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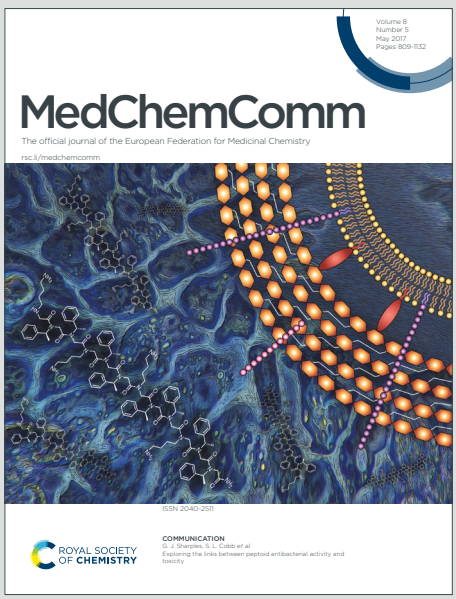

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ARTICLE TYPE

Repositioning Salirasib as new antimalarial agent

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Malaria is a serious tropical disease that kills thousands of people every year, mainly in Africa, due to *Plasmodium falciparum* infections. Salirasib is a promising cancer drug candidate that interferes with the post-translational modification of Ras. This S-farnesyl thiosalycylate inhibits the isoprenyl carboxyl methyltransferase (ICMT), a validated target for cancer drug development. There is a high homology between the human and the parasite enzyme isoforms, in addition to being a druggable target. Looking to repurpose its structure as antimalarial drug, a collection of S-substituted derivatives of thiosalicylic acid were prepared, introducing a 1,2,3-triazole as diversity entry point or by direct alkylation of the thiol. We further investigated the *in vitro* toxicity of FTS analogues to *Plasmodium falciparum* in the asexual stages and in Vero cells. The antiplasmodial activity assay was performed using a simple, high-sensitivity methodology based on nanoluciferase (NLuc)-transfected *P. falciparum* parasites. The results showed that some of the analogs were active at low micromolar concentration, including Salirasib. The most potent member of the series has S-farnesyl and the 1,2,3-triazole moiety substituted with phytyl. However, the compound substituted with methyl-naphthyl show promising physicochemical and activity values. The low cytotoxicity in eukaryotic cells of the most active analogs provided good therapeutic indexes, being a starting-point candidate for future antimalarial drugs development.

Malaria is one of the most important tropical diseases, and the World Health Organization describes malaria as one of the top ten causes of death worldwide.[1] In 2016, malaria infected 216 million and killed more than 400 thousand people; most deaths occurred in Africa and were due to *Plasmodium falciparum* infections. Nowadays, there are no vaccines for malaria immunization. Therefore, the disease prophylaxis, control and treatment are based on the existing chemotherapy and vector control.

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Currently the WHO suggests the use of combination therapies for the treatment of malaria.[2] Unfortunately, the expanding resistance puts at risk the ongoing plans to control the disease.[3] For these reasons, new antimalarial compounds effective against *Plasmodium*'s asexual stages in humans are required to treat infected people and for use in collective eradication programs.[1,4]
To facilitate drug discovery, efforts are being made to develop more sensitive, robust, easier, and less expensive methods for drug screening.[5,6] Two well-known research strategies for the discovery of etiological treatments for parasitic protozoan diseases are drug repositioning and improving drugs' effectiveness through structural modifications.[7]
Salirasib (farnesyl thiosalicylic acid, FTS) is a promising drug candidate that was first reported more than 20 years ago.[8,9] This simple compound is a potent inhibitor of the isoprenylcysteine carboxyl methyltransferase (ICMT) in cell-free systems. Surprisingly, its activity did not correlate in intact cells, being a poor methylation inhibitor. It has been shown that Salirasib acts on the Ras signaling cascade, which is required for cell proliferation and differentiation. This process starts with the removal of all Ras isoforms from their membrane anchoring sites.[10] Since its discovery, different clinical trials have been conducted with Salirasib for pancreatic, colon, lung and breast cancers.[11]
One possible target for the development of potential antimalarial drugs is the isoprenoid biosynthesis.[12]

