IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Research Article
April 2020 Vol.:18, Issue:1
© All rights are reserved by V. Manikandan et al.

Evaluation of Pharmacokinetics, Drug-Likeness, and Medicinal Chemistry Friendliness for Newer Anticancer Drug Molecules by a Predictive Computation Study of the Free Web Tool on Swiss ADME

IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

V. Manikandan*, G. Praveen Kumar, K. Devi

Department of Pharmacy, Annamalai University, Chidambaram, Tamil Nadu, India.

Submission: 20 March 2020
Accepted: 28 March 2020
Published: 30 April 2020

HUMAN JOURNALS
www.ijppr.humanjournals.com

Keywords: Swiss ADME, Pharmacokinetics, Drug-likeness, Medicinal chemistry friendliness

ABSTRACT

The objective of the study was to evaluate the Pharmacokinetics, Drug-likeness and Medicinal Chemistry friendliness of newer Anticancer drug molecules (Pexidartinib, Entrectinib, Fedratinib, Alpelisib, Erdafitinib, Upadacitinib). This study was a predictive computation study of the free web tool of Swiss ADME that is provided by the Swiss Institute of Bioinformatics (SIB). The Swiss ADME web tool enables the computation key of Pharmacokinetics, Drug-likeness and Medicinal chemistry friendliness for one or multiple molecules. The pharmacokinetics predictions were studied by Boiled Egg for GI absorption and BBB permeation. The above drug molecules having appropriate properties, drug-likeness and medicinal chemistry aspects in their web tool. According to the predictive computation range; Erdafitinib, Fedratinib, and Entrectinib are more than 80 % lipid solubility and poorly soluble in water; Pexidartinib, Alpelisib and Upadacitinib are less than 70% of lipid solubility and moderately soluble in water. GI absorption is high at Erdafitinib, Pexidartinib, Entrectinib, and Upadacitinib; GI absorption is low at Alpelisib and Fedratinib respectively. There is no BBB permeation of the above drug molecules. Hence all the drug molecules were within the limit of the computation range that is given by the Swiss ADME web page.

INTRODUCTION

The Swiss ADME is the free web tool that is provided by the Swiss Institute of Bioinformatics (SIB). During the time and resource-consuming process of drug discovery and development, a large number of molecular structures are evaluated according to very diverse parameters to steer the selection of which chemicals to synthesize, test and promote, which the final goal to identify those with the best chance to become an effective medicine for their patients. The molecules must show high biological activity together with low toxicity. The Swiss ADME web tool enables a predictive computation key for pharmacokinetics, drug-likeness and medicinal chemistry friendliness for one or multiple compounds.

MATERIALS AND METHODS:

Accessing http://www.swissadme.ch in a web browser displays directly the submission page that the drug molecule structures are submitted one by one to the web page then accessing the run button, within 5 seconds the web page shows physicochemical properties, lipophilicity, water-solubility, pharmacokinetics, drug-likeness, and medicinal chemistry friendliness properties of those drug molecules.

