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Incorporation of a 3-(2,2,2-Trifluoroethyl)-γ-hydroxy-γ-lactam Motif in the Side Chain of 4-Aminoquinolines. Syntheses and Antimalarial Activities

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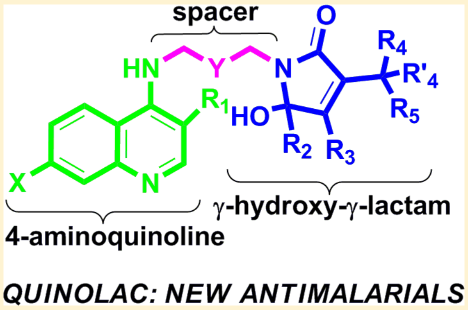
Ⓢ *Supporting Information*

ABSTRACT: In this paper we report the synthesis and antimalarial properties of two series of fluoroalkylated γ-lactams derived from 4-aminoquinoline as potent chemotherapeutic agents for malaria treatment. These molecules obtained in several steps resulted in the identification of very potent structures with in vitro activity against *Plasmodium falciparum* clones of variable sensitivity (3D7 and W2) in the range of 19–50 nM with resistance indices in the range of 1.0–2.5. In addition, selected molecules (**50**, **51**, **58**, **60**, **63**, **70**, **72**, **74**, **78**, **81**, **84**, and **87**) that are representative of the two series of compounds did not show cytotoxicity in vitro when tested against human umbilical vein endothelial cells up to a concentration of 100 μM. The most promising compounds (**82** and **84**) showed significant IC_{50} values close to 26 and 19 nM against the chloroquino-sensitive strain 3D7 and 49 and 42 nM against the multi-drug-resistant strain W2. Furthermore, two model compounds (**50** and **70**) were found to be quite stable over 48 h at pH 7.4 and 5.2. Overall, our preliminary data indicate that this class of structures contains promising candidates for further study.



■ INTRODUCTION

Malaria is an infectious disease that affects approximately 300 million people annually, causing about 1 million deaths (mostly young children). It is most common in tropical and subtropical areas, and 90% of all cases are found in sub-Saharan Africa. Antimalarial drug resistance, particularly the widespread resistance of many *Plasmodium falciparum* strains to most readily available drugs, including the recent artemisin-based combined therapies, hinders malaria control and is therefore a major public health problem. Resistance to antimalarial drugs has increased the global cost of controlling the disease. Resistance, as well as the absence of a vaccine, causes an urgent need for new effective, safe, and affordable drugs. 7-Chloro-4-aminoquinoline derivatives, including chloroquine (CQ) and amodiaquine (AQ), were among the most potent antimalarial drugs,[1−4] and new agents with improved activity against CQ-resistant (CQR) strains have been introduced via synthetic modifications of the CQ side chain.[5−10] Another current strategy to overcome the resistance mechanism of 4-aminoquinolines is to develop dual drugs based on the 7-chloro-4-aminoquinoline skeleton, such as the trioxaquines and other hybrid molecules.[11−14] The search for new CQ analogues that are equally active against CQ-sensitive (CQS) and CQR strains has received increasing attention during recent years. Various studies have revealed that *most* of the structural changes of the 7-chloroquinoline ring in the CQ reduce the activity, whereas alterations of the CQ side chain appear to be a

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promising approach. One modification that is of current interest is to replace the basic tertiary nitrogen atom of CQ with other functionalities which may give rise to molecules with improved metabolic stability and induce better resistance profiles.

For some years we have been developing methodologies to generate fluoroalkylated heterocycles using perfluoroketene dithioacetals as versatile building blocks.[15−24] Among the different heterocyclic structures that have been disclosed, γ-lactams bearing a trifluoroethyl moiety were readily obtained from the reaction of primary amines and several α,β-unsaturated γ-lactones,[18] as well as from the treatment of fluoroalkylated γ-ketothioesters with diisopropylamine followed by addition of various primary amines (Figure 1).[22]

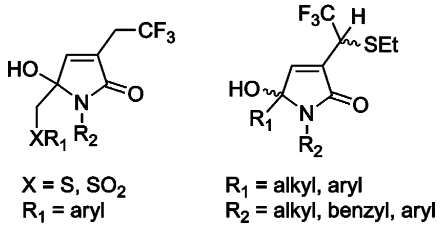


Figure 1. γ-Lactam derivatives with a trifluoroethyl moiety.

The resulting 3-substituted 5-hydroxypyrrolin-2-ones are a class of compounds that are found in many natural products and bioactive derivatives.[25] Interestingly, some, *but a few*, of these γ-hydroxy-γ-lactams from natural sources have been screened as potent antiplasmodial agents, and a number of them displayed interesting antimalarial activities (Figure 2).[26]

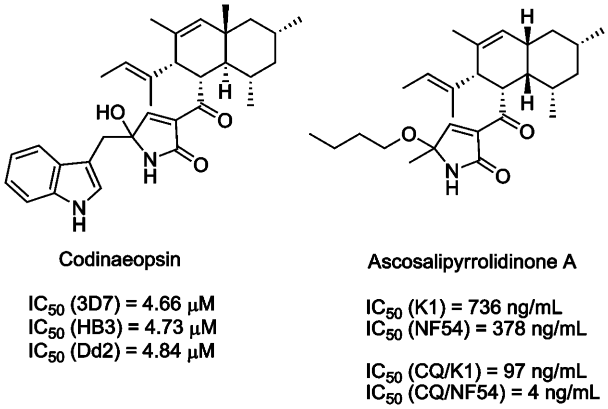


Figure 2. γ-Hydroxy-γ-lactam derivatives from natural sources with known antimalarial activities.

Introducing such γ-lactam scaffolds using our current methodologies,[18,22] with different possible functionalities, including fluorine moieties, in the side chain of 4-aminoquinolines in a first exploratory study, may provide molecules with interesting antimalarial activities, possible new modes of action with an ultimate aim then to extend the syntheses and data generated in this study to other more or less complex structures without the typical 4-aminoquinoline skeleton; such a γ-lactam skeleton may be well adapted to (a) decrease potential metabolic dealkylation processes due to the presence of a tertiary nitrogen, (b) provide simpler analogues than those found in natural products, and (c) generate molecular diversity for structure−activity relationships and hit to lead optimization. To the best of our knowledge, the methodologies presented in this study have not been used before for the design of antiplasmodials, and no synthetic, non-natural γ-hydroxy-γ-lactams have been evaluated as potent antimalarials. When the project was initiated in 2008, only one paper describing the parallel synthesis of 4-aminoquinoline γ-lactams through an intramolecular multicomponent reaction (Ugi three-component four-center reaction, Ugi 3C/4C)[27] using levulinic acid, commercially available *tert*-butyl isocyanide, or cyclohexyl isocyanide and 7-chloroquinoline-derived diamines was considered to be relevant to our study (Figure 3).[28]

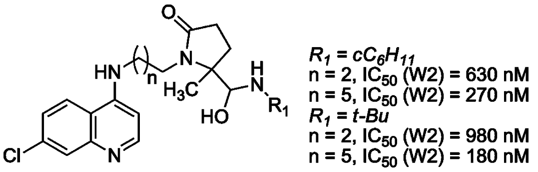


Figure 3. Antimalarial 4-aminoquinoline γ-lactams.

In this paper we present the first results of our efforts directed to the synthesis and antimalarial evaluation of two series (A and B) of new γ-hydroxy-γ-lactams bearing a 4-aminoquinoline skeleton using readily available perfluoroketene dithioacetal building blocks. The general structure of our targets is depicted in Figure 4.

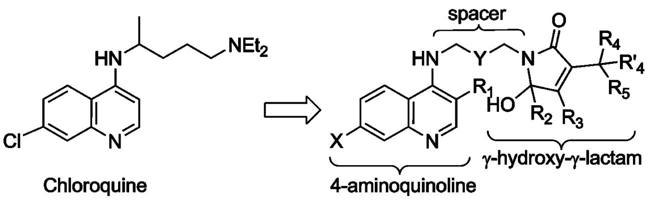


Figure 4. Our targeted 4-aminoquinoline γ-hydroxy-γ-lactams.

