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SAR and Pharmacophore Based Designing of Some Antimalarial and Antiretroviral Agents: An INTERNET Based Drug Design Approach

Soumendranath Bhakat

Department of Pharmaceutical Sciences, Birla Institute of technology, Mesra, Ranchi

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ABSTRACT

With the development of computational chemistry and molecular docking studies SAR and pharmacophore based drug design have been modified to target based drug discovery using sophisticated computational tools which is not very much user friendly and has got many incompatibility issues with many operating systems(OS) and other system configurations. In this paper SAR (Structure Activity Relationship) and pharmacophore based drug design approaches have been described by the used of free internet based tools which are very much user friendly and can almost compatible with any platform. Some antimalarial. And anti retroviral agents have been designed using pharmacophore study and their drug like properties,toxicity,metabolic sites and other parameters are predicted by the free internet based tools.

Keywords: Structure Activity Relationship(SAR),Pharmacophore, Drug Design, OSIRIS Property Explorer,MolSoft,MetaPrint2D,Lazar Toxicity,Antimalarial,Antiretroviral,HIV,AIDS,Miracle Molecule

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INTRODUCTION

In recent years computer aided drug [1],[2],[3],[4],[5] design become a famous tool for rational drug design on the basis of SAR (Structure Activity Relationship) and pharmacophore study. The SAR [6] and pharmacophore [7] based drug design is mainly based on lipski's rule of five [8]. But for higher costs, lengthy and complicated procedure to install and compatibility issues in different systems make the computational softwares difficult to handle for general undergraduate students and sometimes post graduation students because these softwares needs a lot of time and skill to expertise. Most of these softwares are mainly compatible with LINUX and WINDOWS previous versions(WINDOWS XP,WINDOWS 98 etc.) and incompatible with WINDOWS 7 operating system specially in 64 bit OS where it needs some compilation and a lengthy procedure to install and these softwares also show certain incompatible issues with INTEL SECOND generation processors (i3,i5,i7 etc.).

To encounter these difficulties and make drug design more easy and convenient INTERNET based drug design on the basis of SAR and pharmacophore study become a prosperous 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 on fly basis. These JAVA based internet tools can be applied to predict the toxicity, solubility, pKa; lipnski's five rule which are important parameters for structure based rational drug design.

Recently structural analogue based drug discovery become an important tool for designing more potent drug like molecules. In this paper by SAR and pharmacophore study structural analogue based novel drugs e.g. antimalarial, Anti-Retroviral molecules have been designed using internet based tools.

MATERIALS AND METHODS

The structural analogue based drug design has been performed using MOLSOFT molecules in-silico drug likeness and molecular property prediction tool [9]. The new designed molecules on the basis of SAR and pharmacophore study have been inputted in JME molecular editor [10] 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 [11]. OSIRIS property explorer [12] is also used to predict toxicity and other drug like properties. The metabolic sites of these designed drugs have been predicted using MetaPrint2D [13]. All these works have been performed using WINDOWS 7 64-bit operating system having Intel Core 2 duo processor.

