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Original Research Article

Pharmacophore based 3d QSAR studies of some quinoline derivatives as antimalarial agents

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Abstract

Malaria caused by Plasmodium affects millions people worldwide. Plasmodium consumes hemoglobin during its intraerythrocytic stage leaving toxic heme. Parasite detoxifies free heme through formation of hemozoin (β-hematin) pigment. Proteolysis of hemoglobin and formation of hemozoin are two main targets for antimalarial drugs. Quinoline anti-marital drugs and analogs were studied as inhibitors of β-hematin formation. A computer assisted methodology was applied for the construction of pharmacophore and for building 3D QSAR model of novel Isocryptolepine derivatives as a β-hematin Inhibitors. 3D QSAR model of Isocryptolepine derivative based on common featured pharmacophore was developed using BIOVIA Discovery Studio software. A series of 49 analogues of Isocryptolepine derivatives as anti-plasmodial activity against *P. falciparum* (IC50) was selected and used to develop the Pharmacophore based 3D QSAR model. The best pharmacophore model (Hypo1) exhibits all the important chemical features required for β-hematin inhibitors. The correlation coefficient, root mean square deviation (RMSD) and cost difference were 0.864099, 0.948278 1.0719 and 24.272, respectively, suggesting a good predictive ability of the model (Hypo1) among all the ten pharmacophore models that were analyzed.

Keywords: Pharmacophore based 3D QSAR, antimalarial agent, BIOVIA discovery studio, isocryptolepine derivatives

Introduction

About half of the world's population is at risk from the parasitic infectious illness malaria. When a female Anopheles mosquito consumes blood, it spreads this parasite illness to humans. In the subtropical areas, pregnant women and small children are more vulnerable to contracting malaria. There were 214 million infections recorded in 2015, with 438,000 fatalities, 90% of which occurred in the African continent [1-4]. Plasmodium falciparum and Plasmodium vivax account for the bulk of fatalities from malaria, which is brought on by five parasites of the species Plasmodium [1, 4-6]. There are now effective malaria medications available, including quinine, quinoline, mefloquine, and artemisinin. The preferred medication for treating malaria brought on by Plasmodium falciparum was quinoline. The parasite has, however, become resistant to the medication. Different strategies, including combination treatment, have been studied to overcome medication resistance. Combination treatment, which combines two or more antimalarial drugs, was predicted to be the most

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effective way to combat drug resistance to antimalarials more than ten years ago. It has also been used to create molecules with improved efficacy against the majority of malaria stages by combining two separate pharmacophoric properties from existing and novel medications [1, 7]. Antimalarial medications with 4-aminoquinoline scaffolds are excellent starting materials for hybridising with other antimalarials and metal-based compounds [7]. Due to the rarity of drug-drug side effects, hybrid molecules are more efficacious than multi-component medications [8]. The creation of hybrid compounds including derivatives of 4-and 8-aminoquinolines will be the main focus of this review's *in vitro* and *in vivo* experiments [1].
Recognition process between ligand and model is based on spatial distribution of certain structural features of active site being complimentary to those of the interacting ligands and the features common to the ligands would provide the information about the active site. A pharmacophore mapping is the essential step towards understanding of receptor ligand recognition process and is established as one of the successful computational tools in rational drug design [9, 10]. This involves the identification of a three-dimensional arrangement of functional groups which a molecule must possess to be recognized by the receptor. Further, a model is generated by finding chemically important functional groups that are common to the molecules that bind. Pharmacophore can be derived by direct analysis of the structure of known ligand either in the most stable conformer or in the form observed when complexed with the target protein.

Material and Methods

Pharmacophore

Pharmacophore is an analog based method. This word is coined by Paul Ehrlich in the early 1900s referring to a molecular frame work that carries the essential features (phoros) responsible for a drug's (pharmacon) biological activity. In 1977 Peter Gund redefined as "a set of structural features in a molecule that is recognized at a receptor site and is responsible for that molecule's biological activity". A pharmacophore can also be generated from the receptor structures.
In dynamic pharmacophore model based on molecular dynamics trajectories takes care of the binding site dynamics. These models can be used for optimizing known ligands or for screening databases to find potential novel leads suitable for further development 19. Virtual screening: Virtual screening as "automatically evaluating very large libraries of compounds" using computer programs. The aim of virtual screening is to identify molecules of novel chemical structure that bind to the macromolecular target of interest. Virtual screening is very important part of drug design and drug discovery research [13, 14].

