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In – Silico Biological Evaluation of Anticancer Drugs - SWISS ADME

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Abstract

The aim of the present work is to prepare anti-cancer drugs through *In – Silico* Biological Evaluation using SWISS ADME. The new Swiss ADME web tool, which includes in-house expert methods like the BOILED-Egg, Ilogp, and Bioavailability Radar, provides free access to a pool of quick yet reliable predictive models for physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness. It is developed to predict various pharmacodynamics and pharmacokinetics properties of small molecules, helping researchers in the drug discovery and development process. Researchers can use this tool to assess the potential success of a drug in terms of its ADME. Swiss ADME offers predictive model for various pharmacokinetic properties such as solubility, lipophilicity, and bioavailability this helps researchers assess how a drug candidate will be absorbed, distributed, metabolized, and excreted in the body.

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INTRODUCTION

A powerful chemical needs to reach its target in the body at a high enough concentration and remain there in a bioactive form for the anticipated biologic events to occur in order to be successful as a medication1. Drug development entails evaluating excretion, metabolism, distribution, and absorption at progressively early stages of the discovery process, when there are many compounds under consideration but restricted physical sample availability. Computer models are legitimate substitutes for the experiments in that content [1]. The new Swiss ADME web tool, which includes in-house expert methods like the BOILED-Egg, Ilogp, and Bioavailability Radar, provides free access to a pool of quick yet reliable predictive models for physicochemical properties, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness. The user-friendly interface of the website, which requires no login, ensures efficient and easy input and interpretation. Key parameters for a set of compounds can be quickly predicted by experts in cheminformatics or computational chemistry as well as non-experts, to aid in drug discovery efforts [2]. A vast number of molecular

structures are assessed based on a wide range of criteria during the laborious and resource-intensive processes of drug discovery and development. This helps to direct the choice of which compounds to synthesise, test, as well as advance, ultimately aiming to identify those that have the best potential to treat patients. The compounds must have low toxicity in addition to great biological activity. The organism's access to and concentration at the therapeutic target are equally crucial [3]. The conventional approach to pharmacokinetics, or the fate of a medicinal molecule within the organism, involves dissecting the different effects into discrete characteristics that affect the target's accessibility. By using certain techniques, each of these ADME factors can then be assessed independently. It has been shown that estimating ADME early in the discovery phase significantly lowers the percentage of clinical phases that experience pharmacokinetics-related failure. In the early stages of ADME prediction, when there are many chemical structures under investigation but few compounds available, computer models have been promoted as a viable substitute for experimental methods.

The goal of several different silicon approaches is to estimate ADME parameters based on chemical structure. Notably, Lipinski ET al.'s groundbreaking research looked at compounds that were active when taken orally to identify physicochemical ranges that had a high likelihood of becoming an oral medication; this study established the connection between pharmacokinetic as well as physicochemical parameters, and it is known as the "Rule-of-five" [4].

Developed By:

Swiss ADME was developed by a team of experts at the Swiss Institute of Bioinformatics, a renowned institution dedicated to advancing bioinformatics and computational biology, Molecular Modelling Group, Quartier Sorge, Batiment Genopode, and CH-1015 Lausanne Switzerland. It is developed to predict various pharmacodynamics and pharmacokinetics properties of small molecules, helping researchers in the drug discovery and development process. Researchers can use this tool to assess the potential success of a drug in terms of its ADME [5].

HISTORY:

Swiss ADME has a rich history with its origins dating back to the early 2000s when the SIB recognized the need for a comprehensive tool to predict the pharmacokinetic and physicochemical properties of small molecules. Over the years, it has evolved into a sophisticated software package that aids researchers worldwide. It is a powerful software suite developed by the SIB to facilitate drug discovery and development processes [6]. It stands for Absorption, Distribution, Metabolism, Excretion, which are critical aspects in understanding how drugs behave in the human body. The software is known for its user- friendly interface and various modules that predict properties like solubility, bioavailability, drug-likeness.

Early development: Swiss ADME Software began its development in the late 1990 with an initial focus on predicting physicochemical properties, which are essential factors in drug design [7].

Expansion: Over the years, the suite expanded to include various modules and predictive models for ADME. This expansion made it a comprehensive platform for assessing the pharmacokinetic properties of potential drug compounds.

Open access: Swiss ADME software has been made freely available to the scientific community, contributing to its widespread adoption [8].

FUNCTIONS [9-10]

A. Pharmacokinetic Predictions:

Swiss ADME offers predictive model for various pharmacokinetic properties such as solubility, lipophilicity, and bioavailability this helps researchers assess how a drug candidate will be absorbed, distributed, metabolized, and excreted in the body.

B. Toxicity Prediction:

The software can estimate potential toxicity, allowing researchers to identify and modify compounds with adverse effects early in the drug development process.

