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Pyrrolone Antimalarials: Pharmacophoric Analysis using In-Silico Techniques

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Abstract: ***In the present work, extensive pharmacophore modelling has been completed to recognize the consensus and significant structural features having relationship with antimalarial activity of Pyrrolone derivatives. The selected dataset encompasses of sixty-one Pyrrolone derivatives showing the anti-plasmodial activity (EC_{50}) against PfK1strain in the range 0.07 to 33.73 µM. For consensus modelling, out of sixty-one, the five utmost active molecules were aligned using common structural features, followed by pharmacophore modelling using PyMOL. The consensus pharmacophore model identified some vital structural features which could be used in future optimizations of these congeneric molecules.***
Keywords: Pharmacophore modelling, antimalarial activity, Pyrrolone derivatives, Drug design

I. INTRODUCTION

Malaria is a vector borne (Mosquito) deadly parasitic disease with significant presence in undeveloped and developing countries from Africa and Asia. The disease is instigated by parasites of the *Plasmodium* genus, generally by *Plasmodium falciparum*, and accountable for more than 214 million cases in 2015. World Health Organization (WHO) endorses artemisinin combination therapies (ACT) for treatment of malaria. But recent reports indicate the appearance of resistance against ACT, particularly from Southeast Asia [1-4]. Consequently, developing a novel drug for malaria is a necessity. Unfortunately, designing a new drug using conventional methodologies is a hard, 10-15 years long, expensive and often associated with high risks of let-down. Hence, alternate approaches like Computer Aided Drug Design (CADD) should be used with high importance.

CADD is a method of choice due to many advantages like result oriented performance, cheaper, less time and resource consumption, and provides alternative to animal testing. CADD has gained this reputation due to its thriving branches like pharmacophore modelling, QSAR, etc. The technique of pharmacophore modelling provides key features to be retained in future optimizations for drug development [5-7]. Hence, in this analysis, we have developed consensus pharmacophore model for antimalarial activity of Pyrrolone derivatives. Recently, Murugesan *et al* [3] reported antimalarial activity of Pyrrolone derivatives. The newly synthesized molecules were tested for anti-plasmodial activity (EC_{50}) which varies in the range 0.07 to 33.73 µM. Though, SAR (Structure Activity Relationship) were discussed by them, but no attempt was executed to create consensus pharmacophore model. This is first ever attempt to derive consensus pharmacophore model for antimalarial activity of Pyrrolone derivatives using a simple approach. The results could be beneficial to medicinal chemists while developing new drugs for malaria using Pyrrolone derivatives as the starting material.

II. EXPERIMENTAL METHODOLOGY

1) *Dataset:* The dataset consists of sixty-one Pyrrolone derivatives exhibiting the anti-plasmodial activity (EC_{50}) in µM range. The Pyrrolone derivatives possess good variation in substation pattern like the presence of different heterocyclic, aliphatic and aromatic rings, positional isomers and change in linkers [1]. Therefore, the selected dataset is wide enough to develop a consensus pharmacophore model. The dataset has been tabulated in table 1. For the sake of comparison, the EC_{50} have been transformed to pEC_{50}.

Table 1. Five most active Pyrrolone derivatives (SMILES notation) along with reported pEC_{50} used in the present work

S.N.	SMILES notation	pEC_{50}
1.	O=C(OC)C=1C(=O)/C(NC=1C)=C\c3cc(n(c2c(cccc2)C(F)(F)F)c3C)	8.155
2.	O=C(OCC)C=1C(=O)C(/NC=1C)=C\c3cc(C)n(c2ccc(SC(F)(F)F)cc2)	8.097
3.	O=C(OCC)C=1C(=O)C(/NC=1C)=C\c3cc(C)n(c2ccccc2C(F)(F)F)c3C	8.046
4.	O=C(OCC)C=1C(=O)C(/NC=1C)=C\c3cc(C)n(c2ccc(cc2)C(F)(F)F)	7.721
5.	O=C(OCC)C=1C(=O)/C(NC=1C)=C\c3cc(n(c2c(cccc2)C(F)(F)F)c3CC)	7.699

