Substituted Aminoacetamides as Novel Leads for Malaria Treatment

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Herein we describe the optimization of a phenotypic hit against *Plasmodium falciparum* based on an aminoacetamide scaffold. This led to N-(3-chloro-4-fluorophenyl)-2-methyl-2-[[4-methyl-3-(morpholinosulfonyl)phenyl]amino]propanamide (compound 28) with low-nanomolar activity against the intra-erythrocytic stages of the malaria parasite, and which was found to be inactive in a mammalian cell counter-screen up to 25 μM. Inhibition of gametes in the dual gamete activation assay suggests that this family of compounds may also have transmission blocking capabilities. Whilst we were unable to optimize the aqueous solubility and microsomal stability to a point at which the aminoacetamides would be suitable for in vivo pharmacokinetic and efficacy studies, compound 28 displayed excellent antimalarial potency and selectivity; it could therefore serve as a suitable chemical tool for drug target identification.

Introduction

Malaria is a devastating parasitic disease, which is endemic in many parts of the developing world. Human malaria is caused by five species of *Plasmodium*, of which, *P. falciparum* causes the greatest number of deaths, affecting many parts of Africa. *P. vivax* causes severe morbidity and affects mainly Latin America and South East Asia. In 2017, there were 219 million reported cases of malaria, and >400,000 deaths, many of which were in children under the age of five years. The malaria parasite is transmitted to humans through the bite of an infected female anopheles mosquito when taking a blood meal. Following infection, malaria parasites in the form of sporozoites, migrate from the skin to the liver, where they invade and develop into merozoites. When merozoites outgrow liver cells, they are released into the blood stream, invading red blood cells, where they continue to grow and develop, repeating the cycle in the erythrocytes. During the intraerythrocytic stages of infection, some parasites differentiate into the sexual form (gametocytes), while others remain as the asexual form, progressing through multiple stages of development within the blood cells. When the parasites are mature, infected red blood cells burst, releasing parasites into the bloodstream, causing the febrile symptoms associated with malaria. Asexual merozoites are then free to invade other red blood cells, whereas gametocytes may be taken up through the bite of a feeding mosquito and transmitted to another human, perpetuating the malaria parasite life cycle. Current front-line therapies for the treatment of malaria are failing due to the increasing development of drug resistance and new antimalarial treatments are urgently needed. Furthermore, novel therapies that target the malaria parasite in all life-cycle stages are required, to both treat
and prevent the spread of malaria and to help in the process of eliminating this disease.\textsuperscript{[5]}

**Results and Discussion**

**Project initiation**

To develop potential new antimalarials, we focused our attention on the publicly available results of a high-throughput screening (HTS) campaign of nearly two million compounds carried out by GlaxoSmithKline (GSK), to identify new chemical matter with antimalarial activity.\textsuperscript{[6]} The screening campaign identified > 13,500 compounds malaria blood-stage actives (Tres Cantos Antimalarial Set, TCAMS). Chemical filtering and prioritization resulted in 47 different chemotypes with antimalarial potency (EC\textsubscript{50} < 2 µM). Herein we describe the selection of one particular series of inhibitors from the TCAMS library screen and the subsequent optimization of a new class of antimalarials, based on a substituted amidoacetamide core.

**Hit selection**

Amidoacetamide TCMDC-123553 (Series 10)\textsuperscript{[7]} was selected as a new chemical starting point based on good antimalarial potency against chloroquine/pyrimethamine-sensitive and -resistant strains, suitable physicochemical properties for further development\textsuperscript{[8]} and was not subject to drug discovery efforts from any other MMV funded programs. Series 10 comprised a cluster of two compounds: TCMDC-123553 and TCMDC-125117 (Figure 1). The enamide moiety of TCMDC-125117 was flagged as a possible Michael acceptor and with the added risk of epoxidation of the double bond to give a reactive intermediate.\textsuperscript{[9]} Therefore, our focus was directed toward TCMDC-123553 (1) for further in vitro assessment.

