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Optimization of 1,2,3,4-Tetrahydroacridin-9(10*H*)-ones as Antimalarials Utilizing Structure−Activity and Structure−Property Relationships

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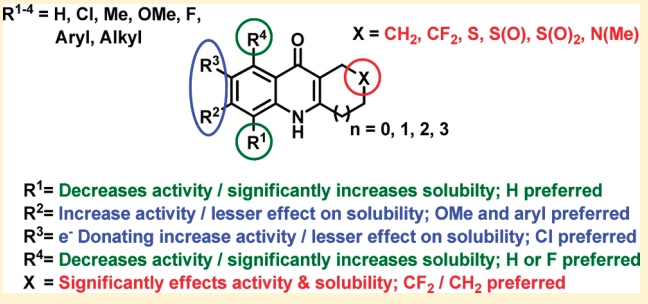
Supporting Information

ABSTRACT: Antimalarial activity of 1,2,3,4-tetrahydroacridin-9(10*H*)-ones (THAs) has been known since the 1940s and has garnered more attention with the development of the acridinedione floxacrine (**1**) in the 1970s and analogues thereof such as WR 243251 (**2a**) in the 1990s. These compounds failed just prior to clinical development because of suboptimal activity, poor solubility, and rapid induction of parasite resistance. Moreover, detailed structure−activity relationship (SAR) studies of the THA core scaffold were lacking and SPR studies were nonexistent. To improve upon initial findings, several series of 1,2,3,4-tetrahydroacridin-9(10*H*)-ones were synthesized and tested in a systematic fashion, examining each compound for antimalarial activity, solubility, and permeability. Furthermore, a select set of compounds was chosen for microsomal stability testing to identify physicochemical liabilities of the THA scaffold. Several potent compounds (EC_{50} < 100 nM) were identified to be active against the clinically relevant isolates W2 and TM90-C2B while possessing good physicochemical properties and little to no cross-resistance.



INTRODUCTION

Malaria's origin, recently estimated to be over 30 million years old,[1] predates mankind and has plagued civilization since the dawn of agriculture.[2] This devastating disease has become one of the most widespread infectious diseases[3] with approximately 243 million cases resulting in approximately 863 000 deaths in 2008.[4] It is believed that ∼40% of the world's population is at risk[3] with the greatest representation of this number being young children. With the widespread emergence of parasite resistance to drug mainstays such as atovaquone, sulfadoxine−pyrimethamine, mefloquine, and even more recently artemisinin,[5,6] the development of new antimalarials has been invigorated and supported by the recent call-to-arms from the Bill and Melinda Gates Foundation and other initiatives.[7] In an effort to curb artemisinin resistance, the World Health Organization (WHO) promoted the use of artemisinin-combination therapies (ACTs)[8] by which two or more antimalarials with different modes of action are taken at the same time.[9] Unfortunately, disturbing reports of emerging resistance to ACTs, which originally have been considered to be reliable treatments for malaria, have emanated in recent studies. Historically, once resistance has manifested itself to one compound, the resistance is conferred to the entire chemotype class. Therefore, much effort has been taken to modify existing drugs to counteract the induced resistance through structural changes.[10,11] Alternatively, new pharmacophores are extremely desirable as platforms for new possibilities in malaria therapy.

Advances in library screening, hit-to-lead optimization, physicochemical understanding of biologically active compounds, and refined understanding in mechanisms of action can lead to overcoming hurdles in previously discovered lead candidates.[12,13] One such example recently arose with the optimization of the 4(1*H*)-quinolone endochin (**3**) into a more robust 3-phenyl-4(1*H*)-quinolone (**4**) that possessed higher solubility, greater microsomal stability, and no cross-resistance with atovaquone.[14] A similarly related example is floxacrine (**1**) and its analogue WR 243251 (**2a**) (Figure 1). The dihydroacridinedione **1** was first discovered by Durckheimer and co-workers in 1975.[15] Though compound **1** had promising characteristics including causal prophylactic activity,[16−18] it suffered from poor solubility,[19] parasite drug-resistance,[20] and dose-dependent chronic periarteritis.[20] Shortly after, a new synthetic analogue **2a** with superior properties devoid of the aforementioned disadvantages of **1** emerged.[19] However, during late preclinical development, compound **2a** was abandoned because of suboptimal stability, cross-resistance with atovaquone,[21] and lingering toxicity.

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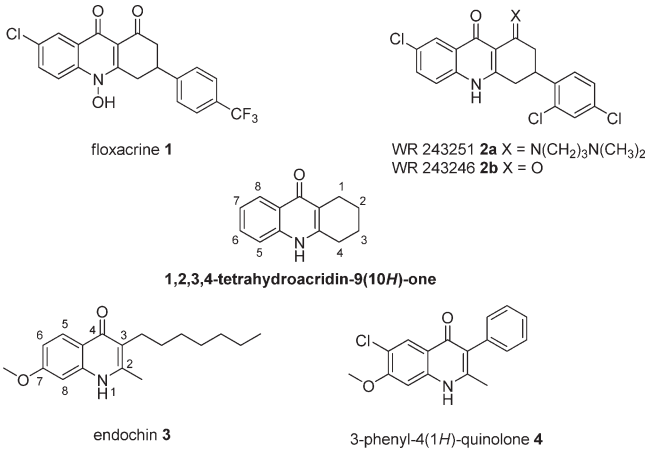


Figure 1. Structures of several antimalarials **1**−**4** and the core 1,2,3,4-tetrahydroacridin-9(10*H*)-one.

Even though 1,2,3,4-tetrahydroacridin-9(10*H*)-ones (THAs) with antimalarial activity were reported initially by Stephen and co-workers in 1947, follow-up optimization studies were relatively limited in comparison to optimizations of other historical antimalarials.[22] Riscoe et al. recently examined acridone analogues as antimalarials, which, however, differ from the THAs with respect to the structure and aromaticity.[23,24] With limited exploration of THA analogues such as **1** and **2a**, as well as recent studies on antimalarial 4(1*H*)-quinolones,[14,25] we were prompted to examine the THA series (Figure 1) for antimalarial efficacy by conducting detailed structure−activity and structure−property relationship (SAR and SPR) studies in parallel. In the past decade, drug discovery and optimization programs focusing on biological activity and physicochemical property data at the early developmental stages have been shown to minimize the risks to fail later. Our synthetic strategy was based in part upon the Topliss operational schemes[26,27] to design THA analogues for routine in vitro testing against *P. falciparum* multidrug resistant strains W2 (resistant to chloroquine and pyrimethamine) and TM90-C2B (resistant to chloroquine, mefloquine, pyrimethamine, and atovaquone). All THAs have undergone in vitro testing for cytotoxicity in mammalian J774 macrophage cells. Furthermore, all compounds have routinely been evaluated for aqueous solubility at pH 2.4, 4.0, and 7.4, permeability at pH 4.0 and 7.4, and log *D* at pH 7.4 to determine which compounds have potential to be advanced into in vivo efficacy experiments. Herein, we report the preparation and thorough examination of a library of 118 THAs as antimalarial agents.

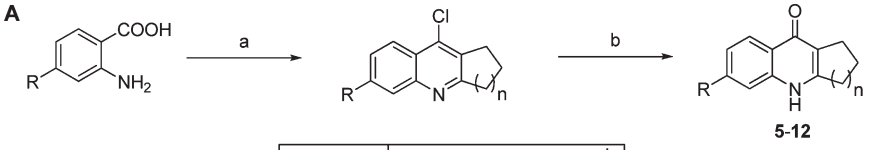
RESULTS AND DISCUSSION

Synthetic Chemistry. Previous optimization studies leading to acridinedione compounds **1** and **2a** demonstrated that a 7-chloro substituent in the benzenoid ring of the acridinedione core was important for antimalarial activity, as well as the imine moiety at the carbonyl carbon C1 in N10-H analogues. Over 200 compounds were prepared and tested; however, the main investigation focused on analogues varying the nature of the aryl ring at the 3 position and analogues possessing various alkylamino imines at the 1-position. Of these aforementioned analogues, the majority of them possessed a 7-chloro substituent with very limited attention paid to benzenoid ring substitution.[19] It is possible that access to a single synthetic route for generating various benzenoid substituents in the acridinedione core was a key factor in the limited scope of compounds tested. For the current optimization study, THAs varying in their substituents at the, 2-, 3-, 5-, 6-, 7-, and/or 8-position have been designed to obtain detailed SAR and SPR data, which complements previous studies potentially overcoming the liabilities of compounds **1** and **2a**.

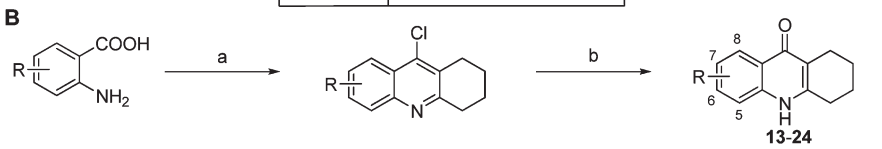
First, a set of THAs was synthesized to determine the optimal size of the saturated ring. On the basis of 3-aryl-substituted 4(1*H*)-quinolones previously developed in our laboratory,[14] five- to eight-membered ring sizes were examined with THAs containing either an electron poor or an electron rich substituent at the 6-position. Structures shown in Figure 1 with aliphatic ring sizes of 5, 7, and 8 are not tetrahydroacridone according to the IUPAC nomenclature. Nevertheless, the inclusive acronym THA (tetrahydroacridone) was used for all analogues based on a six-membered aliphatic ring. These compounds were prepared using 4-methoxyanthranillic acid or 4-trifluoromethylanthranillic acid with $POCl_3$ and the appropriate cycloalkanone to yield 9-chloro-1,2,3,4-tetrahydroacridines. These intermediates were subsequently hydrolyzed using acetic acid in a sealed tube at 200 °C to generate compounds **5**−**12** (Scheme 1). The two-step synthetic sequence proved to be superior over the more frequently reported direct condensation reactions of anthranillic acids and cyclohexanones via azeotropic distillation of water.[28−30] It was observed that these one-step condensations were often incomplete and overall problematic especially those starting from electron rich anthranillic acids. Recently, Elguero and co-workers utilized microwave irradiation to improve the yields through the one-step condensation.[31] Another hurdle of the one-step condensations is the purification of the THA products, as unreacted anthranillic acid and resultant polar side products are very difficult to remove. In contrast, the two-step reaction sequence cleanly provided THA compounds upon precipitation from water which were further recrystallized from either pyridine or DMF. Generally, the use of pyridine provided neutral THA products as opposed to DMF which could yield the corresponding salt forms. It was observed that the hydrolysis undergoes a nucleophilic displacement at the 9-position, providing the 1,2,3,4-tetrahydroacridin-9-yl acetate, which is subsequently hydrolyzed. This observation is in accordance with the known electrophilicity of these 9-chloro-1,2,3,4-tetrahydroacridines, since these intermediates are commonly found in literature to prepare 4-aminoquinolines.[32,33]

Next, a set of compounds was designed to probe the benzenoid ring positions according to the Topliss operational schemes, which are based upon physicochemical parameters related to hydrophobicity, electronics, and sterics.[26,27] Upon determination that the THAs containing the six-membered aliphatic ring were the most potent analogues, chloro-, methyl-, or methoxy-substituted anthranillic acids were combined with cyclohexanone, 3,3-dimethylcyclohexanone, and 4,4,-dimethylcyclohexanone to yield THAs **13**−**50**. Furthermore, a series of monosubstituted THAs **51**−**63** with more electronegative or sterically encumbering benzenoid ring substituents were prepared either by the two-step sequence starting from anthranillic acids and cyclohexanones (Scheme 2, route A) or by a Conrad−Limpach cyclization reactions (Scheme 2, route B).[34] The decision of which route to use for the preparation of a particular THA was based on commercial availability and cost of starting materials as well as the ease in purification of the final product.[35] The preparation of THAs via the Conrad−Limpach synthetic route starting from meta-substituted anilines yields a mixture of 6- and 8-substituted regioisomers, which are difficult to separate. In contrast, the two-step

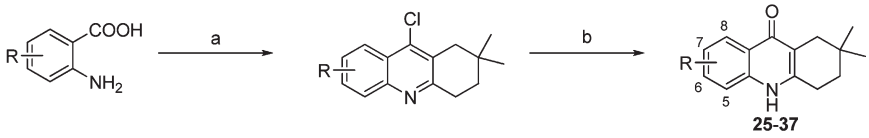
Scheme 1. Synthesis of Varying Ring-Sized 1,2,3,4-Tetrahydroacridin-9(10*H*)-ones 5−50[a]



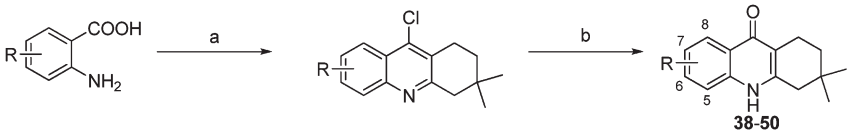
Compound	R	n	Yield[i]
5	-OMe	1	54%
6	-OMe	2	43%
7	OMe	3	38%
8	-OMe	4	32%
9	-CF_3	1	65%
10	-CF_3	2	62%
11	-CF_3	3	57%
12	-CF_3	4	31%



Compound	R	Yield[i]	Compound	R	Yield[i]	Compound	R	Yield[i]
13	H	72%	**17**	5-Me	29%	**21**	5-Cl	60%
14	5-OMe	33%	**18**	6-Me	51%	**22**	6-Cl	65%
6	6-OMe	43%	**19**	7-Me	55%	**23**	7-Cl	68%
15	7-OMe	46%	**20**	8-Me	43%	**24**	8-Cl	43%
16	8-OMe	15%						



Compound	R	Yield[i]	Compound	R	Yield[i]	Compound	R	Yield[i]
25	H	59%	**30**	5-Me	34%	**34**	5-Cl	51%
26	5-OMe	56%	**31**	6-Me	37%	**35**	6-Cl	45%
27	6-OMe	37%	**32**	7-Me	39%	**36**	7-Cl	60%
28	7-OMe	61%	**33**	8-Me	44%	**37**	8-Cl	42%
29	8-OMe	45%						



Compound	R	Yield[i]	Compound	R	Yield[i]	Compound	R	Yield[i]
38	H	43%	**43**	5-Me	32%	**47**	5-Cl	26%
39	5-OMe	21%	**44**	6-Me	41%	**48**	6-Cl	52%
40	6-OMe	39%	**45**	7-Me	38%	**49**	7-Cl	53%
41	7-OMe	21%	**46**	8-Me	75%	**50**	8-Cl	45%
42	8-OMe	46%						

[a] Reaction conditions: (a) $POCl_3$, cycloalkanone, reflux, 1−8 h; (b) AcOH, sealed tube, 200 °C, 24−48 h; (i) yield over two steps after recrystallization from either DMF or pyridine.

reaction sequence with 4-substituted anthranillic acids cleanly produces the desired THA regioisomer. Nevertheless, the Conrad−Limpach reaction is more suitable for THAs that cannot withstand the acetic acid hydrolysis such as compound **63**. Overall, the commercial availability of various anilines compared to anthranillic acids is much greater, making this synthetic route very desirable and valuable.

Investigations then focused on THAs equally disubstituted at the benzenoid ring to probe potential synergistic effects derived from these monosubstituents. By use of the same pair of synthetic routes in Scheme 2, compounds **64**−**83** were prepared from commercially available anilines (Figure 2, route B). Via route B, some anilines generated regioisomeric THAs, whose individual isomers were purified via preparative HPLC and recrystallization as noted in Scheme 2. Furthermore, THAs substituted with two different groups at the 6- and 7-positions were synthesized to test whether a particular benzenoid ring substituent combination exhibits a potency enhancement similar to that observed for the 6-chloro-7-methoxy-4(1*H*)-quinolone antimalarial series (Scheme 3). Simultaneously, THAs containing one heteroatom in the saturated ring were prepared with the intent to increase the solubility, the metabolic stability, or both.

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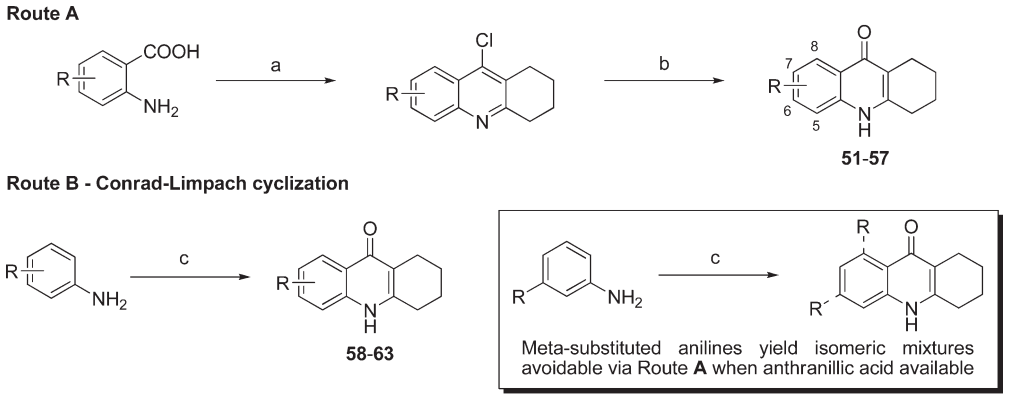
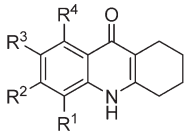
Scheme 2. Synthesis of 1,2,3,4-Tetrahydroacridin-9(10*H*)-ones 51−63 Using Route A or Route B[a]



Compound	R	Yield[i]	Route	Compound	R	Yield[i]	Route
51	6-nitro	54%	**A**	**58**	5-^{t}bu	49%	**B**
52	7-nitro	61%	**A**	**59**	7-^{t}bu	84%	**B**
53	5-fluoro	25%	**A**	**60**	5-CF_3	39%	**B**
54	6-fluoro	55%	**A**	**61**	7-^{i}Pr	11%	**B**
55	7-iodo	49%	**A**	**62**	7-EtO	51%	**B**
56	6-bromo	51%	**A**	**63**	7-CO_2Et	32%	**B**
57	7-bromo	48%	**A**				

[a] Reaction conditions: (a) $POCl_3$, cyclohexanone, reflux, 1−8 h; (b) AcOH, sealed tube, 200 °C, 24−48 h; (c) ethyl 2-oxocyclohexanecarboxylate, AcOH, benzene, Dean−Stark trap, reflux, overnight, then Ph_2O, reflux, 15 min. [i] Route A - yield over two steps after recrystallization from either DMF or pyridine. Route B - yield is reported as the standard Conrad−Limpach conditions described in the experimental section. Some compounds were further purified either via Preparative HPLC or recrystallization, see experimental section.



64-83

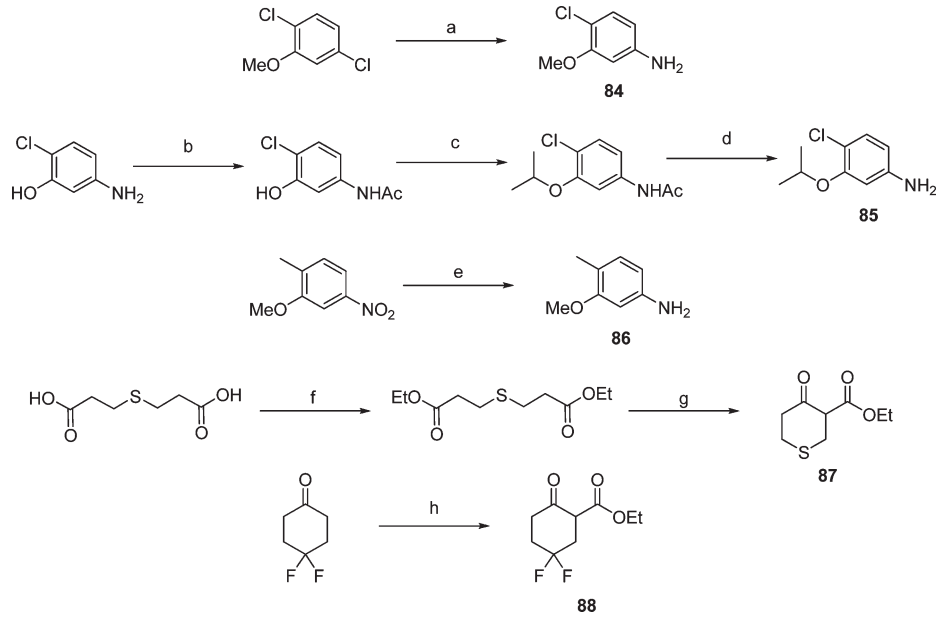
Compound	R^1	R^2	R^3	R^4	Yield[i]	Route	Compound	R^1	R^2	R^3	R^4	Yield[i]	Route
64	-Me	-H	-H	-Me	74%	**B**	**74**	-Cl	-H	-H	-Cl	15%	**B**
65	-Me	-H	-Me	-H	78%	**B**	**75**	-Cl	-H	-Cl	-H	39%	**A**
66	-H	-Me	-H	-Me	31%	**B**	**76**	-H	-Cl	-H	-Cl	47%	**B**
67	-Me	-Me	-H	-H	27%	**B**	**77**	-Cl	-Cl	-H	-H	36%	**B**
68	-H	-Me	-Me	-H	34%	**B**	**78**	-H	-Cl	-Cl	-H	21%	**A**
69	-OMe	-H	-H	-OMe	84%	**B**	**79**	-F	-H	-H	-F	19%	**B**
70	-OMe	-H	-OMe	-H	23%	**B**	**80**	-F	-H	-F	-H	97%	**B**
71	-H	-OMe	-H	-OMe	11%	**B**	**81**	-H	-F	-H	-F	30%	**B**
72	-OMe	-OMe	-H	-H	35%	**B**	**82**	-F	-F	-H	-H	51%	**B**
73	-H	-OMe	-OMe	-H	40%	**A**	**83**	-H	-F	-F	-H	42%	**A**

Figure 2. Compounds **64**−**83** via routes A and B. [i] Route A - yield over two steps after recrystallization from either DMF or pyridine. Route B - yield is reported as the standard Conrad−Limpach conditions described in the experimental section. Some compounds were further purified either via Preparative HPLC or recrystallization, see experimental section.

Starting materials, which are commercially unavailable, have been synthesized prior to the THA syntheses. 4-Chloro-3-methoxyaniline **84** was prepared using sodium amide in liquid ammonia,[36] while 4-chloro-3-isopropoxyaniline **85** was obtained by acetylating 5-amino-2-chlorophenol followed by an alkylation with isopropyl iodide in Cs_2CO_3. Interestingly, K_2CO_3 generated lower yields through a deprotective hydrolysis of the acetamido group. The amide was subsequently hydrolyzed with KOH in EtOH and water (9:1) to provide aniline **85**. 4-Methyl-3-methoxyaniline **86** was generated starting from a solution of 2-methoxy-1-methyl-4-nitrobenzene in MeOH and hydrogenated for 3 h in the presence of 10% Pd/C.[37] The cyclic β-ketoester **87** was prepared by esterifying 3,3′-thiodipropanoic acid to the ethyl ester. Subsequently, this intermediate was intramolecularly cyclized via sodium hydride by refluxing in THF. Ethyl 5,5-difluoro-2-oxocyclohexanecarboxylate **88** was prepared from 4,4-difluorocyclohexanone using NaH and diethyl carbonate.