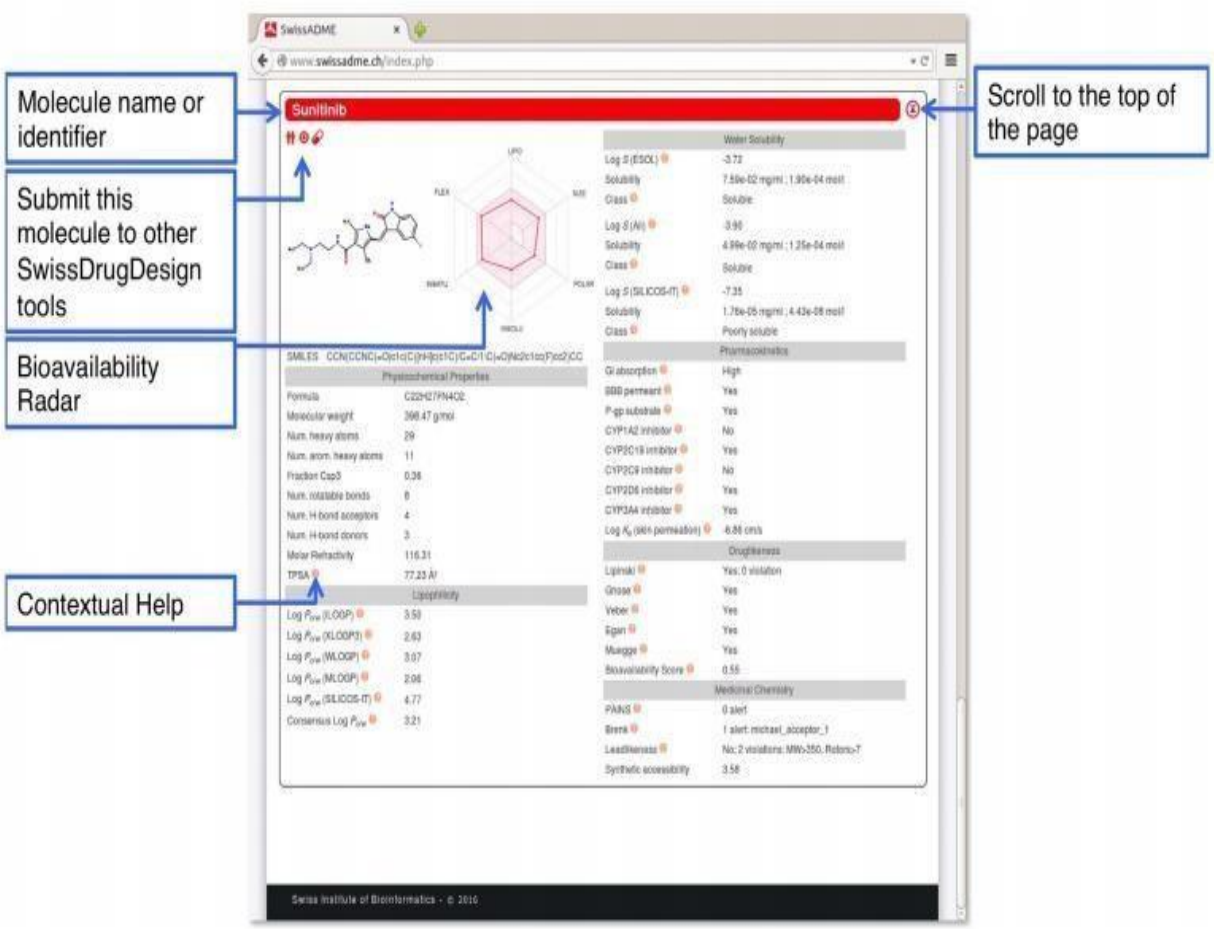


Figure 1 Computed parameter values are grouped in the differentselections of the one-panel-par- molecule Output

C. Bioavailability Optimization:

Swiss ADME assists in optimizing drug candidates for improved bioavailability, increasing the chances of a drug reaching its intended.

A. Lipophilicity.

The standard descriptor for lipophilicity is the partition coefficient Geg P between n-octane as well as water. Because of the critical importance of this physicochemical property for pharmacokinetic drug development, it has its own section in the Swiss ADME. Various computational techniques were created with varying performance on different chemical sets for log Pertinmation. It is standard procedure to employ several predictors to get consensus estimation or to choose the best accurate techniques for a certain chemical series. To improve the prediction accuracy through consent slog P, the predictors' underlying models must be as varied as feasible [11].

B. Water Solubility:

Many drug development operations are considerably aided by the presence of a soluble molecule, chiefly in terms of handling and formulation simplicity." Furthermore, solubility is a key factor affecting absorption in research efforts aimed at oral delivery. A medication intended for parenteral administration must also have a high water solubility to provide an adequate amount of the active component in the small amount of such a pharmaceutical dosage. Swiss ADME includes two topological techniques for predicting water solubility. Ali et al. provided an adaptation for the second me, while the first is an OL model. Since they do not include the melting point parameter—which might be difficult to predict—both deviate from the general solubility equation [12].

C. Pharmacokinetic:

Expert models assess each ADME behaviour of the substance being studied; these predictions are compiled in the Pharmacokinetics section. One panel for every molecule Results: On the same webpage, the output panels are loaded. All of the values for every molecule are compiled into a single panel. One molecule at a time, fills up instantly following the calculation. In this manner, it is feasible to review the initial compound findings without having to wait for the entire list to be processed. This one-panel-per-molecule is separated into many sections and is headed by the name of the molecule [13].

D. Chemical structure and Bioavailability Radar:

The two-dimensional chemical structure as well as canonical SMILES are included in the first section, which is below the title. It displays the chemical form that was used to calculate the predictions. Also shown for a quick evaluation of drug-likeness is our Bioavailability Radar. Descriptors derived from references 23 and 24 were used to determine the six physicochemical ranges on each axis. The descriptors are shown as a pink area on the radar where additional information can be obtained [14].

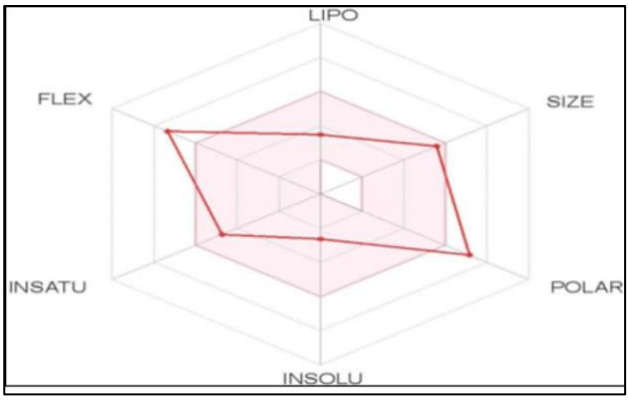


Figure 2 The Bioavailability Radar enables a first glance at the drug-likeness of a molecule

The pink region denotes the ideal range for each property: polarity: TPSA between 20 and 130A2, size: MW between 150 and 500g/mol, flexibility: no more than 9 rotatable bonds, solubility: logs not less than 0.25, and lipophilicity: XLOGP3 between –1.7 and +5.0. A multiple linear regression model is one that attempts to estimate the skin permeability coefficient. It is adapted from Potts and Guy, who discovered a linear correlation between lipophilicity and molecule size and KP. A lower molecule's skin penetration is indicated by a greater negative logKP [15].

On the Swiss ADME results page, click the red button that appears below the sketcher once all input molecules have been processed. This will display the readout of the BOILED-Egg model, an inappropriate graphical classification model that serves as a predictor for both passive human gastrointestinal absorption and blood-brain permeation.Additional binary classification models are presented, centred around the likelihood of a specific small molecule serving as a substrate for proteins that control significant pharmacokinetic behaviours [16].