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Isoprenoid are synthesized in *P. falciparum,* plants plastids and most bacteria (among other organisms) by the 2-C-methyl-D-erythritol-4-phosphate (MEP) pathway.[12] In contrast, most animal cells, several eubacteria, some archaea and fungi synthesize isoprenoid precursors only by the mevalonate pathway. In 2004, Goulart *et al.*[13] showed that, for *P. falciparum* strain 3D7 cultured *in vitro*, FTS possesses a dose-response growth inhibition effect with a half maximum inhibitory concentration (IC_{50}) of 14 μM (confidence interval: 13.61-19.18 μM). The greatest lethal effects were observed between the schizont stage and the formation of rings.[13] The same authors showed that FTS specifically decreased radioactive uptake in immunoprecipitated Ras isoprenylated proteins radiolabeled with [1-(n)-^{3}H] farnesyl pyrophosphate triammonium salt.[13] This effect was only observed in the schizont stage, for which the authors suggested a higher Ras protein expression.[13] It was also suggested that, as it happens in other cell systems, Ras proteins could be involved in cell signaling or proliferation in the parasite.[14,15] Based on those precedents, we envisioned FTS as a promising scaffold to develop new antimalarial agents. To explore this hypothesis, a collection of thiosalicylic acid derivatives were prepared and assayed against *P. falciparum*.

Bioinformatics studies of the molecular target

In order to position the ICMT as a possible molecular target for repositioning drugs, multiple sequence alignments and homology modelling were refined (**Figure S1** Supplementary Information).[16] The primary human and infectious apicomplexans ICMT sequences (in particular, *Toxoplasma* and *Plasmodium* genus) were analyzed. All sequences correspond to functional proteins belonging to the ICMT superfamily containing the conserved the C-terminal substrate-binding site, (particularly, between amino acids 160-279 in *H. sapiens*). There is also complete in the active site amino acids conservation and those interacting with the S-adenosyl methionine cofactor. Particularly, there is a 36% identity and 54% similarity between *Hs*-ICMT and *Pf*-ICMT. These values are considerably higher when the domains involved in the catalytic site are analyzed. Expanding the sequence analysis towards different species, allows us to conclude that the catalytic domain of the enzyme is highly conserved throughout evolution (**Figure S2** Supplementary Information). In addition, the TDR Targets database[17] indicates that ICMT would be a druggable target and is potentially essential in *P. falciparum*. Promisingly, TDR target predicts that Salirasib would be a potential inhibitory drug for *Pf*-ICMT. Based on these facts, ICMT is an interesting molecular target and Salirasib an attractive starting-point for repositioning drug toward *P. falciparum* and liable to consequent reengineering.

Design and synthesis

Salirasib activity has been undoubtedly linked to the presence of the thiosalicylic acid on the structure.[9] The simplicity of its structure only allowed minimal structural modifications to explore a structure-activity relationship and improve the activity. It has been observed that a free carboxyl group is absolutely required for its activity. Introduction of halogenic substitution of the benzene ring implies a decrease or a loss of activity on the target.[18] Therefore, we decided to preserve the 2-mercaptobenzoic acid portion in our design and introduce modifications on the thiol. The diversity was introduced by direct alkylation of the thiol, preparing a collection of thioethers and additionally, further diversity was added by 1,2,3-triazol formation by click chemistry (**Figure 1**).

