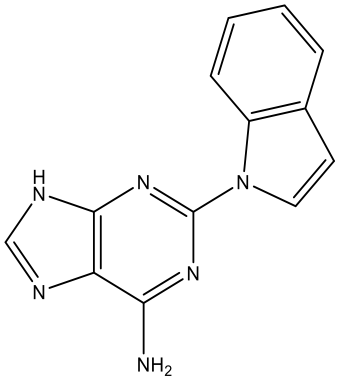
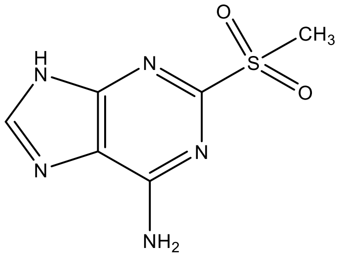
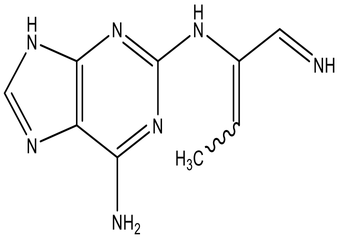
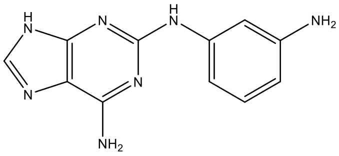
ADS18		2-(2-aminophenyl)-9H-purin-6-amine	C11H10N6	226.24	-0.180772	-7.4456
ADS19		N2-(3-methylbut-2-en-2-yl)-9H-purine-2,6-diamine	C10H14N6	218.26	-51.411712	-7.4363
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular weight**	**AC Score**	**Swiss Param Score**
ADS20		6-amino-9H-purin-2-ol	C5H5N5O	151.13	52.5530	-6.1347
ADS21		2-(4-chlorophenyl)-9H-purin-6-amine	C11H8ClN5	245.67	-1.229971	-71645
ADS22		2-phenoxy-9H-purin-6-amine	C11H9N5O	227.23	-7.188994	-7.1222

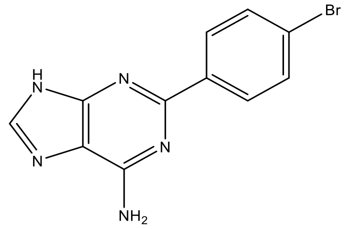
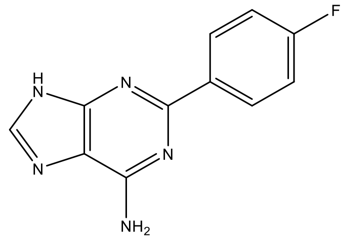
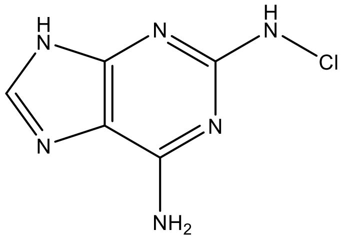
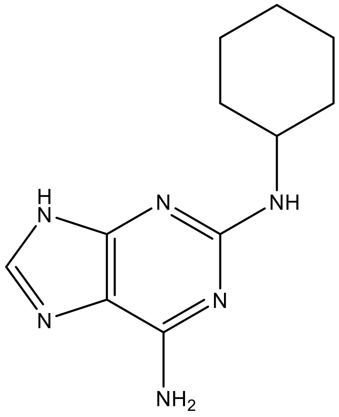
ADS23		2-methyl sulphonyl-9H-Purine-6amine	$C_6H_7N_5O_2S$	213.22	54.646152	-7.0175
ADS24		2-(pyridin-4-yl)-9H-purin-6-amine	$C_{10}H_8N_6$	212.22	-5.857012	-7.1338
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS25		9H-purine-2,6-diamine	$C_5H_6N_6$	150.15	-70.988	-6.3930
ADS26		-	$C_{10}H_8N_{10}$	268.24	19.8607	-7.6815
ADS27		2-(2-iodophenyl)-9H-purin-6-amine	$C_{11}H_8IN_5$	337.12	-9.775953	-7.7000
ADS28		N2-(4-aminophenyl)-9H-purine-2,6-	$C_{11}H_{11}N_7$	241.46	-56.03	-7.5371