**Figure 1.** Compounds from TCAMS Series 10.\textsuperscript{[10]}

As a suitable chemical starting point, TCMDC-123553 (1) displayed good antimalarial activity in vitro and was inactive in a mammalian counter-screen. In a preliminary malaria parasite rate of kill assay (the parasite reduction ratio (PRR) assay\textsuperscript{[10]}), 1 showed a relatively slow rate of kill, intermediate between pyrimethamine and atovaquone (Figure 2). In this assay, parasites were treated with 10×EC\textsubscript{50} concentrations of 1 and samples of parasites taken from treated cultures after 24 and 48 h, and the number of viable parasites determined.

**Optimization of R¹**

Modifications at R¹ (Figure 3 and Table 1) were initially investigated around the substituted phenyl ring. Modifications were focused on improving or retaining activity, whilst increasing metabolic stability and solubility. We envisaged that an increase in metabolic stability could be achieved by modifications to the phenyl ring by the introduction of heteroatoms to both modulate logP and remove potential sites of metabolism. Alternatively, replacement of the phenyl ring with aliphatic polar and/or basic groups, could simultaneously improve met-
abdomic stability and aqueous solubility. Removal of the chlorine atom at the C3 position to afford fluorophenyl 2 decreased lipophilicity and improved solubility, but resulted in a small drop in potency. Removal of the fluorine atom at C4 (4) had little effect on potency, whilst removal of both halogens (3) gave a 10-fold decrease in activity. Furthermore, removal of one or both halogens had little effect on metabolic stability. Synthetic modifications at R1 were then directed toward aromatic heterocycles. Direct replacement of the di-halogenated phenyl of 1 with a pyrazine (5) did not improve solubility or metabolic stability and lost all antimalarial activity. Thiazole (6) and oxazole (7) however, did improve solubility although all antimalarial activity was lost and metabolic stability was not improved.

Despite the relatively low clogP the compounds still showed poor metabolic stability. We then focused on aliphatic heterocycles. Substituting the R2 di-halogenated aniline of 1 for morpholine 8, lost all antimalarial activity, although led to an improvement in metabolic stability. Cyclohexylamine 9 retained some activity, but suffered from ≈20-fold drop in antimalarial potency relative to compound 1, and was metabolically unstable. The difluoro derivative (10) showed similar activity to compound 9, but with significantly improved solubility, possibly due to the difluoro giving a small dipole moment.\[16\] Replacement of the morpholine oxygen atom in 8 with difluoro 11 was also inactive, and lost metabolic stability relative to 8. The addition of a nitrile group on the cyclohexyl ring of 9, as exemplified by 12, led to a loss of activity. Replacement of the R2 amino cyclohexyl moiety of 9 with a piperazine (13) improved metabolic stability and aqueous solubility but not metabolic stability and also lost all antimalarial activity. Substitution at R1 with piperidine 14 afforded a compound with lower solubility and microsomal stability than 13, and again rendered the compound inactive. Efforts to improve potency and physicochemical properties were then directed toward changes at the R2 position.

Table 1. Modifications at R1.