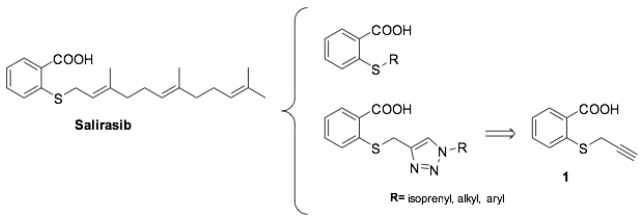
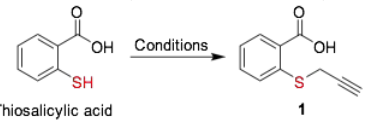


Figure 1. Proposed Salirasib analogs

First, to prepare the thioether collection the selective thiol alkylation was optimized. The propargyl bromide was selected as alkylating agent for that purpose because it was the key intermediate for the 1,2,3-triazole library preparation. (**Scheme 1**) Starting from commercial thiosalicylic acid, different reactions were assayed using different bases and solvents.

The attempts using potassium hydroxide and potassium carbonate in water were unsuccessful (**Table 1**, entries 1-2).



Scheme 1. Alkylation of thiosalicylic acid

When those bases were used, but the solvent was exchanged by MeOH, KOH produced complete product decomposition and with K_2CO_3 alkylated ester product was obtained (**Table 1**, entries 3-4). Fortunately, when using guanidinium carbonate as base in acetone, a complete selectivity was achieved obtaining the S-propagyl thiosalicylic acid **1** as the only product (**Table 1**, entries 5).

Table 1. Optimization of thiosalicylic S-alkylation.

Entry	Reagents[a]	Results
1	KOH (1 eq), H_2O	NR
2	K_2CO_3 (1 eq) H_2O	NR
3	KOH (1 eq), MeOH	Decomposition
4	K_2CO_3 (1 eq), MeOH	S-propargyl propargyl thiosalicylate
5	Guanidinium carbonate (1 eq.) acetone, r.t.	S-propagyl thiosalicylic acid 81% yield

a) thiosalicylic acid (1 eq), propargyl bromide (1eq), reflux, 12 h.

With those conditions optimized, we moved to prepare a collection of analogs. Alkylating agents were selected aiming to cover a wide spectrum of steric and lipophilic demand. Most of the required alkylating agents were commercial. For those not commercially accessible, the bromides were easily prepared from the alcohol precursor by substitution with phosphorous tribromide in Et_2O. The isoprenols (geraniol, farnesol, and phytol) were transformed on the respective chloride through the Corey-Kim modified conditions,[19] using N-chlorosuccinimide, DMS in DCM.

The final collection of the alkylated thiosalicylic acid was prepared

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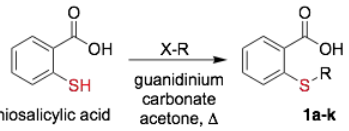
by S-alkylation (**Table 1**, entry 5), using the optimized conditions providing twelve analogs with an average yield of 79% after purification by column chromatography (**Scheme 2, Table 2,** entries 1 to 11).



Thiosalicylic acid **1a-k**

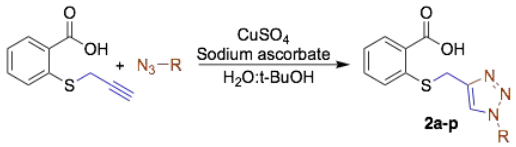
Scheme 2. Alkylated thiosalisylic acid library prepared.

Once the S-alkylated thiosalisylic acid collection was finished, we moved to synthesize the 1,2,3-triazole collection. A pool of azides were selected, following the same chemotype used for the alkylated products, and applied to prepare the new derivatives. Azides were mostly prepared by direct substitution of the bromide with sodium azide in DMF. For the isoprenyl azides, the isoprenol was transformed in one-pot reaction to the azides, whose regioisomers are in equilibrium.[20] The triazoles were synthesized by reaction of S-propargyl thiosalicylate **1** with the azide under conventional conditions using copper sulphate, sodium ascorbate in ^{t}BuOH:H_2O (1:1).[21] The collection of sixteen new products was obtained with an average yield of 81% after purification. (**Scheme 3**, **Table 2** entries 12 to 28)