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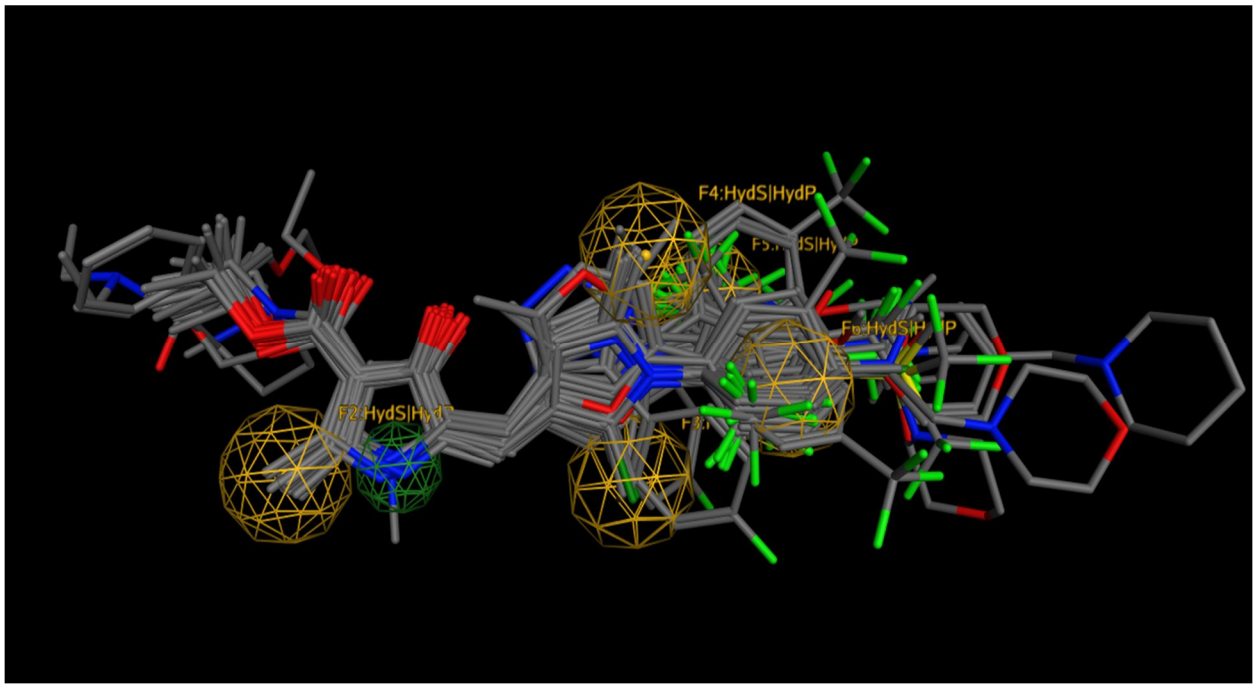
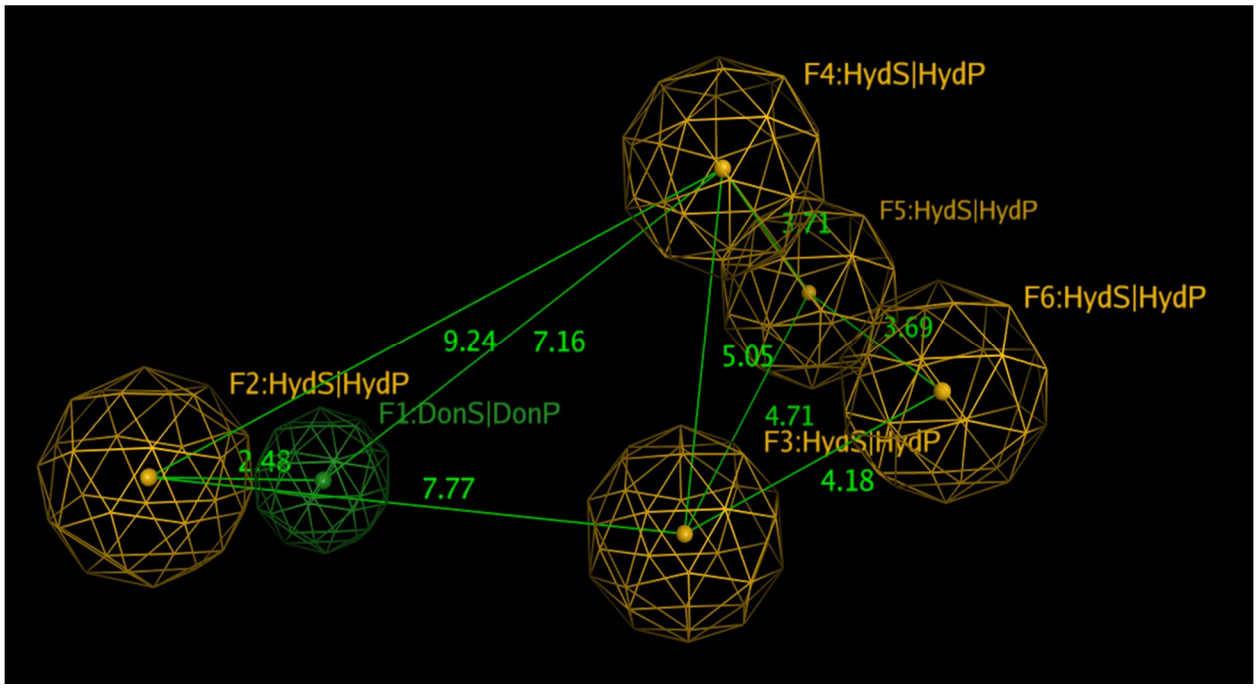
2) *Structure Drawing, Optimization and Alignment [5-7]:* The standard procedure for developing consensus pharmacophore modelling [5-7] has been followed. The four main steps are:

