MedChemComm

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Journal:	*MedChemComm*
Manuscript ID	MD-CAR-08-2015-000343.R1
Article Type:	Concise Article
Date Submitted by the Author:	18-Sep-2015

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Journal Name

COMMUNICATION

Synthesis of fusidic acid bioisosteres as antiplasmodial agents and molecular docking studies in the binding site of Elongation Factor-G

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

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A series of fusidic acid derivatives was synthesized by replacing the carboxylic acid group with various bioisosteres and evaluated *in vitro* against the chloroquine-sensitive NF54 strain of malaria parasite *Plasmodium falciparum*. Most of these derivatives showed a 2-35 fold increase in activity as compared to fusidic acid and had a good selectivity index. Further, docking experiments of fusidic acid and the most active derivative 18 within the active site of plasmodial elongation factor-Gs suggested that the binding orientation of 18 is similar to fusidic acid, but with slightly better docking score.

Introduction

Malaria still exacts a huge toll on human health, imposing a substantial social and economic burden in developing countries. According to the latest WHO malaria report,[1] around 198 million cases of malaria occurred in 2013 causing 584000 deaths worldwide with the heaviest burden in Sub-Saharan Africa and children under the age of 5. The management of this disease is further compounded by the emergence of resistance to the available drug regimens, including the artemisinins – the mainstay of combination therapy in malaria.[2,3] The discovery and development of new antimalarials, particularly those with novel mechanisms of action and no cross resistance to current drugs, is therefore an urgent challenge.

Fusidic acid, an antibiotic isolated from *Fusidium coccineum*[4], has been in clinical use since the 1960s for the management of topical and systemic bacterial infections caused by gram-positive bacteria such as *Staphylococcus aureus.*[5-10] The *in vitro* MIC_{50} of fusidic acid against most gram-positive bacteria lies between 0.1µM – 1µM.[11-14] Its mechanism of action involves inhibition of bacterial protein synthesis by locking elongation factor-G (EF-G) on the ribosome with Guanosine 5'-diphosphate (GDP) in a post-translocational state.[15] Extensive structure-activity relationship (SAR) studies have been carried out on fusidic acid in the antibacterial field.[16-20]

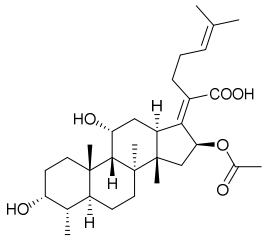

Figure 1. Structure of fusidic acid.

Fusidic acid is also known to have *in vitro* antiplasmodial activity against *P. falciparum*.[21-23] A few studies have suggested that fusidic acid may act by inhibiting plasmodial EF-Gs located in the apicoplast and mitochondria,[22-23]though it is unclear whether other mechanisms of action contribute to this activity. However, the reported IC_{50} (52.8 µM against *P.falciparum* strain D10) is too high for fusidic acid to be clinically useful as an antimalarial. Nevertheless, its precedented clinical use – where it has been shown to have excellent tissue distribution, good oral bioavailability and a low degree of toxicity[24-25] – and the novelty in its mechanism of action, makes it a promising new antiplasmodial scaffold for repositioning *via* medicinal chemistry approaches.

The low *in vitro* antiplasmodial activity of fusidic acid may reflect the influence of many factors including its ability to get to the target site, its concentration at the site of action, its affinity for

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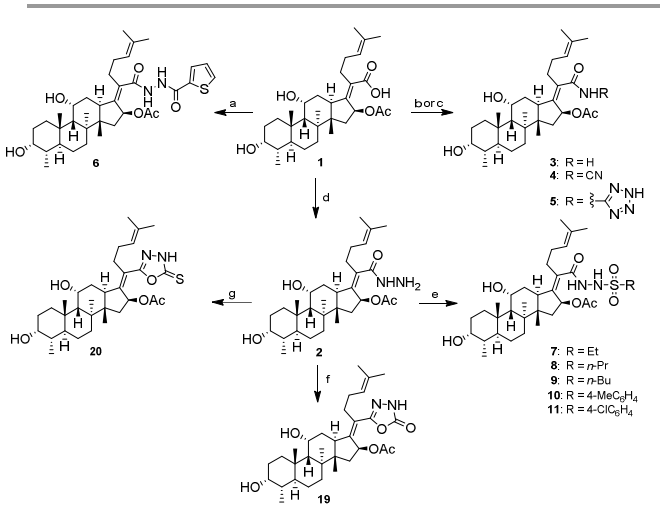
†Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

