JOC The Journal of Organic Chemistry

pubs.acs.org/joc Note

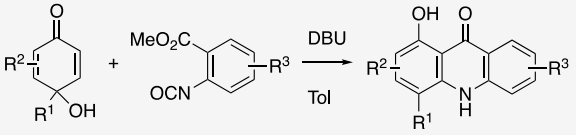
One-Pot Synthesis of 1-Hydroxyacridones from *para*-Quinols and *ortho*-Methoxycarbonylaryl Isocyanates

Jing Wu, Jinzhu Zhang, Ruben Soto-Acosta, Lili Mao, Jiahui Lian, Kenny Chen, Guy Pillon, Guoqi Zhang, Robert J. Geraghty, and Shengping Zheng*

Cite This: *J. Org. Chem.* 2020, 85, 4515−4524 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: A variety of substituted acridones were synthesized via a one-pot, metal-free cascade reaction. In this event, the DBU-mediated addition between quinols and *ortho*-methoxycarbonylaryl isocyanates formed a bicyclic oxazolidinone, followed by a sequence of intramolecular condensation, tautomerization, and decarboxylation, which led to the formation of acridones. The acridones showed mild activity against the human cytomegalovirus.



Acridones are a subclass of acridines with a carbonyl group at the 9 position (10*H*-acridin-9-one). Acridines have become well-known anticancer agents.[1−3] Acridones are key intermediates for the synthesis of acridines.[4] Moreover, acridones are important synthetic targets because of their selective inhibition of diverse human pathogenic viruses.[5−9] In recent years, both naturally occurring and synthetic 1-hydroxyacridones were found to be selective inhibitors of both DNA and RNA viruses. For example, citrusinine-I exhibits potent activity against the herpes simplex virus (HSV);[10] compound A is an inhibitor of the human cytomegalovirus (HCMV);[6] compound B shows inhibitory activity of the bovine viral diarrhea virus (BVDV) and hepatitis C virus (HCV);[8] and RD6-5071 is a selective anti-HIV agent[11] (Figure 1). Though the mechanism of action of these antiviral compounds is not known, it seems that the hydroxyl group and the carbonyl group are critical for the bioactivity from the pattern of the substitution.[12]

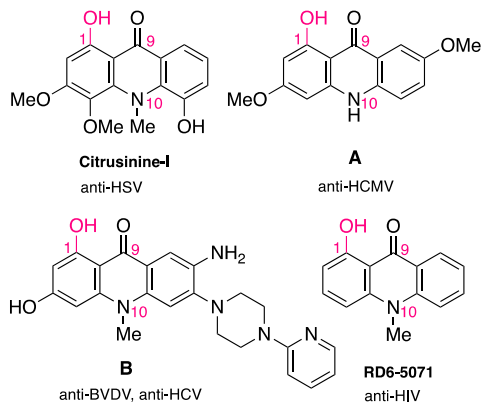
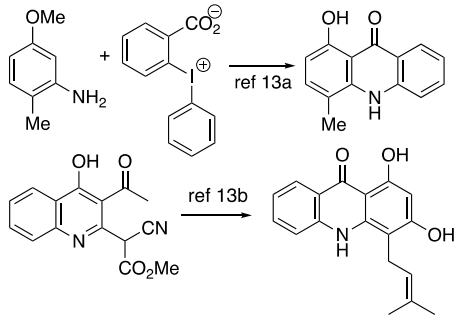


Figure 1. Antiviral 1-hydroxyacridones.

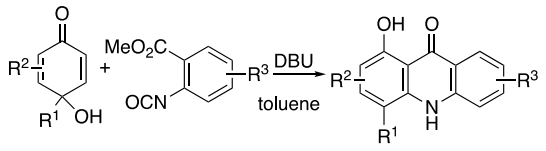
The synthesis of multiple substituted 1-hydroxyacridones is still challenging; for example, the known synthetic routes to 1-hydroxy-4-alkylacridone are lengthy and low-yielding[13] (Scheme 1a). We report herein a rapid synthesis of substituted 1-hydroxyacridones via a one-pot condensation of quinols and

Scheme 1. Synthetic Routes to 1-Hydroxy-4-alkylacridones

a. previous work



b. this work



Received: December 9, 2019
Published: February 19, 2020

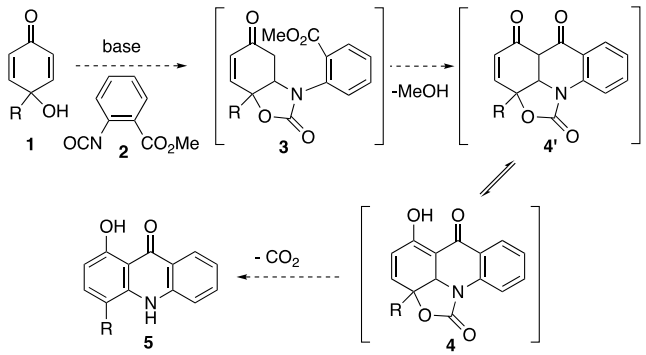
https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524

ortho-(methoxycarbonyl)aryl isocyanates via a carbamation/Michael addition/mixed Claisen condensation/decarboxylative aromatization cascade (Scheme 1b). It should be noted that our method is suitable for the synthesis of substituted 4-alkyl or 4-arylacridones, and hence, it could not be applied to the synthesis of the structures in Figure 1.