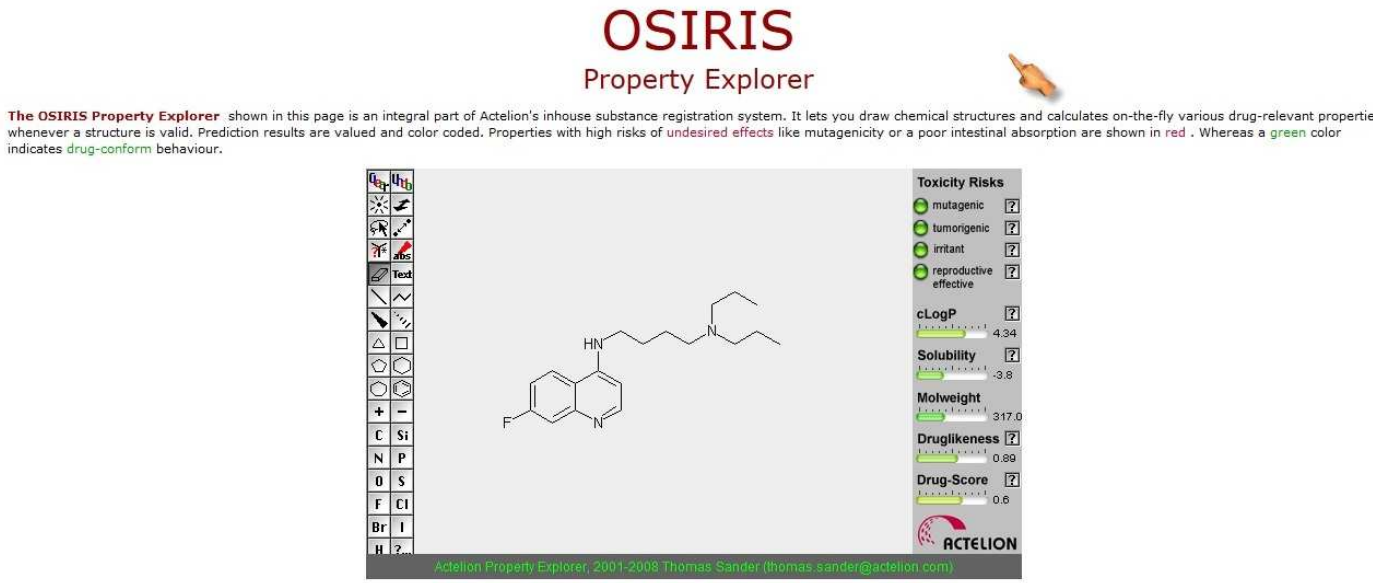


Fig 1. Screenshot of OSIRIS Property Explorer

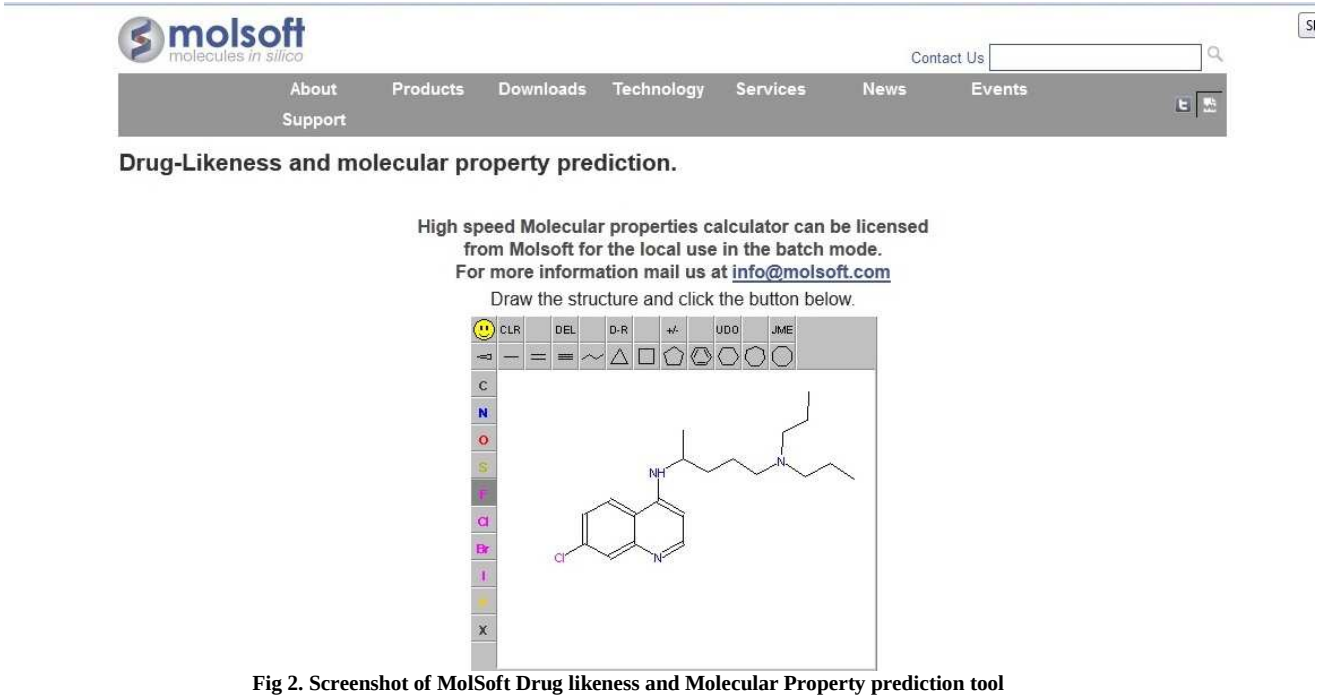


Fig 2. Screenshot of MolSoft Drug likeness and Molecular Property prediction tool

