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Prediction and Comparison of Drug likeliness properties of Primaquine and its structural analogues using *In-Silico* ADME and Toxicity Prediction Tools

Om prakash Tanwar[a], Rikta Saha[a], Akranth Marella[a], Md. Mumtaz Alam[a], Mymoona Akhter[a] and Virendra Kumar Dua*[b]

[a.]Drug Design and Medicinal Chemistry Lab, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Jamia Hamdard, New Delhi 110062 (India)
[b.]National Institute of Malaria Research (ICMR), Sector 8, Dwarka, DELHI-110077 (India)
*Corresponding author;Email:vkdua51@gmail.com

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ABSTRACT:
Five primaquine (PQ) analogues have been isolated by peroxydisulfate oxidation and were tested for antimalarial activity against *Plasmodium yoelli* infected mice. To develop them as promising antimalarial agents *in-silico* drug-likeness studies were carried out. The analogue 6-Methoxy-5,8-di-(4-amino-1-methylbutyl-amino)-quinoline [P1] was found to be promising antimalarial agent as it was found nontoxic in *in-silico* studies and obeys all drug-likeness rules.

The drug likeliness properties of primaquine analogues were determined using various *in-silico* tools like ADMETPredictor™, QikProp, Molinspiration and Osiris drug like property calculators. Each *in-silico* study supported the drugability of analogue P1. Result of *in-silico* studies shows that analogue P1 is safer and can be a drug of choice for radical cure of malaria infection.

Keywords: Malaria, Antimalarial, Primaquine (PQ), QikProp, *Plasmodium yoelli*, and Drug likeness.

1. INTRODUCTION

Malaria pandemic remains one of the most widespread infectious diseases, and stances a great challenge to world health. Malaria kills 1–2 million people each year and 300–500 million new clinical cases of malaria are reported annually. Approximately 40% of the world's population, mostly those living in the world's poorest countries, is at risk of this disease [1, 2]. The quinoline scaffold is prevalent in a variety of synthetic and natural antimalarial compounds. The quinolines are historically among the most important antimalarial drugs ever used. Primaquine (PQ), an 8-aminoquinolone has been used for decades to prevent relapses of infections by *P. vivax* and *P. ovale* (radical cure) and as a gametocidal agent to decrease the transmission of *P. falciparum* in malaria-endemic areas. PQ is useful to fights malaria in three ways e.g. causal

prophylaxis against all species of malaria, terminal prophylaxis for patients extensively exposed to *P. vivax* or *P. ovale*, and radical cure in individuals infected with *P. vivax* or *P. ovale*. [3,4]. PQ is active against both blood and tissue (liver) stages of malaria thus it can eliminate *P. vivax* and *P. falciparum* infections that are developing in the liver (causal prophylaxis) and prevent symptomatic or clinical infection.[4] However, its usefulness is limited by its unwanted effects, it metabolites like 5-hydroxyprimaquine and 6-methoxy-8-aminoquinoline are responsible for hemolytic anemia in humans, which is more dangerous with patients deficient in glucose-6-phosphate dehydrogenase [5]. Moreover, appearance of malaria *vivax* in sub-tropical and tempered areas reinforced the relevance and the need of finding more effective treatments for the disease [6]. Therefore, there is always a recognized need for investigations of new, less toxic drugs for the radical cure of relapsing malaria.

