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BIS/MC ALGORITHM BASED 3D-QSAR FOR RECEPTOR MODELLING TO EXPLORE ANTI-MALARIAL ACTIVITY OF SYNTHETIC PRODIGININES

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Abstract:
3D-QSAR analysis using BiS/MC (Biological Substrate/Multi-Conformational) algorithm has been performed in the present work to explore anti-malarial activity of synthetic prodiginines along with the modelling of the characteristics features of the receptor site. Using the novel approach implemented in the BiS/MC, it has been observed that lipophilic and electrostatic are prominent interactions between the prodiginines and the receptor site. BiS/MC builds statistically sound 3D-QSAR model to construct pseudo-receptor site. The analysis of the generalized self-consistent complementary field constructed within BiS/MC approach reveals introduction of H-bonding capable groups on side chain and lipophilic groups on pyrrole ring B could result in enhancement of anti-malarial activity of prodiginines.

Keywords: Prodiginines, Anti-malarial activity, 3D-QSAR, BiS/MC algorithm

Abbreviations: BiS/MC- Biological Substrate/Multi-Conformational

Introduction:

Malaria, a global health challenge especially for tropical and subtropical countries, kills more than 2 million peoples every year (http://www.who.int/malaria/en/) [1]. The emergence of resistance against existing drugs is worsening the situation. To curb malaria, ongoing modification of existing drugs and search for new therapeutics has lead to identification of novel chemical compounds viz. xanthones,

artimisins, prodiginines etc., a few to mention [2-8], as hopeful anti-malarial agents.

Prodiginines (figure 1), the red pigment tripyrrole derivatives [9], have received considerable attention of researchers due to *in vitro* moderate to high activity against Plasmodium species at a very low concentration, oral administration, marked parasite clearance and cures in some cases without evident weight loss but search for synthetic analogues with better anti-malarial activity and with reduced toxicity persists [9-11]. To achieve these objectives, modern techniques like QSAR, GUSAR, molecular docking, pharmacophore modelling etc. are promising tools [2-8].

Fig. 1. Synthetic prodiginines analysed in present study

The mechanism of action against *P. falciparum* and the receptor with which the prodiginines interact is unknown [9-11] therefore 3D-QSAR could be especially trustworthy. In present work, we have carried out 3D-QSAR analysis using BiS/MC algorithm. BiS/MC, a novel approach for 3D-QSAR, is a superimposing algorithm which allows one to construct a pseudo-atomic model of a receptor and to calculate the interaction energy of each conformer with the obtained model receptor [12-17], whereas the traditional 3D-QSAR approaches like CoMFA, CoMSIA, HASL etc. are able to give idea about the common pattern of fields around the congener series of molecules only. Thus BiS/MC has

additional advantages apropos of receptor site over conventional 3D-QSAR approaches.

2. Results and Discussions

2.1 BiS/MC analysis of anti-malarial activity of Prodiginines:

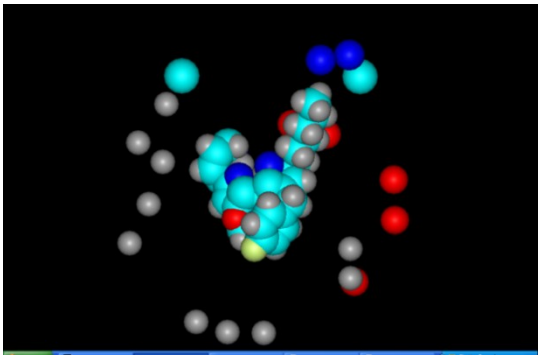
The statistical characteristics for BiS/MC 3D-QSAR analysis for 53 synthetic prodiginines are as follows: R = 0.972, R^2 = 0.945, crossR^2 = 0.884 and S = 0.431. The analysis of the statistical characteristics shows that the model developed by BiS/MC is statistically reliable and can be used as a novel tool for future drug design. A straight line relation between the actual and predicted pIC_{50} indicates that the BiS/MC model has a good predictive efficiency.