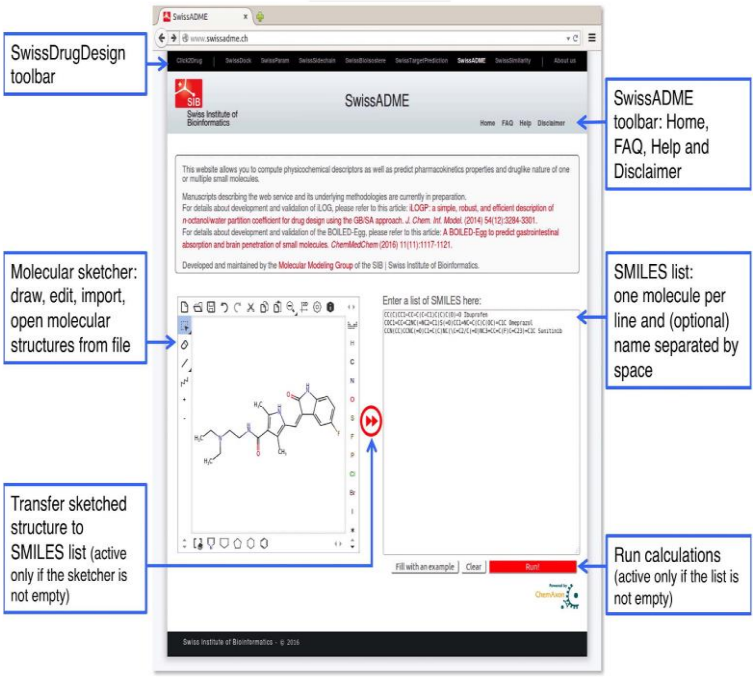

Figure No. 1: Submission page of Swiss ADME

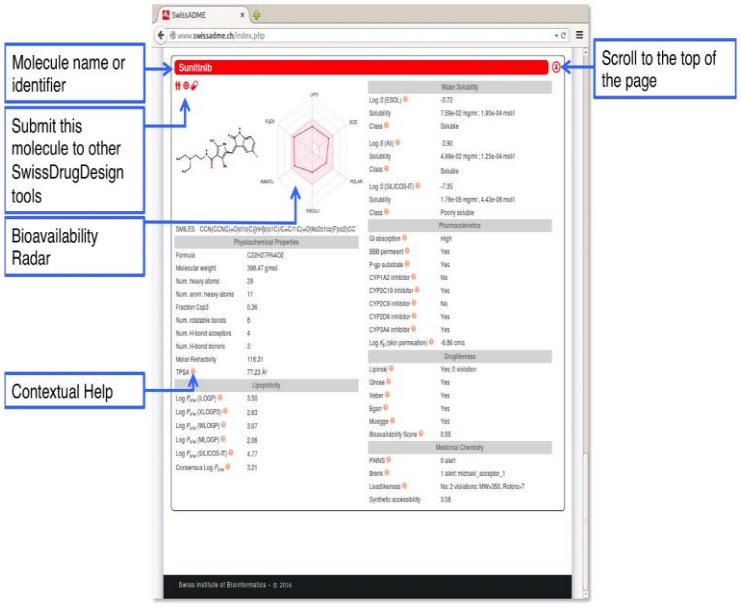

Figure No. 2: The web page shows properties of the drug molecule

RESULTS AND DISCUSSION

Bioavailability Radar:

- *Lipophilicity* : - 0.7 < XLogP3 < 0.5. All drug molecules do not within the limit of lipophilicity (XLogP3).

- *Size* : 150 g/mol < MW < 500 g/mol All drug molecules have within the size of Molecular Weight except Entrectinib and Fedratinib.

- *Polarity* : 20 $Å^2$ < TPSA < 130 $Å^2$. All drug molecules have within the limit of TPSA. Hence, these drugs are containing normal polarity.

- *Insolubility* : 0 < Log S < 6. All drug molecules do not within the limit of insolubility because Erdafitinib, Alpelisib, and Pexidartinib are moderately soluble; Entrectinib and Fedratinib are poorly soluble; Upadacitinib is soluble in water which depends on bioavailability.

- *In saturation* : 0.25 < Fraction Csp^3 < 1. All drug molecules have within the range of Fraction Csp^3. So, these drugs may not be saturated.

➢ *Flexibility* : 0 < No. of rotatable bonds < 9. Alpelisib, Pexidartinib, Entrectinib, Upadacitinib contain normal flexibility; Erdafitinib and Fedratinib have high flexibility due to the high amount of rotatable bonds.

Lipophilicity:

Table No. 1

Drug	LIPOPHILICITY				
	iLogP	**XLogP3**	**WLogP**	**MLogP**	**SILICOS-IT**
Alpelisib	2.14	3.22	4.52	1.18	3.68
Erdafitinib	4.23	3.17	4.18	1.62	3.25
Pexidartinib	2.99	4.49	6.04	3.23	5.57
Entrectinib	3.73	5.72	4.72	4	5.12
Fedratinib	4.22	4.76	5.52	2.47	2.95
Upadacitinib	2.5	2.69	3.79	1.63	1.76

We conclude the overall lipophilicity (Figure. 3) is denoted that Erdafitinib, Fedratinib, Entrectinib are more than 80 %lipid solubility and other drugs are less than 70 % lipid solubility.