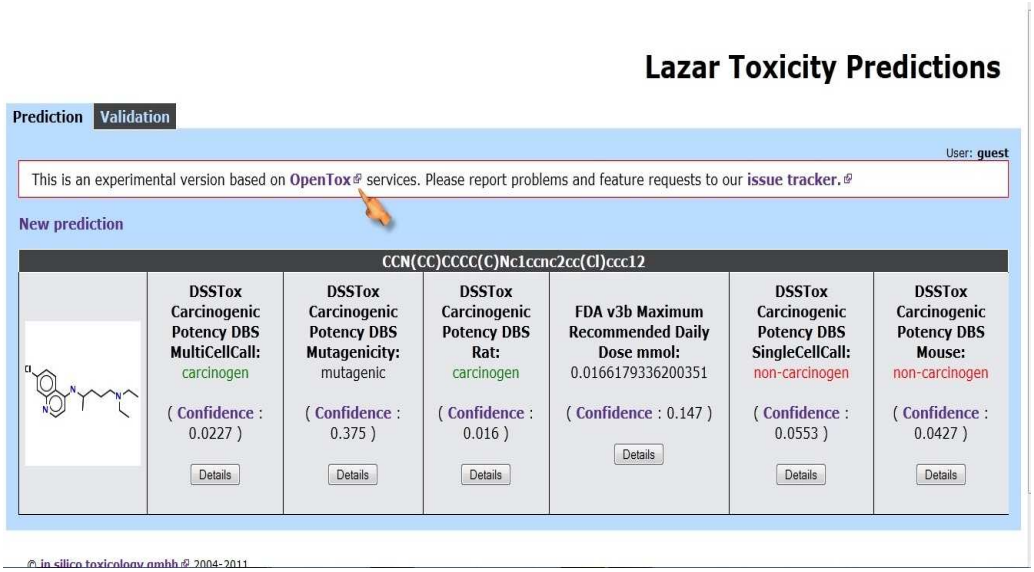


Fig 3. Screenshot of Lazar toxicity prediction tool

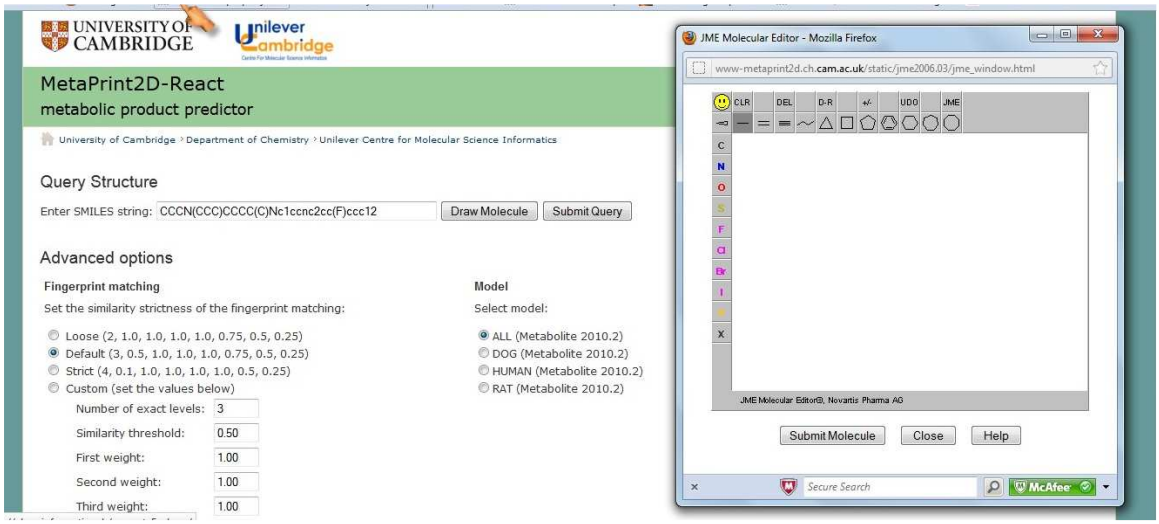


Fig 4. Screenshot of MetaPrint2D metabolic site prediction tool

RESULTS AND DISCUSSION

Designing of New Chloroquine structural analogues as probable Antimalarial agent:

Inexpensive and stable antimalarial drugs such as the chloroquine [14] have kept malaria in check in most regions for decades. However, the rising number of malaria deaths is due in part to increase resistance [15] to chloroquine hence there is a necessity to design some more potent 4 aminoquinoline derivatives to introduce a more potent therapy.

The first type of drug designed using internet based tools using chloroquine as prototype drug having probable antimalarial activity as it consists of 4-aminoquinoline [16] pharmacophore. The structural analogues of chloroquine have been designed in such a way that it will show more drug likeness score than the prototype molecule but having the same pharmacophore essential for the antimalarial activity. The side chain present at 4 position of chloroquine have been modified with alteration of halogen atom in some cases at position 8 to get increased drug likeness score with the MolSoft Drug Likeness and Molecular Property prediction tool. In case of designed molecules AM3, AM4 the chlorine molecule at position 8 have been replaced by –F atom to increase the MolSoft drug likeness score than the prototype molecule chloroquine. The list of designed chloroquine analogues with drug likeness scores, predicted toxicity and other molecular properties have been listed below. The position of R^1 and R^2 in the 4-aminoquinolone ring (Fig 1) are modified in these designed molecules to get increased drug likeness score.

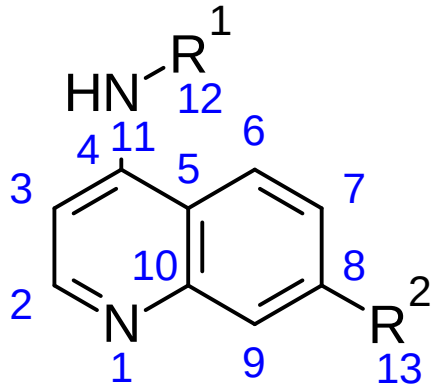


Fig 5. The 4-Amino quinolone pharmacophore, R1,R2=position of substitution

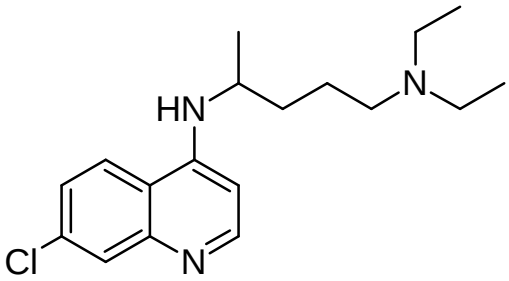
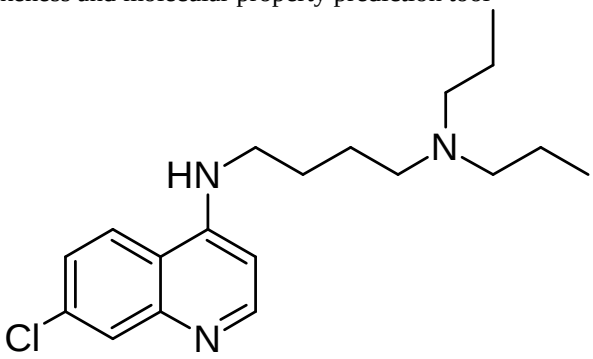
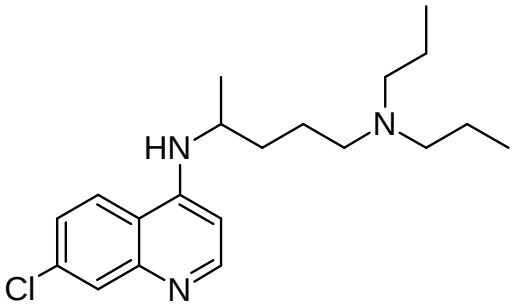


