QSAR Analysis and Toxicity Prediction of Anti-Malarial Drug and Its Derivatives

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Abstract

Malaria is the biggest threat to the tropical countries and, thereforea constant need for the discovery of novel targets and a high rate efficacy of antimalarial molecules are required.High yielding information have been gathered from databaseswhich has aimed towards facilitating novel molecules to be explored, as well as set of algorithms being used for defining the electron density of the molecular structure which has given better drug likeness score and bioactivity score . Moreover, various procedures are employed to analyze the results of logP, melting point, volume, solubility, blood-brain permeability and toxicity prediction of anti-malarial drug and its analogues which played further role used for improvising potency, selectivity and pharmacokinetic properties.

KEYWORDS: electron density, logP, blood-brain permeability, pharmacokinetic properties.

Introduction

The word “malaria” comes from the Italian “mal’aria” for “bad airs.” It was not until the 1880s and 1890s that Alphonse Laveran, Ronald Ross, Battista Grassi, and others were able to identify the malaria parasite and link the transmission of malaria to mosquitoes.
Although the understanding of the mosquito cycle led to a number of new approaches in vector control in the early 20th century, malaria prophylaxis and therapy continued to draw on earlier remedies. Indeed, what is remarkable about malarial fevers is that two herbal treatments, cinchona bark and qinghao, were used to treat malaria effectively for hundreds of years prior to the under-standing
of the mosquito cycle. Today both quinine (derived from the cinchona bark) and artemisinin (from qinghao) remain of prime importance in the control of malaria.
The practice of Western medicine changed dramatically during the 19th and 20th centuries, as herbal remedies were gradually replaced by pure chemical compounds and, later, synthetic drugs. So, thetreatment of malaria undergoes important scientific developments. Malaria was among the first diseases to be treated by a pure chemical compound—quinine—isolated from the cinchona bark in 1820. It was, sub-sequently, the first disease to be treated by a synthetic compound—methylene blue. In addition, malaria parasites were among the first pathogenic microbes to out-smart medical intervention and become drug resistant.Malaria was one of the best-studied diseases in Western medicine until the middle of the 20th century.
Until that time, malaria was still endemic in North America and Europe. It also had great importance because it represented an obstacle to the expansion of European nations into

the tropical world. It also played an important role in the major wars of both the 19th and 20th centuries. The aim of this work is to provide an overview of antimalarial drug resistance with a particular emphasis on the pharmacokinetic features of the drug and its analogues in the reduction of the burden of malaria.

The main target to reduce the heinouseffects of the fatal disease on behalf of predicting the toxicity, solubility of the drugs and its analogues, which have given rise to measure the burden of drug resistance and predicting the impact of strategies . It has been aimed to demonstrate how a bioeconomic model might be developed and deployed to address these issues and to clarify policy options.Emanation of new molecules can be treated with novel biochemical targets which has been resulted from molecular modeling and further validated by the path of molecular dynamics, so as to improve the drug efficacy and eradicating effects of malaria parasite. Though, streamline generation of chemically diverse and effective drugs being used still, there has been a quick resistance in the target sites. Artemisinin along with its derivatives have been used for treating the patients, but their declined affects have been shown in the area where malaria is endemic, for e.g. Thai-Cambodian border. Therefore, amalgamating the studies of Genomics along with the implementation of structure based drug designing hold a breakthrough towards eliminating the infectious disease.

Fatal effects of parasite can be reduced by employing in silico methods where new novel molecules can be designed and generated by chemical library and virtually screening of the molecules to the targets may give an assumption of the best docking result corresponding to its lowest energy value.The science of synthetic organic chemistry underwent a revolution in the late 19th century, partly in response to the need for new antimalarials. In 1856, William Henry Perkins, an 18-yr-old English chemist, set out to synthesize quinine, but failed.

Indeed, the synthesis of quinine was not accomplished until 1944 and, even to this day, has not been achieved on a commercially economic scale. However, Perkins succeeded in synthesizing “mauve,” the first synthetic textile dye that did not wash off in water. This advance sparked the development of a huge German synthetic dye industry.