the target and its ability to block the target once bound. All or one of these factors might be responsible for the high *in vitro* IC_{50} (52.8 μM) of fusidic acid against *P. falciparum*. In view of this, we explored the potential of this compound as an antiplasmodial agent by performing structural modifications aimed at improving selective antiplasmodial activity and synthesized new derivatives of fusidic acid by replacing COOH with its bioisosteres. Bioisosteric replacements are known to improve biological properties of a molecule by modifying its physiochemical properties while maintaining the necessary interactions with the target.[26] Carboxylic acid bioisosteres are one of the most frequently studied bioisosteric replacements in drug discovery.

Herein, we report the synthesis and antiplasmodial activity of fusidic acid bioisosteres and the docking interactions of selected compounds on homology models of plasmodial EF-Gs.

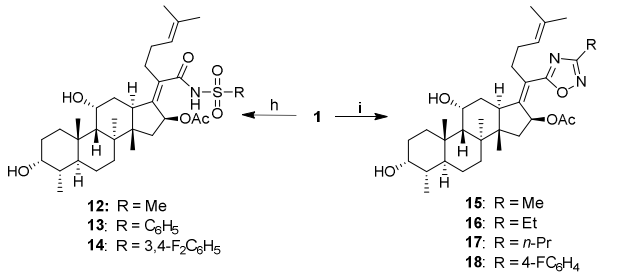
Results and Discussion

The compounds synthesized for this study are presented in Table 1 with the corresponding synthetic routes outlined in Schemes 1-2. Cyclic as well as acyclic bioisosteres of carboxylic acid were selected from literature[26-30] to synthesize a total of 19 fusidic acid derivatives (Table 1). The derivatives **2**,[31] **4** and **5** were obtained in good to moderate yields (98-29%, Table 1) by reacting commercially available fusidic acid **1** with hydrazine hydrate, cyanamide and 5-aminotetrazole respectively, using EDCI/HOBt as a coupling reagent (Scheme 1). Likewise, PyBOP-mediated coupling of **1** with ammonium chloride at room temperature furnished fusidic acid amide **3**[31] (31%, Table 1). The synthesis of compound **6** was accomplished by treating **1** with thiophene-2-carbohydrazide and TBTU in DMF. Sulfonylhydrazinyl derivatives of fusidic acid (**7**-**11**) were obtained in moderate to good yields (25-71%) by reacting compound **2** with respective sulfonyl chloride (aliphatic sulfonyl chlorides with varying carbon chain length for **7**-**9** and 4-substituted aromatic sulfonyl chlorides for **10**-**11**) at room temperature using pyridine as a base and solvent (Scheme 1).



Scheme1. Reagents and reaction conditions: (a) Thiophene-2-carbohydrazide, TBTU, DIPEA, DMF, 25°C, 16 h; (b) PyBOP, HOBt, DIPEA, NH_4Cl, DMF, 25°C, 16 h for compound **3**; (c) RNH_2, EDCI, HOBt, DIPEA, DCM, 25°C, 24 h for compounds **4** and **5**; (d) EDCI, HOBt, CH_3CN, 25°C, 3 h, $NH_2NH_2.H_2O$, 25°C, 16 h; (e) RSO_2Cl, pyridine, 25°C, 1-3 h; (f) CDI, Et_3N, THF, 0°C-25°C, 16 h; (g) CS_2, KOH, EtOH, reflux, 16 h.

