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SWISSADME PREDICTIONS OF PHARMACOKINETICS AND DRUG-LIKENESS PROPERTIES OF 5-FLUOROURACIL (5FU)

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Abstract: Swiss ADME web tool is empolyed for study of Absorption, Distribution, Metabolism and Excretion (ADME) properties of 5-Fluorouracil (5FU). A chemotherapy drug 5-Fluorouracil (5FU) decelerate the growth of cancer cells for treatment of different types of cancer like breast cancer,colon or rectal cancer, pancreatic cancer and stomach cancer

Keywords: 5-Fluorouracil, SwissADME, drug discovery, Lipinski's rule of five

I. INTRODUCTION

5-Fluorouracil(5FU) is an anticancer medication (Fig 1) which interferes with the genetic material (DNA and RNA) of the cancer cells and thereby prevented its growth. 5FU gradually slows growth of these cancer cells and further kills them [1-3]. Fluorouracil interferes with DNA synthesis and it blocks in specific enzyme thymidylate synthase which is essential for DNA replication and leading to cancer cell death[4].

Presently an important concept which is of considerable interest for drugs is computer aided reckoning of ADME (Absorption, Distribution, Metabolism and Excretion). This provided trustworthy information about the drugs before it is experimented[5,6].

II. MATERIALS AND METHODS

Swiss Institute of Bioinformatics developed Swiss ADME software which was accessed by employing website www.swissadme.ch. The web server of this website on Google, provides Submission page of Swiss ADME. The individual ADME behaviors of the compounds can be estimated by utilizing this Swiss ADME software[7]. Schematic diagram of Swiss ADME Software in webpage for 5-Fluorouracil is displayed in Fig.2

Simplified molecular input line entry system (SMILES) is used to describe 5-Fluorouracil. The results were presented in the form of tables, graphs, and an excel spreadsheet, as described by Egan et al. (2000) [8]

The two-dimensional chemical structure with canonical SMILES is presented in the first section and this allowed to assess the drug likeness of the molecule. Six physicochemical properties: lipophilicity (LIPO), size (SIZE), polarity (POLAR), insolubility (INSOLU), insaturation (INSATU), and flexibility (FLEX) were taken into consideration by bioavailability radar.

According to the guidelines established by Daina et al[9], in 2017 , the specific criteria for each property are defined as follows :size should have a molecular weight (MW) between 150 and 500 g/mol, polarity should have a topological polar surface area (TPSA) between 20 and 130 0A2, solubility should have a logarithm of the solubility (log S) not exceeding 6, saturation should have a fraction of carbons in sp3 hybridization not less than 0.25, flexibility should have no more than 9 rotatable bonds and lipophilicity should have an XLOGP3 value between -0.7 and +5.0. All these criteria were considered to determine the drug likeness of the molecule.

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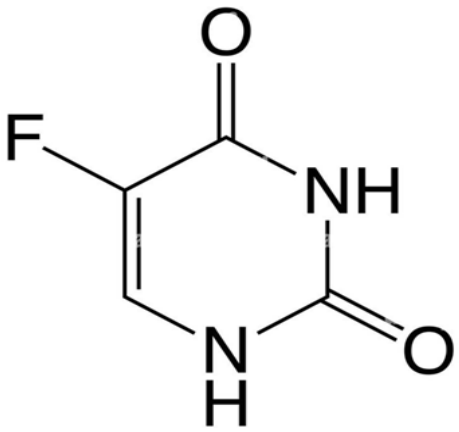

Fig 1. Structure of 5-Fluorouracil (5FU)