The new dye industry helped promote the advancement of medicine. When microbial pathogens were first identified, they were difficult to see under the microscope. Newly synthesized dyes were then used by microbiologists as stains to enhance visualization and classification. Paul Ehrlich, a German scientist, noticed that methylene blue was particularly effective in staining malaria parasites. He reasoned that because the parasite avidly took up the dye, it might be poisoned by it in vivo. In 1891, Ehrlich cured two patients of malaria using methylene blue, the first time a synthetic drug was ever used in humans.

Bayer, one of the leading German dye companies, soon became a leading pharmaceutical company. A team of chemists and biologists was assembled by Bayer to develop new synthetic antimalarials using methylene blue as a prototype. In 1925, they developed plasmoquine (also called pamaquine). Plasmoquine, the first 8-aminoquinoline, proved to be the first compound capable of preventing relapses in vivax malaria. In 1932, they developed mepacrine (atebrine) which was effective againstfalciparum malaria.

MATERIALS AND METHODS

Lipinski’s Rule

Lipinski's rule of five also known as the Pfizer's rule of five or simply the Rule of five (RO5) is a rule of thumb to evaluate drug likeness or determine if a chemical compound with a certain pharmacological or biological activity has properties that would make it a likely orally active drug in humans. The rule was formulated by Christopher A. Lipinski in 1997.

The rule describes molecular properties important for a drug's pharmacokinetics in the human body, including their absorption, distribution, metabolism, and excretion ("ADME")

Components of the Lipinski's rule:

Lipinski's rule states:

- Not more than 5 hydrogen bond donors (nitrogen or oxygen atoms with one or more hydrogen atoms)
- Not more than 10 hydrogen bond acceptors (nitrogen or oxygen atoms)
- A molecular mass less than 500 daltons
- Anoctanal-water partition coefficient log *P* not greater than 5
- No more than one number of violations.

Molinspiration

Molinspiration, web based software was used to obtain parameter such as MiLogP, TPSA, drug likeness. MiLogP, is calculated by the methodology developed by Molinspiration as a sum of fragment based contributions and correction factors [6,7]. MiLog P parameter is used to check good permeability across the cell membrane. TPSA is related to hydrogen bonding potential of compound which should be below 160Å.Calculation of volume developed at Molinspiration is based on group contributors. Number of rotatable bonds measures molecular flexibility. It is a very good descriptor of absorption and bioavailability of drugs. Through drug likeness datas of molecule, it can be checked molecular properties and structure feature in respect to known drugs.

Bioactivity score

Bioactivity of the drug can be checked by calculating the activity score of GPCR ligand, ion channel modulator, nuclear receptor legend, kinase inhibitor, protease inhibitor, enzyme inhibitor. All the parameters were checked with the help of software Molinspiration drug-likeness score online (www.molinspiration.com). Calculated drug likeness score of each compounds and compared with the specific activity of each compound, and the results were compared with standard drug. For organic molecules the probability is if the bioactivity score is (>0), then it is active, if (-5.0-0.0) then moderately active, if (< -5.0) then inactive.

OSIRIS Property Explorer

The OSIRIS Property Explorer shown in this page is an integral part of Actelion's (1) in house substance registration system. It lets you draw chemical structures and calculates on-the-fly various drug-relevant properties whenever a structure is valid. Prediction results are valued and colour coded. Properties with high risks of undesired effects like mutagenicity or a poor intestinal absorption are shown in red. Whereas a green colour indicates drug-conform behaviour.

O CHEM

Online Chemical Modeling Environment is a web-based platform that aims to automate and simplify the typical steps required for QSAR Modeling. The platform consists of two major subsystems: the database of experimental measurements and the modelling framework. A user-contributed database contains a set of tools for easy input, search and modification of thousands of records. The OCHEM database is based on the wiki principle and focuses primarily on the quality and verifiability of the data. The database is tightly integrated with the Modeling framework, which supports all the steps required to create a predictive model: data search, calculation and selection of a vast variety of molecular descriptors, application of machine learning methods, validation, analysis of the model and assessment of the applicability domain.

As compared to other similar systems, OCHEM is not intended to re-implement the existing tools or models but rather to invite the original authors to contribute their results, make them publicly available, and share them with other users and to become members of the growing research community. OCHEM a widely used platform to perform the QSPR/QSAR studies online and share it with other users on the Web.

The ultimate goal of OCHEM is collecting all possible chemoinformatics tools within one simple, reliable and user-friendly resource. The OCHEM is free for web users and it is available online at http://www.ochem.eu.