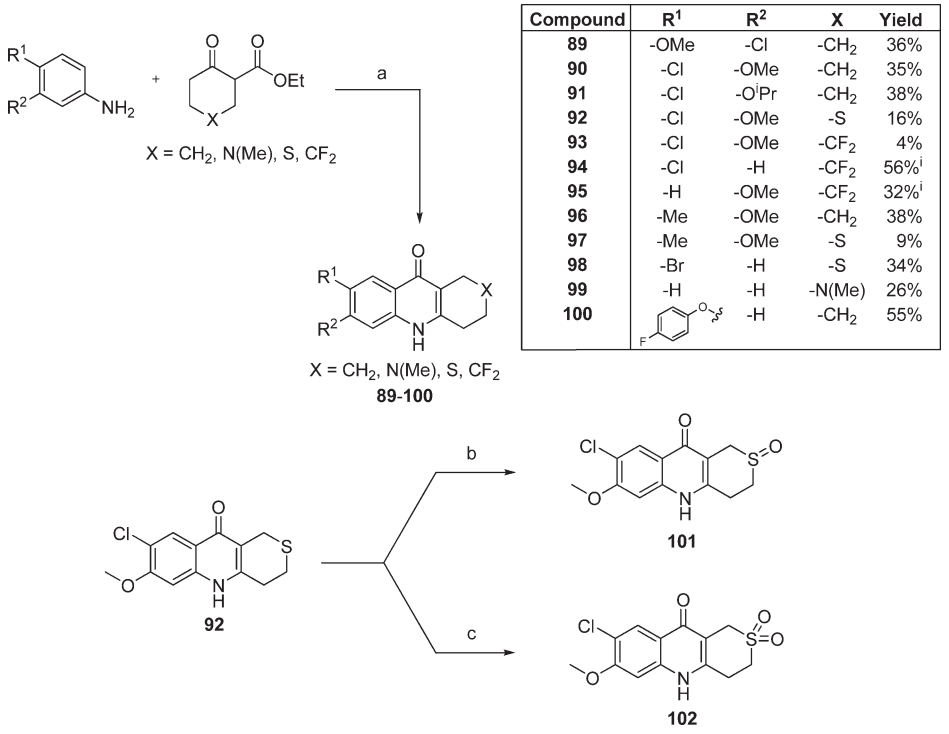
Compounds **89**−**100** were prepared using the Conrad−Limpach reaction conditions used in route B (Scheme 4). THA **100** was synthesized from a commercially available anilinoether to examine whether an aryl ether directly attached to the THA core would improve biological activity. Similarly, this compound provides a different class of ethers as opposed to THAs **62**, **70**, **73**, and **89**−**93**, which contain alkyl ether

Scheme 3. Synthesis of Intermediate Anilines 84−86 and β-Ketoesters 87−88[a]



[a] Reaction conditions: (a) Na, NH_3(l); (b) Ac_2O, AcOH, reflux, 5 min; (c) Cs_2CO_3, ^{i}PrI, DMF, 45 °C, 18 h; (d) KOH, EtOH/H_2O (9:1), reflux, 8 h; (e) Pd/C, H_2(g), MeOH, 3 h; (f) conc H_2SO_4, EtOH, reflux, 4 h; (g) NaH, THF, EtOH (cat.), reflux, 8 h; (h) NaH, diethylcarbonate, benzene, 80 °C, 8 h.

Scheme 4. Synthesis of THAs 89−102[a]



Compound	R^1	R^2	X	Yield
89	-OMe	-Cl	$-CH_2$	36%
90	-Cl	-OMe	$-CH_2$	35%
91	-Cl	-O^{i}Pr	$-CH_2$	38%
92	-Cl	-OMe	-S	16%
93	-Cl	-OMe	$-CF_2$	4%
94	-Cl	-H	$-CF_2$	56%[i]
95	-H	-OMe	$-CF_2$	32%[i]
96	-Me	-OMe	$-CH_2$	38%
97	-Me	-OMe	-S	9%
98	-Br	-H	-S	34%
99	-H	-H	-N(Me)	26%
100		-H	$-CH_2$	55%

[a] Reaction conditions: (a) various ethyl 2-oxo-4-substituted cyclohexanecarboxylates, AcOH, benzene, Dean−Stark trap, reflux, overnight, then Ph_2O, reflux, 15 min; (b) H_2O_2 (aq), 40 °C; (c) *m*-CPBA in $CHCl_3$, 0 °C, 4 h. [i] Route A using corresponding anthranillic acid was used.

substituents. Sulfoxide **101** and sulfone **102** were oxidized from THA **92** using aqueous hydrogen peroxide at 40 °C and *m*-CPBA in $CHCl_3$ at 0 °C, respectively.[38] Finally, a small set of THAs was prepared in which the 2-position possessed a difluoromethylene unit. Compound **93** was prepared using route B from the chloromethoxyaniline **84** and cyclic β-ketoester **88**, while compounds **94** and **95** were generated using route A with 4,4-difluorocyclohexanone.

Finally, a small series of Suzuki−Miyaura coupled THAs (**103**−**118**) was prepared to probe the similarity between the

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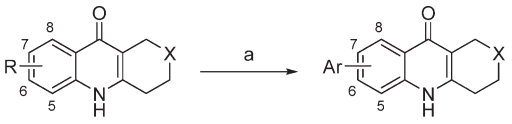
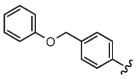
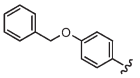
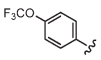
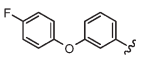
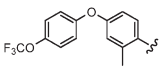
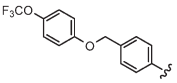
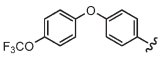
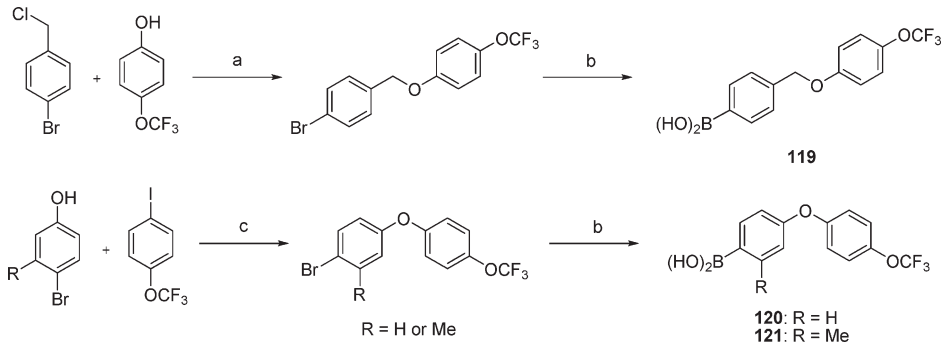
Scheme 5. Synthesis of THAs 100−118 via Suzuki−Miyaura Cross-Coupling[a]



Compound	R	Ar	X	Yield	Compound	R	Ar	X	Yield
103	7-Br		S	31%	**111**	7-Br		S	68%
104	7-Br		S	82%	**112**	7-Br		S	62%
105	7-Br		S	74%	**113**	7-Br		S	71%
106	7-Br		S	70%	**114**	7-I		CH_2	78%
107	7-Br		S	72%	**115**	6-Br		CH_2	81%
108	7-Br		S	79%	**116**	6-Br		CH_2	10%
109	7-Br		S	56%	**117**	6-Br		CH_2	33%
110	7-Br		S	68%	**118**	6-Br		CH_2	37%

[a] Reaction conditions: (a) $Pd_2(dba)_3$, SPHOS, Na_2CO_3 (aq), $ArB(OH)_2$, DMF, 80 °C, 4−36 h.

Scheme 6. Synthesis of Boronic Acids 119−121[a]



[a] Reaction conditions: (a) NaH, DMF (anhyd), 80 °C; (b) $B(O^iPr)_3$, THF (anhyd), −78 °C, then *n*-BuLi (1.6 M), 3 h, then 6 M HCl, rt, 18 h; (c) CuCl, NMP (anhyd), Cs_2CO_3, 2,2,6,6-tetramethylheptane-3,5-dione (22 mol %), 110 °C, 4−6 h.

THAs and the 4(1*H*)-quinolone chemotype (Scheme 5).[14] Notably, THA **100** was promising in terms of activity, prompting the investigation of the position and nature of several aryl moieties at the benzenoid ring. A variety of monosubstituted and biaryl 6- or 7-substituted THAs were prepared. Moreover, recent results from GSK's pyridone project[39,40] and preliminary data generated in our laboratory motivated us to synthesize boronic acids **119**−**121** used in the preparation of **109**, **110**, and **118** (Scheme 6). Of all the Suzuki−Miyaura compounds, the difluoro and pyridyl substrates **103**, **105**, and **116** demonstrated the most sluggish reactivity, requiring long reaction times and providing low yields.

Starting from 1-bromo-4-(chloromethyl)benzene, boronic acid **119** was prepared using 60% NaH in anhydrous DMF at 80 °C. This benzyl intermediate was lithiated using *n*-BuLi

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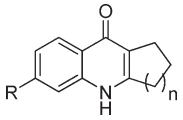
Table 1. SAR Focusing on the Aliphatic Ring Size of the 1,2,3,4-Tetrahydroacridin-9(10*H*)-ones[a]



compd	R	*n*	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)	solubility, pH 7.4 (μM)	P_e, pH 7.4 (10^{-6} cm/s)	log *D*, pH 7.4
1			478	270[b]					
2a			25.0	300	12.0				
2b			8.71	27.8	3.19		1	20	3.1
5	OMe	1	1130	610	0.54	>40	91	11	1.5
6	OMe	2	89.9	99.9	1.11	>40	82	25	1.9
7	OMe	3	171	153	0.89	>20	30	39	2.1
8	OMe	4	146	230	1.58	>40	98	73	2.4
9	CF_3	1	2320	438	0.19	>40	98	60	2.3
10	CF_3	2	120	19.0	0.16	>20	158	73	2.7
11	CF_3	3	4890	>4340	>0.88	>10	17	131	3.0
12	CF_3	4	4740	4230	0.89	>10	13	252	3.2

[a] Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay: DHA (1.8 nM W2 and 0.9 nM TM90-C2B) and CQ (162 nM W2 and 131 nM TM90-C2B) and ATO (0.53 nM W2 and >170 nM TM90-C2B). [b] EC_{50} vs D6.

at −78 °C in anhydrous THF and stirred in the presence of-$B(O^iPr)_3$ for 3 h at −78 °C. The boronate ester was hydrolyzed via the addition of 6 M HCl and subsequently warmed to room temperature and stirred overnight. Boronic acids **120** and **121** were prepared similarly; however, an Ullman cross-coupling was used to generate the halobiaryl intermediate that was subsequently hydrolyzed to the boronic acid as in **119**.

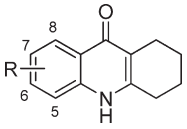
Antimalarial Activity. All synthesized compounds were tested, as previously reported, against the clinically relevant multidrug resistant malarial strains W2 (chloroquine and pyrimethamine resistant) and TM90-C2B (chloroquine, mefloquine, pyrimethamine, and atovaquone resistant).[14] The human malaria parasite *P. falciparum* was grown in vitro in dilute human erythrocytes in RPMI 1640 medium containing 10% heat inactivated plasma, and the potency for each 1,2,3,4-tetrahydroacridin-9(10*H*)-one against the individual strains has been calculated as the 50% effective concentration (EC_{50}).[41] The emergence of resistance and cross-resistance with atovaquone is a concern for new antimalarials that target the parasite mitochondria (e.g., atovaquone), and the resistance index (RI) of each compound was calculated as the ratio of the effective concentrations for W2 and TM90-C2B (RI = EC_{50}(TM90-C2B)/EC_{50}(W2)).[14] Compounds with RI = 0.3−3.0 are considered acceptable in regards to risk of cross-resistance with atovaquone, whereas compounds with RI > 10 or RI < 0.1 are likely to have clinically relevant levels of cross-resistance with atovaquone and are not candidates for additional preclinical studies.[42,43]

Structure−Activity Studies. THA **1** has been reported to display EC_{50} of 478 nM for W2 (chloroquine and pyrimethamine resistant) and 270 nM for D6 (drug susceptible strain), while the EC_{50} of compound **2a** (racemic mixture) for W2 is 25 nM, EC_{50} for D6 is 11 nM, EC_{50} for TM91 (chloroquine, quinine, and mefloquine resistant) is 51 nM, and EC_{50} for TM90-C2B is 300 nM.[21,44] Great strides were taken to improve the efficacy of compound **1**. Hundreds of analogues were prepared and tested, culminating in compound **2a**, a prodrug of **2b**.[19,45,46] Though these optimization attempts resulted in several compounds with single digit nanomolar activities to as low as 730 pM, these efforts were lacking in a systematic SAR and accompanying SPR studies. In the end, the development of compound **2a** and analogues thereof were abandoned, since these compounds suffered from drug resistance,[21] poor aqueous solubility, and lingering toxicity issues.[18,47] Similarly, in 1947 Stephen and co-workers examined THAs for antimalarial activity using an in vivo assay against *P. gallinaceum* infections in chickens without determining key physicochemical properties.[22] Six monosubstituted THAs and one disubstituted compound, which for confirmatory purposes have also been reevaluated by us, were tested, and compound **14** was identified by Kesten and co-workers to be the most potent compound. Interestingly, at the time that Stephen and co-workers initiated their studies on THAs, endochin had just been discovered and its in vivo antimalarial activity against *P. gallinaceum* was superior to that of most of the THAs.

The majority of the analogues of **1** and **2a** that were previously screened contained a 7-chloro substituent. Kesten and co-workers reported that the monochloro substituent was a necessity to achieve the highest levels of activity, while an unsubstituted or a disubstituted benzenoid ring resulted in greatly reduced antimalarial activities. In contrast, recent work by our laboratory demonstrates a substantial increase of potency in endochin analogues that are disubstituted at the benzenoid ring with a 6-chloro-7-methoxy substituent pair.[14] Just as important, this synergistic pair of substituents also improved the RI for W2 and TM90-C2B and the aqueous solubility. Furthermore, in the past, the aliphatic THA ring was moderately evaluated. Thus, a systematic approach to investigate the benzenoid ring and the saturated ring simultaneously was considered to be of highest priority to initiate our studies expanding upon the findings of Stephen and Kesten. A small series of THAs containing saturated ring sizes with five to eight carbons was prepared utilizing the appropriate commercially available cycloalkanones (Table 1).

THAs **5**−**8** contained one electron rich methoxy substituent at the benzenoid ring, while **9**−**12** were substituted with one

Table 2. SAR Focusing on Monosubstituted Benzenoid Ring Containing Unsubstituted Aliphatic Ring[a]



compd	R	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)	solubility, pH 7.4 (μM)	P_e, pH 7.4 (10^{-6} cm/s)	log *D*, pH 7.4
13	H	719	325	0.45	>40	24	10	3.0
14	5-OMe	4770	4560	0.95	>20	99	16	1.7
6	6-OMe	89.9	99.9	1.11	>40	82	25	1.9
15	7-OMe	2440	2530	1.03	>40	78	16	1.5
16	8-OMe	8970	5940	0.66	>20	76	17	1.2
17	5-Me	2200	888	0.40	>40	47	26	1.9
18	6-Me	150	152	1.01	>40	89	27	2.0
19	7-Me	449	656	1.46	>40	44	19	1.7
20	8-Me	6250	4570	0.73	>20	99	87	2.1
21	5-Cl	1350	>9000	>7.9	>20	107	107	2.2
22	6-Cl	137	122	0.89	>10	15	75	2.2
23	7-Cl	99.4	63.4	0.63	>2	4	57	2.0
24	8-Cl	368	447	1.22	>5	99	47	1.8

[a] Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay: DHA (1.8 nM W2 and 0.9 nM TM90-C2B) and CQ (162 nM W2 and 131 nM TM90-C2B) and ATO (0.53 nM W2 and >170 nM TM90-C2B).

electron-poor trifluoromethyl group. Regardless of the benzenoid ring substituent, THAs **6** and **10** containing a six-membered saturated ring were the most potent compounds against both W2 and TM90-C2B. Compounds **5** and **9** with the five-membered aliphatic ring and THAs **7**, **8**, **11**, and **12** with ring sizes of seven or larger were less potent than **6** and **10**. Furthermore, the RI value was not found to significantly depend on the aliphatic ring size. With the exception of compounds **9** and **10**, acceptable RI values have been calculated for all other THAs **5**−**8**, **11**, and **12**. In fact, the significant potency differences related to the two different benzenoid ring substitutents were determined to be of greater importance than the size of the saturated ring. Thus, the results of the subset of the methoxy-substituted THAs **5**−**8** urged us to focus on the further optimization of compounds containing six-membered saturated rings exclusively.

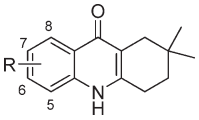
Next, an investigation was designed to explore the THA's benzenoid ring with various substituents at the 5-, 6-, 7-, and 8-positions. Following the Topliss operational scheme for aromatic substituents, the first compound set focused on groups probing electronic and steric factors. Monosubstituted THAs **6**, **13**−**24** containing a methyl, a methoxy, or a chloro substituent were tested (Table 2).

The unsubstituted THA **13** was used as a reference compound to assess whether a particular substituent of **14**−**24** has a favorable or an adverse effect on the antimalarial activity. Furthermore, two additional compound series were designed in which the 2- or 3-position of the saturated ring possesses *gem*-dimethyl substitution in combination with a methyl, a methoxy, or a chloro substituent on the benzenoid ring. These analogues not only probe the 2- and 3-position for sterics but also provide information on the saturated ring, since the methyl substituents influence the ring conformation. All possible combinations of 2,2-dimethyl substituted THAs **25**−**37** (Table 3) and 3,3-dimethyl-substituted compounds **38**−**50** (Table 4) have been tested against W2 and TM90-C2B. Analogues **25** and **38** have been prepared as reference compounds to reliably conclude whether the 2-position, the 3-position, or both are suitable for structural modifications.

Of compounds **6**, **13**−**24**, the 7-chloro-THA **23** exhibiting EC_{50} of 99.4 nM for W2 and 63.4 nM for TM90-C2B is the most active analogue, which is closely followed in activity by 6-methoxy- and 6-methyl-substituted THAs, **6** and **18**, respectively. Compound **6** with a methoxy group at the 6-position was the most potent compound of all the methoxy-substituted THAs, **6** and **14**−**16** with EC_{50} values of 89.9 nM for W2 and 99.9 nM for TM90-C2B. Thus, depending on the tested strain, THA **6** is approximately 3- to 7-fold more potent compared to the unsubstituted reference compound **13**. In contrast, methoxy substitution at the 5-, 7-, or 8-position provides THAs **14**, **15**, and **16** with diminished antimalarial activities in the micromolar range. Testing of THAs **17**−**24** identified that the 6- and 7-positions, when populated with a methyl or chloro substituent, improve the antimalarial activity by a factor of 2−7. The 6-methyl-THA **18** was approximately 2 to 4-fold more potent than the 7-methyl-substituted analogue **19**, while the 7-chloro-substituted THA **23** was twice as active as the 6-chloro-THA **22**.

The 2,2-dimethyl- or the 3,3-dimethyl-substituted THAs **25**−**50** were overall less active than the THA series **13**−**24** containing an unsubstituted saturated ring. The methyl groups appear to be less tolerated at the 3-position than at the 2-position with an average of a 4-fold difference in antimalarial activity. Furthermore, the 2,2-dimethyl- and 3,3-dimethyl-THAs **25**−**50** display a more pronounced strain selectivity with less favorable RI values in comparison to THAs **13**−**24** with an unsubstituted saturated ring. Especially THA **31**, which was shown to be potent against W2 with an EC_{50} of 166 nM and fairly inactive against TM90-C2B, and its analogues **18** and **44** are striking examples demonstrating that a small variance in structure can significantly impact the strain dependence. Regarding the benzenoid ring substituents of the 2,2-dimethyl- or the 3,3-dimethyl-substituted THAs **25**−**50**, potency trends were observed that are similar to

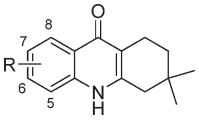
Table 3. SAR Focusing on Monosubstituted Benzenoid Ring Containing 2-*gem*-Dimethyl Aliphatic Ring[a]



compd	R	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)	solubility, pH 7.4 (μM)	P_e, pH 7.4 (10^{-6} cm/s)	log *D*, pH 7.4
25	H	421	295	0.70	>20	35	43	1.8
26	5-OMe	1990	620	0.31	>40	91	95	2.4
27	6-OMe	54.3	175	3.22	>40	61	88	2.2
28	7-OMe	8400	>9720	>1.16	>20	38	73	2.0
29	8-OMe	5240	3500	0.67	>20	83	54	1.9
30	5-Me	791	531	0.67	>40	38	90	2.3
31	6-Me	166	1980	11.9	>40	75	82	2.4
32	7-Me	474	2180	4.60	>40	52	84	2.4
33	8-Me	3020	4130	1.37	>40	45	269	2.7
34	5-Cl	4670	4730	1.01	>20	62	427	2.9
35	6-Cl	240	829	3.45	>40	1	62	2.8
36	7-Cl	256	118	0.46	>40	1	63	2.6
37	8-Cl	373	599	1.61	>40	23	117	2.4

[a] Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay: DHA (1.8 nM W2 and 0.9 nM TM90-C2B) and CQ (162 nM W2 and 131 nM TM90-C2B) and ATO (0.53 nM W2 and >170 nM TM90-C2B).

Table 4. SAR Focusing on Monosubstituted Benzenoid Ring Containing 3-*gem*-Dimethyl Aliphatic Ring[a]



compd	R	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)	solubility, pH 7.4 (μM)	P_e, pH 7.4 (10^{-6} cm/s)	log *D*, pH 7.4
38	H	1870	335	0.18	>40	64	43	1.9
39	5-OMe	6540	2490	0.38	>20	91	114	2.4
40	6-OMe	355	112	0.32	>40	92	64	2.2
41	7-OMe	>9720	>9720	ND	>5	9.2	128	2.3
42	8-OMe	>9720	4100	<0.42	>20	64	43	1.7
43	5-Me	2370	1750	0.74	>40	60	88	2.3
44	6-Me	1460	965	0.66	>10	17	53	2.49
45	7-Me	587	319	0.54	>2	4	78	2.4
46	8-Me	>9990	>9990	ND	>5	9	240	2.8
47	5-Cl	6700	>9550	>1.42	>20	20	407	3.0
48	6-Cl	1080	645	0.60	>1	1	0	2.9
49	7-Cl	215	538	2.50	>1	2	96	2.7
50	8-Cl	2990	5330	1.78	>5	6	103	2.5

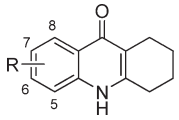
[a] Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay: DHA (1.8 nM W2 and 0.9 nM TM90-C2B) and CQ (162 nM W2 and 131 nM TM90-C2B) and ATO (0.53 nM W2 and >170 nM TM90-C2B).

those of the THA analogues **13**−**24**. The 6-methoxy- or 7-chloro-containing compounds **27**, **36**, **40**, and **49** were considerably more potent compared to the nonsubstituted reference compounds **25** and **38**, while methyl or chloro substituents in the 5- or 8-position resulted in compounds with poor activity with EC_{50} in the micromolar range.

The loss in potency and the adverse effect on the RI observed with the *gem*-dimethyl-THAs **25**−**50** motivated us to restrict the compound design to THAs possessing an unsubstituted aliphatic ring only. A selection of THAs **51**−**63** was prepared with the intent of exploring additional benzenoid ring substituents of distinct steric or electronic withdrawing nature (Table 5). Most compounds of this series displayed poor antimalarial activity with EC_{50} in the high-nanomolar or micromolar range. The 6-fluoro and the 6-bromo THAs **54** and **56** were the best analogues inhibiting the drug-susceptible strain W2 and the resistant strain

dx.doi.org/10.1021/jm200015a |*J. Med. Chem.* 2011, 54, 4399–4426

Table 5. SAR Focusing on Benzenoid Ring Substituted with Various Electronegative and/or Bulky Substituents[a]



compd	R	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)	solubility, pH 7.4 (μM)	P_e, pH 7.4 (10^{-6} cm/s)	log *D*, pH 7.4
51	6-NO_2	1050	959	0.91	>2	3	63	1.5
52	7-NO_2	3160	379	0.12	>5	8	6.9	1.5
53	5-F	536	2910	5.43	>40	109	17	1.5
54	6-F	67.7	119	1.76	>20	46	21	1.7
55	7-I	378	167	0.44	>20	4	96	2.3
56	6-Br	77.7	115	1.48	>10	14	70	2.8
57	7-Br	197	64.7	0.32	>2	2	63	2.1
58	5-^{t}Bu	>9790	>9790	ND	>10	90	553	3.3
59	7-^{t}Bu	78.7	325	4.13	>5	5	165	2.8
60	5-CF_3	>9350	>9350	ND	>20	116	246	2.6
61	7-^{i}Pr	879	732	0.83	>40	30	100	2.2
62	7-OEt	265	226	0.85	>5	5	52	1.9
63	7-CO_2Et	153	58.3	0.38	>5	8	63	2.1

[a] Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay: DHA (1.8 nM W2 and 0.9 nM TM90-C2B) and CQ (162 nM W2 and 131 nM TM90-C2B) and ATO (0.53 nM W2 and >170 nM TM90-C2B).