Understanding how chemicals interact with cytochromes P450 is also crucial. Through metabolic biotransformation, this superfamily of isoenzymes plays a crucial role in drug clearance. It has been proposed that P-gp and CYP can work together to metabolise small compounds in a way that enhances tissue and organism protection. It is estimated that between 50 and 90 per cent of therapeutic compounds are substrates of the five main isoforms that have been found. Swiss ADME makes it possible to estimate if a substance is a P-gp substrate or an inhibitor of the most significant CYP isoenzymes. We used the support vector machine approach on massive data sets of known substrates that had been carefully cleansed. SVM was shown to outperform other machine-learning methods for binary classification in comparable situations. If the molecule under investigation has a higher probability of being a P-gp substrate, the model returns either Yes or No. When compared to earlier SVM models on the same targets, the statistical performance of the classification models is provided in the table. We limited the benchmark to cutting-edge techniques that were released after 2010 [17].

APPLICATIONS [18-19]

Swiss ADME finds extensive applications in both academic research and the pharmaceutical industry:

Drug Discovery: It aids in the selection and optimization of potential drug candidates, saving time and resources.

Lead Optimization: Researchers use Swiss ADME to fine-tune molecular structures to enhance a compounds chance of becoming a successful drug.

Early Toxicity Screening: The software helps identify compounds withtoxic potential early in development, reducing the risk of late-stage failures.

Chemo informatics: It plays a crucial role in various chemo informatics tasks, controlling library design and compound selection.

Medicinal Chemistry: This section's goal is to assist medicinal chemists in their ongoing efforts to find new drugs. Parts that can be problematic can be identified using two complementary pattern recognition techniques. PAINS, also known as frequent hits or promiscuous chemicals, are molecules with substructures that exhibit a strong assay response regardless of the protein target. Baell et al. analysed six orthogonal assays and separated the molecules active on two or more assays into 481 recurring pieces, which are thought to potentially lead to promiscuous chemicals. These fragments, generating false positive biological output, were identified. If the molecule being examined contains such moieties, Swiss ADME returns warnings.

Aiding in the selection of the most promising virtual molecules to be synthesised and submitted to biological assays or other tests is one of the main goals of CADD operations. One important thing to keep in mind during this choosing process is synthetic accessibility. Medicinal chemists are the best qualified to determine SA for a decent number of compounds. On the other hand, silicon estimates can be utilised for pre-filtering when an expert evaluation is hindered by an excessive number of molecule structures.

A fingerprint-based method for SA estimation was proposed by Ertl and Schuffelhauer, although our tool's easy implementation is hindered by the presence of closed-source fingerprint-defining information. Consequently, we have developed our fragmental approach through the analysis of over 13 million molecules that are promptly deliverable by vendors sets: several external molecules; b number of chemical markers; c mean average error; d root mean square error; e coefficient of linear correlation. Based on our extensive collection, we deduced that the majority of the molecular fragments likely indicate a high SA, whereas the rarer fragments suggest a sophisticated synthesis. For a given molecule, the parameters describing size and complexity, such as macrocycles, chiral centres, or Ertl-defined Spiro functions, add up and correct the fragmental contributions to SA. There is no denying that the subjective nature of human assessment of synthetic complexity depends on the training and expertise of individual chemists.

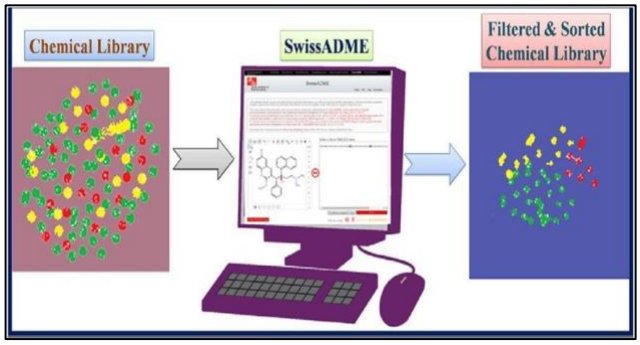


Figure 1 Swiss ADME

Graphical output [20]:

Following the completion of all calculations, the graphical output is displayed on the same page by clicking the red "Show BOILED-Egg" button beneath the sketcher. The BOILED-Egg is a simple and easy way to predict two important ADME characteristics at the same time: brain access and passive gastrointestinal absorption. This categorization model was carefully constructed with consideration for statistical significance and robustness, although having a very simple conceptual basis—it only relies on two physicochemical descriptors. The grey area outside represents chemicals with characteristics suggesting anticipated low absorption and restricted brain penetration, and the two compartments are not mutually exclusive. Practical experience with the BOILED- Egg in drug development contexts has demonstrated its easy interpretation and effective translation to molecular design. Consequently, by color-coding (blue dots for P-gp substrates (PGP+) and red dots for P-gp non-substrate (PGP-), the user may quickly acquire an overall evaluation concerning passive absorption, passive brain access, and active efflux from the central nervous system or to the gastrointestinal lumen on the same graph. Additional capacities were included to enable interactive navigation and easy evaluation, in