SYBYL-X

SYBYL-X is a program that allows us to create molecular modelling from sequence through lead optimization. The program has capabilities for small molecule modelling and simulation, macromolecular modelling and simulation, chemo informatics and lead identification.Predictive models that cover all of the parameters relevant to successful clinical outcome are needed to design drugs which balance multiple criteria efficiently. Recent advances in SYBYL-X's 3D QSAR capabilities make modeling multiple biological endpoints quick and easy.

TopomerCoMFA, SYBYL-X's latest QSAR method, enables researchers to create 3D QSAR models in minutes instead of weeks, and to automatically generate 100's to 1000's of predictive QSAR models for chemogenomic studies by mining large databases of chemical and biological data.

Results

Physiochemical properties

The physicochemical properties as melting point, molecular formula of the compounds,

attached functional group (R), SMILES of the compounds (1a-1p) are summarized in Table 1, moreover, compound code has been given to every single compound, according to which chemical structure of each and every compounds have been described in figure 1.

Drug likeness calculation on the basis of Lipinski rule of five and bioactivity score

The drug likeness score was calculated by considering milogP(partition coefficient), molecular weight, number of heavy atoms, number of hydrogen donor, number of hydrogen acceptor and number of violation, number of rotatable bonds, volume. The drug likeness score and the calculated value of various parameters of the isolated compounds (1-17) are in Table 2.

The bioactivity scores of the isolated compounds (1a-1p) are compared with standard drug on the basis of GPCR ligand, ion channel modulator, nuclear receptor ligand, kinase inhibitor, protease inhibitor, enzyme inhibitor in Table 3. Calculated drug likeness of each compound and compared with specific activity of each compound and results were compared with standard drug. In case of activeness of organic compound, probability of bioactivity has to be (> 0), for moderate activeness it has to be (-5.0-0.0) and inactive after (< -5.0).

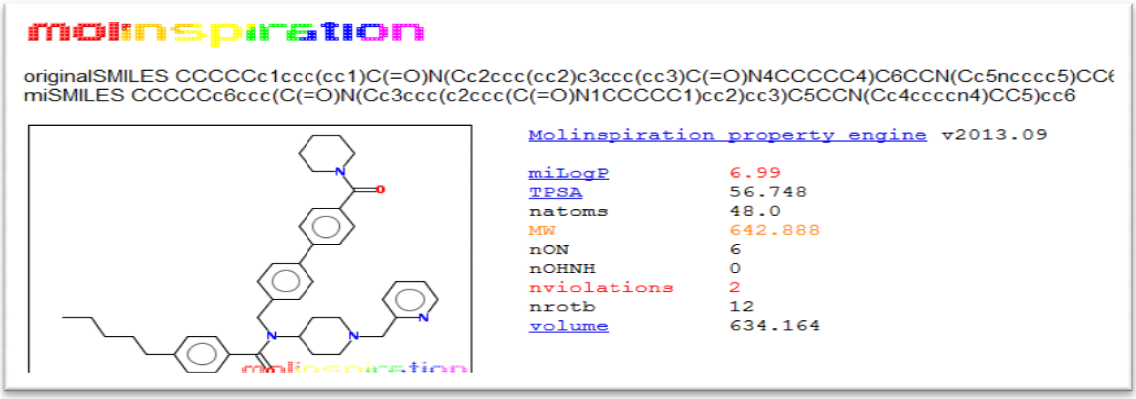


Figure 1: showinga1t drug (i.e. 1a in table1) through molinspiration, predicting properties like miLogP, TPSA, n atoms, MW and etc.