2.3 Analysis of BiS/MC output:

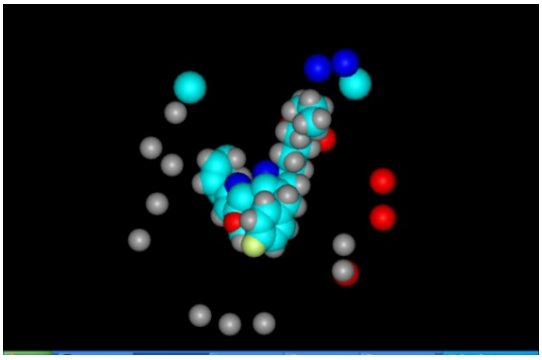
Figure 2 represents the output of BiS/MC for anti-malarial activity of prodiginines. Though the BiS/MC analysis was carried for all 53 synthetic prodiginines, only four most active and four least active have been depicted as representatives in figure 3 for comparison purpose.

From figure 2, it is clear that the major factors which govern the interactions of prodiginines with receptor are lipophilic and electrostatic in nature. In the case of the most active compounds number **40** and **41**, though the interactions are appearing identical, but the difference in their IC_{50} values (0.9 and 1.3 nM respectively) reveals that some other factors like log$P$, pKa etc. should be considered. Similar explanations can be applied for compound number **27** and **28** with identical IC_{50} (-0.23 nM), even though there is a considerable difference in their structure and it emerges out that they interact with same atoms of the receptor in an identical manner.

Fig. 2. Output of BiS/MC



Molecule no. 40:



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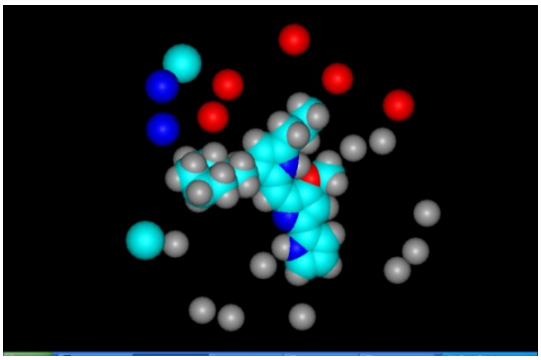
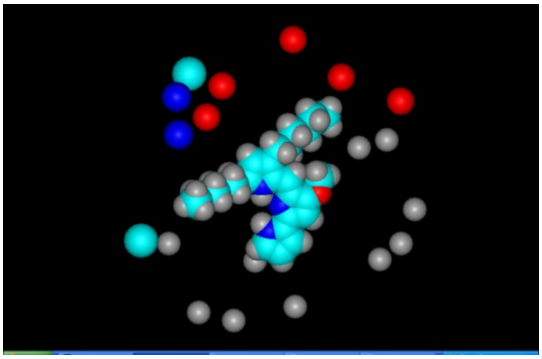
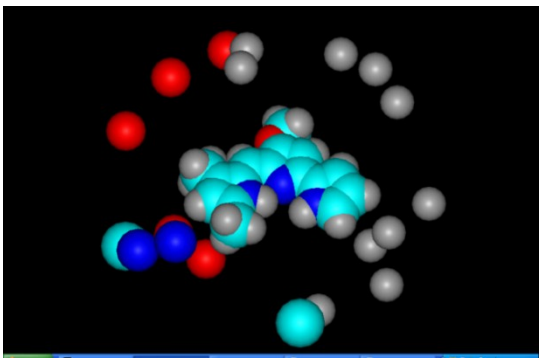


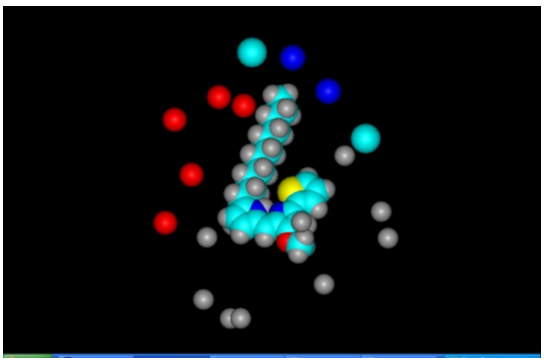
Molecule no. 27:



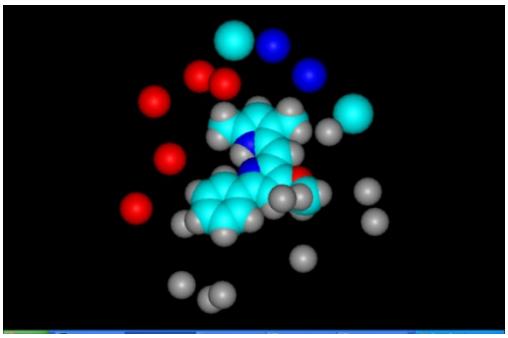
Molecule no. 28:



Molecule no. 24:



Molecule no. 6:



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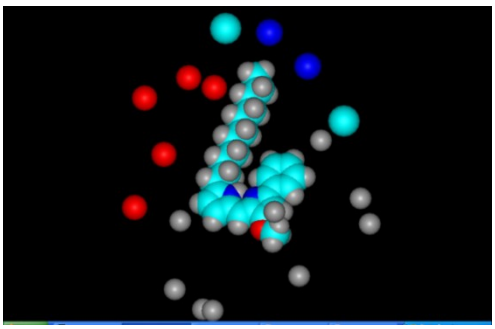

Molecuel no. 3:

A possible explanation for different probe spheres is: Red is negatively charged pseudo-atom (oxygen-like); blue is also negatively charged pseudo-atom but with less charge and greater radius (nitrogen-like); gray is positively charged pseudo-atom (like a hydrogen of -OH, -NH, -COOH groups); cyan is non-charged "lipophilic" pseudoatom (like alkyl carbon or hydrogen) [12-17].

3. Materials and methods:

3.1 Data set: In present work, fifty three structurally diverse synthetic prodiginines possessing substituents like –F, –Cl, alkyl, -NH_2, etc. at different positions were selected from literature [9]. All were assayed for their *in vitro* anti-malarial activity against *P. falciperum* pansensitive D6 with chloroquine (CQ) as a reference drug. To obtain a symmetrically distributed data for smoother BiS/MC analysis, the data reported as IC_{50} was converted to $-\log IC_{50}$ (pIC_{50})[10]. A complete list of compounds is presented in table 1 along with experimental IC_{50} (nM). The experimental pIC_{50} along with predicted pIC_{50} by BiS/MC are listed in table 1.

Table 1 Experimental data and predicted IC_{50} by BiS/MC

Molecule no.	R_1	R_2	R_3	IC_{50}(nM) D6	Actual pIC_{50}	Predicted pIC_{50}
1		CH_3	CH_3	4250	-3.628	-3.65013
2		n-$C_{11}H_{23}$	H	4060	-3.608	-3.76422
3		n-$C_{11}H_{23}$	H	10470	-4.019	-3.67714
4		CH_3	CH_3	19410	-4.288	-3.92714
5		n-$C_{11}H_{23}$	H	2920	-3.465	-3.17274
6		CH_3	CH_3	>25000	-3.773	-3.47111
7		n-$C_{11}H_{23}$	H	5940	-3.361	-3.32064
8		CH_3	CH_3	>25000	-3.25	-3.58345

9	n-C_3H_7	H	2300	-2.574	-2.06819
10	n-C_4H_9	H	1780	-1.903	-2.17415
11	n-C_6H_{13}	H	375	-2.477	-2.85857
12	n-C_8H_{17}	H	80	-3.23	-3.39469
13	n-$C_{16}H_{33}$	H	300	-3.653	-3.5456
14	n-$C_{11}H_{22}NH_2$	H	1700	-2.662	-2.40882
15	H	$(CH_2)_3COOCH_3$	4500	-1.903	-2.23137
16	H	$CH_2CH(CH_3)_2$	460	-1.447	-1.16215
17	H	n-C_4H_9	80	-0.662	-0.9224
18	H	n-C_6H_{13}	28	-0.903	-1.01716
19	H	n-C_8H_{17}	4.6	-1.919	-1.84772
20	H	n-$C_{10}H_{21}$	8.0	-2.23	-2.35412
21	H	n-$C_{16}H_{33}$	>25000	-1.812	-1.62018
22	H	$C_6H_5CH_2$	83	-1.954	-2.2573
23	H	4-$OCH_3C_6H_4CH_2$	170	-1.748	-1.72893