Aliphatic (**12**), unsubstituted (**13**) as well as substituted aromatic (**14**) sulfonamide derivatives of fusidic acid were obtained in moderate yields (30-55%, Table 1) through EDCI-mediated coupling of **1** with the respective sulfonamide (Scheme 2). Reaction of **1** with the respective aliphatic and aromatic amidoximes in the presence of EDCI/HOBt in CH_3CN furnished intermediates, which upon reaction with sodium acetate in ethanol under microwave irradiation furnished 3-substituted-1,2,4-oxadiazole derivatives **15**-**18** in relatively lower yields (14-24%, Scheme 2, Table 1). The synthesis of 2-oxo-1,3,4-oxodiazole **19** was accomplished by reacting compound **2** with CDI and Et_3N at room temperature in THF (Scheme 1). On the other hand, the reaction of **2** with carbon disulphide and potassium hydroxide in refluxing ethanol furnished 2-thioxo-1,3,4-oxadiazole **20** in moderate yield (56%, Table 1). All target compounds were purified using column chromatography and fully characterized by analytical and spectroscopic techniques (see ESI†).



Scheme 2. Reagents and reaction conditions: (h) EDCI, DMAP, DCM, 25°C, 48 h; (i) (1) EDCI, HOBt, CH_3CN, 25°C, 3 h, Amidoxime, 80°C, 12 h; (2) NaOAc, EtOH, MW, 100°C, 2 h.

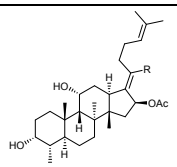
All the synthesized compounds were evaluated for their *in vitro* antiplasmodial activity against the chloroquine-sensitive (CQS) NF54 strain of *P. falciparum* and for cytotoxicity against the mammalian cell line, Chinese Hamster Ovarian (CHO) (Table 1). CQ and artesunate were used as the reference drugs. The stability of fusidic acid under the assay conditions was assessed and no instability was observed over the 48hrs in which the assay was conducted.

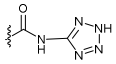
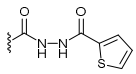
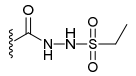
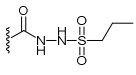
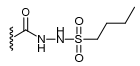
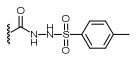
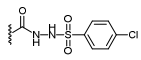
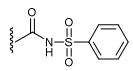
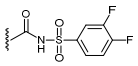
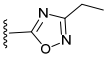
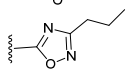
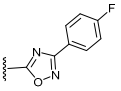
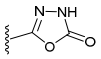
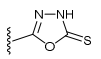
The inhibitory concentration value (IC_{50}) of fusidic acid **1** was found to be 59 μM, which is comparable to that reported for the D10 strain.[22] Most of these derivatives exhibited micromolar potencies against the NF54 strain of *P. falciparum*, with 16 of the 19 compounds having IC_{50} value between 1.7-35.9 μM (Table 1).

First, we investigated the effect of acyclic bioisosteric replacements of carboxylic acid and synthesized various amide and hydrazide derivatives (**1**-**14**). Hydrazide derivatives were found to display better activity (IC_{50} 5.7-31.3 μM) than amide