Fig 6. Prototype molecule chloroquine having MolSoft drug likeness score of 1.17

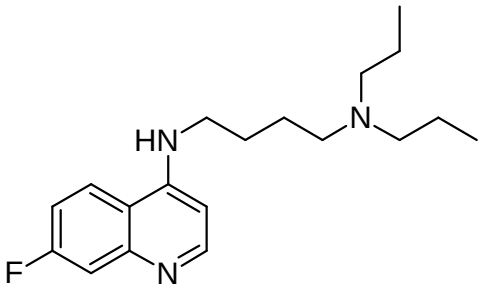
List of designed chloroquine analogues with MolSoft Drug likeness score and predicted molecular property
*Predicted by MolSoft Drug likeness and molecular property prediction tool



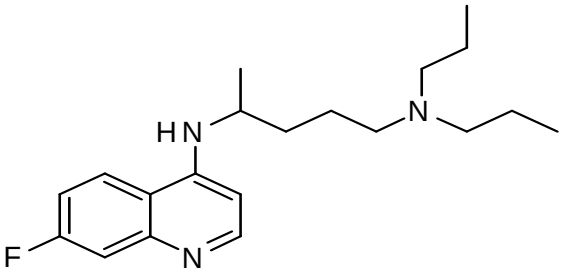
Drug likeness* score 1.38 Molecule ID: AM1
Molecular property* of AM1
Molecular formula: C_{19} H_{28} Cl N_3
Molecular weight: 333.20
Number of HBA: 2
Number of HBD: 1
MolLogP : 5.90 (> 5)
MolLogS : -5.71 (in Log(moles/L)) 0.65 (in mg/L)
MolPSA : 24.58 A^2
MolVol : 343.53 A^3
Number of stereo centers: 0



Drug likeness* score 1.25
Molecule ID:AM2
Molecular property* of AM2
Molecular formula: C_{20} H_{30} Cl N_3
Molecular weight: 347.21
Number of HBA: 2
Number of HBD: 1
MolLogP : 5.35 (> 5)
MolLogS : -5.89 (in Log(moles/L)) 0.44 (in mg/L)
MolPSA : 24.04 A^2
MolVol : 359.14 A^3
Number of stereo centers: 1



Drug likeness* score 1.23 Molecule ID:AM3
Molecular property* of AM3
Molecular formula: C_{19} H_{28} F N_3
Molecular weight: 317.23
Number of HBA: 2
Number of HBD: 1
MolLogP : 5.27 (> 5)
MolLogS : -5.13 (in Log(moles/L)) 2.37 (in mg/L)
MolPSA : 24.58 A^2
MolVol : 332.26 A^3
Number of stereo centers: 0



Drug likeness score* 1.20
Molecule ID: AM4
Molecular Property* of AM4
Molecular formula: C_{20} H_{30} F N_3
Molecular weight: 331.24
Number of HBA: 2

Number of HBD: 1
MolLogP : 4.72
MolLogS : -5.31 (in Log(moles/L)) 1.61 (in mg/L)
MolPSA : 24.04 A^2
MolVol : 347.87 A^3
Number of stereo centers: 1

Table 1. OSIRIS Property explorer values of designed chloroquine analogues

Molecule ID	cLogP value	Solubility	Molecular Weight	Drug Likeness	Drug Score
AM1	4.89	-4.22	333.0	3.27	0.59
AM2	5.3	-4.60	347.0	5.56	0.53
AM3	4.34	-3.8	317.0	0.89	0.60
AM4	4.74	-4.18	331.0	3.36	0.61

All parameters in OSIRIS property explorer shows "green" colour for all designed drugs which indicates the drug confirm behavior of these designed chloroquine analogues.

Phase I Metabolic site prediction using MetaPrint2D by setting the strictness of the fingerprint matching in "DEFAULT" and selecting model "ALL (Metabolite 2010.2)":

The colour highlighting an atom indicates its normalised occurrence ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database. The normalised occurrence ratio does not indicate how likely a molecule is to be metabolised, but rather the relative likelihood of metabolism occurring at a particular site in the molecule, assuming it is metabolised.

The Indication of colours which denotes predicted metabolic sites:
Red0.66 <= NOR <= 1.00 Orange0.33 <= NOR < 0.66 Green0.15 <= NOR < 0.33 White0.00 <= NOR < 0.15 Grey-Little/no data