| R1     | EC50 [μM] | M, [Da] | clogP | Mouse microsomal Clint [mL·min⁻¹·(g liver)⁻¹] | Sol. [μM] |
|--------|-----------|--------|-------|--------------------------------------------|----------|
|        | PF(3D7)   | HepG2  |       |                                            |          |
| 1      | 0.14 (n=6) | > 50 (n=3) | 442  | 2.4                                        | > 50     | 164 |
|        | CI 0.18–0.10 |          |      |                                            |          |     |
| 2      | 0.42 (n=4) | > 25 (n=2) | 407  | 2.1                                        | 45       | > 250 |
|        | CI 0.52–0.34 |          |      |                                            |          |     |
| 3      | 1.45 (n=4) | > 25 (n=2) | 389  | 2.0                                        | 42       | 183 |
|        | CI 1.51–1.31 |          |      |                                            |          |     |
| 4      | 0.19 (n=4) | > 25 (n=2) | 424  | 2.3                                        | > 50     | 219 |
|        | CI 0.28–0.13 |          |      |                                            |          |     |
| 5      | > 50 (n=5) | 4.98 (n=3) | 391  | 1.5                                        | 42       | 55 |
|        | CI 17.59–1.64 |          |      |                                            |          |     |
| 6H     | > 50 (n=3) | > 25 (n=2) | 396  | 1.6                                        | 32       | > 250 |
|        |            |          |      |                                            |          |     |
| 7      | > 50 (n=3) | > 25 (n=2) | 380  | 1.3                                        | 9.7      | > 250 |
|        |            |          |      |                                            |          |     |
| 8      | > 50 (n=3) | > 25 (n=2) | 395  | 2.2                                        | 3.8      | 110 |
|        |            |          |      |                                            |          |     |
| 9H     | 2.67 (n=3) | > 25 (n=3) | 383  | 0.8                                        | 37       | 20 |
|        | CI 3.37–2.17 |          |      |                                            |          |     |
| 10     | 1.71 (n=6) | > 25 (n=3) | 431  | 2.2                                        | 19       | > 250 |
|        | CI 2.24–1.21 |          |      |                                            |          |     |
| 11     | > 50 (n=3) | > 25 (n=2) | 417  | 1.7                                        | 10       | > 250 |
|        |            |          |      |                                            |          |     |
| 12     | > 50 (n=3) | > 25 (n=2) | 406  | 1.2                                        | 4.6      | > 250 |
|        |            |          |      |                                            |          |     |
| 13     | > 50 (n=5) | > 25 (n=3) | 382  | 0.6                                        | 1.1      | > 250 |
|        |            |          |      |                                            |          |     |
| 14     | > 50 (n=3) | > 25 (n=2) | 381  | 1.7                                        | 11       | > 250 |

(a) n: number of screening replicates; CI: 95% confidence interval. [b] Values were calculated using StarDrop\[\textsuperscript{16}\] from Optibrium. [c] Kinetic solubility in water. [d] Purity: 84%. [e] Purity: 81%.
Optimization of R²

Substitution of the methyl group of 1 at R² with fluorine to afford 16, displayed a small drop in potency, but 16 was still rapidly metabolized (Table 2). Replacement of the methyl group on R² with a chlorine atom (15), displayed a moderate improvement in potency, but aqueous solubility and metabolic stability were still poor. Removal of the methyl group altogether with 17, did not improve metabolic stability or solubility and gave rise to a ≈100-fold drop in potency. Modifications at R² were then directed toward replacement of the morpholine sulfonamide moiety. Removal of the morpholine oxygen atom from 1 gave the piperidinesulfonamide 18, which showed similar potency but increased lipophilicity and decreased aqueous solubility. The smaller and less lipophilic diethyl sulfonamide (19) and dimethyl sulfonamide (20) did not improve metabolic stability or solubility relative to 1, although 19 retained potency, and 20 only showed a small drop. Replacement of the sulfonamide morpholine group of 1 with a morpholine amide (21), led to a loss of activity. However, compound 21 showed increased solubility, although the metabolic stability was still too high. To try and recover potency, we removed the carbonyl group of morpholine amide 21 to afford benzyl morpholine 22. We envisaged that free rotation of the alkyl-linked morpholine around the phenyl ring of R² may allow the morpholine group to find an optimal interaction with the unknown biological target. However, 22 was inactive against malaria parasites. When explored the bridged morpholine sulfonamide moiety 23, to decrease the planarity of the molecule, with a view to increasing solubility through the possible disruption of crystal packing[17]. Compound 23 retained only a slightly reduced potency relative to compound 1, and may have shown an marginal improvement in solubility but was very unstable with microsomes. We then moved to the,