derivatives (IC_{50} 7.3-35.9 μM). Fusidic acid amide **3** exhibited 2-fold increase in activity (IC_{50} 35.9 μM) as compared to fusidic acid, though with a poor selectivity index (SI) (Table 1). Replacing the carboxylic acid moiety with a cyanamide group augmented the antiplasmodial activity by 5 times (**4**, IC_{50} 10.8 μM) with a SI value of >17. A tetrazole moiety, which has a pKa similar to –COOH group (4.5-4.9 vs 4.2-4.4) and is known to increase lipophilicity of the molecules,[32-33] was also introduced but was found to be inactive at the highest concentration tested (**5**, IC_{50} >15 μM). A possible reason for poor activity of this molecule may be the presence of the amide linkage between fusidic acid and tetrazole core. An attempt to replace the –COOH group with tetrazole was unsuccessful. Amongst sulfonamide derivatives (**12**-**14**), alkyl (**12**) and unsubstituted aromatic (**13**) derivatives were found to be inactive at the highest concentration tested. On the contrary, substitution of the phenyl ring restored the activity as 3,4-difluorophenylsulfonamide derivative **14** (IC_{50} 7.3 μM) was found to be the most active among amide derivatives, displaying an 8-fold increase in activity compared to fusidic acid with a SI value of 11. Amidst the hydrazide derivatives, substituted ones (**6**-**11**) demonstrated better activity than the unsubstituted derivative **2**. Further, aliphatic sulfonyl hydrazides (**7**-**9**) were found to be more active than their aromatic analogues (**10**-**11**). The antiplasmodial activity of the aliphatic sulfonyl hydrazides increased from 12.4 μM (**7**) to 5.7 μM (**8**) with increase in carbon chain length from ethyl to propyl and then decreases with insertion of one more $–CH_2$-spacer (**9**, IC_{50} 8.0 μM). Introduction of heterocyclic aromatic thiophene-2-carbohydrazinyl group resulted in a compound (**6**, IC_{50} 8.4 μM) with activity comparable to its aliphatic analogues. Propyl sulfonylhydrazide **8** being the most active (IC_{50} 5.7 μM) among hydrazide derivatives demonstrated a 10-fold increase in activity compared to fusidic acid with a SI value of 14. Replacement of the carboxylic acid group of fusidic acid with less acidic and similar molecular-size bioisosteres like an oxadiazole was also explored. Oxadiazole rings can exist in three regioisomeric forms; 1,2,4-oxadiazoles, 1,3,4-oxadiazoles and 1,2,5-oxadiazoles, the first two being most common and recurrent motifs in dug-like molecules. However, these two isomeric forms offer different physiochemical profiles e.g. lipophilicity, aqueous solubility, metabolic stability, hERG toxicity and thereby resulting in diverse biological activities.[34] 1,2,4-Oxadiazole derivatives **15**-**18** substituted at the 3-position with aliphatic and aromatic substituents displayed superior antiplasmodial activity (15-35 fold higher) relative to fusidic acid. Introduction of a 4-fluorophenyl group at the 3-position of the 1,2,4-oxadiazole ring (**18**, IC_{50} 1.7 μM) conferred a 35-fold increase in potency with the best SI value of 46. 5-Oxo-1,3,4-oxadiazole derivative **19** (IC_{50} 9.2 μM) and its thio analogue **20** (IC_{50} 7.0 μM) also showed improvement in antiplasmodial activity by 6- and 8-fold respectively, but were found to be less active than 1,2,4-oxadiazole derivatives.

Table 1. Yield, *in vitro* antiplasmodial activity, cytotoxicity and selectivity index of fusidic acid bioisosteres.



Comp	R	Yield (%)	Antiplasmodial activity (NF54) IC_{50} (μM)	Cytotoxicity (CHO) IC_{50} (μM)	SI[a]
1	-COOH	-	59.0	>194.0	>3
2	$-CONHNH_2$	98	21.3	112.0	5
3	$-CONH_2$	31	35.9	113.0	3
4	-CONHCN	53	10.8	>185.0	>17
5		29	>15	>171.0	ND
6		50	8.4	78.8	9
7		45	12.4	77.3	6
8		25	5.7	79.7	14
9		71	8.0	49.9	6
10		46	13.4	48.2	4
11		65	31.3	53.2	2
12		55	>15	>169.0	ND
13		38	>15	96.1	ND
14		30	7.3	81.4	11
15		24	3.8	47.8	13
16		23	1.9	71.7	38
17		14	2.1	68.2	32
18		20	1.7	77.4	46
19		24	9.2	82.0	9
20		56	7.0	70.0	10
	CQ		16 nM		
	Artesunate		4 nM		
	Emetine			0.4	

[a]SI (Selectivity index) = IC_{50} CHO/IC_{50} NF54; ND = not determined; CQ = Chloroquine.

In summary, bioisosteric replacement of the carboxylic acid group led to better antiplasmodial activity, with the best activity observed with 1,2,4-oxadiazoles. In addition, cyclic bioisosteres of fusidic acid were in general more active than their acyclic counterparts. The improved biological activity on replacement of carboxylic acid with other moieties also suggests that the free carboxylic group is not essential for antiplasmodial activity. This is in contrast to its antibacterial activity where a free carboxylic acid is reported to be essential.[35]

