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# Boron trifluoride etherate promoted microwave-assisted synthesis of antimalarial acridones†

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A microwave-assisted, rapid and efficient method using boron trifluoride etherate ($BF_3.Et_2O$) for the synthesis of acridones, *via* an intramolecular acylation of *N*-phenylanthranilic acid derivatives, has been developed. The reaction proceeds under solvent-free conditions, tolerates a wide range of functional groups, and provides rapid access to a range of acridones in good to excellent yields. Several of the synthesized acridones exhibited potent antimalarial activities against CQ sensitive and multi-drug resistant (MDR) parasites.



## Introduction

Acridones are one of the important classes of heteroaromatic compounds and they have ubiquitous structural motifs in biologically active molecules. The natural and synthetic acridone products (Fig. 1) are of worldwide interest because of their wide range of biological properties, including antitumor, anticancer, antimalarial, anti-HIV, antiviral, and antifungal activities.[1–13] The intriguing structural features and therapeutic importance of acridone scaffold has attracted the great attention of organic and medicinal chemists to discover new synthetic routes[14–18] for the generation of novel acridones to be evaluated for biological activities and structure–activity relationships (SAR).

As part of an ongoing interest in developing new antiparasitic agents, we recently discovered a novel acridone chemotype that demonstrates efficacy against both liver and blood stage malaria.[11,12] Of the many conventional methods available for the synthesis of acridones from *N*-phenylanthranilic acid and ester derivatives, the most widely used is the strong acid catalyzed intramolecular Friedel–Crafts cyclization in the presence of either sulfuric acid ($H_2SO_4$), polyphosphoric acid (PPA), or Eaton's acid (Scheme 1).[12,19,20] In 2006, Nadaraj *et al.* demonstrated the use of several other catalysts (*e.g.* PTSA, $ZnCl_2$, $AlCl_3$ and PPA) in the synthesis of acridones under microwave irradiation.[21] Recently, Zhang *et al.* reported the intramolecular acylation of *N*,*N*-diphenylanthranilic acids in the presence of $BF_3.Et_2O$, under conventional conditions (Scheme 1, top panel),[22] however, they did not explore the substrate scope of the reaction. To date, there has not been any report of synthetic method for acridones under a non-conventional pathway using microwave irradiation in the presence of $BF_3.Et_2O$.

The currently available methods for the synthesis of acridones, which lack either the aryl or alkyl moiety at *N*-10 position of the middle ring, have some limitations, such as low yields, long reaction times, functional group intolerance, harsh reaction conditions, usage of larger amount of catalysts and, solvents and tedious workup procedures. An efficient and improved synthetic method for the synthesis of acridones to overcome the aforementioned disadvantages is highly desirable but remains a challenge for organic chemists. In our ongoing drug discovery program to produce new antimalarial chemotypes, our synthetic efforts focused on the development of new and efficient synthetic methods towards the generation of a large library of antimalarial acridones. In this work we report a facile, versatile, eco-friendly, and cost-effective synthetic method that is microwave-assisted for the synthesis of various acridones. In addition, we report the potent antimalarial activities of the newly generated acridones.

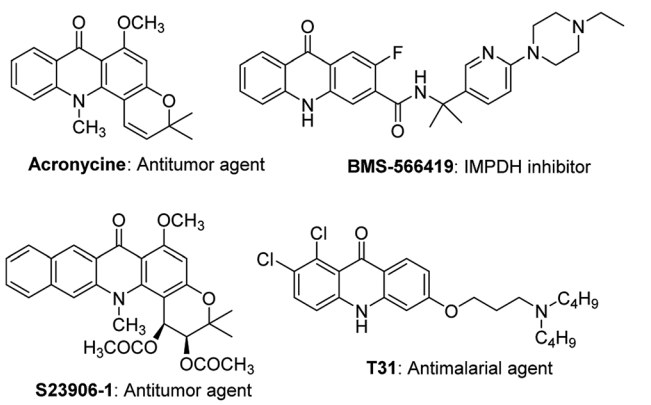


Fig. 1 Biologically active natural and synthetic acridones.

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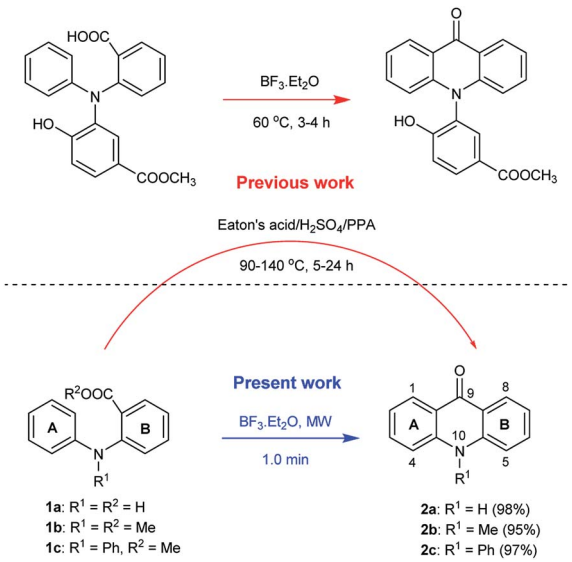
† Electronic supplementary information (ESI) available: Copies of $^1$H and $^{13}$C-NMR spectra of the final products. See DOI: 10.1039/c9ra09478d




Scheme 1 Present and previous synthetic methods for the synthesis of acridones.

## Results and discussion

To evaluate the broad scope of boron trifluoride etherate ($BF_3.Et_2O$) as a catalyst/reagent for the synthesis of various acridones, including (10*H*)-9-acridones, *N*-alkyl-9-acridones and *N*-aryl-9-acridones, we started the initial investigation with *N*-phenylanthranilic acid (**1a**) as the pilot substrate. First a careful investigation of the reaction conditions, including reaction temperature and solvent selection was carried out without the use of microwave irradiation. No desired acridone **2a** formation was observed at room temperature under solvent free conditions, and in 1,4-dioxane, DMF and acetonitrile (Table 1, entries 1–4). However, the acridone **2a** was formed with low yield (10%) when the reaction was performed in 1,4-dioxane under reflux conditions for 6 h (Table 1, entry 5). Acridone **2a** was produced with 30% yield when the reaction was conducted under solvent free conditions at 80 °C for 24 h (Table 1, entry 6). The yield of **2a** was enhanced to 65% when the reaction was performed at 130 °C for 5 h (Table 1, entry 7).

