Electronic Supplementary Material (ESI) for RSC Advances

SUPPLEMENTARY INFORMATION

From the Natural Compound (+)-Epigallocatechin Gallate to a Simplified Synthetic Analogue as a Cytoadherence Inhibitor for *Plasmodium falciparum*

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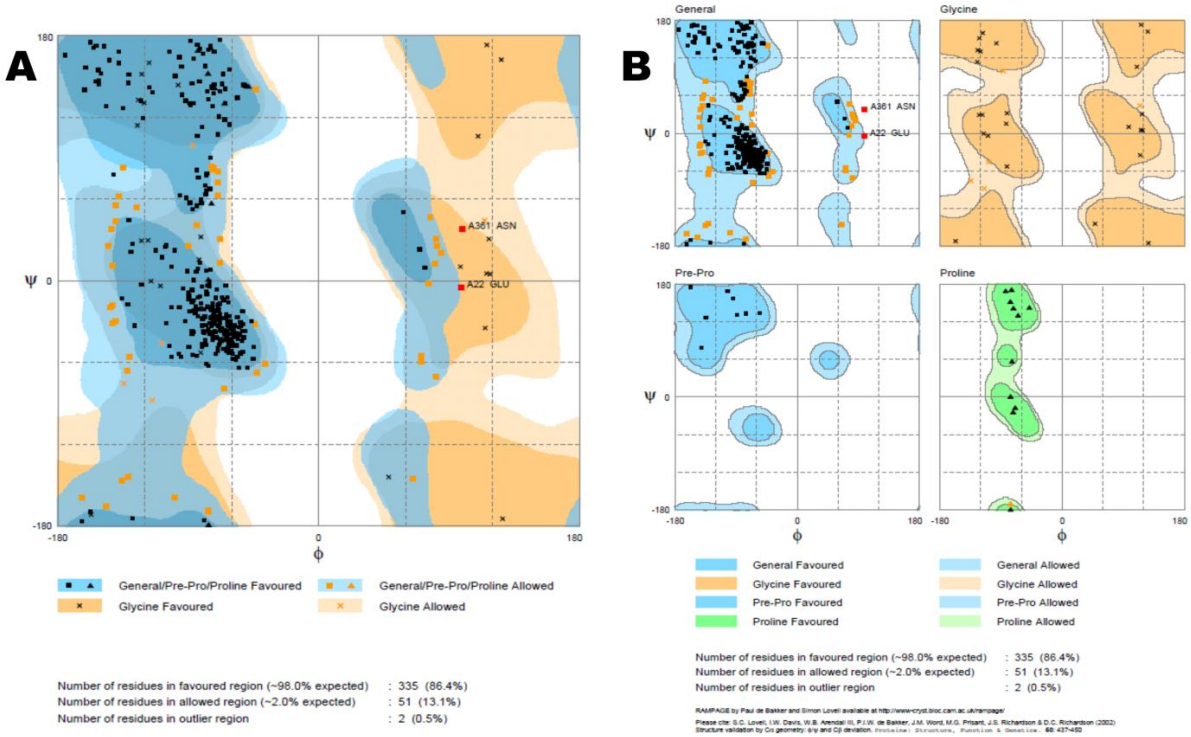

Figure S1. Ramachandran Plot analysis of the modeled DBLβ domain from PfEMP1 protein. (A): general panel; (B): representation of the placement of residues in the homology model for general Gly, Pre-Pro, Pro. The residues N361 and E22 corresponding to N1171 and E832 in the full length protein sequence. The reported plot is referred to the homology model minimized by means of Method-1 MM-PPW. The Ramachandran Plot performed on the DBLβ domain minimized by means of Method-2 PPW-MM does not display any significant change (data not shown).