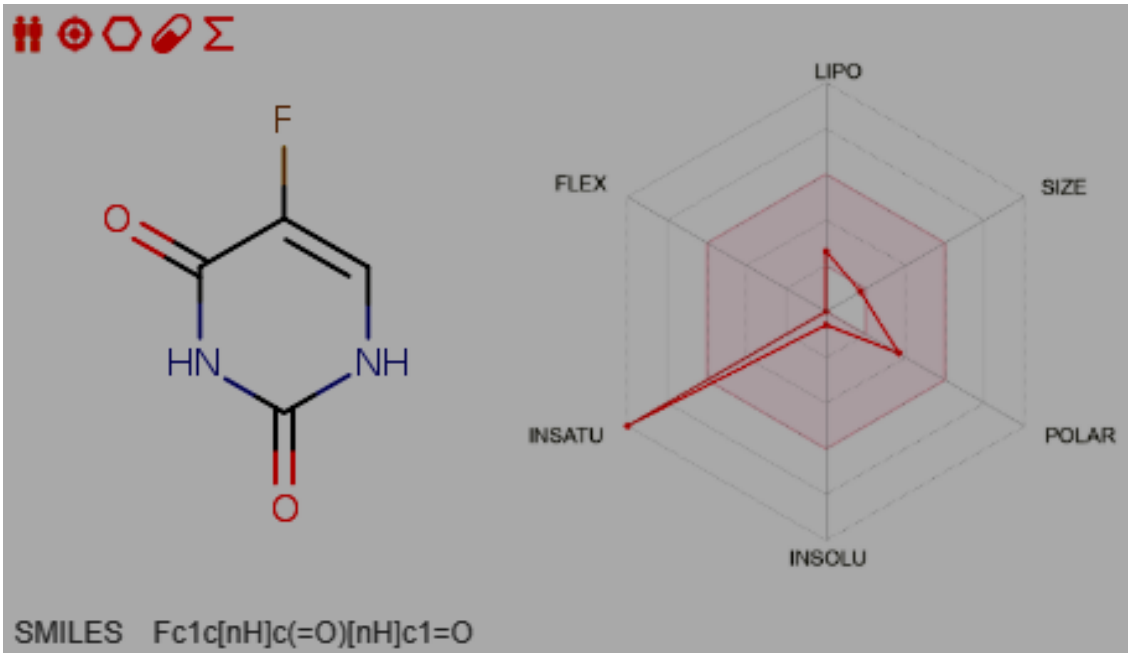

Fig.2 Schematic diagram of Swiss ADME Software in webpage for 5-Fluorouracil

General Characteristics of 5-Fluorouracil	
molecule	**5-Fluorouracil**
Pubchem ID	**CID 3385**
Molecular formula	**C4H3FN2O2**
Canonical SMILES	**Fc1c[nH]c(=O)[nH]c1=O**
Molecular weight	**130.08 g·mol^{-1}**

Table 1. General Characteristics of 5-Fluorouracil

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The General Characteristics of the compound 5-Fluorouracil were incorporated in this section. Pubchem ID ,Molecular formula, Canonical SMILES, Molecular weight of 5-Fluorouracil were determined (Table 1)

BOILED-Egg model of 5-Fluorouracil molecule

BOILED-Egg model is employed for evaluation of passive gastrointestinal absorption (HIA) and brain penetration (BBB)[10-14]. In this model white region indicates the high probability for passive absorption by GIT and the yellow region the high probability of brain penetration.

Apart from this red coloured points are indicative for molecules which are not to be effluated from the central nervous system by the P-glycoprotein

The molecule of 5-Fluorouracil 5FU as indicated by fig 3 is present in the region outside the prediction site. It is found in the white region of the BOILED-Egg therby suggesting high passive absorption of GIT. 5-Fluorouracil molecule as shown by fig 4. is denoted by red dot indicating that it is non-substrate of P-gp.