24	H	4-$ClC_6H_4CH_2$	65	-3.949	-4.14314
25	H	4-$BrC_6H_4CH_2$	90	-0.653	-0.91314
26	H	2-NaphthylCH$_2$	56	-0.462	-0.31924
27	CH_3	CH_3	8900	-0.23	-0.21539
28	n-C_6H_{13}	n-C_3H_7	4.5	-0.23	-0.42776
29	n-C_8H_{17}	n-C_3H_7	2.9	-0.322	-0.39323
30	n-C_3H_7		1.7	-0.69	-1.18937
31	n-C_6H_{13}	n-C_6H_{13}	1.7	-0.792	-0.7877
32	n-C_7H_{15}	n-C_6H_{13}	2.1	-1.963	-1.00539
33	n-C_6H_{13}	n-C_8H_{17}	4.9	-0.724	-0.793
34	n-C_7H_{15}	n-C_8H_{17}	6.2	-0.799	-0.17955
35	n-C_8H_{17}	n-C_8H_{17}	92	-0.477	-0.90233
36			5.3	-0.301	-0.40445
37	C_2H_5	4-$ClC_6H_4CH_2$	6.3	-0.447	-0.452
38	n-C_3H_7	4-$ClC_6H_4CH_2$	3	-1.204	-0.73575

39	n-C_6H_{13}	4-$ClC_6H_4CH_2$	2	-0.591	-0.6225
40	n-C_7H_{15}	4-$ClC_6H_4CH_2$	2.8	0.045	0.03333
41	n-C_8H_{17}	4-$ClC_6H_4CH_2$	16	-0.113	-0.36213
42	4-$ClC_6H_4CH_2$		3.9	-0.462	-0.5408
43	n-C_6H_{13}	4-$FC_6H_4CH_2$	0.9	-0.602	-0.95763
44	n-C_8H_{17}	4-$FC_6H_4CH_2$	1.3	-0.785	-0.95104
45	n-C_6H_{13}	4-$BrC_6H_4CH_2$	2.9	-0.748	-0.71502
46	n-C_8H_{17}	4-$BrC_6H_4CH_2$	4	-1.146	-1.15627
47	4-$ClC_6H_4CH_2$	4-$ClC_6H_4CH_2$	6.1	-0.785	-0.87856
48	4-$FC_6H_4CH_2$	4-$FC_6H_4CH_2$	5.6	-0.919	-0.78514
49	4-$BrC_6H_4CH_2$	4-$BrC_6H_4CH_2$	14	-0.755	-0.93336
50	4-$FC_6H_4CH_2$	4-$ClC_6H_4CH_2$	6.1	-1.1	-0.72488
51	4-$BrC_6H_4CH_2$	4-$ClC_6H_4CH_2$	8.3	-1.167	-0.66199
52	4-$BrC_6H_4CH_2$	4-$FC_6H_4CH_2$	5.7	-0.707	-1.01513
53	2,4-$Cl_2C_6H_3CH_2$	2,4-$Cl_2C_6H_3CH_2$	12.6	-0.556	-0.8125

3.2 BiS/MC computations: The structures were drawn using ACD ChemSketch 12 freeware followed by optimization. The structures along with their experimental pIC_{50} data were used in BiS/MC. The standard procedure provided with BiS/MC was used to get the best results.

4. Conclusions:

The results of the analysis shows the following: (1) BiS/MC is very successful in building statistically robust 3D-QSAR models. (2) BiS/MC provides idea about the characteristics of receptor site. (3) Introduction of H-bonding capable groups on side chain and lipophilic groups on pyrrole ring B could result in enhancement of anti-malarial activity of prodiginines. (4) Lipophilic and electrostatic are prominent interactions between prodiginines and receptor site. The results of present analysis could be fruitful for future modifications in prodiginines to augment their anti-malarial activity.

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6. Conflict of interest: Authors declare no conflict of interests.

7. References:

http://www.who.int/malaria/en/

R.D. Jawarkar, V.H. Masand, K.N. Patil, D.T. Mahajan, M.H. Youssoufi, T.B. Hadda, and S.L. Kumbhare, (2010). 3D-QSAR Study on Coumarin Analogues as Potent Inhibitors of MAO-B using a COMFA Approach, Der Pharma Chemica. 2(6) 302-310.

D.T. Mahajan, R.D. Jawarkar, K.N. Patil, V.H. Masand, and G.M. Nazerruddin, (2010). 3D-QSAR studies on xanthone derivatives to understand pharmacological activities as MAO inhibitors, Der Pharma Chemica 2(4) 298-308.