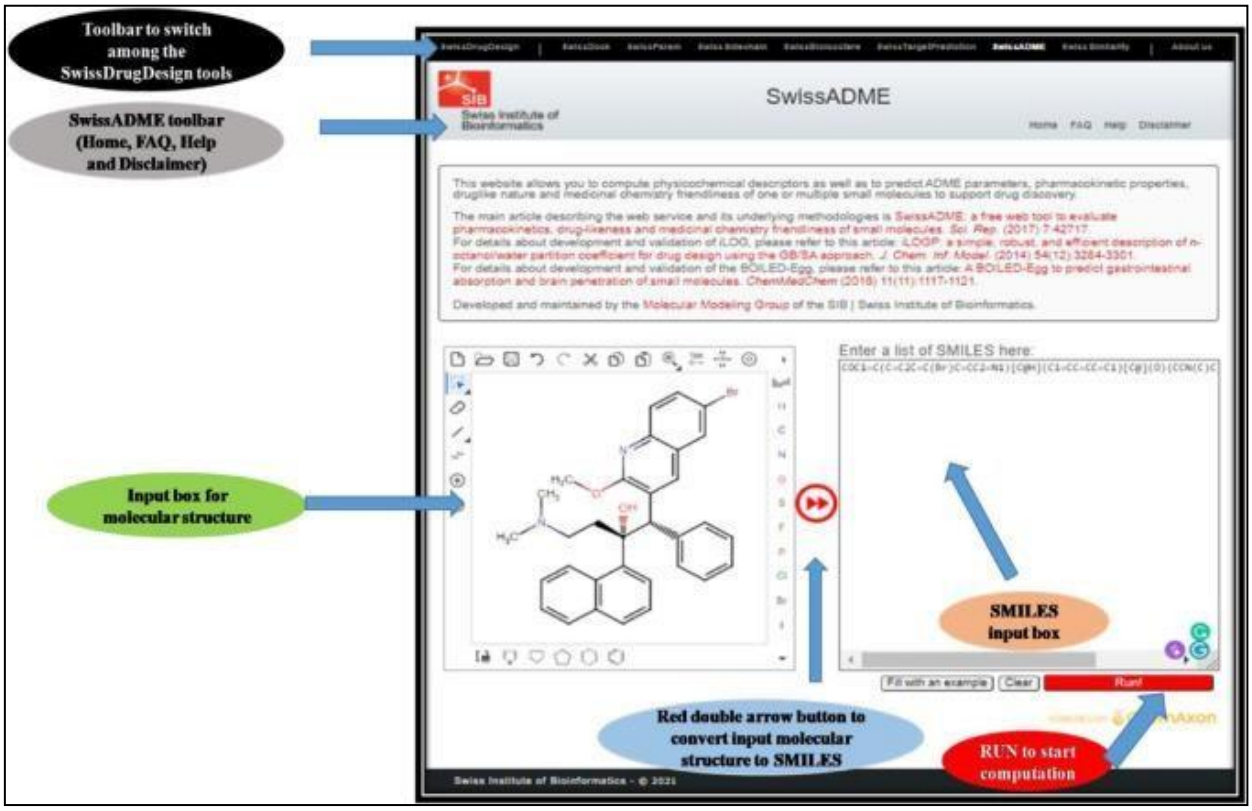


Figure 4 Swiss ADME Representation

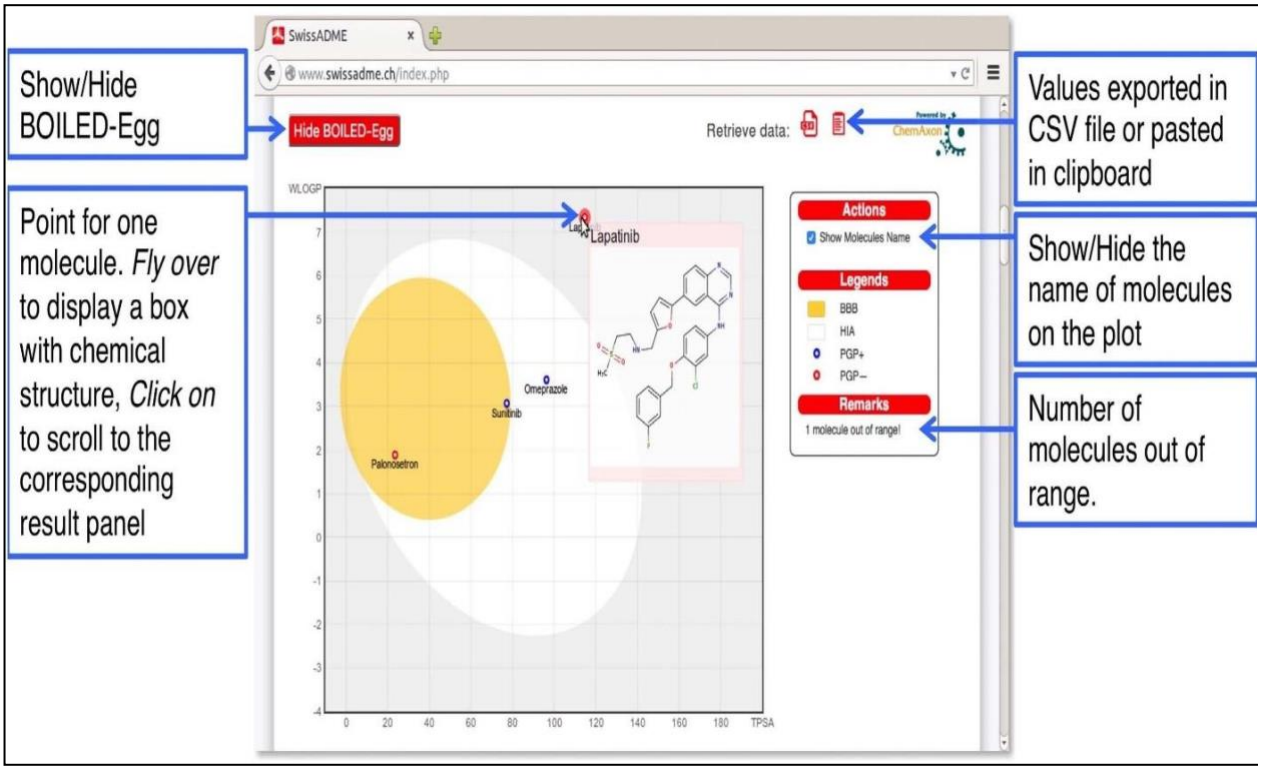


Figure 5: The WLOGP-versus-TPSA referential molecules' functions enable the intuitive assessment of passive gastrointestinal absorption and brain penetration using the BOILED-Egg.

contrast to the one-panel-per-molecule idea for other metrics. The graphical output comprises prediction for all molecules for all molecules submitted to Swiss ADME. When a point is passed over, a semi-transparent box containing the molecule's name and structure appears.

There is a high likelihood of brain penetration in the yellow region and a high likelihood of passive absorption by the gastrointestinal system in the white zone. White areas and the folk are not mutually exclusive. Furthermore, the spots are coloured red if P-gp is projected to be non-substrate and blue if P-gp is predicted to be actively effluxed. When performing an interactive analysis, the user can click on a dot to scroll to the relevant output panel by leaving the mouse pointer over the dot that displays the molecule's structure. In this instance, it is anticipated that Lapatinib will be efficiently absorbed but not reach the bran and PGP+, Sunitinib will passively cross the blood-brain barrier but be pumped out of the brain, and Palonosetron will enter the brain but not be actively effluxed.

They enable the molecule to be submitted with just one click to websites for Swiss Target Prediction, Swiss Similarity, and Swiss Drug Design. These websites also feature the Swiss ADME pill icon, which can be used to estimate the pharmacokinetics of ADME, rug-likeness, and medicinal chemistry friendliness of a small molecule output from any CADD process.