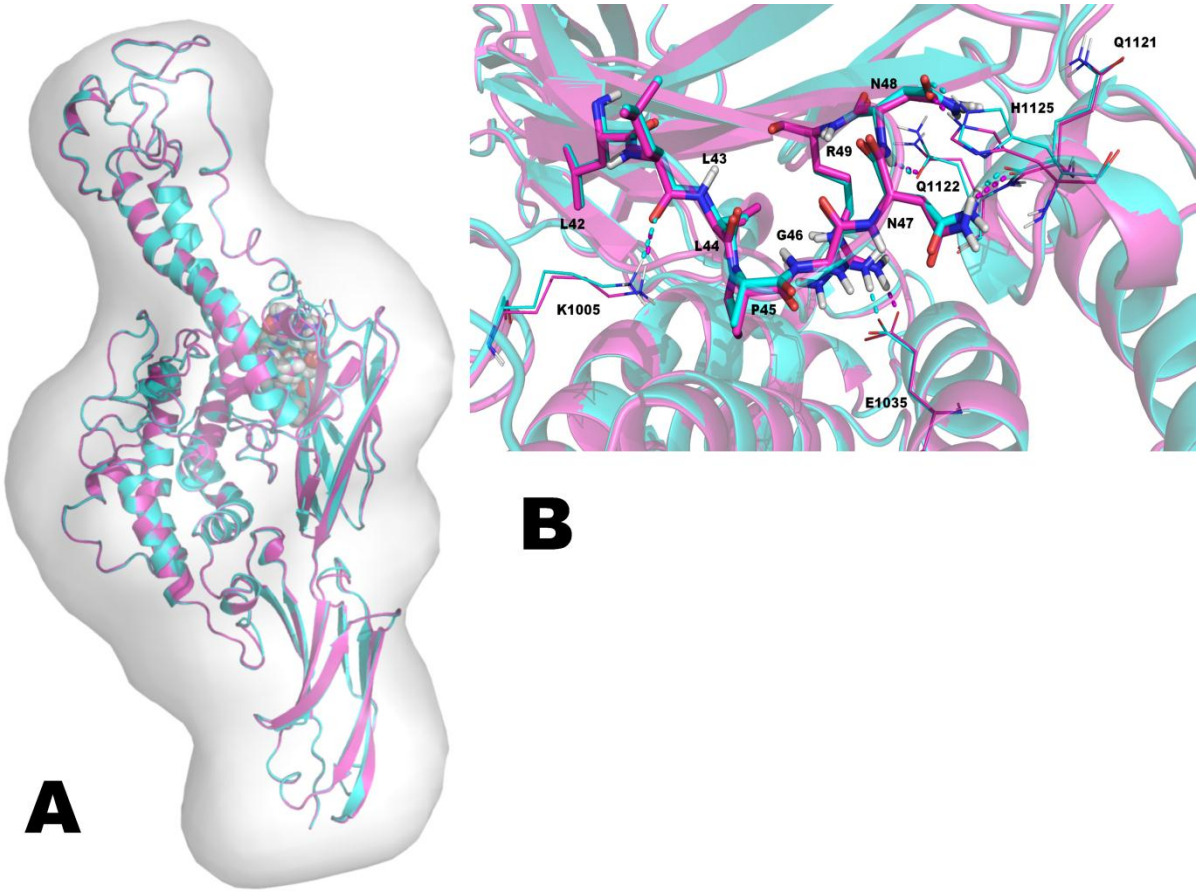

Figure S2. (A) Superposition between the structures of DBLβ-ICAM^{D1D2} generated by HADDOCK web server and the experimental SAXS data. In cyan it is reported the original model presented in the Main Text of the manuscript, while in magenta is represented the calculation performed using the reviewer suggestion. Accordingly, before the HADDOCK calculation, the model was first treated with protein preparation wizard and subsequently with MacroModel. (B) Superposition of the binding sites between the structures of DBLβ-ICAM^{D1D2}. The original structure is in cyan color, while the structure obtained by the new procedure is depicted in magenta. The residues of the loops are represented by sticks while the key residues in the binding sites are represented by lines. The non-polar hydrogen atoms were omitted for the sake of clarity. H-bonds for the original model are reported by cyan dotted lines, while H-bonds for the model obtained by the new procedure are reported by magenta dotted lines. Notably, in either case, no significant differences can be found in the binding mode or in relevant contacts between DE-loop and the interacting residues of the DBLβ domain.