Encouraged by these results, we next evaluated this reaction under microwave irradiation using 1,4-dioxane, DMF and acetonitrile as solvent and solvent free conditions at various temperatures (Table 1, entries 8–15). Great improvement was observed as acridone **2a** was obtained with 98% yield in the presence of $BF_3.Et_2O$ (2.0 eq.), with a short reaction time (1.0 min) (Scheme 1 and Table 1, entry 15). Remarkably, this reaction was very efficient under solvent free conditions and generated no side products. Having now changed several reaction parameters, we wished to determine whether $BF_3.Et_2O$ was still the best reagent for the model reaction, so we then screened the reaction with other Lewis acids $SnCl_4$, $TiCl_4$, $FeCl_3$, $Pd(OAc)_2$, $PdCl_2$ and $I_2$ under microwave irradiation at 150 °C (Table 1, entries 16–23). All these reactions failed to provide the desired product **2a** even at longer reaction time (3.0 min). A trace amount of the acridone **2a** was observed with $SnCl_4$ and $TiCl_4$ in 1,4-dioxane (Table 1, entries 17 and 19), however, in both cases, the reaction mixture turned into a black tar. On the basis of all of these experiments, the optimal reaction

Table 1 Screening of various reaction conditions and reagents of Friedel–Crafts intramolecular cyclization of *N*-phenylanthranilic acid (**1a**)

| Entry | Reaction conditions | Reagent (no. eq.) | Solvent | Reaction time | Yield[b] (%) **2a** |
|---|---|---|---|---|---|
| 1 | RT[a] | $BF_3.Et_2O$ (2.0) | — | 24 h | NR[c] |
| 2 | RT | $BF_3.Et_2O$ (1.0) | 1,4-Dioxane | 24 h | NR |
| 3 | RT | $BF_3.Et_2O$ (1.0) | DMF | 24 h | NR |
| 4 | RT | $BF_3.Et_2O$ (1.0) | Acetonitrile | 24 h | NR |
| 5 | 100 °C | $BF_3.Et_2O$ (1.0) | 1,4-Dioxane | 6 h | 10 |
| 6 | 80 °C | $BF_3.Et_2O$ (2.0) | — | 24 h | 30 |
| 7 | 130 °C | $BF_3.Et_2O$ (2.0) | — | 5 h | 65 |
| 8 | MW[d], 100 °C | $BF_3.Et_2O$ (1.0) | 1,4-Dioxane | 1.0 min | 10 |
| 9 | MW, 130 °C | $BF_3.Et_2O$ (1.0) | 1,4-Dioxane | 1.0 min | 20 |
| 10 | MW, 150 °C | $BF_3.Et_2O$ (1.0) | 1,4-Dioxane | 1.0 min | 45 |
| 11 | MW, 150 °C | $BF_3.Et_2O$ (1.0) | DMF | 1.0 min | NR |
| 12 | MW, 150 °C | $BF_3.Et_2O$ (1.0) | Acetonitrile | 1.0 min | 33 |
| 13 | MW, 100 °C | $BF_3.Et_2O$ (2.0) | — | 1.0 min | 25 |
| 14 | MW, 130 °C | $BF_3.Et_2O$ (2.0) | — | 1.0 min | 60 |
| **15** | **MW, 150 °C** | **$BF_3.Et_2O$ (2.0)** | **—** | **1.0 min** | **98** |
| 16 | MW, 150 °C | $SnCl_4$ (2.0) | — | 3.0 min | NR |
| 17 | MW, 150 °C | $SnCl_4$ (2.0) | 1,4-Dioxane | 3.0 min | Trace[e] |
| 18 | MW, 150 °C | $TiCl_4$ (2.0) | — | 3.0 min | NR |
| 19 | MW, 150 °C | $TiCl_4$ (2.0) | 1,4-Dioxane | 3.0 min | Trace[e] |
| 20 | MW, 150 °C | $FeCl_3$ (2.0) | 1,4-Dioxane | 3.0 min | NR |
| 21 | MW, 150 °C | $Pd(OAc)_2$ (2.0) | 1,4-Dioxane | 3.0 min | NR |
| 22 | MW, 150 °C | $PdCl_2$ (2.0) | 1,4-Dioxane | 3.0 min | NR |
| 23 | MW, 150 °C | $I_2$ (2.0) | 1,4-Dioxane | 3.0 min | NR |

[a] RT; room temperature. [b] Isolated yield. [c] NR; no reaction. [d] MW; microwave. [e] Formed black tar.

Table 2 Substrate scope of the reaction

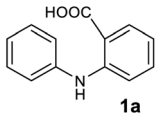
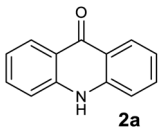
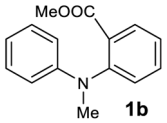
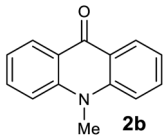
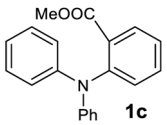
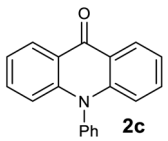
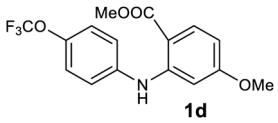
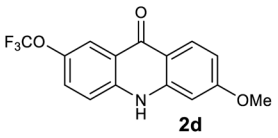
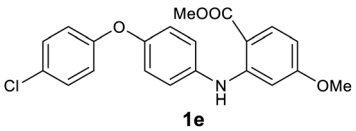
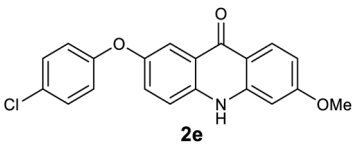
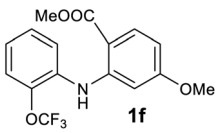
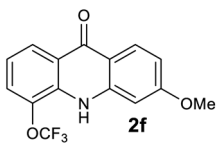
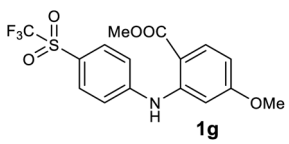
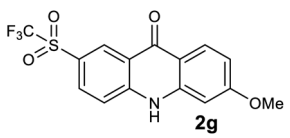
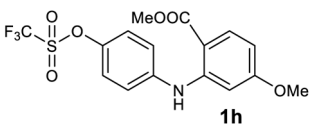
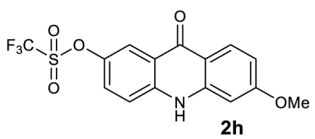
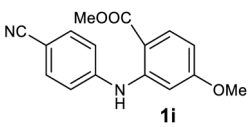
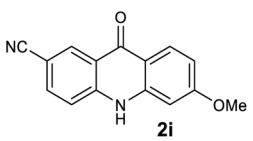
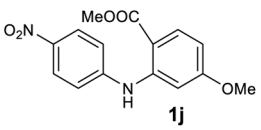
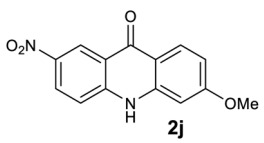
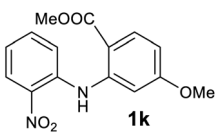
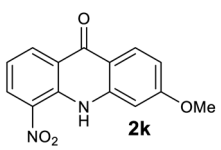
| Entry | Substrate | Product | Yield[a] (%) |
|---|---|---|---|
| 1 |  1a |  2a | 98 |
| 2 |  1b |  2b | 95 |
| 3 |  1c |  2c | 97 |
| 4 |  1d |  2d | 97 |
| 5 |  1e |  2e | 96 |
| 6 |  1f |  2f | 95 |
| 7 |  1g |  2g | 97 |
| 8 |  1h |  2h | 98 |
| 9 |  1i |  2i | 97 |
| 10 |  1j |  2j | 96 |
| 11 |  1k |  2k | 95 |