Advantages [21]:

Comprehensive: Swiss ADME provides a wide range of predictive models, offering a holistic view of a compound ADME properties.

Time and Cost Savings: It accelerates the drug development process by guiding researchers toward compounds with higher chances of success.

User-Friendly Interface: The software is designed to be user-friendly, making new comers in the field.

Predictive Capabilities: Swiss ADME can predict various pharmacokinetics and physicochemical properties of compounds, helping researchers assess a drug's viability.

Integration: The tool can be integrated into larger drug discovery workflows, enhancing its utility in the pharmaceutical research.

Batch Processing: Users can submit multiple compounds for analysis in a single run, saving time and effort.

Visualization: The software provides 2Dand 3D molecular structure visualization, helping users better understanding the properties of their compounds. It is important to note that while Swiss ADME is a powerful tool, it should be used in conjunction with other experimental and computational methods to comprehensively assess drug candidates.

Cost-efficacy: By identifying potential issues with compounds before conducting costly experimental studies, Swiss ADME can lead to significant cost savings in the drug development.

Board applicability: It is valuable not only in pharmaceutical research but also in areas like agrochemicals, food chemistry and environmental science.

It is important to note that while Swiss ADME is a powerful tool, it should be used in conjunction with other experimental and computational methods to comprehensively assess drug candidates.

Disadvantages [22]:

Data quality: The accuracy of predictions heavily relies on the quality ofinput data and errors in the compound information can lead to unreliable results.

Limited to small molecules: Its primarily designed for small organic molecules and may not be suitable for large biologics or peptides.

Limited accuracy: Swiss ADME predictions may not always be highly accurate, especially for compounds with unusual or properties.

Limited Predictive Power: Predictive accuracy may vary for different properties, and the software might not perform equally well for all compounds or endpoints.

Lack of customization: Users have limited control over the underlyingalgorithms models, making it less flexible for specific research needs.

Single compound Focus: It's more suitable for assessing individual compounds rather than complex mixtures or interactions between multiplecompounds.

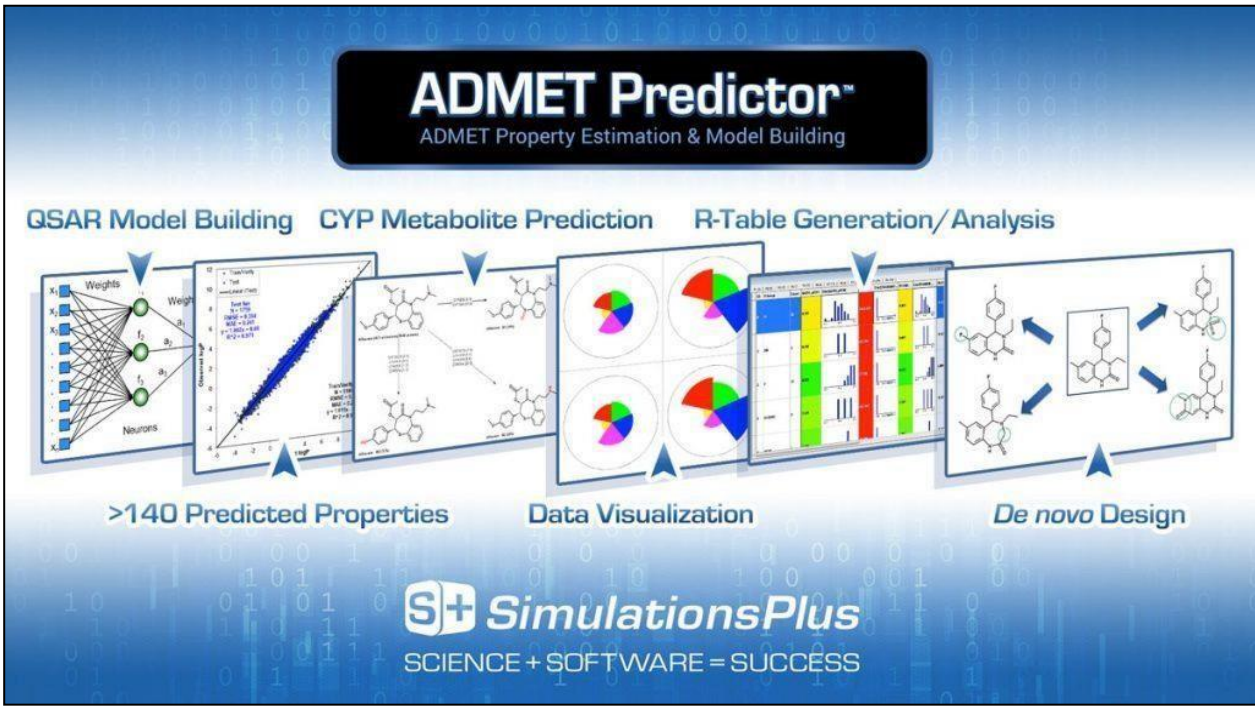


Figure 6: ADMER Predictor

Commercial Licensing: While there is a free version, some advanced features of Swiss ADME may require a commercial license, which can becostly.

Lack of Mechanistic Insights: Swiss ADME provides predictions but does not offer detailed mechanist insights into the predicted properties, which may be crucial in some drug development scenarios. Despite these disadvantages, Swiss ADME remains a valuable tool for early – stage drug discovery and optimization, especially for small molecules with well characterized properties.

ADME predictor is a machine learning software tool that quickly and accuratelypredicts over

175 properties, including solubility, pka, logP sites of CYP metabolism and Ame's mutagenicity.