Previous studies[22-23] have shown that plasmodial EF-Gs located in the apicoplast and mitochondria are the possible targets of fusidic acid and this formed the basis for our docking study. In order to comprehend the probable interactions of fusidic acid and its bioisosteres with plasmodial EF-G, docking calculations of both fusidic acid and its most active derivative **18** were performed on the validated models of apicoplast (*Pf*EF-G_{Ap}) and mitochondrial (*Pf*EF-G_{Mit}) EF-Gs, using a validated Autodock Vina program.[36] The crystal structure of *T. thermophilus* EF-G (*Tt*EF-G; PDB code: 4V5F, Y chain) bound to fusidic acid was used as a template to build both *Pf*EF-G_{Ap} and *Pf*EF-G_{Mit} models.[37] The validated homology models of *Pf*EF-G_{Ap} and *Pf*EF-G_{Mit} were then prepared for docking studies using Protein Preparation Wizard of Schrödinger suite (see ESI†).[38] Autodock Vina docks ligands and ranks them according to their docking score. Fusidic acid exhibited docking scores of -6.7 and -6.3 kcal/mol for *Pf*EF-G_{Ap} and *Pf*EF-G_{Mit}, respectively, while compound **18** showed slightly better scores of -7.5 and -7.1 kcal/mol. The docking score of both compounds were slightly better in *Pf*EF-G_{Ap} than *Pf*EF-G_{Mit} suggesting that they may be more sensitive to the former as mentioned in previous studies.[23] The plausible binding modes of fusidic acid and compound **18** with *Pf*EF-G_{Ap} and *Pf*EF-G_{Mit} are depicted in Figure 2 and 3, respectively. The comparable orientation and slightly better docking score of **18** to fusidic acid in *Pf*EF-G_{Ap} as well as in *Pf*EF-G_{Mit} suggests that its improved antiplasmodial activity may be a result of better binding to *Pf*EF-Gs. However, the contribution of other factors such as improved permeability or activity through a different target cannot be ruled out. Both fusidic acid and **18** exhibit non-covalent interactions with *Pf*EF-Gs, with largely electrostatic and van der Waals bindings of residues with ligands. Fusidic acid interacted with Ile66, Pro93, Gly94, Val96, Asp545, Lys426 residues in *Pf*EF-G_{Ap} and Ile66, Gly91, Pro96, Lys387, Glu505, Asp506 residues in *Pf*EF-G_{Mit} as shown in figures 2 (A) and 3 (E) respectively. Whereas, compound **18** displayed interactions with Ile22, Asp23, Pro93, Val96, Asp545, His568 residues in *Pf*EF-G_{Ap} (Figure 2C), and Ile19, Asp20, Pro90, Glu505, Ile532 residues in *Pf*EF-G_{Mit} (Figure 3G). Importantly, the substituted aromatic moiety in **18** interacts with hydrophobic residues in both *Pf*EF-G_{Ap} and *Pf*EF-G_{Mit}, such as Thr, Gly and Ile, which is the reason for the slightly better docking score. Interestingly, Thr92 and Phe98 in *Pf*EF-G_{Ap} and Thr89 and Phe95 in *Pf*EF-G_{Mit} interact directly with both fusidic acid and **18** (Figure 2 and 3**)**, these interactions have been suggested to be responsible for fusidic acid resistance and sensitivity in *Tt*EF-G.[37]

Conclusions

In conclusion, novel fusidic acid derivatives were synthesized by replacing the carboxylic acid group with various bioisosteres and evaluated for their *in vitro* antiplasmodial activity against the CQ-sensitive NF54 strain of the malaria parasite *P. falciparum*. These bioisosteric replacements yielded compounds with a marked (2-35 fold) increase in antiplasmodial activity as compared to fusidic acid which suggests that free carboxylic group is not essential for antiplasmodial activity. 3-Substituted 1,2,4-oxadiazoles were found to be the most promising with the 3-(4-fluorophenyl)-substituted-1,2,4-oxadiazole derivative **18** being found to be the most active and selective. Further, homology structural models of the *Pf*EF-G_{Ap} and *Pf*EF-G_{Mit} were constructed and used for docking calculations of fusidic acid and compound **18**. The results of these calculations, which need to be validated experimentally, indicated an energetic preference for the binding of bioisostere **18** over fusidic acid within the active site of the *Pf*EF-G. The contribution of other mechanisms of action, however, cannot be discounted, at this stage. Overall, this work demonstrates the potential of fusidic acid as a promising novel antimalarial template for repositioning purposes.

Acknowledgements

The University of Cape Town, South African Medical Research Council, and South African Research Chairs initiative of the Department of Science and Technology administered through the South African National Research Foundation are gratefully acknowledged for support (KC).

