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In silico- internet and analogue based drug design of new anticancer agent

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Abstract
As now a day there is development and importance of computational chemistry including molecular docking and a SAR study which deals with pharmacophore based drug design approach. As the methodology linked with modification of the target based drug discovery by using sophisticated computational tools which are generally not very easy to understand and also got many incompatibility issues with many operating systems (OS) and other system configurations. Thus, the present study deals with the SAR (Structure Activity Relationship) study and pharmacophore based drug design approaches with the use of free internet based tools which are much user friendly and almost compatible with any platform. Here, in this paper attempts are made to design some daunomycin analogues using pharmacophore study as more potent or equivalent anticancer agents and their drug like properties, toxicity, metabolic sites and some other parameters that are predicted by the free internet based tools.

Keywords: computational chemistry, molecular docking, operating systems (OS), pharmacophore, daunomycin, SAR (Structure Activity Relationship), anticancer agents

Introduction
In today's era the biggest scientific challenges is to design a potent anticancer agent [1, 2]. For that now a day structure based drug designing becomes increasingly much in use to design potent drug like molecules [3, 4, 5, 6]. But the main problem of this Structure based drug design is the use of high price computational software because these high price software are not easily available to individuals also they are incompatible with many modern operating systems such as WINDOWS 7 64-bit, ANDRIOD OS, Chromium OS etc. Also many modern processors such as i5, i7 etc. have some compatibility issues with this modern computational drug design software. For the same reasons INTERNET based drug designing becomes a popular tool for design of new potent drug like molecules as they are independent of operating system and processors. INTERNET based drug design on the basis of SAR [7] (Structure activity relationship) and pharmacophore [8] study becomes a fruitful tool for modern structure based rational drug design. This INTERNET based tools are easy to handle because it uses JAVA platform to input structure and calculate the drug likeness and molecular properties. These JAVA based internet tools can be applied to predict the toxicity, solubility, pKa, lipnski's five rules which are important parameters for structure based rational drug design [9].
The present communication deals with the use of this INTERNET based drug design tool to design some potent or equivalent drug like anticancer agents. Daunomycin has been taken as a prototype to design new drug like molecules. Daunomycin (trade name cerubidine) is a drug used in cancer chemotherapy. It is the natural product and anthracycline antibiotics, works by intercalating DNA. It is commonly used in the treatment of a wide range of cancers, including hematological malignancies, many types of carcinoma, and soft tissue sarcomas. INTERNET based drug design tools have been used to analysis the structural analogues of daunomycin for their drug like behavior.

Materials and methods
Daunomycin is an anthracyclic antibiotic having the following molecular structure.

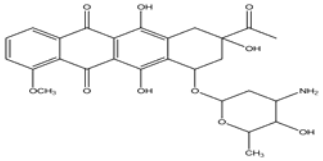


Fig 1: Daunomycin molecular structure

The new designed drug like molecules has been designed by taking Daunomycin as prototype and substituting the R_1, R_2 andR_3 position of the Daunomycin skeleton.

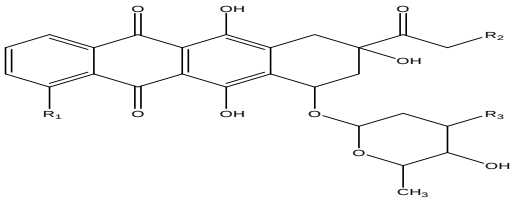


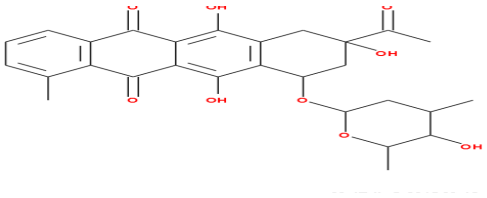
Fig 2: Daunomycin skeleton with R_1, R_2 and R_3.

In case of Daunomycin the R_1, R2 and R_3 positions are substituted by $–OCH_3$, -H and $–NH_2$ respectively. By using SAR and pharmacophore study the positions of R_1, R_2 and$R_3$of the structural analogues of daunomycin are substituted to get high degree likeness score than that of prototype Daunomycin. The structural an analogues based drug design has been performed using MOLSOFT molecules *in silico* drug likeness and molecular property prediction tool [11]. The new designed molecules on the basis of SAR and pharmacophore study have been inputted in JME molecular editor [12] and different properties have been calculated. The lazar toxicity of all these designed drugs have been performed using *in silico* internet based lazar toxicity prediction tool [13]. OSIRIS property explorer [14] is also used to predict toxicity and other drug like properties. The metabolic sites of these designed drugs have been predicted using metaprint2D [15]. ADME and toxicity was predicted by using preADMET server [16]. These works have been performed by using WINDOWS 7 64-bit operating system having Intel core 2 duo processor.