Table 2 (*Contd.*)

| Entry | Substrate | Product | Yield[a] (%) |
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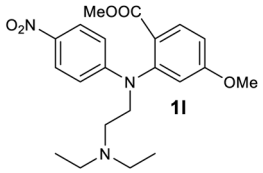
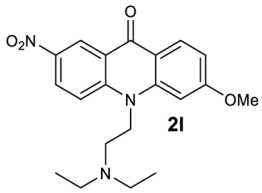
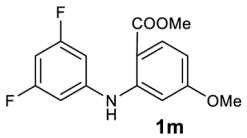
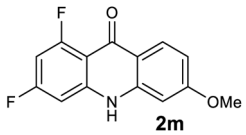
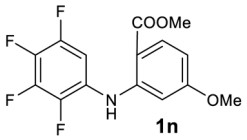
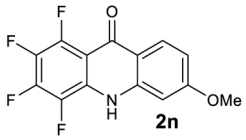
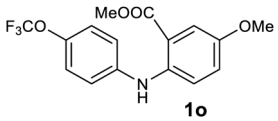
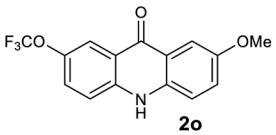
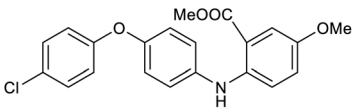
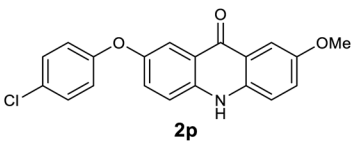
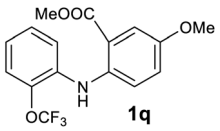
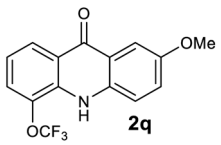
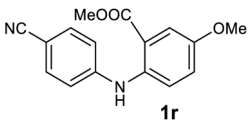
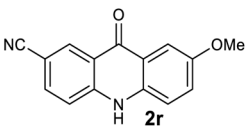
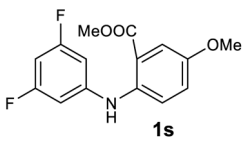
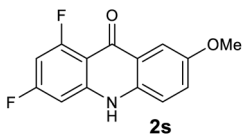
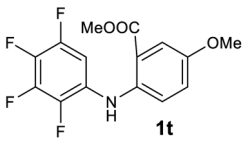
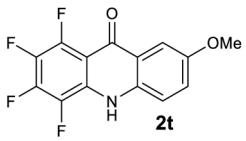
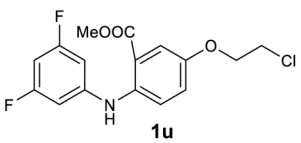
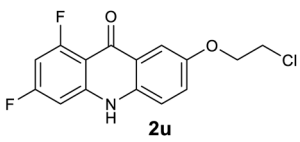
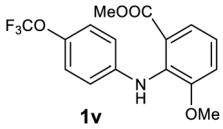
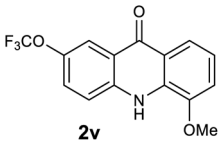
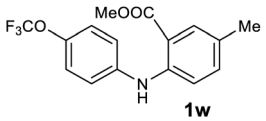
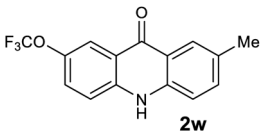
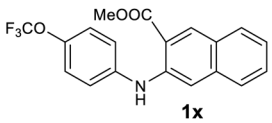
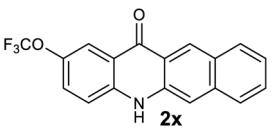
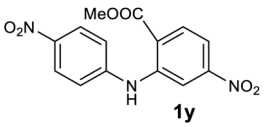
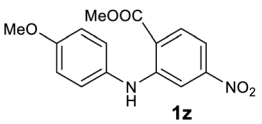
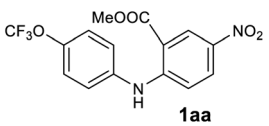
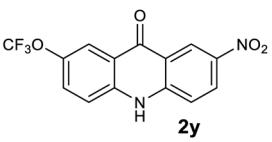
| 12 |  **1l** |  **2l** | 94 |
| 13 |  **1m** |  **2m** | 85 |
| 14 |  **1n** |  **2n** | 67 |
| 15 |  **1o** |  **2o** | 69 |
| 16 |  **1p** |  **2p** | 56 |
| 17 |  **1q** |  **2q** | 65 |
| 18 |  **1r** |  **2r** | 60 |
| 19 |  **1s** |  **2s** | 64 |
| 20 |  **1t** |  **2t** | 32 |
| 21 |  **1u** |  **2u** | 72 |

Table 2 (*Contd.*)

| Entry | Substrate | Product | Yield[a] (%) |
|---|---|---|---|
| 22 |  **1v** |  **2v** | 71 |
| 23 |  **1w** |  **2w** | 86 |
| 24 |  **1x** |  **2x** | 45 |
| 25 |  **1y** | — | NR[b] |
| 26 |  **1z** | — | NR[b] |
| 27 |  **1aa** |  **2y** | Trace[c] |

[a] Isolated yield. [b] NR; no reaction, recovered the substrate at 150 °C, but decomposed at 200 °C. [c] Trace amount of **2y** was observed along with other side products at 170 °C, and decomposed at 200 °C.

conditions were identified as no added solvent at 150 °C for 1.0 min under microwave irradiation mediated by $BF_3.Et_2O$ (2.0 eq.).

