3D-QSAR COMMON FEATURE PHARMACOPHORE MODEL FOR POLYPHENOLS AS POTENTIAL ANTI-MALARIAL AGENTS

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Introduction

Malaria and FAS –II pathway

- Approximately 300-400 million people worldwide now have malaria, and each year 1 to 3 million people mostly children die from this infectious disease[1,2].
- Malaria is caused by protozoan parasites of the genus *Plasmodium* (phylum Apicomplexa). In humans malaria is caused by *P. falciparum, P. malariae, P. ovale,* and *P. vivax*. *P. falciparum* is the most common cause of infection and is responsible for about 80% of all malaria cases, and is also responsible for about 90% of the deaths from malaria.
- The chemotherapeutic cure of this disease is becoming more difficult because of the rapidly increasing multidrug resistance of the *Plasmodium falciparum* malarial parasites to antifolates and to standard quinoline antimalarial drugs like chloroquine[3].
- The need of new drug development approaches are therefore required to combat malaria and in this context polyphenols as FAS-II inhibitors have proved quite efficient.

Polyphenols as potent FAS-II inhibitor

- **Polyphenols** are a group of chemical substances found in plants, characterized by the presence of more than one phenol unit or building block per molecule.
- The largest and best studied polyphenols are the flavonoids, which include several thousand compounds, among them the flavonols, flavones, catechins, flavanones, anthocyanidins, and isoflavonoids.
- Recently luteolin-7-O-glucoside a flavonoid glycoside has been selected as natural antimalarial agent targeting FAS-II pathway. This prompted us to select polyphenol series as antimalarials.
- It is quite interesting to notice that individual compounds can inhibit three enzymes in the same pathway thus increasing the efficacy and decreased risk of developing resistance.
- Another healthy reason in case of flavonoid kind of polyphenols is that they show very low toxicity to humans and can be considered safe.

3D –QSAR Study

Objectives and strategy

The reported series of polyphenols as FAS II antagonists with their smaller activity range makes this "quantitative" hypothesis (Hypogen) generation method inappropriate.

For this type of training set, the common-feature hypothesis generation, also called HipHop, is more suitable. HipHop generates hypotheses consisting only of identification and overlay of common features (without the use of activity data).

The objective of this work is to derive feature-based 3D models using HipHop from a set of seven molecules, covering different structural scaffolds.

Material and method

Data set :

- The 3D-QSAR studies were performed using 33 molecules reported by Remo *et al.*[4]
- Out of **33** molecules, **seven** molecules were taken for the common feature pharmacophore model as they are the most active molecules of the dataset.

Common feature Hypothesis generation

The structures of seven compounds which were used for common feature hypothesis generation using **Catalyst/ HipHop program** are given below

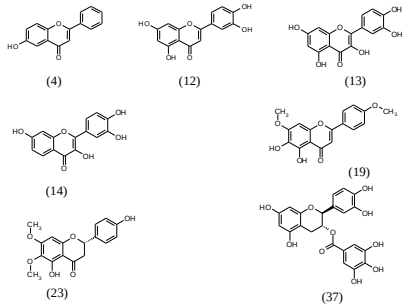
The conformations generated (255 for each compound) were used to generate pharmacophoric hypotheses.

Table 1: Settings used for hypothesis generation

Comp. No.	Principal	MaxOmitFeat
4	2	0
12	1	2
13	1	1
14	1	1
19	1	1
23	1	1
37	2	0

Principal = 2 means that this is a reference compound. MaxOmitFeat = 1 means one feature of a compound may not be mapped to a hypothesis model

Figure 1: Molecules Used for Common Feature Pharmacophore Generation



Result & Disscussion

A preparative test was performed with HDA, RAA, RDA, HAA . Potential hypothesis models were produced with the minimum permitted interfeature spacing of 2.97 Å generating alignments of common features.

It was found that hypotheses contain good correlation with HDA. The results of the generated best ten hypotheses are listed in Table . All the hypotheses have 3 features. The ranking scores ranges from 55.734 to 57.411. The molecules of different series were mapped onto the generated hypothesis using best fit option and it was found that the hypothesis 1 ranked the compounds in a better manner than others.