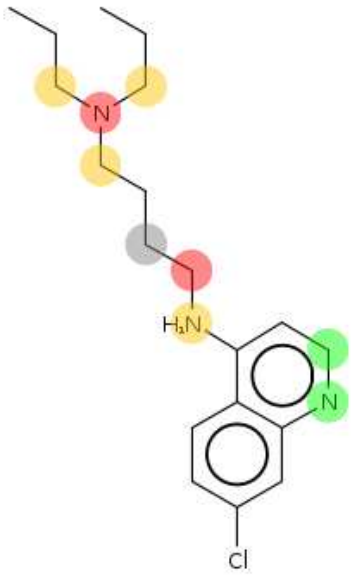


Fig 7a. Predicted Phase I metabolic sites of AM1

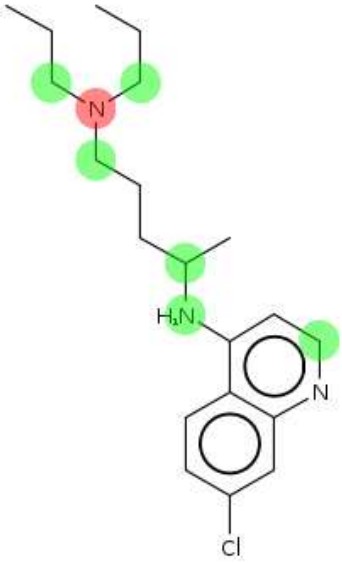


Fig 7b. Predicted Phase I metabolic sites of AM2

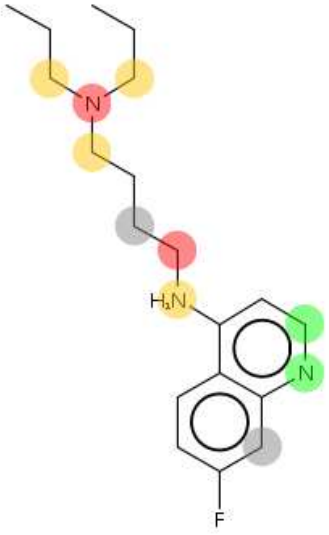


Fig 7c, Predicted Phase I metabolic sites of AM3

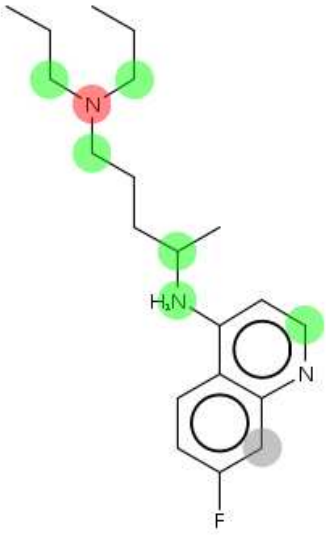


Fig 7d, Predicted Phase I metabolic sites of AM4

Table 2. Predicted toxicity of chloroquine analogues using in-silico lazar toxicity prediction tool
http://lazar.in-silico.de/predict

Molecule ID	**DSSTox Carcinogenic Potency DBS MultiCellCall**	**DSSTox Carcinogenic Potency DBS Mutagenicity**	**DSSTox Carcinogenic Potency DBS Rat**	**FDA v3b Maximum Recommended Daily Dose mmol**	**DSSTox Carcinogenic Potency DBS SingleCellCall****	**DSSTox Carcinogenic Potency DBS Mouse****
AM1	**Carcinogen Confidence:0.0219**	**Mutagenic Confidence:0.375**	**Carcinogen Confidence:0.0101**	0.0178807218776623 Confidence:0.143	**Non-carcinogen Confidence:0.0762**	**Non-carcinogen Confidence:0.0628**
AM2	Carcinogen Confidence:0.0104	Mutagenic Confidence:0.375	Carcicnogen Confidence:0.016	0.0151183201990332 Confidence:0.141	Non-carcinogen Confidence:0.0788	Non-carcinogen Confidence:0.0427
AM3	Non-Carcinogen Confidence:0.0835	Mutagenic Confidence:0.316	Non-carcinogen Confidence:0.0796	0.0115127173023031 Confidence:0.101	Non-carcinogen Confidence:0.0762	Non-carcinogen Confidence:0.0628
AM4	Non-carcinogen Confidence:0.0678	Mutagenic Confidence:0.0316	Non-carcinogen Confidence:0.083	0.0121710340126146 Confidence:0.124	Non-carcinogen Confidence:0.0788	Non-carcinogen Confidence:0.0427
Chloroquine	Carcinogen Confidence:0.0227	Mutagenic Confidence:0.375	Carcinogen Confidence:0.016	0.0166179336200351 Confidence:0.147	Non-carcinogen Confidence:0.0553	Non-carcinogen Confidence:0.0427

On the basis of predicted lazar toxicity it is clear that the molecules AM3 and AM4 are more potent than chloroquine,AM1 and AM2. But as the toxicity level of the drugs AM1 and AM2 have almost similar with chloroquine and in some cases the confidence value for the predicted toxicity is more than that of chloroquine (the confidence value for the non-carcinogenic property of AM1 and AM2 in case of SingleCellCall** and Mouse** parameters are more than that of chloroquine) hence they are believed to be more potent than chloroquine as well.

Designed Artemisinin analogues as antimalarial agents

Artemisinin [17] (Fig. 8) is a drug that posses the most rapid action of all current drugs against Plasmodium falciparum malaria. To increase the potency(the main aim is to cure Artemisinin resistant malaria [18] and make this drug more broad spectrum antimalarial agent the carbon at position 10 of Artemisinin is replaced by nitrogen with a side chain having a analogous chloroquine like side chain and a chlorine atom is attached with position 15 of Artemisinin. The new designed drug like molecules have been found to have more drug likeness score than that of the prototype drug Artemisinin(Artemisinin has a drug likeness score that of 1.22). The toxicity and metabolic sites of these designed drugs have been predicted using the toxicity, metabolic site prediction tools.

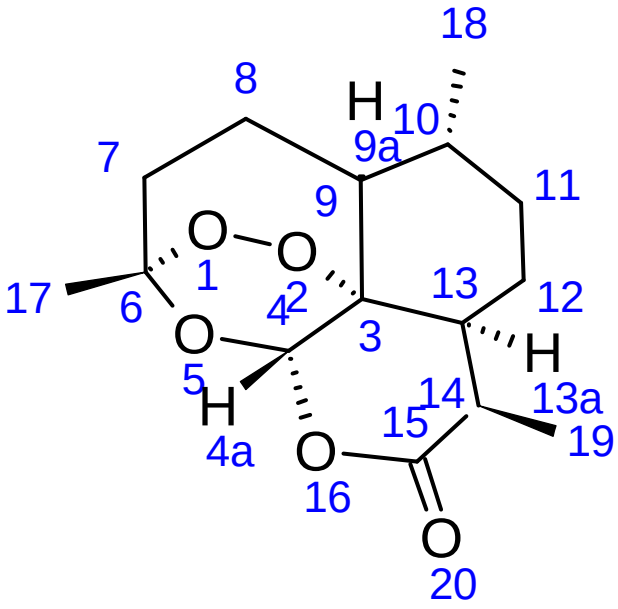
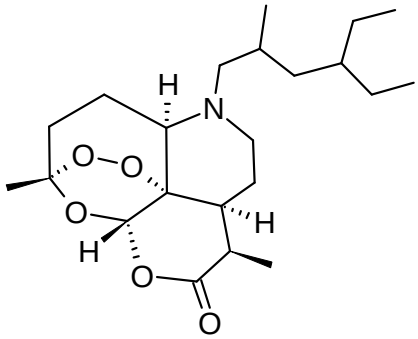