Biological activity

In vitro* activity against *P. falciparum

The NanoLuc Luciferase (NLuc) method for drug screening was applied and validated with results previously obtained[6] by the Malaria SYBR Green I Fluorescence assay (MSF). While the fluorescence-based method relied on quantifying fluorescence on parasite cultures previously incubated with the DNA intercalating dye, the most sensitive and affordable NLuc method involves quantifying bioluminescence in NLuc expressing transgenic parasites.[22] In order to confirm that IC_{50}s determined by both methods are similar and that the transgenic NLuc expressing parasites are not more resistant to known antimalarials, wild type 3D7 strain and parasites transfected with the pEF-NLuc expressing vector[22] were cultured in serially diluted concentrations of artesunate for 48h and growth was quantified by MSF and/or NLuc assay. Non-linear regression of growth values generated by both methods produced similar IC_{50} values suggesting results are comparable (**Table S1** Supplementary Information)



2a-p

Scheme 3. 1,2,3-triazolyl thiosalicylate derivatives.

One NLuc assay was validated an initial screening was performed to select the most effective compounds. For this purpose, parasites were cultured with FTS or its analogues at 200 µM concentration. Growth was quantified daily by NLuc assay and compared to parasites cultured with the solvent control ethanol. Because most compounds are soluble in ethanol, 200 µM is approximately the highest assayable drug concentration that does not produce significant effects due to ethanol toxicity (0.5-1% at maximum). The inhibition percentage caused by FTS and its analogues at the 200 µM concentration (as compared to an untreated control) was calculated three times. We also performed quality controls with antimalarial drugs, including 200 µM of clindamycin (which is a delayed-effect antimalarial compound), 200 nM of both artesunate and chloroquine (as supralethal controls) and 3.125 nM of artesunate (as a sublethal control). Compounds **2k** and **2m** showed haemolysis at 200 µM but not at 100 µM; for this reason, the inhibition percentage study was performed at 100 µM. The results showed that clindamycin, as well as FTS and most of its derivatives, had higher inhibitory effect at 72 h than after one or two days (**Figure S3** Supplementary Information). On the other hand, inhibition by either sub- or supralethal artesunate concentrations was similar from 1-3 days. Considering the assays initiated with ring stage parasites, the compounds likely act on late stage parasites as previously reported for FTS.

The IC_{50} was determined for FTS analogues which inhibited parasites growth >90% after 72 h, an effect like the observed inhibition of antimalarial control drugs at supralethal concentrations (**Tables 2**, **Figure S4** Supplementary Information). The IC_{50}s of chloroquine and artesunate were determined as positive and quality controls. The IC_{50} was calculated at 72 h because produced the best antimalarial effect and to be comparable with previous FTS. We used an initial lethal maximum concentration of 200 µM for FTS (100 µM for compounds **2k** and **2m**); and its analogues, or 200 nM for chloroquine and artesunate, in addition to several smaller concentrations prepared by serial dilutions.

We also checked all the compounds for which the calculated IC_{50} values indicated that they may have been directly interfering with nLuc luminescence emission (**Figure S3** Supplementary Information). For this purpose, we added a 200 µM concentration of each prepared analog to 100 µL of parasite lysate prepared as previously described from unsynchronized cultures (parasitaemia 1%, haematocrit 2%); we then counted the emitted luminescence with respect to a control without added experimental compounds. The results showed few luminescence modifications which is comparable to those results obtained by other authors' homologous assays for antimalarial drug screenings.[4,5] Again, in this assay all samples had $Z > 0.5$.

In vitro antimalarial activity of the collection of S-alkylated thiosalicylic acid (Compounds **1a-k**) is shown on the **Table 2** (entries 1-11). Most of the derivatives of this collection were inactive at the maximum concentration tested of 200 µM, including the key intermediate S-propargyl thiosalicylic acid **1**.