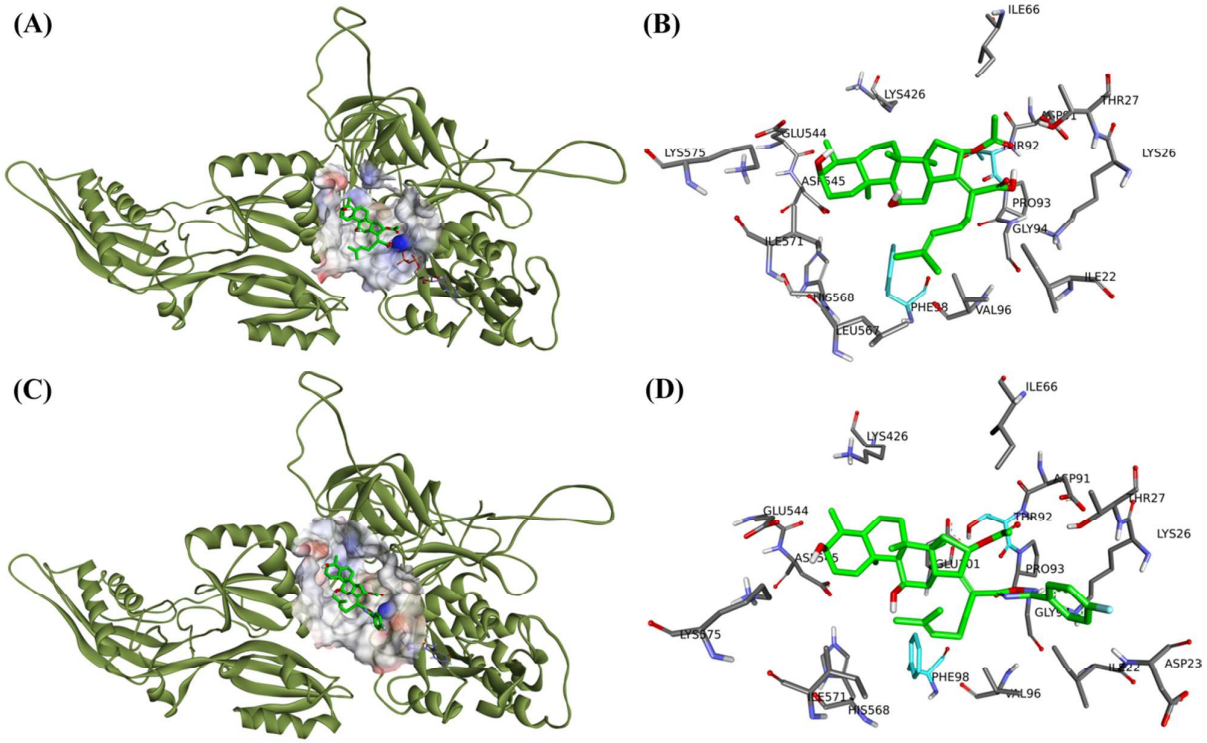


Figure 2. Fusidic acid (**A**) and compound **18** (**C**) in the binding site of *Pf*EF-G_{Ap}. Surfaces of binding site are colored by their charges. Red color represents negative charge, blue represents positive charge and grey color represents neutral charge. The interacting residues are shown within 5 Å based on fusidic acid (green color) **(B)** and compound **18** (green color) **(D)**. The residues that proposed to interact directly with *Tt*EF-G are highlighted by cyan color.