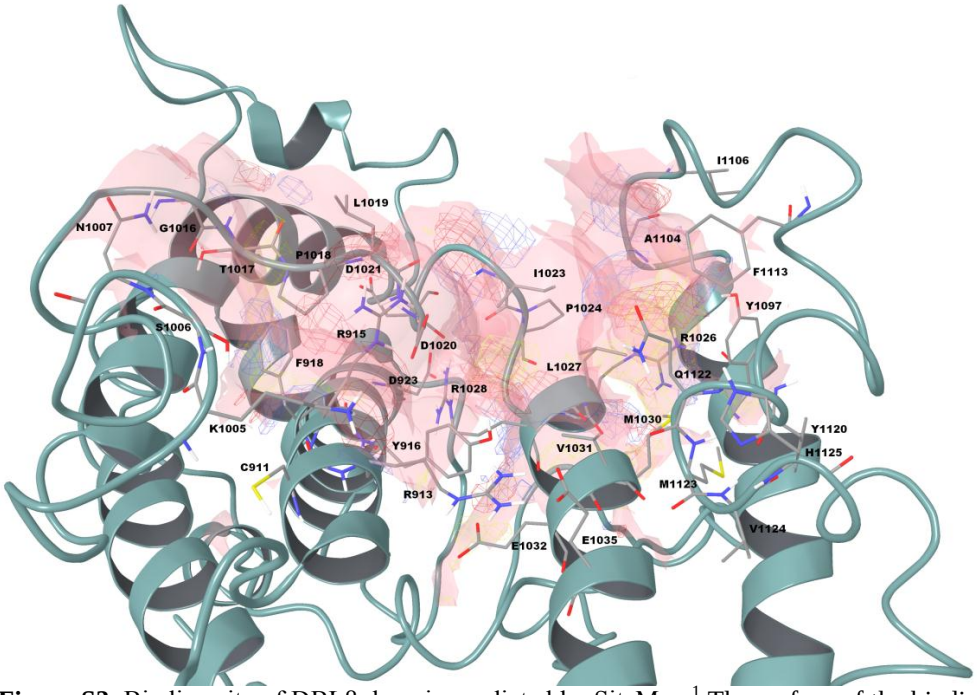

Figure S3. Binding site of DBLβ domain predicted by SiteMap.[1] The surface of the binding site is represented as solid in pink color. The maps of binding site for a potential ligand interaction are represented as solid mesh (red=acceptor; blue=donor; yellow=hydrophobic). Residues comprised by surface are represented by thin tubes. These residues are considered as active residues for protein-protein docking performed by means of HADDOCK web server.[2] The picture was generated by Maestro.[3]

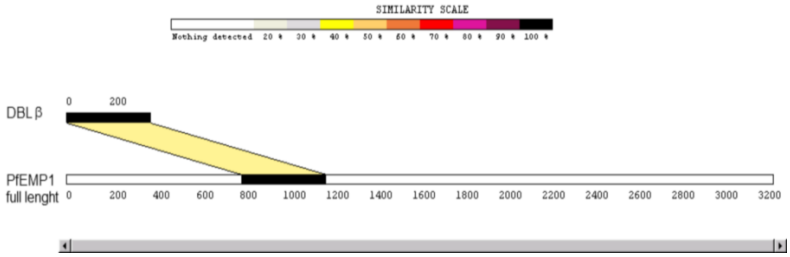

Figure S4. Alignment between the sequence of DBLβ domain and of full length PfEMP1 IT4VAR13, highlighting the numbering of DBLβ sequence reported in this study. The alignment was performed by means of SIM-alignment tool for protein sequence.[4] The visualization of the output was performed by means of LALNVIEW.[5]