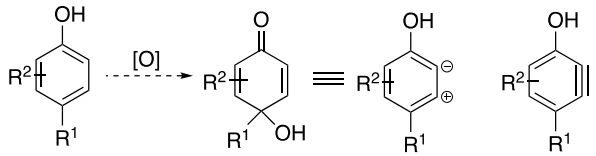
Quinols are 2,5-cyclohexadienones, which serve as useful synthetic building blocks.[14] They can be made in one step via the dearomatization of *para*-substituted phenols.[15,16] Recently, we were interested in new methodology development from the nucleophilic addition to 2,5-cyclohexadienones.[16−19] From our preliminary results in the synthesis of oxazolidinones from isocyanates,[16] we envisioned that acridones could be synthesized from quinols and commercial *ortho*-methoxycarbonylphenyl isocyanate via a carbamation/Michael addition/mixed Claisen condensation/decarboxylative aromatization sequence (Scheme 2a). In our strategy, quinols act as a

Scheme 2. Synthetic Strategy

a. Proposed synthesis of 1-hydroxyacridones



b. Quinols act as regiospecifically differentiated benzyne equivalents.



regiospecifically differentiated equivalent of benzynes[20−25] (Scheme 2b). In contrast to substituted benzynes,[26] quinols are more readily prepared and have controlled regiospecific chemistry.

To test our idea, the addition of 0.15 equiv of 1,8-diazabicycloundecene (DBU) to a solution of premixed quinol **1a** (R═CH_3) and commercially available *ortho*-(methoxycarbonyl)phenyl isocyanate **2** in cold CH_2Cl_2 and a further reaction at room temperature for 1 h resulted in complete consumption of **1a** to form the Michael addition intermediate **3a** (R═CH_3); no new spot appeared on the thin-layer chromatography (TLC) after stirring 6 h at room temperature or under reflux for another 20 h. Eventually, after removal of the solvent, the addition of 1.1 equiv of NaOMe in THF to the reaction mixture at room temperature and refluxing for 6 h produced acridone **5a** (R═CH_3) in a trace amount and enol **4a** (R═CH_3) in 42% yield along with recovery of 19% of oxazolidinone **3a** (R═CH_3) (see Table S1 in the Supporting Information). When **4a** was treated with DBU and refluxed in toluene, **5a** was obtained in a quantitative yield. Structures of **4a** and **5a** were confirmed by X-ray diffraction analysis (cf the Supporting Information).

With the initial results in hand, we focused our efforts on the effective conversion of **1** to **5** via a homogeneous one-pot procedure, and the results are summarized in Table 1. When excess NaOMe was used after the formation of oxazolidinone **3a**, 79% of **4a** was obtained along with 3% of acridone **5a** (entry 1). An improvement followed by applying toluene as the solvent (entry 2), the addition of a stoichiometric amount DBU seemed to facilitate the formation of enol **4a** and the following decarboxylation to afford acridone **5a** (entries 3 and 4); microwave (μW) radiation provided a comparable yield with a higher efficiency (entry 5), whereas bulkier alkyl substituents resulted in lower yields of acridones **5b** and **5c** (entries 7 and 10). Heating under reflux failed to improve yields of **5b** and **5c** even with the application of prolonged reaction times (entries 8 and 11). Optimization led to the use of sealed tube conditions at 130 °C for 6 h and proved to be reliable to deliver acridones **5a−c** (entries 6, 9, and 12).