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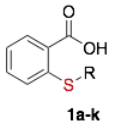
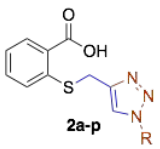
Table 2. *In vitro* antimalarial activity and yield of alkylated thiosalicylic acid derivatives and of 1,2,3-triazolyl thiosalicylic acid derivatives.

Entry	Cmpd	R	Yield (%)	*P. falciparum* * IC_{50} μM	Z value	R^2
1	**1**	Propargyl	81	> 200		
2	**1a**	Cyclohexyl	87	> 200		
3	**1b**	Benzyl	73	> 200		
4	**1c**	3-phenyl-propyl	75	> 200		
5	**1d**	Cinnamyl	68	> 200		
6	**1e**	Octyl	83	> 200		
7	**1f**	Decyl	81	> 200		
8	**1g**	$CH_2CH_2CO_2CH_3CH_3$	78	> 200		
9	**1h**	Prenyl	72	> 200		
10	**1i**	Geranyl	88	> 200		
11	**1j**	Farnesyl (Salirasib)	79	20.34±5.52	0.93±0.06	0.95±0.02
12	**1k**	Phytyl	85	13.40±1.53	0.93±0.06	0.98±0.02
13	**2a**	Cyclohexyl	84	> 200		
14	**2b**	Benzyl	80	> 200		
15	**2c**	3-phenyl-propyl	88	> 200		
16	**2d**	Cinnamyl	86	65.33±10.71	0.89±0.09	0.87±0.01
17	**2e**	Octyl	78	> 200		
18	**2f**	Decyl	88	> 200		
19	**2g**	$CH_2CH_2CO_2CH_2CH_3$	91	> 200		
20	**2h**	Prenyl	89	> 200		
21	**2i**	Geranyl	84	> 200		
22	**2j**	Farnesyl	90	25.97±1.32	0.94±0.06	0.96±0.02
23	**2k**	Phytyl	83	9.75±1.97	0.92±0.06	0.98±0.01
24	**2l**	$CH_2CO_2CH_2CH_3$	92	> 200		
25	**2m**	Cetyl	81	14.44±5.43	0.93±0.06	0.97±0.01
26	**2n**	Tridecanyl	55	19.83±5.14	0.88±0.08	0.97±0.02
27	**2o**	2-phenyl-ethyl	94	> 200		
28	**2p**	Naphthyl	33	20.54±5.45	0.92±0.06	0.96±0.04
	CQ			8.15±1.83 nM	0.75±0.18	0.96±0.02
	ART			1.64±0.08 nM	0.86±0.11	0.96±0.03



1a-k



2a-p

CQ=Chloroquine, ART=Artesunate, *evaluated by NanoLuc Luciferase method

Interestingly the only active compounds of the series were the prenylated analogs **1j** and **1k**. Compound **1j** (R=*E,E*-farnesyl, Salirasib) and **1k** (R=phytyl) has IC_{50} of 20.34 and 13.40 μM, respectively. The derivatives with smaller prenyl chains (**1h** R=prenyl and **1i** R=geranyl) were inactive at 200 μM linking the activity with the number of isoprene units. That is not surprising having in mind that early studies of thiosalicylic as prenylated protein methyl transferase inhibitors shown to be very sensitive to nature of the prenyl chain, being inactive for geranylated analogs.[18,23]

On the other hand, it is interesting to note that only the most voluminous molecules of this family that contain fatty acid chain (**1j** and **1k**) are active in *P. falciparum*. Members with shorter chains are inactive (**1e** and **1f**). Finally, the remaining inactive analogs that has aromatic, carbocyclic or alkyl esters put some limits to possible stereo-electronic variations on the structure.

In vitro antimalarial activity of the collection of the 1,2,3-triazolyl thiosalicylic acid derivatives (Compounds **2a-p**) are presented on the **Table 2 (**entries 13-28**)**. The behavior of this collection is similar to the S-alkylated analogs with long fatty substituents providing better activity. A detailed look on the activities shown that compounds **2a**, **2b**, **2c**, **2e**, **2f**, **2g**, **2h**, **2i**, **2l** and **2o** did not display activity on *P. falciparum* at the maximum concentration tested (200 μM).