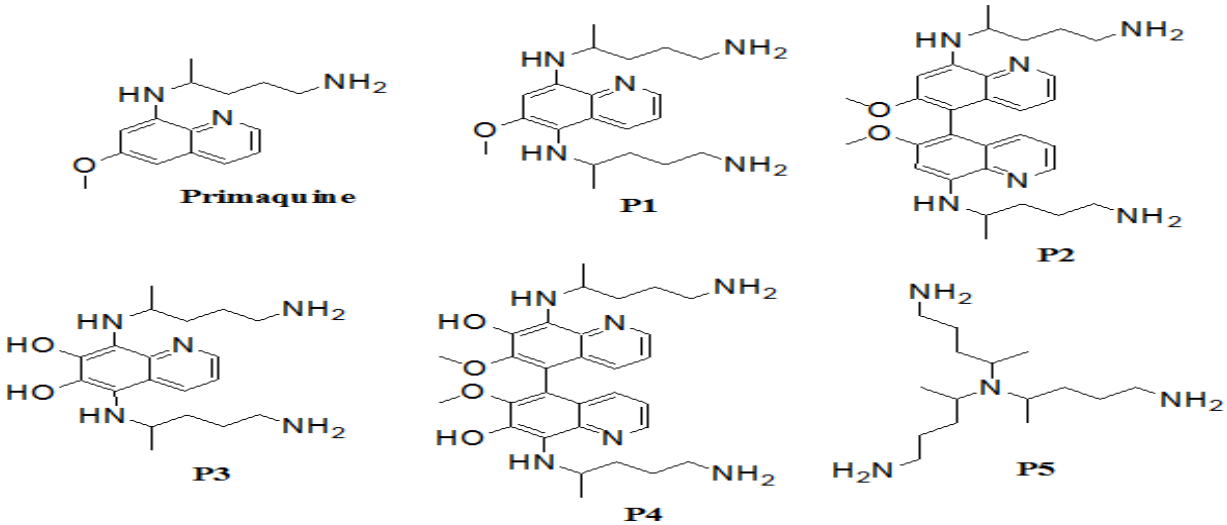
The current study is initiated with an objective to reinforce and explore PQ analogues as promising new antimalarial agents. We have isolated five oxidative products of PQ [7] **(Figure-1)**. Of the five PQ compounds isolated the analogue P1 was found to possess better gametocytocidal potency as compared to PQ, against *Plasmodium yoelli in-vivo* and *in-vitro*. The *in-vivo* gamatocidal concentration of analogue P1 has been found 0.026 (mg/well) and that of PQ is 0.115 (mg/well).

Figure-1 PQ and its structural analogue isolated from oxidation of primaquin

Drug-likeness may be defined as a model of various molecular properties and structure features which determine whether particular molecule can be a potential drug or not. Drug-likeness is a broad term used to define absorption distribution metabolism excretion and toxic (ADMET) properties of a drug molecule. Chris Lipinski of Pfizer in 1997, derived an easy rule ‘known as rule of thumb' for drug-likeness in molecules after surveying the world’s marketed drugs [8a]. The majority of drugs fail to reach into the market due to non-drug-likeness characters resulting in ADME-tox problems [8b-d]. *In-vivo* evaluation of ADMET properties of a molecule is very expensive and time consuming while the *in-silico* methods are very economical and fast. ADME–Tox evaluation into early stages of drug discovery is a cost effective and time savings approach therefore, one should go for *in-silico* ADME–Tox evaluations before *in-vivo* evaluations. The molecules which pass the multi-objective optimization criteria of ADME/Tox properties should be further evaluated [8e]. In this paper we tried to evaluate the *in-silico* properties of PQ analogues to develop them as potential antimalarial drugs of future.

2. MATERIAL AND METHODS

The peroxydisulfate oxidation products of PQ



have been isolated and tested them for their *in-vitro* schizontocidal and gametocytocidal activity at different concentrations by Dua et al. The study reported that the analogue with two side chains amino [4-amino-1-methylbutyl-amino (analogue P1)] has better gametocytocidal potential than PQ [7]. In order to develop analogue P1 as promising new antimalarial agent *In-silico* ADMET studies were carried out using ADMETPredictor™ from simulations plus, QikProp from Schrödinger, Molinspiration and Osiris drug like property calculator.

ADMET Predictor calculations:

In-silico properties of PQ and its analogues have been calculated by using ADMETPredictor™ version 5.0.0012 [9]. ADMET Predictor, designed to estimate certain ADMET (Absorption, Distribution, Metabolism, Elimination, and Toxicity) properties of drug-like chemicals from their molecular.

The ADMET properties of all six compounds including PQ were calculated at pH 7.4 using the default values of *ADMET Predictor*. The structures were drawn on MedChem Designer module of the same software.