The scope of the reaction was further explored with the newly optimized conditions. Under the same reaction conditions (as in Table 1, entry 15), *N*-methyl-*N*-phenylanthranilic acid methyl ester (**1b**) and *N*,*N*-diphenylanthranilic acid methyl ester (**1c**) also provided the *N*-methyl-9-acridone (**2b**) and *N*-phenyl-9-acridone (**2c**), respectively, in high yields (Scheme 1 and Table 2, entries 2 and 3). It is noteworthy that this is a unique synthetic strategy to generate various acridones, such as (10*H*)-9-acridones, *N*-alkyl-9-acridones and *N*-aryl-9-acridones.

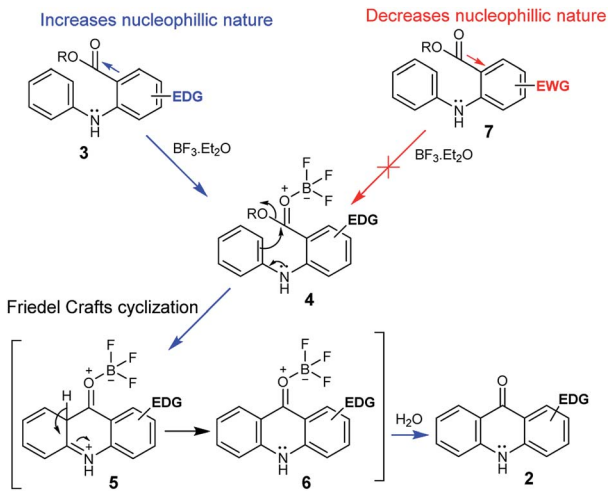
We next examined the scope of the reaction by verifying the functional groups positioned on both aryl rings (A and B) (Table 2). *N*-phenylanthranilic acid analogues **1d–1k** (Table 2, entries 4–11) bearing an electron-donating methoxy group at the *para*-position to the methyl ester on ring-B, and various electron-donating and electron-withdrawing groups on ring-A produced the corresponding acridones **2d–2k** in excellent yields (95–98%). Notably, *N*-phenylanthranilic acid methyl ester **1l** (Table 2, entry 12) bearing (diethylamino)ethyl moiety at *N*-10 position of the middle ring also responded well under the optimized conditions to provide the desired acridone **2l** in excellent yield (94%). Together, it was demonstrated that the *N*-phenylanthranilic acid analogues bearing an alkyl, aryl and alkyl-amine moieties at *N*-10 position of the middle ring, and electron-donating and electron-withdrawing groups on ring-A are well tolerated producing desired products with great efficiency. A decrease in yield was observed in the case of acridone **2m** and **2n** (Table 2, entries 13 and 14) with *N*-phenylanthranilic acid methyl ester bearing multiple fluoro substitutions on ring-A as a substrate.

Next, the effect of substituents at *meta*-position to the methyl ester on ring-B was studied. *N*-phenylanthranilic acid analogues **1o–1v** (Table 2, entries 15–22) bearing an electron-donating groups at *meta*-position to the methyl ester on ring-B and various electron-donating and electron-withdrawing groups on ring-A were converted to their corresponding acridones with good yields. However, the yields of acridones **2o–2v** were roughly 25% lesser than the corresponding positional acridones **2d–2n**. In contrast, the *N*-phenylanthranilic acid analogue (**1w**) with the methyl instead of methoxy group provided the

corresponding acridone **2w** in higher yield (86%). Of note, during the reaction with substrates **1o–1w** small amount of side products were observed (not isolated). The extended conjugation on ring-B as with substrate **1x** significantly reduced the yield of acridone **2x** (45%). Disappointingly, when substrates **1y** and **1z** bearing a strong electron-withdrawing nitro group at 6 positon of the ring-B were used, no desired acridones were obtained even at elevated temperatures (170 °C and 200 °C) and longer reaction time (3.0 min) (Table 2, entries 25 and 26). However, a trace amount of the acridone **2y** was observed (not isolated) along with other side products at 170 °C, when substrate **1aa** containing a nitro group at 7 positon of the ring-B, was used. All these results demonstrated that the electron-withdrawing groups (EWGs) on the ring-B, are not tolerated in this methodology.

The possible mechanistic pathway involves an intramolecular Friedel–Crafts cyclization, and we propose that initially the $BF_3.OEt_2$ coordinates with the oxygen of a carbonyl of the substrate **3** to form the key intermediate **4**. The following intramolecular Friedel–Crafts cyclization proceeds *via* the intermediates **5** and **6**, and the subsequent hydrolysis provides the desired acridone **2** (Scheme 2). In fact, it appears that the electron-donating group (EDG) on the ring-B of **3** significantly enhances the nucleophilic nature at the oxygen of the carbonyl group, which facilitates toward the formation of the $BF_3$ complex **4**. Conversely, electron-withdrawing group (EWG) on the ring-B of **7** diminishes the nucleophilic nature at the oxygen of the carbonyl group, which prevents the formation of $BF_3$ complex (Scheme 2). It is noteworthy that the formation of key intermediate **4** is vital in this transformation.

To demonstrate the feasibility of the present protocol, a larger-scale reaction (5 g × 5) was performed with **1a**. Significantly, our reaction has shown excellent efficiency even at a larger scale reaction with >95% yield. This reaction was also carried out under domestic microwave conditions obtaining the corresponding acridones with excellent yields.




Scheme 2 Possible reaction mechanism for $BF_3.Et_2O$ mediated Friedel–Crafts cyclization.