The remaining six analogs displayed IC_{50}s in the range of 65.33 μM, for the cinnamyl derivative **2d**, to 9.75 μM for the phytyl analog **2k**, the most active compounds of both collections (twice as active as Salirasib). A detailed look on the nature of the substituent that provide better activities revealed again that farnesyl (**2j**), phytyl (**2k**), and long alkyl linear chains (**2m**=cetyl and **2n**=tridecanyl) are between the most active. But in this case, the aromatic substituted derivatives **2d** (cinnamyl) and **2p** (methyl naphthyl) also appeared between the most active, while compounds **2b** (benzyl), **2c** (3-phenyl propyl) and **2o** (2-phenyl ethyl) are not active at concentrations below at 200 μM.

In vitro cytotoxicity assay in Vero cells.

The collection prepared was assayed against Vero cells (ATCC CCL-81, already available in our laboratory) to determine the selectivity against the *P. falciparum*. The initial screening showed that all the compounds were non-cytotoxic at the maximum concentration tested of 4.75 μg/mL. Then, a selection of the most active analogs was submitted to a full analysis to determine the IC_{50}.

Compounds **1j**, **1k**, **2d**, **2j**, **2k**, **2m**, **2n** and **2p** were assayed showing different degree of cytotoxicity as was expected because they have an anticancer origin (**Table 3**). The most toxic compound, analog **2l**, has an IC_{50} of 34 μM where the less toxic analogs, compounds **1j**, **2d** and **2j**, were inactive at the maximum concentration tested of 200 μM. A detailed analysis on the activities shows that compounds with long aliphatic or prenyl chains are the most cytotoxic derivatives. That is the case for analogs **1k**, **2k**, **2m**, **2n** and **2p** that has IC_{50}s below 60 μM, but in no case the selectivtivy index is lower than 1.8. Taking into consideration those values, the selected hits of the series were compounds **1j**, **2j** and **2p** that have therapeutic indexes of 10.3, >7.70 and 6.95, respectively. According with those values, the analogues can be considered as promising starting-point candidates[24] to move to further *in vivo* studies.

Table 3. Cytotoxicity of selected analogs

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Entry	Cmpd	Family / R	Vero cells IC_{50} μM	SI
1	**1j**	S-Alk/farnesyl	210 ± 5	10.3
2	**1k**	S-Alk/phytyl	52 ± 4	3.87
3	**2d**	123T/cinnamyl	> 200	> 3.06
4	**2j**	123T/farnesyl	> 200	> 7.70
5	**2k**	123T/phytyl	34 ± 1	3.67
6	**2m**	123T/cetyl	27 ± 4	1.86
7	**2n**	123T/tridecanyl	59 ± 4	2.99
8	**2p**	123T/naphthyl	143 ± 6	6.95

SI= Selectivity index. Calculated as IC_{50}Vero cells / IC_{50}*P. falciparum*

ADME-Tox calculations

An oral drug requires good bioavailability than can be achieved by balancing their partitioning and solubility properties. Those properties are difficult to achieve on any drug development pipeline. Indeed, one third of new chemical entities have poor pharmacokinetics properties and have not been able to reach the clinical trial phase. To avoid these problems an early estimation of ADME-Tox properties seems mandatory in any drug discovery program. The *in silico* ADME-Tox gave substantial information for the feasible and pharmacotherapeutic use of the chemical library.