TM90-C2B at 100 nM or lower concentrations. Compound **63** containing an ethyl ester moiety at the 7-position was potent against TM90-C2B with an EC_{50} of 58.3 nM, which is consistent with previous observations that an electron-withdrawing group at the 7-position enhances activity. Analogues **58** and **60** containing substitutions at the 5-position were both devoid of activity. 7-Ethoxy-THA **62** was approximately 5-fold more potent when compared to the 7-methoxy analogues **15**, **28**, and **41**, suggesting that THAs with substituents at the 7-position may have potential to occupy a hydrophobic pocket of the biological target.[21,47,48]

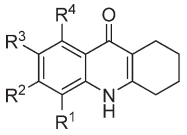
Subsequently, a methodical approach to test the benzenoid ring positions, which are substituted with two identical groups, was devised to explore the synergistic potential of **64**−**83** (Table 6). This study was accompanied by a second THA series having two different groups at the benzenoid ring or containing one heteroatom in the aliphatic ring, **89**−**102** (Table 7). The majority of the dimethyl-, dimethoxy-, dichloro-, and difluoro-substituted THAs **64**−**83** lacked submicromolar antimalarial activity. Nevertheless, five compounds with EC_{50} lower than 300 nM suggested that disubstitution patterns could be effective. The dimethyl and the dichloro analogues **68** and **78** substituted at the 6- and 7-positions were moderately potent with EC_{50} of 216−341 nM, whereas the 6,7-difluoro analogue **83** exhibited slightly better activities with EC_{50} in the 100 nM range for W2 and TM90-C2B. In contrast, the 6,8-dichloro analog **76** with EC_{50} of 87.8−96.2 nM and especially the 6,8-difluoro analog **81** with EC_{50} of 16.5−45.0 nM were approximately 5-fold more potent than their congeners **78** and **83**. However, compound **81** has an RI of 2.72, which just falls into the acceptable range for a resistance index figure but is still much more active in the drug susceptible strain. Eight disubstituted THA analogues containing an R^4 substituent possessed activities between 1 and 10 μM, except compounds **76** and **81** which also maintained a 6-substituent. The 6,7-disubstituted benzenoid moiety was manifested in terms of potency while maintaining excellent RIs of 0.82, 1.06, and 0.91 in compounds **68**, **78**, and **83**, respectively. Antimalarial activities of THAs **68**, **81**, and **83** are further evidence that a particular combination of substituents can provide not only a potent compound but one that could perhaps be free of multidrug resistance.

On the basis of the SAR of compounds **5**−**83**, a series was developed with the majority of the analogues containing a 6-methoxy-7-substituted THA core, with various substitutions on the aliphatic chain, **89**−**102** (Table 7). Compound **91** was the most potent against W2 (21.3 nM) but displayed a RI of 4.88, well above the desired range. Compounds **90**, **92**, **96**, and **97** were all 113 nM or less in activity against W2, with **92** having a 26.3 nM activity. These analogues support the observation that the 6-methoxy-7-substituted (generally chloro) substitution pattern is very important for potency. The RIs of these compounds are all in the acceptable range with exception of compound **92**, which has a good activity with the drug-susceptible strain. Compound **100** is interesting in that it has an RI just out of the acceptable range of 0.28 but an affinity for the drug-resistant line of 47 nM (TM90-C2B) and 169 (W2). This *O*-aryl ether was one of a possible series that we decided to pursue. These compounds can be assembled using a number of synthetic pathways. However, their synthesis is outside the scope of this manuscript. Nonetheless, this analogue highlights the potential for aryl-substituted scaffolds on the THA core. Compounds **90** and **96** were the most potent analogs against TM90-C2B with 24.1 and 16.2 nM, respectively. Compound **90** displayed an acceptable RI as observed with other analogues possessing this substitution pattern.[14]

3-Aryl substitution was shown to improve potency in the 4(1*H*)-quinolone series.[14] Analogous to the 4(1*H*)-quinolones, a small THA series was prepared to examine whether substitutions at the 6- and 7-positions of the benzenoid ring have potential to improve antimalarial activity, solubility, or both (Table 8).

The electronic nature of the aryl ring has been shown to be important for overall efficacy. All of the benzenoid positions in

Table 6. SAR of Disubstituted THAs[a]



compd	R^1	R^2	R^3	R^4	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)	solubility, pH 7.4 (μM)	P_e, pH 7.4 (10^{-6} cm/s)	log *D*, pH 7.4
64	Me	H	H	Me	3070	2390	0.78	>20	122	263	2.6
65	Me	H	Me	H	1070	768	0.72	>40	108	58	2.2
66	H	Me	H	Me	3130	4830	1.54	ND	17	218	2.4
67	Me	Me	H	H	3920	2280	0.58	>5	8	42	2.2
68	H	Me	Me	H	262	216	0.82	>20	41	46	2.1
69	OMe	H	H	OMe	>9640	>9640	ND	>20	105	9	1.5
70	OMe	H	OMe	H	>9640	7980	<0.83	>20	152	51	1.9
71	H	OMe	H	OMe	>7290	2590	<0.36	>40	188	13	1.4
72	OMe	OMe	H	H	6340	3460	0.55	>20	175	19	1.8
73	H	OMe	OMe	H	8970	3390	0.38	>20	88	1	1.3
74	Cl	H	H	Cl	>9320	>9320	ND	>20	108	288	2.6
75	Cl	H	Cl	H	>9320	>9320	ND	>1	1	252	3.0
76	H	Cl	H	Cl	87.8	96.2	1.10	>5	8	134	2.5
77	Cl	Cl	H	H	6330	>9330	>1.47	>20	41	348	2.9
78	H	Cl	Cl	H	321	341	1.06	>1	1	180	2.6
79	F	H	H	F	804	1320	1.64	>40	159	12	1.3
80	F	H	F	H	2690	405	0.15	>40	66	29	1.7
81	H	F	H	F	16.5	45.0	2.72	>2	3	13	1.5
82	F	F	H	H	1050	378	0.36	>40	93	38	1.9
83	H	F	F	H	129	118	0.91	>10	18	28	1.9

[a] Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay: DHA (1.8 nM W2 and 0.9 nM TM90-C2B) and CQ (162 nM W2 and 131 nM TM90-C2B) and ATO (0.53 nM W2 and >170 nM TM90-C2B).

the THA scaffold could be decorated with an appropriate halide to be used as a Suzuki coupling precursor; however, the focus would be on the 6- and 7-position because of the preliminary SAR emerging from Tables 1−7. Choice of boronic acid was based on the desire to probe a broad chemical space with electronic differences in the rings. 7-Pyridyl analogues **103** and **104** displayed poor activities in the micromolar range. 7-Substituted aromatic analogues, especially **106**, which has a 34.6 nM activity against W2 and a 23.2 nM activity against TM90-C2B, displayed good potencies. Next, 7-biaryl ether and 7-benzylaryl ether substituted analogues were tested. Compounds **108**−**112** showed good activities against W2 but a pronounced decline against TM90-C2B, suggesting the presence of resistance in these extended biaryl ethers. Alternatively, compound **118** displayed excellent activities against both strains with EC_{50} of 12.2 and 9.1 nM against W2 and TM90-C2B, respectively. The 6-dimethylaminobenzene substituted analogue **117** displayed activities of 99.2 and 161 nM against W2 and TM90-C2B. As a direct comparison of analogues substituted at the 6- and 7-position and the necessity of a sulfur containing aliphatic ring, analogues **113**−**115** were prepared. These three compounds were all active in the lower nanomolar range with the 6-trifluoromethylphenyl substituent being the most potent at 34.9 and 8.70 nM against W2 and TM90-C2B, respectively. This highlights the slight increase in activity of a strictly carbon aliphatic ring versus a heteroatom containing ring; however, the solubilities and half-lives of these analogues varied (see below). Overall, the aryl analogues exhibit increased activities in comparison to the mono- and disubstituted THAs. These analogues make for a large area of opportunity for diversification and improvements of the THA chemotype.

Resistance Index and Cytotoxicity. Through in vitro studies one can determine the strain dependence of individual compounds, which in turn can generate a proportion known as the resistance index (RI). As previously mentioned, RI > 3 has been linked to chemical resistance in atovaquone and chloroquine,[42,43] while a THA with an RI between 3 and 0.3 is desired (Figure 3).

The initial SAR probing aliphatic ring size revealed an interesting trend showing that electron withdrawing substituents at the 6-position were more potent against TM90-C2B, the chemically resistant strain, while the 6-methoxy substituted with six-membered rings showed an RI very close to 1. Generally the aryl-substituted THA series (Table 8) is more potent against W2 in comparison to TM90-C2B with a few of the compounds displaying RIs close to 1. This stands in contrast to the rest of the THA library (Tables 1−7) whose analogues are slightly more potent against the TM90-C2B strain than W2. Compound **90** is one of the most active THAs with EC_{50}(W2) of 30.6 nM and EC_{50}(TM90-C2B) of 24.1 nM with an RI of 0.79. Nevertheless, the RI is sensitive to structural changes among analogues similar to THA **90**. For example, THA **92** containing a sulfur in the aliphatic ring has an RI of almost 5, while replacement of the methoxy substituent by an isopropoxy group shifts the RI to almost 5 as well. Alternatively, for analogues **96** and **97**, in which

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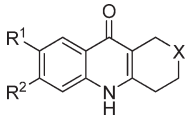
Table 7. SAR of Various THAs Including Heteroatom Containing Aliphatic Ring[a]



Compound	R^1	R^2	X	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)	Solubility pH 7.4 (μM)	Pe pH 7.4 (10^{-6} cm/s)	Log D pH 7.4
89	-OMe	-Cl	$-CH_2$	35.2	11.5	0.33	>20	33	24	1.3
90	-Cl	-OMe	$-CH_2$	30.6	24.1	0.79	>10	17	85	2.2
91	-Cl	$-O^iPr$	$-CH_2$	21.3	104	4.88	>0.1	0.3	0	2.9
92	-Cl	-OMe	-S	26.3	130	4.94	>10	13	101	1.0
93	-Cl	-OMe	$-CF_2$	76.7	5.60	0.07	>10	10	107	2.1
94	-Cl	-H	$-CF_2$	148	226	1.52	>2	4	62	2.0
95	-H	-OMe	$-CF_2$	343	351	1.02	>10	14	39	1.6
96	-Me	-OMe	$-CH_2$	34.8	16.2	0.46	>20	23	50	2.0
97	-Me	-OMe	-S	113	96.9	0.86	>10	14	68	0.9
98	-Br	-H	-S	667	>8440	N.D.	>10	17	6.3	0.9
99	-H	-H	-N(Me)	>9990	>9990	N.D.	>20	33	21	1.0
100		-H	$-CH_2$	169	47.0	0.28	>5	8	0	2.8
101	-Cl	-OMe	-S(O)	4710	1360	0.29	>40	45	0	1.3
102	-Cl	-OMe	$-S(O)_2$	4710	8410	1.76	>20	24	0	1.0

[a] Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay: DHA (1.8 nM W2 and 0.9 nM TM90-C2B) and CQ (162 nM W2 and 131 nM TM90-C2B) and ATO (0.53 nM W2 and >170 nM TM90-C2B).

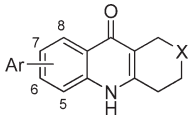
the 7-chloro has been replaced with a 7-methyl substituent, the RIs revert back to 0.46 and 0.86, respectively. Interestingly, the 6-chloro and 7-methoxy analogues **94** and **95**, respectively, which contain a $-CF_2$ group in the aliphatic ring, display acceptable RIs while compound **93** combining the two benzenoid ring substituents with the CF_2 unit yields a RI of less than 0.1. Ultimately, the placement of benzenoid substituents in conjunction with the other favorable aliphatic ring features is critical for developing a molecule with an acceptable RI. All compounds were finally tested for cytotoxicity against J774 mammalian cells in a 96-well plate format, which has been previously reported (see Experimental Section for details). Generally, the THAs do not display signs of cytotoxicity at concentrations lower than 20 μM, rendering cytotoxicity indices (CI = EC_{50}(J774)/EC_{50}(TM90-C2B)) of 100 or more. These results indicate that most of the THAs are selective and nontoxic agents.[14]

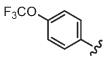
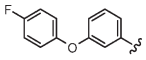
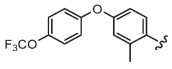
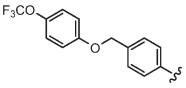
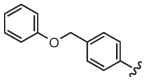
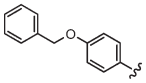
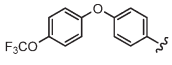
Structure−Property Studies. In parallel to the antimalarial activity testing, standard physicochemical properties were determined to identify potential compound liabilities prior to the time-consuming and costly development and optimization of analogues that will ultimately fail within in vivo efficacy experiments. Compound **2b** was prepared, using the procedure of Kesten et al., as a reference compound for comparison of solubility, permeability, and log $D_{7.4}$ (Table 1).[19] Analogue **2b** does not possess the imine moiety of prodrug **2a** and hence is structurally more similar to THAs **5**−**118**. Interestingly, compound **2b** displayed poor solubility and a log $D_{7.4}$ just out of the acceptable range. Compounds **5**−**118** were routinely assessed in parallel for aqueous solubility, partition coefficient (log $D_{7.4}$), and permeability (P_e) at various pH (Tables 1−8). Protein and plasma binding assays were regarded as redundant, since the in vitro antimalarial activity assay is conducted in 10% heat inactivated plasma. Furthermore, a selection of promising THAs has also been tested for murine microsomal stability to determine potential metabolic liabilities (Table 9).

The determination of aqueous solubility and log $D_{7.4}$ was conducted using HPLC-based protocols, which were previously utilized for the 3-substituted 4(1*H*)-quinolone series (see Experimental Section for details).[14,49] The distribution coefficients of all THAs are in the acceptable range ($1 < \log D_{7.4} < 4$), whereby a plot of in vitro activity against log $D_{7.4}$ implies that potency against both strains weakly correlates with lipophilicity (Figure 4). The most potent compound **118** also possess the greatest lipophilicity with a log $D_{7.4}$ of 3.6.

Overall, for the majority of the THAs, the solubilities are in the acceptable range of 40 μM or higher and no significant pH dependence on the aqueous solubility has been observed (Tables 1−8). Comparison of the solubility of compounds **5**−**118** suggests that THAs containing a five- or six-membered aliphatic ring exhibit greater solubility than the analogues with a

Table 8. SAR of Suzuki−Miyaura Cross-Coupled THAs[a]



Compound	Position	Ar	X	EC_{50} W2 (nM)	EC_{50} TM90-C2B (nM)	RI	EC_{50} J774 (μM)	Solubility pH 7.4 (μM)	Pe pH 7.4 (10^{-6} cm/s)	Log D pH 7.4
103	7		-S	6210	4990	0.80	>20	45	15	0.8
104	7		-S	7620	8490	1.11	>20	37	3	0.8
105	7		-S	193	78.4	0.41	>5	7	10	3.6
106	7		-S	34.6	23.2	0.67	>2	2	<1	2.4
107	7		-S	95.1	58.0	0.61	>1	1	<1	2.5
108	7		-S	40.9	143	3.50	>0.1	0.3	2	2.8
109	7		-S	27.7	326	11.8	>5	7	<1	3.6
110	7		-S	129	2840	22.0	>10	12	3	3.5
111	7		-S	44.5	706	15.9	>1	1	7	2.8
112	7		-S	35.9	370	10.3	>1	1	<1	2.8
113	7		-S	101	293	2.90	>10	10	<1	2.4
114	7		$-CH_2$	58.2	44.9	0.77	>2	2	36	3.6
115	6		$-CH_2$	34.9	8.70	0.24	>2	3	250	2.45
116	6		$-CH_2$	72.3	25.3	0.35	>0.1	0.3	339	3.0
117	6		$-CH_2$	99.2	161	1.62	>10	11	199	1.3
118	6		$-CH_2$	12.2	9.10	0.75	>0.1	0.1	18	3.8

[a] Dihydroartemisinin (DHA), chloroquine (CQ), and atovaquone (ATO) are internal controls for each in vitro assay: DHA (1.8 nM W2 and 0.9 nM TM90-C2B) and CQ (162 nM W2 and 131 nM TM90-C2B) and ATO (0.53 nM W2 and >170 nM TM90-C2B).

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seven- or eight-membered saturated ring. The solubility also depends on the nature and position of substituents on the benzenoid ring. For example, the 5-chloro-THAs **21**, **34**, **47** and the 8-chloro-THAs **24**, **37**, **50** possess significantly increased solubility in comparison to the 6- or 7-chloro-substituted analogues **22**, **23**, **35**, **36**, **48**, and **49**. A more pronounced difference in solubility is observed for the compound pair **58** and **59**, which is monosubstituted with one *tert*-butyl group at the 5- or 7-position. Though THAs **58** and **59** are similar in electronics, the divergence in solubility is purely derived by the position of the bulky alkyl group. A similar observation can be made by analyzing the THAs disubstituted on the benzenoid ring, **64**−**83**, and especially the dichloro compounds **74**−**78**, in which the 5,8-dichloro analogue **74** is much more soluble than compounds **75**−**78**. Strikingly, the extent of the solubility increase for the 5- or 8-substituted analogues stands in contrast to the distribution coefficient log $D_{7.4}$ determined to be in the range of 2.4−3.0 for all monochloro- or dichloro-THAs **21**−**24**, **34**−**37**, **47**−**50**, and **74**−**78** (see Supporting Information, Figure S1).

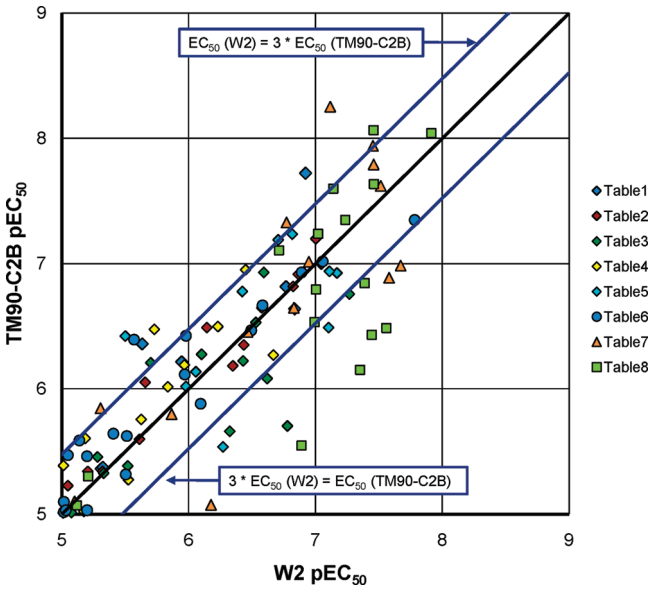

Figure 3. Plot of pEC_{50} (TM90-C2B) versus pEC_{50} (W2).

Table 9. In Vitro Metabolic Stability Using Murine Liver Microsomes

compd	$t_{1/2}$ (min)	compd	$t_{1/2}$ (min)
6	6.8	**95**	15.8
13	18.2	**101**	990
17	6.4	**102**	CNC[a]
18	20.1	**106**	8.4
27	77	**109**	15.1
40	24.8	**113**	11.2
81	3.6	**114**	C.N.C.[a]
93	8.5	**115**	C.N.C.[a]
94	40.8	**118**	173.3

[a] C.N.C. compounds that underwent such a minimal degradation that half-lives could not be calculated.

Analogous solubility trends for the dimethyl- or the dimethoxy-substituted THAs **64**−**73** were determined; however, these results are less pronounced in comparison to the dichloro compounds **74**−**78**. These data support the notion that the THA's solubility is strongly influenced by a tight crystal packing. A chloro group at the 5- or 8-position or both positions creates steric hindrance that presumably weakens the strength of the intermolecular hydrogen bonding between the carbonyl and the amino groups of the THA scaffold. ^{1}H NMR N−H chemical shift trends also seem to support such a weakening of hydrogen bonding with respect to DMSO in solution. The unsubstituted THA **13** (N−H δ 11.3 ppm) is similarly shifted as 5-chloro-THA **21** (N−H δ 10.4 ppm), 5-fluoro-THA **53** (N−H δ 11.2 ppm), and 5-methoxy-THA **14** (N−H δ 10.7 ppm). However, the 5-methyl-THA **17** (N−H δ 10.0 ppm) shows a large upfield shift while the 5-*tert*-butyl-THA **58** (N−H δ 8.7 ppm) is even further shifted, almost 3 ppm compared to the unsubstituted THA **13**. This trend suggests the THA N−H chemical shift is much more dependent on the local steric environment than electronics/σ-effect, especially when considering that either electron poor or electron rich analogues have chemical shifts similar to those of the unsubstituted THA **13**. This conclusion is further supported by the increased solubility and dramatic loss of antimalarial activity as seen in THAs **14**, **17**, **21**, **58**, **64**, **69**, and **74** possessing a sterically encumbered substituent at the 5- or 8-positions (see Supporting Information, Figure S1).

The crucial role of the benzenoid ring substituents at the 6- and 7-positions on antimalarial activity also motivated us to study

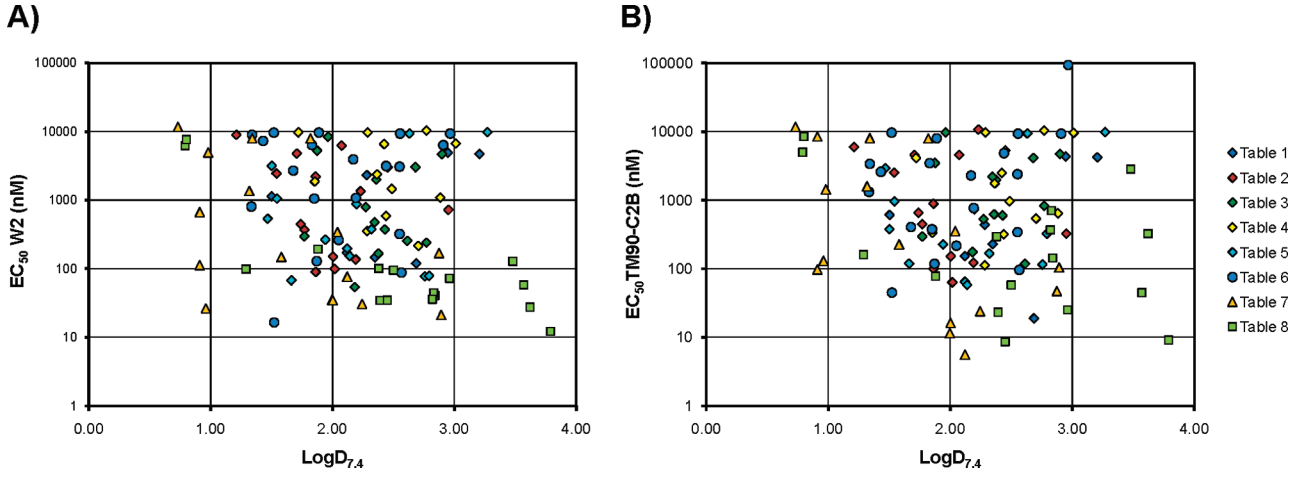

Figure 4. Plots of activities of W2 and TM90-C2B versus log D (pH 7.4).