Table 3 *In vitro* blood-stage antimalarial activity and cytotoxicity of acridones

| | *In vitro* activity[a] ($IC_{50}$ nM) | | | |
|---|---|---|---|---|
| Compd | D6 | Dd2 | 7G8 | Cytotoxicity[a] (nM) *vs.* HepG2 |
| **2d** | 0.103 | 1.10 | 1.51 | >200000 |
| **2e** | 8.84 | 11.7 | 13.5 | >200000 |
| **2f** | 782 | 753 | 1138 | >200000 |
| **2g** | 11.6 | 11.6 | 22.2 | >200000 |
| **2h** | 57.7 | 60.7 | 56.6 | >200000 |
| **2i** | 100 | 177 | 228 | >200000 |
| **2j** | 84.1 | 98.1 | 35.0 | >200000 |
| **2l** | 405 | 684 | 462 | 12 296 |
| **2n** | 257 | 325 | 41.8 | >200000 |
| **2o** | 632 | 425 | 437 | >200000 |
| **2p** | 573 | 513 | 911 | >200000 |
| **2q** | 1493 | 1678 | >2500 | >200000 |
| **2r** | 983 | 932 | >2500 | >200000 |
| **2s** | 0.05 | 0.29 | 0.20 | >200000 |
| **2t** | >2500 | 1954 | 393 | >200000 |
| **2u** | 11.6 | 0.91 | 1.22 | >200000 |
| **2v** | 27.7 | 15.5 | 46.3 | 139435 |
| **2w** | 63.1 | 49.2 | 109 | >200000 |
| **2x** | 7.03 | 0.563 | 16.5 | >200000 |
| ATV | 0.10 | 0.10 | 0.20 | 23 160 |
| CQ | 15.0 | 163 | 172 | 37 577 |

[a] $IC_{50}$ values are the average of at least three determinations, each carried out in triplicate (±10%). D6: CQ-sensitive; Dd2: MDR strain with Old World genetic background; 7G8: MDR strain with New World genetic background; ATV: atovaquone; CQ: chloroquine.

All newly synthesized acridones were then evaluated for their *in vitro* antimalarial blood stage activity against a panel of *Plasmodium falciparum* malaria parasites with different geographic and genetic backgrounds using a SYBR Green based assay.[23] Standard antimalarials chloroquine (CQ) and atovaquone (ATV) were used as reference drugs. In parallel, the cytotoxicity of acridones was tested against human hepatic HepG2 cancer cell line.[24] The results are summarized in Table 3. Majority of the acridones have shown great antimalarial activity ($IC_{50}$ < 100 nM). Significantly, acridones **2d**, **2e**, **2g**, **2s**, **2u**, **2v** and **2x** exhibited excellent activity against all tested strains with a high therapeutic index (the ratio of cytotoxicity to antimalarial therapeutic efficacy), as demonstrated in Table 3. In general, the activity and structure–activity relationship (SAR) analyses demonstrate that the electron donating groups at 2 position of ring-A, and 6 position of ring-B are well tolerated. Conversely, the electron withdrawing groups on ring-A have an adverse effect on antimalarial potency.

## Conclusions

In conclusion, we developed an efficient, simple and convenient synthetic method for the synthesis of acridones in good to excellent yields for the first time in the presence $BF_3.Et_2O$ under microwave irradiation conditions. The advantages of this method are: simple experimental and workup procedures, short duration of reaction (1.0 min), proceeds under solvent free

conditions, the use of mild and low cost catalyst/reagent, replacement of the strong acid catalysts, and tolerance of large variety functional groups. This synthetic method has the potential to be carried out on a large scale and is suited for the generation of an extensive library of acridones and their precursors. Significantly, a number of newly generated acridones exhibited potent antimalarial activity with great selectivity. The preparation of a large library containing structurally diversified second generation acridones is currently underway in our laboratory.

## Experimental section

### General

NMR spectra were recorded on Bruker AMX-400 spectrometer at 400 MHz ($^1$H) and 100 MHz ($^{13}$C). Experiments were recorded in $CDCl_3$ and DMSO-$d_6$ at 25 °C. Chemical shifts are given in parts per million (ppm) downfield from internal standard $Me_4Si$. High-resolution mass spectrometry (HRMS) (electrospray ionization (ESI)) were recorded on a high-resolution (140 000) Q Exactive Orbitrap mass spectrometer. The microwave reactions were conducted using Biotage® Initiator+ microwave synthesizer and domestic microwave. Unless otherwise stated, all reagents and solvents were purchased from commercial suppliers and used without further purification. Reactions that required the use of anhydrous, inert atmosphere techniques were carried out under an atmosphere of argon/nitrogen. Chromatography was executed on CombiFlash instrument, using silica gel (230–400 mesh) as the stationary phase and mixtures of ethyl acetate (EtOAc) and hexane or dichloromethane (DCM) and methanol as eluents. Substrate **1a** was obtained from commercial sources and **1b** was synthesized from **1a** *via* standard methylation reaction. Substrate **1c** was synthesized from methyl 2-bromobenzoate *via* a copper-mediated substitution reaction with diphenylamine.[25] Substrates **1d–1z**, and **1aa** were synthesized using Buchwald–Hartwig cross-coupling methods.[12,26]

### Representative procedure for the synthesis of acridin-9(10H)-one (2a)[21]

$BF_3.Et_2O$ (580 μL, 4.69 mmol) was added to a microwave reaction vial containing *N*-phenylanthranilic acid (**1a**) (500 mg, 2.34 mmol). Then the reaction mixture was exposed to microwave irradiation for 1.0 min at 150 °C. After cooling to room temperature, the reaction mixture was poured into water (25 mL) and allowed to stir for 5 min. The solid material was filtered by a sintered funnel and washed with water (50 mL) and methanol (5 mL) to afford the desired acridone **2a** (448 mg. 98%). $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.74 (s, 1H), 8.23 (dd, $J$ = 8.2, 1.4 Hz, 2H), 7.73 (m, 2H), 7.54 (d, $J$ = 8.2 Hz, 2H), 7.26 (m, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 177.2, 141.4 (2C), 133.9 (2C), 126.5 (2C), 121.5 (2C), 120.9 (2C), 117.8 (2C); HRMS (ESI) calcd for $C_{13}H_{10}N_1O_1$ $(M + H)^+$ 196.0757, found 196.0754.

