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Pharmacophore and SAR Based Designing of Podophyllotoxin Analogues: An Internet Based Drug Design Approach

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ABSTRACT

In recent years, the use of computers in chemistry have been developed greatly. The molecular docking, computer based drug designing, etc. has proved the efficiency of computers in computational chemistry. With the use of sophisticated computational tools and techniques the drugs discovery has been accelerated in the form of target based drug discovery rather than rational methods. In the current scenario the software used for drug designing are very expensive, so in this paper the power of internet and open source community has been used for performing SAR and Pharmacophore based drug design approaches as they are free to use. Using SAR and Pharmacophore study here some derivatives of Podophyllotoxin have been designed by understanding their toxicity, metabolic sites and drug like properties.

Keywords: Pharmacophore, SAR, Podophyllotoxin

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INTRODUCTION

The SAR of a drug describes the activity by changing the chemical groups in the pharmacophore of the drugs. Use of computer has made this tough job easy [1-4]. Easily by applying Lipinski rule of five in SAR and pharmacophore drug design one can predict the drug like properties of the compound[5-8]. But the necessary software are expensive and require some computational skill to install them. Also some of the software use old operating systems and hardware that are difficult to find these days. The materials and tools used here were not compatible in the new operating systems like windows 10, 7, 8 and also showed incompatibility issues with modern hardware like current generation Intel and AMD processor. As the tools used here are internet based that required old NPAPI java plugin support that are also incompatible with latest web browsers.

To tackle these difficulties internet explorer 7 with Java Run time environment was used. The internet based tools used JRE to function and work. These tools are capable of calculating drug likeness and molecular properties in real time when the SMILES codes of the structures are input. They also provide the facility to draw the chemical structure in the JAVA molecular editor. These Java based internet tools use large database to predict the toxicity, solidibility, pKa and all other parameters.

Podophyllotoxin is a natural product obtained from Podophyllum that is used in various cancer treatments[9]. The structure mainly contains five rings of which four are fused (A,B,C & D) and the fifth ring E is not. The changes can be done at 4^{th} carbon atom by replacing the glycone part to some other group. However based on the analysis the functional group has to be sterically and electrostatically compatible with environment of DNA minor groove.

Lipinski rule of five is a rule of thumb to evaluate drug likeness, however it does not predict if a compound is pharmacologically active or not[5]. Using the applications that work on Lipinski rule here we predicted the drug like properties of few derivatives of Podophyllotoxin. As the derivatives act by binding to Topoisomerase II during late S and early G2 phase, the basic five ring system is required for the activity.[10,11] The changes can be done on the 4-OH position of ring C only the –I groups in the substituent ring showed greater drug like properties but if ether linkage is removed the derivatives show good drug score. The toxicity were also done using online tools and the derivatives showed lower level of carcinogenicity and mutagenicity with good confidence.

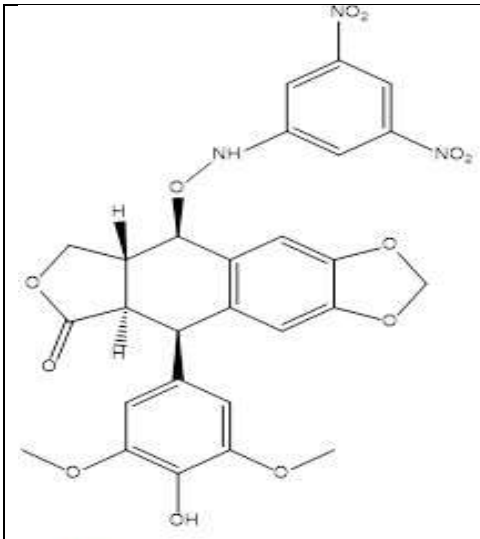
MATERIALS AND METHOD

There are various online tools have been used in the whole work. Chemdraw V12 was used to draw the structures and to copy the SMILES codes as it was very hard to draw the chemical

structures in JME (JAVA molecular editor). Mainly four online free tools were used in the study. LAZAR toxicity prediction was used in order to study the toxicity (carcinogenic and mutagenic) effects of the derivatives and Etoposide[12]. Molsoft was used for drug likeness and for molecular property prediction[13]. Osiris property explorer was used to predict toxicity and drug like properties[14]. The above mentioned tools allowed inserting the SMILES codes, so it was very easy after drawing the structures in Chemdraw and copying the SMILES code for use in the tools. All the calculations were done in 32 bit Windows 7 OS having Intel Atom processor with 2 GB RAM.