1. PRINCIPLE [23]

Swiss ADME software principles refer to the principles and methodologies used in software tools designed to predict the pharmacokinetic properties of small molecules in the drug discovery and development.64These principles typically encompass the following:

a. Data Integration: Swiss ADME software integrates various data sources, including chemical structures, physicochemical properties, and biological data, to provide comprehensive predictions.

b. Pharmacokinetic Modeling: These tools employ mathematical models and algorithms to simulate how a drug compound will be absorbed, distributed, metabolized, and excreted in the body.

c. Structure-Activity Relationships (SAR): Swiss ADME software often uses SAR analysis to link chemical structures to pharmacokinetic properties, helping to predict how structural changes impact drug behavior in the body.

d. Predictive Algorithms: These tools utilize predictive algorithms based on historicaldata to estimate properties such as solubility, permeability, and half-life.

e. Data Validation: Validated and curated datasets are crucial for accurate predictions, ensuring that the software's results are reliable. User-Friendly Interfaces: User-friendly interfaces and visualization tools make it easier for researchers to input data, interpret results, and make informed decisions.

f. Machine Learning and AI: Some Swiss ADME software incorporates machine learning and artificial intelligence techniques to improve

prediction accuracy and handle complex data relationships.

g. **User-Friendly Interfaces:** User-friendly interfaces and visualization tools make it easier for researchers to input data, interpret results, and make informed decisions.

h. **Customization:** Flexibility to customize models and parameters to suit specific research needs or drug development goals is often a key feature.

i. **Compliance:** Swiss ADME software may adhere to regulatory guidelines and standards to ensure that the predictions align with industry requirements for drug development.

j. **Data Privacy:** Ensuring the confidentiality and security of proprietary drug data iscritical in these tools.

These principles are applied to help researchers assess the potential of drug candidatesby predicting how they will behave within the human body, ultimately aiding in the selection and optimization of compounds with desirable pharmacokinetic properties.

2. WORKING [24]

a. **Input**: Users input the chemical structure of a compound in the form of a 2D or 3D molecular structure file.

b. **Prediction**: Swiss ADME uses a variety of computational models and algorithms to predict key ADME properties such as lipophilicity, water solubility, permeability, and more. It also estimates the potential for metabolism by cytochrome P450 enzymes.

c. **Results:** The software provides a report with the predicted ADME parameters and related information for the input compound.

d. **Interpretation:** Users can interpret the results to assess the compound's suitability for drug development. For face challenges in metabolism or excretion.

e. **Decision Support:** Swiss ADME assists researchers in making decisions about whether to proceed with the development of a particular compound, considering its pharmacokinetic properties.

Export: Users can export the results for further analysis and reporting. Swiss ADME is a valuable tool in the drug discovery process as it helps pharmacokinetics researchers and pharmaceutical companies quickly assess the drug likeness and potential issues.

Activity:

Anticancer drugs are made to treat a variety of cancer types. The unchecked growth of cells that obstruct the development of healthy cells is known as cancer. Radiation, chemotherapy (treatment with anticancer medications), surgery, or a combination of these are the main cancer treatments.

Anti-cancer medications are intended to prevent and treat a variety of cancers, including testicular seminomas, Hodgkin's and non-Hodgkin's lymphomas, cervical cancer, breast cancer, small cell lung cancer, head and neck cancer, ovarian cancer, osteosarcoma, and lymphoblastic leukaemia.

Anti-Cancer Drugs' Common Mechanism of Action:

a. They could work by causing harm to malignant cells' DNA. Anticancer drugs can result in the production of nonsense DNA or RNA or cause single-strand and double-strand breaks in DNA. This group of medications includes, among others, etoposide, daunorubicin, doxorubicin, mitomycin C, and cisplatin.
b. They prevent the synthesis of new DNA to prevent cell replication, which promotes tumour growth. There are several methods in which these agents function.
c. They halt mitosis, which is the process by which the original cell divides into two new cells. Reversing mitosis prevents cancer cells from proliferating, or dividing, and may eventually stop the cancer from spreading [25].

There are various categories into which anti-cancer agents can be classified [26]:

DNA ALKYLATING AGENTS:

- Clorambucil
- Cyclophosphamide
- Ifosfamide
- Mechlorethamine

Table 1: Alkylating agents

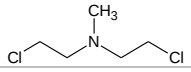
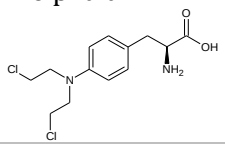
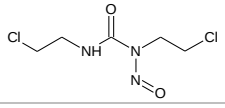
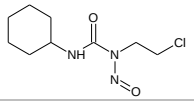
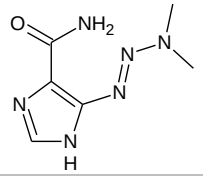
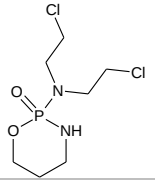
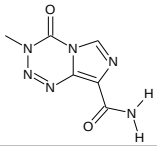
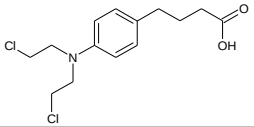
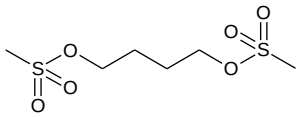
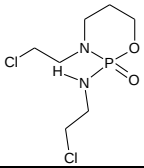
S.No	Name of the Drug & Structure	IUPAC Name	Smiles Notation
1.	Mechlorethamine 	*N*-(2-chloroethyl)-*N*- methylpropan-1-amine	CCCN(C)CCCl
2.	Melphalan 	(1H) - [(2*S*)-2-amino-3-{4-[bis(2-chloroethyl) amino] phenyl}-1-hydroxypropylidene] dioxidanium	O\[O+]=C(/O)[C@@H](N)Cc1ccc (cc1)N(CCCl)CC Cl
3.	Carmustine 	1,3-bis(2-chloroethyl)-1- nitrosourea	O=C(NCCCl)N(CCCl)N=O
4.	Lomustine 	1-(2-chloroethyl)-3- cyclohexyl-1-nitrosourea	O=C(NC1CCCCC1) N(CCCl)N=O
5.	Dacarbazine 	5-[(1*E*)-3,3-dimethyltriaz-1- en-1-yl]-1*H*-imidazole-4- carboxamide	O=C(N)c1ncnc1/N=N/N(C)C
6.	Cyclophosphamide 	*N*, *N*-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2- oxide	O=P1(NCCCO1) N(CCCl)CCCl
7.	Temozolomide 	4-methyl -5-oxo-2,3,4,6,8-pentazabicyclo [4.3.0]nona- 2,7,9-triene-9-carboxamide	NC(=O) c2ncn1c2N=[N+] =NC1=O
8.	Chlorambucil 	Butane-1,4-diyl dimethanesulfana-te	O=[SH2+] (=O) OCCCCO[SH2+] (=O) =O
9.	Busulfan 	Butane-1,4-diyl dimethanesulfana-te	O=[SH2+] (=O) OCCCCO[SH2+] (=O) =O
10	Ifosfamide 	*N*,3-bis(2-chloroethyl)-1,3,2-oxazaphosphinan-2-amine 2- oxide	O=P1(NCCCl)OCCCN1CCCl