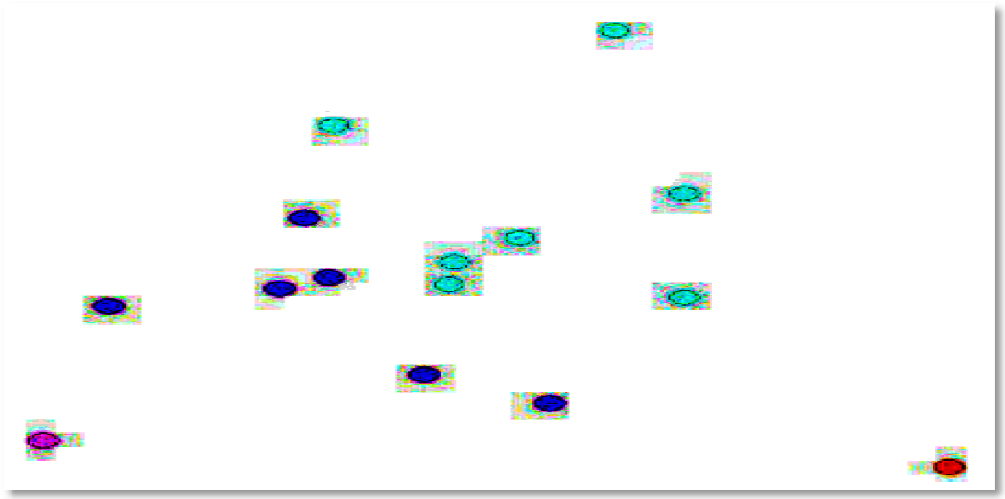
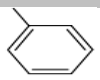
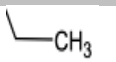
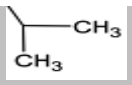
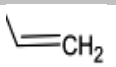
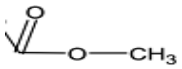
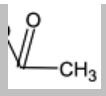
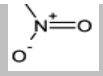


Figure 2: Structure activity relation map of drug and its analogues, where color similarity represents structural resemblance.

Table 1: Compound code, side chain, Molecular formula and m.p. of drugs and its analogues.

Compound code	R	m.p.	Molecular formula	SMILE
1a	-CH_3	117.4	$C_{42}H_{50}N_4O_2$	CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1b		138	$C_{47}H_{52}N_4O_2$	O=C(N1CCCCC1)c2ccc(cc2)c3ccc(cc3)CN(C5CCN(Cc4ncccc4)CC5)C(=O)c7ccc(CCCCc6ccccc6)cc7
1c		119	$C_{42}H_{47}F_3N_4O_2$	FC(F)(F)CCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1d		112	$C_{43}H_{52}N_4O_2$	CCCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1e		111.7	$C_{43}H_{50}N_4O_2$	C=CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1f		95.9	$C_{43}H_{50}N_4O_2$	C=CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1g		121	$C_{41}H_{47}ClN_4O_2$	ClCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1h		144	$C_{42}H_{47}N_5O_2$	N#CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6

1i		201	$C_{42}H_{48}N_4O_3$	O=CCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1j		130.9	$C_{43}H_{50}N_4O_4$	O=C(OC)CCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1k		118.4	$C_{43}H_{50}N_4O_3$	CC(=O)CCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1l		178	$C_{41}H_{47}FN_4O_2$	FCCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1m		159.8	$C_{41}H_{49}N_5O_2$	O=C(N1CCCCC1)c2ccc(cc2)c3ccc(cc3)CN(C5CCN(Cc4ncccc4)CC5)C(=O)c6ccc(CCCCN)cc6
1n		159.8	$C_{41}H_{50}N_5O_2$	O=C(N1CCCCC1)c2ccc(cc2)c3ccc(cc3)CN(C5CCN(Cc4ncccc4)CC5)C(=O)c6ccc(CCCC[NH3+])cc6
1o		142.8	$C_{41}H_{47}N_5O_4$	O=N(=O)CCCCc1ccc(cc1)C(=O)N(Cc2ccc(cc2)c3ccc(cc3)C(=O)N4CCCCC4)C6CCN(Cc5ncccc5)CC6
1p		126	$C_{41}H_{47}N_4O_3$	O=C(N1CCCCC1)c2ccc(cc2)c3ccc(cc3)CN(C5CCN(Cc4ncccc4)CC5)C(=O)c6ccc(CCCCO)cc6