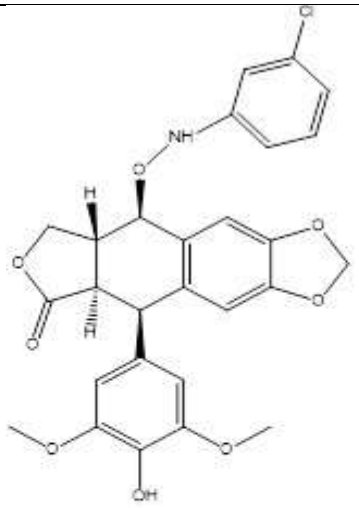
RESULTS AND DISCUSSION

Etoposide and Teniposide, two semi synthetic Podophyllotoxin derivatives, are used in the treatment of small cell lung cancer, testicular sarcoma, lymphoma and Koposi's sarcoma. Another derivative GL-331 having p-Nitro Aniline as the substituent in ring has undergone through clinical trials for treatment of various cancers. Here Etoposide has been taken as the reference drug with respect to that other drugs have been designed and the properties have been calculated. The derivatives have some other groups in place of the glycone part and rest pharmacophore was kept unchanged as it is essential for binding with Topoisomerase-II enzyme. In Molsoft Drug likeness tool, Etoposide shows a drug score of 0.73 but the derived molecules shown lesser drug score as ET1 having -0.11, ET2 having 0.12, ET3 having 0.01, ET4 having 0.37 and ET5 having drug score of 0.11.



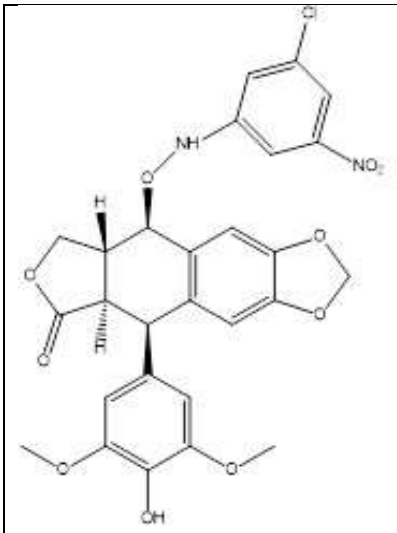
ET1

Drug-likeness model score: -0.11
Molecular formula: C27 H23 N3 O12
Molecular weight: 581.13 (> 500)
MolLogP : 3.09
MolLogS : -8.10 (in Log(moles/L)) 0.00 (in mg/L)



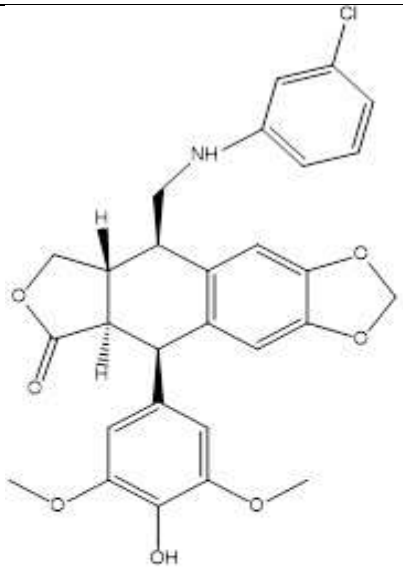
ET2

Drug-likeness model score: 0.12
Molecular formula: C27 H24 Cl NO8
Molecular weight: 525.12 (> 500)
MolLogP : 4.47
MolLogS : -7.47 (in Log(moles/L)) 0.02 (in mg/L)



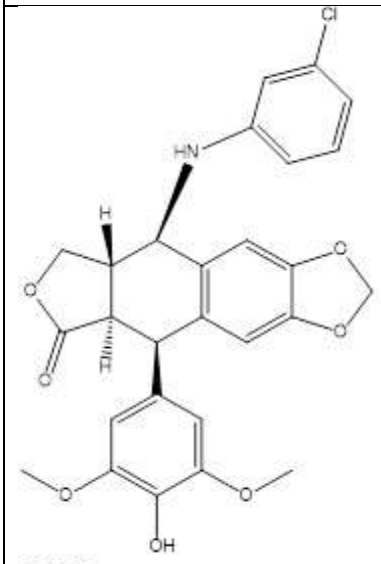
ET3

Drug-likeness model score: 0.01
Molecular formula: C27 H23 Cl N2 O10
Molecular weight: 570.10 (> 500)
MolLogP : 4.19
MolLogS : -7.86 (in Log(moles/L)) 0.01 (in mg/L)



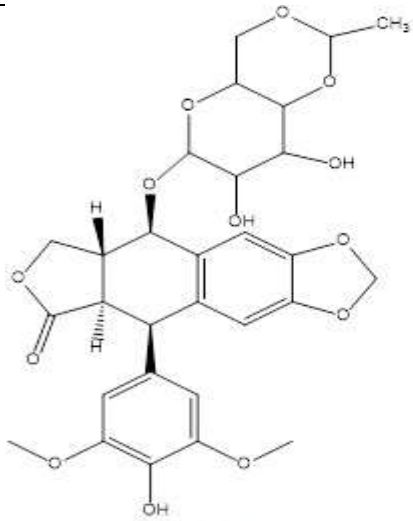
ET4

Drug-likeness model score: 0.24
Molecular formula: C28 H26 Cl N O7
Molecular weight: 523.14 (> 500)
MolLogP : 5.18 (> 5)
MolLogS : -7.94 (in Log(moles/L)) 0.01 (in mg/L)