To rationalize the profile of our analogs computational studies of all the synthesized compounds were performed to predict their absorption, distribution, metabolism and excretion (ADME) properties, Lipinski's rule of five, toxicity liabilities and drug likeness. The calculation was performed using the web-based software Molinspiration,[25] Osiris,[26] ChemAxon,[27] and SwissADME.[28] The Molinspiration platform uses a sum of fragment-based contributions and correction factors being able to calculate parameters of most of the organic and even organometallic molecules. The analysis of the collection revealed that only two compounds have a MW > 500. Almost half of those (13 analogs) violated the rule with logP > 5. However, our library contains ionizable groups that are charged at physiological pH, which make logD a better descriptor of the lipophilicity of these molecules. The calculated logD at physiological pH (7.4) of the collection shows that 93% of the library being ≤ 5 (-1.62 to 6.31). Finally, all compounds fulfill the restrictions on the number of hydrogen donors and acceptors. The physicochemical profile and distribution of the prepared compounds based on molecular weight, polar surface area, logD and octanol/water partition coefficient are displayed on **Figure 2**.

The OSIRIS Property Explorer platform was used to perform a toxicology analysis also providing the drug likeness and a drug score. The results revealed that none of the products prepared are potentially mutagenic, irritant, teratogenic or toxic for sexual reproduction. The solubility is a critical property which aids in the circulation of a drug after the administration and into the bloodstream. The calculated drug likeness shows a variable profile with thirteen derivatives with a poor profile (<-3), but the remaining derivatives fall between -3 and 0. The combination of solubility, logP, MW and toxicity risk are used to calculate the drug score, that were from moderate to good compared with a standard drug (0.13-0.61).

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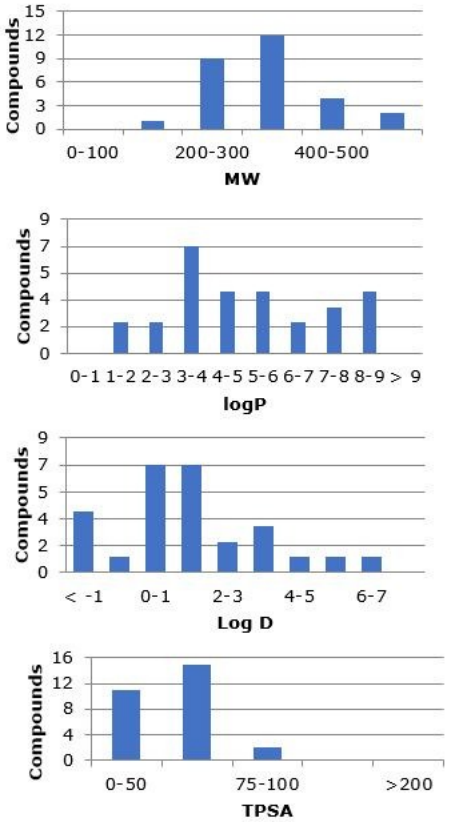

Figure 2. Distribution of physicochemical parameters of the chemical library.

Even though there are diverse routes of drug administration, oral dosing is highly preferred, especially for tropical diseases. Early estimation of oral bioavailability (for example, the fraction of the dose that reaches the bloodstream after oral administration) is very useful in drug development pipeline. Bioavailability is highly multifactorial but is primarily driven by gastrointestinal absorption. SwissADME use the BOILED-Egg method to predict gastrointestinal absorption and brain penetration of small molecules. In this point, among all the active compounds, the one that stands out the most is compound **2p**.

A good proportion of the analogs did not comply the logP requirement. However, the analogs contain ionizable groups, so the logD calculated at physiological pH are more adequate. We wanted to find a correlation between the compound activity and its partition coefficient. A chart correlating the *P. falciparum* IC_{50} vs. logD presented on **Figure 3** (on top) showed a clear pattern. An interesting outcome of this chart is the location of the most active compounds. On the one hand, a region of "high activity" can be defined being all the compounds with logD > 3. On the other hand, the remaining analogs were inactive except for the methyl-naphthyl derivative **2p**. The tendency shows that the highest activity for the library is concentrated for the analogs with logD between 4.7 to 6.5, with a maximum value in 6 (**Figure 3**, bottom). The analog **2p** seems to conjugate good activity, excellent ADMETox values and proper physicochemical parameters. Likewise, the difference in the physicochemical properties with respect to the other active molecules of the family suggest that the compound **2p** would exert a different mechanism of action.