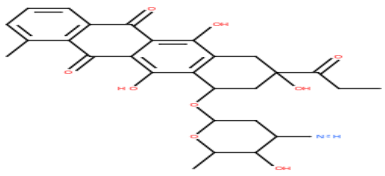
Result and discussion

Drug likeness score of Daunomycin analogues

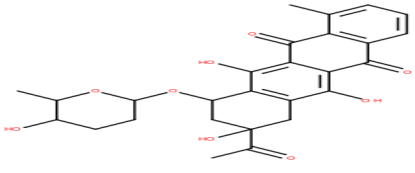
New drug like Daunomycin analogues have been listed below. Drug likeness score is predicted by molsoft. By SAR and pharmacophore study the R_1, R_2 and R_3 positions are substituted in such a way that the drug likeness score of new drug like molecules are near that of the prototype.



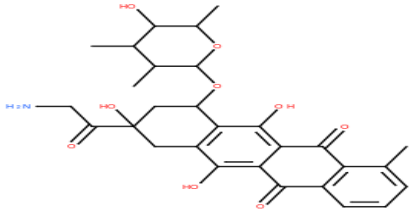
Molsoft drug likeness score: 0.90; molecule ID: Daunomycin 1



Molsoft Drug likeness score: 1.26: Molecule ID: Daunomycin 2



Molsoft Drug likeness score: 1.01 molecule ID: Daunomycin 3



Molsoft Drug likeness score: 1.21: Molecule ID: daunomycin 4

Table 1: OSIRIS Property explorer score

Molecule ID	cLogP	Solubility	Molecular weight	Drug likeness	Drug score
Daunomycin	2.54	5.79	527	5.68	0.48
Daunomycin 1	4.82	6.85	506	4.52	0.32
Daunomycin 2	4.62	6.69	492	3.65	0.35
Daunomycin 3	2.32	5.61	525	7.42	0.47
Daunomycin 4	2.56	5.85	523	7.42	0.47

The above data shows that substitution at position R1or R2 or R3 increases the drug likeness score that of the prototype drug Daunomycine when calculated by MolSoft. All these new drug molecules also judge by using OSIRIS property explorer for their drug score, drug likeness score & other physiochemical & toxicity parameters [table 1].

Toxicity of all these new Daunomycin analogues has been predicted by preADMET server which is listed below.

Pre ADMET toxicity prediction of the molecule Daunomycin 1

	Name	Value
Ames test		
	TA100-10 RLI	Negative
	TA100-NA	Negative
	TA1535-10 RLI	Negative
	TA1535-NA	Negative
Carcinogenicity		
	Carcinogenicity (mouse)	Negative
	Carcinogenicity (rat)	Negative

Pre ADMET toxicity prediction of the molecule Daunomycin 2

	Name	Value
Ames test		
	TA100-NA	Negative
	TA100-NA	Negative
	TA1535-10 RLI	Negative
	TA1535- NA	Negative
Carcinogenicity		
	Carcinogenicity (mouse)	Positive
	Carcinogenicity (rat)	Positive

Pre ADMET toxicity prediction of the molecule Daunomycin 3

	Name	Value
Ames test		
	TA100-10RLI	Negative
	TA-100NA	Negative
	TA1535-10RLI	Negative
	TA1535-NA	Negative
Carcinogenicity		
	Carcinogenicity (mouse)	Positive
	Carcinogenicity (rat)	Negative

Pre ADMET toxicity prediction of the molecule Daunomycin 4

	Name	Value
Ames test		
	TA100-10RLI	Negative
	TA100-NA	Negative
	TA1535-10RLI	Negative
	TA1535-NA	Negative
Carcinogenicity		
	Carcinogenicity (mouse)	Negative
	Carcinogenicity (rat)	Negative