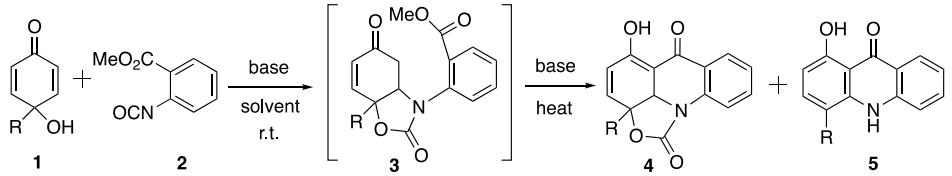
Under the optimized reaction conditions (sealed tube, 130 °C, 6 h, toluene) using a wide range of quinols, we explored the scope of this one-pot acridone synthesis with *ortho*-substituted phenyl isocyanate **2a**. Representative results are summarized in Table 2. Generally, 1-hydroxyacridones **5a−5i** were formed with good to excellent overall yields (entries 1−9). For sterically hindered quinols **1j** and **1k** (entries 10 and 11), acridones **5j** and **5k** were obtained in moderate yields. For quinol **1l**, the desired acridone **5l** was obtained in a good yield (entry 12). Unlike quinol **11**, where Michael addition occurred at the less substituted double bond, Michael addition took place at the more substituted sp^2 hybridized carbon of quinol **1m**, presumably due to the release of the ring strain,[27] to afford a pentacyclic product **4m** (entry 13). For quinols **1n−1q** with a substituent other than the alkyl group on the double bond, acrdiones **5n−5q** were obtained in moderate to good yields. For hydroxylcyclohexenones **1r** and **1s**, acridones **5r** and **5s** were obtained in moderate to good yields through an elimination/aromatization mechanism (entries 18 and 19).

Annelated quinol **1t** afforded acridone **5t** in a good yield[27b] (entry 20). However, quinols **1u** and **1v** led to oxazoloacridones **4u** and **4v** in moderate yields (entries 21 and 22). Compounds **4u** and **4v** were obtained because the aromatization could not be easily achieved. For quinol **1w** with a strong electron-withdrawing methoxycarbonyl, acridone **5a** was formed in 64% yield; presumably, the Michael addition occurred on the more electrophilic double bond, followed by demethoxycarboxylation through a methanol attack to produce the acridone **5a** instead (entry 23). Although tetracyclic intermediates were isolated (entries 21 and 22) when the α-carbon or β-carbon was substituted by a methyl group so that the decarboxylation/aromatization step was blocked; decarboxylative demethylation could occur when the system was overheated to give 3,4-dimethyl acridone **5i** from 3,4,5 trimethyl quinol **1v**. These results strongly support the proposed mechanism.

We further investigated the substrate scope of this reaction in terms of the substituted phenyl isocyanates. To this end, commercial anilines were transformed into the corresponding isocyanates, which were trapped with quinol **1b** to furnish the acridone transformation. A typical procedure involved the reaction of a disubstituted aniline with 0.4 equiv of triphosgene in a mixture of saturated aqueous $NaHCO_3$ and CH_2Cl_2 in an

https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524

Table 1. Optimization of the Reaction Conditions



entry	quinol 1 (R)	base (equiv)	solvent	temp (°C)[a]	condition/time (h)[b]	% yield of 5 (4)[c]
1[d]	R = Me	DBU (0.15)/NaOMe (2.2)	CH_2Cl_2/THF	RT/66	reflux (12)	3 (79)
2	R = Me	DBU (0.15)	tol	RT/111	reflux (12)	44 (trace)[e]
3	R = Me	DBU (1.1)	tol	RT/111	reflux (12)	76 (trace)[f]
4	R = Me	DBU (2.2)	tol	RT/111	reflux (12)	87
5	R = Me	DBU (2.2)	tol	RT/115	μW (1)	81
6	R = Me	DBU (2.2)	tol	RT/130	sealed tube (6)	96
7	R = Et	DBU (2.2)	tol	RT/115	μW (1)	83 (trace)
8	R = Et	DBU (2.2)	tol	RT/111	reflux (20)	60 (13)
9	R = Et	DBU (2.2)	tol	RT/130	sealed tube (6)	95
10	R = c-Hex	DBU (2.2)	tol	RT/115	μW (1)	54 (28)
11	R = c-Hex	DBU (2.2)	tol	RT/111	reflux (20)	67 (18)
12	R = c-Hex	DBU (2.2)	tol	RT/130	sealed tube (6)	92

[a]The reaction was performed at room temperature until the formation of **3** along with complete consumption of **1**, monitored by TLC. An elevated temperature was then applied with a different heat source. [b]The time required for the transformation of **3** to **5**. [c]Isolated yields of **5** and **4** from silica gel column chromatography purification. [d]See Table S1 in Supporting Information for a detailed experimental procedure. [e]**3a** was isolated in 13% yield. [f]**3a** was isolated in 5% yield.

ice bath for 1 h, followed by the separation and evaporation of the methylene chloride solvent and then the addition of quinol **1b** and DBU in toluene to the *in situ* made arylisocyanate under the protocol reported above. The reaction proceeded smoothly to afford the acridones **5x**–**5z** in good overall yields (Scheme 3).