Various ADMET properties were calculated for all compounds. **Physico-chemical and biopharmaceutical properties** include ionization constants (pKa), LogP, solubility, qualitative blood-brain barrier permeability, percent unbound to blood plasma proteins, and pharmacokinetic volume of distribution in human model. **Metabolic properties;** Metabolic properties calculation comprise of inhibition of HIV Integrase, Kinetic Michaelis-Menten constants of metabolism mediated by CYP 1A2, 2C19, 2C9, 2D6, and 3A4 enzymes in human, general and specific inhibition of metabolism mediated by CYP 1A2, 2C9, 2D6, and 3A4 enzymes in human and probability of Phase II metabolism mediated by UGT 1A1, 1A3, 1A4, 1A6, 1A9, 1A10, and 2B7 enzymes in human. **Toxicity properties**; calculation include maximum recommended therapeutic dose administered as an oral dose, assessment of estrogen receptor toxicity, assessment of allergenic skin sensitization, Cardiac (hERG) toxicity, lethal dose at 50% concentration, tumor induction dose, liver toxicity in relation to elevation in the levels of GGT, LDH, SGOT and SGPT enzymes and assessment of mutagenicity. Also, Number of toxic functional groups/reactive functionalities present in the structures was calculated by ADMET predictor. The properties calculates by ADMETPredictor are summarized in **Table 1.**

Molinspiration calculations [10, 11]:

Molinspiration was used to calculate logP, molecular polar surface area, molecular weight, molecular volume, number of rotatable bonds and bioactivity etc. Octanol/water partition coefficient (logP) is calculated as a sum of fragment based contributions and correction factors (**Table 2**). Total Molecular Polar Surface Area (TPSA) is calculated based on the methodology published by Ertl et al. [12] as a sum of fragment contributions [13] O-and N-centered polar fragments are considered. Other drug likeliness properties calculated like Number of nonhydrogen atoms (Natoms), molecular weight (MW), number of hydrogen-bond acceptors (nON), number of hydrogen-bond donors (nOHNH groups), number of rule of 5 violations (nviolations), number of rotatable bonds (nrotb) and molecular volume. The bioactivity data also comprise of GPCR ligand, ion channel modulator, kinase inhibitor, and nuclear receptor ligand

Osiris calculations [11]

Toxicity related risks (tumorogenicity, mutagenicity, irritation, and reproduction effectivity) and various physico-chemical properties (clogP, solubility, drug-likeness and drug score) can be calculated by the methodology developed by Osiris. The toxicity risk predictor locates fragments within a molecule, which indicate a potential toxicity risk.

Properties calculated by OSIRIS Property Explorer are summarized in in **Table 3**. The calculated logP value, aqueous solubility and

molecular weight of analogue P1 is under the acceptable criteria. The drug score combines drug-likeness, cLogP, logS, molecular weight and toxicity risks in one handy value than may be used to judge the compound's overall potential to qualify for a drug. This value is calculated by multiplying contributions of the individual properties with the first equation:

$$ds = \pi\left(\frac{1}{2} + \frac{1}{2}si\right).\pi ti$$

$$s = \frac{1}{1+e^{ap+b}}$$

ds is the drug score. si are the contributions calculated directly from of cLogP, logS, molweight and drug-likeness (pi) via the second equation which describes a spline curve. Parameters **a** and **b** are (1, -5), (1, 5), (0.012, -6) and (1, 0) for cLogP, logS, molweight and drug-likeness, respectively. ti are the contributions taken from the 4 toxicity risk types. The ti values are 1.0, 0.8 and 0.6 for no risk, medium risk and high risk, respectively [14]

QikProp calculations:

QikProp from Schrödinger is a quick, accurate, easy-to-use ADME prediction program designed by Professor William L. Jorgensen. QikProp predicts physically significant descriptors and pharmaceutically relevant properties of organic molecules, either individually or in batches. In addition to predicting molecular properties QikProp also provides ranges for comparing a particular molecule's properties with those of 95% of known drugs. [15].