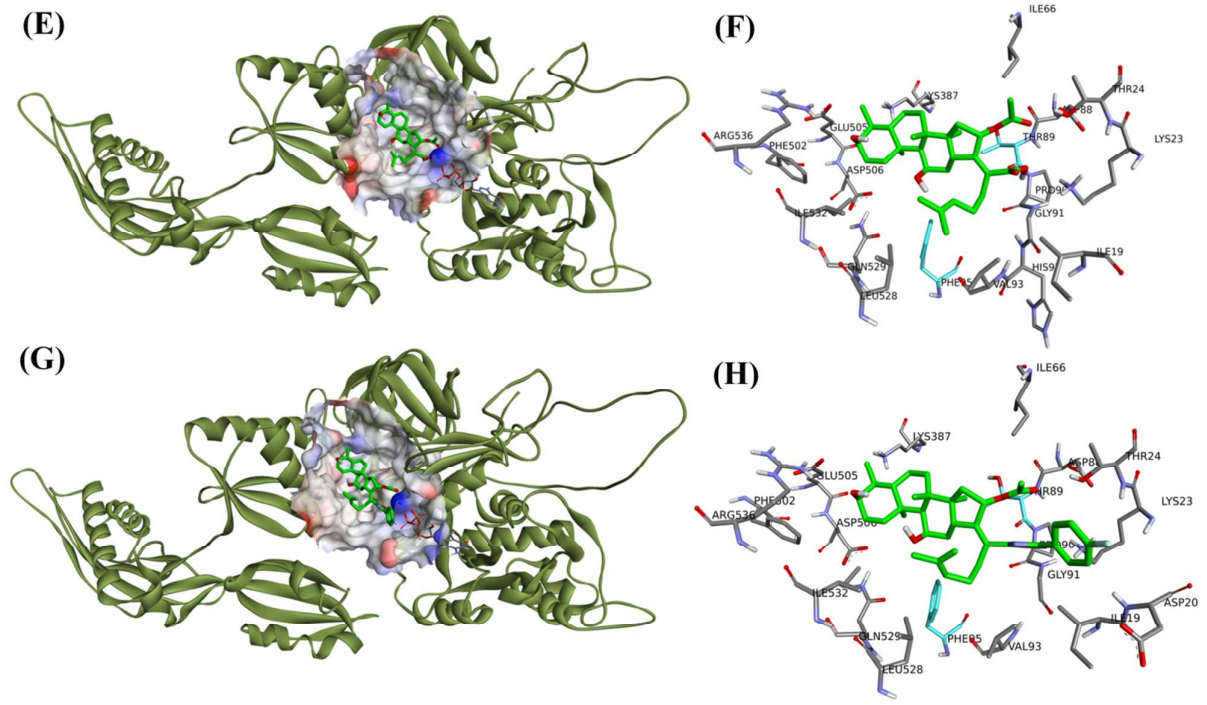


Figure 3. Fusidic acid (**E**) and compound **18** (**G**) in the binding site of *Pf*EF-G_{Mit}. Surfaces of binding site are colored by their charges. Red color represents negative charge, blue represents positive charge and grey color represents neutral charge. The interacting residues are shown within 5 Å based on fusidic acid (green color) **(F)** and compound **18** (green color) **(H).** The residues that proposed to interact directly with *Tt*EF-G are highlighted by cyan color.

Notes and references

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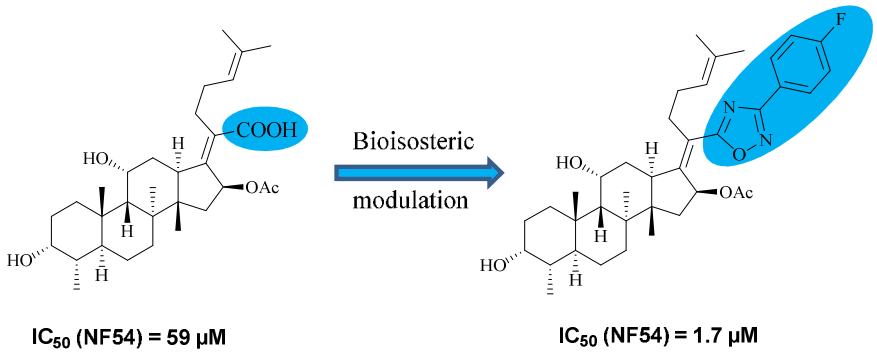
Graphical Abstract

Synthesis of fusidic acid bioisosteres as antiplasmodial agents and molecular docking studies in the binding site of Elongation Factor-G

Gurminder Kaur, Kawaljit Singh, Elumalai Pavadai, Mathew Njoroge, Marlene Espinoza-Moraga, Carmen De Kock, Peter J. Smith, Sergio Wittlin and Kelly Chibale



IC_{50} (NF54) = 59 µM

IC_{50} (NF54) = 1.7 µM