Table 2: Heavy Atoms

Codes	No. heavy atoms	No.arom Heavy atoms	Fraction Csp3
Mechlorethamine	8	0	1.00
Melphalan	20	6	0.46
Carmustine	12	0	0.80
Lomustine	9	0	0.86
Dacarbazine	13	5	0.33
Cyclophos phamide	7	0	1.00
Temozolomide	3	0	0.00
Chlorambucil	12	6	0.30
Busulfan	2	0	0.30
Ifosfamide	14	0	1.00

No. rotatable bonds	No. H-bonds acceptors	Molar Refractivity	TPSA
4	1	38.65	3.24 A^2
8	4	81.54	86.79 A^2
7	3	46.77	61.77 A^2
2	1	37.04	29.10 A^2
3	4	44.77	99.73 A^2
0	3	31.22	61.80 A^2
0	1	10.22	43.09 A^2
4	2	47.60	37.30 A^2
0	1	10.84	36.28 A^2
5	4	62.60	51.38 A^2

Lipophilicity characteristics

Table 3: Lipophilicity Characteristics [28]

Code	iLOGP	XLOGP3	WLOGP
Mechlorethamine	2.41	1.75	1.57
Melphalan	-3.07	2.17	1.93
Carmustine	1.72	1.53	1.16
Lomustine	1.61	1.36	1.07
Dacarbazine	0.24	-0.56	0.07
Cyclophosphamide	0.52	-0.69	0.01
Temozolomide	0.24	-0.85	-0.90
Chlorambucil	1.69	2.42	2.09
Busulfan	1.69	2.42	2.09
Ifosfamide	2.08	0.86	1.50

MLOGP	SILICOS-IT	Consensus Log Po/w
1.89	1.28	1.78
-0.05	0.62	0.32
0.99	0.66	1.21
1.23	1.32	1.32
-0.66	-0.09	-0.20
-0.83	2.30	0.26
-1.13	-0.47	-0.62
2.29	2.23	2.14
2.29	2.23	2.14
0.97	1.13	1.31

Water Solubility

Table 4: Water Solubility [29]

Code	ESOL			
	Log S (ESOL)	Solubility		Class
		mg/ml	mol/L	
Mechlorethamine	-1.52	4.10e+00	3.02w-02	VS
Melphalan	-2.90	4.07e-01	1.26e-03	S
Carmustine	-1.67	4.59e+00	2.14e-02	VS
Lomustine	-1.35	5.64e+00	4.43e-02	VS
Dacarbazine	-0.70	3.61e+01	1.98e-01	VS
Cyclophosphamide	-0.16	8.45e+01	6.98e-01	VS
Temozolomide	0.42	1.17e+02	2.61e+00	HS
Chlorambucil	-2.49	5.33e-01	3.25e-03	S
Busulfan	-2.49	5.33e-01	3.25e-03	S
Ifosfamide	-1.67	5.58e+00	2.14e-02	VS

Code	Ali			
	Log S (Ali)	Solubility		Class
		mg/ml	mol/L	
Mechlorethamine	-1.44	4.98e+	3.67e-02	VS
Melphalan	-3.63	7.63e-02	2.37e-04	S
Carmustine	-2.44	7.84e-01	3.66e-03	S
Lomustine	-1.57	3.40e+00	2.67e-02	VS
Dacarbazine	-1.06	1.57e+01	8.62e-02	VS
Cyclophosphamide	-0.13	8.91e+01	7.36e-01	VS
Temozolomide	0.43	1.20e+02	2.67e+00	HS
Chlorambucil	-2.85	2.34e-01	1.43e-03	S
Busulfan	-2.85	2.34e-01	1.43e-03	S
Ifosfamide	-1.52	7.84e+00	3.00e-02	VS

Code	SILICOS-IT			
	Log S (SILICOS-IT)	Solubility		Class
		mg/ml	mol/L	
Mechlorethamine	-2.19	8.68e-01	6.40e-03	S
Melphalan	-3.61	7.96e-02	2.47e-04	S
Carmustine	-2.03	2.01e+004	9.40e-03	S
Lomustine	-1.28	6.74e+00	5.30e-02	S
Dacarbazine	-1.03	1.69e+01	9.29e-02	S
Cyclophosphamide	-0.47	4.08e+01	3.37e-01	S
Temozolomide	0.76	2.60e+02	5.77e+00	S
Chlorambucil	-2.98	1.74e-01	1.06e-03	S
Busulfan	-2.98	1.74e-01	1.06e-03	S
Ifosfamide	-2.71	5.08e-01	1.95e-03	S

Pharmacokinetics

Table 5: Pharmacokinetics

Code	GI absorption	BBB permeant	P-gp substrate	CYP1A 2 inhibitor
Mechlorethamine	Low	No	No	No
Melphalan	High	No	Yes	No
Carmustine	High	Yes	No	No
Lomustine	High	Yes	No	No
Dacarbazine	High	No	No	No
Cyclophosphamide	High	No	No	No
Temozolomide	High	No	No	No
Chlorambucil	High	Yes	No	No
Busulfan	High	Yes	No	No
Ifosfamide	High	Yes	No	No

CYP2C 19 inhibitor	CYP2C 9 inhibitor	CYP2D 6 inhibitor	CYP3A 4 inhibitor	Log K_p (Skin permeation) (cm/s)
No	No	No	No	-5.88
No	No	No	No	-6.72
No	No	No	No	-6.52
No	No	No	No	-6.11
No	No	No	No	-7.81
No	No	No	No	-7.53
No	No	No	No	-7.18
No	No	No	No	-5.58
No	No	No	No	-5.58
No	No	No	No	-7.28

Drug likeness

Table 6: Drug Likeness

Code	Lipinski	Ghose	Veber
Mechlorethamine	Yes; 0 violation	No;2 violations	Yes
Melphalan	Yes; 0 violation	Yes	Yes
Carmustine	Yes; 0 violation	Yes	Yes
Lomustine	Yes; 0 violation	No;2 violations	Yes
Dacarbazine	Yes; 0 violation	Yes	Yes
Cyclophosphamide	Yes; 0 violation	No;3 violations	Yes
Temozolomide	Yes; 0 violation	No;4 violations	Yes
Chlorambucil	Yes; 0 violation	Yes	Yes
Busulfan	Yes; 0 violation	Yes	Yes
Ifosfamide	Yes; 0 violation	Yes	Yes