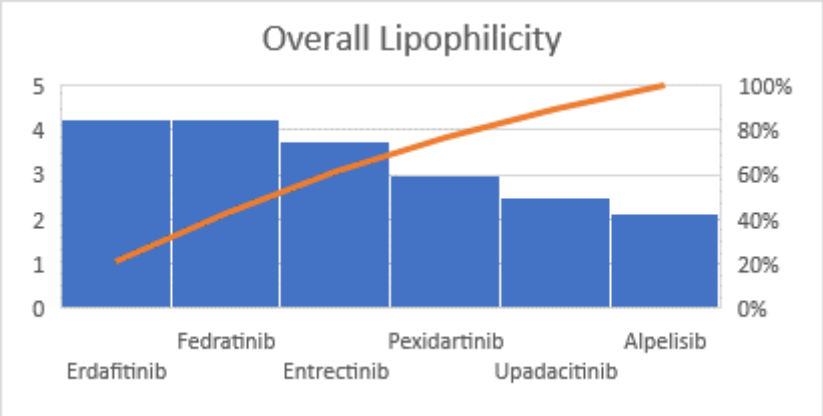

Figure No. 3: Overall Lipophilicity

Water Solubility:

Table No. 2

Drug	Water Solubility Log S		
	ESOL	ALI	SILICOS-IT
Alpelisib	-4.42	-5.61	-5.22
Erdafitinib	-4.48	-4.46	-7.92
Pexidartinib	-5.4	-5.61	-9.47
Entrectinib	-6.77	-7.28	-9.78
Fedratinib	-5.73	-6.94	-9.15
Upadacitinib	-3.83	-3.99	-4.61

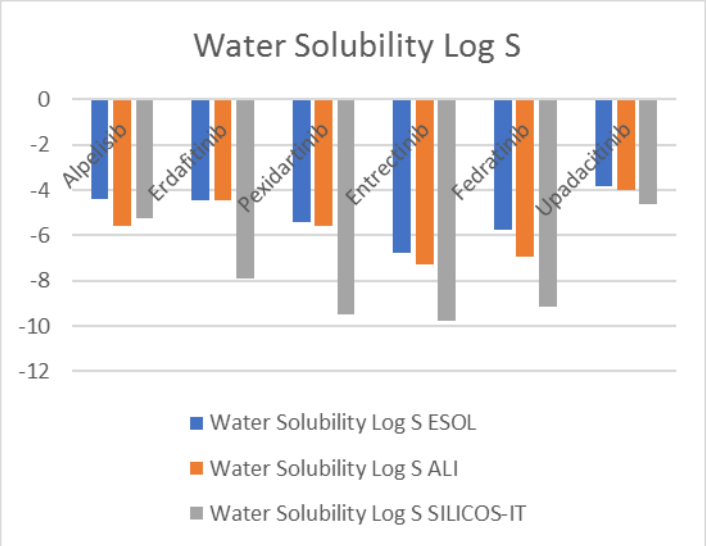

Figure No. 4: Water Solubility

The above graphical (Figure. 4) representation concludes the water solubility that Erdafitinib, Alpelisib, and Pexidartinib are moderately soluble; Entrectinib, Fedratinib, and Upadacitinib are poorly soluble; which depends on their computation range.

Pharmacokinetics:

The Boiled egg experiment denotes that GI absorption and BBB permeant. This experiment also available on their web page. We concluded the experiment, GI absorption is high at Erdafitinib, Pexidartinib, Entrectinib, and Upadacitinib; GI absorption is low at Alpelisib and Fedratinib respectively. There is no BBB permeant of all drugs (Alpelisib, Erdafitinib, Pexidartinib, Entrectinib, Fedratinib, Upadacitinib). P-GP substrate is predicted in all drugs

except Fedratinib. Drugs may prevent another metabolic pathway from compensating for the CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4 inhibition respectively.

Drug-likeness:

➢ *Lipinski* : All drug molecules have complied with Lipinski (Pfizer) filter.