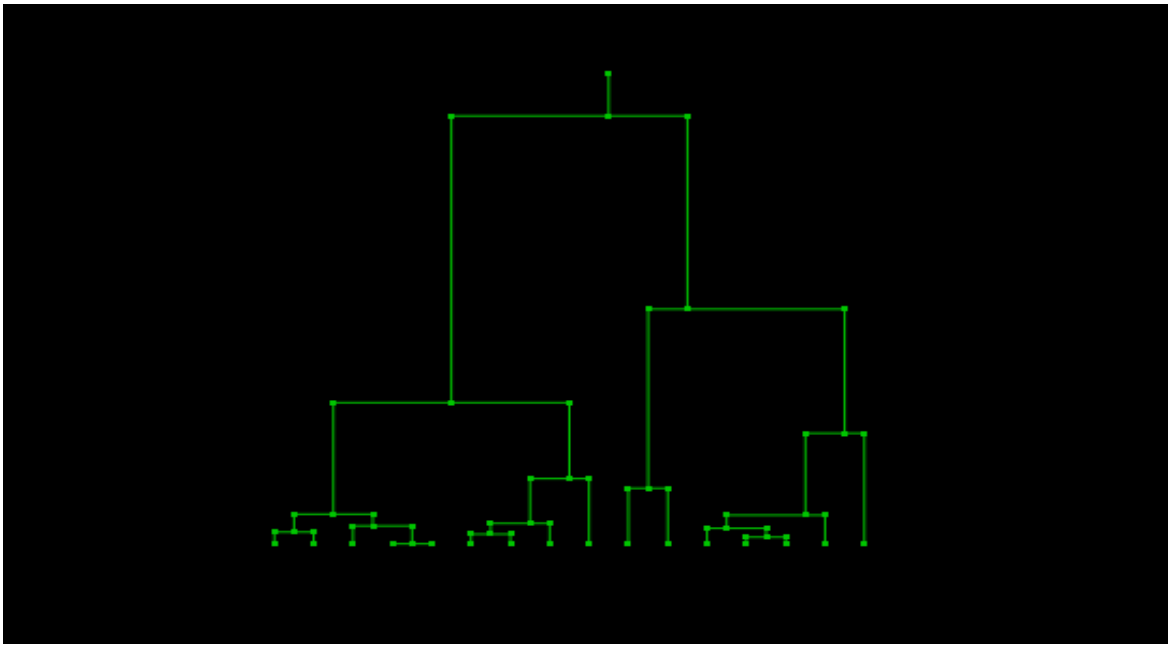


Figure 3: The dig. Shows hierarchical tree generation of analogues from lead compound.

Table 2: Drug likeness score for compound

Compound code	mi log P	TPSA	nAtoms	M.W.	nOH	nOHNH	nViolation	nrot b	Volume
1a	6.99	56.74	48	642	6	0	2	12	634
1b	7.64	56.74	53	704.9	6	0	2	13	689
1c	7.01	56.74	51	696.8	6	0	2	13	648.9
1d	7.5	56.74	49	656.9	6	0	2	13	650.9
1e	7.47	56.74	50	670.9	6	0	2	13	667.5
1f	6.97	56.74	49	654.8	6	0	3	13	645.3
1g	6.194	56.74	48	663	6	0	2	12	631
1h	5.28	80.54	49	656.8	7	0	2	12	634
1i	5.9	73.8	49	656.8	7	0	2	13	636.5
1j	5.6	83.05	51	686	8	0	2	14	662
1k	5.63	73.8	50	670.8	7	0	2	13	653
1l	5.8	56	48	646.8	6	0	2	12	622.5
1m	4.3	82.7	48	643.8	7	2	1	12	628
1n	2.2	84.3	48	644.8	7	3	1	12	629.69
1o	5.37	102.5	50	673.8	9	0	2	13	640.9
1p	4.95	76.97	48	644	7	1	1	12	625.6