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their effect on solubility. In comparison to the unsubstituted compound **13**, the presence of a 6- methoxy group as in analogue **6** increases the solubility by a factor of 3, while 7-chloro-THA **23** is 6-fold less soluble. The combination of both substituents in the same compound (**90**) not only improves the antimalarial activity but also restores the compound's solubility to that similar to **13**. Replacement of the 7-chloro group in **90** by a 7-methyl group yields analogue **96** and restores the aqueous solubility to a range similar to that of analogue **13**. The 7-chloro substituent improves the hydrogen bond donor capacity of the THA's amine, while the 6-methoxy group enhances the carbonyl's ability as a hydrogen bond acceptor, which possibly strengthens the intramolecular hydrogen bonding in the crystal packing.

Compounds substituted at the benzenoid ring with an aromatic residue at the 6- or 7-position belong to another major compound series that in general displayed poor solubility with a few exceptions. Nevertheless, the solubility of biaryl ether **108** is improved by the out-of-plane *o*-methylaryl group in **109**, depending on the pH in which the aqueous solubility has been determined, by a factor 6 or higher. Furthermore, the pyridyl analogues **103** and **104** were extremely soluble at low pH (>80 μM each) and at pH 7.4 (>40 μM each); unfortunately, they were devoid of activity.

Finally, the aliphatic ring has been considered to be a suitable site for improving the aqueous solubility by perturbing the crystal packing and/or increasing the compound polarity. In comparison to the THAs **13**−**24**, the 2,2-dimethyl-THAs **25**−**37** and the 3,3-dimethyl-substituted analogues **38**−**50** have been designed with the idea of introducing subtle steric entities while minimally increasing the distribution coefficients. Overall, the 2,2-dimethyl-THAs **25**−**37** are similar or less soluble than the THAs **13**−**24**, while the 3,3-dimethyl-substituted compounds are less soluble. The strategy to improve the solubility by steric differences at the aliphatic ring was abandoned given that the 2,2-dimethyl- and 3,3-dimethyl-THAs **25**−**50** did not improve the aqueous solubility. However, replacement of a methylene unit in the aliphatic ring by a nitrogen or a sulfur yielded analogues varying in solubility and potency. The tertiary amine in THA **99** significantly enhances the solubility across all pHs, while the antimalarial activity is completely abolished. In contrast, the solubility of thioether compounds varies depending on the benzenoid ring substituents. 7-Aryl-substituted thioether **113** is approximately 5-fold more soluble than its methylene congener **114**, while 6-methoxy-substituted thioethers **92** and **97** are less soluble than the aliphatic THAs **90** and **96**. Nevertheless, oxidation of the sulfur atom of **92**, leading to sulfoxide **101** and sulfone **102**, restores the aqueous solubility of 20 μM or higher. Replacement of the same methylene by a CF_2 unit was synthesized mainly as a probe for examining microsomal stability; however, upon comparison of the solubility of these three analogues **93**, **94**, and **95**, an interesting trend emerged. The 7-chloro is the least soluble while the 6-methoxy is the most soluble at all three pHs. The 6-chloro-7-methoxy compound's solubility is comparable to the 6-methoxy compound but with an approximate 63-fold increase in potency against TM90-C2B.

The permeabilities of the majority of the compounds have been determined and are not considered to be a major liability for the THA compound series. A plot of the permeability against solubility at pH 4.0 and pH 7.4 demonstrates an insignificant pH dependence (see Supporting Information, Figure S2). Furthermore, it also shows that most of the tested THAs possess acceptable solubilities (20−100 μM) and acceptable permeabilities (10×10^{-6} to 100×10^{-6} cm/s).

Microsomal stability was determined for a select set of compounds to systematically determine the structural features of the THA core that are most susceptible to microsomal degradation (Table 9). Compounds that underwent such a minimal degradation that half-lives could not be calculated are listed as CNC.

The unsubstituted THA **13** had a half-life of 18 min, while substitution at the 5-position with a methyl as in **17** or disubstitution at the 6- and 8- position as in **81** with a fluorine decreased the half-lives to less than 7 min. Comparison of geminally disubstituted methoxy analogues **27** and **40** revealed that the 2,2-dimethyl analogue had a half-life of 77 min, which corresponds to a 3-fold increase of stability over the 3,3-dimethyl congener. Sulfoxide containing THA **101** had a half-life of 990 min, while the sulfone **102** was minimally degraded. Next, the aryl substituted analogues were tested, showing that THAs **106**, **109**, and **113** with sulfur containing aliphatic rings displayed the poorest half-lives of 8.3, 15.1, and 11.2 min, respectively. The THA **118** substituted at the 6-position with a biaryl ether demonstrated an improved half-life of 173 min, while the 6- and 7-trifluoromethylphenyl substituted analogues **115** and **114** showed minimal degradation. Finally, three compounds were prepared in which the methylene at the 2-position was replaced by a CF_2 unit with intentions of gaining a contrasting result to the sulfur containing aliphatic ring. The most stable analogue was **94**, which is monosubstituted with a chloro at the 7-position. The half-life of the 6-methoxy analogue **95** was decreased by a factor of 3, whereas the half-life of the 7-chloro-6-methoxy-THA was less. The fluoromethylene compound **93**, which was shown to increase potency while slightly decreasing solubility, maintained a similar microsomal stability as the reference THA **13**. The aryl-substituted analogues **106**, **109**, **113**−**115**, and **118** vary in half-lives from 8 min to minimally detectable degradation. The trifluoromethylphenyl was shown to be the superior substituent in terms of stability compared to the other aryl analogues, and substitution at the 6-position appeared to be slightly more stable compared to the 7-substituted analogue.

CONCLUSIONS

Upon examination of the shortcomings of compounds **1**, **2a**, and **2b**, a set of compounds was prepared to probe the ring size of the aliphatic ring of the THA core and to examine whether heteroatoms in the aliphatic ring are tolerated. In addition, a library of THA analogues was prepared to systematically identify the key positions and substitutions of the benzenoid ring by loosely following the Topliss operational schemes. Generally, the best antimalarial activities with acceptable RI values were obtained if (a) the 5-position was unsubstituted, (b) the 6-position was substituted with an electron donating or electron withdrawing group, (c) the 7-position was substituted with an electron donating group, (d) the 8-position was fluorinated or unsubstituted, and (e) the THA core contained a six-membered aliphatic ring. Furthermore, it was shown that replacement of the C-2 methylene unit by one CF_2 group or one sulfur was tolerated, while introduction of other heteroatoms in the aliphatic ring significantly reduced the THA's antimalarial activity. The best substituents were combined in follow-up optimization studies leading to the identification of several THAs with improved antimalarial activity against multidrug resistant strains W2 and the TM90-C2B. THAs **89** and **90**, which are disubstituted in 6- and 7-positions with one electron withdrawing and one electron

donating group, and 6,8-difluoro-substitued THA **81** are among the most potent compounds with EC_{50} of 45 nM or lower. Furthermore, THAs such as **106**, **114**, **115**, and **118**, substituted with an aryl ring either in the 6- or 7-position, demonstrated comparable or improved antimalarial activity. Of all THAs tested, biaryl ether **118** with EC_{50} of 12.2 nM for W2 and 9.1 nM for TM90-C2B was the most potent compound, also possessing an acceptable resistance index (RI) of 0.75. Overall, this SAR study demonstrated that most of the THA compounds possess RI values in the acceptable range and thus lack, in contrast to atovaquone or chloroquine, any cross-resistance. Furthermore, the entire THA series did not show any cytotoxicity to J774 mammalian cells at 20 μM, yielding cytotoxicity indices (CIs) of 100 or more for the most potent antimalarial THAs **89**, **90**, **106**, **114**, **115**, and **118**.

All THAs have also been examined for aqueous solubility, log $D_{7.4}$, and permeability. In general, the permeability, the log $D_{7.4}$, and the aqueous solubility of most of the THAs have been determined to be in the acceptable ranges. Nevertheless, the more potent THAs tend to possess increased log $D_{7.4}$ values and decreased aqueous solubility, which is consistent with the previous report on antimalarial 4(1*H*)-quinolones.[14] Importantly, in comparison to reference compound **2b**, THAs such as **89**, **90**, **114**, and **115** are similar in antimalarial activity; however, they possess a better solubility or an improved permeability or both.

Furthermore, a selection of THAs has been tested for murine microsomal stability and most of the tested THAs suffer from short half-lives of 3−20 min. The aliphatic ring and several groups of the benzenoid ring have been identified to be the major sites for metabolism. Nevertheless, THAs **114**, **115**, and **118**, which are substituted with an aryl group in the 6- or 7-position, possess excellent half-lives of 3 h or longer.

The improved physicochemical properties in conjunction with the potent antimalarial activity and lack of cross-resistance make the aryl-substituted THAs attractive for further optimization and development. Even though no THA with optimal antimalarial activity and optimal physicochemical properties has been identified, the herein presented study strongly suggests that THAs **114**, **115**, and possibly **89**, **90**, and **118** are well suited for further development. Studies are currently ongoing to assess whether these frontrunner compounds demonstrate in vivo efficacy in rodent malaria models as well as exoerythrocytic stage activity. The discovery that the 6- or 7-position of the THA scaffold tolerates aryl substituents provides opportunities for next generation designs. The herein presented ease of the palladium catalyzed cross-coupling conditions to prepare 6- or 7-aryl-substituted THAs in combination with the large number of commercially available boronic acids is attractive for future lead optimization.

EXPERIMENTAL SECTION

All anhydrous solvents were obtained from Aldrich Chemical Co. and used without further purification unless otherwise noted. 2,5-Dichloroanisole, 4,4-dimethylcyclohexanone, and 3,3-dimethylcyclohexanone were bought from Alfa Aesar. 4-Fluoro-3-methoxyaniline was bought from Oakwood Products, Inc., while 4-bromo-3-methoxyaniline was bought from TCI America. Anthranillic acids were purchased from Oakwood Products, Inc. or Aldrich. $POCl_3$, 2-methoxy-1-methyl-4-nitrobenzene, 3,3′-thiodipropanoic acid, cycloalkanones, and all other anilines were purchased from Aldrich. 1-Bromo-4-(chloromethyl)benzene, 1-iodo-4-(trifluoromethoxy)benzene, and all phenols were purchased from Matrix Scientific. All palladium catalysts and ligands were purchased from Strem. All boronic acids were purchased from Frontier Scientific. The identity of all title compounds were verified via ^{1}H NMR, ^{13}C NMR, and HPLC/HRMS. The chemical purity of the titled compounds was determined using the following conditions: an Agilent 1100 series LC/MSD with an Eclipse XDB-C18 (4.6 mm × 100 mm, 5 μm) reversed phase column; method, 10% (v/v) of acetonitrile (+0.05% TFA) in 90% (v/v) of H_2O (+0.05% TFA), ramped to 100% acetonitrile (+0.05% TFA) over 9 min, and holding at 100% acetonitrile for 4 min with a flow rate of 0.7 mL/min; UV detector, 254 nm. The purity of each compound was ≥95% in this analysis. NMR spectra were recorded at ambient temperature on a 400 or 500 MHz Varian NMR spectrometer in the solvent indicated. All ^{1}H NMR experiments are reported in δ units, parts per million (ppm) downfield of TMS, and were measured relative to the signals for chloroform (7.26 ppm) and dimethylsulfoxide (2.50 ppm). All ^{13}C NMR spectra were reported in ppm relative to the signals for chloroform (77 ppm) and dimethylsulfoxide (39.5 ppm) with ^{1}H decoupled observation. Data for ^{1}H NMR are reported as follows: chemical shift (δ ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), integration, and coupling constant (Hz). ^{13}C NMR analyses were obtained at 101 MHz and reported in terms of chemical shift. NMR data were analyzed by using MestReNova software, version 5.3.2-4936. High resolution mass spectrometry (HRMS) was performed on an Agilent LC/MSD TOF system G3250AA. Isomers were separated by reverse phase HPLC system (Waters Prep LC 4000 system with Waters 996 photodiode array detector, Agilent column Eclipse XDB-C18, 5 μm, 9.4 mm × 250 mm). Compounds were eluted using a gradient elution of 70/30 to 50/50 A/B over 30 min at a flow rate of 5.0 mL/min, where solvent A was water and solvent B was acetonitrile. Analytical thin layer chromatography (TLC) was performed on silica gel 60 F254 precoated plates (0.25 mm) from EMD Chemical Inc., and components were visualized by ultraviolet light (254 nm). Silicycle silica gel 230−400 (particle size 40−63 μm) mesh was used for all flash column chromatography experiments.

General Procedure A: $POCl_3$ Cyclization of Anthranillic Acids. Anthranillic acid (0.25 g, 1.7 mmol) is added to a dried flask, followed by cycloalkanone (0.23 g, 1.87 mmol). This flask is cooled to 0 °C, and $POCl_3$ (1.4 mL) is added. The mixture is allowed to reflux for 1−8 h. Upon completion the mixture is poured onto ice and water. The solution is brought to pH 10 using saturated K_2CO_3 . Next ethyl acetate or chloroform is added and the organic layer is removed and washed with brine (50 mL) followed by water (50 mL). Next the organic layer is dried over Na_2SO_4 and concentrated in vacuo. The crude oil is purified further via flash chromatography (hexane/EtOAc). A few representative examples of these compounds were characterized by NMR; however, most were considered as intermediates and were taken on to acetic acid hydrolysis upon identification using LC−MS.

General Procedure B: Hydrolysis of 9-Chloro-1,2,3,4-tetrahydroacridine. 9-Chloro-1,2,3,4-tetrahydroacridine (0.15 g, 0.69 mmol) was dissolved in AcOH (1.5 mL) and heated in a sealed tube at 200 °C for 24−48 h. Upon completion via LC−MS analysis, the crude material is poured onto ice and water. The mixture is filtered, and the solid is recrystallized from either pyridine or DMF.

General Procedure C: Conrad−Limpach Cyclization Using Ethyl 2-Oxocyclohexanecarboxylate. An oven-dried 100 mL round-bottom flask attached to a Dean−Stark trap equipped with a reflux condenser was charged with an aniline (0.025 mol), corresponding cyclohexanone carboxylate (0.025−0.05 mol), benzene (25 mL), and glacial acidic acid (1 mL). The mixture was heated at 100 °C until no more water was separated (3−24 h). The benzene was distilled under reduced pressure, and the resulting crude intermediate was then used in the next step without further purification. Biphenyl ether (30 mL) was stirred and heated at reflux, while the crude intermediate was added rapidly through the dropping funnel. Stirring and refluxing continued for

10−15 min until no more ethanol separated within the Dean−Stark trap. The mixture was then allowed to cool to room temperature while precipitation arose. The solid was filtered off and washed with hexane and acetone. Ice cold methanol washing may be necessary in some cases. In most cases no further purification was needed, however in some cases recrystallization from DMF was employed. Furthermore, compounds **68**, **78**, and **89** which produced regioisomers were isolated using preparative HPLC as previously described.

General Procedure D: Suzuki Coupling of Halotetrahydroacridone. An oven-dried Schlenk tube was flame-dried and backfilled with argon (3×). The tube was then charged with 6-bromo-1,2,3,4-tetrahydroacridin-9(10*H*)-one (0.1 g, 0.36 mmol), $Pd_2(dba)_3$ (0.01 g, 7 mol %), SPHOS (0.013 g, 14 mol %), and boronic acid (0.102 g, 0.54 mmol). A rubber septum was then placed on the tube, and 1 M Na_2CO_3 (1 mL) and DMF (5 mL) were added. The tube was then purged of air by argon for about 1 min while the mixture was stirred and then heated at 80 °C until reaction completion by HPLC analysis (3−24 h). After completion, the mixture was boiled with 1:1 MeOH/$CHCl_3$ and filtered over Celite. The Celite was then rinsed with boiling hot DMF. The filtrate was then evaporated on silica gel purified via flash chromatography.

6-Methoxy-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-9(4*H*)-one (5). Following general procedures A and B, the title compound was prepared to provide 54% yield as a brown powder. ^{1}H NMR (400 MHz, DMSO) δ 7.92 (s, 1H), 6.83 (d, J = 32.8 Hz, 2H), 3.76 (s, 3H), 2.87 (br s, 2H), 2.44 (br s, 2H), 1.95 (br s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 161.58, 153.93, 142.55, 126.95, 119.35, 112.52, 99.65, 55.40, 32.13, 28.09, 21.72. HRMS (ESI) calcd for $C_{13}H_{14}NO_2$ $[M + H]^+$, 216.1019; found, 216.1018.

6-Methoxy-1,2,3,4-tetrahydroacridin-9(10*H*)-one (6). Following general procedures A and B, the title compound was prepared to provide 43% yield as an off-white powder, mp = 283−287 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 7.97 (d, J = 8.7 Hz, 1H), 6.85 (d, J = 10.0 Hz, 2H), 3.83 (s, 3H), 2.66 (d, J = 5.8 Hz, 2H), 2.41 (t, J = 5.4 Hz, 2H), 1.76−1.65 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.74, 162.10, 147.41, 141.57, 127.25, 118.14, 115.67, 113.14, 98.86, 55.97, 27.79, 22.55, 22.24, 22.13. HRMS (ESI) calcd for $C_{14}H_{16}NO_2$[M + H]$^+$, 230.1176; found, 230.1171.

3-Methoxy-7,8,9,10-tetrahydro-5*H*-cyclohepta[*b*]quinolin-11(6*H*)-one (7). Following general procedures A and B, the title compound was prepared to provide 38% yield as a brown crystal, mp = 284−285 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.98 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.03−6.86 (m, 2H), 3.84 (s, 3H), 2.88 (br s, 2H), 2.79 (br s, 2H), 1.79 (br s, 2H), 1.66 (br s, 2H), 1.46 (br s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 172.38, 161.53, 154.31, 140.25, 126.79, 120.02, 117.02, 113.92, 98.63, 55.45, 33.51, 31.70, 27.00, 25.66, 23.06. HRMS (ESI) calcd for $C_{15}H_{18}NO_2$ $[M + H]^+$, 244.1332; found, 244.1330.

3-Methoxy-6,7,8,9,10,11-hexahydrocycloocta[*b*]quinolin-12(5*H*)-one (8). Following general procedures A and B, the title compound was prepared to provide 32% yield as a brown powder, mp = 266−268 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.66 (s, 1H), 8.12 (d, J = 8.3 Hz, 1H), 7.12 (s, 1H), 6.99 (d, J = 8.0 Hz, 1H), 3.85 (s, 3H), 2.91 (br s, 2H), 2.74 (br s, 2H), 1.75 (br s, 2H), 1.55 (br s, 2H), 1.35 (br s, 4H). ^{13}C NMR (101 MHz, DMSO) δ 171.34, 161.68, 152.63, 140.83, 126.34, 117.78, 116.29, 114.60, 98.50, 55.48, 30.12, 29.72, 29.15, 25.85, 25.45, 22.57. HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$, 258.1489; found, 258.1490.

6-Trifluoromethyl-2,3-dihydro-1*H*-cyclopenta[*b*]quinolin-9(4*H*)-one (9). Following general procedures A and B, the title compound was prepared to provide 65% yield as a gray powder, mp = 283−284 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.57 (s, 1H), 8.29 (d, J = 8.0 Hz, 1H), 7.87 (s, 1H), 7.57 (d, J = 7.8 Hz, 1H), 3.03 (s, 2H), 2.73 (s, 2H), 2.07 (d, J = 6.2 Hz, 2H). ^{19}F NMR (376 MHz, DMSO) δ −61.82. ^{13}C NMR (101 MHz, DMSO) δ 172.41, 155.98, 139.50, 130.55 (q, J = 31.3 Hz), 126.54, 123.74 (q, J = 273.1 Hz),120.94, 118.28, 115.44, 31.83, 27.49, 21.26. HRMS (ESI) calcd for $C_{13}H_{11}F_3NO$ $[M + H]^+$, 254.0787; found, 254.0785.

6-Trifluoromethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (10). Following general procedures A and B, the title compound was prepared to provide 62% yield as a brown crystal, mp = 324−328 °C. ^{1}H NMR (400 MHz, DMSO) δ 12.09 (s, 1H), 8.26 (d, J = 8.4 Hz, 1H), 7.88 (s, 1H), 7.52 (d, J = 8.4 Hz, 1H), 2.75 (t, J = 5.7 Hz, 2H), 2.46 (t, J = 5.8 Hz, 2H), 1.80−1.66 (m, 4H). ^{19}F NMR (376 MHz, DMSO) δ −62.16. ^{13}C NMR (101 MHz, DMSO) δ 175.00, 164.60, 161.89, 149.63, 141.41, 139.16, 133.55, 131.50 (q, J = 32.3 Hz), 130.08, 127.25, 125.26, 124.47 (q, J = 273.7 Hz,), 118.57, 117.76, 115.76, 27.92, 22.32, 22.20, 21.85. HRMS (ESI) calcd for $C_{14}H_{13}F_3NO$ $[M + H]^+$, 268.0944; found, 268.0943.

3-Trifluoromethyl-7,8,9,10-tetrahydro-5*H*-cyclohepta[*b*]quinolin-11(6*H*)-one (11). Following general procedures A and B, the title compound was prepared to provide 57% yield as a brown crystal, mp = 332−333 °C. ^{1}H NMR (500 MHz, DMSO) δ 8.27 (d, J = 8.8 Hz, 1H), 8.23 (s, 1H), 7.88 (d, J = 7.6 Hz, 1H), 3.19 (dd, J = 15.4, 8.5 Hz, 4H), 1.83 (dd, J = 11.1, 5.7 Hz, 2H), 1.69 (dd, J = 11.2, 5.4 Hz, 4H). ^{13}C NMR (126 MHz, DMSO) δ 167.07, 145.26, 138.64, 136.72, 130.0 (q, J = 25 Hz), 127.01, 126.65 (q, J = 12.5 Hz), 126.49, 124.3 (q, J = 275 Hz), 122.88 (q, J = 3.75 Hz), 39.79, 31.38, 30.22, 27.27, 26.69. HRMS (ESI) calcd for $C_{15}H_{15}F_3NO$ $[M + H]^+$, 282.1100; found, 282.1099.

3-Trifluoromethyl-6,7,8,9,10,11-hexahydrocycloocta[*b*]quinolin-12(5*H*)-one (12). Following general procedures A and B, the title compound was prepared to provide 31% yield as a brown powder, mp = 241−242 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.94 (s, 1H), 8.25 (d, J = 6.3 Hz, 1H), 7.88 (s, 1H), 7.52 (d, J = 6.4 Hz, 1H), 2.84 (s, 2H), 2.70 (s, 2H), 1.55 (s, 2H), 1.37 (s, 4H). ^{19}F NMR (376 MHz, DMSO) δ −61.51. ^{13}C NMR (101 MHz, DMSO) δ 174.50, 151.87, 139.20, 131.09 (q, J = 27.3 Hz), 127.43, 125.53, 124.28 (q, J = 273.7 Hz), 120.52, 118.32, 115.75, 30.70, 29.96, 29.57, 26.43, 25.97, 23.21.

1,2,3,4-Tetrahydroacridin-9(10*H*)-one (13). Following general procedures A and B, the title compound was prepared to provide 72% yield as an off-white powder, mp = 341−343 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.30 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.55 (dd, J = 11.1, 4.0 Hz, 1H), 7.45 (d, J = 8.3 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 2.69 (t, J = 6.0 Hz, 2H), 2.43 (t, J = 6.0 Hz, 2H), 1.77−1.67 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 176.60, 147.41, 139.92, 131.57, 125.49, 123.88, 122.60, 118.00, 116.18, 27.79, 22.56, 22.34, 22.18. HRMS (ESI) calcd for $C_{13}H_{14}NO$ $[M + H]^+$, 200.1070; found, 200.1073.

5-Methoxy-1,2,3,4-tetrahydroacridin-9(10*H*)-one (14). Following general procedures A and B, the title compound was prepared to provide 27% yield as a light yellow powder, mp = 273−276 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.69 (s, 1H), 7.64−7.58 (m, 1H), 7.15 (d, J = 5.0 Hz, 2H), 3.97 (s, 3H), 2.76 (t, J = 5.8 Hz, 2H), 2.42 (t, J = 6.0 Hz, 2H), 1.74−1.65 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.66, 147.91, 146.72, 130.09, 124.02, 121.64, 116.19, 116.01, 110.28, 56.00, 27.12, 21.80, 21.78, 21.51. HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$, 230.1176; found, 230.1171.