ET5

Drug-likeness model score: 0.11
Molecular formula: C27 H24 Cl N O7
Molecular weight: 509.12 (> 500)
MolLogP : 5.04 (> 5)
MolLogS : -7.18 (in Log(moles/L)) 0.03 (in mg/L)



Etoposide

Drug-likeness model score: 0.73
Molecular formula: C29 H32 O13
Molecular weight: 588.18 (> 500)
MolLogP : 0.90
MolLogS : -4.55 (in Log(moles/L)) 16.73 (in mg/L)

In ET1,ET2 and ET3 there ether linkage is present that gives lower drug likeness score over Etoposide but the logP value is greater that indicates the compound is higher lipophillic in nature. In the ET4 erther linkage is removed yet CH2 bridge is present, the compound shows a good drug likeness score of 0.24 and higher logP value, solubility. In the compound ET5 the CH2 is also removed but it does not show a significant improvement over the others in Molsoft program.

In Osiris property explorer Etoposide shows a drug score of 0.39 and drug likeness of -0.28. Here ET4 represents a slight lower drug score of 0.37 but greater drug likeness of 3.57 and ET5 shows greater drug score of 0.42 and also good drug likeness of 3.01. Here results show that ET5 and ET4 both represent a good drug like properties with good solubility, partition coefficient and drug likeness. The partition coefficient of ET4 is about 4.26 and ET5 is 3.79 that states that both compounds are higher lipophillic when compared to the reference compound.

Table 1: Osiris Property Explorer values of designed Etoposide analogues

Molecule ID	cLogP value	Solubility	Drug Likeness	Drug score
Etoposide	0.67	-3.95	-0.28	0.39
ET1	2.5	-5.61	-8.04	0.21
ET2	4.95	-5.42	2.61	0.22
ET3	4.03	-5.88	-6.7	0.11
ET4	4.26	-6.17	3.57	0.37
ET5	3.79	-5.76	3.01	0.42

Table 2: Predicted toxicity of Etoposide analogues using in silico lazar toxicity prediction tool.

Molecule ID	DSSTox Carcinogenic Potency DBS Mutagenicity	DSSTox Carcinogenic Potency DBS Rat	FDA v3b Max Recommended Daily Dose mmol	DSSTox Carcinogenic potency Single Cell Call	DSSTox Carcinogenic Potency DBS Mouse
Etoposide	Non Mutagenic (Confidence) 0.184	Non Carcinogen (Confidence) 0.0603	0.00157946877902165, 0.0943 (Confidence)	Non Carcinogen (Confidence) 0.143	Non Carcinogen (Confidence) 0.14
ET1	Non Mutagenic (Confidence) 0.159	Non Carcinogen (Confidence) 0.0715	0.00542689777074487, 0.158 (Confidence)	Non Carcinogen (Confidence) 0.0611	Non Carcinogen (Confidence) 0.195
ET2	Non Mutagenic (Confidence) 0.155	Non Carcinogen (Confidence) 0.0543	0.00742897442507395, 0.15 (Confidence)	Non Carcinogen (Confidence) 0.0635	Non Carcinogen (Confidence) 0.195
ET3	Non Mutagenic (Confidence) 0.154	Non Carcinogen (Confidence) 0.0521	0.00742897442507395, 0.15 (Confidence)	Non Carcinogen (Confidence) 0.0611	Non Carcinogen (Confidence) 0.195
ET4	Non Mutagenic (Confidence) 0.186	Non Carcinogen (Confidence) 0.0549	0.005469617934188, 0.119 (Confidence)	Non Carcinogen (Confidence) 0.063	Non Carcinogen (Confidence) 0.187
ET5	Non Mutagenic (Confidence) 0.156	Non Carcinogen (Confidence) 0.0524	0.003925, 0.137 (Confidence)	Non Carcinogen (Confidence) 0.0641	Non Carcinogen (Confidence) 0.151

On the basis of Lazar toxicity prediction it is clear that the above derivatives show similar toxicity levels as Etoposide. In DBS mouse all the derivatives showed greater potency over the reference drug Etoposide of which ET1, ET2, ET3 showed much higher potency than the others, still the rest two ET4 and ET5 have greater potency than Etoposide.

CONCLUSION

The derivatives prepared all showed greater potency than the reference drug in Lazar toxicity prediction tool but as per drug likeness and drug score prediction only two derivatives were found to be good that are ET4 and ET5. Although the two derivatives having good drug like score their partition coefficient is greater that lead to higher lipophillicity. If the higher lipophillic nature may lead to some problems it can be overcome by other methods. The compounds can be further studied for metabolic transformation using in sillico approaches and also the molecular docking of these compounds can be studied by using such online free tools. The study of new compounds that can act like drugs can be fastened by applying these kind of approaches. By understanding the skills of computational chemistry and having knowledge of open source online tools is good for computational chemist as they are easy to handle and also the cost for the study is nearly zero. The drug designing on the basis of SAR and pharmacophore by using these kind of free online tools is great.

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