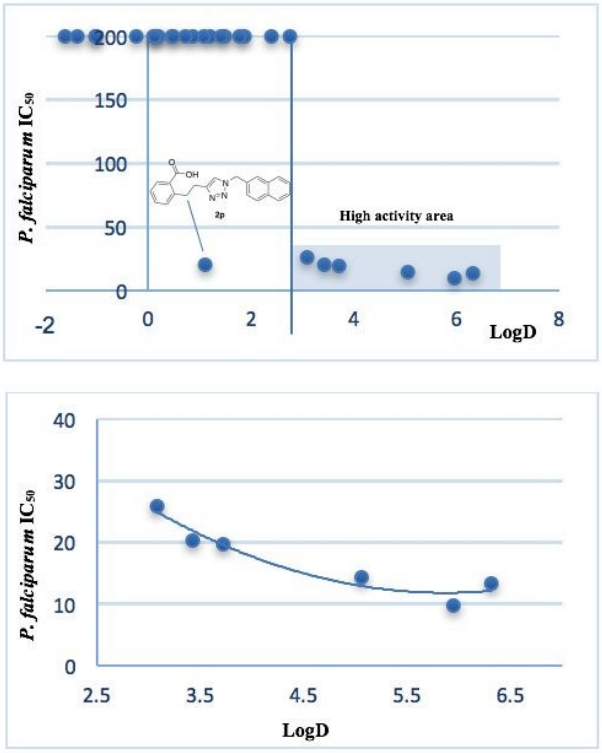

Figure 3. Top: Correlation between the *in vitro* antimalarial activity and the logD. Bottom: Expansion of "high activity" area and tendency.

Conclusions

Drug reposition has emerged as a valuable strategy for the development of new treatment against tropical diseases including malaria. Drug repurpose and reengineering have been shown as efficient strategies to reduce the cost and time of drug development. Almost 40% of drugs registered by the US FDA found new uses in the treatment of several human conditions.[29] Based on that premise, we selected Salirasib as a starting point to reengineer the anticancer drug as a new antimalarial agent, preparing a library of new 28 thiosalycilic acid derivatives. The whole collection was tested against *P. falciparum*, the etiological agent of malaria. The selectivity towards *P. falciparum* in comparison with Vero cells could point Salirasib as an example of drug repositioning. Moreover, an island of high activity was found for derivatives substituted with long alkyl chains or the farnesyl terpene derivative. Compound **2k** is the most active structure against *P. falciparum* (IC_{50} 9.75 µM, SI 3.67). Some compounds have high logP values breaking Lipinsky´s rules, but logD calculated at physiological pH seems to be a better descriptor, based ionizable groups on the prepared analogs. The naphthyl derivative **2p** has an antimalarial activity profile similar to Salirasib, good ADME-T parameters and excellent drug score being the best candidate as antiplasmodial agent. The lack of toxicity of **2p** (predicted *in silico* and validated on Vero cells) together with its structural simplicity, prompted us to point out this new analog as a starting-point candidate for future antimalarial drug development. The most active members of the collection have activity values are comparable to other examples of drug

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repositioning towards malaria, such as verteporfin, amlodipine besylate, triamterene, rocuronium bromide, or apoptozole.[30,31] Same conclusion can be reached if examples of repositioning towards other parasitic diseases are analyzed.[32,33] However, in some cases the selectivity index is low, or they break more than one of the Lipinsky's rules. Finally, further optimization would be required for series to become a serious contender for future drug development.

Conflicts of interest

There are no conflicts to declare.

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Repurposing strategies represent an enormous advantage for drug discovery, especially in malaria, where resources are scarce.

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