QikProp also calculate number of parameters for the small molecules like functional group detection, molecular weight, LogP, CNS permeability, dipole moment of the molecule, number of hydrogen bonds donors and acceptors in the molecules, aqueous solubility, predicted IC_{50} value for blockage of HERG K+ channels, oral absorption, and skin permeability etc. In addition to this, it also calculates reactive functional groups accurately. The presence of these groups can lead to false positives in HTS assays and to decomposition, reactivity, or toxicity problems *in-vivo*. The following reactive functional groups which contribute to toxicity of the molecules: acyl halide, hetero-halogen bond, NAS substrate, alkyl halide, halogen alpha to W-group, heteroatom in 3-ring, activated cyclopropane, aluminum present (toxic), silicon present (toxic), hetero-hetero single bond, azo, diazo, or azide, acceptor carbonyl or derivative, anhydride or analog, unhindered ester, sulfonate or relative, phosphonate or relative, acetal or analog, carbonate, thiol—oxidation possible, and carbonyl in 3-ring. [15]

3. RESULTS AND DISCUSSION

In-silico ADMET property calculations are useful in predicting the drug likeliness properties of a new chemical entity as it helps to identify the potential lead compound with minimal unwanted effects. We have carried out *In-silico* ADMET studies on PQ and its analogues isolated form peroxydisulfate oxidation of PQ to develop them as potential antimalarial agent. The results of present study are very encouraging and indicate that the analogue P1 can be a good clinical compound.

Properties calculated by ADMET Predictor shows that PQ and P1 have similar type of physico-chemical and biopharmaceutical properties. Blood brain permeability for PQ and P1 are low and *p*Ka of P1 is greater than PQ. The log P value of analogue P1 being 2.64 making it less permeable to brain as indicated by low blood brain barrier permeability. The concentration of unbound drug in blood plasma protein for analogue P1 is more, suggesting that the amount of free drug is more which means that low dose shall be required for antimalarial action.

Inhibition of cytochrome enzymes is responsible for drug interaction. Both PQ and P1 were found to inhibit most of the cytochrome family accept CYP2C9 and CYP3A4. Glucuronidation by various UDP glucuronosyltransferase 1A and 2B

family does not modify PQ and P1 structures except 1A6 which metabolize PQ.

Toxic properties of PQ and analogue P1 are somewhat different as the toxic dose for analogue P1 (1026.94 mg/kg) which is greater than toxic dose of PQ (561.14 mg/kg) suggests that P1 is more tolerable than PQ. However analogue P1 is more toxic than PQ for LC_{50} for fathead minnow lethal toxicity after 96 hours of exposure. The higher dose of toxic effect shows that analogue P1 has higher therapeutic window than PQ which is a good sign for a molecule to be converted to a drug candidate. Elevation of various enzymes are responsible for multiple organ toxicities like liver kidney etc. results show that PQ and P1 do not elevate the level of Alkaline Phosphatase enzyme, GGT enzyme, LDH enzyme, SGOT enzyme, SGPT enzyme. Thus it is supposed that analogue P1 can be well tolerated and is safe as PQ. Mutagenic potential of PQ and analogue P1 is also similar and both were found to be toxic only for TA97 and/or TA1837 strains of S. Typhimurium.

ADMET Predictor calculates the ADMET_Risk for the molecule which is an indicator of oral bioavailability and follows the Lipinski's rule of five. PQ and analogue P1 show similar potential for oral absorption. This means that the analogue P1 will be absorbed orally in similar manner as that of PQ. It is interesting to note here that both PQ and analogue P1 are devoid of different reactive functionalities.

Molinspiration calculation:

For PQ and P1 the calculated log P values were below 5 which is an indication for good water solubility. The polar surface area (PSA) is calculated from number of oxygen and nitrogen atoms and by hydrogen atoms attached to them. Thus, the PSA imitates the hydrogen bonding characteristic for a compound. PSA has been shown to be a very good descriptor characterizing drug absorption, including intestinal absorption, bioavailability, Caco-2 permeability and blood-brain barrier penetration. Lipophilicity (log P value) and polar surface area (PSA) values are two important properties for the prediction of per oral bioavailability of drug molecules [16,17]. Molecules with PSA values of 140Å or greater are supposed to exhibit poor intestinal absorption. [17] P1 has one violation from the drug likeliness rule of 5 however, one violation is acceptable for oral bioavailability [8]. Analogue P1 has similar bioactivity values to that of PQ therefore it can be assumes that P1 is expected to have similar activity. Values of other Molinspiration properties like Natoms, MW, nON, nOHNH, nrotb and molecular volume are under the acceptable limits.