From the toxicity prediction it was found that all designed drug is non-toxic (as shows negative Ames [17] test in almost all parameters and found to be non-mutagenic and non-carcinogenic) except molecules Daunomycin 2 and Daunomycin 3 is carcinogenic toxic to rat and mouse and Phase 1 metabolic site prediction of Daunomycin analogues using metaprint2D by setting the strictness of the fingerprint matching in "DEFAULT" and selecting model "ALL (metabolite 2010.2)": The color highlighting an atom indicates its normalized occurrence ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database. The normalized occurrence ratio does not indicate how likely a molecule is to be metabolized, but rather the relative likelihood of metabolism occurring at a particular site in the molecule, assuming it is metabolized. Predicted metabolic sites will be useful to determine the binding site of the designed molecules with suitable targets.

Red	0.66 <= NOR <= 1.00
Orange	0.33 <= NOR < 0.66
Green	0.15 <= NOR < 0.33
White	0.00 <= NOR < 0.15
Grey	Little/no data

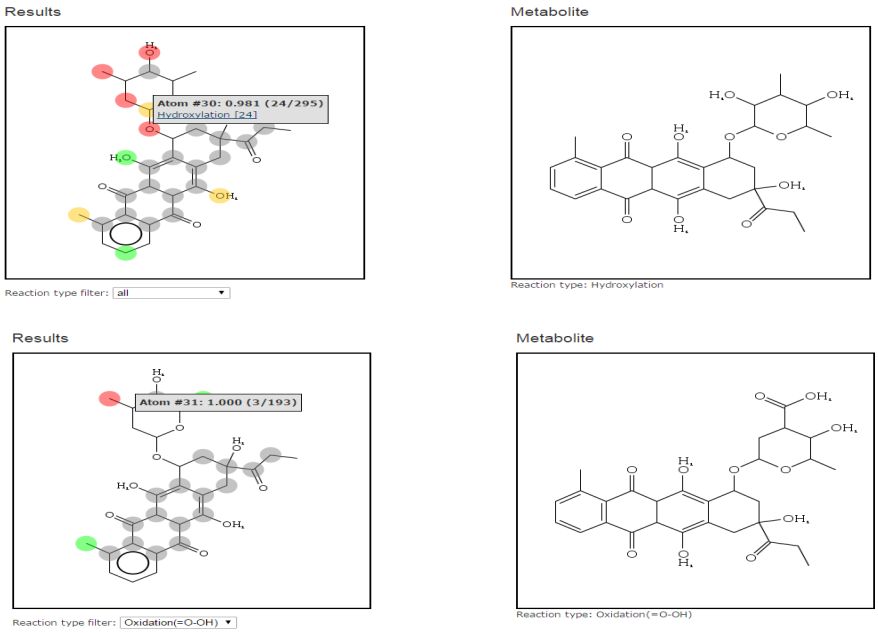


Fig 3: predicted phase 1 metabolic site of Daunomycin 1

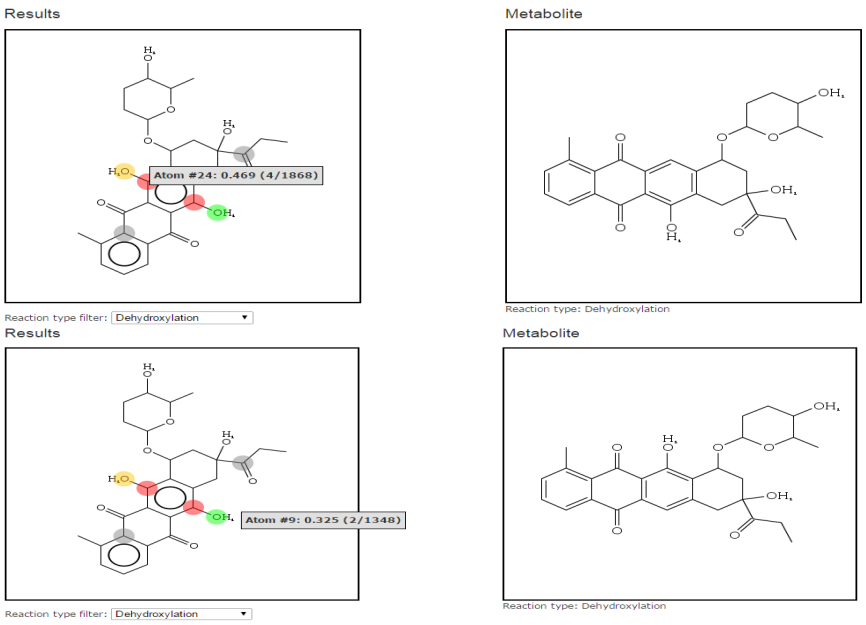


Fig 4: Predicted phase 1 metabolic site of daunomycin 2

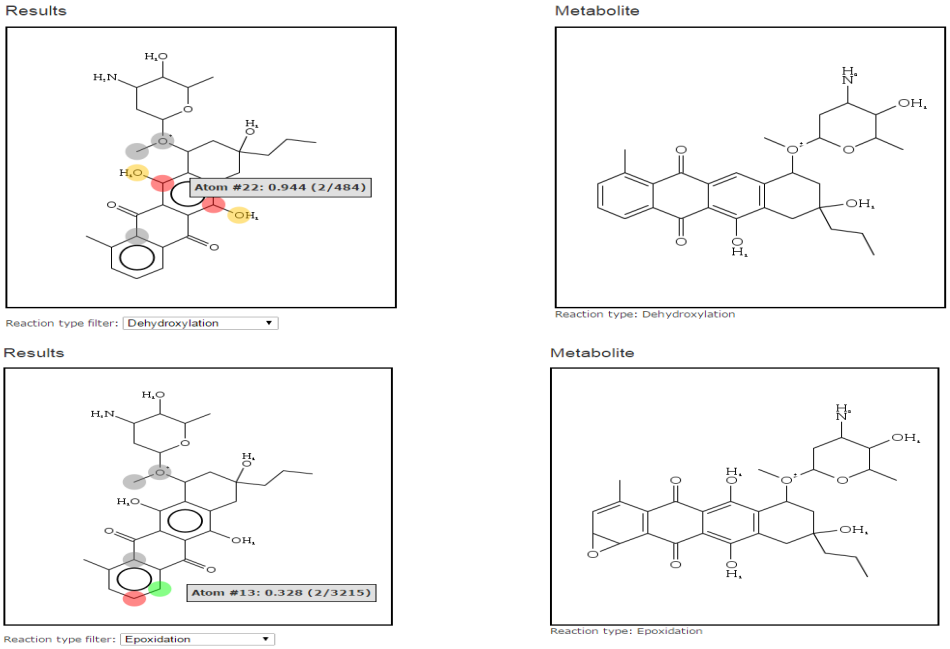


Fig 5: Predicted phase 1 metabolic site of daunomycin3

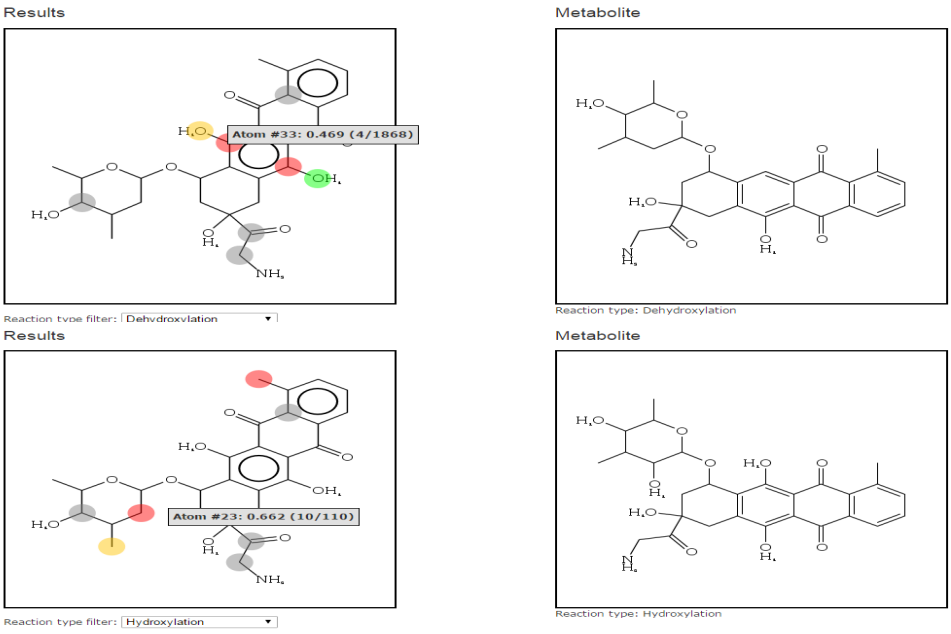


Fig 6: Predicted phase 1 metabolic site of daunomycin 4

Lazar toxicity of all these molecules have been predicted using *in silico* lazar toxicity prediction tool (http://lazar.in.silico.de/predict/).