The design of these new molecules was based on different structural variations that can lead to the generation of a diverse set of molecules. Overall, our study was expected to establish which primary substitutions are tolerated on the γ-lactam and the 4-aminoquinoline moieties and how these modifications provide potential hits with low cytotoxicity and a good resistance profile. Molecules thus generated were based on (a) the variation of the length of the spacer, (b) the introduction of a basic nitrogen moiety(ies) in the spacer to potentially increase food vacuole accumulation and also to generate a hydrogen bond acceptor as well as induce better solubility via possible salt formulation, (c) substitution on the quinoline ring at the C-3 position (R_1 = H or $COCF_3$) since we already know from our previous work[29] that 7-chloro-3-(trifluoroacetyl)-4-((3-(dimethylamino)propyl)amino)-quinoline showed an antimalarial effect against *Plasmodium berghei* in mice with a 2-fold intraperitoneal injection dose of 100 mg/kg with a 60% survival rate after 14 days and an infection rate of erythrocytes of 2.1% after three days and 16.6% after seven days (for comparison CQ has 0% and <1% infection rates after three and seven days) as well as at the C-7 position (X = Cl, H),[29] (d) the introduction of different aromatic, aliphatic, benzyl, or heteroraryl moieties (R_2, R_3, R_4, and R'_4) to study the impact of hydrophobic and lipophilic moieties on activity, and (e) the introduction of a fluoroalkylated moiety (R_5) that may help to some extent to

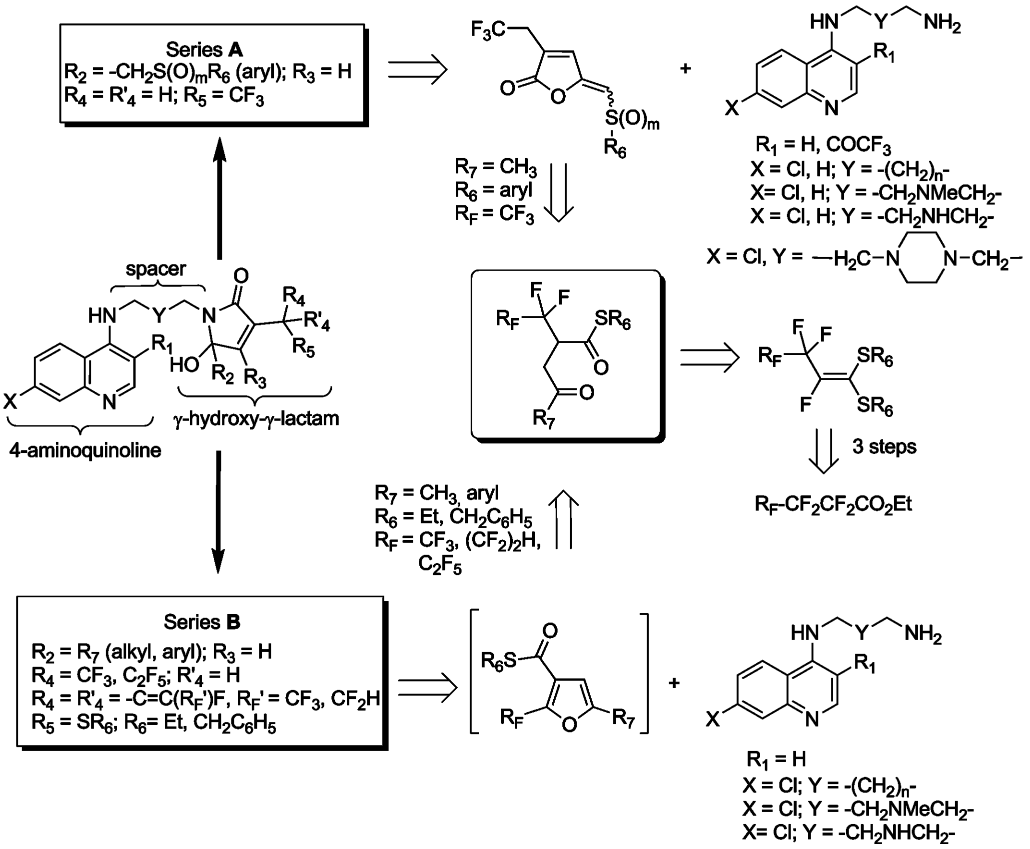


Figure 5. Targeted molecules, series A and B, and retrosynthetic analysis.

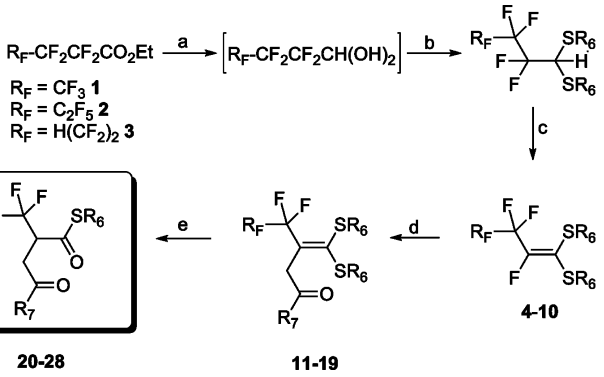
decrease some possible metabolism processes as well as to potentially increase bioavailability.[30]

■ CHEMISTRY

On the basis of our experience with the synthesis of fluorinated γ-lactams,[18,22] we envisaged to prepare two series of structures, A and B (Figure 5). The two sets of molecules differ in their substitutions on the γ-lactam and quinoline rings to generate more diversity. They are prepared in 7–8 steps from commercially available perfluoroalkyl esters **1**–**3**. The first key perfluoroketene dithioacetal building blocks **4**–**10**[17,18,21,22,24] (**6** and **8** are new compounds) were obtained in three steps (Scheme 1) using our published procedures from the reduction of the esters **1**–**3** using lithium aluminum hydride in diethyl ether at 0 °C followed by aqueous acid hydrolysis to give the corresponding aldehyde hydrates, which are directly treated with appropriate thiols in the presence of $TiCl_4$ in dichloromethane to provide the corresponding dithioacetals. HF elimination of the latter in the presence of potassium hydroxide under phase transfer catalysis yielded the compounds **4**–**10**. These intermediates were purified by distillation under reduced pressure or were pure enough to be used directly in the two next steps to provide the γ-ketothioesters **20**–**28**[21,22,24] (**24**–**27** are new compounds) by substitution of the vinylic fluoride with the appropriate potassium enolate of ketones in THF at 0 °C and final hydrolysis in the presence of trifluoroacetic acid and water under refluxing conditions (Scheme 1 and Table 1).

Appropriate amines **33**–**35** (Scheme 2) bearing a trifluoroacetyl moiety were prepared using our published procedure,[31] via the trifluoroacetylation of 4-(dimethylamino)quinoline starting materials **29**[31] and **30**[29,32] with 1-(trifluoroacetyl)-4-(dimethylamino)pyridinium trifluoroacetate (generated in situ) followed by aromatic nucleophilic substitution (N–N exchange reaction) of the 4-dimethylamino moiety with commercially available diamines. The 4-aminoquinoline amines **33**–**35** were obtained in 76–92% isolated yields and were found to be pure enough to be engaged in the final step of the synthesis (traces of the corresponding dimers were observed by mass spectrometry, but these impurities were removed at the latest stage of the chemical synthesis). Amines **36**–**38**[28,34,35] (**39**–**41** are new compounds; **41** was mentioned in a patent without the

Scheme 1[a]



[a]Reagents and conditions: (a) $LiAlH_4$ in Et_2O at 0 °C, then aq H_2SO_4, EtOH; (b) R_6SH (2.0 equiv) + $TiCl_4$ (3 equiv) in CH_2Cl_2; (c) aq KOH + cat Bu_4NBr in CH_2Cl_2; (d) R_7COMe/KH in THF at 0 °C; (e) CF_3CO_2H/H_2O, reflux (see Table 1 for the different substitutions and yields).

Table 1. Synthesis of γ-Ketothioesters 20−28

γ-ketothioester	R_F	R_7	R_6	yield[a] (%)
20	CF_3	CH_3	C_6H_5	60
21	CF_3	CH_3	p-ClC_6H_4	62
22	CF_3	CH_3	p-BrC_6H_4	51
23	CF_3	CH_3	C_2H_5	86
24	CF_3	CH_3	$CH_2C_6H_5$	53
25	CF_3	C_6H_5	C_2H_5	64
26	CF_3	p-BrC_6H_4	C_2H_5	72
27	C_2F_5	CH_3	C_2H_5	65
28	$H(CF_2)_2$	CH_3	C_2H_5	61

[a] Overall isolated yield for the last two steps (from compounds **4−10**).

procedure and spectral data[36]) were prepared following known procedures (the piperazine diamine precursor to prepare **41** was prepared as described in the literature[33]).

The γ-ketothioesters **20−22**, when treated with diisopropylamine in diethyl ether, give rise to sulfides **42−44** and sulfones **45−47** (after *m*CPBA oxidation in dichloromethane), γ-lactones, according to our published methodology[18,21] or furan intermediates from γ-ketothioesters **23−28** using our standard conditions in the presence of diisopropylamine in diethyl ether.[22] The coupling reactions (lactamization) in anhydrous THF (room temperature or refluxing conditions) of amines **33−41** with γ-lactones **42−47** gave final target compounds of series A (**48−68,** Table 2), while furan intermediates, which are usually not isolated (their formation can be followed by ^{19}F NMR analysis of the reaction mixture), can be in situ trapped with appropriate amines **36** and **38−40** to give the final target compounds **69−83** of series B (Table 3). γ-Lactams containing a fluoroalkene moiety (**74−76**) were obtained from in situ base induced HF elimination. Aqueous soluble citrate salts **84−88** were finally obtained in excellent yields from the reaction of **58**, **59**, **62**, **72**, and **83** with citric acid in acetone (Scheme 3).