Osiris calculation:

OSIRIS property calculator is used mainly in drug discovery for knowing the mutagenic and tumorogenic potentials of new chemical entities. Results of OSIRIS property calculator indicate that the analogue P1 has no mutagenic and tumorogenic potentials however, PQ is showing mutagenicity. Mutagenic potential of PQ has been established by various publications [18-20]. All the studies showed that PQ has mutagenic effect in TA97 strain of *Salmonella Typhimurium* with and without S9 mix. This also has been proved with the help of ADMET predictor.

The overall drug score (DS) for PQ and analogue P1 have been compared. The drug score for analogue P1 0.7 which is more than the PQ 0.4 suggesting that analogue P1 can be developed as potential antimalarial drug. Both compounds have no effect on reproductive system. Other drugs like properties are under the acceptable limits

Quickprop properties:

QikProp bases its predictions on the full 3D molecular structure; unlike fragment-based approaches, QikProp can provide equally accurate results in predicting properties for molecules with novel scaffolds as for analogs of well-known drugs. The results show that P1 has poor central nervous system activity which in agreement with the ADMET calculation of low permeability. Dipole moment play a role in binding a lead compound to a binding site and the value of computed dipole moment for P1 is greater than

PQ. So it is assumed that bind due to its greater binding to the active site P1 is more potent than PQ. H bond donor, acceptor and predicted octanol/water partition coefficient are under the acceptable limits for both PQ and P1. The value of predicted skin permeability of P1 is lesser than PQ so it is supposed to less skin permeable. Predicted percent human oral absorption of P1 is less than PQ so it may have poor oral absorption. Nevertheless, the tetraphosphate salt of P1 can overcome this problem and can be 100 % bioavailable. Violations from Lipinski's rule of five are similar to that of molinspiration calculations.

4. CONCLUSION

The present study establishes and compares the drug like behavior of P1 analogue of PQ. The study shows that analogue P1 follow the Lipinski's rule. The study has been validated with different softwares and platforms for drug discovery tools. P1 and Pq are similar in ADME properties and while former is showing lower *in-silico* toxicities than latter. The *in-vivo* Gamatocidal concentration of analogue P1 is better than PQ. In conclusion it can be stated that the analogue P1 can be a potential drug candidate for total eradication of malaria parasite.

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Table 1 Properties of PQ and its analogues calculated by ADMETPredictor

PROPERTIES	PQ	P1	P2	P3	P4	P5
Physico-chemical and Biopharmaceutical Module						
pKa	9.79	10.14	10.05	9.54	9.03	10.97
octanol-water partition coefficient (LogP)	2.8	2.64	4.92	1.64	3.59	0.04
Permeability through rabbit cornea [cm/s x 10^7]	162.09	154.42	167.18	99.36	108.07	121.98
Qualitative assessment of blood-brain barrier permeability	Low	Low	Low	Low	Low	Low
Percent unbound to blood plasma proteins	42.44	48.89	14.25	62.18	15.52	79.3
Pharmacokinetic volume of distribution in human	2.69	3.34	5.27	3.4	6.37	2.11
Blood-to-plasma concentration ratio in human	0.95	0.86	0.75	0.95	0.71	1.16
Metabolic properties						
Qualitative model of a general inhibition of the CYP 1A2 enzyme	Inhibitor	Inhibitor	Inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor
Qualitative model of a general inhibition of the CYP 2C9 enzyme	Non-inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor	Inhibitor	Non-inhibitor