Quantitative Structure Activity Relationship (QSAR): Quantitative structure activity relationships (qsar) represent an attempt to correlate structural or property descriptors of compounds with activities. Sufficient number of ligands active against target of intrest should be available to develop the structure activity relationships. The equations that are parameterized for one target do not apply to another.

Alignment of Molecules

For 3D QSAR study all the molecules in data set must have relative conformation that can be aligned over their common scaffold. All the molecules in the data set bear a common basic scaffold i.e. isocriptolepine as quinoline derivative (figure-1). Alignment can be done using pharmacophore based molecular alignment protocols for the present study.

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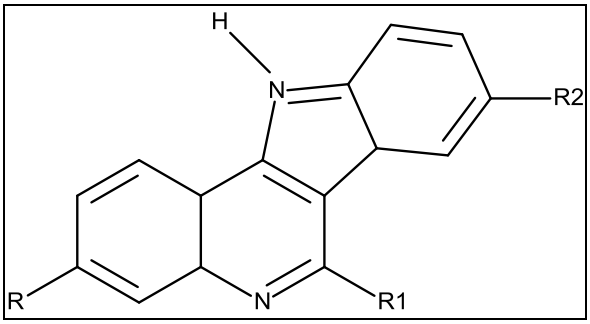

Fig 1: Basic Structure of Isocriptolepine as B-Hematin Inhibitor

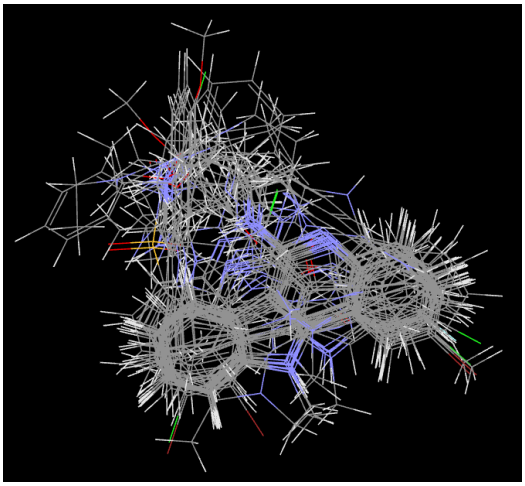

Fig 2: Alignment of the All Molecules with Common Pharmacophore

Results and Discussion

pharmacophore, common feature pharmacophore method with 5 high energy molecules was selected from 30 β-hematin inhibitors. Then 3D-QSAR Pharmacophore-Generation ten 3D-QSAR pharmacophore were generated based on the 30 compounds of literature (N. Wang *et al*.) by HYPOGEN-algorithm using Discovery Studio 2021.

Pharmacophore

Table 1: Following 6 features were found in feature mapping

Sr. No.	Pharmacophore Features	Showed as colour
1.	Hydrogen Bond Acceptor	Green
2.	Hydrogen Bond Donor	Magenta
3.	Hydrophobic Feature	Cyan
4.	Negative Ionizable Feature	Blue
5.	Positive Ionizable Feature	Red
6.	Aromatic Ring	Orange

Generation of Pharmacophore Models

- First of all, auto pharmacophore was generated. Auto pharmacophore generated all the features associated with all the structures superimposed (i.e., Hydrogen Bond Acceptor, Hydrophobic, Positive Ionizable, Negative Ionizable and Ring Aromatic).
- *Common feature pharmacophore* had been generated after auto pharmacophore. Top ranked Common feature pharmacophore showed four features i.e., Hydrogen Bond Acceptor, Hydrophobic, Positive Ionizable, Hydrophobic Aliphatic.
- *3D QSAR pharmacophore* was generated after common feature pharmacophore generation. 3D QSAR pharmacophore showed two features i.e., Hydrogen Bond Acceptor, Hydrophobic.