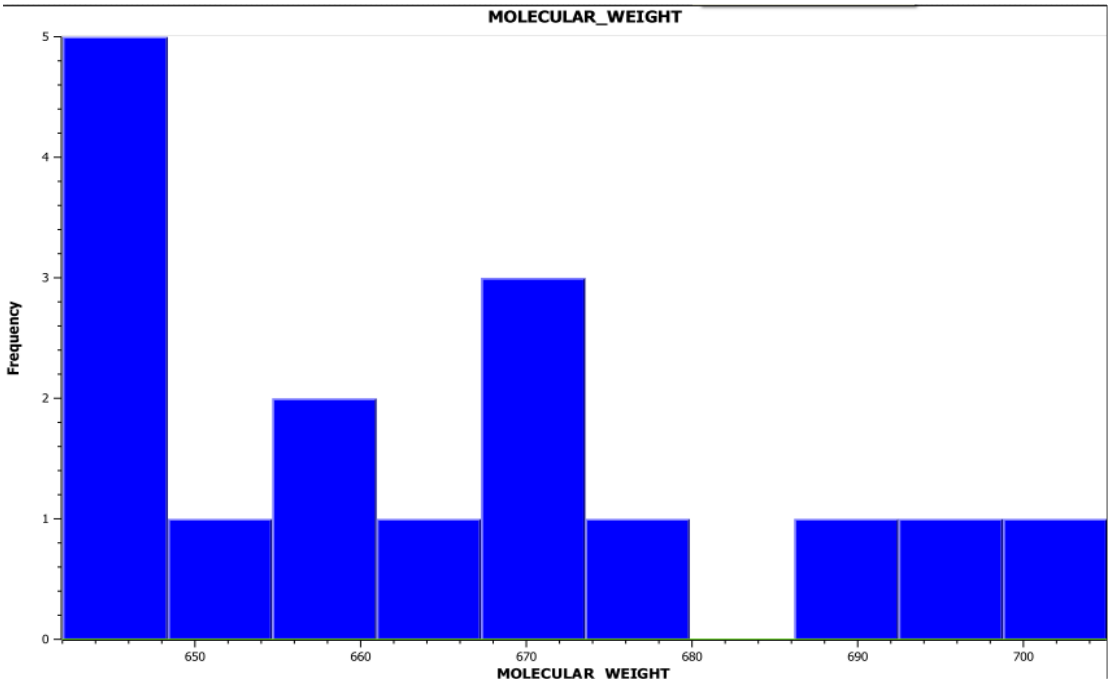


Figure 4: Comparative analysis of molecular weights of drug and its derivatives. Out of which the least value of mol. wt. has validated the Lipinski's rule.

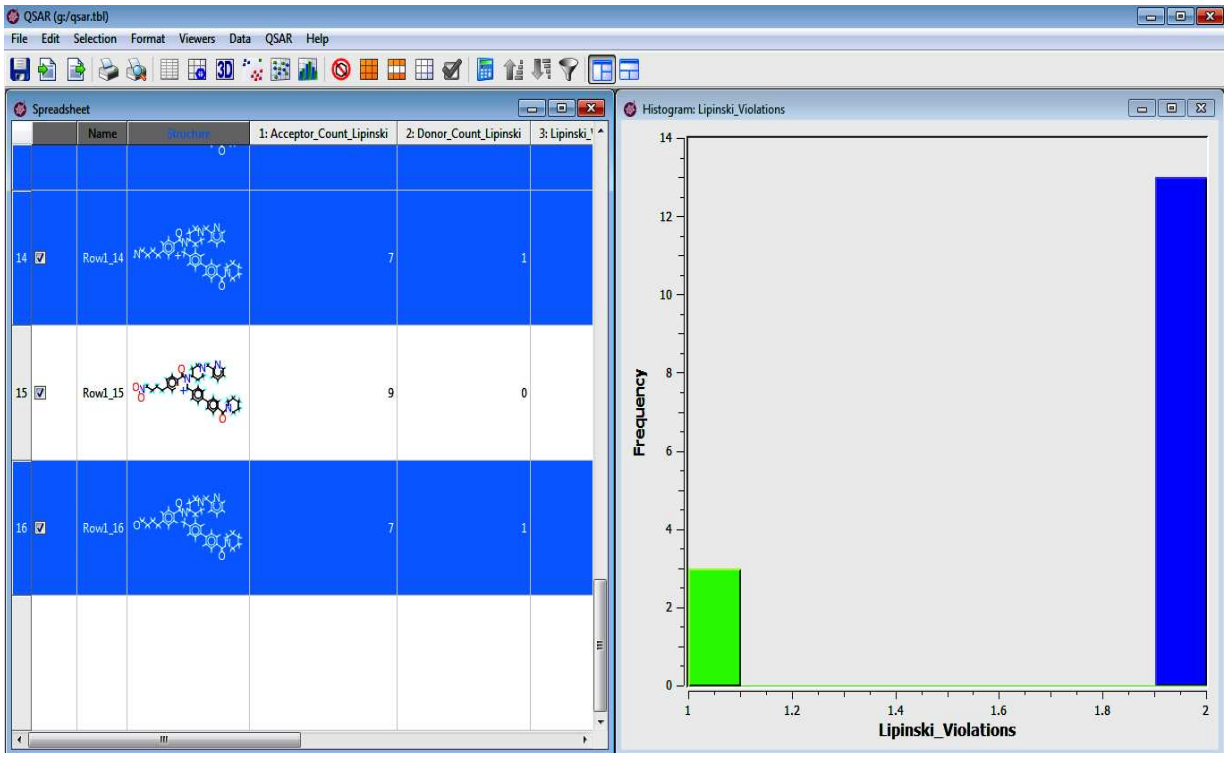


Figure 5: compounds violating lipinskis rule are under blue color and green color shows the highlighted analogues which are validating Lipinskis rule and they are represented in spread sheet.