**10-Methylacridin-9(10*H*)-one (2b).**[14] $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 8.34 (d, $J$ = 8.2 Hz, 2H), 7.84 (m, 4H), 7.33 (m, 2H), 3.93 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 177.0, 142.8 (2C), 134.5 (2C), 127.0 (2C), 122.1 (2C), 121.6 (2C), 116.6 (2C), 34.1; HRMS (ESI) calcd for $C_{14}H_{12}N_1O_1$ $(M + H)^+$ 210.0913, found 210.0910.

**10-Phenylacridin-9(10*H*)-one (2c).**[27] $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 8.62 (d, $J$ = 7.9 Hz, 2H), 7.72 (m, 3H), 7.53 (m, 2H), 7.40 (d, $J$ = 7.5 Hz, 2H), 7.30 (m, 2H), 6.88 (d, $J$ = 8.6 Hz, 2H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 178.1, 143.2, 139.0, 133.4 (2C), 131.1 (2C), 130.0 (2C), 129.7 (2C), 127.3 (2C), 121.7 (2C), 121.6 (2C), 118.8 (2C); HRMS (ESI) calcd for $C_{19}H_{14}N_1O_1$ $(M + H)^+$ 272.1070, found 272.1066.

**6-Methoxy-2-(trifluoromethoxy)acridin-9(10*H*)-one (2d).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.86 (s, 1H), 8.13 (m, 1H), 8.03 (d, $J$ = 1.3 Hz, 1H), 7.71 (dd, $J$ = 9.0, 2.6 Hz, 1H), 7.61 (d, $J$ = 9.0 Hz, 1H), 6.90 (m, 2H), 3.91 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.6, 164.1, 143.3, 142.6, 140.0, 128.4, 127.2, 122.0, 121.1, 120.0, 117.5, 114.9, 112.7, 98.4, 56.0; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_1O_3$ $(M + H)^+$ 310.0686, found 310.0681.

**2-(4-Chlorophenoxy)-6-methoxyacridin-9(10*H*)-one (2e).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.75 (s, 1H), 8.10 (d, $J$ = 8.9 Hz, 1H), 7.65 (d, $J$ = 2.8 Hz, 1H), 7.55 (m, 1H), 7.51 (m, 1H), 7.45 (m, 2H), 7.09 (dd, $J$ = 6.8, 2.2 Hz, 2H), 6.87 (m, 2H), 3.90 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.6, 163.8, 156.5, 150.9, 143.2, 138.0, 130.4 (2C), 128.4, 127.7, 126.4, 121.8, 120.6 (2C), 120.0, 114.9, 113.9, 112.3, 98.3, 55.9; HRMS (ESI) calcd for $C_{20}H_{15}Cl_1N_1O_3$ $(M + H)^+$ 352.0735, found 352.0733.

**3-Methoxy-5-(trifluoromethoxy)acridin-9(10*H*)-one (2f).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.32 (s, 1H), 8.22 (d, $J$ = 8.1 Hz, 1H), 8.14 (d, $J$ = 8.9 Hz, 1H), 7.80 (d, $J$ = 7.8 Hz, 1H), 7.39 (d, $J$ = 2.1 Hz, 1H), 7.30 (m, 1H), 6.91 (dd, $J$ = 8.9, 2.1 Hz, 1H), 3.91 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.5, 164.2, 143.4, 136.6, 134.4, 128.3, 125.6, 125.2, 123.0, 122.1, 120.8, 115.4, 113.1, 99.3, 56.0; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_1O_3$ $(M + H)^+$ 310.0686, found 310.0679.

**6-Methoxy-2-((trifluoromethyl)sulfonyl)acridin-9(10*H*)-one (2g).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.40 (s, 1H), 8.75 (d, $J$ = 2.1 Hz, 1H), 8.20 (m, 2H), 7.78 (d, $J$ = 8.9 Hz, 1H), 7.00 (dd, $J$ = 8.9, 2.3 Hz, 1H), 6.95 (d, $J$ = 2.2 Hz, 1H), 3.93 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.3, 164.7, 146.5, 143.1, 132.8, 132.0, 128.7, 121.6, 120.7, 120.3, 120.2, 116.1, 113.6, 99.7, 56.2; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_1O_4S_1$ $(M + H)^+$ 358.0355, found 358.0351.

**6-Methoxy-9-oxo-9,10-dihydroacridin-2-yl-trifluoromethanesulfonate (2h).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.96 (s, 1H), 8.12 (m, 2H), 7.81 (dd, $J$ = 9.2, 3.0 Hz, 1H), 7.65 (d, $J$ = 9.2 Hz, 1H), 6.92 (d, $J$ = 2.4 Hz, 1H), 6.90 (s, 1H), 3.91 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.3, 164.2, 143.5, 143.3, 140.7, 128.4, 126.9, 121.2, 120.4, 120.3, 118.2, 115.0, 112.9, 98.7, 56.0; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_1O_5S_1$ $(M + H)^+$ 374.0305, found 374.0300.

**6-Methoxy-9-oxo-9,10-dihydroacridine-2-carbonitrile (2i).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.05 (s, 1H), 8.51 (d, $J$ = 1.9 Hz, 1H), 8.14 (d, $J$ = 8.9 Hz, 1H), 7.99 (dd, $J$ = 8.7, 2.0 Hz, 1H), 7.58 (d, $J$ = 8.7 Hz, 1H), 6.94 (m, 2H), 3.91 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.2, 164.4, 143.6, 143.2, 135.0, 132.3, 128.6, 120.7, 119.4, 119.0, 115.9, 113.0, 103.3, 99.1, 56.1; HRMS (ESI) calcd for $C_{15}H_{11}N_2O_2$ $(M + H)^+$ 251.0815, found 251.0812.

**6-Methoxy-2-nitroacridin-9(10H)-one (2j).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 8.92 (d, $J$ = 2.5 Hz, 1H), 8.42 (dd, $J$ = 9.2, 2.6 Hz,

1H), 8.13 (d, $J$ = 8.9 Hz, 1H), 7.60 (d, $J$ = 9.2 Hz, 1H), 6.96 (dd, $J$ = 9.0, 2.0 Hz, 1H), 6.92 (d, $J$ = 1.9 Hz, 1H), 3.91 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.7, 164.5, 145.0, 143.1, 141.2, 128.6, 127.5, 123.3, 119.9, 119.0, 115.6, 113.4, 99.4, 56.1; HRMS (ESI) calcd for $C_{14}H_{11}N_2O_4$ $(M + H)^+$ 271.0713, found 271.0709.