7-Methoxy-1,2,3,4-tetrahydroacridin-9(10*H*)-one (15). Following general procedure A, the title compound was prepared to provide 46% yield as a brown crystal, mp = 299−301 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.29 (s, 1H), 7.45 (d, J = 2.8 Hz, 1H), 7.42 (d, J = 9.0 Hz, 1H), 7.21 (dd, J = 9.0, 2.8 Hz, 1H), 3.80 (s, 3H), 2.68 (t, J = 5.8 Hz, 2H), 2.44 (t, J = 5.9 Hz, 2H), 1.77−1.67 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.23, 154.64, 145.85, 133.95, 123.99, 121.41, 119.06, 114.48, 104.05, 55.19, 27.05, 21.95, 21.79, 21.54. HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$, 230.1176; found, 230.1179.

8-Methoxy-1,2,3,4-tetrahydroacridin-9(10*H*)-one (16). Following general procedures A and B, the title compound was prepared to provide 15% yield as a brown powder. ^{1}H NMR (400 MHz, DMSO) δ 11.1 (s, 1H), 7.37−7.30 (m, 1H), 7.16 (d, J = 8.0, 1H), 6.78 (d, J = 6.8, 1H), 2.82 (s, 3H), 2.60 (t, J = 5.1, 2H), 2.43 (t, J = 5.0, 2H), 1.70−1.60

(m, 4H). HRMS (ESI) calcd for $C_{14}H_{16}NO_2$ $[M + H]^+$, 230.1176; found, 230.1167.

5-Methyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (17). Following general procedure and B, the title compound was prepared to provide 29% yield as a brown powder, mp = 314−317 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.16 (s, 1H), 7.94 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 6.8 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 2.80 (t, J = 5.6 Hz, 2H), 2.5 (s, 3H), 2.46−2.42 (m, 2H), 1.72 (br m, J = 23.1, 5.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 176.00, 147.35, 137.91, 131.89, 125.43, 123.28, 122.78, 121.81, 115.66, 27.32, 21.78, 21.76, 21.57, 17.49. HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$, 214.1226; found, 214.1229.

6-Methyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (18). Following general procedures A and B, the title compound was prepared to provide 51% yield as a tan crystal, mp = 330−332 °C. ^{1}H NMR (250 MHz, DMSO) δ 11.17 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.21 (s, 1H), 7.03 (dd, J = 8.3, 1.1 Hz, 1H), 2.67 (t, J = 5.8 Hz, 2H), 2.45−2.35 (m, 5H), 1.78−1.62 (m, 4H). ^{13}C NMR (63 MHz, DMSO) δ 175.83, 146.44, 140.87, 139.45, 124.85, 123.74, 121.29, 116.57, 115.26, 27.11, 21.91, 21.65, 21.53, 21.33. HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$, 214.1226; found, 214.1226.

7-Methyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (19). Following general procedures A and B, the title compound was prepared to provide 55% yield as a beige crystal, mp = 352−356 °C. ^{1}H NMR (250 MHz, DMSO) δ 11.24 (s, 1H), 7.84 (s, 1H), 7.37 (s, 2H), 2.67 (t, J = 5.4 Hz, 2H), 2.42 (t, J = 5.7 Hz, 2H), 2.37 (s, 3H), 1.83−1.61 (m, 4H). ^{13}C NMR (63 MHz, DMSO) δ 175.75, 146.37, 137.37, 132.36, 130.97, 124.02, 123.15, 117.30, 115.20, 27.11, 21.95, 21.74, 21.54, 20.75. HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$, 214.1226; found, 214.1219.

8-Methyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (20). Following general procedures A and B, the title compound was prepared to provide 43% yield as an off-white powder, mp = 340−342 °C. ^{1}H NMR (250 MHz, DMSO) δ 11.06 (s, 1H), 7.39−7.32 (m, 1H), 7.26 (d, J = 8.0, 1H), 6.88 (d, J = 6.8, 1H), 2.79 (s, 3H), 2.62 (t, J = 5.1, 2H), 2.36 (t, J = 5.0, 2H), 1.75−1.65 (m, 4H). ^{13}C NMR (63 MHz, DMSO) δ 178.44, 145.16, 140.85, 138.90, 130.01, 124.31, 121.55, 116.67, 115.53, 26.70, 23.34, 21.99, 21.76, 21.48. HRMS (ESI) calcd for $C_{14}H_{16}NO$ $[M + H]^+$, 214.1226; found, 214.1222.

5-Chloro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (21). Following general procedures A and B, the title compound was prepared to provide 60% yield as a light yellow powder, mp = 265−266 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.46 (s, 1H), 8.05 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 7.6 Hz, 1H), 7.24 (t, J = 7.8 Hz, 1H), 2.82 (t, J = 5.9 Hz, 2H), 2.43 (t, J = 6.0 Hz, 2H), 1.75−1.67 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.44, 148.06, 135.79, 131.26, 124.69, 124.25, 122.38, 120.54, 116.59, 27.28, 21.71, 21.56, 21.39. HRMS (ESI) calcd for $C_{13}H_{13}ClNO$ $[M + H]^+$, 234.0680; found, 234.0681.

6-Chloro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (22). Following general procedures A and B, the title compound was prepared to provide 65% yield as an off-white crystal, mp = 362−365 °C. ^{1}H NMR (250 MHz, DMSO) δ 11.38 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.46 (s, 1H), 7.22 (dd, J = 8.6, 1.8 Hz, 1H), 2.68 (t, J = 5.6 Hz, 2H), 2.41 (t, J = 5.7 Hz, 2H), 1.79−1.66 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.38, 147.31, 139.92, 135.51, 127.22, 122.37, 121.77, 116.39, 116.30, 27.11, 21.70, 21.55, 21.36. HRMS (ESI) calcd for $C_{13}H_{13}ClNO$ $[M + H]^+$, 234.0680; found, 234.0683.

7-Chloro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (23). Following general procedures A and B, the title compound was prepared to provide 68% yield as an off-white powder, mp = 359−361 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.51 (s, 1H), 7.97 (d, J = 2.2 Hz, 1H), 7.59 (dd, J = 8.8, 2.2 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 2.70 (t, J = 5.8 Hz, 2H), 2.43 (t, J = 5.9 Hz, 2H), 1.76 (d, J = 5.1 Hz, 2H), 1.70 (d, J = 5.2 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 174.70, 147.32, 137.77, 131.04, 126.51, 124.07, 123.68, 119.83, 116.01, 27.10, 21.71, 21.63, 21.37. HRMS (ESI) calcd for $C_{13}H_{13}ClNO$ $[M + H]^+$, 234.0680; found, 234.0677.

8-Chloro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (24). Following general procedures A and B, the title compound was prepared to provide 43% yield as a tan powder, mp = 329−330 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.35 (s, 1H), 7.48−7.38 (m, 2H), 7.16 (d, J = 7.3, 1H), 2.65 (t, J = 5.9, 2H), 2.36 (t, J = 5.8, 2H), 1.78−1.66 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.16, 145.67, 141.72, 131.74, 130.65, 124.56, 119.07, 117.36, 116.94, 26.71, 21.77, 21.31. HRMS (ESI) calcd for $C_{13}H_{13}ClNO$ $[M + H]^+$, 234.0680; found, 234.0680.

2,2-Dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (25). Following general procedures A and B, the title compound was prepared to provide 59% yield as a white crystal. ^{1}H NMR (400 MHz, DMSO) δ 11.34 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.56 (t, J = 8.1 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.21 (t, J = 7.4 Hz, 1H), 2.71 (t, J = 6.5 Hz, 2H), 2.25 (s, 2H), 1.55 (t, J = 6.6 Hz, 2H), 0.97 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 176.17, 145.59, 139.23, 130.91, 124.80, 123.11, 121.87, 117.30, 114.54, 35.42, 33.89, 28.51, 27.93, 24.60. HRMS (ESI) calcd for $C_{15}H_{18}NO$ $[M + H]^+$, 228.1383; found, 228.1376.

5-Methoxy-2,2-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (26). Following general procedure A and B, the title compound was prepared to provide 56% yield as a yellow powder solid. ^{1}H NMR (400 MHz, DMSO) δ 10.75 (s, 1H), 7.67−7.58 (m, 1H), 7.15 (s, 2H), 3.97 (s, 3H), 2.78 (s, 2H), 2.24 (t, J = 6.1 Hz, 2H), 1.51 (t, J = 6.1 Hz, 2H), 0.95 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.91, 147.92, 145.58, 130.11, 123.94, 121.61, 116.20, 115.09, 110.29, 56.02, 35.56, 33.93, 28.35, 27.91, 24.63. HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$, 258.1487; found, 258.1478.

6-Methoxy-2,2-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (27). Following general procedures A and B, the title compound was prepared to provide 37% yield as a yellow powder solid, mp = 301−303.5 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.17 (s, 1H), 7.94 (d, J = 8.6 Hz, 1H), 6.82 (d, J = 9.9 Hz, 2H), 3.82 (s, 3H), 2.66 (t, J = 6.1 Hz, 2H), 2.22 (s, 2H), 1.52 (t, J = 6.2 Hz, 2H), 0.95 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.81, 161.34, 145.04, 140.91, 126.65, 117.66, 114.06, 112.00, 98.15, 55.23, 35.30, 33.89, 28.51, 27.92, 24.55. HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$, 258.1489; found, 258.1484.

7-Methoxy-2,2-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (28). Following general procedures A and B, the title compound was prepared to provide 61% yield as a yellow powder, mp = 206−208 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.34 (s, 1H), 7.46−7.40 (m, 2H), 7.22 (dt, J = 8.9, 3.2 Hz, 1H), 3.80 (s, 3H), 2.71 (s, 2H), 2.26 (s, 2H), 1.54 (t, J = 6.1 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.51, 154.64, 144.74, 133.98, 123.92, 121.50, 119.08, 113.58, 104.03, 55.22, 35.60, 33.95, 28.56, 27.97, 24.52. HRMS (ESI) calcd $C_{16}H_{20}NO_2$ $[M + H]^+$, 258.1489; found, 258.1492.

8-Methoxy-2,2-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (29). Following general procedures A and B, the title compound was prepared to provide 45% yield as a white powder. ^{1}H NMR (400 MHz, DMSO) δ 11.04 (s, 1H), 7.39 (t, J = 8.2 Hz, 1H), 6.96 (d, J = 8.3 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 3.76 (s, 3H), 2.62 (t, J = 6.4 Hz, 2H), 2.14 (s, 2H), 1.50 (t, J = 6.5 Hz, 2H), 0.94 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 176.72, 159.92, 143.99, 142.68, 131.75, 116.82, 114.31, 110.11, 103.72, 56.10, 36.33, 34.54, 29.28, 28.68, 24.86. HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$, 258.1489; found, 258.1500.

2,2,5-Trimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (30). Following general procedures A and B, the title compound was prepared to provide 34% yield as a yellow crystal. ^{1}H NMR (400 MHz, DMSO) δ 10.15 (s, 1H), 7.93 (d, J = 7.9 Hz, 1H), 7.41 (d, J = 6.8 Hz, 1H), 7.12 (t, J = 7.4 Hz, 1H), 2.81 (t, J = 6.0 Hz, 2H), 2.50 (s, 3H), 2.25 (s, 2H), 1.54 (t, J = 6.0 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 176.47, 145.99, 137.95, 131.86, 125.39, 123.31, 122.83, 121.68, 114.72, 35.51, 34.02, 28.37, 27.93, 24.79, 17.53. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1537.

2,2,6-Trimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (31). Following general procedures A and B, the title compound was prepared to provide 37% yield as a white crystal, mp = 329−330 °C. ^{1}H NMR (250 MHz, DMSO) δ 11.22 (s, 1H), 7.92 (d, J = 8.2 Hz, 1H), 7.21 (s, 1H), 7.03 (dd, J = 8.3, 1.3 Hz, 1H), 2.69 (t, J = 6.5 Hz, 2H), 2.39 (s, 3H), 2.23 (s, 2H), 1.53 (t, J = 6.6 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 176.07, 145.26, 140.84, 139.43, 124.82, 123.65, 121.20, 116.53, 114.28, 35.40, 33.91, 28.51, 27.94, 24.60, 21.30. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1533.

2,2,7-Trimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (32). Following general procedures A and B, the title compound was prepared to provide 39% yield as a yellow crystal, mp = 334−335 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.28 (s, 1H), 7.83 (s, 1H), 7.42−7.33 (m, 2H), 2.70 (t, J = 6.5 Hz, 2H), 2.37 (s, 3H), 2.25 (s, 2H), 1.54 (t, J = 6.5 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.93, 145.22, 137.34, 132.34, 130.92, 123.97, 123.02, 117.26, 114.23, 35.49, 33.91, 28.52, 27.95, 24.57, 20.71. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1547.

2,2,8-Trimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (33). Following general procedures A and B, the title compound was prepared to provide 44% yield as a yellow crystal, mp = 308−309 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 7.35 (t, J = 7.7 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 6.88 (d, J = 7.0 Hz, 1H), 2.79 (s, 3H), 2.65 (t, J = 6.3 Hz, 2H), 2.18 (s, 2H), 1.51 (t, J = 6.4 Hz, 2H), 0.95 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 178.64, 143.98, 140.84, 138.88, 130.00, 124.24, 121.48, 115.72, 115.50, 35.54, 33.87, 28.57, 27.99, 24.24, 23.31. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1531.

5-Chloro-2,2-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (34). Following general procedures A and B, the title compound was prepared to provide 51% yield as a light yellow crystal, mp = 244−246 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.52 (s, 1H), 8.05 (s, 1H), 7.75 (s, 1H), 7.24 (s, 1H), 2.84 (s, 2H), 2.25 (s, 2H), 1.53 (s, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.69, 146.96, 135.81, 131.29, 124.63, 124.28, 122.36, 120.54, 115.65, 35.42, 33.83, 28.25, 27.85, 24.82. HRMS (ESI) calcd for $C_{15}H_{17}ClNO$ $[M + H]^+$, 262.0993; found, 262.0998.

6-Chloro-2,2-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (35). Following general procedures A and B, the title compound was prepared to provide 45% yield as a off-white crystal, mp = 341−343 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.43 (s, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 1.6 Hz, 1H), 7.23 (dd, J = 8.6, 1.7 Hz, 1H), 2.70 (t, J = 6.4 Hz, 2H), 2.23 (s, 2H), 1.54 (t, J = 6.5 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 176.29, 146.87, 140.60, 136.19, 127.90, 122.99, 122.37, 117.07, 116.00, 35.96, 34.44, 29.15, 28.58, 25.33. HRMS (ESI) calcd for $C_{15}H_{17}ClNO$ $[M + H]^+$, 262.0993; found, 262.0996.

7-Chloro-2,2-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*-one (36). Following general procedures A and B, the title compound was prepared to provide 60% yield as an off-white powder, mp = 324−325 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.55 (s, 1H), 7.97 (s, 1H), 7.59 (dd, J = 8.7, 1.8 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 2.72 (t, J = 6.2 Hz, 2H), 2.25 (s, 2H), 1.54 (t, J = 6.3 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 174.98, 146.24, 137.78, 131.07, 126.48, 123.99, 123.70, 119.83, 115.07, 35.37, 33.77, 28.47, 27.90, 24.62. HRMS (ESI) calcd for $C_{15}H_{16}ClNONa$ $[M + Na]^+$, 284.0813; found, 284.0810.

8-Chloro-2,2-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (37). Following general procedures A and B, the title compound was prepared to provide 42% yield as a tan crystal. ^{1}H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 7.47−7.38 (m, 2H), 7.16 (d, J = 7.2 Hz, 1H), 2.67 (t, J = 6.2 Hz, 2H), 2.18 (s, 2H), 1.52 (t, J = 6.4 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.38, 144.55, 141.73, 131.75, 130.66, 124.51, 119.01, 116.93, 116.41, 35.49, 33.70, 28.54, 27.94, 24.28. HRMS (ESI) calcd for $C_{15}H_{17}ClNO$ $[M + H]^+$, 262.0993; found, 262.0987.

3,3-Dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (38). Following general procedures A and B, the title compound was prepared to provide 43% yield as a white crystal, mp = 301−302 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.27 (s, 1H), 8.05 (d, J = 7.3 Hz, 1H), 7.56 (t, J = 7.6 Hz, 1H), 7.45 (d, J = 8.2 Hz, 1H), 7.22 (t, J = 7.5 Hz, 1H), 2.48−2.43 (m, 4H), 1.50 (t, J = 6.6 Hz, 2H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.77, 145.97, 139.39, 130.89, 124.77, 123.23, 121.98, 117.33, 114.04, 40.57, 34.48, 28.99, 27.55, 19.48. HRMS (ESI) calcd for $C_{15}H_{18}NO$ $[M + H]^+$, 228.1383; found, 228.1386.

5-Methoxy-3,3-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (39). Following general procedures A and B, the title compound was prepared to provide 21% yield as a tan powder, mp = 317 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 10.65 (s, 1H), 7.63 (t, J = 4.5 Hz, 1H), 7.16 (d, J = 3.3 Hz, 2H), 3.97 (s, 3H), 2.57 (s, 2H), 2.45 (t, J = 6.1 Hz, 2H), 1.48 (t, J = 6.1 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.54, 147.94, 145.99, 130.28, 124.05, 121.74, 116.14, 114.59, 110.28, 56.00, 40.54, 34.40, 28.95, 27.63, 19.65. HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$, 258.1489; found, 258.1495.

6-Methoxy-3,3-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (40). Following general procedures A and B, the title compound was prepared to provide 39% yield as a tan crystal, mp = 309−311 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.10 (s, 1H), 7.94 (d, J = 9.3 Hz, 1H), 6.83 (s, 2H), 3.82 (s, 3H), 2.42 (d, J = 9.5 Hz, 4H), 1.48 (t, J = 6.0 Hz, 2H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.43, 161.32, 145.42, 141.07, 126.62, 117.76, 113.57, 112.13, 98.20, 55.25, 40.52, 34.53, 28.98, 27.56, 19.36. HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$, 258.1489; found, 258.1483.

7-Methoxy-3,3-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (41). Following general procedures A and B, the title compound was prepared to provide 21% yield as a yellow crystal, mp = 318−320 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.27 (s, 1H), 7.47−7.38 (m, 2H), 7.24−7.17 (m, 1H), 3.81 (s, 3H), 2.47 (s, 4H), 1.49 (t, J = 5.9 Hz, 2H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.11, 154.71, 145.12, 134.12, 124.05, 121.40, 119.09, 113.03, 104.04, 55.21, 40.54, 34.55, 29.00, 27.55, 19.60. HRMS (ESI) calcd for $C_{16}H_{19}NO_2$ $[M + H]^+$, 258.1489; found, 258.1485.

8-Methoxy-3,3-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (42). Following general procedures A and B, the title compound was prepared to provide 46% yield as a white powder, mp = 365 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 10.95 (s, 1H), 7.40 (t, J = 7.9 Hz, 1H), 6.96 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 7.6 Hz, 1H), 3.76 (s, 3H), 2.37 (d, J = 16.8 Hz, 4H), 1.46 (s, 2H), 0.97 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.81, 159.43, 143.63, 142.16, 131.17, 115.64, 113.95, 109.43, 103.15, 55.55, 40.44, 34.63, 28.96, 27.58, 19.62. HRMS (ESI) calcd for $C_{16}H_{20}NO_2$ $[M + H]^+$, 258.1489; found, 258.1493.

3,3,5-Trimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (43). Following general procedures A and B, the title compound was prepared to provide 32% yield as a white powder, mp = 280 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 10.15 (s, 1H), 7.93 (d, J = 8.0 Hz, 1H), 7.41 (d, J = 6.8 Hz, 1H), 7.12 (t, J = 7.2 Hz, 1H), 2.81 (t, J = 6.0 Hz, 2H), 2.25 (s, 3H), 1.54 (t, J = 6.0 Hz, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 176.74, 147.02, 138.78, 132.48, 126.10, 124.10, 123.45, 122.43, 114.85, 41.43, 35.06, 29.70, 28.33, 20.23, 18.11. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1530.

3,3,6-Trimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (44). Following general procedures A and B, the title compound was prepared to provide 41% yield as a tan crystal, mp = 339−341 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.13 (s, 1H), 7.93 (d, J = 8.2 Hz, 1H), 7.21 (s, 1H), 7.04 (d, J = 8.2 Hz, 1H), 2.47−2.41 (m, 4H), 2.39 (s, 3H), 1.49 (t, J = 6.5 Hz, 2H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.48, 145.99, 141.02, 139.58, 124.78, 123.97, 121.21, 116.65, 113.83, 40.62, 34.50, 29.03, 27.60, 21.34, 19.49. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1531.

3,3,7-Trimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (45). Following general procedures A and B, the title compound was prepared to provide 38% yield as a white crystal, mp = 342−344 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.20 (s, 1H), 7.84 (s, 1H), 7.38 (q, J = 8.3 Hz, 2H), 2.44−2.48 (m, 4H), 2.38 (s, 3H), 1.49 (t, J = 6.0 Hz, 2H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.57, 145.56, 137.49, 132.30, 131.01, 123.94, 123.16, 117.28, 113.69, 40.55, 34.52, 28.98, 27.56, 20.71, 19.51. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1530.

3,3,8-Trimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (46). Following general procedures A and B, the title compound was prepared to provide 75% yield as a white crystal, mp = 327−329 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.03 (s, 1H), 7.36 (t, J = 7.7 Hz, 1H), 7.26 (d, J = 8.2 Hz, 1H), 6.89 (d, J = 7.0 Hz, 1H), 2.80 (s, 3H), 2.39 (dd, J = 13.1, 6.4 Hz, 4H), 1.47 (t, J = 6.5 Hz, 2H), 0.97 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 178.31, 144.39, 141.02, 138.92, 129.99, 124.35, 121.58, 115.54, 115.21, 40.21, 34.64, 28.95, 27.56, 23.29, 19.60. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1529.

5-Chloro-3,3-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (47). Following general procedures A and B, the title compound was prepared to provide 26% yield as an off-white powder, mp = 255−256 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.52 (s, 1H), 8.05 (s, 1H), 7.75 (s, 1H), 7.24 (s, 1H), 2.84 (s, 2H), 2.25 (s, 2H), 1.53 (s, 2H), 0.96 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.32, 147.30, 135.97, 131.26, 124.73, 124.22, 122.47, 120.61, 115.17, 40.64, 34.15, 28.96, 27.60, 19.55. HRMS (ESI) calcd for $C_{15}H_{17}ClNO$ $[M + H]^+$, 262.0993; found, 262.0993.

6-Chloro-3,3-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (48). Following general procedures A and B, the title compound was prepared to provide 52% yield as a white powder, mp = 346−349 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.36 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.47 (d, J = 1.7 Hz, 1H), 7.24 (dd, J = 8.6, 1.7 Hz, 1H), 3.17 (s, 2H), 2.43 (d, J = 6.5 Hz, 2H), 1.49 (t, J = 6.5 Hz, 2H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.26, 146.54, 140.09, 135.52, 127.20, 122.44, 121.82, 116.44, 114.87, 48.58, 34.34, 28.99, 27.54, 19.40. HRMS (ESI) calcd for $C_{15}H_{17}ClNO$ $[M + H]^+$, 262.0993; found, 262.0998.

7-Chloro-3,3-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (49). Following general procedures A and B, the title compound was prepared to provide 53% yield as a white crystal, mp = 337−339 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.48 (s, 1H), 7.98 (d, J = 2.1 Hz, 1H), 7.60 (dd, J = 8.8, 2.1 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 2.48−2.44 (m, 4H), 1.49 (t, J = 6.4 Hz, 2H), 0.98 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 174.61, 146.61, 137.95, 131.07, 126.61, 124.13, 123.68, 119.88, 114.61, 40.54, 34.33, 28.99, 27.54, 19.48. HRMS (ESI) calcd for $C_{15}H_{17}ClNO$ $[M + H]^+$, 262.0993; found, 262.0989.