We conducted a preliminary screening of the antiviral activity of several compounds synthesized by this method. It is found that some, notably **5a**, exhibited anti-HCMV activity at 10 μM, albeit with a slight reduction in cell viability. Other compounds, such as **5c** and **5h**, inhibited HCMV with no effect on cell viability (Table 3). These preliminary results suggest, that along with the bulkiness of the alkyl substituents, the nature and position of functionalities can be optimized for antiviral effects. We envision that such compounds could lead to the development of a new class of anti-HCMV molecules with potential benefits against drug-resistant cell strains.

In summary, we have developed a highly efficient synthetic pathway to acridones from a wide range of quinols in moderate to excellent yields. This one-pot process represents a direct and practical method to 1-hydoxyl-4-alkyl/aryl-acridones from commercially available phenols in two steps. During this process, quinols act as a traceless benzyne equivalent. Furthermore, the acridones showed mild activity against the human cytomegalovirus. More work on the synthesis of various heterocycles and their antiviral activity will be reported in due course.

EXPERIMENTAL SECTION

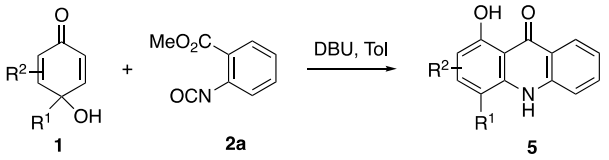
General Information. All reactions were carried out under dry nitrogen in oven-dried glassware, unless the procedure states otherwise. Anhydrous methylene chloride (CH_2Cl_2) was distilled from phosphorus pentoxide, toluene (tol) was distilled from sodium, and tetrahydrofuran (THF) was distilled from sodium under a nitrogen atmosphere. All reactions were performed under nitrogen protection, and the gas exchange was done with a nitrogen balloon and house vacuum. Reagents purchased from commercial sources were used as received or synthesized following literature procedures and were recrystallized if it was applicable. Reactions were monitored by thin-layer chromatography (TLC), which was developed on Silicycle SiliaPlate TLC glass-backed plates with precoated silica gel 60 bearing an F-254 UV indicator and visualized by exposure to ultraviolet light or stained with ceric ammonium molybdate, followed by heating on a heat gun. Preparative thin-layer chromatography (prep TLC) was done on the same TLC plates with the proper thickness. Column chromatography was performed over silica gel with a porosity of 60 Å and a particle size of 40–63 μm. ^{1}H and ^{13}C NMR spectra were recorded on Bruker 400, 500, and 600 MHz spectrometers. Chemical shifts (δ values) were reported in ppm with a reference to residual solvent peaks ($CHCl_3$ in $CDCl_3$, 7.26 ppm; DMSO in $(CD_3)_2SO$, 2.54 for ^{1}H NMR, 77.36 and 40.45 ppm for ^{13}C NMR, respectively). Mass spectrometric data were measured by the late Dr. Cliff Soll and Dr. Barney Yoo at the Hunter College mass spectrometry facility and taken on an Agilent 6520A Q-TOF spectrometer using electrospray ionization. The X-ray crystallography experiments were performed on a Bruker Kappa X8 Apex II diffractometer by Dr. Michelle Neary at the Hunter College X-ray facility and on a Bruker AXS Smart Apex II single-crystal diffractometer by Dr. Chunhua Hu at the Department of Chemistry, New York University. Microwave reactions were conducted on a CEM Discover SP reactor, where pressurized vessels were used, and the reaction temperature was monitored by an internal probe.

Experimental Procedures. Known quinols were prepared according to the literature procedures.[15a,16,28−32] For the reported spectral data, see: **1a**, **1b**, **1d**, **1j**;[28] **1c**;[16] **1e**, **1f**, **1g**;[29] **1h**, **1i**, **1k**, **1l**, **1n**, **1r**, **1u**;[15a] **1o**;[30] **1q**;[31] and **1s**.[32]

*General Procedure for the Synthesis of p-Quinols **1k**, **1m**, **1p**, **1t**, and **1w** (Method A).*[16] A solution of the corresponding alkylphenol (1 equiv) in MeCN/H_2O (3:1) was cooled to 0 °C in an ice bath, and phenyliodine(III) diacetate (PIDA) (1.5 equiv) was added in small portions. The reaction mixture was stirred at 0 °C until full consumption of the starting material (monitored by TLC), then diluted with EtOAc, and quenched with saturated aq $NaHCO_3$, and the layers were separated. The aqueous layer was extracted three times with EtOAc. The organic layers were combined and washed with water and brine, dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography to provide the desired product.