Table 3:Bioactivity Score of the compound

Comp. code	GPCR Ligand	Ion Channel Modulator	Kinase Inhibitor	Nuclear Reactor Ligand	Protease Inhibitor	Enzyme Inhibitor
1a	-0.22	-1.06	-0.71	-0.85	-0.07	-0.61
1b	-0.88	-1.97	-1.52	-1.72	-0.55	-1.36
1c	-0.56	-1.55	-1.18	-1.28	- 0.28	-1.00
1d	-0.33	-1.23	-0.85	-1.00	-0.14	-0.74
1e	-0.45	-1.39	-1.02	-1.15	-0.19	-0.88
1f	-0.34	-1.22	-0.87	-0.97	-0.15	-0.73
1g	-0.30	-1.17	-0.75	-0.91	-0.13	-0.64

1h	-0.39	-1.32	-0.86	-1.09	-0.15	-0.77
1i	-0.30	-1.12	-0.83	-0.98	-0.05	-0.67
1j	-0.59	-1.59	-1.20	-1.33	-0.32	-1.03
1k	-0.50	-1.42	-1.13	-1.15	-0.26	-0.27
1l	-0.08	-0.98	-0.59	-0.70	0.06	-0.57
1m	-0.17	-0.99	-0.61	-0.87	-0.02	-0.56
1n	**-0.17**	**-0.99**	**-0.61**	**-0.82**	**-0.04**	**-0.58**
1o	-0.53	-1.48	-1.04	-1.21	-0.28	-0.86
1p	-0.21	-1.05	-0.66	-0.82	-0.04	-0.58

Table 4:Toxicity prediction of drugs and its analogues.

Comp .code	solubility	m.p.(2-D descriptors)	Environmental toxicity	AMES test	CYP3A4 test
1a	7.9	193	0.56	0.09	0.3
1b	8.29	217	0.56	0.12	0.38
1c	7.7	195	-0.05	0.08	0.39
1d	8.23	191	0.63	0.02	0.33
1e	8.32	177	0.55	-0.02	0.27
1f	8.11	152	0.3	0.23	0.34
1g	7.7	168	0.49	0.04	0.3
1h	7.29	217.7	0.13	0.2	0.27
1i	7.25	137.6	0.31	0.31	0.31
1j	7.16	193.9	0.16	0.05	0.12
1k	7.2	223	0.39	0.16	0.28
1l	6.95	155.2	0.3	0.32	0.31
1m	6.3	139.4	-0.08	-0.01	0.3
1n	**6.3**	**139.4**	**-0.08**	**-0.01**	**0.3**
1o	7.13	237.9	0.28	0.25	0.34
1p	6.9	227.6	0.17	0.13	0.23

DISCUSSION

These properties are calculated and discussed on the basis of Lipinski's rule and its component. The compound code 1n containing $–NH_3^+$ group fulfil Lipinski's rule and shows good drug likeness score (Table 2.) .Milog P of this compound was found below 5 that means this shows good permeability across cell membrane. TPSA below 160 Å2, *n* violations =1or <0 that means compound easily binds to receptor, only exception is molecular mass >500, *n* rotb< 5, No. hydrogen bond donors ≤ 5 (The sum of OHs and NHs), No. hydrogen bond acceptor≤ 10 (The sum of Os and Ns). Compound1a-1p was taken for further calculation of bioactivity score from Table 3 where compounds 1a-1p showed good bioactivity score with moderately activeness as the values are less than 0. Compound code (1n) showed good drug likeness score and bioactivity score, than other compounds and also showed least environmental toxicity i.e. -0.08.