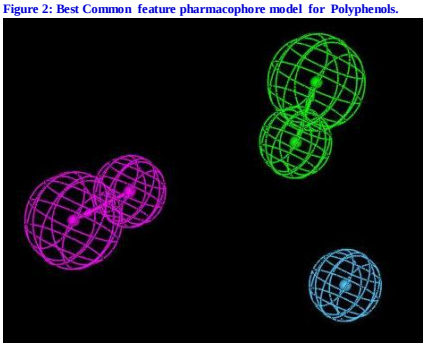
Therefore **hypothesis 1** (Fig. 2) was chosen for further study. The common binding features in these compounds as identified by the **Catalyst/ HipHop program** suggest the requirement of one Hydrophobe aromatic site ,one H bond donor site and one H bond acceptor site.

Table 2: Results of the best ten generated hypotheses

Hypothesis	Features	Rank Score	Direct Hit	Partial Hit	Max Fit
1	HDA	57.411	1111111	0000000	3
2	HDA	57.390	1111111	0000000	3
3	RAA	57.203	1111111	0000000	3
4	RDA	56.899	1111111	0000000	3
5	RAA	56.234	1111111	0000000	3
6	RAA	56.234	1111111	0000000	3
7	HAA	56.011	1111111	0000000	3
8	HAA	56.011	1111111	0000000	3
9	RDA	56.000	1111111	0000000	3
10	RDA	55.734	1111111	0000000	3

R=Ring Aromatic, H= Hydrophobic A= acceptor, D= Donor, Direct Hit=all the features are mapped. Direct Hit=1 means Yes; Partial Hit= partial mapping of the hypothesis. Partial Hit=0 means No

Figure 2: Best Common feature pharmacophore model for Polyphenols.



Blue Colour = Aromatic Hydrophobe , Pink Colour =Hydrogen Bond Donor ,Green Colour =Acceptor

Figure 3 : (A) Mapping of the most active compound (37); (B) Mapping of least active compound (34)

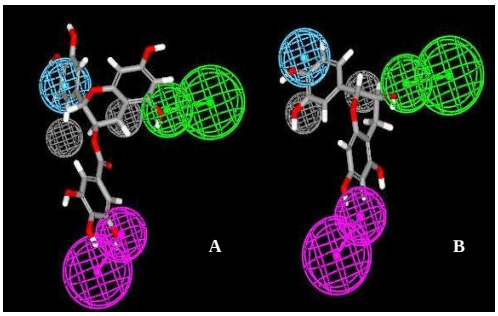
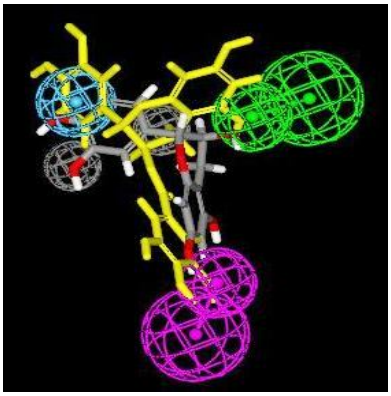


Figure 4: Mapping of the most active compound (Fit value=2.704 in yellow) and the least active compound (Fit value=.009 in grey colour).



Conclusion

- The present generated model show the important essential structural requirements for FAS II inhibitory activity molecular characteristics which are essential for a molecule to show activity.
- Important features such as a Hydrobhobe Aromatic, one H bond donor and one H bond acceptor were found important for FAS II antagonists.
- It was found that the most active compounds map well to all the features of the hypotheses while the least active compounds do not map to all the feature of the generated pharmacophore model.
- Their lack of activity may be due to their inability to achieve an energetically favorable conformation as well as the structural features :one H bond acceptor one hydrophobic (aromatic) and one H bond donor
- Therefore this HipHop model may provide new scaffolds that may used to design and develop New Chemical Entities (NCEs) as potent FAS-II inhibitors for Malarial chemotherapy.

Reference

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