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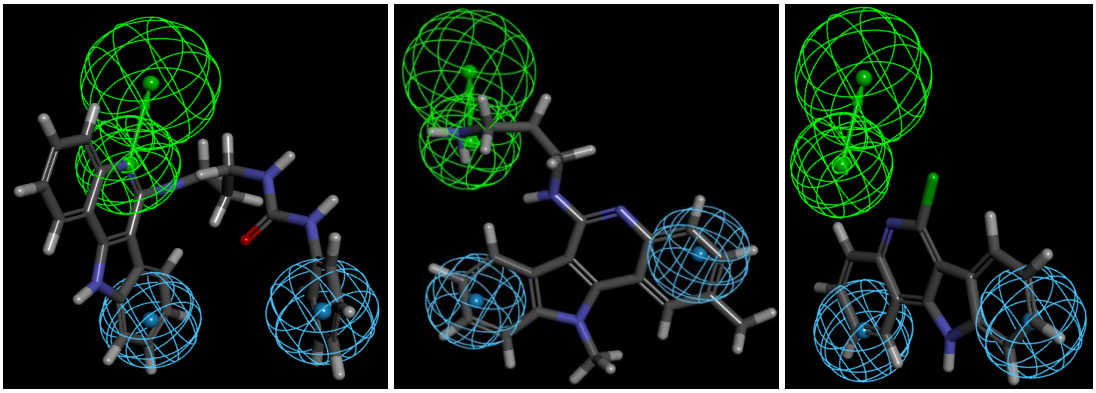
- *Auto Pharmacophore Generation* Auto Pharmacophore model for a set of 30 β-hematin inhibitors (Dataset) was generated by ligand-based pharmacophore generation process.
- In pharmacophore, common feature pharmacophore method with 5 high energy molecules was selected from 30 β-hematin inhibitors. Then 3D-QSAR Pharmacophore-Generation ten 3D-QSAR pharmacophore were generated based on the 30 compounds of literature (N. Wang *et al*.) by HYPOGEN-algorithm using Discovery Studio2021. Among ten hypothesis produced, Hypothesis 1 was carefully chosen on the basis of Cost Function Analysis and Corelation Coefficient. Hypothesis 1 exhibited highest correlation-coefficient value of 0.864099 and difference between hypothesis 1 total cost and null hypothesis cost was 129.847. The best hypothesis, hypothesis-1, have four-point features, two hydrogen bond-acceptor, two hydrophobic.
- The auto pharmacophore method. Pharmacophore 1 showed 3 features i.e., Hydrogen bond-donner, HBD, HYDROPHOB Aromatic, HYDROPHOBIC. From the dataset 3 compounds which are most active (PR-22), moderate active (PR-20) and least active (PR-1) are shown in figure below.



(A) **(B)** **(C)**

Fig 3: Pharmacophore mapping of the most active, moderate active, less active compounds in the training set. (a) hypo 1 mapped on to the most active compound (pr-22), (b) hypo 1 mapped on to the moderate active compound (pr-20), (c) hypo 1 mapped on to the least active compound (pn-1)

Table 1: Hiphop Exporting Hypotheses from Hiphop Algorithm

SL. No.	Features	Rank	Direct Hit	Partial Hit	Max. FIT
01	YYH	220.970	11111	00000	3
02	YYH	213.343	11111	00000	3
03	YZH	213.305	11111	00000	3
04	YZH	213.305	11111	00000	3
05	YZH	208.725	11111	00000	3
06	YZA	207.305	11111	00000	3
07	YZH	207.017	11111	00000	3
08	YYH	202.033	11111	00000	3
09	YYA	199.769	11111	00000	3
10	YZA	196.904	11111	00000	3

Table 2: Hypogen Exporting Hypotheses from Hypogen Algorithm

Hypothesis number	Total cost	Cost difference	Error	RMS	Correlation (r)	Features
1.	129.847	24.272	-2.2000	0.948278	0.864099	HBD, HBD, Hydrophob Aromatic, Hydrophobic
2.	130.816	23.303	1.5000	0.905906	0.883767	HBA_lipid, HBD, HBD
3.	131.221	22.898	1.4000	0.997028	0.848405	HBD, HBD, Hydrophob

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						Aromatic, Hydrophobic
4.	131.326	22.793	1.1000	1.00061	0.847214	HBD, HBD, Hydrophobic, Hydrophobic
5.	131.329	22.790	1.1000	1.00072	0.847175	HBD, HBD, Hydrophob Aromatic, Hydrophobic
6.	131.752	22.367	-1.1000	1.01462	0.842506	HBD, HBD, Hydrophobic, Hydrophobic
7.	132.009	22.110	-3.5000	0.986321	0.855013	HBD, HBD, Hydrophob Aromatic, Hydrophobic
8.	132.106	22.013	-3.3000	0.999838	0.849556	HBD, HBD, Hydrophob Aromat, Hydrophob Aromatic, Hydrophobic
9.	132.231	21.888	3.5000	1.02867	0.837758	HBD, HBD, Hydrophobic
10.	132.302	21.817	-6.4000	1.02848	0.838008	HBD, HBD, Hydrophob Aromatic, Hydrophobic