Qualitative model of a general inhibition of the CYP 2D6 enzyme	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
Qualitative model of a general inhibition of the CYP 3A4 enzyme	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor	Inhibitor
Qualitative model of a specific inhibition of the CYP 3A4-mediated metabolism of midazolam and testosterone	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor	Non-inhibitor
Qualitative model of a glucuronidation by the UDP glucuronosyl transferase 1A3 enzyme, UDP glucuronosyl transferase 1A4 enzyme, UDP glucuronosyl transferase 1A10 enzyme and UDP glucuronosyl transferase 2B7 enzyme	No	No	No	No	No	No
Qualitative model of a glucuronidation by the UDP glucuronosyltransferase 1A6 enzyme	Yes	No	No	No	No	No
Qualitative model of a glucuronidation by the UDP glucuronosyltransferase 1A1 enzyme	No	No	Yes	No	No	No
Qualitative model of a glucuronidation by the UDP glucuronosyltransferase 1A9 enzyme	No	No	Yes	No	No	No
Toxicity properties						
Qualitative assessment of the Maximum Recommended Therapeutic Dose administered as an oral dose [mg/kg/day]	<3.16	<3.16	<3.16	<3.16	<3.16	<3.16
Qualitative assessment of estrogen receptor toxicity in rats	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Toxic	Nontoxic
Skin sensitization in mice	Yes	Yes	Yes	Yes	Yes	Yes
LC_{50} for fathead minnow lethal toxicity after 96 hours of exposure [mg/L]	8.48	0.98	0.01	0.54	0.03	35.54
$pIGC_{50}$ for Tetrahymena pyriformis growth inhibition toxicity [mmol/L]	0.959	1.10	1.25	1.25	1.4	0.31
IC_{50} as a measure of affinity towards hERG K+ channel and potential for cardiac toxicity [mol/L]	5.24	5.71	6.02	5.02	5.24	5.23
LD_{50} for lethal rat acute toxicity [mg/kg]	561.14	1026.94	1176.9	1252.84	1501.95	1455.96
TD_{50} which is defined as the oral dose of a compound required to induce tumors in 50 percent of a rat population after exposure over a standard lifetime	34.1	135.17	64.58	614.88	922.81	374.49
Human liver adverse effect as the likelihood of causing elevation in the levels of Alkaline Phosphatase enzyme, GGT enzyme, LDH enzyme, SGOT enzyme, SGPT enzyme, Qualitative assessment of mutagenicity of the pure compound in TA98 strain of S. Typhimurium, TA100 strain of S. Typhimurium, TA1535 strain of S. Typhimurium, TA102 strain of S.	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic	Nontoxic

Typhimurium and/or WP2 uvrA strain of E. coli Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA98 strain of S. Typhimurium, TA100 strain of S. Typhimurium, TA102 strain of S. Typhimurium and/or WP2 uvrA strain of E. coli, TA1535 strain of S. Typhimurium						
Qualitative assessment of mutagenicity of the pure compound in TA97 and/or TA1537 strains of S. Typhimurium	Toxic	Toxic	Toxic	Toxic	Toxic	Nontoxic
Qualitative assessment of mutagenicity of the compound and its microsomal rat liver metabolites in TA97 and/or TA1537 strains of S. Typhimurium	Toxic	Toxic	Toxic	Toxic	Toxic	Nontoxic
Other properties						
ADMET_Risk (computational filter for oral absorption in human analogous to the "Rule of Five")	1	1	2	1	3	1
Number of rings	2	2	4	2	4	0
Number of Hydrogen Bond Donors	2	4	4	6	6	3
Number of Hydrogen Bond Acceptors	4	6	8	7	10	4
Number of reactive/unwanted functional groups*	0	0	0	0	0	0

- Number of reactive/unwanted functional groups: Thiol groups, Thiocarbonyl groups, Sulfide groups, Sulfonium groups, Phosphine groups, Hydroxyamine groups, Oxime groups, Nitroso groups, N-oxide groups, Hydrazine groups, Hydrazone groups, Azo groups, Diazo groups, Thioamine groups, Disulfide groups, Sulfoxide groups, Thioxime groups, Nitro groups, Nitrite groups, Nitrosamine groups, Azoxy groups, Azide groups, Sulfone groups, Sulfinate groups, Phosphorate groups, Triazo groups, Oxadiazo groups, Thiadiazo groups, Triazene groups, Nitrate groups, N-connected nitro groups, Sulfonate groups, Sulfite groups, Sulfonamide groups, Primary Sulfonamide groups, Phosphonate groups, Thiolophosphonate groups, Phosphite groups, Tetrazo groups, Oxadiazooxide groups, N-nitrosohydroxylamine groups, Sulfamide groups, Sulfate groups, Thiosulfate groups, Phosphate groups, ThioloPhosphate O=P(X)(X)X groups (X = S,O), ThioPhosphate groups, ThioThioloPhosphate S=P(X)(X)X groups (X = S,O), Phosphamide O=P(X)(X)X groups (X = N,O), Diphosphate groups, Triphosphate groups, Aliphatic Carboxyl groups, Aromatic Carboxyl groups, Ester groups, Amide groups, Thioamide groups, Amidine groups, Isocyanate groups, Thiocyanate groups, Isothiocyanate groups, Urea groups, Carbamate groups, Guanidine groups, Imide groups