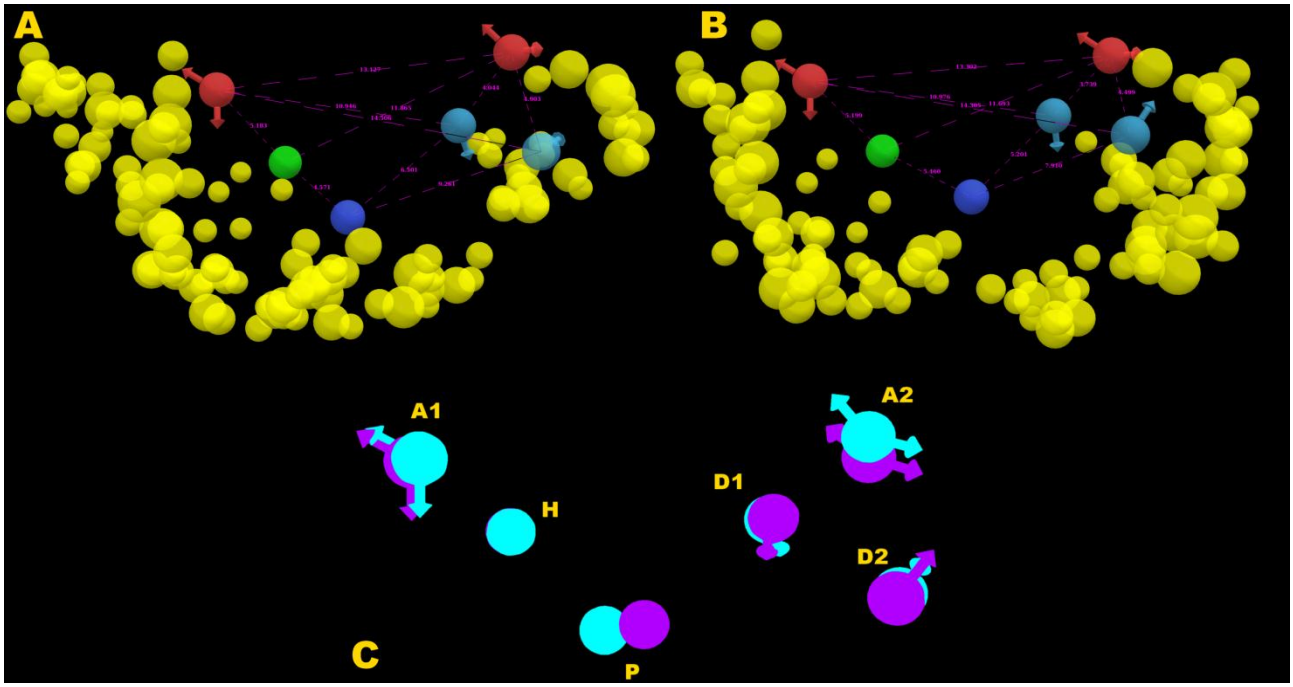

Figure S5. (A) AADDHP Pharmacophore obtained by Phase with excluded volumes and with its inter-feature distances in Å, using a complex generated by using Method-1 MM-PPW as reported in the paper Main Text. (B) AADDHP Pharmacophore obtained by Phase with excluded volumes and with its inter-feature distances in Å, using a complex generated by using Method-2 PPW-MM. (C) Superposition between the two pharmacophore hypothesis. In particular, the original pharmacophore is depicted in cyan, while the new pharmacophore, generated using a complex minimized by reviewer's suggestion, is reported in magenta. The picture was generated by Maestro.[3]

Table S1. Comparison between the fitness values obtained by using the two pharmacophore models.

Compound	**Fitness values (Method-1MM-PPW)**		**Fitness values (Method-2PPW-MM)**	
(+)-EGCG (**1**)	2.13		2.21	
	R	***S***	***R***	***S***
2a	0.91	0.99	0.90	0.97
2n	1.37	1.39	1.39	1.40

Fitness values were calculated as reported in the Main Text.