a) *Step-1:* The structures were drawn using ChemSketch 2010 freeware
b) *Step-2:* Optimization using PM3 semi-empirical method using MOPAC 2012
c) *Step-3:* Alignment of molecules using Open3dAlign software
d) *Step-4:* Using the default settings, consensus pharmacophore model was created using PyMOl 1.8.6

III. RESULTS AND DISCUSSION



(a)



(b)

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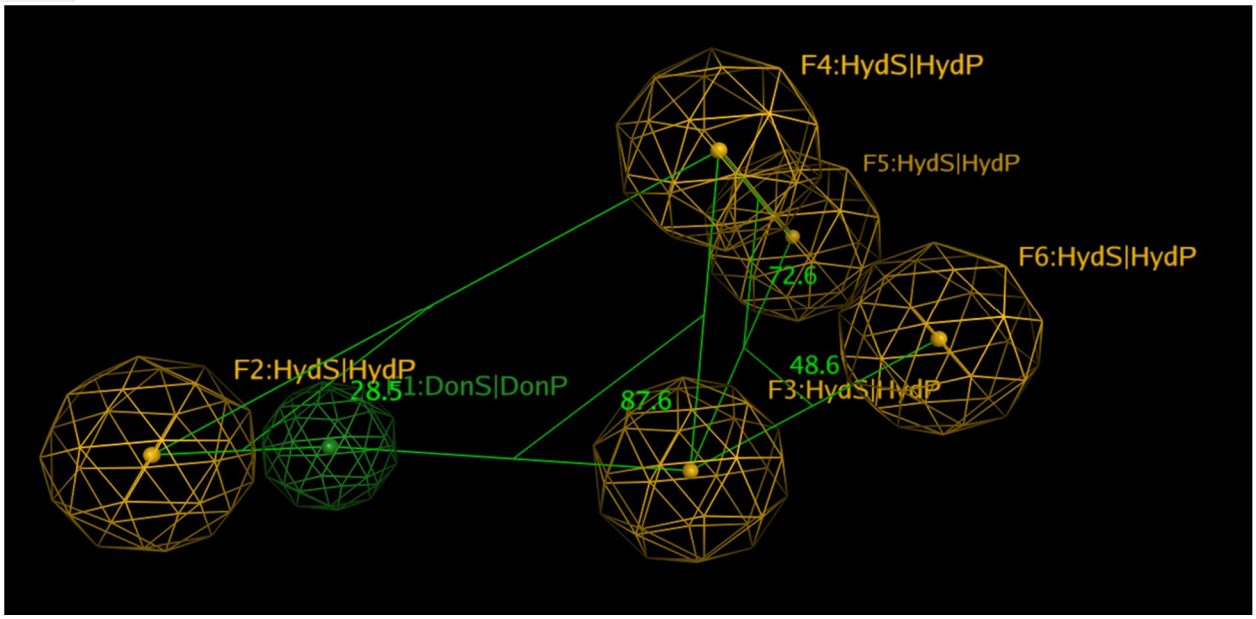

(c)

Figure 1. 3D- representation of consensus pharmacophoric pattern using all molecules (Yellow: Hydrophobic, Green: H-Bond donor regions) (a) All molecules with pharmacophore model (b) Distances between pharmacophoric regions (c) Angles between pharmacophoric regions

The consensus pharmacophore modelling identified six important regions in the molecules which have correlation with anti-malarial activity of Pyrrolone derivatives. The most prominent regions are: (1) five hydrophobic regions (shown by yellow contours), (2) A H-bond donor region (shown by green contour). These regions are spread across the molecules with three aromatic/hydrophobic regions in the close proximity of each other. In future optimizations these regions should be retained for good activity.