**3-Methoxy-5-nitroacridin-9(10*H*)-one (2k).**[28] $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.37 (s, 1H), 8.63 (m, 2H), 8.09 (d, $J$ = 8.9 Hz, 1H), 7.62 (d, $J$ = 2.4 Hz, 1H), 7.39 (t, $J$ = 8.0 Hz, 1H), 6.94 (dd, $J$ = 8.9, 2.4 Hz, 1H), 3.90 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.1, 164.6, 142.8, 135.5, 135.4, 135.0, 131.5, 128.2, 123.8, 120.4, 115.4, 114.0, 101.0, 56.3; HRMS (ESI) calcd for $C_{14}H_{11}N_2O_4$ $(M + H)^+$ 271.0713, found 271.0710.

**10-(2-(Diethylamino)ethyl)-6-methoxy-2-nitroacridin-9(10*H*)-one (2l).** $^1$H NMR ($CDCl_3$, 400 MHz) $\delta$ 9.23 (d, $J$ = 2.8 Hz, 1H), 8.37 (m, 2H), 7.53 (d, $J$ = 9.5 Hz, 1H), 6.89 (m, 2H), 4.36 (t, $J$ = 7.3 Hz, 2H), 3.90 (s, 3H). 2.85 (t, $J$ = 7.3 Hz, 2H), 2.62 (q, $J$ = 7.2 Hz, 4H), 1.02 (t, $J$ = 7.2 Hz, 6H); $^{13}$C NMR ($CDCl_3$, 100 MHz) $\delta$ 175.7, 165.0, 145.4, 143.5, 141.2, 130.0, 127.3, 124.2, 121.5, 116.9, 115.9, 111.2, 98.9, 55.7, 50.0, 47.9 (2C), 46.8, 12.1 (2C); HRMS (ESI) calcd for $C_{20}H_{24}N_3O_4$ $(M + H)^+$ 370.1761, found 370.1758.

**1,3-Difluoro-6-methoxyacridin-9(10*H*)-one (2m).**[12] $^1$H-NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.78 (s, 1H), 8.06 (d, $J$ = 8.9 Hz, 1H), 7.02–6.93 (m, 2H), 6.88 (dd, $J$ = 8.9, 2.3 Hz, 1H), 6.82 (d, $J$ = 2.1 Hz, 1H), 3.89 (s, 3H). HRMS (ESI) calcd for $C_{14}H_{10}F_2N_1O_2$ $(M + H)^+$ 262.0674, found 262.0672.

**1,2,3,4-Tetrafluoro-6-methoxyacridin-9(10*H*)-one (2n).** $^1$H-NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.75 (s, 1H), 8.07 (d, $J$ = 9.0 Hz, 1H), 7.21 (d, $J$ = 2.2 Hz, 1H), 6.94 (dd, $J$ = 9.0, 2.3 Hz, 1H), 3.89 (s, 3H); HRMS (ESI) calcd for $C_{14}H_8F_4N_1O_2$ $(M + H)^+$ 298.0486, found 298.0484.

**2-Methoxy-7-(trifluoromethoxy)acridin-9(10*H*)-one (2o).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.00 (s, 1H), 8.06 (s, 1H), 7.72 (dd, $J$ = 9.0, 2.5 Hz, 1H), 7.65 (d, $J$ = 9.1 Hz, 1H), 7.61 (d, $J$ = 2.9 Hz, 1H), 7.56 (d, $J$ = 9.0 Hz, 1H), 7.45 (dd, $J$ = 9.1, 2.9 Hz, 1H), 3.87 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 176.0, 154.8, 142.5, 139.5, 136.1, 127.3, 125.3, 122.0, 121.0, 120.4, 119.9, 119.4, 117.4, 105.1, 55.8; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_1O_3$ $(M + H)^+$ 310.0686, found 310.0681.

**2-(4-Chlorophenoxy)-7-methoxyacridin-9(10*H*)-one (2p).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.89 (s, 1H), 7.68 (d, $J$ = 2.1 Hz, 1H), 7.58 (m, 3H), 7.43 (m, 4H), 7.08 (d, $J$ = 8.7 Hz, 2H), 3.84 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 176.0, 156.5, 154.6, 150.7, 137.6, 136.1, 130.4 (2C), 127.7, 126.8, 125.1, 120.7, 120.6 (2C), 120.5, 120.4, 119.8, 113.6, 105.0, 55.8; HRMS (ESI) calcd for $C_{20}H_{15}Cl_1N_1O_3$ $(M + H)^+$ 352.0735, found 352.0731.

**2-Methoxy-5-(trifluoromethoxy)acridin-9(10*H*)-one (2q).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.48 (s, 1H), 8.25 (t, $J$ = 7.3 Hz, 1H), 7.92 (d, $J$ = 9.2 Hz, 1H), 7.81 (m, 1H), 7.63 (d, $J$ = 3.0 Hz, 1H), 7.46 (dd, $J$ = 9.1, 3.0 Hz, 1H), 7.29 (t, $J$ = 8.0 Hz, 1H), 3.87 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 176.0, 155.1, 136.9, 136.0, 133.9, 125.7, 125.2, 125.1, 122.1, 122.0, 121.6, 120.5, 120.4, 105.2, 55.9; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_1O_3$ $(M + H)^+$ 310.0686, found 310.0680.

**7-Methoxy-9-oxo-9,10-dihydroacridine-2-carbonitrile (2r).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 12.16 (s, 1H), 8.55 (d, $J$ = 1.9 Hz, 1H), 7.98 (dd, $J$ = 8.8, 2.0 Hz, 1H), 7.61 (dd, $J$ = 6.6, 3.6 Hz, 2H), 7.55 (d, $J$ = 9.0 Hz, 1H), 7.46 (dd, $J$ = 9.0, 2.9 Hz, 1H), 3.87 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 175.8, 155.4, 142.8, 135.8, 134.8, 132.6, 125.4, 122.1, 120.2, 119.5, 119.4, 119.3, 105.6, 103.0, 55.9; HRMS (ESI) calcd for $C_{15}H_{11}N_2O_2$ $(M + H)^+$ 251.0815, found 251.0812.