https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524

Table 2. Substrate Scope of Quinols



entry	quinol	product/yield	entry	quinol	product/yield
1 2 3 4 5	**1a** (R=Me) **1b** (R=Et) **1c** (R= c-Hex) **1d** (R=Pr) **1e** (R=Ph)	**5a** (R=Me)/96% **5b** (R=Et)/95% **5c** (R=c-Hex)/92% **5d** (R=Pr)/72% **5e** (R=Ph)/88%	14 15 16 17	**1n** (R=OMe) **1o** (R=F) **1p** (R=Cl) **1q** (R=Br)	**5n** (R=OMe)/87% **5o** (R=F)/79% **5p** (R=Cl)/75% **5q** (R=Br)/41%
6 7	**1f** (R = CN) **1g** (R=Br)	**5f** (R=CN)/68% **5g** (R=Br)/89%	18	**1r**	**5r**/70%
8	**1h**	**5h**/87%	19	**1s**	**5s**/57%
9	**1i**	**5i**/94%	20	**1t**	**5t**/80%
10 11	**1j** (R=H) **1k** (R=Me)	**5j** (R=H)/55% **5k** (R=Me)/42%	21	**1u**	**4u**/44%
12	**1l**	**5l**/83%	22	**1v**	**4v**/54%
13	**1m**	**4m**/84%	23	**1w**	**5a**/64%

4-Hydroxy-4-isopropyl-3-methylcyclohexa-2,5-dien-1-one (***1k***): 1.9 g, 56% yield, colorless needle-like crystals; R_f = 0.2 (EtOAc/hexane = 1:4); mp = 65−69 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (d, J = 10.2 Hz, 1H), 5.98 (dd, J = 10.2, 1.6 Hz, 1H), 5.81 (s, 1H), 4.24 (br, s, 1H), 1.97 (s, J = 6.8 Hz, 1H), 1.85 (s, 3H), 0.98 (d, J = 7.1 Hz, 3H), 0.48 (d, J = 7.0 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 186.4, 163.9, 150.3, 128.9, 126.9, 74.5, 35.3, 18.1, 16.9, 16.7; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{10}H_{14}O_2$ 167.1067, found 167.1062; [M + Na]$^+$ calcd for $C_{10}H_{12}O_2Na$ 189.0886, found 189.0882.

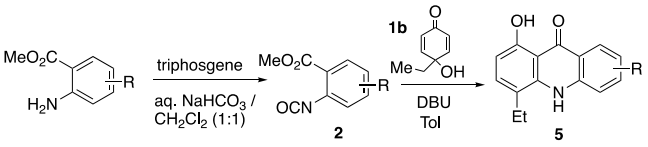
7a-Hydroxy-1,2,3,7a-tetrahydro-5H-inden-5-one (***1m***): 1.0 g, 44% yield, white solid; R_f = 0.2 (EtOAc/hexane = 1:2); mp = 74−77 °C; ^{1}H NMR (600 MHz, CDCl3) δ 6.98 (d, J = 10.0 Hz, 1H), 6.01 (d, J = 10.0 Hz, 1H), 5.90 (s, 1H), 3.07 (br s, 1H), 2.87 (t, J = 14.3 Hz, 1H), 2.46−2.41 (m, 1H), 2.26−2.18 (m, 1H), 2.04 (dd, J = 8.0, 13.4 Hz, 1H), 1.94−1.88 (m, 1H), 1.59−1.54 (m, 1H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 187.3, 170.1, 148.0, 128.6, 122.1, 73.5, 35.7, 28.8, 21.8; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_9H_{10}O_2$ 151.0754, found 151.0755.

2-Chloro-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (***1p***): 0.3 g, 57% yield, pale yellow solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.05 (d, J = 2.9 Hz, 1H), 6.90 (dd, J = 10.0, 2.9 Hz, 1H), 6.18 (d, J = 10.0 Hz, 1H), 2.82 (br s, 1H), 1.51 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $CDCl_3$) δ 178.9, 152.9, 148.5, 131.7, 126.2, 69.6, 26.9; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_7H_7ClO_2$ 159.0207, found 159.0205.

7-Hydroxy-7-methyl-1,2,3,7-tetrahydro-4H-inden-4-one (***1t***): 1.5 g, 66% yield, white solid; R_f = 0.2 (EtOAc/hexane = 1:2); mp = 48−51 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (d, J = 9.9 Hz, 1H), 5.95 (d, J = 9.9 Hz, 1H), 3.19 (br s, 1H), 2.83−2.77 (m, 1H), 2.66−2.59 (m, 1H), 2.53 (t, J = 7.5 Hz, 2H), 1.99−1.83 (m, 2H), 1.38 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 185.4, 165.7, 153.5, 136.6,

https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524

Scheme 3. Substrate Scope of Isocyanates



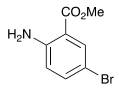
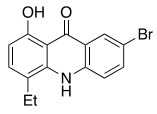
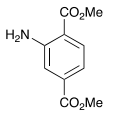
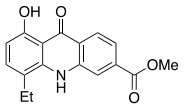
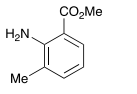
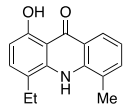
entry	aniline	product		yield
1			**5x**	82%
2			**5y**	73%
3			**5z**	85%