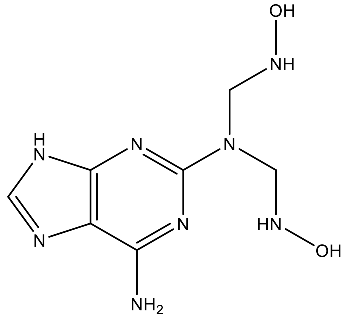
		diamine				
ADS29		2-(4-aminophenyl)-9H-purin-6-amine	C11H10N6	226.24	-4.5581	-7.4292
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS30		N2,N2-dimethyl-9H-purine-2,6-diamine	C7H10N6	178.20	-60.420007	-6.8221
ADS31		2-(pyrimidin-4-yl)-9H-purin-6-amine	C9H7N7	213.20	24.908895	-7.4445
ADS32		(6-amino-9H-purin-2yl)methanol	C6H7N5O	165.16	10.690453	-6.5034

ADS33		2-(amino methyl)-9H-purin-6-amine	C6H8N6	164.08	16.992752	-6.5274
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS34		2-(1H-imidazol-1-yl)-9H-purin-6-amine	C8H7N7	201.19	-4.998699	-7.1119
ADS35		N2-butyl-9H-purine-2,6-diamine	C9H14N6	206.25	-76.802217	-6.9363
ADS36		N2-(chloro methyl)-9H-purine-2,6-diamine	C6H7ClN6	198.61	84.443034	-6.5170

ADS37		(6-amino-9H-purin-2-yl)phosphonic dichloride	C5H4Cl2N5OP	251.99	7.5555	-4.965
ADS38		2-cyclopentyl-9H-purin-6-amine	C10H13N5	203.25	-19.143436	-7.0722
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS39		N2-(1H-pyrrol-1-yl)-9H-purine-2,6-diamine	C9H9N7	215.22	-89.749715	-75827
ADS40		N2-cyclopentyl-9H-purine-2,6-diamine	C10H14N6	218.16	-12.4356	-5.833
ADS41		2-benzyl-9H-purin-6-amine	C12H11N5	225.26	1.208978	-7.3918

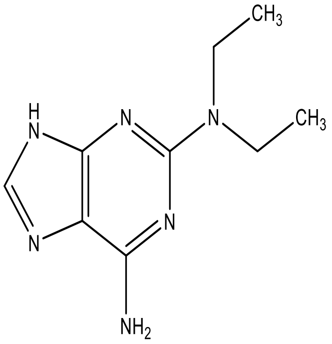
ADS42		2-(1H-indol-1-yl)-9H-purin-6-amine	C13H10N6	250.27	20.6842	-7.5765
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss pram Score**
ADS43		2-(methylsulfonyl)-9H-purin-6-amine	C6H7N5O2S	213.22	56.4589	-6.8740
ADS44		N2-(1-iminobut-2-en-2-yl)-9H-purine-2,6-diamine	C9H11N7	217.24	-36.579571	-7.3174
ADS45		N2-(3-aminophenyl)-9H-purine-2,6-diamine	C11H11N7	241.66	-56.039330	-7.5371

ADS46		2-(4-bromophenyl)-9H-purin-6-amine	C11H8BrN5	290.12	-5.480959	-7.5896
ADS47		2-(4-fluorophenyl)-9H-purin-6-amine	C11H8FN5	229.22	-3.927267	-7.44
Molecular code	**Molecular Structure**	**IUPAC Name**	**Molecular Formula**	**Molecular Weight**	**AC Score**	**Swiss param Score**
ADS48		N2-chloro-9H-purine-2,6-diamine	C5H5ClN6	184.59	-88.038925	-6.9390
ADS49		N2-cyclohexyl-9H-purine-2,6-diamine	C11H16N6	232.92	17.15	-6.003

ADS50		N2,N2-bis((hydroxyamino)methyl)-9H-purine-2,6-diamine	C7H12N8O2	240.23	-100.487086	-7.4406

ADMET Study

ADMET (Absorption, Distribution, Metabolism, Excretion, and Toxicity) studies in molecular modeling are critical for predicting a compound's behavior in the human body, filtering out weak candidates early to reduce costly, late-stage development failures. In silico ADMET prediction optimizes drug-likeness by assessing safety, solubility, and permeability, thereby accelerating lead optimization, reducing animal testing, and enhancing the probability of clinical success.