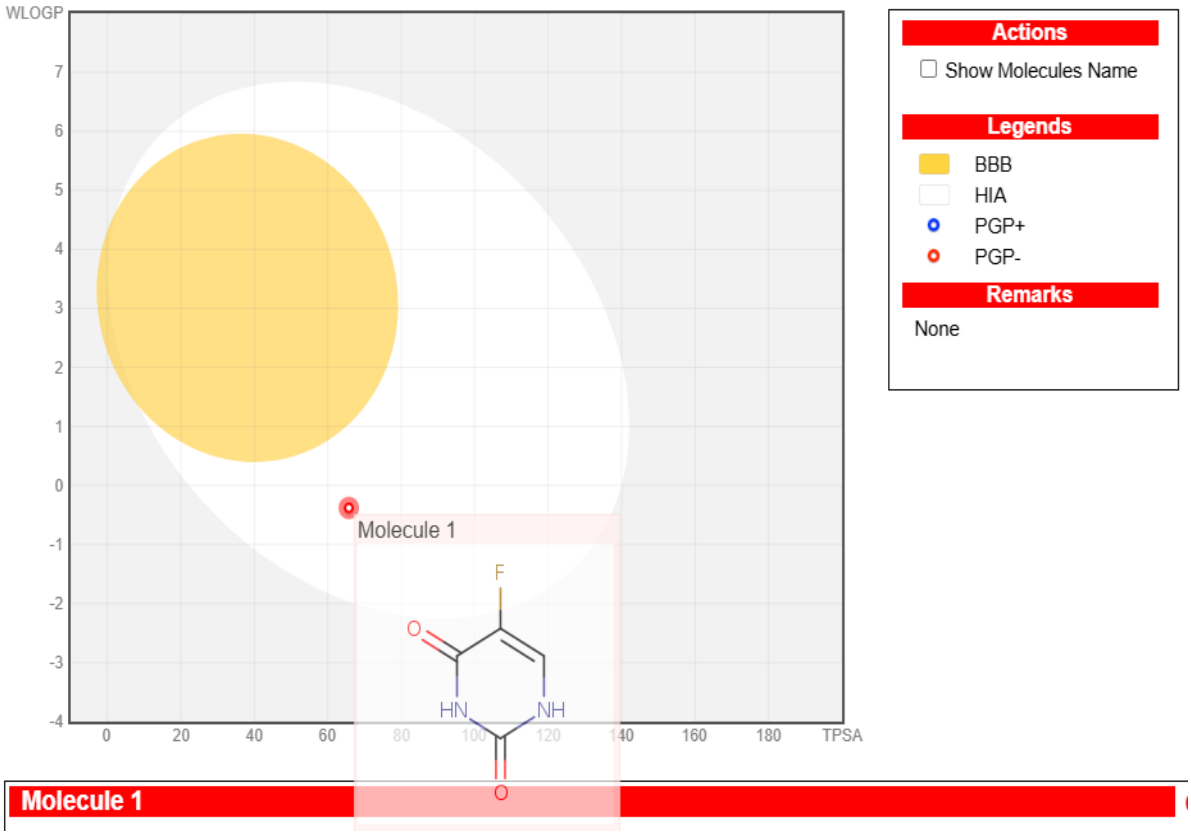

Fig 3: Schematic representation of perceptive evaluation of passive gastrointestinal absorption (HIA) and Brain penetration (BBB) with 5-Fluorouracil molecules in the WLOGP-versus-TPSA using BOILED-Egg.

Physicochemical properties of 5-Fluorouracil

The values of molecular and physicochemical characteristics of 5-Fluorouracil were computed [15,16] by employing using open babel version 2.3.0.

Details of molecular formula, molecular weight, number of heavy atoms, number of aromatic heavy atoms, fraction csp3, number of rotatable bonds, number of H-bond acceptors, number of H-bond donors, molar refractivity, TPSA of 5-Fluorouracil were presented in Table 2.

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Physicochemical properties of 5-Fluorouracil (5FU)	
Formula	**C4H3FN2O2**
Molecular weight	**130.08 g/mol**
Num. heavy atoms	**9**
Num. arom. heavy atoms	**6**
Fraction Csp3	**0.00**
Num. rotatable bonds	**0**
Num. H-bond acceptors	**3**
Num. H-bond donors	**2**
Molar Refractivity	**27.64**
TPSA	**65.72 Å²**

Table 2. Physicochemical properties of 5-Fluorouracil (5FU)

Liphophilicity of 5-Fluorouracil

Lipophilicity is considered as the most informative and instructive physicochemical property in medicinal chemistry[17] and in drug discovery and design[18]. It is determined experimentally in terms of partition coefficients (log P) or distribution coefficients (log D)

Log P represents partition equilibrium of an un-ionized solute between water and an immiscible organic solvent[19] Lipophilicity of the compound [20] is evaluated by means of five freely available models such as XLOGP3, WLOGP, MLOGP, SILICOS-IT, and iLOGP provided by Swiss ADME software. Table 3 represents Lipophilicity of 5-Fluorouracil (5FU) as obtained by above models.

Higher log P values correspond to greater lipophilicity. Log *P*o/w (SILICOS-IT) value of 5-Fluorouracil (5FU) is 1.78 thereby confirming the greater lipophilicity of 5-Fluorouracil (5FU)

Liphophilicity of 5-Fluorouracil (5FU)	
Log *P*o/w (iLOGP)	**0.44**
Log *P*o/w (XLOGP3)	**-0.89**
Log *P*o/w (WLOGP)	**-0.38**
Log *P*o/w (MLOGP)	**-0.32**
Log *P*o/w (SILICOS-IT)	**1.78**
Consensus Log *P*o/w	**0.13**

Table 3. Liphophilicity of 5-Fluorouracil (5FU)

Water solubility of 5-Fluorouracil (5FU)

Swiss ADME provides two topological approaches in order to predict water solubility. one approach involves the use of ESOL model and based on this model solubility is classified in terms of logarithmic scale as follows. Insoluble<-10, Poorly soluble<-6, Moderately soluble<-4, Soluble<-2, Very soluble<-10, Poorly soluble<- 6, Moderately soluble<-4, Soluble<-2, Very soluble< 0. log S values are Predicted values which are displayed in the decimal logarithm of the molar solubility in water. Solubility values in mol/l and mg/ml, as well as qualitative solubility classes[21] of 5-Fluorouracil (5FU) as given by Swiss ADME are displayed in Table 4.

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LogS (ESOL) of 5-Fluorouracil (5FU) is -0.58(Table 4) which is less than 0 indicates that 5FU is very soluble.SILICOS- IT developed another predictor for Swiss ADME and based on this solubility is classified in terms the logarithmic scale as (Insoluble<-10, Poorly soluble<- 6, Moderately soluble<-4, Soluble<-2, Very soluble <0 with the linear coefficient being corrected by molecular weight (R2=0.75)[22,23].Log *S* (SILICOS-IT) of 5-Fluorouracil (5FU) is -1.71 which is also less than 0 thereby indicating Very soluble nature of 5FU.