IV. CONCLUSIONS

The present work revealed important pharmacophoric patterns for anti-malarial activity of Pyrrolone derivatives.

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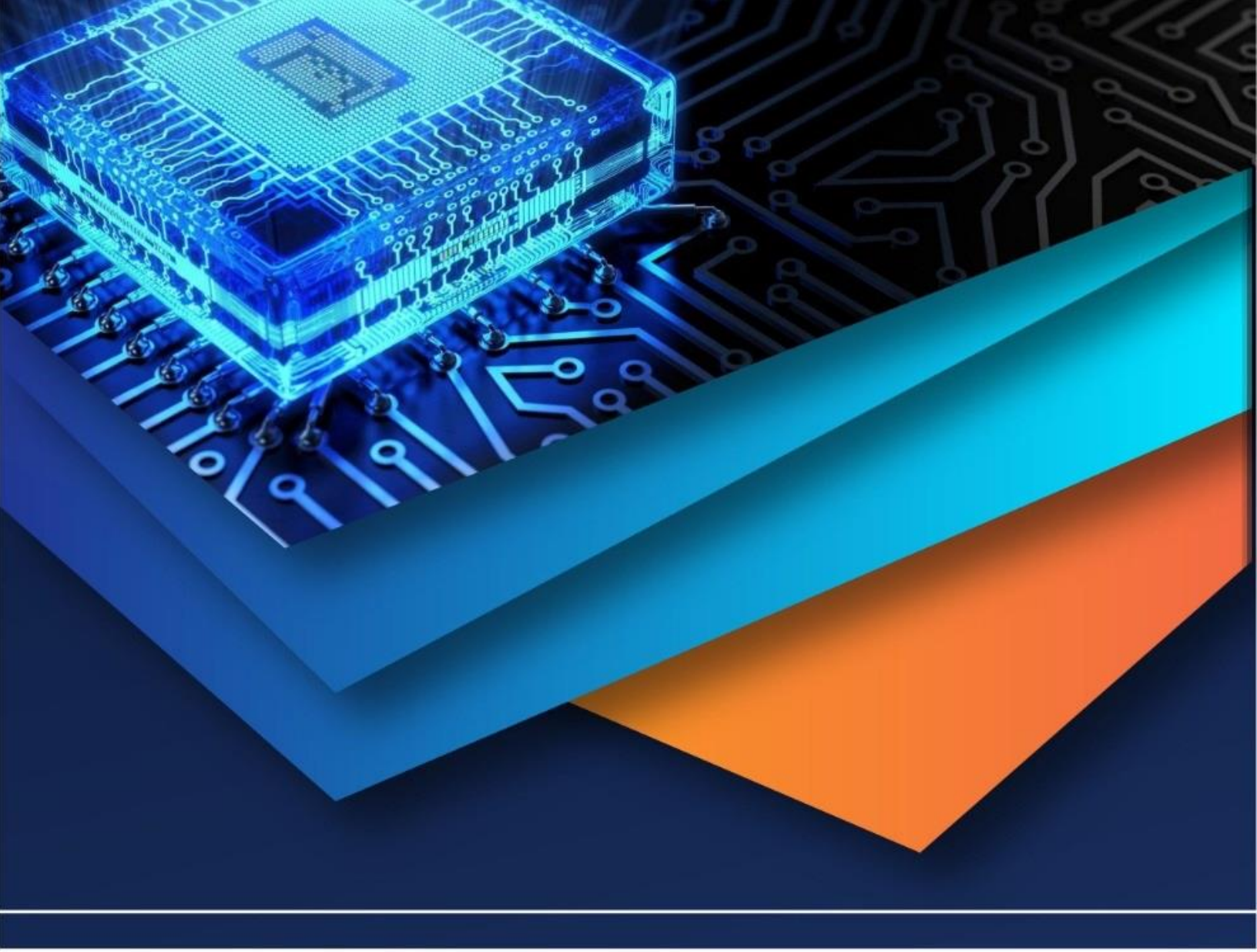

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