Table 3. Anti-HCMV Screening and Cytotoxicity of 1-Hydroxyacridones

compound	% inhibition (10 μM)[a]	% viable cells (10 μM)[a]
ganciclovir	89 ± 1.6	101 ± 3.0
letermovir[b]	86 ± 1.5	104 ± 4.6
5a	83 ± 2.7	68 ± 2.9
5c	50 ± 0.1	104 ± 3.0
5e	61 ± 2.0	77 ± 6.1
5f	17 ± 13	100 ± 2.5
5h	46 ± 3.7	96 ± 2.8
5i	58 ± 5.9	79 ± 1.4
4u	13 ± 3.0	101 ± 2.5
5x	74 ± 4.1	86 ± 1.9
5a′[c]	78 ± 0.8	76 ± 2.0

[a]Compared to DMSO-treated cells. [b]At 1 μM. [c]**5a′** is the *N*-methylation product of **5a**.

127.4, 68.1, 32.7, 29.8, 25.8, 21.8; HRMS (ESI/Q-TOF) *m*/*z* [M + H]$^+$ calcd for $C_{10}H_{12}O_2$ 165.0910, found 165.0909.

*Methyl 3-Hydroxy-3-methyl-6-oxocyclohexa-1,4-diene-1-carboxylate (**1w**).* Instead of PIDA, 1.5 equiv of [bis(trifluoroacetoxy)-iodo]benzene (PIFA) was used as an oxidant. Compound **1w**: 0.1 g, 54% yield, white solid; R_f = 0.4 (EtOAc/hexane = 1:1); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, *J* = 3.06 Hz, 1H), 6.84 (dd, *J* = 10.1, 3.1 Hz, 1H), 6.03 (d, *J* = 10.1 Hz, 2H), 3.76 (s, 3H), 3.71 (br s, 1H), 1.46 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 181.6, 164.9, 157.5, 151.7, 129.2, 127.4, 67.2, 52.7, 26.8; HRMS (ESI/Q-TOF) *m*/*z* [M + H]$^+$ calcd for $C_9H_{10}O_4$ 183.0652, found 183.0649; [M + Na]$^+$ calcd for $C_9H_{10}O_4Na$ 205.0471, found 205.0471.

For known quinols, spectroscopic data were in agreement with those previously reported in the literature. Some representative data are reported below.

*4-Hydroxy-4-methylcyclohexa-2,5-dien-1-one (**1a**):* 1.5 g, 67% yield, white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, *J* = 10.1 Hz, 2H), 6.14 (d, *J* = 10.1 Hz, 2H), 2.02 (br s, 1H), 1.49 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 185.6, 152.2, 127.7, 67.6, 27.1.

*4-Ethyl-4-hydroxycyclohexa-2,5-dien-1-one (**1b**):* 0.7 g, 63% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 10.1 Hz, 2H), 6.20 (d, *J* = 10.1 Hz, 2H), 2.43 (br s, 1H), 1.82 (q, *J* = 7.5 Hz, 2H), 0.88 (t, *J* = 7.5 Hz, 3H).

*1-Hydroxy-[1,1′-bi(cyclohexane)]-2,5-dien-4-one (**1c**):* 1.2 g, 54% yield, white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.79 (d, *J* = 10.2 Hz, 2H), 6.11 (d, *J* = 10.2 Hz, 2H), 3.15 (br s, 1H), 1.85−1.82 (m, 2H), 1.75−1.72 (m, 2H), 1.64−1.57 (m, 2H), 1.21−1.13 (m, 2H), 1.09−1.00 (m, 1H), 0.93−0.85 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 186.6, 151.6, 128.7, 72.2, 46.9, 27.3, 26.6, 26.5.

*4-Hydroxy-4-propylcyclohexa-2,5-dien-1-one (**1d**):* 0.7 g, 64% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.82 (d, *J* = 10.2 Hz, 2H), 6.19 (d, *J* = 10.2 Hz, 2H), 1.76−1.72 (m, 2H), 1.34−1.25 (m, 2H), 0.93 (t, *J* = 7.2 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 186.4, 152.9, 127.5, 69.8, 42.0, 16.9, 14.2.

*1-Hydroxy-[1,1′-biphenyl]-4(1H)-one (**1e**):* 1.8 g, 83% yield, white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49−7.47 (m, 2H), 7.39−7.36 (m, 2H), 7.34−7.31 (m, 1H), 6.90 (d, *J* = 10.0 Hz, 2H), 6.19 (d, *J* = 10.0 Hz, 2H), 3.37 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 186.4, 151.6, 138.98, 129.2, 128.7, 126.98, 125.6, 71.3.