Water solubility of 5-Fluorouracil (5FU)	
LogS (ESOL)	**-0.58**
Solubility	**3.43e+01 mg/ml ; 2.64 e-01 mol/l**
Class	**Very soluble**
Log *S* (Ali)	**-0.01**
Solubility	**1.28e+02 mg/ml ; 9.82e-01 mol/l**
Class	**Very soluble**
Log *S* (SILICOS-IT)	**-1.71**
Solubility	**2.54e+00 mg/ml ; 1.95e-02 mol/l**
Class	**Soluble**

Table 4. Water solubility of 5-Fluorouracil (5FU)

Pharmacokinetics of 5-Fluorouracil (5FU)

The highest concentration of well absorbed molecules represented by the circular region is known as the Egan egg. The model's ability to predict passive GI absorption and brain is predicted by utilizing this Egan egg. This is accessed by means of passive diffusion resulting in the creation of the BOILED-Egg (Brain or Intestina L Estimate D permeation predictive model). BOILED-Egg model's ability predicts quick and effective passive GI absorption and this in turn benefited Drug research and discovery[24]. The highest chance of penetrating to the brain is indicated by the space of the yellow region (the yolk). The space filled by molecules that absorb more by the GI tract is reflected by the white region.[25]

Pharmacokinetics of 5-Fluorouracil (5FU)	
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 Kp (skin permeation)	**-7.73cm/s**

Table 5. Pharmacokinetics parameters of 5-Fluorouracil (5FU)

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CYP1A2, CYP3A4, CYP2C9, CYP2C 19, CYP2D6 are five major isoforms by means of which more than 50%-90% of therapeutic molecules are biotransformed. Table 5. Shows that GI absorption of 5-Fluorouracil (5FU) is high.

Swiss ADME utilizes the support vector machine algorithm which enabled to analyze datasets that have substrates /non-substrates or inhibitors / non-inhibitors. Depending on whether it has the potential to be both P-gp and CYP substrates the molecule that emerges will be classified as either 'Yes' or 'No'. Pharmacokinetics parameters of 5-Fluorouracil is classified as 'No' for CYP1A2, CYP3A4, CYP2C9, CYP2C 19, CYP2D6 isoforms thereby indicating that 5FU is inhibitor for these isoforms.

Medicinal Chemistry of 5-Fluorouracil

Results of this section of medicinal Chemistry as given by SwissADME are very much considered by Medicinal chemists foccussing on drug discovery. Molecules that show potent response in assays irrespective of the protein targets are Pan Assay Interference compounds (PAINS)[26-29].SwissADME analysis did not assign any PAINS alert for **5-Fluorouracil** molecule

As interpreted by Brenk rule compounds which are smaller ,hydrophobic and those not following “Lipinski’s rule of 5” ” can show Leadlikeness. SwissADME results shows that compound 5FU does not follow brenks rule and failed Leadlikeness(Table 6).

Medicinal Chemistry of 5-Fluorouracil (5FU)	
PAINS	**0 alert:**
Brenk	**0 alert**
Leadlikeness	**No;1 violations: MW < 250**
Synthetic accessibility	**1.52**

Table 6. Medicinal Chemistry of 5-Fluorouracil (5FU)

Druglikeness of 5-Fluorouracil (5FU)

5-Fluorouracil (5FU) followed the filtered rule of Lipinski’s rule of 5 as invoked in the SwissADME satisfying all the requirements (Table 7) and no the violation shown[30]. Hence 5-Fluorouracil (5FU) is considered as an efficient in vivo Drug.

Log Kp (skin permeation) of 5-Fluorouracil is -7.73cm/s. SwissADME of 5-Fluorouracil molecule showed Log Kp value of -7.73cm/s and hence it is considered to be of less skin permeation.

Druglikeness of 5-Fluorouracil (5FU)	
Lipinski	**Yes; 0 violations**
Ghose	**No; 3 violations : MW < 160, MR<40, #atoms<20**
Veber	**Yes**
Egan	**Yes**
Muegge	**No; 2 violations : MW <200, #C<5**
Bioavailability Score	**0.55**

Table 7. Druglikeness parameters of 5-Fluorouracil (5FU)

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III. CONCLUSION

In the present study SwissADME web tool is employed to evaluate biophysical parameters like lipophilicity, drug likeness, water solubility and medicinal chemistry of 5-Fluorouracil (5FU). Anti cancer properties of 5-Fluorouracil were appraised in this analysis . In this research article knowledge of ADME properties which is a a computational approach strongly assures that 5-Fluorouracil can be used both as in vitro and in vivo prescription drug primarily for cancer treatment.

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