Table S2. Superposition between all compounds used in this study (**2a-n**, *R*- and *S*-enantiomers) with the structure-based pharmacophore hypothesis AADDHP. The pictures were generated by Maestro.[3]

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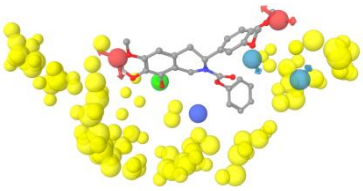
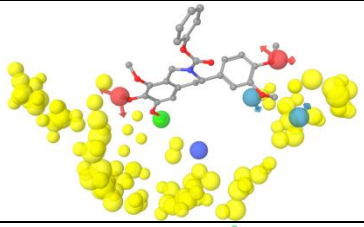
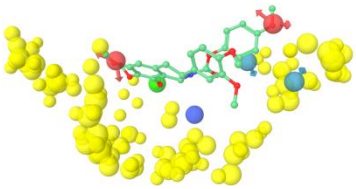
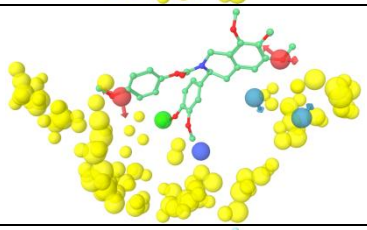
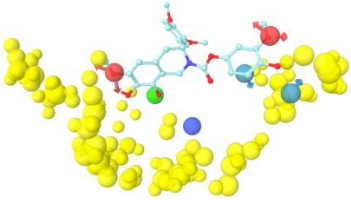
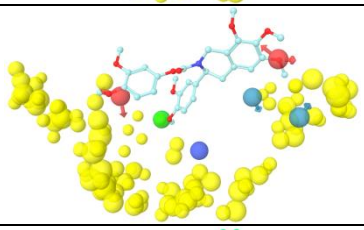
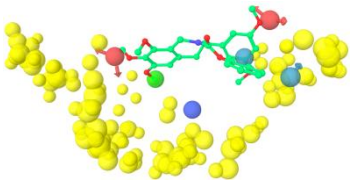
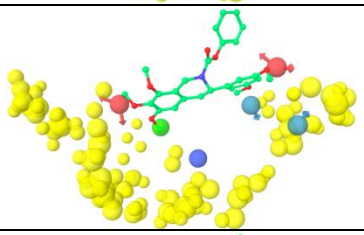
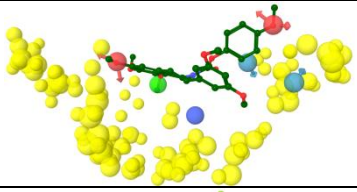
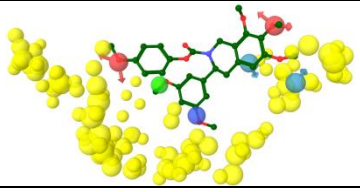
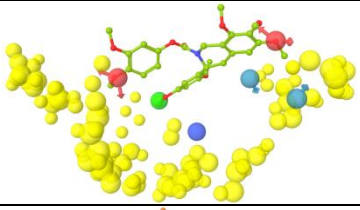
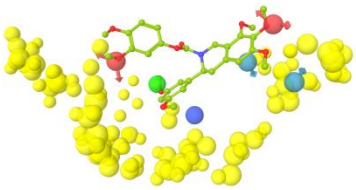
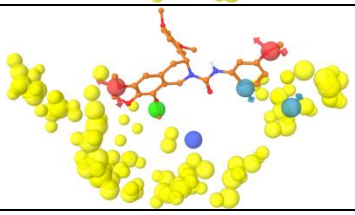
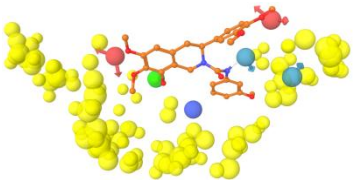