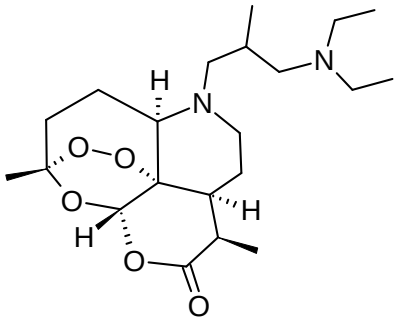
Fig 8. The prototype drug Artemisinin

List of designed Artemisinin analogues with MolSoft Drug likeness score and predicted molecular property



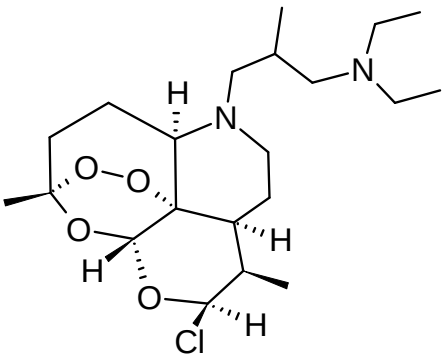
Molecule ID: AMM1
Drug-likeness score of AMM1: 1.97
Molecular Properties of AMM1

Molecular formula: C_{22} H_{37} N O_5
Molecular weight: 395.27
Number of HBA: 6
Number of HBD: 0
MolLogP : 5.46 (> 5)
MolLogS : -2.52 (in Log(moles/L)) 1202.47 (in mg/L)
MolPSA : 51.18 A^2
MolVol : 445.00 A^3
Number of stereo centers: 7



Molecule ID: AMM2
Drug-likeness score of AMM2: 1.90
Molecular Properties of AMM2

Molecular formula: C_{21} H_{36} N_2 O_5
Molecular weight: 396.26
Number of HBA: 7
Number of HBD: 0
MolLogP : 3.71
MolLogS : -1.10 (in Log(moles/L)) 31431.52 (in mg/L)
MolPSA : 55.19 A^2
MolVol : 443.65 A^3
Number of stereo centers: 7



Molecule ID:AMM3
Drug likeness model score of AMM3:1.46
Molecular Properties of AMM3

Molecular formula: C_{21} H_{37} Cl N_2 O_4
Molecular weight: 416.24
Number of HBA: 6
Number of HBD: 0
MolLogP : 4.23
MolLogS : -1.62 (in Log(moles/L)) 10018.30 (in mg/L)
MolPSA : 42.77 A^2
MolVol : 446.57 A^3
Number of stereo centers: 8

Table 3.OSIRIS Property explorer values of designed Artemisinin analogues

Molecule ID	cLogP value	Solubility	Molecular Weight	Drug Likeness	Drug Score
AMM1	4.62	-3.93	395.0	1.71	0.12
AMM2	2.55	-2.41	396.0	3.37	0.17
AMM3	4.08	-2.97	416.0	0.53	0.12
Prototype drug, Artemisinin	2.37	-3.29	282.0	-1.97	0.10

Artemisinin and all its analogues have shown mutagenic, tumorigenic and irritant property as it shows in “red colour” in OSIRIS Property Explorer but all of their designed analogues have more drug score than that of Artemisinin hence it is predicted that these newly designed drug like molecules have much more potency than that of the prototype drug Artemisinin.

Phase I Metabolic site prediction using MetaPrint2D by setting the strictness of the fingerprint matching in "DEFAULT" and selecting model "ALL (Metabolite 2010.2)":
The colour highlighting an atom indicates its normalised occurrence ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database. The normalised occurrence ratio does not indicate how likely a molecule is to be metabolised, but rather the relative likelihood of metabolism occurring at a particular site in the molecule, assuming it is metabolised.