*1′-Hydroxy-4′-oxo-1′,4′-dihydro-[1,1′-biphenyl]-4-carbonitrile (**1f**):* 0.4 g, 81% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.6 Hz, 2H), 7.62 (d, *J* = 8.6 Hz, 2H), 6.86 (d, *J* = 10.0 Hz, 2H), 6.26 (d, *J* = 10.0 Hz, 2H), 3.53 (br s, 1H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 185.3, 149.6, 144.2, 133.1, 128.1, 126.6, 118.7, 112.7, 71.2.

*4-Hydroxy-3,4-dimethylcyclohexa-2,5-dien-1-one (**1i**):* 2.2 g, 65% yield, white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.87 (d, *J* = 10.0 Hz, 1H), 6.09−6.06 (m, 1H), 5.97 (d, *J* = 1.4 Hz, 1H), 0.85 (br s, 1H), 2.08 (s, 3H), 1.44 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 186.3, 162.5, 153.2, 127.1, 126.1, 69.4, 26.3, 18.4.

*4-Hydroxy-4-isopropylcyclohexa-2,5-dien-1-one (**1j**).* Method A was followed, and $CaCO_3$ (3 equiv) was added to obtain **1j**: 72 mg, 63% yield, white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.81 (d, *J* = 10.3 Hz, 2H), 6.17 (d, *J* = 10.3 Hz, 2H), 2.85 (br s, 1H), 1.98 (sept, *J* = 6.9 Hz, 1H), 0.93 (t, *J* = 7.1 Hz, 6H).

*4a-Hydroxy-5,6,7,8-tetrahydronaphthalen-2(4aH)-one (**1l**):* 0.8 g, 58% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (d, *J* = 10.0 Hz, 1H), 5.97 (dd, *J* = 10.0, 2.0 Hz, 1H), 5.84 (t, *J* = 1.7 Hz, 1H), 3.52 (br s, 1H), 2.64 (tdd, *J* = 13.1, 4.9, 1.6 Hz, 1H), 2.22 (apparently d, *J* = 12.3 Hz, 1H), 2.05−2.00 (m, 1H), 1.97−1.82 (m, 2H), 1.58−1.54 (m, 1H), 1.32−1.18 (m, 2H).

*2-Fluoro-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (**1o**):* 0.36 g, 69% yield, orange greenish solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.89 (dd, *J* = 10.0, 2.6 Hz, 1H), 6.41 (dd, *J* = 12.3, 2.7 Hz, 1H), 6.10 (dd, *J* = 10.0, 7.1 Hz, 1H), 2.90 (br s, 1H), 1.53 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 178.9 (d, *J* = 22.3 Hz), 153.6 (d, *J* = 2.7 Hz), 152.5 (d, *J* = 267.5 Hz), 128.0 (d, *J* = 9.6 Hz), 125.9 (d, *J* = 3.7 Hz), 69.7 (d, *J* = 8.4 Hz), 27.3 (d, *J* = 2.1 Hz).

*2-Bromo-4-hydroxy-4-methylcyclohexa-2,5-dien-1-one (**1q**):* 0.7 g, 67% yield, white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 2.8 Hz, 1H), 6.91 (dd, *J* = 10.0, 2.8 Hz, 1H), 6.26 (d, *J* = 10.0 Hz, 1H), 2.10 (br s, 1H), 1.53 (s, 3H).

*4-Hydroxy-3,4,5-trimethylcyclohexa-2,5-dien-1-one (**1v**):* 0.6 g, 54% yield, white solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.72 (s, 2H), 4.42 (br s, 1H), 1.94 (s, 6H), 1.27 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 186.2, 165.2, 125.1, 71.5, 26.3, 18.3.

*General Procedure for the Synthesis of p-Quinols **1n** and **1r** (Method B).*[15a] A solution of the corresponding phenol (1 equiv) in MeCN/H_2O (3:1) was vigorously stirred at room temperature, and a mixture of Oxone (8 equiv) and $NaHCO_3$ (15 equiv) was added in small portions. A septum with an empty balloon was immediately placed into the flask to trap the generated singlet oxygen. The mixture was kept stirring until full consumption of the starting material (monitored by TLC), then quenched with water, and extracted three times with EtOAc. Combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was diluted with water, and solid $Na_2S_2O_3$ (15 equiv) was added in portions, and the mixture was stirred for 30 min. The reaction mixture was quenched with water and extracted with EtOAc. The combined organic layers were dried, filtered, and concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography to provide the desired product.