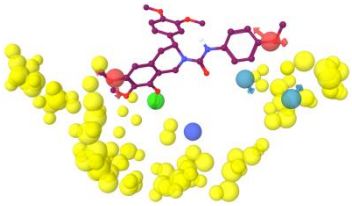
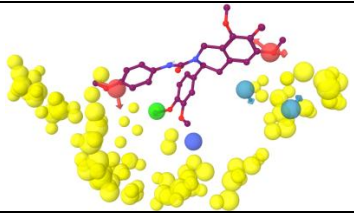
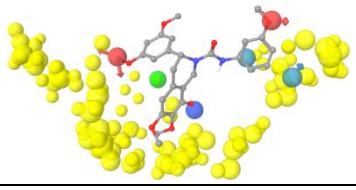
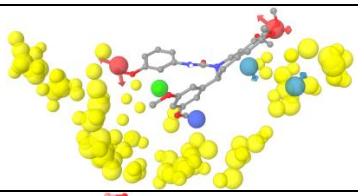
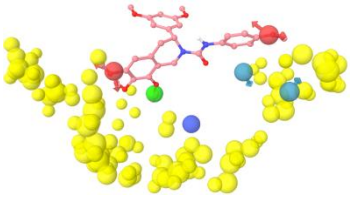
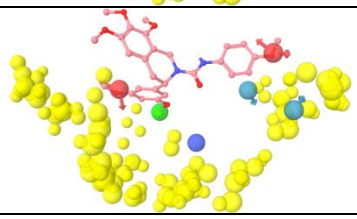
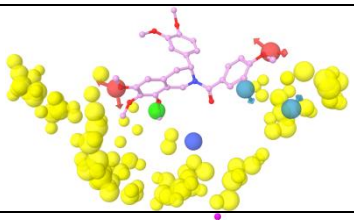
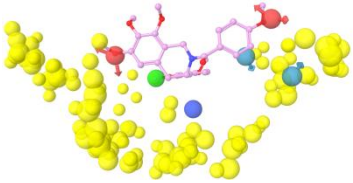
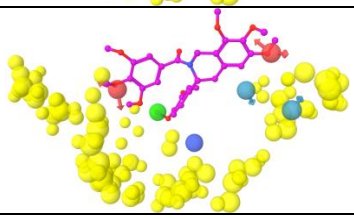
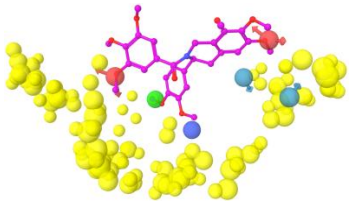
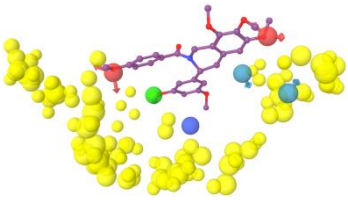
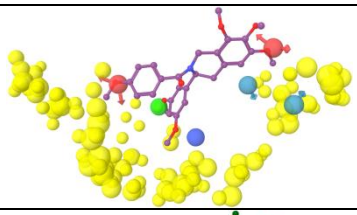
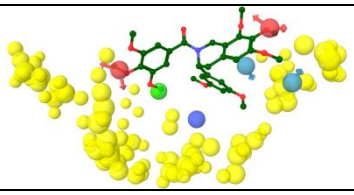
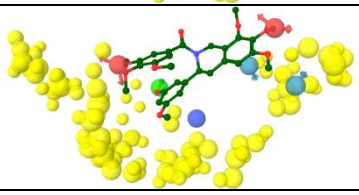
2a		
2b		
2c		
2d		
2e		
2f		
2g		
2h		

2i		
2j		
2k		
2l		
2m		
2n		

References

1. SiteMap, version 2.5, Schrödinger, LLC, New York, NY, 2011.
2. S. J. de Vries, M. van Dijk and A. M. Bonvin, *Nat. Protoc.*, 2010, **5**, 883-897.
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