| R² | EC₅₀ [μM][a] | Mᵣ [Da] | clogP[b] | CLᵣ [mL min⁻¹ (g liver)] | Sol. [μM][c] |
|----|-------------|---------|---------|---------------------|-----------|
| 1  | 0.14 (n = 6) | > 25 (n = 3) | 442 | 2.4 | > 50 |
| 15 | 0.06 (n = 7) | > 25 (n = 3) | 25.72 (n = 3) | 462 | 2.5 |
| 16 | 0.58 (n = 3) | > 25 (n = 2) | 446 | 2.3 | 48 |
| 17 | 11 (n = 5) | > 25 (n = 5) | 427 | 2.1 | > 50 |
| 18 | 0.22 (n = 4) | > 25 (n = 5) | 24.03 (n = 3) | 440 | 3.2 |
| 19 | 0.27 (n = 4) | > 25 (n = 2) | 428 | 2.2 | > 50 |
| 20 | 0.69 (n = 4) | > 25 (n = 2) | 400 | 2.3 | > 50 |
| 21 | > 50 (n = 3) | > 25 (n = 2) | 405 | 2.3 | 5.6 |
| 22 | > 50 (n = 5) | > 25 (n = 3) | 392 | 3.2 | 4.1 |
| 23 | > 50 (n = 3) | > 25 (n = 3) | 454 | 2.7 | > 50 |
| 24 | > 50 (n = 5) | > 25 (n = 2) | 468 | 2.9 | > 50 |

[a] n: number of screening replicates; CI: 95% confidence interval. [b] Values were calculated using StarDrop from Optibrium. [c] Kinetic solubility in water. [d] Compound 17 was only weakly active, with two of five replicates returning an EC₅₀ value greater than the top concentration tested. [e] Purity: 83%. [f] Purity: 88%.
bridged homomorpholino to investigate if we could modulate activity with a larger sulfonamide. Compound 24 displayed similar potency to 23, but decreased solubility. We then investigated changes to the linker functionality, to improve potency and modulate physicochemical properties.

Increasing antimalarial activity: modifications to the linker

Initial changes to the aliphatic linker sought to determine the importance of the linker hydrogen bond donors for antimalarial activity, through the systematic methylation of each NH functionality. Methylation of the R¹ amide NH (25) gave rise to a loss in potency. However, methylation of the R² aniline NH (26) was tolerated although aqueous solubility and metabolic stability were not improved compared with 1. Removal of the amide carbonyl to afford 27 resulted in > 100-fold drop in potency and also decreased aqueous solubility. We then investigated if the metabolic instability of 1 was associated with metabolism α to the carbonyl, which would also be N-dealkylation, a known phase 1 biotransformation. A common approach to decrease metabolic instability is the geminal dimethylation of metabolically labile regions. The dimethylated analogue 28 did not show improved metabolic stability but displayed an approximate 20-fold improvement in potency relative to hit compound 1 (Table 3).

Met ID studies

To understand what was causing the microsomal instability, we sought to identify the chemical functional groups that were susceptible to metabolism, incubating mouse liver microsomes in the presence 1 and monitoring for metabolites by mass spectrometry. Two main metabolites were identified, [M + H]+ 458 and [M + H]+ 440, suggesting hydroxylation and dehydration. However, the exact sites of metabolism and metabolite structures were not clear from our Met ID experiments.

Combining key SAR

A final attempt was made to investigate different combinations of previously tried functional groups, to improve physicochemical characteristics as well as potency against P. falciparum (Table 4). Substitution of the linker moiety with a geminal dimethyl group, combined with bridged morpholine analogues at R², afforded 29 and 32. Both gave a 10-fold increase in potency relative to 1. However, solubility and metabolic stability were not improved. New combinations at R², replacing the methyl group with methoxy as exemplified by 30, also resulted in a 10-fold increase in potency and improved solubility relative to 1, although again, metabolic stability was not improved. Substitution of the R² morpholine on 1 with the spirocyclic morpholine sulfonamide of 31 displayed similar potency to 1 but the desired increased levels of metabolic stability and aqueous solubility were not obtained.