8-Chloro-3,3-dimethyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (50). Following general procedures A and B, the title compound was prepared to provide 45% yield as an off-white powder, mp = 339−341 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.30 (s, 1H), 7.48−7.38 (m, 2H), 7.17 (d, J = 7.0 Hz, 1H), 2.43 (s, 2H), 2.39 (t, J = 6.2 Hz, 2H), 1.48 (t, J = 6.4 Hz, 2H), 0.97 (s, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.05, 144.91, 141.90, 131.76, 130.64, 124.62, 119.10, 116.97, 115.95, 40.16, 34.43, 28.90, 27.52, 19.62. HRMS (ESI) calcd for $C_{15}H_{17}ClNO$ $[M + H]^+$, 262.0993; found, 262.0995.

6-Nitro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (51). Following general procedures A and B, the title compound was prepared to provide 54% yield as a yellow powder, mp = 330−331 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.74 (s, 1H), 8.29 (s, 1H), 8.22 (d, J = 8.7 Hz, 1H), 7.93 (d, J = 8.6 Hz, 1H), 2.71 (br s, 2H), 2.43 (br s, 2H), 1.74 (dd, J = 25.7, 5.0 Hz, 4H). HRMS (ESI) calcd for $C_{13}H_{13}N_2O_3$ $[M + H]^+$, 245.0921; found, 245.0925.

7-Nitro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (52). Following general procedures A and B, the title compound was prepared to provide 61% yield as a yellow powder, mp = 358−359 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.82 (s, 1H), 8.77 (s, 1H), 8.31 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 9.0 Hz, 1H), 2.69 (s, 2H), 2.42 (s, 2H), 1.73 (dd, J = 26.3, 4.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.49, 148.16, 142.76, 141.74, 125.15, 121.86, 121.70, 119.06, 117.53, 27.08, 21.46, 21.20. HRMS (ESI) calcd for $C_{13}H_{13}N_2O_3$ $[M + H]^+$, 245.0921; found, 245.0926.

5-Fluoro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (53). Following general procedure C, the title compound was prepared to provide 25% yield as an off-white powder, mp = 308−310 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.21 (s, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.44 (dd, J = 11.4, 7.9 Hz, 1H), 7.17−7.12 (m, 1H), 2.70 (t, J = 5.7 Hz, 2H), 2.39 (t, J = 5.7 Hz, 2H), 1.71−1.62 (m, 4H). ^{19}F NMR (376 MHz, DMSO) δ −131.26. ^{13}C NMR (101 MHz, DMSO) δ 175.09, 151.14 (d, J = 248.5 Hz), 147.40, 128.54 (d, J = 13.13 Hz), 125.24, 121.40 (d, J = 6.1 Hz), 120.53, 116.45, 115.45 (d, J = 17.2 Hz), 27.08, 21.68, 21.65, 21.34. HRMS (ESI) calcd for $C_{13}H_{13}FNO$ $[M + H]^+$, 218.0976; found, 218.0969.

6-Fluoro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (54). Following general procedures A and B, the title compound was prepared to provide 55% yield as a white powder, mp = 359 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.35 (s, 1H), 8.08 (dd, J = 8.8, 6.6 Hz, 1H), 7.15 (dd, J = 10.3, 2.2 Hz, 1H), 7.06 (td, J = 8.8, 2.2 Hz, 1H), 2.67 (t, J = 6.0 Hz, 2H), 2.40 (t, J = 6.0 Hz, 2H), 1.76−1.66 (m, 4H). ^{19}F NMR (376 MHz, DMSO) δ −109.41. ^{13}C NMR (101 MHz, DMSO) δ 175.38, 163.46 (d, J = 247.5 Hz), 147.24, 140.45 (d, J = 12.12 Hz), 128.12 (d, J = 10.1 Hz), 120.27, 115.78, 110.79 (d, J = 24.24 Hz), 102.22 (d, J = 25.25 Hz), 27.05, 21.75, 21.49, 21.38. HRMS (ESI) calcd for $C_{13}H_{13}FNO$ $[M + H]^+$, 218.0976; found, 218.0967.

7-Iodo-1,2,3,4-tetrahydroacridin-9(10*H*)-one (55). Following general procedures A and B, the title compound was prepared to provide 49% yield as a white powder. ^{1}H NMR (400 MHz, DMSO) δ 11.45 (s, 1H), 8.32 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.28 (d, J = 8.7 Hz, 1H), 2.68 (s, 2H), 2.41 (s, 2H), 1.72 (d, J = 18.6 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.39, 147.29, 138.89, 138.36, 133.30, 124.99, 119.94, 116.22, 86.02, 27.12, 21.70, 21.65, 21.35. HRMS (ESI) calcd for $C_{13}H_{12}INONa$ $[M + Na]^+$, 347.9856; found, 347.9851

6-Bromo-1,2,3,4-tetrahydroacridin-9(10*H*)-one (56). Following general procedures A and B, the title compound was prepared to provide 51% yield as a yellow powder. ^{1}H NMR (400 MHz, DMSO) δ 11.37 (s, 1H), 7.96 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.35 (d, J = 8.3 Hz, 1H), 2.68 (s, 2H), 2.41 (s, 2H), 1.72 (d, J = 20.6 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.36, 147.34, 140.08, 127.23, 125.09, 124.32, 121.95, 119.48, 116.32, 27.13, 21.69, 21.57, 21.35. HRMS (ESI) calcd for $C_{13}H_{13}BrNO$ $[M + H]^+$, 278.0175; found, 287.0179.

7-Bromo-1,2,3,4-tetrahydroacridin-9(10*H*)-one (57). Following general procedure C, the title compound was prepared to provide 48% yield as a yellow crystal, mp = 252−253 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.50 (s, 1H), 8.12 (s, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.43 (d, J = 8.7 Hz, 1H), 2.69 (t, J = 6.0 Hz, 2H), 2.42 (t, J = 6.1 Hz, 2H), 1.72 (dd, J = 24.8, 5.7 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.53, 147.39, 138.04, 133.64, 126.90, 124.47, 120.05, 116.13, 114.45, 27.12, 21.70, 21.65, 21.36. HRMS (ESI) calcd for $C_{13}H_{13}BrNO$ $[M + H]^+$, 278.0175; found, 287.0167.

5-*tert*-Butyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (58). Following general procedure C, the title compound was prepared to provide 49% yield as an off-white crystal, mp = 176−177 °C. ^{1}H NMR (400 MHz, DMSO) δ 8.74 (s, 1H), 8.05 (d, J = 7.9 Hz, 1H), 7.55 (d, J = 7.0 Hz, 1H), 7.17 (d, J = 7.4 Hz, 1H), 2.87 (d, J = 5.4 Hz, 2H), 2.44 (s, 2H), 1.78−1.66 (m, 4H), 1.50 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 177.11, 147.11, 137.58, 136.90, 128.98, 125.30, 124.44, 122.61, 115.94, 34.81, 31.16, 28.56, 22.40, 22.25, 22.20. HRMS (ESI) calcd for $C_{17}H_{22}NO$ $[M + H]^+$, 256.1696; found, 256.1703.

7-*tert*-Butyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (59). Following general procedure C, the title compound was prepared to

provide 84% yield as a white crystal, mp = 316−319 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.25 (s, 1H), 8.04−7.97 (m, 1H), 7.66 (ddd, J = 8.7, 2.3, 1.4 Hz, 1H), 7.40 (dd, J = 8.7, 0.8 Hz, 1H), 2.67 (t, J = 5.9 Hz, 2H), 2.43 (t, J = 6.0 Hz, 2H), 1.77−1.67 (m, 4H), 1.32 (s, 9H). ^{13}C NMR (101 MHz, DMSO) δ 175.97, 146.32, 144.25, 137.30, 129.03, 122.64, 119.78, 117.19, 115.17, 34.27, 31.14, 27.07, 21.93, 21.72, 21.53. HRMS (ESI) calcd for $C_{17}H_{22}NO$ $[M + H]^+$, 256.1696; found, 256.1700.

5-(Trifluoromethyl)-1,2,3,4-tetrahydroacridin-9(10*H*)-one (60). Following general procedure C, the title compound was prepared to provide 39% yield as a yellow powder, mp = 226−230 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.00 (s, 1H), 8.40 (d, J = 7.9 Hz, 1H), 7.99 (d, J = 7.3 Hz, 1H), 7.39 (t, J = 7.6 Hz, 1H), 2.84 (s, 2H), 2.44 (s, 2H), 1.72 (dd, J = 14.8, 6.6 Hz, 4H). ^{19}F NMR (376 MHz, DMSO) δ −59.13. ^{13}C NMR (101 MHz, DMSO) δ 175.18, 148.45, 135.21, 130.51, 129.57 (d, J = 5.05 Hz), 124.41, 123.79 (d, J = 276.7 Hz), 121.42, 117.16, 27.61, 21.59, 21.43. HRMS (ESI) calcd for $C_{14}H_{13}F_3NO$ $[M + H]^+$, 268.0944; found, 268.0940.

7-Isopropyl-1,2,3,4-tetrahydroacridin-9(10*H*)-one (61). Following general procedure C, the title compound was prepared to provide 11% yield as a tan powder, mp = 275−277 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.24 (s, 1H), 7.88 (s, 1H), 7.48 (d, J = 7.9 Hz, 1H), 7.39 (d, J = 8.0 Hz, 1H), 2.96 (d, J = 6.0 Hz, 1H), 2.68 (s, 2H), 2.43 (s, 2H), 1.72 (d, J = 19.1 Hz, 4H), 1.23 (d, J = 5.9 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 176.54, 147.00, 142.62, 138.31, 130.68, 123.74, 121.75, 118.06, 115.81, 33.69, 27.76, 24.59, 22.61, 22.40, 22.21. HRMS (ESI) calcd for $C_{16}H_{20}NO$ $[M + H]^+$, 242.1539; found, 242.1540.

7-Ethoxy-1,2,3,4-tetrahydroacridin-9(10*H*)-one (62). Following general procedure C, the title compound was prepared to provide 51% yield as a yellow powder, mp = 291−292 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.28 (s, 1H), 7.42 (dd, J = 11.0, 5.8 Hz, 2H), 7.19 (dd, J = 8.9, 2.8 Hz, 1H), 4.05 (q, J = 6.9 Hz, 2H), 2.68 (t, J = 5.7 Hz, 2H), 2.43 (d, J = 5.5 Hz, 2H), 1.75−1.63 (m, 4H), 1.35 (t, J = 6.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 175.93, 154.57, 146.51, 134.56, 124.69, 122.41, 119.72, 115.13, 105.38, 63.87, 27.74, 22.65, 22.49, 22.24, 15.29. HRMS (ESI) calcd for $C_{15}H_{18}NO_2$ $[M + H]^+$, 244.1332; found, 244.1323.

9-Oxo-5,6,7,8,9,10-hexahydroacridine-2-carboxylic Acid Ethyl Ester (63). Following general procedure C, the title compound was prepared to provide 32% yield as an off-white crystal, mp = 325−326 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.60 (s, 1H), 8.68 (d, J = 1.3 Hz, 1H), 8.06 (dd, J = 8.6, 1.5 Hz, 1H), 7.52 (d, J = 8.7 Hz, 1H), 4.33 (q, J = 7.0 Hz, 2H), 2.69 (d, J = 5.9 Hz, 2H), 2.42 (d, J = 5.4 Hz, 2H), 1.73 (dd, J = 25.3, 4.9 Hz, 4H), 1.34 (t, J = 7.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO) δ 176.57, 166.08, 148.25, 142.67, 131.42, 128.12, 123.83, 122.98, 118.58, 117.55, 61.31, 27.77, 22.31, 22.25, 22.02, 14.90. HRMS (ESI) calcd $C_{16}H_{18}NO_3$ $[M + H]^+$, 272.1281; found, 272.1275.

5,8-Dimethyl-1,3,4,10-tetrahydro-2*H*-acridin-9-one (64). Following general procedure C, the title compound was prepared to provide 74% yield as a yellow crystal, mp = 246−248 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.66 (s, 1H), 7.20 (d, J = 7.3 Hz, 1H), 6.80 (d, J = 7.3 Hz, 1H), 2.74 (br m, 5H), 2.41 (s, 3H), 2.37 (t, J = 5.9 Hz, 2H), 1.69 (br m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 178.77, 145.46, 139.30, 136.53, 130.96, 124.10, 122.78, 121.68, 116.94, 26.92, 23.49, 21.93, 21.81, 21.57, 17.56. HRMS (ESI) calcd $C_{15}H_{18}NO$ $[M + H]^+$, 228.1383; found, 228.1376.

5,7-Dimethyl-1,3,4,10-tetrahydro-2*H*-acridin-9-one (65). Following general procedure C, the title compound was prepared to provide 78% yield as an off-white crystal, mp = 323−326 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 7.06 (s, 1H), 6.74 (s, 1H), 2.79 (s, 3H), 2.64 (s, 2H), 2.38 (s, 2H), 2.34 (s, 3H), 1.72 (br d, J = 15.4 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 178.28, 144.84, 141.08, 139.66, 138.73, 126.06, 119.63, 116.40, 114.83, 26.72, 23.18, 22.04, 21.74, 21.52, 21.01. HRMS (ESI) calcd for $C_{15}H_{18}NO$ $[M + H]^+$, 228.1383; found, 228.1377.

6,8-Dimethyl-1,3,4,10-tetrahydro-2*H*-acridin-9-one (66). Following general procedure C, the title compound was prepared to provide 31% yield as a white powder, mp = 292−294 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.97 (s, 1H), 7.06 (s, 1H), 6.74 (s, 1H), 2.79 (s, 3H), 2.64 (s, 2H), 2.38 (s, 2H), 2.34 (s, 3H), 1.72 (br d, J = 15.4 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 178.28, 144.84, 141.08, 139.66, 138.73, 126.06, 119.63, 116.40, 114.83, 26.72, 23.18, 22.04, 21.74, 21.52, 21.01. HRMS (ESI) calcd for $C_{15}H_{18}NO$ $[M + H]^+$, 228.1383; found, 228.1381.

5,6-Dimethyl-1,3,4,10-tetrahydro-2*H*-acridin-9-one (67). Following general procedure C, the title compound was prepared to provide 27% yield as a white crystal, mp = 340−343 °C. ^{1}H NMR (400 MHz, DMSO) δ 9.93 (s, 1H), 7.83 (d, J = 8.2 Hz, 1H), 7.06 (d, J = 8.2 Hz, 1H), 3.32 (d, J = 0.9 Hz, 3H), 2.78 (t, J = 5.9 Hz, 2H), 2.42 (t, J = 5.5 Hz, 2H), 2.39 (s, 2H), 2.36 (s, 2H), 1.72 (dd, J = 23.8, 5.9 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 176.21, 146.99, 138.82, 138.00, 124.46, 122.77, 122.05, 121.91, 114.99, 27.33, 21.84, 21.66, 21.63, 20.39, 12.94. HRMS (ESI) calcd for $C_{15}H_{17}NONa$ $[M + Na]^+$, 250.1202; found, 250.1195.

6,7-Dimethyl-1,3,4,10-tetrahydro-2*H*-acridin-9-one (68). Following general procedure C, the title compound was prepared to provide 34% yield as a white powder. ^{1}H NMR (400 MHz, DMSO) δ 11.13 (s, 1H), 7.78 (s, 1H), 7.20 (s, 1H), 2.66 (s, 2H), 2.41 (s, 2H), 2.29 (d, J = 9.1 Hz, 6H), 1.75−1.67 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 146.69, 141.04, 138.51, 131.36, 125.19, 122.28, 117.82, 115.62, 27.77, 22.64, 22.38, 22.23, 20.57, 19.86. HRMS (ESI) calcd for $C_{15}H_{18}NO$ $[M + H]^+$, 228.1383; found, 228.1379.

5,8-Dimethoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (69). Following general procedure C, the title compound was prepared to provide 84% yield as a yellow-green powder, mp = 215−219 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.25 (s, 1H), 7.03 (d, J = 8.6 Hz, 1H), 6.55 (d, J = 8.6 Hz, 1H), 3.89 (s, 3H), 3.71 (s, 3H), 2.70 (s, 2H), 2.34 (s, 2H), 1.66 (br d, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.66, 152.65, 144.61, 141.47, 132.17, 117.75, 114.67, 110.58, 102.85, 56.16, 26.71, 21.90, 21.47. HRMS (ESI) calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$, 260.1281; found, 260.1272.

5,7-Dimethoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (70). Following general procedure C, the title compound was prepared to provide 23% yield as a tan powder, mp = 226−230 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.67 (s, 1H), 7.04 (s, 1H), 6.79 (s, 1H), 3.95 (s, 3H), 3.80 (s, 3H), 2.74 (t, J = 5.3 Hz, 2H), 2.43 (t, J = 5.3 Hz, 2H), 1.68 (d, J = 3.6 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.94, 154.78, 149.16, 145.77, 125.34, 124.31, 115.14, 101.88, 95.19, 56.16, 55.21, 27.04, 21.92, 21.89, 21.54. HRMS (ESI) calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$, 260.1281; found, 260.1283.

6,8-Dimethoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (71). Following general procedure C, the title compound was prepared to provide 11% yield as a white powder, mp = 267−270 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.89 (s, 1H), 6.44 (s, 1H), 6.24 (s, 1H), 3.82 (s, 3H), 3.77 (s, 3H), 2.59 (s, 2H), 2.33 (s, 2H), 1.71 (br d, J = 15.8 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.40, 161.27, 160.78, 143.77, 143.25, 116.56, 109.04, 93.46, 90.60, 55.46, 55.05, 26.49, 21.99, 21.58, 21.45. HRMS (ESI) calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$, 260.1281; found, 260.1273.

5,6-Dimethoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (72). Following general procedure C, the title compound was prepared to provide 35% yield as a light yellow powder, mp = 206−207 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.59 (s, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.10 (d, J = 9.0 Hz, 1H), 3.95 (s, 3H), 3.87 (s, 3H), 2.79 (s, 2H), 2.44 (s, 2H), 1.73 (br d, J = 14.5 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.70, 152.76, 147.14, 134.98, 134.04, 120.67, 118.58, 114.75, 108.68, 60.57, 56.08, 27.22, 21.84, 21.67, 21.53. HRMS (ESI) calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$, 260.1281; found, 260.1280.

6,7-Dimethoxy-1,2,3,4-tetrahydroacridin-9(10*H*)-one (73). Following general procedures A and B, the title compound was prepared to provide 40% yield as a yellow powder, mp = 252−254 °C. ^{1}H NMR

(400 MHz, DMSO) δ 11.15 (s, 1H), 7.40 (s, 1H), 6.88 (s, 1H), 3.82 (d, J = 14.2 Hz, 6H), 2.65 (t, J = 5.5 Hz, 2H), 2.41 (t, J = 5.8 Hz, 2H), 1.71 (dd, J = 21.9, 5.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.51, 153.13, 146.48, 145.85, 135.57, 117.71, 115.03, 104.89, 99.12, 56.20, 56.07, 27.68, 22.68, 22.41, 22.23. HRMS (ESI) calcd for $C_{15}H_{18}NO_3$ $[M + H]^+$, 260.1281; found, 260.1284.

5,8-Dichloro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (74). Following general procedure C, the title compound was prepared to provide 15% yield as a off-white powder, mp = 229−231 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.23 (s, 1H), 7.65 (d, J = 8.3 Hz, 1H), 7.18 (d, J = 8.3 Hz, 1H), 2.76 (d, J = 5.7 Hz, 2H), 2.36 (t, J = 5.3 Hz, 2H), 1.69 (dd, J = 11.3, 5.3 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.77, 146.66, 137.78, 131.09, 130.81, 124.67, 120.09, 119.61, 118.45, 26.92, 21.77, 21.48, 21.21. HRMS (ESI) calcd for $C_{13}H_{12}Cl_2NO$ $[M + H]^+$, 268.0291; found, 268.0281.

5,7-Dichloro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (75). Following general procedure C, the title compound was prepared to provide 39% yield as a yellow crystalline powder, mp = 302−305 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.68 (s, 1H), 7.96 (d, J = 24.3 Hz, 2H), 2.84 (s, 2H), 2.44 (s, 2H), 1.73 (d, J = 16.2 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.89, 149.30, 135.41, 131.50, 126.92, 125.65, 123.97, 122.87, 117.70, 27.97, 22.40, 22.10, 21.98. HRMS (ESI) calcd for $C_{19}H_{12}Cl_2NO$ $[M + H]^+$, 268.0291; found, 268.0286.

6,8-Dichloro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (76). Following general procedure C, the title compound was prepared to provide 47% yield as a white powder. ^{1}H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 7.41 (s, 1H), 7.23 (s, 1H), 2.63 (s, 2H), 2.34 (s, 2H), 1.70 (d, J = 17.9 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 203.73, 175.33, 146.66, 142.67, 135.02, 134.25, 124.69, 118.78, 116.66, 27.39, 22.32, 21.88. HRMS (ESI) calcd for $C_{13}H_{12}Cl_2NO$ $[M + H]^+$, 268.0290; found, 268.0278.

5,6-Dichloro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (77). Following general procedure C, the title compound was prepared to provide 36% yield as a white powder, mp = 320−322 °C. ^{1}H NMR (400 MHz, DMSO) δ 10.56 (s, 1H), 8.05 (d, J = 8.7 Hz, 1H), 7.47 (d, J = 8.7 Hz, 1H), 2.85 (s, 2H), 2.45 (s, 2H), 1.75 (br d, J = 17.2 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.02, 148.58, 136.99, 134.43, 125.14, 125.06, 123.15, 122.89, 117.09, 27.28, 21.58, 21.40, 21.29. HRMS (ESI) calcd for $C_{13}H_{12}Cl_2NO$ $[M + H]^+$, 268.0290; found, 268.0286.

6,7-Dichloro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (78). Following general procedure C, the title compound was prepared to provide 21% yield as a brown powder. ^{1}H NMR (400 MHz, DMSO) δ 9.93 (s, 1H), 7.83 (1H), 7.06 (1H), 2.78 (d, J = 5.8 Hz, 2H), 2.34 (d, J = 4.9 Hz, 2H), 1.78−1.66 (m, 4H). HRMS (ESI) calcd for $C_{13}H_{12}Cl_2NO$ $[M + H]^+$, 268.0290; found, 268.0296.

5,8-Difluoro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (79). Following general procedure C, the title compound was prepared to provide 19% yield as a yellow powder, mp = 304.4−306.3 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.20 (s, 1H), 7.56−7.39 (m, 1H), 6.94−6.79 (m, 1H), 2.71 (t, J = 5.8 Hz, 2H), 2.36 (t, J = 5.8 Hz, 2H), 1.73−1.64 (m, 4H). ^{19}F NMR (376 MHz, DMSO) δ −119.28, −134.70. ^{13}C NMR (101 MHz, DMSO) δ 174.02, 156.28 (d, J = 256.5 Hz), 147.04 (dd, J = 245.4, 5.05 Hz), 146.72, 118.22, 115.47 (dd, J = 19.19, 10.1 Hz), 106.64 (dd, J = 24.24, 7.07 Hz), 26.83, 21.56, 21.22. HRMS (ESI) calcd for $C_{13}H_{12}F_2NO$ $[M + H]^+$, 236.0882; found, 236.0880.

5,7-Difluoro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (80). Following general procedure C, the title compound was prepared to provide 97% yield as a white powder, mp = 328−331 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.38 (s, 1H), 7.66−7.58 (m, 1H), 7.53 (dd, J = 9.1, 0.9 Hz, 1H), 2.73 (t, J = 5.8 Hz, 2H), 2.42 (t, J = 5.8 Hz, 2H), 1.76−1.64 (m, 4H). ^{19}F NMR (376 MHz, DMSO) δ −117.71, −125.75. ^{13}C NMR (101 MHz, DMSO) δ 174.15, 156.13 (dd, J = 244.4, 11.11 Hz), 151.42 (dd, J = 252.5, 12.12 Hz), 147.70, 125.66 (d, J = 12.12 Hz), 124.94 (d, J = 6.06 Hz), 116.00, 106.07 (dd, J = 29.3, 20.0 Hz), 106.5 (d, J = 22.2 Hz), 27.06, 21.68, 21.57, 21.27. HRMS (ESI) calcd for $C_{13}H_{12}F_2NO$ $[M + H]^+$, 236.0882; found, 236.0874.