Table 2 Drug-likeness properties and bioactivity properties calculations for PQ and P1-P5 analogues using molinspiration web based tool.

Drug-likeness properties						
Properties	**PQ**	**P1**	**P2**	**P3**	**P4**	**P5**
miLogP	2.104	2.535	4.527	1.968	3.944	-0.631

TPSA	60.18	98.23	120.35	129.45	160.81	81.31
Natoms	19	26	38	26	40	19
MW	259.35	359.52	516.69	361.49	548.69	272.48
nON	4	6	8	7	10	4
nOHNH	3	6	6	8	8	6
nviolations	0	1	2	1	2	1
Nrotb	6	11	13	10	13	12
Volume	256.91	364.40	501.19	354.89	517.22	310.67
Bioactivity results						
GPCR ligand	0.18	0.22	0.06	0.12	-0.08	0.41
Ion channel modulator	-0.23	-0.18	-0.42	-0.09	-0.67	0.25
Kinase inhibitor	-0.21	-0.15	-0.28	-0.18	-0.38	-0.12
Nuclear receptor ligand	-1.21	-0.81	-0.55	-0.54	-0.49	-0.49

Table3: Toxicity related and physico-chemical properties calculated by OSIRIS Property calculator

Properties	**PQ**	**P1**	**P2**	**P3**	**P4**	**P5**
Mutagenic	yes	**No**	no	No	no	no
Tumorogenicity	no	**No**	no	No	no	no
Irritation	no	**No**	no	No	no	no
Reproduction Effectivity	no	**No**	no	No	no	no
clogP	2.04	**1.88**	3.77	1.39	3.17	1.02
Solubility	-3.19	**-4.03**	-6.84	-3.42	-6.25	-2.17
Molweight	259.0	**359.0**	516	361.0	548.0	272.0
Drug-likeness	1.37	**1.31**	1.31	1.19	1.26	0.77
Drug Score	0.48	**0.7**	0.33	0.73	0.34	0.79

Table 4 Properties of PQ and its analogues calculated by QikProp

Properties	**Range or recommended values**	**PQ**	**P1**	**P2**	**P3**	**P4**	**P5**
Predicted central nervous system activity on	a –2 (inactive) to +2 (active) scale.	0	-1	-2	-2	-2	-2
Molecular weight of the molecule.	(130.0 – 725.0)	259.35	359.514	516.685	361.486	548.684	272.476
Computed dipole moment of the molecule.	(1.0 – 12.5)	1.508	2.423	2.848	3.284	3.279	1.777
Estimated number of hydrogen bonds donors	(0.0 – 6.0)	3	6	6	8	8	6
Estimated number of hydrogen bonds acceptors	(2.0 – 20.0)	3.75	5.75	7.5	6.5	9	5
Predicted octanol/water partition coefficient.	(–2.0 – 6.5)	2.141	2.006	3.888	0.485	2.46	-0.505
Predicted aqueous solubility, log S.	(–6.5 – 0.5)	-2.504	-1.798	-4.123	-0.548	-2.712	2

Predicted skin permeability	(log *K*p. –8.0 to –1.0)	-3.75	-6.464	-6.04	-7.87	-7.218	-7.762
Predicted qualitative human oral absorption	1, 2, or 3 for low, medium, or high.	3	1	1	1	1	1
Predicted Percent human oral absorption	on 0 to 100% scale	86.122	51.654	48.778	29.635	29.158	17.41
Number of nitrogen and oxygen atoms.	2 – 15	4	6	8	7	10	4
Violations from Lipinski's rule of five	Maximum is 4	0	1	2	1	2	1