V.H. Masand, R.D. Jawarkar, K.N. Patil, D.T. Mahajan, T.B. Hadda, and G.H. Kurhade, (2010). COMFA Analysis and toxicity risk assessment of coumarin analogues as MAO-A Inhibitors: Attempting better insight in drug design, Der Pharm Lettre 2(6) 350-357.

V.H. Masand, R.D. Jawarkar, D.T. Mahajan, T.B. Hadda, A.M. Manikrao, P.N. Khatale, and J.V. Vyas, (2011). Presuming the Probable Anti-inflammatory Mechanism of Ursolic Acid: a plant derived pentacyclic triterpenoid, using molecular docking, J. Comput. Method. Mol. Design. 1(2) 9-13.

V.H. Masand, R.D. Jawarkar, K.N. Patil, G.M. Nazerruddin, and S.O. Bajaj, (2010). Correlation potential of Wiener index vis-à-vis molecular refractivity: Antimalarial activity of xanthone derivatives, Org. Chem. An Ind. J. 6(1) 30-38.

V.H. Masand, R.D. Jawarkar, D.T. Mahajan, T.B. Hadda, J. Sheikh, and K.N. Patil, (2011). QSAR and CoMFA studies of biphenyl analogs of the anti-tuberculosis drug (6S)-2-nitro-6-{[4-(trifluoromethoxy)benzyl]oxy}-6,7-dihydro-5H-imidazo[2,1-b][1,3]oxazine(PA-824), Med. Chem. Res., DOI:10.1007/s00044-011-9787-x

V.H. Masand, D.T. Mahajan, K.N. Patil, K.D. Chinchkhede, R.D. Jawarkar, T. Ben Hadda, A.M. Alafeefy, and I.G. Shibi, (2012). k-NN, quantum mechanical and field similarity based analysis of xanthone derivatives as α-glucosidase inhibitors, Med. Chem. Res, 1-12, DOI:10.1007/s00044-012-9995-z

K. Papireddy, M. Smilkstein, J.X. Kelly, Shweta, S.M. Salem, M. Alhamadsheh, S.W. Haynes, G.L. Challis, and K.A. Reynolds, (2011). Antimalarial Activity of Natural and Synthetic Prodiginines. J. Med. Chem. 54 : 5296–5306.

N.R. Williamson, P.C. Fineran, F.J. Leeper, and G.P.C. Salmond, (2006). The biosynthesis and regulation of bacterial prodiginines. Nature Reviews 4: 887-899.

P.A. Gale, and W. Dehaen, (2010). Anion Recognition in Supramolecular Chemistry (Topics in Heterocyclic Chemistry)**,** Springer, New York.

M.A. Grishina, A.A. Pogrebnoi, V.A. Potemkin, and T.Y. Zrakova, (2005). Molecular-biological problems of drug design and mechanism of drug action theoretical study of the substrate specificity of cytochrome P-450 isoforms, Pharm. Chem. J. 39(10) 509-513.

M.A. Grishina, and V.A. Potemkin, (2008). A new paradigm for pattern recognition of drugs, J Comput Aided Mol Des 22 : 489–505.

A.A. Pogrebnoi, M.A. Grishina, V.A. Potemkin, and D.A. Sysakov, (2010). Molecular-biological problems of drug design and mechanism of drug action modeling complexes of substrates with cytochrome P-450 2C9, Pharm. Chem. J. 44(5) 237-240.

M.A. Grishina, A.A. Pogrebnoi, V.A. Potemkin, and N.N. Ivshina, (2008). A Study of Conformational States of Substrates of Isoform 3A4 of Cytochrome P-450, Mol. Biophys. 53(5) 758-765.

V.A. Potemkin, R.M. Arslambekov, E.V. Bartashevich, M.A. Grishina, A.V. Belik, S. Perspicace, and S. Guccione, (2002). Multiconformational method for analyzing the biological activity of molecular structures, J. Struct. Chem. 43(6) 1045-1049.

A.A. Pogrebnoi, M.A. Grishina, and V.A. Potemkin, (2009). Modeling of complexes between cytochrome p450 1a2 and substrates, J. Struct. Chem. 50(5) 814-820.