BIOLOGICAL TESTING

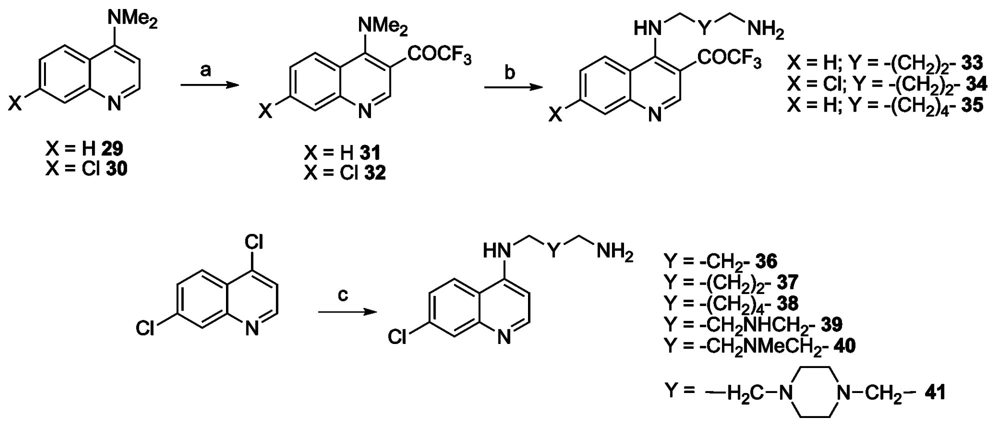
All the compounds thus synthesized (40 new derivatives) were evaluated against 3D7 chloroquino-sensitive and W2 chloroquino-resistant strains of *P. falciparum* (Table 4). All experiments were carried out twice with wells in triplicate. Data are reported as mean IC_{50} values (Figures S1−S2 of the Supporting Information).

Selected compounds (**50**, **51**, **58**, **60**, **63**, **70**, **72**, **74**, **78**, **81**, **84**, and **87**) were also tested for cytotoxicity against human umbilical vein endothelial cell (HUVEC) lines. Endothelial cells were used for these experiments to reproduce the physiological conditions associated with the use of an antimalarial drug against blood stage parasites. These cells are the major target of parasitized red blood cells, and any additional injury may counteract the beneficial effect of antimalarial drugs. The lack of cytotoxicity against endothelial cells is expected to be a major benefit for any new drug. All experiments were carried out twice.

Finally, the stability of two representative compounds (**50** and **70**) in pH 5.2 and 7.4 buffers was evaluated over 48 h using LC/MS (Figures S3−S7 of the Supporting Information).

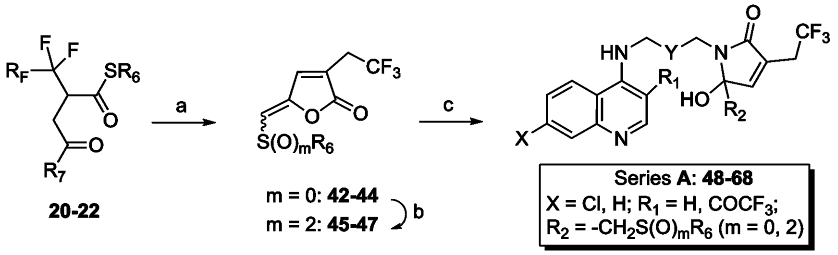
Of the 40 compounds tested, 10 compounds showed reasonable potency (IC_{50} < 100 nM) against the CQ-sensitive 3D7 strain and CQ-resistant W2 strain with roughly equipotent activity against the two strains. Two compounds (**85**, **87**) exhibited high activity (IC_{50} = 49 and 42 nM, respectively) against the CQ-resistant W2 strain, while the activity against CQ-sensitive 3D7 was on the same order as that of chloroquine (IC_{50} = 26 and 19 nM, respectively). The length of the spacer had generally a dramatic influence on the activity, with three methylene spacers better than four and six methylene spacers; introduction of a basic nitrogen in the spacer (−NMe, −NH, and piperazine, **58**, **60**, **61**, **63**, **72**, and **83**) greatly improved the activity on both strains, as long as the R_2 moiety was not a sulfonyl one, which induced decreased reactivity on the CQ-resistant W2 strain. The beneficial effect of such a basic nitrogen as well as the length of the spacer has already been demonstrated in other studies.[7−9] The sulfur atom in series A and B may raise some concern for potential in vivo metabolization to the sulfoxide and sulfone; while we have not yet prepared the sulfoxide analogues, our current data indicate that the sulfonyl derivatives (at least in series A) are less active on the CQ-resistant W2 strain but not to a great extent and have almost similar activity on the CQ-sensitive 3D7 strain. The trifluoroacetyl moiety in **64−68** was a "poor"

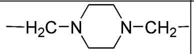
Scheme 2[a]



[a] Reagents and conditions: (a) 1-(trifluoroacetyl)-4-(dimethylamino)pyridinium trifluoroacetate in xylene, reflux, **31** (87%), **32** (95%); (b) $H_2NCH_2YCH_2NH_2$ (5.0 equiv) in acetonitrile, room temperature or reflux, **33** (92%, reflux, 1 h), **34** (76%, room temperature, 2 h), **35** (83%, room temperature, 2 h); (c) $H_2NCH_2YCH_2NH_2$ (3.0−3.5 equiv), neat, 90−135 °C, 2−4 h, **36** (>90%), **37** (>90%), **38** (>90%), **39** (23%), **40** (>95%), **41** (76%).

Table 2. 4-Aminoquinoline-Derived γ-Hydroxy-γ-lactams, Series A[a]



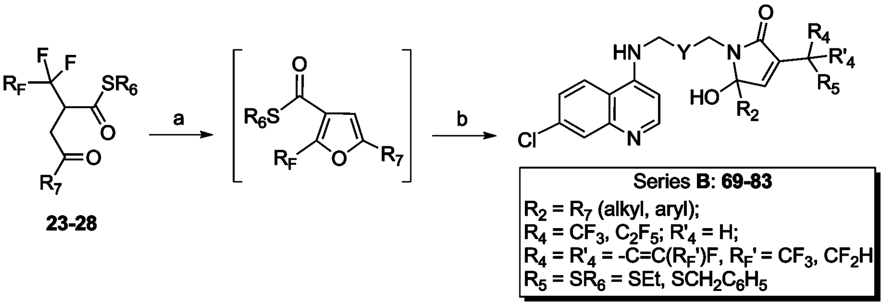
Compound	X	R_1	Y	R_2	Yield (%)[b]
48	Cl	H	$-CH_2-$	$-CH_2-S-Ph$	66
49	Cl	H	$-CH_2-$	$-CH_2-SO_2-Ph$	64
50	Cl	H	$-CH_2-$	$-CH_2-S-C_6H_4-p-Br$	47
51	Cl	H	$-CH_2-$	$-CH_2-SO_2-C_6H_4-p-Br$	62
52	Cl	H	$-(CH_2)_2-$	$-CH_2-S-Ph$	69
53	Cl	H	$-(CH_2)_2-$	$-CH_2-SO_2-Ph$	58
54	Cl	H	$-(CH_2)_2-$	$-CH_2-SO_2-C_6H_4-p-Cl$	36
55	Cl	H	$-(CH_2)_4-$	$-CH_2-S-Ph$	48
56	Cl	H	$-(CH_2)_4-$	$-CH_2-S-C_6H_4-p-Cl$	62
57	Cl	H	$-(CH_2)_4-$	$-CH_2-SO_2-C_6H_4-p-Cl$	47
58	Cl	H	$-CH_2NMeCH_2-$	$-CH_2-S-Ph$	46
59	Cl	H	$-CH_2NMeCH_2-$	$-CH_2-SO_2-Ph$	86
60	Cl	H	$-CH_2NMeCH_2-$	$-CH_2-S-C_6H_4-p-Cl$	35
61	Cl	H	$-CH_2NMeCH_2-$	$-CH_2-S-C_6H_4-p-Br$	28
62	Cl	H	$-CH_2NHCH_2-$	$-CH_2-S-Ph$	63
63	Cl	H		$-CH_2-S-Ph$	21
64	Cl	$-COCF_3$	$-(CH_2)_2-$	$-CH_2-SO_2-Ph$	48
65	H	$-COCF_3$	$-(CH_2)_2-$	$-CH_2-S-Ph$	30
66	H	$-COCF_3$	$-(CH_2)_2-$	$-CH_2-SO_2-Ph$	73
67	H	$-COCF_3$	$-(CH_2)_4-$	$-CH_2-SO_2-Ph$	75
68	H	$-COCF_3$	$-(CH_2)_4-$	$-CH_2-SO_2-C_6H_4-p-Cl$	51