6,8-Difluoro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (81). Following general procedure C, the title compound was prepared to provide 30% yield as an off-white powder, mp = 315 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.45 (s, 1H), 6.99 (dd, J = 24.9, 10.2 Hz, 2H), 2.67 (s, 2H), 2.38 (s, 2H), 1.74 (d, J = 19.6 Hz, 2H), 0.00 (dd, J = 24.9, 10.2 Hz, 2H). ^{19}F NMR (376 MHz, DMSO) δ −106.67, −109.20. HRMS (ESI) calcd for $C_{13}H_{12}F_2NO$ $[M + H]^+$, 236.0882; found, 236.0871.

5,6-Difluoro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (82). Following general procedure C, the title compound was prepared to provide 51% yield as an off-white powder, mp = 327−331 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 7.95−7.85 (m, 1H), 7.28 (dd, J = 16.9, 9.0 Hz, 1H), 2.76 (s, 2H), 2.44 (s, 2H), 1.74 (br d, J = 15.9 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.64, 150.21 (dd, J = 248.5, 9.09 Hz), 147.97, 138.51 (dd, J = 250.5, 15.15 Hz), 129.97, 121.45, 121.04, 116.47, 110.94 (d, J = 19.19 Hz), 27.05, 21.52, 21.23. HRMS (ESI) calcd for $C_{13}H_{11}F_2NONa$ $(M + Na)^+$, 258.0701; found, 258.0700.

6,7-Difluoro-1,2,3,4-tetrahydroacridin-9(10*H*)-one (83). Following general procedures A and B, the title compound was prepared to provide 42% yield as a tan powder, mp = 357−358 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.47 (s, 1H), 7.86 (t, J = 9.7 Hz, 1H), 7.37 (dd, J = 10.6, 6.8 Hz, 1H), 2.67 (s, 2H), 2.40 (s, 2H), 1.71 (d, J = 19.1 Hz, 5H). ^{19}F NMR (376 MHz, DMSO) δ −133.05, −144.44. ^{13}C NMR (101 MHz, DMSO) δ 174.55, 151.68 (dd, J = 255.53, 15.15 Hz), 147.54, 146.08 (dd, J = 245.43, 14.14 Hz), 136.08 (d, J = 11.11 Hz), 119.93, 115.38, 111.77 (d, J = 16.16 Hz), 105.26 (d, J = 20.2 Hz), 27.03, 21.65, 21.50, 21.29. HRMS (ESI) calcd for $C_{13}H_{12}F_2NO$ $[M + H]^+$, 236.0882; found, 236.0885.

4-Chloro-3-methoxyaniline (84). An amount of 900 mL of ammonia is condensed at −78 °C. Then 1 g of thinly shaven strips of sodium was added followed by 1.0 g of iron(III) nitrate nonahydrate. Upon disappearance of the deep blue color 25 g of thinly shaven strips of sodium was added. After the mixture is stirred for 30 min at −78 °C, 50 g of 2,5-dichloroanisole is added as a solution in hexane (70 mL) dropwise and the mixture is warmed to −45 °C for 2 h. Upon completion the ammonia is allowed to evaporate. The crude pot is then diluted in chloroform, and 100 g of NH_4Cl is added slowly. The combines are taken up in a separatory funnel and washed with H_2O (×3) followed by brine (×1). The organic layer is dried over Na_2SO_4 and concentrated in vacuo. The resulting solid can be used without further purification. Yield: 99%. ^{1}H NMR (400 MHz, DMSO) δ 6.98 (d, J = 8.4, 1H), 6.34 (d, J = 1.8, 1H), 6.16 (dd, J = 8.4, 1.9, 1H), 5.23 (s, 2H), 3.74 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 154.90, 149.16, 129.68, 107.02, 106.74, 98.66, 55.38. HRMS (ESI) calcd for C_7H_8ClNO $[M + H]^+$, 157.0367; found, 157.0361.

4-Chloro-3-isopropoxyaniline (85). To 13.9 mmol of 5-amino-2-chlorophenol, 1.3 mL of acetic anhydride and 8 mL of acetic acid were added. After 5 min at reflux, the mixture was allowed to cool. Product was filtered and used without purification. To the product described above were added 25.6 mmol of isopropyl iodide, 25.6 mmol of Cs_2CO_3, and 65 mL of DMF. After 18 h of reflux, the product was purified via flash chromatography. This product was refluxed with 121.5 mmol of KOH, 15 mL of water, and 135 mL of ethanol overnight. Flash chromatography afforded 4-chloro-3-isopropoxyaniline in 75% yield over three steps. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.07 (d, J = 8.4, 1H), 6.28 (d, J = 2.5, 1H), 6.21 (dd, J = 8.4, 2.6, 1H), 4.45 (dt, J = 12.2, 6.1, 1H), 3.62 (s, 2H), 1.34 (d, J = 6.1, 3H).

3-Methoxy-4-methylaniline (86). A solution of 2-methoxy-1-methyl-4-nitrobenzene (12 mmol) in 30 mL of ethyl acetate was stirred with 75 mg of 10% palladium on carbon under 1.4 atm of hydrogen for 5 h. The catalyst was filtered and the solution was concentrated to afford **86** in 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.91 (d, J = 8.0 Hz, 1H), 6.29−6.16 (m, 2H), 3.79 (s, 3H), 3.57 (s, 2H), 2.12 (s, 3H). ^{13}C NMR

(101 MHz, DMSO) δ 158.54, 145.66, 131.08, 116.62, 106.91, 98.66, 55.27, 15.44.

Ethyl 4-Oxotetrahydro-2*H*-thiopyran-3-carboxylate (87). To 15 mmol of 3-(2-carboxyethylsulfanyl)propionic acid, 5 mL of concentrated sulfuric acid in 900 mL of ethanol was added. The mixture was allowed to reflux for 4 h. After cooling, the mixture was concentrated to ∼20% of its initial concentration followed by the addition of 600 mL of EA. The solution was extracted using 50% sodium bicarbonate twice and once with brine. After flash chromatography, the resulting compound was added in 30 mL of Et_2O to a flamed dried flask containing 193 mmol of 60% NaH, 350 mL of Et_2O, and catalytic ethanol. After the mixture was refluxed for 8 h, the reaction was quenched with 200 mL of 3.1 N aqueous AcOH. After extraction with ether 3 times, the organic layers were washed with sodium bicarbonate, dried, and concentrated. After purification via flash chromatography, the titled compound was afforded in 68% yield over two steps as a mixture of keto and enol forms. ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.51 (d, *J* = 3.6 Hz, 2H), 4.16 (qd, *J* = 7.0, 3.4 Hz, 8H), 3.59 (ddd, *J* = 7.7, 3.8, 3.1 Hz, 1H), 3.28−3.25 (m, 4H), 3.25−3.16 (m, 1H), 3.02−2.92 (m, 1H), 2.92−2.73 (m, 4H), 2.70 (td, *J* = 6.0, 3.5 Hz, 6H), 2.53−2.48 (m, 4H), 1.28−1.12 (m, 15H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.27, 171.46, 168.54, 97.29, 61.42, 60.66, 60.58, 60.53, 58.59, 43.50, 37.42, 32.50, 32.44, 30.76, 30.31, 29.61, 25.17, 24.63, 23.44, 14.17, 14.05.

Ethyl 5,5-Difluoro-2-oxocyclohexanecarboxylate (88). To a flamed-dried flask, 7.5 mmol of 4,4-difluorocyclohexanone in 3 mL of benzene was added along with 22.3 mmol of NaH in 30 mL of benzene and 18.6 mmol of diethyl carbonate. After the mixture was refluxed for 2 h, the reaction was quenched by the addition of crushed ice, brine, and 6 mL of acetic acid. The mixture was washed with DCM twice, and the organic layers were dried and concentrated. The oil was purified via column chromatography to afford the titled compound in 22% yield.

6-Chloro-7-methoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (89). Following general procedure C, the title compound was prepared to provide 36% yield as a mixture of isomers. The desired compound was further purified by preparative HPLC. ^{1}H NMR (400 MHz, DMSO) δ 11.19 (s, 1H), 7.49−7.39 (m, 2H), 3.86 (s, 3H), 2.62 (d, *J* = 5.6 Hz, 3H), 2.35 (t, *J* = 5.6 Hz, 2H), 1.74−1.64 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.90, 150.85, 145.83, 136.52, 120.60, 118.85, 118.10, 117.77, 116.81, 57.48, 27.39, 22.60, 22.57, 22.04. HRMS (ESI) calcd for $C_{14}H_{15}ClNO_2$ $(M + H)^+$, 264.0786; found, 264.0777.

7-Chloro-6-methoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (90). Following general procedure C, the title compound was prepared to provide 42% yield as a mixture of isomers. The desired compound was further purified by preparative HPLC to afford an off-white powder, mp = 316−317 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.31 (s, 1H), 7.96 (s, 1H), 6.99 (s, 1H), 3.93 (s, 1H), 2.66 (s, 2H), 2.40 (s, 2H), 1.72 (br d, *J* = 20.3 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.46, 156.27, 146.66, 139.43, 125.63, 117.69, 117.22, 115.41, 99.07, 56.20, 27.03, 21.75, 21.49, 21.37. HRMS (ESI) calcd for $C_{14}H_{15}ClNO_2$ $[M + H]^+$, 264.0786; found, 264.0781.

7-Chloro-6-isopropoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (91). Following general procedure C, the title compound was prepared to provide 35% yield as a white powder, mp = 345−346 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.22 (s, 1H), 7.95 (s, 1H), 7.01 (s, 1H), 4.66 (s, 1H), 2.65 (s, 2H), 2.39 (s, 2H), 1.75−1.68 (m, 4H), 1.38 (d, *J* = 5.7 Hz, 6H). ^{13}C NMR (101 MHz, DMSO) δ 175.19, 155.24, 147.37, 140.10, 126.50, 118.85, 118.26, 115.98, 101.48, 72.16, 40.83, 40.62, 40.41, 40.20, 39.99, 39.78, 39.57, 27.74, 22.49, 22.15. HRMS (ESI) calcd for $C_{16}H_{19}ClNO_2$ $[M + H]^+$, 292.1099; found, 292.1097.

7-Chloro-6-methoxy-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (92). Following general procedure C, the title compound was prepared to provide 16% yield as a brown powder, mp = 324 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.46 (s, 1H), 7.96 (s, 1H), 6.98 (s, 1H), 3.93 (s, 3H), 3.54 (s, 2H), 2.91 (dd, *J* = 13.5, 4.5 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 174.02, 157.29, 147.38, 140.03, 126.42, 118.45, 118.28, 114.49, 99.86, 56.98, 29.27, 24.25, 23.01.

7-Chloro-2,2-difluoro-6-methoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (93). Following general procedure C, the title compound was prepared to provide 4% yield as a dark brown powder. ^{1}H NMR (400 MHz, DMSO) δ 11.66 (s, 1H), 7.97 (s, 1H), 7.00 (s, 1H), 3.93 (s, 3H), 2.90 (d, *J* = 15.6 Hz, 4H), 2.29 (s, 2H). ^{19}F NMR (376 MHz, DMSO) δ −94.75. ^{13}C NMR (101 MHz, DMSO) δ 174.01, 157.13, 144.74, 139.80, 126.03, 124.13, 118.42, 117.67, 99.64, 56.84, 31.67 (t, *J* = 25.3 Hz), 29.08 (t, *J* = 25.3 Hz), 25.74. HRMS (ESI) calcd for $C_{14}H_{13}ClF_2NO_2$ $[M + H]^+$, 300.060 29; found, 300.060 24.

7-Chloro-2,2-difluoro-1,3,4,10-tetrahydro-2*H*-acridin-9-one (94). Following general procedures A and B, the title compound was prepared to provide 55% yield as a brown powder, mp = 351 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.83 (s, 1H), 7.98 (d, *J* = 2.1 Hz, 1H), 7.64 (dd, *J* = 8.8, 2.1 Hz, 1H), 7.52 (d, *J* = 8.8 Hz, 1H), 2.96 (d, *J* = 5.9 Hz, 4H), 2.34−2.27 (m, 2H). ^{19}F NMR (376 MHz, DMSO) δ −94.75. ^{13}C NMR (101 MHz, DMSO) δ 174.69, 145.68, 138.34, 132.14, 127.63, 124.22, 124.03, 120.52, 111.66, 31.75 (t, *J* = 25.3 Hz), 29.25 (t, *J* = 25.3 Hz), 25.70 (t, *J* = 5 Hz). HRMS (ESI) calcd for $C_{13}H_{11}ClF_2NO$ $[M + H]^+$, 270.04972; found, 270.04968.

2,2-Difluoro-6-methoxy-1,3,4,10-tetrahydro-2*H*-acridin-9-one (95). Following general procedures A and B, the title compound was prepared to provide 36% yield as a light brown powder, mp = 327 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.48 (s, 1H), 7.96 (d, *J* = 8.8 Hz, 1H), 6.86 (dt, *J* = 6.8, 2.3 Hz, 2H), 3.84 (s, 3H), 2.96−2.87 (m, 4H), 2.27 (dt, *J* = 20.6, 7.0 Hz, 2H). ^{19}F NMR (376 MHz, DMSO) δ −94.73. ^{13}C NMR (101 MHz, DMSO) δ 175.05, 161.78, 144.18, 141.11, 126.58, 117.24, 112.74, 110.36, 98.40, 55.35, 31.25 (t, *J* = 25.3 Hz), 28.50 (t, *J* = 25.2 Hz), 25.23. HRMS (ESI) calcd for $C_{14}H_{14}F_2NO_2$ $[M + H]^+$, 266.09926; found, 266.09933.

6-Methoxy-7-methyl-1,3,4,10-tetrahydro-2*H*-acridin-9-one (96). Following general procedure C, the title compound was prepared to provide 38% yield as a white powder. ^{1}H NMR (400 MHz, DMSO) δ 11.09 (s, 1H), 7.77 (s, 1H), 6.81 (s, 1H), 3.85 (s, 3H), 2.64 (s, 2H), 2.39 (s, 2H), 2.20 (s, 3H), 1.71 (d, *J* = 19.9 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.33, 159.92, 145.62, 139.46, 125.89, 121.81, 117.16, 114.86, 96.44, 55.39, 27.03, 21.98, 21.60, 21.53, 16.00. HRMS (ESI) calcd for $C_{15}H_{18}NO_2$ $[M + H]^+$, 244.1332; found, 244.1326.

6-Methoxy-7-methyl-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (97). Following general procedure C, the title compound was prepared to provide 9% yield as a pink crystalline powder, mp = 328 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.27 (s, 1H), 7.79 (s, 1H), 6.83 (s, 1H), 3.87 (s, 3H), 3.52 (d, *J* = 19.9 Hz, 2H), 2.90 (dd, *J* = 14.6, 5.0 Hz, 4H), 2.21 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.12, 160.25, 145.68, 139.37, 125.97, 122.48, 117.07, 113.24, 96.54, 55.47, 28.54, 23.67, 22.43, 15.98. HRMS (ESI) calcd for $C_{14}H_{16}NO_2S$ $[M + H]^+$, 262.0896; found, 262.0895.

7-Bromo-3,4-dihydro-1*H*-thiopyrano[4,3-*b*]quinolin-10(5*H*)-one (98). Following general procedure C, the title compound was prepared to provide 34% yield as a yellow crystal, mp = 298 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.66 (s, 1H), 8.13 (d, *J* = 2.2 Hz, 1H), 7.74 (dd, *J* = 8.8, 2.3 Hz, 1H), 7.45 (d, *J* = 8.8 Hz, 1H), 3.57 (s, 2H), 2.97 (d, *J* = 5.6 Hz, 2H), 2.90 (t, *J* = 5.8 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.45, 147.35, 137.90, 134.11, 127.00, 124.48, 120.16, 114.94, 114.44, 28.66, 23.57, 22.40. HRMS (ESI) calcd for $C_{12}H_{10}BrNOSNa$ $[M + Na]^+$, 317.9556; found, 317.9571.

2-Methyl-1,3,4,5-tetrahydro-2*H*-benzo[*b*][1,6]naphthyridin-10-one (99). Following general procedure C, the title compound was prepared to provide 26% yield as a yellow powder. ^{1}H NMR (400 MHz, DMSO) δ 12.31 (s, 1H), 8.07 (d, *J* = 7.9 Hz, 1H), 7.66 (dd, *J* = 11.0, 4.0 Hz, 1H), 7.60 (d, *J* = 8.1 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 1H), 4.07 (s, 2H), 3.48 (s, 2H), 3.16 (s, 2H), 2.93 (s, 3H). ^{13}C NMR (101 MHz,

DMSO) δ 174.24, 143.62, 139.38, 124.62, 124.54, 123.22, 122.86, 118.11, 109.49, 49.65, 49.13, 42.76, 24.79. HRMS (ESI) calcd for $C_{13}H_{15}N_2O$ $[M + H]^+$, 215.1179; found, 215.1170.

7-(4-Fluorophenoxy)-1,3,4,10-tetrahydro-2*H*-acridin-9-one (100). Following general procedure C, the title compound was prepared to provide 55% yield as an off-white powder, mp = 306−308 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 7.51 (s, 1H), 7.44 (s, 1H), 7.36 (dd, *J* = 8.7, 2.0 Hz, 1H), 7.23 (t, *J* = 8.5 Hz, 2H), 7.08 (dd, *J* = 8.5, 4.4 Hz, 2H), 2.67 (d, *J* = 5.7 Hz, 2H), 2.40 (s, 2H), 1.70 (dd, *J* = 24.6, 5.0 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.12, 158.19 (d, *J* = 249.47 Hz), 152.80, 152.31, 146.61, 135.49, 123.98, 123.30, 120.64, 119.72, 116.57 (d, *J* = 24.24 Hz), 114.90, 111.09, 27.08, 21.83, 21.67, 21.47. HRMS (ESI) calcd for $C_{19}H_{17}FNO_2$ $[M + H]^+$, 310.1238; found, 310.1232.

7-Chloro-6-methoxy-2-oxo-1,3,4,10-tetrahydro-2*H*-2l4-thia-10-aza-anthracen-9-one (101). A flame-dried 5 mL round-bottom flask was charged with 2 mL of 27% aq H_2O_2 and 7-chloro-6-methoxy-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (0.142 mmol). The mixture was heated at 40 °C for 10 h and the resulting solid was filtered and purified by preparatory HPLC to give a white crystal. ^{1}H NMR (400 MHz, DMSO) δ 11.80 (s, 1H), 7.97 (s, 1H), 7.05 (s, 1H), 3.95 (s, 3H), 3.84 (d, *J* = 16.0 Hz, 2H), 3.65 (d, *J* = 16.6 Hz, 2H), 3.20 (d, *J* = 12.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 174.36, 156.85, 145.41, 139.42, 125.66, 118.12, 117.54, 105.92, 99.39, 56.40, 42.86, 41.15, 19.64. HRMS (ESI) calcd for $C_{13}H_{13}ClNO_3S$ $[M + H]^+$, 298.0299; found, 298.0295.

7-Chloro-6-methoxy-2,2-dioxo-1,3,4,10-tetrahydro-2*H*-2l6-thia-10-aza-anthracen-9-one (102). A flame-dried 25 mL round-bottom flask was charged with *m*-CPBA (0.553 mmol), 4.7 mL of anhydrous $CHCl_3$, and 7-chloro-6-methoxy-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (0.142 mmol). The reaction slurry was allowed to stir at room temperature for 22 h. It was then quenched by adding a few drops of water and filtered. The resulting solid was then purified by preparatory HPLC to give a white crystal. ^{1}H NMR (400 MHz, DMSO) δ 11.92 (s, 1H), 7.99 (s, 1H), 7.05 (s, 1H), 4.06 (s, 2H), 3.95 (s, 3H), 3.49 (d, *J* = 6.5 Hz, 2H), 3.30 (d, *J* = 6.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 173.23, 157.05, 144.24, 139.76, 125.60, 118.51, 117.05, 108.82, 99.60, 56.44, 46.71, 45.62, 28.02. HRMS (ESI) calcd for $C_{13}H_{13}ClNO_4S$ $[M + H]^+$, 314.0248; found, 314.0244.

7-Pyridin-4-yl-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (103). Following general procedure D, the title compound was prepared to provide 31% yield as a yellow powder, mp = 348 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.66 (s, 1H), 8.65 (s, 2H), 8.44 (s, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.76 (s, 2H), 7.61 (d, *J* = 8.5 Hz, 1H), 3.61 (s, 2H), 3.00 (s, 2H), 2.92 (d, *J* = 5.1 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 175.15, 150.56, 147.58, 140.06, 140.03, 131.41, 130.27, 123.70, 123.59, 121.43, 119.13, 114.97, 29.12, 24.08, 22.92. HRMS (ESI) calcd for $C_{17}H_{15}N_2OS$ $[M + H]^+$, 295.0900; found, 295.0904.

7-Pyridin-3-yl-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (104). Following general procedure D, the title compound was prepared to provide 82% yield as a yellow powder, mp = 327 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.64 (s, 1H), 8.94 (s, 1H), 8.58 (s, 1H), 8.33 (s, 1H), 8.13 (d, *J* = 7.1 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.61 (d, *J* = 8.8 Hz, 1H), 7.58−7.30 (m, 1H), 3.61 (s, 2H), 3.01 (d, *J* = 5.2 Hz, 2H), 2.93 (d, *J* = 5.3 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 174.67, 148.29, 147.42, 146.99, 138.87, 135.00, 134.02, 131.17, 130.12, 123.97, 123.40, 122.80, 118.62, 114.29, 28.68, 23.66, 22.49. HRMS (ESI) calcd for $C_{17}H_{15}N_2OS$ $[M + H]^+$, 295.0900; found, 295.0889.

8-(2,4-Difluorophenyl)-3,4-dihydro-1*H*-thiopyrano[4,3-*b*]quinolin-10(5*H*)-one (105). Following general procedure D, the title compound was prepared to provide 74% yield as a yellow powder, mp = 341 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.64 (s, 1H), 8.19 (s, 1H), 7.82−7.74 (m, 1H), 7.65 (td, *J* = 8.9, 6.7 Hz, 1H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.42−7.35 (m, 1H), 7.21 (td, *J* = 8.5, 2.7 Hz, 1H), 3.61 (s, 2H), 3.02 (t, *J* = 5.5 Hz, 2H), 2.92 (t, *J* = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 174.60, 161.62 (dd, *J* = 241.9, 6.8 Hz), 159.09 (dd, *J* = 242.9, 7.3 Hz), 147.03, 138.56, 133.05−130.30 129.10−127.80 (m), 124.90 (d, *J* = 3.3 Hz), 124.24 (dd, *J* = 13.1, 3.6 Hz), 123.05, 118.04, 114.24, 112.15 (dd, *J* = 21.2, 3.7 Hz), 104.56 (dd, *J* = 26.9, 25.9 Hz), 28.65, 23.67, 22.46. HRMS (ESI) calcd for $C_{18}H_{14}F_2NOS$ $[M + H]^+$, 330.0759; found, 330.0749.

7-(4-Chloro-2-methylphenyl)-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (106). Following general procedure D, the title compound was prepared to provide 70% yield as an orange powder, mp = 329 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.62 (s, 1H), 7.96 (s, 1H), 7.65−7.58 (m, 1H), 7.56 (d, *J* = 8.6 Hz, 1H), 7.41 (s, 1H), 7.33 (d, *J* = 8.1 Hz, 1H), 7.26 (d, *J* = 8.2 Hz, 1H), 3.60 (s, 2H), 3.00 (d, *J* = 5.4 Hz, 2H), 2.92 (d, *J* = 5.2 Hz, 2H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.64, 146.94, 139.51, 138.20, 137.39, 134.10, 132.35, 131.81, 131.30, 129.91, 125.92, 124.78, 122.91, 117.61, 114.11, 28.67, 23.69, 22.45, 19.97. HRMS (ESI) calcd for $C_{19}H_{16}ClNOSNa$ $[M + Na]^+$, 364.0533; found, 364.0532.