[a]The cost difference between null cost and total cost; null cost is 258.686 bits; fixed cost is 77.5618 bits; configuration cost is 15.4729 bits.
[b]Abbreviation used for features: HBA: H-bond acceptor; HBD: H-bond donor; HyAr: hydrophobic aromatic.

Table 3: It Shows the Best Hypothesis of Hypogen Training Set

Name	Fit	Est	Act	Err	Status	Mapping
PR22	7.9800	1.1000	2.4	-2.2000	active	[22 18 7 27]
PR17	6.7400	19	6.2	3.1000	active	[19 23 8 11]
PR15	6.1500	75	8.1	9.300	active	[1*11 20]
PR8	6.9900	11	9.4	1.100	active	[26 10 21 32]
PR31	7.0400	9.8000	11	-1.1000	active	[25 5 21 32]
PR4	6.7100	21	13	1.6000	active	[25 9 15 2]
PR2	6.1900	68	14	5	active	[24 *18 6]
PR5	6.9100	13	15	-1.1000	active	[26 4 10 21]
PR27	6.6100	26	17	1.5000	active	[24 20 19 30]
PR12	6.9700	11	19	-1.600	active	[8 17 24 5]
PR20	6.9900	11	22	-2	moderately active	[18 1 7 23]
PR19	6.5800	28	25	1.1000	moderately active	[19 25 18 11]
PR6	5.9300	120	26	4.7000	moderately active	[9 *23 16]
PR18	6.9200	13	30	-2.3000	moderately active	[19 6 18 22]
PR40	6.1400	76	31	2.4000	moderately active	[20 24* 19]
PR47	6.1700	71	31	2.3000	moderately active	[8 12* 3]
PR16	6.3500	47	36	1.3000	moderately active	[19 23 18 11]
PR34	6.2800	55	41	1.3000	moderately active	[11 16 22 5]
PR46	6.0600	92	53	1.7000	moderately active	[*24 12 19]
PR41	5.9800	110	58	1.9000	moderately active	[20 26* 19]
PR33	6.7300	20	72	-3.7000	moderately active	[22 18 7 29]
PR39	5.7300	200	93	2.1000	moderately active	[7 * 23 18]
PR11	6.4600	37	110	-3.1000	moderately active	[6 2 1810]
PR9	6.0500	94	140	-1.5000	moderately active	[22 *12 16]
PR10	6.2100	66	230	-3.4000	moderately active	[24 23 14 6]
PR38	5.4100	410	270	1.5000	moderately active	[17*6 24]
PR24	6.3400	49	290	-5.9000	moderately active	[19 25 29 1]
PR13	5.9700	110	320	-2.8000	moderately active	[11 20 17 8]
PR36	4.0600	9200	7400	1.2000	moderately active	[* * 7 17]
PR1	4.1500	7500	100000	-14	Inactive	[* * 6 18]

3D-QSAR Pharmacophore-Generation

Ten 3D-QSAR pharmacophore were generated based on the 30 compounds of literature by

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HYPOGEN-algorithm using Discovery Studio 2021 (https://biovia-discovery-studio-64-bit-client.software.informer.com/). Among ten hypothesis produced, Hypothesis 1 was carefully chosen on the basis of Cost Function Analysis and Correlation Coefficient. Hypothesis 1 exhibited highest correlation-coefficient value of 0.864099 and difference between hypothesis 1 total cost and null hypothesis cost was 154.119. The best hypothesis, hypothesis-1, have Three-point features, two hydrogenbond-donner, one HYDROPHOB Aromatic one hydrophobic.

Overall Results

Table 4: Summary of Run Parameters

1. Summary of Run Parameters:

HypoGen Parameters	
Spacing	300
Variable Weight	No
Variable Tolerance	No

Features Constraints		
Name	Min	Max
HBA	0	5
HBA_lipid	0	5
HBD	0	5
HYDROPHOBIC	0	5
HYDROPHOBAromati	0	5
Total	1	5

2. Overall Results:

Pharmacophore Space: 1.977239e+04

Best records in pass: 3.