CONCLUSION

With the increase in drug-resistant strains of the malaria parasite, its affects cause scourge to mankind. Though, information regarding availability of the genome sequence provides a wide range of novel targets for drug design along with a collaborative knowledge of Parasite Biology, Genomics and Combinatorial Chemistry have played into existence. The application of functional genomic tools with modern approaches such as structure-based drug design and combinatorial chemistry have lead to develop effectively new molecules against drug-resistant malarial strains and therefore generating analogue with code (1n) which has showed better results rather than the drug which has been available in the market

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REFERENCES

1. Luxemburger C, Kyaw Ley Thew, White NJ, Webster HK, Kyle DE, Maelankiri L, Chongsuphajaisiddhi T, Nosten F: The epidemiology of malaria in a Karen population on the western border of Thailand.Trans R Soc Trop Med Hyg 1996, 90:105-111.

2. Drakeley C, Sutherland C, Bousema JT, Sauerwein RW, Targett GA: The epidemiology ofPlasmodium falciparum gametocytes: weapons of mass dispersion.TrendsParasitol 2006, 22:424-430.

3. Ansell J, Hamilton KA, Pinder M, Walraven GE, Lindsay SW: Short-range attractiveness of pregnant women to Anopheles gambiaemosquitoes.Trans R Soc Trop Med Hyg 2002, 96:113-116.

4. Murphy MW, Dunton RF, Perich MJ, Rowley WA: Attraction of Anopheles (Diptera: culicidae) to volatile chemicals in Western Kenya.J Med Entomol 2001, 38:242-244.

5. Schneider P, Bousema JT, Gouagna LC, Otieno S, Vegte-Bolmer M, Omar SA, SauerweinRW: Submicroscopic Plasmodium falciparum gametocyte densities frequently result in mosquito infection.Am J Trop Med Hyg 2007, 76:470-474.

6. McKenzie FE, Jeffery GM, Collins WE: Plasmodium vivax blood-stage dynamics.JParasitol 2002, 88:521-535.

7. McKenzie FE, Jeffery GM, Collins WE: Plasmodium malariae blood-stage dynamics.JParasitol 2001, 87:626-637.

8. Collins WE, Jeffery GM: A retrospective examination of sporozoite-induced and trophozoite-induced infections with Plasmodium ovale : development of parasitologic and clinical immunity during primary infection.Am J Trop Med Hyg 2002, 66:492-502.

9. Pukrittayakamee S, Imwong M, Stepniewska K, Day NPJ, White NJ: The effects of different antimalarial drugs on gametocyte carriage in P. vivaxmalaria.Am J Trop Med Hyg 2008, 79:378-384.

10. Pukrittayakamee S, Chotivanich K, Chantra A, Clemens R, Looareesuwan S, White NJ:Activities of artesunate and primaquine against asexual- and sexual-stage parasites in falciparum malaria.Antimicrob Agents Chemother 2004, 48:1329-1334.

6. Pukrittayakamee S, Imwong M, Looareesuwan S, White NJ: Therapeutic responses to antimalarial and antibacterial drugs in vivaxmalaria.Acta Trop 2004, 89:351-356.

7. White NJ: Assessment of the pharmacodynamic properties of the antimalarial drugs in-vivo.Antimicrob Agents Chemother 1997, 41:1413-1422.

8. International Artemisinin Study Group: Artesunate combinations for treatment of malaria: meta- analysis.Lancet 2004, 363:9-17.

9. White NJ: Antimalarial drug resistance.JClin Invest 2004, 113:1084-92.

10. Govere JM, Durrheim DN, Mngomezulu NM, Barnes K, Sharp B: Infectivity ofPlasmodium falciparum gametocytes to Anopheles arabiensis after treatment with sulfadoxine-pyrimethamine.Trans R Soc Trop Med Hyg 2003, 97:707-708.

11. vonSeidlein L, Greenwood BM: Mass administrations of antimalarial drugs.TrendsParasitol 2003, 19:452-460.

12. Paddon CJ, Keasling Jay D: Semi-synthetic artimisinin : A model for the useof synthetic

Biology in pharmaceutical development. Nature reviews Microbiology 2014, 355-367.

13.Tu Y: The discovery of artimisinin and gifts from Chinese medicine.Nature Medicine 2011, 2471.

14.Salas PD, Herrmann C, Orvig C : Metalloantimalarials. Chemical reviews 2011, 3450-3492