➢ *Ghose* : Alpelisib, Erdafitinib, and Upadacitinib have complied with Ghose filter. Then Pexidartinib, Entrectinib, and Fedratinib do not comply with Ghose filter. The reasons are following,

- Pexidartinib : 1 violation (WLogP > 5.6)
- Entrectinib: 3 violations (MW > 350, Rotors > 7, XLogP3 >3.5)
- Fedratinib : 3 violations (MW > 480, MR > 130, atoms > 70)

➢ *Veber* : All drug molecules have complied with Veber (GSK) filter except Fedratinib. Because it consists 1 violation (Rotors > 10).

➢ *Egan* : All drug molecules have complied with Egan (Pharmacia) filter except Pexidartinib. Because it consists 1 violation (WLogP > 5.8).

➢ *Muegge* : All drug molecules have complied with Muegge (Bayer) filter except Entrectinib. Because it consists 1 violation (XLogP3 > 5).

➢ *Bioavailability score* : All drug molecules have complied with the bioavailability score within the limit of 55 %.

Medicinal chemistry:

➢ *PAINS & Brenk* : There is no structural modification in our selected drugs.

➢ *Lead likeness* : All drug molecules do not comply with the lead likeness property. Because these drugs contain some violations is there.

- Alpelisib : 1 violation (MW > 350)
- Erdafitinib : 2 violations (MW > 350, rotors > 7)

- Pexidartinib : 2 violations (MW > 350, XLogP3 > 3.5)
- Entrectinib : 3 violations (MW > 350, XLogP3 > 3.5, rotors > 7)
- Fedratinib : 3 violations (MW > 350, XLogP3 > 3.5, rotors > 7)
- Upadacitinib : 1 violation (MW > 350)

CONCLUSION

All selected drug molecules (Erdafitinib, Alpelisib, Pexidartinib, Entrectinib, Fedratinib, and Upadacitinib) were evaluated by the Swiss ADME web tool which was provided by SIB (Swiss Institute of Bioinformatics). These drug molecules were within the limits of a predictive computation range. Hence, this proposed method will easy to evaluate the newer drug molecules, at the end of the drug discovery program.

REFERENCES

1. Antoine Daina., Olivier Michielin & Vincent Zoete. 03/03/2017 Available from: www.nature.com/swissadme.scientificreport.
2. Swiss Institute of Bioinformatics (2019) Available from: www.swissadme.ch.
3. Hay, M., Thomas, D. W., Craighead, J. L., Economides, C. & Rosenthal, J. Clinical development success rates for investigational drugs. Nature Biotechnol. 32, 40–51 (2014).
4. Dahlin, J. L., Inglese, J. & Walters, M. A. Mitigating risk in academic preclinical drug discovery. Nature Rev. Drug Discov. 14, 279–294 (2015).
5. Tian, S. et al. The application of in silico drug-likeness predictions in pharmaceutical research. Adv Drug Deliv Rev 86, 2–10 (2015).
6. Lipinski, C. A., Lombardo, F., Dominy, B. W. & Feeney, P. J. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. Adv. Drug. Deliv. Rev. 46, 3–26 (2016).
7. Brenk, R. et al. Lessons learnt from assembling screening libraries for drug discovery for neglected diseases. Chem Med Chem 3, 435–444 (2016).

Image *Author -1*	***Author Name – Corresponding Author*** *MANIKANDAN V* *Fourth B. Pharm Student* *Department of Pharmacy, Annamalai University,* *Annamalai Nagar, Chidambaram,* *Cuddalore, Tamil Nadu, India.*
Image *Author -2*	***Author Name*** *Dr. K. DEVI* *Assistant Professor,* *Department of Pharmacy, Annamalai University,* *Annamalai Nagar, Chidambaram,* *Cuddalore, Tamil Nadu, India.*
Image *Author -3*	***Author Name*** *PRAVEEN KUMAR G* *Fourth B. Pharm Student* *Department of Pharmacy, Annamalai University,* *Annamalai Nagar, Chidambaram,* *Cuddalore, Tamil Nadu, India.*