Physicochemical Properties	
Formula	C9H14N6
Molecular weight	206.25 g/mol
Num. heavy atoms	15
Num. arom. heavy atoms	9
Fraction Csp3	0.44
Num. rotatable bonds	3
Num. H-bond acceptors	3
Num. H-bond donors	2
Molar Refractivity	59.91

TPSA	83.72 Å^2
Lipophilicity	
Log $P_{o/w}$ (iLOGP)	1.37
Log $P_{o/w}$ (XLOGP3)	0.94
Log $P_{o/w}$ (WLOGP)	0.79
Log $P_{o/w}$ (MLOGP)	0.01
Log $P_{o/w}$ (SILICOS-IT)	0.46
Consensus Log $P_{o/w}$	0.72
Water Solubility	
Log S (ESOL)	-1.96
Solubility	2.28e+00 mg/ml ; 1.10e-02 mol/l
Class	Very soluble
Log S (Ali)	-2.28
Solubility	1.07e+00 mg/ml ; 5.19e-03 mol/l
Class	Soluble
Log S (SILICOS-IT)	-2.73
Solubility	3.81e-01 mg/ml ; 1.85e-03 mol/l
Class	Soluble
Pharmacokinetics	
GI absorption	High
BBB permeant	No
P-gp substrate	No
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No

CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-6.89 cm/s
Druglikeness	
Lipinski	Yes; 0 violation
Ghose	Yes
Veber	Yes
Egan	Yes
Muegge	Yes
Bioavailability Score	0.55
Medicinal Chemistry	
PAINS	0 alert
Brenk	0 alert
Leadlikeness	No; 1 violation: MW<250
Synthetic accessibility	2.32

Result:

Using Swiss Dock, 50 adenine derivatives (ADS1–ADS50) were docked to the Adenosine A2A receptor (PDB) based on crystallographic structure described). Docking employed grid-based exhaustive search, generating poses with AC (docking energy) and Swiss Param (physicochemical) scores. Lower values indicate better binding affinity and drug-likeness.

1	**ADS14**	**-105.14**	**-7.167.7**	**206.13**	**Diethylamine**
2	ADS50	-100.487086	-7.6924	240.23	Bis(hydroxyamino)amino
3	ADS39	-89.749715	- 7.5827	215.22	hydrazinyl-pyrrole

4	ADS48	- 88.0389	-6.9390	184.59	chloroamino
5	ADS35	-76.802217	-6.9363	206.17	Propylanimo
6	ADS15	-75.291493	-7.0483	192.23	Ethylamino
7	ADS25	-70.988	-6.3930	150.15	Amino
8	ADS11	-64.1777	-7.0597	192.2	Ethylmethyl diamine
9	ADS30	-60.42007	-6.8221	178.20	Dimethylamine
10	ADS45	-56.03933	-7.5371	241.66	3-aminophenyl amino

Result Table

Discussion :

Key Findings : ADS14 and ADS50 showed the best binding due to C2-position modifications that enhance receptor antagonism and metabolic stability. These modifications block adenosine signalling that suppresses immune attack on skin cancer cells.

Significance : The results validate adenine as an excellent scaffold for A2A receptor antagonists. Better docking scores correlate with structural features known to improve selectivity and potency against skin cancer.

Limitations : Computational predictions need experimental validation through synthesis and cell-based assays.

Conclusion :

Adenine derivatives ADS14 and ADS50 emerged as promising leads for skin cancer therapy by blocking A2A receptors and potentially restoring immune function. These computational hits provide a strong foundation for synthesis and preclinical testing to develop novel anticancer agents.

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