Results Colour Scheme

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

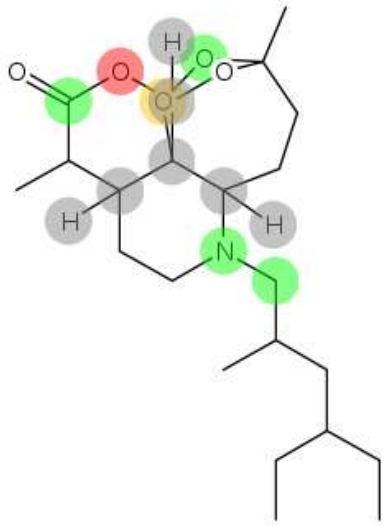


Fig 8a. Predicted phase I metabolic site of AMM1

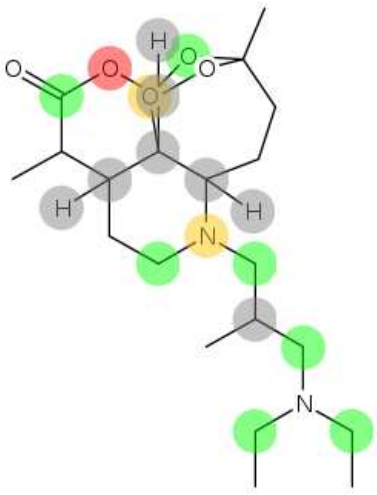


Fig 8b. Predicted Phase I metabolic site of AMM2

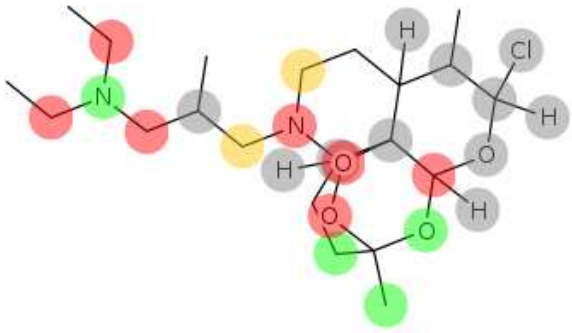


Fig 8c. Predicted Phase I metabolic site of AMM3

Table 4. Predicted toxicity of Artemisinin analogues using in-silico lazar toxicity prediction tool
http://lazar.in-silico.de/predict

Molecule ID	DSSTox Carcinogenic Potency DBS MultiCellCall	DSSTox Carcinogenic Potency DBS Mutagenicity	DSSTox Carcinogenic Potency DBS Rat	FDA v3b Maximum Recommended Daily Dose mmol	DSSTox Carcinogenic Potency DBS SingleCellCall**	DSSTox Carcinogenic Potency DBS Mouse**
AMM1	Non-Carcinogen Confidence:0.0647	Non-Mutagenic Confidence:0.133	Non-Carcinogen Confidence:0.0637	0.00132777597200338 Confidence:0.1	Non-carcinogen Confidence:0.0617	Non-carcinogen Confidence:0.12
AMM2	Non-Carcinogen Confidence:0.0647	Non-Mutagenic Confidence:0.133	Non-Carcicnogen Confidence:0.0637	0.00145083067169408 Confidence:0.115	Non-carcinogen Confidence:0.0617	Non-carcinogen Confidence:0.12
AMM3	Non-Carcinogen Confidence:0.0854	Non-Mutagenic Confidence:0.0837	Non-carcinogen Confidence:0.0682	0.00145717569177769 Confidence:0.114	Non-carcinogen Confidence:0.0535	Non-carcinogen Confidence:0.114
Artemisinin	Non-Carcinogen Confidence:0.0823	Non-Mutagenic Confidence:0.158	Non-Carcinogen Confidence:0.0682	0.00059399502380091 8 Confidence:0.112	Non-carcinogen Confidence:0.0679	Non-carcinogen Confidence:0.0951

All designed Artemisinin analogues have been predicted as non carcinogen as well as non-mutagenic by the internet based lazar toxicity prediction tool this confirms that the rational and effective drug like molecules have been designed by SAR and pharmacophore study.

Design of some lamivudine derivatives as potent Anti-Retroviral agents:
Lamivudine is a potent nucleoside analogue reverse transcriptase inhibitor [19]. To increase the potency of lamivudine as anti-HIV agent the –R part of lamivudine (Fig. 9) is substituted to get more potent designed drug like molecule having increased drug likeness score in MolSoft drug likeness and property explorer tool. The prototype drug lamivudine has a drug likeness score of 1.05 and the designed drug like molecules have greater drug likeness score that of lamivudine

The toxicity, metabolic sites and other properties have been predicted using earlier prediction methods using internet based tools.

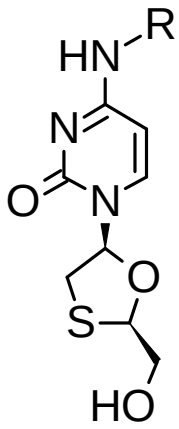
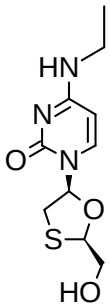


Fig 9. The pharmacophore of lamivudine

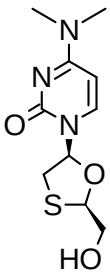
List of designed Lamivudine analogues with MolSoft Drug likeness score and predicted molecular property



4-(ethylamino)-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one

Molecule ID: LMA1
Drug-likeness score of LMA1: 1.16
Molecular Properties of LMA1

Molecular formula: $C_{10}H_{15}N_3O_3S$
Molecular weight: 257.08
Number of HBA: 5
Number of HBD: 2
MolLogP : 0.35
MolLogS : -2.12 (in Log(moles/L)) 1955.97 (in mg/L)
MolPSA : 62.24 A^2
MolVol : 256.18 A^3
Number of stereo centers: 2

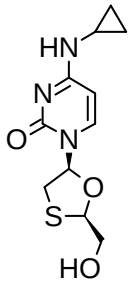


4-(dimethylamino)-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one

Molecule ID:LMA2
Drug-likeness score of LMA2: 1.23
Molecular Properties and Drug-likeness.

Molecular formula: $C_{10}H_{15}N_3O_3S$
Molecular weight: 257.08
Number of HBA: 5

Number of HBD: 1
MolLogP : -0.71
MolLogS : -1.81 (in Log(moles/L)) 3975.81 (in mg/L)
MolPSA : 53.16 A^2
MolVol : 259.27 A^3
Number of stereo centers: 2



4-(cyclopropylamino)-1-[(2*R*,5*S*)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]pyrimidin-2(1*H*)-one

Molecule ID:LMA3
Drug-likeness score of LMA3: 1.30
Molecular Properties and Drug-likeness.