Conclusions

Through iterative rounds of drug design and synthesis, we were able to improve the antimalarial potency of 1 by > 10-fold to afford 28, which displayed single digit nanomolar potency against P. falciparum and good cellular selectivity. It should be noted, however, that not all compounds in this series inhibited growth of P. falciparum to 100% in vitro. Unfortunately, we were unable to identify compounds that combined both potency and good metabolic stability to progress to in vivo pharmacokinetic studies. Furthermore, we were not able to understand the reasons for the metabolic instability. Within this series, only compounds with very low lipophilicity (clogP < 1) displayed the desired levels of microsomal stability (< 5 mL/min/g liver). Unfortunately, these compounds lost all antiparasitic activity. Therefore, during the optimization of the aminocetamides, lowering lipophilicity was not sufficient to significantly decrease microsomal instability to the required levels. It should also be noted that compounds with very low logP values are likely to have a large free unbound fraction, which could lead to higher levels of clearance in vivo.

Table 3. Modification of linker.

| Linker | EC50 [µM] | Mᵢ [Da] | clogP | Mouse microsomal CLint [mL/min/g liver] | Sol. [µM] |
|--------|-----------|---------|-------|--------------------------------------|----------|
|        | P(3D7)    | HepG2   |       |                                      |          |
| 1      | 0.14 (n=6) |         | 0.18-0.10 | 25 (n=3) | 442 | 2.4 | >50 | 164 |
| 25     | >50 (n=5)  | >25 (n=3) | 456 | 2.2 | 39 | 180 |
| 26     | 0.29 (n=3) | >25 (n=2) | 456 | 2.8 | >50 | 142 |
| 27     | 22.57 (n=3) | >25 (n=2) | 428 | 2.6 | 37 | 39 |
| 28     | 0.007 (n=7) | >25 (n=7) | 470 | 3.0 | >50 | 110 |

[a] n: number of screening replicates; CI: 95% confidence interval. [b] Values were calculated using StarDrop® from Optibrium. [c] Kinetic solubility in water.
Given the excellent antimalarial activity and selectivity of 28, mode of action studies to determine the molecular target of this series may be valuable. These results may open new avenues to identify novel chemotypes with improved metabolic stability, aqueous solubility and potent antimalarial activity.

Conflict of interest

C.d.C., B.C., F.I.G., and L.M.S. are employees of GlaxoSmithKline and own shares of the company.

Keywords: aminoacetamides • antimalarial agents • hit optimization • malaria • Plasmodium falciparum

Experimental Section

Please refer to the Supporting Information for all experimental details.

The human biological samples were sourced ethically, and their use in research was in accord with the terms of the informed consents under an IRB/EC-approved protocol.

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Table 4. Combining SAR.

| No. | Key compounds | EC$_{50}$ [μM]$^{[a]}$ | M, [Da] | clogP$^{[a]}$ | Mouse microsomal CL$_{irr}$ (mL min$^{-1}$(g liver)$^{-1}$) | Sol. [μM]$^{[b]}$ |
|-----|---------------|------------------------|--------|-------------|-----------------------------------------------|----------------|
| 1   |               | 0.14 (n = 6) CI: 0.18–0.10 | >25 (n = 3) | 442 | 2.4 | >50 | 164 |
| 28  |               | 0.007 (n = 7) CI: 0.015–0.003 | >25 (n = 8) | 470 | 3.0 | >50 | 110 |
| 29  |               | 0.035 (n = 6) CI: 0.08–0.01 | >25 (n = 3) | 496 | 3.5 | >50 | 157 |
| 30  |               | 0.014 (n = 3) CI: 0.02–0.01 | >25 (n = 2) | 470 | 3.0 | 40 | 219 |
| 31  |               | 0.12 (n = 3) CI: 0.14–0.10 | >25 (n = 2) | 470 | 3.0 | 22 | 167 |
| 32  |               | 0.014 (n = 5) CI: 0.02–0.01 | >25 (n = 3) | 482 | 3.3 | >50 | 143 |

[a] n: number of screening replicates; CI: 95% confidence interval. [b] Values were calculated using StarDrop from Optibrium. [c] Kinetic solubility in water.

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