[a] Reagents and conditions for the reaction: (a) i-Pr_2NH (2 equiv), Et_2O, rt, 15 h, **42** (51%), **43** (72%), **44** (27%); (b) mCPBA (3 equiv), CH_2Cl_2, room temperature, 16 h, **45** (76%), **46** (65%), **47** (67%); (c) appropriate amine (2 equiv), THF, room temperature, 6 h (for **45**–**47**), or reflux, 20–36 h (for **42**–**44**). [b] Isolated yield.

substitution since the compounds were not active up to 1600 nM; this may be due to a lack of protonation of the nitrogen of the quinoline ring (N-1) that resulted from the mesomeric effect of the lone pair of the –NH on the electron-withdrawing $COCF_3$ substituent. Within this set of molecules bearing the trifluoroacetyl moiety, molecules having either a chlorine or a hydrogen were devoid of activity. Halogen substitution on the aryl moiety R_6 in series A has no great influence on activity if compared to hydrogen (see, for example, **61** versus **60** and **58**); such halogens may offer some advantage in blocking potential metabolization (for example, through cytochrome P450 oxidation), but may also increase the lipophilicity and potential liability, especially with a bromine atom. A fluorine substitution will be preferred, but these types of molecules have not yet been synthesized. Generally, the compounds produced from series B are to some degree less active than those generated in series A. Fluoroalkene moieties in **74**–**76** seem not appropriate since IC_{50} values higher than 100 nM were observed; this may be due to their prononced reactivity (as possible Michael acceptors) toward endogeneous nucleophiles that can produce less potent and/or toxic metabolites.

Selected representative compounds (**50**, **51**, **58**, **60**, **63**, **70**, **72**, **74**, **78**, **81**, **84**, and **87**) were evaluated against a mammalian cell line (HUVECs) using final concentrations ranging from

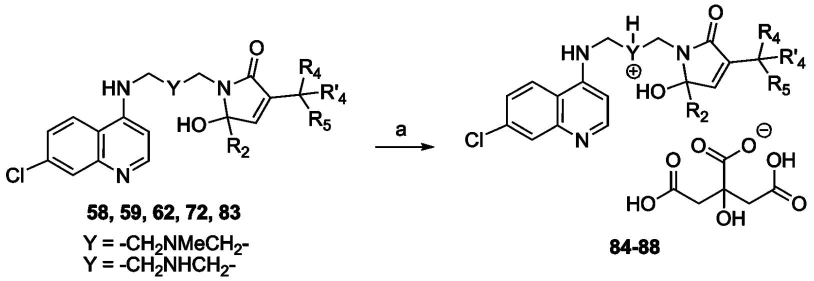
Table 3. 4-Aminoquinoline-Derived γ-Hydroxy-γ-lactams, Series B[a]



compd	Y	R_2	R_5	R_4	R'_4	yield[b] (%)
69	$-CH_2-$	CH_3	$-SC_2H_5$	CF_3	H	36[c]
70	$-(CH_2)_2-$	CH_3	$-SC_2H_5$	CF_3	H	25[c]
71	$-(CH_2)_4-$	CH_3	$-SC_2H_5$	CF_3	H	52[c]
72	$-CH_2NMeCH_2-$	CH_3	$-SC_2H_5$	CF_3	H	26[c]
73	$-CH_2NHCH_2-$	CH_3	$-SC_2H_5$	CF_3	H	19[c]
74	$-CH_2-$	CH_3	$-SC_2H_5$	$-CR_4R'_4 = -C{=}CFCF_2H$[d]		22
75	$-(CH_2)_4-$	CH_3	$-SC_2H_5$	$-CR_4R'_4 = -C{=}CFCF_2H$[d]		22
76	$-CH_2-$	CH_3	$-SC_2H_5$	$-CR_4R'_4 = -C{=}CFCF_3$[d]		18
77	$-CH_2-$	CH_3	$-SC_2H_5$	$-CF_2CF_3$	H	17[c]
78	$-CH_2-$	CH_3	$-SCH_2Ph$	CF_3	H	28[c]
79	$-CH_2-$	C_6H_5	$-SC_2H_5$	CF_3	H	46[c]
80	$-(CH_2)_4-$	C_6H_5	$-SC_2H_5$	CF_3	H	37[c]
81	$-CH_2-$	p-BrC_6H_4	$-SC_2H_5$	CF_3	H	20[c]
82	$-(CH_2)_4-$	p-BrC_6H_4	$-SC_2H_5$	CF_3	H	16[c]
83	$-CH_2NMeCH_2-$	p-BrC_6H_4	$-SC_2H_5$	CF_3	H	18[c]

[a] Reagents and conditions for the reaction: (a) i-Pr_2NH (2 equiv), Et_2O, room temperature, 15 h; (b) appropriate amine (1.2 equiv), MeOH, room temperature, 8−17 h. [b] Isolated yield from γ-ketothioester. [c] Diastereoisomeric mixture (for the ratio, see the Experimental Section). [d] *E* stereoisomer.

Scheme 3[a]



[a] Reagents and conditions: (a) citric acid (1.0 equiv) in acetone at room temperature for 24 h, **84** (salt of **58**, 93%), **85** (salt of **59**, 97%), **86** (salt of **62**, 94%), **87** (salt of **72**, 93%), **88** (salt of **83**, 76%).

0.01 to 100 μmol/L. We did not detect significant cytotoxicity, and no relevant IC_{50} could be obtained in the concentration range tested. On the basis of these data, we extrapolate a minimum cytotoxicity value over the 10−100 μmol/L range for all tested coumpounds, leading to an excellent selectivity against parasites (both strains).

Two model compounds (**50** and **70**) were found to be quite stable at pH 5.2 and 7.4 over 48 h with LC/MS monitoring; the hemiaminal function in these series does not seem to be a critical issue at these pH values since no dehydrated compound or ring-opening product was observed (Figures S3−S7 of the Supporting Information). For both compounds at pH 7.4, there is an indication of formation of traces of new species; in the case of **50** ($[M + H]^+ = 600.0$) the new species at 15.0 min has a molecular weight of $[M + H]^+ = 412.1$ (**89**, Figure S4), which may correspond to a loss of the p-bromothiophenol moiety. As for compound **70** ($[M + H]^+ = 488.1$), the new species at 15.9 min has a molecular weight of $[M + H]^+ = 468.1$ (**90**, Figures S6 and S7), which may correspond to the loss of a HF molecule. Since these two species (**89** and **90**) are observed in very minor amounts, no attempts to isolate them and to confirm their structures have been made so far. In addition, for compound **70**, the ratio of diastereomers did not change significantly for both pH values, with an equilibration of the ratio of such isomers at pH 7.4 after 48 h (Figure S5).

Calculated physicochemical properties of the most potent structures (not the citrate salts) were obtained (Table 5) using ChemAxon software[37] to assess if they were compliant with the Lipinski "rule of five" criteria[38] (Table 5); the data showed that all molecules have (a) a molecular weight in the range of 517−658, which is higher than the accepted 500, (b) a log P close to or higher than 5.0, which may indicate that the compounds are too lipophilic, and (c) a log D at pH 7.4 (permeability) usually in the range of 1.2−2.8 except for two molecules with values

Table 4. In Vitro Data of Compounds 48−88

compound	$IC_{50}(W2)^a$ (nM)	$IC_{50}(3D7)^a$ (nM)	$IC_{50}(W2)/IC_{50}(3D7)^b$
chloroquine	750	30	25.0
48	110	107	1.0
49	210	102	2.1
50	302	351	0.9
51	810	297	2.7
52	391	273	1.4
53	>1000	>1000	
54	796	800	1.0
55	395	335	1.2
56	391	275	1.4
57	391	500	0.8
58	55	47	1.2
59	360	75	4.8
60	57	55	1.0
61	42	45	0.9
62	211	89	2.4
63	51	43	1.2
64	>1000	>1000	
65	>1000	>1000	
66	>1000	>1000	
67	>1000	>1000	
68	>1000	>1000	
69	283	141	2.0
70	413	377	1.1
71	226	180	1.3
72	73	56	1.3
73	496	58	8.6
74	667	351	1.9
75	298	270	1.1
76	266	168	1.6
77	125	87	1.4
78	178	138	1.3
79	290	250	1.2
80	306	326	0.9
81	79	79	1.0
82	97	99	1.0
83	74	58	1.3
84	287	86	3.3
85	49	26	1.9
86	233	41	5.7
87	42	19	2.2
88	135	118	1.2

[a] Values are means determined from at least two experiments. Effective concentration for 50% inhibition. [b] Resistance index (RI) = $IC_{50}(W2)/IC_{50}(3D7)$.