**1,3-Difluoro-7-methoxyacridin-9(10*H*)-one (2s).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.88 (s, 1H), 7.56 (d, $J$ = 2.8 Hz, 1H), 7.47 (d, $J$ = 9.0 Hz, 1H), 7.40 (dd, $J$ = 9.0, 2.9 Hz, 1H), 7.03 (dd, $J$ = 10.3, 2.3 Hz, 1H), 6.95 (m, 1H), 3.85 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 174.5, 155.1, 143.7, 135.3, 124.7, 122.7, 119.3, 105.7, 98.8, 98.6, 97.6, 97.4, 97.1, 55.9; HRMS (ESI) calcd for $C_{14}H_{10}F_2N_1O_2$ $(M + H)^+$ 262.0674, found 262.0672.

**1,2,3,4-Tetrafluoro-7-methoxyacridin-9(10*H*)-one (2t).** $^1$H-NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.90 (s, 1H), 7.76 (d, $J$ = 9.1 Hz, 1H), 7.54 (d, $J$ = 2.6 Hz, 1H), 7.45 (dd, $J$ = 9.1, 2.8 Hz, 1H), 3.86 (s, 3H); HRMS (ESI) calcd for $C_{14}H_8F_4N_1O_2$ $(M + H)^+$ 298.0486, found 298.0484.

**7-(2-Chloroethoxy)-1,3-difluoroacridin-9(10*H*)-one (2u).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.91 (s, 1H), 7.58 (s, 1H), 7.45 (m, 2H), 7.03 (d, $J$ = 10.3 Hz, 1H), 6.95 (t, $J$ = 11.4 Hz, 1H), 4.34 (t, $J$ = 4.5 Hz, 2H), 3.99 (t, $J$ = 4.5 Hz, 2H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 174.5, 153.7, 143.6, 135.6, 124.9, 122.6, 119.4, 107.6, 106.9, 98.8, 98.6, 97.7, 97.4, 97.2, 68.9, 43.5; HRMS (ESI) calcd for $C_{15}H_{11}Cl_1F_2N_1O_2$ $(M + H)^+$ 310.0441, found 310.0437.

**5-Methoxy-2-(trifluoromethoxy)acridin-9(10*H*)-one (2v).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.50 (s, 1H), 8.08 (t, $J$ = 9.2 Hz, 2H), 7.81 (d, $J$ = 8.2 Hz, 1H), 7.75 (dd, $J$ = 9.1, 2.1 Hz, 1H), 7.37 (d, $J$ = 7.7 Hz, 1H), 7.24 (t, $J$ = 8.0 Hz, 1H), 4.06 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 176.5, 148.4, 142.9, 139.8, 132.3, 127.4, 122.0, 121.8, 121.4, 121.1, 121.0, 117.4, 117.2, 113.2, 56.7; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_1O_3$ $(M + H)^+$ 310.0686, found 310.0682.

**2-Methyl-7-(trifluoromethoxy)acridin-9(10*H*)-one (2w).**[27] $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.93 (s, 1H), 8.05 (m, 2H), 7.73 (dd, $J$ = 6.4, 2.6 Hz, 1H), 7.65 (d, $J$ = 9.1 Hz, 1H), 7.62 (dd, $J$ = 8.5, 2.0 Hz, 1H), 7.49 (d, $J$ = 8.5 Hz, 1H), 2.43 (s, 3H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 176.4, 142.5, 139.9, 139.4, 135.9, 131.4, 127.5, 125.4, 122.0, 120.7, 120.3, 119.5, 118.0, 117.5, 21.0; HRMS (ESI) calcd for $C_{15}H_{11}F_3N_1O_2$ $(M + H)^+$ 294.0736, found 294.0732.

**2-(Trifluoromethoxy)benzo[*b*]acridin-12(5*H*)-one (2x).** $^1$H NMR (DMSO-$d_6$, 400 MHz) $\delta$ 11.89 (s, 1H), 8.95 (s, 1H), 8.18 (d, $J$ = 8.3 Hz, 1H), 8.09 (d, $J$ = 1.7 Hz, 1H), 8.02 (d, $J$ = 8.5 Hz, 1H), 7.97 (s, 1H), 7.77 (dd, $J$ = 9.0, 2.7 Hz, 1H), 7.65 (d, $J$ = 9.2 Hz, 1H), 7.60 (t, $J$ = 7.3 Hz, 1H), 7.45 (t, $J$ = 7.3 Hz, 1H); $^{13}$C NMR (DMSO-$d_6$, 100 MHz) $\delta$ 178.0, 142.0, 141.3, 138.0, 136.4, 130.1, 129.2, 128.4, 127.8, 127.0, 124.9, 122.0, 121.0, 119.9, 119.5, 119.2, 118.0, 112.8; HRMS (ESI) calcd for $C_{18}H_{11}F_3N_1O_2$ $(M + H)^+$ 330.0736, found 330.0733.

### *In vitro* blood stage antimalarial activity assay

*In vitro* antimalarial activity was determined by the Malaria SYBR Green I-based Fluorescence (MSF) assay described previously with minor modifications, and expressed as the compound concentration inhibiting growth by 50% ($IC_{50}$).

**HepG2 cytotoxicity assay**

The general cytotoxic effect of acridones on host mammalian cells was assessed by functional assay as described previously, using hepatic HepG2 cells. Drugs were dissolved in DMSO to make 10 mM stock solutions. Human hepatocarcinoma cells (HepG2) were maintained on RPMI-1640 medium supplemented with 10% fetal bovine serum at 37 °C in a humidified 5% $CO_2$ atmosphere. Cells were seeded at a density of $2 \times 10^4$ per well in 96-well flat-bottom tissue culture plates containing complete medium in a total volume of 160 μL per well. The cells were allowed to attach at 37 °C overnight. On the following day, drug solutions (40 μL per well) were serially diluted with complete culture medium across the plate. The plates were then incubated at 37 °C and 5% $CO_2$ for another 24–36 h. Afterward, the medium was aspirated and replaced with complete RPMI medium (200 μL per well), and the plates were incubated for an additional 24 h at 37 °C and 5% $CO_2$. An aliquot of a stock solution of resazurin (Alamar Blue, prepared in 1 × PBS) was then added at 20 μL per well (final concentration 10 μM), and the plates were returned to the incubator for 3 h. After this period, fluorescence in each well, indicative of cellular redox activity was measured in a Gemini EM plate reader with excitation wavelength at 560 nm and emission wavelength at 590 nm. $IC_{50}$ values were determined by nonlinear regression analysis of logistic concentration–fluorescence intensity curves (GraphPad Prism software).

## Conflicts of interest

There are no conflicts to declare.

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