Egan	Muegge	Bioavailability score	Egan
Yes	No;2 violation	0.55	Yes
Yes	Yes	0.55	Yes
Yes	Yes	0.55	Yes
Yes	No;2 violation	0.55	Yes
Yes	No; 1 violation	0.55	Yes
Yes	No;2 violation	0.55	Yes
Yes	No;2 violation	0.55	Yes
Yes	No;1 violation	0.85	Yes
Yes	No; 1 violation	0.85	Yes
Yes	Yes	0.55	Yes

Medicinal Chemistry:

Table 7: Medicinal Chemistry [30]

Code	PAINS	Brenk	Leadlikeness	Synthestic accessibility
Mechlorethamine	0 alert	1 alert	No; 1 violation	1.50
Melphalan	1 alert	3 alerts	No; 1 violation	2.67
Carmustine	0 alert	2 alerts	No; 1 violation	2.42
Lomustine	0 alert	1 alert	No; 1 violation	1.00
Dacarbazine	1 alert	1 alert	No; 1 violation	2.65
Cyclophosphamide	0 alert	1 alert	No; 1 violation	3.79
Temozolomide	0 alert	1 alert	No; 1 violation	1.00
Chlorambucil	0 alert	0 alert	No; 1 violation	1.00
Busulfan	0 alert	0 alert	No; 1 violation	1.00
Ifosfamide	0 alert	2 alerts	Yes	4.07

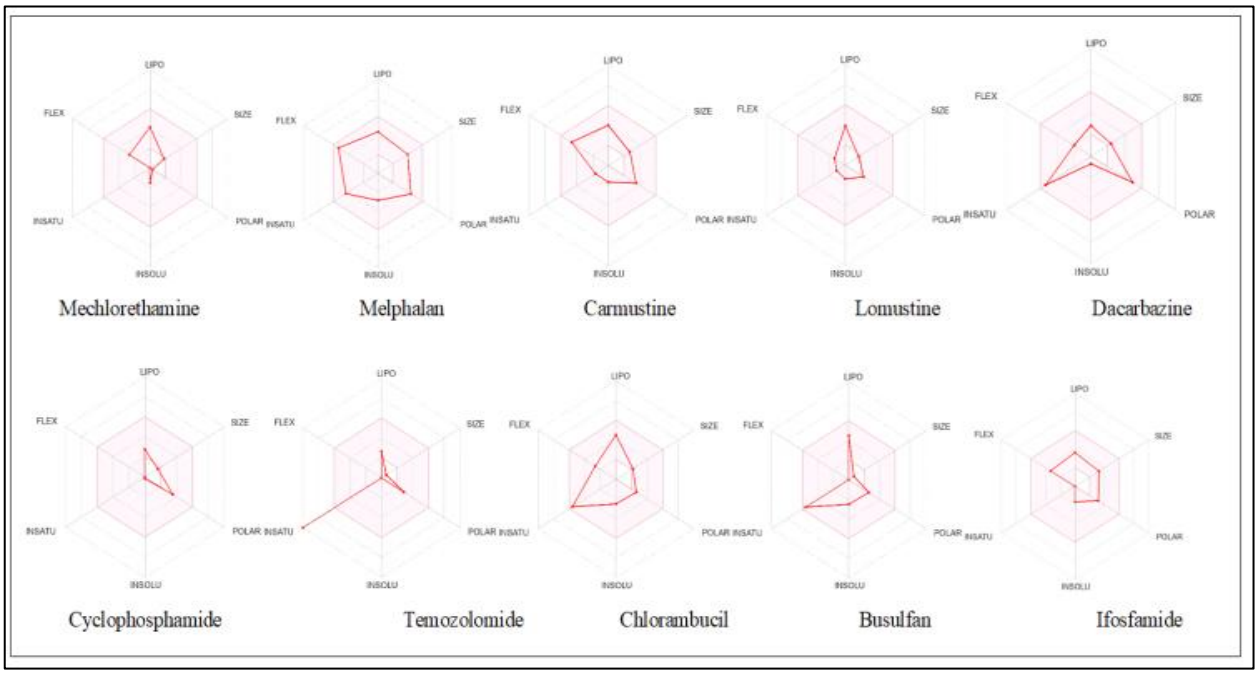


Figure 7: Alkalyting Agents Structural Formulas

- Melphalan
- Cisplatin
- Oxaliplatin
- Satraplatin
- Carmustine
- Lomustine
- Dacarbazine

ANTIMETABOTILES:

- Cladribine
- Clofarabine
- Cytarabine
- Gemcitabine
- Pyrimidine antagonists
- Capecitabine
- Floxuridine
- Methotrexate

ANTIBIOTICS:

- Bleomycin
- Dactinomycin
- Daunorbicin
- Doxorubicin
- Mitomycin
- Valrubicin

MITOSIS INHIBITORS:

- Docetaxel
- Etoposide
- Paclitaxel

- Teniposide
- Topotecan
- Vincristine
- Vinorelbine

ORGANOPLATINUM COMPLEXES:

- Carboplatin

ALKYLATING AGENTS:

The main atoms with which these alkylating chemicals react cytotoxically in biological systems are those found in proteins and DNA. These compounds react with electron-rich atoms to generate strong chemical bonds. When it comes to biological toxicity, reactions involving DNA constituents are the most significant, with RNA and proteins having a secondary role.

It has been reported that mitomycin C, which has been effectively used to treat a variety of cancers, including gastric, pancreatic, breast, non-small cell lung, cervical, prostate, and bladder cancers, has a quinine chemical structure, which produces OH through a series of bio-reductive processes. High-reactivity radicals were thought to have the ability to directly harm cells' DNA and other macromolecules.

3. MECHANISM [27]:

Alkylating agents are substances that react with biologic molecules' electron-rich atoms to create covalent bonds. These agents are often classified into two groups: those that interact with biologic molecules directly and those that combine to generate a reactive intermediate that subsequently interacts with the biologic molecule. Next, stop cells from splitting DNA in two different ways: Bifunctional alkylation: an irreversible bond is formed between two base pairs in the DNA chain by the drug's insertion. This process disrupts the cells' ability to replicate and repair its DNA, ultimately leading to cell death. These are used to treat various types of cancer by preventing the controlled growth and division of cancer cells. Some commonly used alkylating agents include cyclophosphamide and temozolomide.

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