From lazar toxicity prediction study it is evident that the entire new designed drug like molecules are found to be non-carcinogenic in multicell call and carcinogenic in rats.

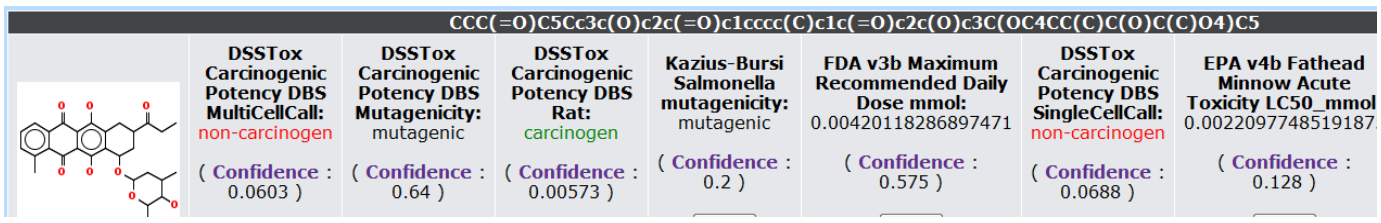


Fig 7: Predicted lazar toxicity of Daunomycin 1

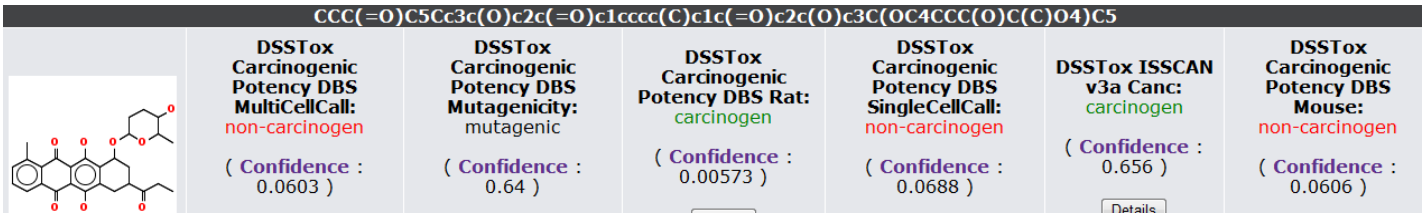


Fig 8: Predicted lazar toxicity of Daunomycin 2

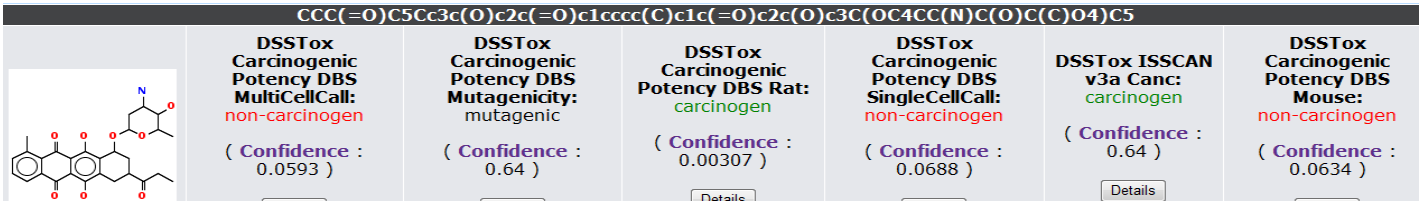


Fig 9: Predicted lazar toxicity of daunomycin 3

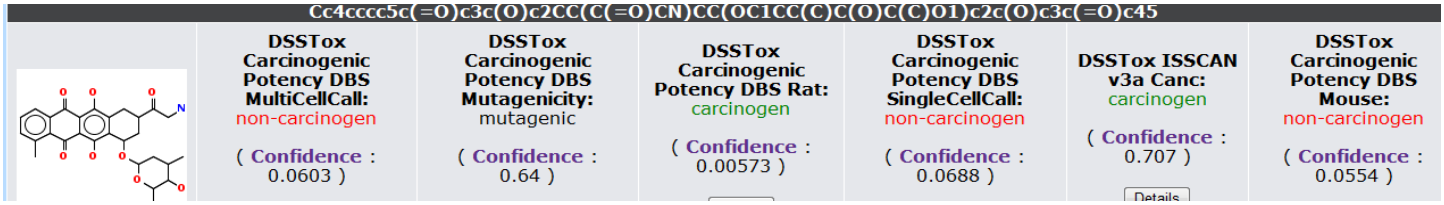


Fig 10: Predicted lazar toxicity of Daunomycin 4

Table 2: predicted lazar toxicity of the new designed daunomycin analogues

Molecule ID	DSSTox carcinogenic potency DBS multi cell call	DSSTox carcinogenic potency DBS Rat	DSSTox carcinogenic potency DBS single cell call	DSSTox carcinogenic property DBS Mouse
Daunomycin 1	Non-carcinogenic	Carcinogenic	Non-carcinogenic	Non-carcinogenic
Daunomycin 2	Non-carcinogenic	Carcinogenic	Non-carcinogenic	Non-carcinogenic
Daunomycin 3	Non-carcinogenic	Carcinogenic	Non-carcinogenic	Non-carcinogenic
Daunomycin 4	Non-carcinogenic	Carcinogenic	Non-carcinogenic	Non-carcinogenic

Absorption and distribution parameters of all the new designed daunomycin analogues have been predicted using ADME prediction tool by preADMET server which is listed below.

Pre ADMET server ADME prediction of Daunomycin 1

	Name	Value
Absorption		
Absorption	Human intestinal absorption (HIA, %)	92.238040
Absorption	In vitro caco-2 cell permeability	20.7855
Absorption	In vitro MDCK cell permeability	0.0436747
Absorption	In vitro skin permeability	3.65086
Distribution		
Distribution	In vitro plasma protein binding (%)	83.930591
Distribution	In vivo blood-brain barrier penetration (C.brain/C.blood)	0.0616283
Pgp inhibition	In vitro plasma glycoprotein inibhition	Inhibitor

Pre ADMET server ADME prediction of Daunomycin 2

	Name	Value
Absorption		
Absorption	Human intestinal absorption (HIA, %)	91.775549
Absorption	In vitro caco-2 cell permeability	18.3371
Absorption	In vitro MDCK cell permeability	0.0692636