Molecular formula: $C_{11}H_{15}N_3O_3S$
Molecular weight: 269.08
Number of HBA: 5
Number of HBD: 2
MolLogP : 0.17
MolLogS : -2.15 (in Log(moles/L)) 1885.47 (in mg/L)
MolPSA : 62.37 A^2
MolVol : 272.08 A^3
Number of stereo centers: 2

Table 5. OSIRIS Property explorer values of designed Lamivudine derivatives

Molecule ID	cLogP value	Solubility	Molecular Weight	Drug Likeness	Drug Score
LMA1	0.0	-1.57	257.0	1.27	0.51
LMA2	-0.21	-0.91	257.0	2.34	0.55
LMA3	4.08	-2.04	269.0	1.46	0.51
Prototype drug, Lamivudine	2.37	-1.36	229.0	-2.12	0.26

All the designed drug like molecules taking the pharmacophore of lamivudine are found to have more drug score than that of the prototype drug lamivudine which leads to confirm that all newly drug like molecules might have increased and more potent activity than that of lamivudine.

Phase I Metabolic site prediction using MetaPrint2D by setting the strictness of the fingerprint matching in "DEFAULT" and selecting model "ALL (Metabolite 2010.2)":

The colour highlighting an atom indicates its normalised occurrence ratio (NOR). A high NOR indicates a more frequently reported site of metabolism in the metabolite database. The normalised occurrence ratio does not indicate how likely a molecule is to be metabolised, but rather the relative likelihood of metabolism occurring at a particular site in the molecule, assuming it is metabolised.

Results Colour Scheme

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 9a. Predicted Phase I metabolic site of LMA1

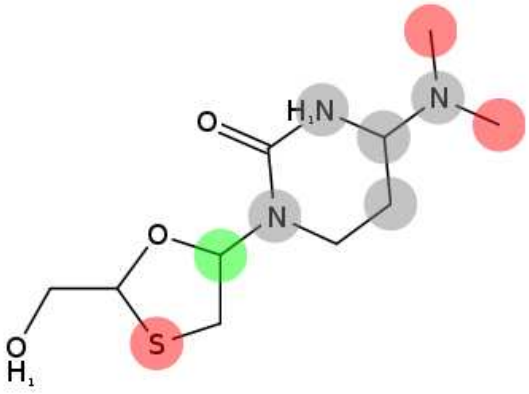


Fig 9b. Predicted Phase I metabolic site of LMA2

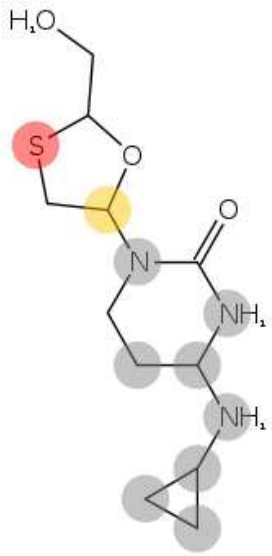


Fig 9c. Predicted Phase I metabolic site of LMA3

Table 6. Predicted toxicity of Artemisinin analogues using in-silico lazar toxicity prediction tool
http://lazar.in-silico.de/predict

Molecule ID	DSSTox Carcinogenic Potency DBS MultiCellCall	DSSTox Carcinogenic Potency DBS Mutagenicity	DSSTox Carcinogenic Potency DBS Rat	FDA v3b Maximum Recommended Daily Dose mmol	DSSTox Carcinogenic Potency DBS SingleCellCall**	DSSTox Carcinogenic Potency DBS Mouse**
LMA1	Carcinogen Confidence:0.317	Non-Mutagenic Confidence:0.005	Carcinogen Confidence:0.0744	0.0218096608207519 Confidence:0.596	Carcinogen Confidence:0.106	Carcinogen Confidence:0.363
LMA2	Carcinogen Confidence:0.0251	Non-Mutagenic Confidence:0.0503	Non-Carcicnogen Confidence:0.0276	0.114833628875105 Confidence:0.0698	Non-carcinogen Confidence:0.0291	Non-carcinogen Confidence:0.0565
LMA3	Carcinogen Confidence:0.0166	Mutagenic Confidence:0.0242	carcinogen Confidence:0.0905	0.0218096608207519 Confidence:0.596	carcinogen Confidence:0.0644	carcinogen Confidence:0.293
Lamivudine	Carcinogen Confidence:0.0317	Mutagenic Confidence:0.005	Carcinogen Confidence:0.0744	0.0218096608207519 Confidence:0.596	Carcinogen Confidence:0.106	Carcinogen Confidence:0.43

From predicted lazar toxicity it is clear that the most effective design drug like molecule is LMA2 which posses lower predicted toxicity level as compare with other designed analogues and of lamivudine. But all other design molecules will have be more effective than that of lamivudine as LMA1 and LMA3 as both of these drugs have lower predicted lazar toxicity than that of lamivudine (as compared by the "confidence" value generated by the lazar toxicity prediction tool, lower confidence value of predicted toxicity of LMA1 and LMA3 than that of prototype drug lamivudine suggests that they are less toxic than lamivudine).

CONCLUSION

These entire designed drug like molecules designed on the basis of SAR and pharmacophore study predicted to be more effective and potent in nature than that of all prototype molecules. The predicted metabolic sites will be beneficial for computational chemists for docking analysis of these drugs and in choosing suitable targets. The internet based tools used in this study for calculating drug score, drug likeness, toxicity and other drug like and molecular properties are easy to handle and user friendly. Designing of these drug like molecules by the pharmacophore study and prediction of drug like properties of these molecules by the internet based tools hope to speed up basic drug design research as all these tools are user friendly. Currently work is going on the development of a "Miracle Molecule" by the use of internet based drug design tools which can be act as an antimalarial,antiviral,antiretroviral,anticancer,antibacterial agent as it will contain all the pharmacophores necessary for these activities and the work will be reported in near future.

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