8-(4-(Trifluoromethoxy)phenyl)-3,4-dihydro-1*H*-thiopyrano[4,3-*b*]quinolin-10(5*H*)-one (107). Following general procedure D, the title compound was prepared to provide 72% yield as a yellow powder, mp = 319 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.63 (s, 1H), 8.31 (s, 1H), 7.95 (d, *J* = 8.6 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 2H), 7.59 (d, *J* = 8.6 Hz, 1H), 7.46 (d, *J* = 8.2 Hz, 2H), 3.61 (s, 2H), 3.00 (d, *J* = 5.2 Hz, 2H), 2.92 (t, *J* = 5.5 Hz, 2H). ^{19}F NMR (376 MHz, DMSO) δ −56.96. ^{13}C NMR (101 MHz, DMSO) δ 174.67, 147.70, 146.95, 138.77, 138.69, 132.80, 130.10, 128.35, 123.30, 122.56, 121.50, 120.10 (q, *J* = 256.2 Hz), 118.48, 114.19, 28.67, 23.65, 22.47. HRMS (ESI) calcd for $C_{19}H_{15}F_3NO_2S$ $[M + H]^+$, 378.0770; found, 378.0764.

8-(3-(4-Fluorophenoxy)phenyl)-3,4-dihydro-1*H*-thiopyrano[4,3-*b*]quinolin-10(5*H*)-one (108). Following general procedure D, the title compound was prepared to provide 79% yield as an off-white powder, mp = 338 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.61 (s, 1H), 8.26 (d, *J* = 2.1 Hz, 1H), 7.92 (dd, *J* = 8.7, 2.1 Hz, 1H), 7.57 (d, *J* = 8.7 Hz, 1H), 7.55−7.44 (m, 2H), 7.34−7.21 (m, 3H), 7.21−7.11 (m, 2H), 7.11−6.83 (m, 2H), 3.60 (s, 2H), 3.13−2.91 (m, 4H), 2.90 (s, 1H). ^{19}F NMR (376 MHz, DMSO) δ −119.90. ^{13}C NMR (101 MHz, DMSO) δ 174.69, 157.81, 158.27 (d, *J* = 239.4 Hz), 152.43, 146.89, 141.51, 138.68, 133.44, 130.72, 130.09, 123.26, 122.39, 121.50, 120.85 (d, *J* = 8.5 Hz), 118.42, 116.80 (d, *J* = 13.4 Hz), 116.50, 115.93, 114.13, 28.65, 23.64, 22.46. HRMS (ESI) calcd for $C_{24}H_{19}FNO_2S$ $[M + H]^+$, 404.1115; found, 404.1122.

7-[2-Methyl-4-(4-trifluoromethoxyphenoxy)phenyl]-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (109). Following general procedure D, the title compound was prepared to provide 56% yield as an off-white powder, mp = 350 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.61 (s, 1H), 7.97 (s, 1H), 7.63 (d, *J* = 8.2, 1H), 7.56 (d, *J* = 8.6, 1H), 7.40 (d, *J* = 8.4, 2H), 7.29 (d, *J* = 8.2, 1H), 7.17 (d, *J* = 9.0, 2H), 7.05 (s, 1H), 6.96 (d, *J* = 8.0, 1H), 3.60 (s, 2H), 2.97 (d, *J* = 37.9, 4H), 2.23 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 174.67, 155.73, 155.23, 146.87, 143.58, 138.02, 137.21, 136.57, 134.66, 132.55, 131.33, 124.81, 122.93, 120.71, 119.73, 117.51, 116.54, 114.02, 28.67, 23.69, 22.45, 20.26. HRMS (ESI) calcd for $C_{26}H_{21}F_3NO_3S$ $[M + H]^+$, 484.1189; found, 484.1173.

8-(4-((4-(Trifluoromethoxy)phenoxy)methyl)phenyl)-3,4-dihydro-1*H*-thiopyrano[4,3-*b*]quinolin-10(5*H*)-one (110). Following general procedure D, the title compound was prepared to provide 68% yield as a light yellow powder, mp = 301 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.60 (s, 1H), 8.33 (s, 1H), 7.96 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 2H), 7.57 (dd, *J* = 12.5, 8.6 Hz, 3H), 7.31 (d, *J* = 8.7 Hz, 2H), 7.13 (d, *J* = 8.9 Hz, 2H), 5.18 (s, 2H), 3.62 (s, 2H), 3.00 (d, *J* = 5.2 Hz, 2H), 2.92 (d, *J* = 5.2 Hz, 2H). ^{19}F NMR (376 MHz, DMSO) δ −57.38. ^{13}C NMR (101 MHz, DMSO) δ 174.76, 157.16, 146.82, 141.85, 139.08, 138.54, 135.75, 133.86, 130.09, 128.44, 126.57, 123.36,

122.50, 122.26, 120.15 (d, J = 255.2 Hz), 118.38, 116.00, 114.08, 69.35, 28.67, 23.67, 22.50.

7-(4-Phenoxymethyl-phenyl)-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (111). Following general procedure D, the title compound was prepared to provide 68% yield as a off-white powder, mp = 323 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.60 (s, 1H), 8.32 (d, J = 2.0 Hz, 1H), 7.96 (dd, J = 8.7, 2.1 Hz, 1H), 7.74 (d, J = 8.1 Hz, 2H), 7.57 (dd, J = 12.9, 8.5 Hz, 3H), 7.30 (t, J = 7.9 Hz, 2H), 7.03 (d, J = 8.0 Hz, 2H), 6.95 (s, 1H), 5.16 (s, 2H), 3.61 (s, 2H), 3.00 (d, J = 5.2 Hz, 2H), 2.92 (t, J = 5.6 Hz, 2H). ^{13}C NMR (101 MHz, DMSO) δ 174.74, 158.28, 146.82, 138.92, 138.51, 136.23, 133.91, 130.10, 129.47, 128.35, 126.52, 123.36, 122.23, 120.70, 118.37, 114.77, 114.07, 68.72, 28.67, 23.67, 22.49. HRMS (ESI) calcd for $C_{25}H_{22}NO_2S$ $[M + H]^+$, 400.1366; found, 400.1357.

8-(4-(Benzyloxy)phenyl)-3,4-dihydro-1*H*-thiopyrano[4,3-*b*]quinolin-10(5*H*)-one (112). Following general procedure D, the title compound was prepared to provide 62% yield as a yellow powder, mp = 310 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 11.57 (s, 1H), 8.25 (s, 1H), 7.90 (d, J = 8.1 Hz, 1H), 7.65 (d, J = 8.1 Hz, 2H), 7.56 (d, J = 8.7 Hz, 1H), 7.48 (d, J = 7.0 Hz, 2H), 7.42−7.39 (m, 2H), 7.35 (d, J = 6.9 Hz, 1H), 7.12 (d, J = 7.7 Hz, 2H), 5.16 (s, 2H), 3.61 (s, 2H), 3.00 (s, 2H), 2.91 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 174.54, 157.91, 146.81, 138.02, 137.02, 134.10, 132.04, 129.89, 128.41, 127.80, 127.63, 127.61, 123.30, 121.41, 118.29, 115.38, 113.90, 69.25, 28.68, 23.66, 22.49. HRMS (ESI) calcd for $C_{25}H_{22}NO_2S$ $[M + H]^+$, 400.1366; found, 400.1377.

7-(4-Trifluoromethylphenyl)-1,3,4,10-tetrahydro-2-thia-10-aza-anthracen-9-one (113). Following general procedure D, the title compound was prepared to provide 71% yield as a dark green powder, mp = 304 °C, dec. ^{1}H NMR (400 MHz, DMSO) δ 8.38 (d, J = 2.2 Hz, 1H), 8.00 (dd, J = 8.7, 2.2 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.4 Hz, 2H), 7.62 (d, J = 8.7 Hz, 1H), 3.62 (s, 2H), 3.01 (t, J = 5.5 Hz, 2H), 2.92 (t, J = 5.7 Hz, 2H). ^{19}F NMR (376 MHz, DMSO) δ −61.09. ^{13}C NMR (101 MHz, DMSO) δ 174.57, 147.44, 143.49, 139.47, 132.39, 129.98, 127.18, 125.88, 125.84, 123.43, 123.02, 118.96, 114.28, 28.91, 23.73, 22.52.

7-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroacridin-9(10*H*)-one (114). Following general procedure D, the title compound was prepared to provide 78% yield as a white solid, mp > 364 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.48 (s, 1H), 8.37 (d, J = 2.2 Hz, 1H), 7.97 (dd, J = 8.7, 2.3 Hz, 1H), 7.94 (d, J = 8.2 Hz, 2H), 7.82 (d, J = 8.3 Hz, 2H), 7.59 (d, J = 8.7 Hz, 1H), 2.72 (t, J = 6.0 Hz, 2H), 2.46 (t, J = 6.1 Hz, 2H), 1.81−1.69 (m, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.86, 147.06, 143.61, 139.24, 132.08, 129.72, 127.15, 125.86, 123.32, 122.95, 118.48, 116.05, 109.55, 27.15, 21.81, 21.71, 21.46. ^{19}F NMR (376 MHz, DMSO) δ −60.89. HRMS (ESI) calcd for $C_{20}H_{16}F_3NONa$ $[M + Na]^+$, 366.1076; found, 366.1076.

6-(4-(Trifluoromethyl)phenyl)-1,2,3,4-tetrahydroacridin-9(10*H*)-one (115). Following general procedure D, the title compound was prepared to provide 81% yield as a yellow powder, mp = 352−354 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.43 (s, 1H), 8.15 (d, J = 8.5 Hz, 1H), 7.90 (dd, J = 19.8, 8.3 Hz, 4H), 7.73 (s, 1H), 7.57 (d, J = 8.4 Hz, 1H), 2.72 (t, J = 5.9 Hz, 2H), 2.45 (t, J = 6.0 Hz, 2H), 1.74 (dd, J = 25.2, 6.0 Hz, 4H). ^{19}F NMR (376 MHz, DMSO) δ −61.09. HRMS (ESI) calcd for $C_{20}H_{17}F_3NO[M + H]^+$, 344.1257; found, 344.1251.

6-(2,6-Difluorophenyl)-1,2,3,4-tetrahydroacridin-9(10*H*)-one (116). Following general procedure D, the title compound was prepared to provide 10% yield as a yellow powder, mp = 318−320 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.42 (s, 1H), 8.14 (d, J = 8.3 Hz, 1H), 7.53 (dd, J = 9.9, 3.1 Hz, 2H), 7.28 (t, J = 8.2 Hz, 3H), 2.71 (d, J = 6.2 Hz, 2H), 2.46 (t, J = 5.9 Hz, 2H), 1.75 (dd, J = 23.2, 4.8 Hz, 4H). ^{19}F NMR (376 MHz, DMSO) δ −114.70. ^{13}C NMR (101 MHz, DMSO) δ 176.01, 160.88, 147.69, 139.46, 131.37, 131.03, 125.48, 124.26, 123.16, 119.38, 116.52, 112.76, 112.51, 27.61, 22.26, 22.11, 21.90. HRMS (ESI) calcd for $C_{19}H_{16}F_2NO$ $[M + H]^+$, 312.1195; found, 312.1183.

6-(4-(Dimethylamino)phenyl)-1,2,3,4-tetrahydroacridin-9(10*H*)-one (117). Following general procedure D, the title compound was prepared to provide 33% yield as a light brown powder, mp > 364 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.24 (s, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 1.9 Hz, 2H), 7.56 (s, 1H), 7.47 (dd, J = 8.5, 1.7 Hz, 1H), 6.84 (d, J = 8.9 Hz, 2H), 2.96 (s, 6H), 2.70 (t, J = 6.0 Hz, 2H), 2.44 (t, J = 5.9 Hz, 2H), 1.73 (dd, J = 25.6, 4.8 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.74, 150.30, 146.68, 142.67, 139.86, 127.35, 126.32, 125.45, 121.32, 120.18, 115.45, 112.78, 112.60, 27.16, 21.92, 21.67, 21.52. HRMS (ESI) calcd for $C_{21}H_{23}N_2O$ $[M + H]^+$, 319.1805; found, 319.1795.

6-(4-(4-(Trifluoromethoxy)phenoxy)phenyl)-1,2,3,4-tetrahydroacridin-9(10*H*)-one (118). Following general procedure D, the title compound was prepared to provide 37% yield as a yellow powder, mp = 311−313 °C. ^{1}H NMR (400 MHz, DMSO) δ 11.39 (s, 1H), 8.11 (d, J = 8.4 Hz, 1H), 7.76 (s, 1H), 7.74 (s, 1H), 7.66 (s, 1H), 7.52 (d, J = 8.5 Hz, 1H), 7.44 (s, 1H), 7.41 (s, 1H), 7.24−7.17 (m, 4H), 2.72 (t, J = 5.9 Hz, 2H), 2.45 (t, J = 5.9 Hz, 2H), 1.74 (dd, J = 25.5, 6.1 Hz, 4H). ^{13}C NMR (101 MHz, DMSO) δ 175.62, 156.49, 155.29, 147.09, 143.92, 141.73, 139.67, 134.92, 128.70, 125.71, 123.04, 122.07, 120.87, 120.24, 119.30, 115.82, 114.55, 27.20, 21.86, 21.68, 21.48. HRMS (ESI) calcd for $C_{26}H_{21}F_3NO_3$ $[M + H]^+$, 452.1468; found, 452.1467.

4-((4-(Trifluoromethoxy)phenoxy)methyl)phenylboronic Acid (119). To a flame-dried flask back-filled with argon (×2) are added 4-(trifluoromethoxy)phenol (20 mmol, 3.64 g), anhydrous DMF (3 mL), and NaH (32.3 mmol, 0.77 g) at 0 °C. This suspension is allowed to stir for 30 min, at which time a solution of 1-bromo-4-(chloromethyl)benzene (19 mmol, 4 g) dissolved in 3 mL of DMF is added dropwise. The mixture is stirred overnight at 80 °C and quenched by pouring onto ice and water. The resulting slurry is extracted by EtOAc (×3) and washed with water followed by brine and subsequently dried over Na_2SO_4. The crude bromide is purified further via flash chromatography (hexane/EtOAc 10:1) to afford 1-bromo-4-((4-(trifluoromethoxy)phenoxy)methyl)-benzene as a colorless oil in 90% yield. To a solution of 1-bromo-4-((4-(trifluoromethoxy)phenoxy)methyl)benzene (7.2 mmol, 2.5 g) and triisopropyl borate (9.4 mmol, 2.15 mL) in dry THF (65 mL) at −78 °C was added dropwise 1.6 M BuLi (5.4 mL) in hexanes over 10 min. The mixture was stirred for 3 h at −78 °C, at which point 10 mL of 6 M HCl is added and the solution is allowed to warm to room temperature and stir overnight. The reaction mixture was diluted with EtOAc (150 mL) and water (150 mL). The organic layer is taken separately and rinsed with water (150 mL), followed by brine (150 mL) and then dried over Na_2SO_4. The EtOAc is then concentrated in vacuo to afford a waxy solid which is then treated with 2 M NaOH (40 mL). The mixutre is stirred for 15 min, diluted with water (300 mL), and stirred for 20 min. The solution is then filtered and the filtrate washed with hexane (3 × 100 mL). The aqueous layer was carefully acidified to pH 1 with 6 M HCl. The resulting white solid was filtered and dried on a high vacuum overnight to afford the titled compound in 67% yield.

4-(4-(Trifluoromethoxy)phenoxy)phenylboronic Acid (120). The titled compound was prepared exactly as Yeates et al.[39] described. A flame-dried 25 mL Schlenk tube was back-filled with argon (×3). To a solution of 4-bromophenol (0.346 g, 2 mmol) in *N*-methylpyrrolidine (8 mL) under an argon atmosphere were added 4-(trifluoromethoxy)-iodobenzene (0.626 mL, 4 mmol), 2,2,6,6-tetramethylheptane-3,5-dione (0.092 mL, 0.44 mmol), and cesium carbonate (1.30 g, 4 mmol). The slurry was degassed by bubbling argon for 15 min, and CuCl (0.099 g, 1 mmol) was then added. The reaction mixture was again degassed and then warmed to 100 °C for 7 h. After the mixture was cooled to room temperature, Et_2O (75 mL) was added slowly. The resulting slurry was filtered and the solid washed with Et_2O (3 × 50 mL). The combined filtrates were washed with 2 M NaOH (100 mL), water (100 mL), 1 M aq HCl (100 mL), water (100 mL), and saturated brine (100 mL), then subsequently dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified via flash

chromatography with 100% hexane. This column chromatography was repeated three times, combining the purest fractions each column elution to obtain pure material due to similarly eluting 4-(trifluoromethoxy)-iodobenzene to afford 1-bromo-4-(4-(trifluoromethoxy)phenoxy)-benzene (0.15 g, 45%) as a colorless liquid. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.45 (m, 2H), 7.20 (m 2H), 6.99 (m 2H), 6.90 (m 2H). To a solution of 1-bromo-4-(4-(trifluoromethoxy)phenoxy)benzene (2.1 mmol, 0.7 g) and triisopropyl borate (2.7 mmol, 0.63 mL) in dry THF (15 mL) at −78 °C was added dropwise 2.5 M BuLi (6.5 mL) in hexanes over 5 min. The mixture was stirred for 3 h at −78 °C, at which point 10 mL of 6 M HCl is added and the solution is allowed to warm to room temperature and stir overnight. The reaction mixture was diluted with EtOAc (150 mL) and water (150 mL). The organic layer is taken separately and rinsed with water (150 mL) followed by brine (150 mL) and then dried over Na_2SO_4. The EtOAc is then concentrated in vacuo to afford a waxy solid which is then treated with 2 M NaOH (40 mL). The mixture is stirred for 15 min, diluted with water (300 mL), and stirred for 20 min. The solution is then filtered and the filtrate washed with hexane (3 × 100 mL). The aqueous layer was carefully acidified to pH 1 with 6 M HCl. The resulting white solid was filtered and dried on a high vacuum overnight to afford the titled compound in 67% yield. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01 (bs, 2H), 7.85−7.78 (m, 2H), 7.43−7.33 (m, 2H), 7.15−7.07 (m, 2H), 7.02−6.94 (m, 2H).

2-Methyl-4-(4-(trifluoromethoxy)phenoxy)phenylboronic Acid (121). The titled compound is prepared similarly to **120** in 36% yield over two steps as an off-white solid. ^{1}H NMR (400 MHz, DMSO) δ 7.92 (d, J = 7.9 Hz, 1H), 7.36 (d, J = 8.9 Hz, 2H), 7.12−7.07 (m, 2H), 6.82 (d, J = 9.0 Hz, 2H), 2.64 (s, 3H). ^{13}C NMR (101 MHz, DMSO) δ 156.91, 155.63, 146.05, 143.50, 136.70, 135.43, 122.82, 120.03, 119.75, 119.57, 114.87, 21.97.

J774 Cytotoxicity Assay. Mouse macrophage cell line J774 was cultured in RPMI 1640 medium with phenol red containing L-glutamine and then supplemented with 10% fetal bovine serum, penicillin (50 U/mL), and streptomycin (50 μg/mL). For seeding into 96-well plates the J774 cells were diluted to 5 × 10^5 cells/mL. Cells were dispensed into 96-well plates at a volume of 100 μL/well, giving a final concentration of 5 × 10^4 cells/well. Plates were incubated for 24 h at 37 °C and 5% CO_2 to allow the attachment of J774 to the bottom of the plate wells. Test compounds were prepared by diluting to 10 μg/mL or 20 nM followed by 1:2 serial dilutions over 11 concentrations. After 24 h the medium was removed from the wells and serially diluted test compounds were added to each well. Positive and negative control wells were included on each assay plate. Plates containing cells and test compounds were then incubated for 72 h at 37 °C and 5% CO_2. After the incubation period, cell proliferation was assessed using CellTiter 96 Aqueous One solution cell proliferation assay reagent (Promega). To each well 20 μL of reagent was added followed by incubation for 4 h at 37 °C and 5% CO_2. A Spectramax M2e (Molecular Devices) plate reader was used to read absorbance at 490 nM. IC_{50} values were determined using a custom database manager (Dataspects, Inc.). Nonlinear regression analysis was used to calculate IC_{50}.

In Vitro Parasite Culturing. *P. falciparum* clone W2/Indochina and TM90C2B/Thailand were grown in continuous culture using RPMI 1640 medium containing 10% heat-inactivated type A+ human plasma, sodium bicarbonate (2.4 g/L), HEPES (5.94 g/L), and 4% washed human type A+ erythrocytes. Cultures were gassed with a 90% N_2, 5% O_2, and 5%CO_2 mixture followed by incubation at 37 °C.

Assay Preparation. Test compounds at 5 mg/mL in DMSO were diluted at least 1:400 and then serially diluted in duplicate over 11 concentrations. *P. falciparum* cultures with >70% ring stage parasites were diluted to 0.5−0.7% parasitemia and 1.5% hematocrit in RPMI 1640 medium. In 96-well plates a volume of 90 μL/well of parasitized erythrocytes was added on top of 10 μL/well of the test compound. A separate plate containing chloroquine, dihydroartemisinin, and atovaquone was added to each set of assay plates as control drugs. A Beckman Coulter Biomek 3000 was used to dispense test compounds, control drugs, and parasitized erythrocytes into the microtiter plates. Positive and negative controls were included in each plate. Positive controls consisted of drug-free parasitized erythrocytes, and negative controls consisted of parasitized erythrocytes dosed with a high concentration of chloroquine or dihydroartemisinin that ensured 100% parasite death. Assay plates were placed into a plastic gassing chamber and equilibrated with 90% N_2, 5% O_2, and 5%CO_2 mixture and then incubated at 37 °C for 72 h. After 72 h of incubation the assay plates were frozen at −80 °C until later processed for parasite growth determinations.

SYBR Green I Processing. Assay plates were removed from −80 °C and allowed to thaw at room temperature. By use of the Beckman Biomek 3000, 100 μL was transferred from the assay plates into 96-well black assay plates. Next, 100 μL of SYBR green I (Invitrogen) in 2× lysis buffer (0.2 μL of SYBR green I/mL of 2× lysis buffer [0.008% saponin, 0.08% Triton X-100, 20 mM Tris, and 5 mM EDTA]) was dispensed into each well of the 96-well black assay plate using the Beckman Coulter Biomek 3000. Upon addition of SYBR green I the microtiter plates were incubated for 1 h in the dark. Relative fluorescence units (RFU) were read using a Molecular Devices Spectramax microplate reader.

Data Analysis. Data analysis was performed using a custom database manager (Dataspects, Inc.). Nonlinear regression analysis was used to calculate EC_{50}.

■ ASSOCIATED CONTENT

Supporting Information. Additional experimental details; SPR, activity, and permeability data; ^{1}H NMR, ^{13}C NMR, and ^{19}F NMR characterizations for all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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■ ABBREVIATIONS USED

EC_{50}, half-maximal effective concentration; ED_{50}, half-maximal effective dose; ACT, artemisinin combination therapy; WRAIR, Walter Reed Army Institute of Research; SAR, structure−activity relationship; SPR, structure−property relationship; SPHOS, dicyclohexyl(2′,6′-dimethoxybiphenyl-2-yl)phosphine; TEA, triethylamine; Bn, benzyl; DCM, dichloromethane; $Pd_2(dba)_3$,

tris(dibenzylideneacetone)dipalladium(0); Ph, phenyl; DMF, *N*,*N*-dimethylformamide; HPLC, high performance liquid chromatography; RPMI, Roswell Park Memorial Institute; RI, resistance index; Ac, acetyl; rt, room temperature; CI, cytotoxicity index

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