Table 5. Calculated Physical Properties of the Best Active Antimalarial Compounds

compd	MW	log D^a (pH 7.4)	log P^a	no. of H-bond donors	no. of H-bond acceptors	no. of Lipinski violations
CQ	319.9	0.88	3.93	1	3	0
58	**565.0**	**1.18**	**4.69**	**2**	**6**	**1**
60	599.5	1.78	5.30	2	6	2
61	643.9	1.95	5.46	2	6	2
63	620.1	1.08	4.54	2	6	1
72	**517.0**	**2.81**	**3.57**	**2**	**6**	**1**
81	628.9	6.36	6.60	2	5	3
83	657.9	5.29	6.05	2	6	3

[a] All calculations were performed using MarvinSketch 5.8.1 from ChemAxon.

higher than 5.0. All derivatives are compliant with hydrogen bond properties. The compounds that are almost compliant with the Lipinski rule of five criteria are **58** and **72** (data shown in bold in Table 5), which are not the most active in vitro (Table 4). The results of this informative analysis do not suggest that any of the compounds should be discarded from this computational assessment and should be taken into account when progressing further potential hits.

CONCLUSION

Two new series of 4-aminoquinoline derivatives bearing a γ-hydroxy-γ-lactam in the side chain were synthesized using methodologies that have not been previously used in the design of potent antimalarials; a number of such molecules were found to be quite potent when tested in vitro against *P. falciparum* clones of variable sensitivity (3D7 and W2) with activities in the range of 19−50 nM.[39] None of the tested molecules were found to be cytotoxic, and resistance indexes were usually close to 1.0−2.0. Two model compounds were found to be chemically stable at pH 5.2 and 7.4 over 48 h. Overall, our data for these new series demonstrate that the incorporation of a γ-lactam plays a significant role in biological activity. Therefore, these results warrant further effort and studies. Work is now under way to (a) demonstrate in vivo oral efficacy of our best derivatives as well as optimize the current structures especially by reducing the log *P* and also study a murine model of their pharmacokinetics, (b) establish the mechanism of action especially by checking if the molecules are found to inhibit β-hematin production as the current 4-aminoquinolines do, and (c) extend the in vitro data to a more comprehensive series of *P. falciparum* clones (Dd2, NF54, HB3, 7G8) to establish if the molecules are not impaired by the chloroquine resistance phenotype. Synthetic current efforts have already been successful in producing (a) a new family of 7-chloro-4-aminoquinolines bearing a *different* γ-hydroxy-γ-lactam in the side chain with excellent in vitro activity, a good resistance index, and no relevant cytotoxicity, demonstrating that the combination of these two skeletons yields new potent antimalarials, and (b) other new pharmacophores not bearing the 7-chloro-4-aminoquinoline skeleton based on a γ-lactam unit that shows very promising activities. These results will be published in forthcoming papers.

EXPERIMENTAL SECTION

Chemistry. Solvents were of the highest purity and anhydrous and were purchased from Acros Organics and Sigma-Aldrich. Reagents were obtained commercially (Acros Organics, Sigma-Aldrich) and used without further purification. Infrared spectra were recorded on an FT-IR Perkin-Elmer PARAGON 500 with a KBr pellet for a solid and a film for an oil. ^1H, ^{19}F, and ^{13}C NMR spectra were recorded with a Bruker Avance 300 or a DRX300 spectrometer (in acetone-d_6, $CDCl_3$, CD_3OD, or DMSO-d_6) at 300, 282, and 75 MHz, respectively. Chemical shifts are given in parts per million (ppm) relative to the residual peak of the solvent or $CFCl_3$ (^{19}F). The following abbreviations are used to describe peak patterns: s (singlet), d (doublet), dd (double doublet), t (triplet), m (multiplet), q (quadruplet), and br (broad). Coupling constants are given in hertz. High- and low-resolution mass spectra were recorded using a FINIGAN MAT 95 (electronic ionization (EI) and chemical ionization (CI) modes) and MicroTOF-Q II (electrospray ionization (ESI) mode). The purities of the target compounds were ≥95%, measured by LC/MS, which was performed on an Agilent 1200 series HPLC system connected to a Bruker MicroTOF-Q II (Bremen, Germany) mass spectrometer. Separations were carried out on a Macherey Nagel Nucleodur C18 HTec column (3 μm, 2 × 125 mm) with a flow rate of 0.4 mL/min at 20 °C. Two mobile phases (mobile phase A, 100% water with 0.1% acetic acid; mobile phase B, 100% methanol with 0.1% acetic acid) were employed to run a gradient condition from 95% A and 5% B to 100% B in 30 min which was held for 5 min, and back to the initial conditions in 5 min, which was held for 5 min. An injection volume of 10 μL was used. The mass spectra were acquired by scanning from 50 to 1000 amu in the positive ion mode with a spray voltage of 5 kV. The calibration of the mass spectrometer was performed by using formiate buffer; the measured mass precision is less than 5 ppm. Samples were prepared by mixing 10 μL of a 1 mg/mL concentration of the compound in methanol in 1 mL of water. Thin-layer chromatography (TLC) was performed on silica gel GF254 plates. Macherey-Nagel silica gel 60M (0.04−0.063 mm) was used for silica gel chromatography. Melting points (uncorrected) were determined in capillary tubes on a Büchi apparatus.

General Procedure for the Preparation of γ-Lactams 48−68. To a solution of γ-lactones **42**−**47** (0.126 mmol) in THF (20 mL) under an inert atmosphere were added the appropriate amines (0.252 mmol, 2 equiv). The reaction mixture was stirred at room temperature for 6 h (for γ-lactones **45**−**47**) or was refluxed for 20−36 h (for γ-lactones **42**−**44**) until total conversion (the reactions were monitored by ^{19}F NMR). After evaporation of the solvent, the residue was purified by silica gel column chromatography and recrystallized, affording the desired γ-lactams **48**−**68**.

1-(3-((7-Chloroquinolin-4-yl)amino)propyl)-5-hydroxy-5-[(phenylthio)methyl]-3-(2,2,2-trifluoroethyl)-1*H*-pyrrol-2(5*H*)-one (48). The yield was 66% after purification by silica gel column chromatography (AcOEt, R_f = 0.58) followed by recrystallization (petroleum ether/MeOH), solid, mp 180 °C. ^{1}H NMR ($CDCl_3$): δ 2.03 (m, 2H, NCH_2CH_2), 3.1−3.3 (m, 3H, CH_2CF_3 + NCH_AH_B), 3.42 (d, J = 13.9 Hz, 1H, CH_AH_BS), 3.3−3.5 (m, 3H, NCH_2 + NCH_AH_B), 3.52 (d, J = 13.9 Hz, 1H, CH_AH_BS), 6.52 (d, J = 5.9 Hz, 1H quinoline), 6.84 (s, 1H, =CH lactam), 7.1−7.3 (m, 5H Ph), 7.42 (dd, J = 9.0 and 2.2 Hz, 1H quinoline), 7.78 (d, J = 2.2 Hz, 1H quinoline), 8.10 (d, J = 9.0 Hz, 1H quinoline), 8.32 (d, J = 5.9 Hz, 1H quinoline). ^{19}F NMR ($CDCl_3$): δ −65.1 (t, J = 11.6 Hz). ^{13}C NMR ($CDCl_3$): δ 28.3 (s, NCH_2CH_2), 30.3 (q, J = 31.5 Hz, CH_2CF_3), 37.5 (s, CH_2), 40.9 (s, CH_2), 41.4 (s, CH_2), 92.3 (s, C_q, COH), 99.7 (s, CH quinoline), 118.8 (s, C_q quinoline), 124.3 (s, CH quinoline), 126.1 (s, CH quinoline), 126.9 (q, J = 276.1 Hz, CF_3), 127.5 (s, CH quinoline), 127.8 (s, CH Ph), 130.1 (s, 2 × CH Ph), 130.3 (q, J = 3.3 Hz, CCH_2CF_3), 131.4 (s, 2 × CH Ph), 136.4 (s, C_q quinoline), 137.1 (s, C_q, Ph), 147.8 (s, =CH lactam), 149.6 (s, C_q quinoline), 152.4 (s, CH quinoline), 152.6 (s, C_q quinoline), 171.0 (s, C_q, CO). IR (KBr, cm^{-1}): 3401, 2925, 1678, 1590, 1458, 1370, 1269, 1139. MS (ESI$^+$): m/z = 522 [M + H]$^+$, 524 [M(^{37}Cl) + H]$^+$. HRMS (ESI$^+$): m/z calcd for [M + H]$^+$ $C_{25}H_{23}ClF_3N_3O_2S$ 522.1230, found 522.1235.