Absorption	In vitro skin permeability	3.75648
Distribution		
Distribution	In vitro plasma protein binding (%)	83.022838
Distribution	In vivo blood-brain barrier penetration (C.brain/C.blood)	0.0604728
Pgp inhibition	In vitro plasma glycoprotein inhibition	Inhibitor

Pre ADMET server ADME prediction of Daunomycin 3

	Name	Value
Absorption		
Absorption	Human intestinal absorption (HIA, %)	81.406169
Absorption	In vitro caco-2 cell permeability	17.7687
Absorption	In vitro MDCK cell permeability	0.231587
Absorption	In vitro skin permeability	4.67354
Distribution		
Distribution	In vitro plasma protein binding (%)	39.975856
Distribution	In vivo blood-brain barrier penetration (C.brain/C.blood)	0.027312
Pgp inhibition	In vitro plasma glycoprotein inhibition	Non

Pre ADMET server ADME prediction of Daunomycin 4

	Name	Value
Absorption		
Absorption	Human intestinal absorption (HIA, %)	89.218217
Absorption	In vitro caco-2 cell permeability	20.3518
Absorption	In vitro MDCK cell permeability	0.0550549
Absorption	In vitro skin permeability	4.23284
Distribution		
Distribution	In vitro plasma protein binding (%)	79.273479
Distribution	In vivo blood-brain barrier penetration (C.brain/C.blood)	0.085321
Pgp inhibition	In vitro plasma glycoprotein inhibition	Non

Conclusion

All the above designed and developed drug like molecules are designed on the basis of SAR studies and Pharmacophore study. The molecule 4 (Daunomycin 4) predicted to be more

effective or equivalent anticancer agents. Also the predicted molecule found to have non- carcinogenic, non-mutagenic in nature with low level of toxicity. Predicted metabolic sites are useful for computational chemist for docking analysis of drug for choosing suitable target. The internet based tool here used is found to be easy to use and compatible. The molecule designed above and the method is novel and hope the present tool might be useful for initiating the new era for designing new anti-cancer drugs with low cost.

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