Fixed Cost: 116.304

Null Cost: 154.119

Cost Analysis (Fixed/Null distance = 37.8 bits)	
Index	Null Cost Distance
1	24.272
2	23.303
3	22.898
4	22.793
5	22.790
6	22.367
7	22.110
8	22.013
9	21.888
10	21.817

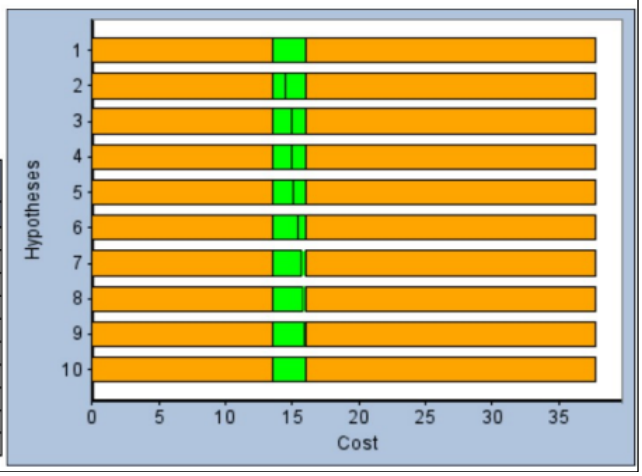

Table 5: Hypothesis 1 Results

3. Hypotheses Results:

Hypothesis 1

Results	
Maximum Fit	8.39669
Total Cost	129.847
RMS	0.948278
Correlation	0.864099

Description	
Features	Weights
HBD	2.09917
HBD	2.09917
HYDROPHOBAromatic	2.09917
HYDROPHOBIC	2.09917

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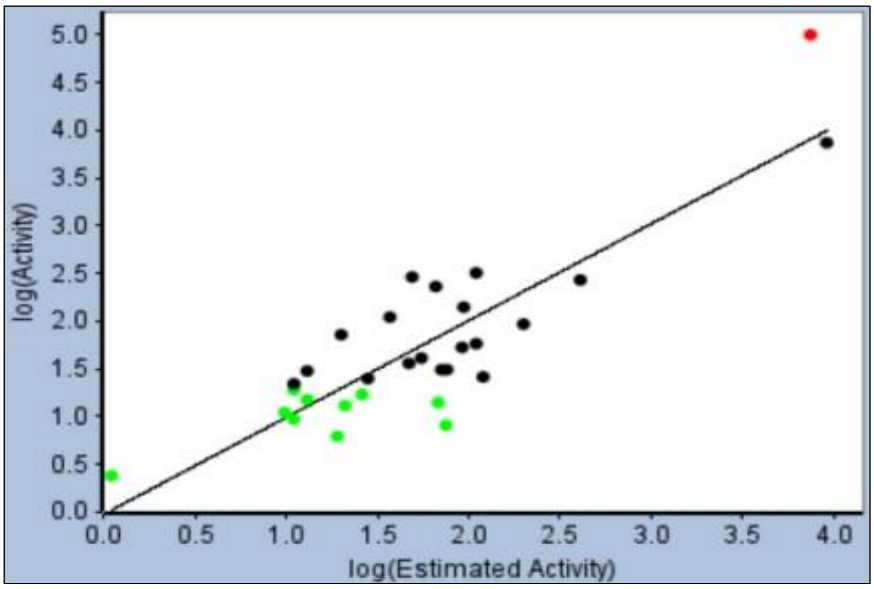

Fig 4: Graph Between Log activity and Log estimated activity

Conclusion

In silico drug design studies considered for β-hematin inhibitors. The algorithms such as PHARMACOPHORE and 3D-QSAR were used. These algorithms showed good results and further investigation for the drug collaboration can be done. Results concluded that PN-22 compound having g a good potential, best fit with other molecules and best fit with our pharmacophore result. So, this compound may be a drug molecule for β-hematin inhibitors as anti-plasmodial activity against *P. falciparum*. Lead optimization and lead to the generation of a highly potent series of β-hematin inhibitors with good drug like properties. However, the scope for fine tuning and optimizing this potent class of β-hematin inhibitors could lead to the generation of new therapeutic agents.

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