1-(2-((2-((7-Chloroquinolin-4-yl)amino)ethyl)methylamino)ethyl)-5-hydroxy-5-((phenylsulfanyl)methyl)-3-(2,2,2-trifluoroethyl)-1*H*-pyrrol-2(5*H*)-one (58). The yield was 46% after purification by silica gel column chromatography (MeOH, R_f = 0.6), viscous oil. ^{1}H NMR ($CDCl_3$): δ 2.35 (s, 3H, NCH_3), 2.35 (m, 1H, CH_2), 2.70−3.05 (m, 6H, 2 × CH_2 + CH_2CF_3), 3.28−3.41 (m, 4H, CH_2 + CH_2S), 3.66 (dt, J = 15.3 and 2.7 Hz, 1H, CH_2), 5.68 (br s, 1H, OH or NH), 6.28 (d, J = 5.4 Hz, 1H, CH quinoline), 6.75 (br s, 1H, =CH lactam), 7.20−7.28 (m, 5H, Ph), 7.35 (dd, J = 9.0 and 2.1 Hz, 1H, CH quinoline), 7.86 (d, J = 9.0 Hz, 1H, CH quinoline), 7.93 (d, J = 2.1 Hz, 1H, CH quinoline), 8.48 (d, J = 5.4 Hz, 1H, CH quinoline). ^{19}F NMR ($CDCl_3$): δ −65.4 (t, J = 10.7 Hz). ^{13}C NMR (CD_3OD): δ 29.4 (q, J = 31.5 Hz, CH_2CF_3), 36.9 (s, CH_2), 39.7 (s, CH_2), 41.2 (s, CH_2S), 41.6 (s, NCH_3), 55.5 (s, CH_2), 56.1 (s, CH_2), 89.1 (s, C_q, $C(OH)CH_3$), 98.6 (s, CH quinoline), 117.2 (s, C_q quinoline), 122.4 (s, CH quinoline), 125.1 (q, J = 276.7 Hz, CF_3), 125.0 (s, CH quinoline), 126.9 (s, CH Ph), 127.6 (s, CH quinoline), 127.9 (q, J = 2.7 Hz, C_q, CCH_2CF_3), 129.0 (s, 2 × CH Ph), 130.5 (s, 2 × CH Ph), 134.9 (s, C_q Ph), 135.4 (s, C_q quinoline), 146.5 (s, =CH lactam), 148.5 (s, C_q quinoline), 149.9 (s, C_q quinoline), 151.3 (s, CH quinoline), 168.5 (s, C_q, CO). MS (ESI$^+$): m/z = 565 [M + H]$^+$, 567 [M(^{37}Cl) + H]$^+$. HRMS (ESI$^+$): m/z calcd for [M + H]$^+$ $C_{27}H_{29}ClF_3N_4O_2S$ 565.1652, found 565.1659. Anal. Calcd for $C_{27}H_{28}ClF_3N_4O_2S$: C, 57.39; H, 4.99; N, 9.92. Found: C, 57.65; H, 4.98; N, 9.72.

1-(2-((2-((7-Chloroquinolin-4-yl)amino)ethyl)piperazin-1-yl)ethyl)-5-hydroxy-5-((phenysulfanyl)methyl)-3-(2,2,2-trifluoroethyl)-1*H*-pyrrol-2(5*H*)-one (63). The yield was 21% after purification by silica gel column chromatography (MeCN/MeOH = 80/20, R_f = 0.2), viscous oil. ^{1}H NMR ($CDCl_3$): δ 2.38 (dm, J = 15.4 Hz, 1H, CH_2), 2.44−2.97 (m, 12H, 6 × CH_2), 3.12 (q, J = 10.6 Hz, 2H, CH_2CF_3), 3.26 (d, J = 14.0 Hz, 1H, SCH_AH_B), 3.31 (m, 2H, CH_2), 3.43 (d, J = 14.0 Hz, 1H, SCH_AH_B), 3.73 (dm, J = 15.4 Hz, 1H, CH_2), 5.79 (br s, 1H, NH), 6.37 (d, J = 5.4 Hz, 1H, CH quinoline), 6.83 (s, 1H, =CH lactam), 7.19−7.34 (m, 5H, Ph), 7.37 (dd, J = 9.0 and 1.9 Hz, 1H, CH quinoline), 7.63 (d, J = 9.0 Hz, 1H, CH quinoline), 7.96 (d, J = 1.9 Hz, 1H, CH quinoline), 8.53 (d, J = 5.4 Hz, 1H, CH quinoline), 9.07 (br s, 1H, OH). ^{19}F NMR ($CDCl_3$): δ −65.3 (t, J = 10.6 Hz). ^{13}C NMR ($CDCl_3$): δ 29.9 (q, J = 31.6 Hz, CCF_3), 36.5 (s, CH_2), 39.0 (s, CH_2), 41.7 (s, CH_2S), 51.9 (s, 2 × CH_2 piperazine), 53.2 (br s, 2 × CH_2 piperazine), 55.4 (s, CH_2), 57.0 (s, CH_2), 89.0 (s, C_q, $C(OH)CH_3$), 99.4 (s, CH quinoline), 117.4 (s, C_q quinoline), 121.0 (s, CH quinoline), 125.3 (q, J = 276.6 Hz, CF_3), 125.4 (s, CH quinoline), 127.0 (s, CH Ph), 128.0 (q, J = 3.0 Hz, C_q lactam), 128.8 (s, CH quinoline), 129.1 (s, 2 × CH Ph), 130.7 (s, 2 × CH Ph), 134.9 (s, C_q Ph), 135.6 (s, C_q quinoline), 146.4 (s, =CH lactam), 149.0 (s, C_q quinoline), 149.6 (s, C_q quinoline), 152.1 (s, CH quinoline), 168.6 (s, CO). HRMS (ESI$^+$): m/z calcd for [M + H]$^+$ $C_{30}H_{34}ClF_3N_5O_2S$ 620.2074, found 620.2064. Anal. Calcd for $C_{30}H_{33}ClF_3N_5O_2S$: C, 58.10; H, 5.36; N, 11.29. Found: C, 58.29; H, 5.51; N, 11.05.

Typical Procedure for the Preparation of γ-Lactams 69−83. To a solution of γ-ketothioester **23** (120 mg, 0.48 mmol) in diethyl ether (3 mL) was added diisopropylamine (134 μL, 0.96 mmol). The reaction mixture was stirred at room temperature for 15 h (the formation of a furan intermediate was monitored by ^{19}F NMR of the crude). Amine **36** (170 mg, 0.72 mmol) and MeOH (0.5 mL) were added to the reaction mixture. After total conversion (monitoring by ^{19}F NMR), the solvents were evaporated under reduced pressure, and then the residue was purified by silica gel column chromatography (AcOEt/MeOH = 95/5, R_f = 0.32) followed by recrystallization (CH_2Cl_2/petroleum ether), affording the desired γ-lactam **69**.

1-(3-((7-Chloroquinolin-4-yl)amino)propyl)-3-(1-(ethylsulfanyl)-2,2,2-trifluoroethyl)-5-hydroxy-5-methyl-1*H*-pyrrol-2(5*H*)-one (69). The yield was 36% as a mixture (52/48) of nonseparated diastereomers, solid. The following are *data for the major diastereomer*. ^{1}H NMR ($CDCl_3$): δ 1.26 (t, J = 7.5 Hz, 3H, CH_3CH_2), 1.62 (s, 3H, $C(OH)CH_3$), 1.9−2.1 (m, 2H, CH_2CH_2N), 2.7−2.9 (m, 2H, CH_2S), 3.0−3.8 (m, 4H, $NCH_2CH_2CH_2N$), 4.28 (m, 1H, $CHCF_3$), 6.06 (d, J = 5.8 Hz, 1H, CH quinoline), 6.4−6.6 (br s, 1H, OH or NH), 6.99 (br s, 1H, =CH lactam), 7.2 (m, 1H, CH quinoline), 7.61 (d, J = 9.0 Hz, 1H, CH quinoline), 7.79 (d, J = 1.9 Hz, 1H, CH quinoline), 8.11 (d, J = 5.8 Hz, 1H, CH quinoline). ^{19}F NMR ($CDCl_3$): δ −69.1 (d, J = 8.8 Hz). ^{13}C NMR ($CDCl_3$): δ 14.3 (s, CH_3CH_2S), 22.8 (s, CH_2CH_2N), 23.7 (s, $CH_3C(OH)$), 27.4 (s, CH_2S), 36.1 (s, CH_2N), 40.3 (s, CH_2N), 41.5 (m, $CHCF_3$), 89.0 (s, C_q, C(OH)), 98.3 (s, CH quinoline), 110.0 (s, C_q quinoline), 117.0 (s, C_q quinoline), 115−125 (CF_3), 122.4 (s, CH quinoline), 125.7 (s, CH quinoline), 126.2 (s, CH quinoline), 130.6 (s, C_q, $CCHCF_3$), 135.9 (s, C_q quinoline), 146.7 (s, =CH lactam), 149.7 (s, CH quinoline), 151.0 (s, C_q quinoline), 168.0 (s, C_q, CO). The following are *selected data for minor diastereomer*: ^{1}H NMR ($CDCl_3$): δ 1.34 (t, J = 7.4 Hz, 3H, CH_3CH_2), 1.63 (s, 3H, $C(OH)CH_3$), 1.9−2.1 (m, 2H, CH_2CH_2N), 2.7−2.9 (m, 2H, CH_2S), 3.0−3.8 (m, 4H, $NCH_2CH_2CH_2N$), 4.28 (m, 1H, $CHCF_3$), 6.04 (d, J = 5.8 Hz, 1H, CH quinoline), 6.4−6.6 (br s, 1H, OH or NH), 6.99 (br s, 1H, =CH lactam), 7.2 (m, 1H, CH quinoline), 7.56 (d, J = 9.0 Hz, 1H, CH quinoline), 7.81 (d, J = 1.9 Hz, 1H, CH quinoline), 8.10 (d, J = 5.8 Hz, 1H, CH quinoline). ^{19}F NMR

(CDCl$_3$): δ −68.7 (d, J = 8.8 Hz). ^{13}C NMR (CDCl$_3$): δ 14.2 (s, CH_3CH$_2$S), 22.8 (s, CH_2CH$_2$N), 23.7 (s, CH_3C(OH)), 27.4 (s, CH_2S), 36.1 (s, CH_2N), 40.3 (s, CH_2N), 41.5 (m, CHCF$_3$), 89.2 (s, C$_q$, C(OH)), 98.3 (s, CH quinoline), 110.0 (s, C$_q$ quinoline), 117.0 (s, C$_q$ quinoline), 115−125 (CF$_3$), 122.4 (s, CH quinoline), 125.7 (s, CH quinoline), 126.2 (s, CH quinoline), 130.6 (s, C$_q$, CCHCF$_3$), 135.9 (s, C$_q$ quinoline), 146.9 (s, =CH lactam), 149.7 (s, CH quinoline), 151.0 (s, C$_q$ quinoline), 168.0 (s, C$_q$, CO). IR (KBr, cm^{-1}): 3383, 3070, 2935, 1686, 1585, 1453, 1254, 1147. MS (ESI$^+$): m/z = 474 [M + H]$^+$, 476 [M(^{37}Cl) + H]$^+$. HRMS (ESI$^+$): m/z calcd for [M + H]$^+$ $C_{21}H_{24}ClF_3N_3O_2S$ 474.1230, found 474.1233.

1-(2-((2-((7-Chloroquinolin-4-yl)amino)ethyl)methylamino)ethyl)-3-(1-(ethylsulfanyl)-2,2,2-trifluoroethyl)-5-hydroxy-5-methyl-1*H*-pyrrol-2(5*H*)-one (72). The yield was 26% (from γ-ketothioester **23**) as a mixture (0.85/1) of nonseparated diastereomers after purification by silica gel column chromatography (MeOH, R_f = 0.55), solid. The following NMR data are for the mixture of diastereomers. ^{1}H NMR (CDCl$_3$): δ 1.10 (t, J = 7.5 Hz, 3H, CH_3CH$_2$ major), 1.26 (t, J = 7.5 Hz, 3H, CH_3CH$_2$ minor), 1.52 (s, 2 × 3H, 2 × CH$_3$), 2.34 (s, 3H, NCH$_3$ minor), 2.36 (s, 3H, NCH$_3$ major), 2.44−2.90 (m, 6H, 2 × CH$_2$ + CH$_2$S), 3.23−3.35 (m, 3H, CH$_2$), 3.96 (m, 1H, CH$_2$), 4.15 (m, 1H, CHCF$_3$), 5.94 (br s, 1H, OH or NH), 6.26 (d, J = 5.4 Hz, 1H, CH quinoline minor), 6.27 (d, J = 5.4 Hz, 1H, CH quinoline major), 6.95 (br s, 1H, =CH lactam), 7.28−7.35 (m, 1H, CH quinoline), 7.84−7.89 (m, 2H, CH quinoline), 8.42 (d, J = 5.4 Hz, 1H, CH quinoline). ^{19}F NMR (CDCl$_3$): δ −68.9 (d, J = 8.2 Hz, minor), −69.0 (d, J = 8.2 Hz, major). ^{13}C NMR (CDCl$_3$): δ 13.9 (s, CH_3CH$_2$S major), 14.0 (s, CH_3CH$_2$S minor), 24.0 (s, 2 × C(OH)CH_3), 27.2 (s, CH_2 major), 27.3 (s, CH_2 minor), 36.8 (s, CH_2), 39.9 (s, CH_2 minor), 40.0 (s, CH_2 major), 41.1 (q, J = 31.6 Hz, CHCF$_3$ major), 41.2 (q, J = 31.6 Hz, CHCF$_3$ minor), 41.7 (s, NCH$_3$ minor), 41.9 (s, NCH$_3$ major), 55.7 (s, CH_2 minor), 55.8 (s, CH_2 major), 56.2 (s, CH_2 major), 56.6 (s, CH_2 minor), 87.1 (s, C$_q$, C(OH)CH$_3$ major), 87.3 (s, C$_q$, C(OH)CH$_3$ minor), 98.6 (s, CH quinoline), 117.2 (s, C$_q$ quinoline minor), 117.3 (s, C$_q$ quinoline major), 120.2 (s, C$_q$ quinoline minor), 120.3 (s, C$_q$ quinoline major), 122.4 (s, CH quinoline minor), 122.5 (s, CH quinoline major), 125.8 (q, J = 278.9 Hz, CF$_3$), 127.4 (s, CH quinoline minor), 127.5 (s, CH quinoline major), 129.5 (s, C$_q$ quinoline), 135.1 (m, C$_q$, CCHCF$_3$), 146.8 (s, =CH lactam), 148.2 (s, CH quinoline minor), 148.3 (s, CH quinoline major), 150.1 (s, C$_q$ quinoline), 151.1 (s, CH quinoline), 167.0 (s, CO major), 167.1 (s, CO minor). MS (ESI$^+$): m/z = 517 [M + H]$^+$, 519 [M(^{37}Cl) + H]$^+$. HRMS (ESI$^+$): m/z calcd for [M + H]$^+$ $C_{23}H_{29}ClF_3N_4O_2S$ 517.1652, found 517.1657. Anal. Calcd for $C_{23}H_{28}ClF_3N_4O_2S$: C, 53.43; H, 5.46; N, 10.84. Found: C, 53.68; H, 5.43; N, 11.06.

5-(4-Bromophenyl)-1-(2-((2-((7-chloroquinolin-4-yl)amino)ethyl)methylamino)ethyl)-3-(1-(ethylsulfanyl)-2,2,2-trifluoroethyl)-5-hydroxy-1*H*-pyrrol-2(5*H*)-one (83). The yield was 18% (from γ-ketothioester **26**) as a mixture (50/50) of nonseparated diastereomers after purification by silica gel column chromatography (EtOH, R_f = 0.55), solid. The following NMR data are for the mixture of diastereomers. ^{1}H NMR (CDCl$_3$): δ 1.16 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 1.31 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 2.22 (s, 3H, NCH_3), 2.25 (s, 3H, NCH_3), 2.34 (m, 1H, CH$_2$), 2.63−2.95 (m, 6H, CH$_2$), 3.47 (m, 2H, CH$_2$), 3.98 (m, 1H, CH$_2$), 4.24 (q, J = 8.2 Hz, 1H, CHCF$_3$), 5.8 (br s, 1H, OH or NH), 6.36 (m, 1H, CH quinoline), 6.91 (br s, 1H, =CH lactam), 6.93 (br s, 1H, =CH lactam), 7.24 (d, J = 8.5 Hz, 2H, p-BrC$_6$H$_4$), 7.37 (m, 1H, CH quinoline), 7.51 (d, J = 8.5 Hz, 2H, p-BrC$_6$H$_4$), 7.90−7.96 (m, 2H, CH quinoline), 8.51 (m, 1H, CH quinoline). ^{19}F NMR (CDCl$_3$): δ −68.9 (d, J = 8.2 Hz), −69.1 (d, J = 8.2 Hz). ^{13}C NMR (CDCl$_3$): δ 14.0 (s, CH_3CH$_2$S), 14.1 (s, CH_3CH$_2$S), 27.3 (s, CH$_3$$CH_2$S), 27.4 (s, CH$_3$$CH_2$S), 37.5 (s, CH$_2$), 39.9 (s, CH$_2$), 41.0 (s, N$CH_3$), 41.2 (s, N$CH_3$), 41.2 (q, J = 31.5 Hz, CHCF$_3$), 41.4 (q, J = 31.5 Hz, CHCF$_3$), 89.6 (s, C$_q$, C(OH)CH$_3$), 89.7 (s, C$_q$, C(OH)CH$_3$), 98.5 (s, CH quinoline), 98.6 (s, CH quinoline), 117.1 (s, C$_q$ quinoline), 117.2 (s, C$_q$ quinoline), 122.6 (s, CH quinoline), 122.7 (s, CH quinoline), 123.0 (s, C$_q$, p-BrC$_6$H$_4$), 123.1 (s, C$_q$, p-BrC$_6$H$_4$), 125.5 (s, CH quinoline), 125.6 (s, CH quinoline), 125.8 (q, J = 278.9 Hz, CF$_3$), 126.7 (s, C$_q$, p-BrC$_6$H$_4$), 126.8 (s, C$_q$, p-BrC$_6$H$_4$), 127.9 (s, 2 × CH p-BrC$_6$H$_4$), 129.0 (s, C$_q$ quinoline), 129.1 (s, C$_q$ quinoline), 132.1 (s, 2 × CH p-BrC$_6$H$_4$), 135.6 (m, C$_q$, CCHCF$_3$), 137.1 (s, C$_q$ quinoline), 137.3 (s, C$_q$ quinoline), 146.3 (s, =CH lactam), 146.8 (s, =CH lactam), 150.2 (s, CH quinoline), 150.3 (s, CH quinoline), 150.5 (s, C$_q$ quinoline), 150.6 (s, C$_q$ quinoline), 168.1 (s, CO), 168.2 (s, CO). HRMS (ESI$^+$): m/z calcd for [M + H]$^+$ $C_{28}H_{30}BrClF_3N_4O_2S$ 657.0913, found 657.0904. Anal. Calcd for $C_{28}H_{29}BrClF_3N_4O_2S$: C, 51.11; H, 4.44; N, 8.52. Found: C, 51.09; H, 4.43; N, 8.47.

Typical Procedure for the Preparation of Citric Salts 84−88. To a solution of aminoquinoline derivative **58** (22 mg, 0.04 mmol) in anhydrous acetone (1 mL) was added a solution of citric acid (8 mg, 0.04 mmol) in anhydrous acetone (1 mL). The corresponding ammonium salt precipated spontaneously, and then the resulting suspension was left for 1 day at room temperature until full precipitation. After removal of the solvent, the solid was washed with acetone (1 mL) and dried under reduced pressure, affording the desired citric salt **84** (28 mg, yield 93%).

1-(2-((2-((7-Chloroquinolin-4-yl)amino)ethyl)amino)ethyl)-5-hydroxy-5-((phenylsulfanyl)methyl)-3-(2,2,2-trifluoroethyl)-1*H*-pyrrol-2(5*H*)-one Citrate (84). The title compound was a solid. ^{1}H NMR (DMSO-d_6): δ 2.54 (d, J = 15.3 Hz, 2H, 2 × CH_AH$_B$ citrate), 2.63 (d, J = 15.3 Hz, 2H, 2 × CH$_A$$H_B$ citrate), 3.03−3.53 (m, 12H, 6 × CH$_2$), 6.62 (d, J = 5.4 Hz, 1H, CH quinoline), 6.92 (br s, 1H, =CH lactam), 7.19−7.30 (m, 5H, Ph), 7.55 (dd, J = 9.0 and 1.9 Hz, 1H, CH quinoline), 7.84 (d, J = 1.9 Hz, 1H, CH quinoline), 8.25 (d, J = 9.0 Hz, 1H, CH quinoline), 8.47 (d, J = 5.4 Hz, 1H, CH quinoline). ^{19}F NMR (DMSO-d_6): δ −63.4 (t, J = 10.3 Hz). Anal. Calcd for $C_{32}H_{34}ClF_3N_4O_9S$: C, 51.72; H, 4.61; N, 7.54. Found: C, 51.97; H, 4.59; N, 6.93.

5-(4-Bromophenyl)-1-(2-((2-((7-chloroquinolin-4-yl)amino)ethyl)methylamino)ethyl)-3-(1-(ethylsulfanyl)-2,2,2-trifluoroethyl)-5-hydroxy-1*H*-pyrrol-2(5*H*)-one citrate (88). The yield was 76% as a mixture (50/50) of nonseparated diastereomers, solid. The following NMR data are for the mixture of diastereomers. ^{1}H NMR (DMSO-d_6): δ 1.19 (t, J = 7.5 Hz, 3H, CH_3CH$_2$), 2.21 (s, 3H, NCH$_3$), 2.58 (d, J = 15.3 Hz, 2H, 2 × CH_AH$_B$ citrate), 2.67 (d, J = 15.3 Hz, 2H, 2 × CH$_A$$H_B$ citrate), 2.50−2.78 (m, 6H, 3 × CH$_2$), 2.85−2.95 (m, 1H, CH$_2$), 3.45 (m, 3H, CH$_2$), 4.47−4.60 (m, 1H, CHCF$_3$), 6.66 (d, J = 5.4 Hz, 1H, CH quinoline), 6.93 (br s, 1H, =CH lactam), 6.95 (br s, 1H, =CH lactam), 7.17−7.22 (m, 2H, p-BrC$_6$H$_4$), 7.56−7.63 (m, 3H, 2 × CH p-BrC$_6$H$_4$ + CH quinoline), 7.86 (m, 1H, CH quinoline), 8.34 (d, J = 9.0 Hz, 1H, CH quinoline), 8.48 (d, J = 5.4 Hz, 1H, CH quinoline). ^{19}F NMR (DMSO-d_6): δ −67.1 (d, J = 8.2 Hz), −67.5 (d, J = 8.2 Hz). Anal. Calcd for $C_{34}H_{37}BrClF_3N_4O_9S$: C, 48.04; H, 4.39; N, 6.59. Found: C, 48.38; H, 4.37; N, 6.18.

In Vitro Drug Sensitivity Assay with Cultured Parasites. After they were taken out of liquid nitrogen, the cultured parasites were grown for 10−12 days until a predominance of ring-stage parasites of no less than 70% was reached. These parasites were used for the drug sensitivity assays. Once the parasitemia levels of the in vitro cultures reached an optimum density of 5−8%, the infected red blood cells were centrifuged at 350g for 5 min; the supernatant was aspirated; and the cells were suspended in RPMI with and without phenol red (Invitrogen, Carlsbad, CA) supplemented with 0.5% Albumax I (0.005 g/mL), HEPES (5.94 g/L), and NaHCO$_3$ (2.4 g/L). An aliquot of the culture was diluted to reduce the parasitemia to 0.5%, and the hematocrit was added to plates preloaded with serial dilution of tested drugs. Negative control (RPMI) and positive control (chloroquine) were systematically added to each plate. All tests were conducted in triplicate, and the experiments were reproduced twice. The plates were incubated in a humidified modular incubator chamber (Flow Laboratories, Irvine, CA) at 37 °C under a gas mixture of 5% O$_2$, 5% CO$_2$, and 90% N$_2$ for 72 h.

IC$_{50}$ Determination by the SYBR Green I Assay. Following incubation, the plates were frozen and stored at −80 °C until the SYBR green I assay was performed. The plates were thawed for 2 h at room temperature, and each sample was mixed by pipetting. Briefly, a total of 100 μL of the culture was transferred to a new 96-well plate, followed by the addition of 100 μL of SYBR green I (Molecular

Probes, Invitrogen, Carlsbad, CA) in lysis buffer (0.2 μL of SYBR green I/mL of lysis buffer, which consisted of Tris 20 mM (pH 7.5), EDTA (5 mM), saponin (0.008%, w/v), and Triton X-100 (0.08%, w/v)).[40] The plates were covered and incubated at room temperature for 1 h. The fluorescence intensity was measured from below with a Twinkle fluorometer (Berthold, Thoiry, France) at excitation and emission wavelengths of 485 and 535 nm, respectively. The IC_{50} values obtained after incubation times of 48 and 72 h were calculated by using the HN-nonlin V1.05 Beta program.

Cytotoxicity. The cytotoxicity of the chemical compounds was tested against HUVECs. Cells were maintained in cell medium EBM-2 (endothelial cell basal medium 2; Lonza) under a humidified atmosphere in 5% CO_2 at 37 °C. HUVECs were seeded in a 96-well microplate in their exponential phase of growth (50 000 cells/mL). The cells were incubated for 24 h with serial dilutions of the compounds from 100 to 0.01 μmol/L. The stock solution of the compounds was 200 mM in DMSO, and the successive dilutions were made in culture medium. The DMSO final concentration in the well never exceeded 0.5%. Growth controls were obtained using medium alone and cytotoxicity controls using DMSO. After the incubation period, 20 μL of Tryptan Blue dye (0.4%) was added to each well during 3 min. Then the dye was removed, and the plates were observed using an optical microscope. Blue-stained cells were considered as dead. The proportion of dead cells in each well was compared to the proportion of dead cells in the growth control.

■ ASSOCIATED CONTENT

Supporting Information

Additional experimental details and description of compounds, additional in vitro data, and LC/MS pH stability profile of compounds **50** and **70**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ ABBREVIATIONS USED

AQ, amodiaquine; CQ, chloroquine; CQS, chloroquino-sensitive; CQR, chloroquino-resistant; CC_{50}, concentration for 50% cytotoxicity; IC_{50}, concentration of inhibitor resulting in 50% inhibition; HUVECs, human umbilical vein endothelial cells; SAR, structure−activity relationship; RI, resistance index (ratio IC_{50}(W2)/IC_{50}(3D7))

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