*4-Hydroxy-2-methoxy-4-methylcyclohexa-2,5-dien-1-one (**1n**):* 0.2 g, 40% yield, white solid; ^{1}H NMR (600 MHz, $CDCl_3$) δ 6.87 (dd, *J* = 10.0, 2.5 Hz, 1H), 6.11 (d, *J* = 10.0 Hz, 1H), 5.78 (d, *J* = 2.1 Hz, 1H), 3.65 (s, 3H), 2.41 (br s, 1H), 1.51 (s, 3H); ^{13}C{^{1}H} NMR

https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524

(150 MHz, $CDCl_3$) δ 181.1, 153.2, 149.9, 126.3, 119.4, 69.3, 55.2, 28.2.

*3a-Hydroxy-3,3a,7,7a-tetrahydrobenzofuran-6(2H)-one (**1r**):*[28] 0.1 g, 38% yield, white solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.74 (dd, J = 10.2, 1.5 Hz, 1H), 5.96 (dd, J = 10.2 Hz, 1H), 4.22−4.19 (m, 1H), 4.06−4.00 (m, 1H), 3.93−3.87 (m, 1H), 3.39 (br s, 1H), 2.75 (dd, J = 16.9, 4.7 Hz, 1H), 2.57 (dd, J = 16.9, 5.5 Hz, 1H), 2.30 (ddd, J = 15.0, 8.4, 6.6 Hz, 1H), 2.21−2.15 (m, 1H).

*Methyl 2-(7a-Methyl-2,5-dioxo-3a,4,5,7a-tetrahydrobenzo[d]-oxazol-3(2H)-yl)benzoate (**3a**).* To a solution of quinol **1a** (60 mg, 0.48 mmol) and **2a** (94 mg, 0.53 mmol) in CH_2Cl_2 (5 mL) was added DBU (11 mg, 0.07 mmol) dropwise, the reaction mixture was stirred at an ambient temperature for 30 min until the complete consumption of *p*-methyl quinol, monitored by TLC analysis. The reaction mixture was diluted with EtOAc (5 mL), quenched by saturated aq NH_4Cl (10 mL), and then extracted with EtOAc (2 × 10 mL). The organic layer was combined and washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography to provide oxazolidinone **3a** (122 mg, 0.41 mmol, 84%) as colorless needle-like crystals: R_f = 0.2 (EtOAc/hexane = 1:1); mp = 121−126 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (dd, J = 7.8, 1.0 Hz, 1H), 7.56 (td, J = 7.7, 1.4 Hz, 1H), 7.43 (t, J = 7.7 Hz, 1H), 7.03 (d, J = 7.8 Hz, 1H), 6.66 (dd, J = 10.4 1.5 Hz, 1H), 6.19 (d, J = 10.4 Hz, 1H), 4.63 (br s, 1H), 3.86 (s, 3H), 2.62 (dd, J = 17.5, 4.1 Hz, 1H), 2.56 (dd, J = 17.5, 2.1 Hz, 1H), 1.78 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 194.6, 166.0, 156.0, 145.7, 135.7, 133.8, 132.6, 130.9, 129.3, 129.1, 128.9, 63.7, 52.8, 36.8, 29.9, 23.4; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{15}NO_5$ 302.1023, found 302.1011; [M + Na]$^+$ calcd for $C_{16}H_{15}NO_5Na$ 324.0842, found 324.0839.

*5-Hydroxy-2a-methyl-2a,2a1-dihydro-1H,6H-oxazolo[5,4,3-de]-acridine-1,6-dione (**4a**).* To a solution of quinol **1a** (50 mg, 0.4 mmol) and methyl 2-isocyanatobenzoate **2a** (78 mg, 0.44 mmol) in CH_2Cl_2 (10 mL) was added DBU (9 mg, 0.06 mmol) dropwise at an ambient temperature. The reaction was monitored by TLC to complete the consumption of **1a**, after which the solvent was evaporated under reduced pressure; NaOMe (48 mg, 0.89 mmol) was added in small portions to the residue in THF at 0 °C, and the reaction mixture was heated under reflux for 12 h. After cooling, the mixture was diluted with EtOAc (10 mL), quenched by saturated aq NH_4Cl (10 mL), and then extracted with EtOAc (2 × 10 mL). The organic layer was combined and washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by silica gel flash column chromatography to provide enol **4a** (86 mg, 0.32 mmol, 79%) as a white solid: R_f = 0.5 (EtOAc/hexane = 1:1); mp = 187−190 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 13.65 (br s, 1H), 7.98 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 8.2 Hz, 1H), 7.62 (t, J = 7.9 Hz, 1H), 7.36 (t, J = 7.6 Hz, 1H), 6.53 (d, J = 10.2 Hz, 1H), 6.31 (d, J = 10.2 Hz, 1H), 4.75 (s, 1H), 1.77 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 176.6, 173.5, 153.0, 139.1, 138.0, 134.4, 129.1, 126.9, 126.3, 123.8, 123.2, 98.9, 74.2, 58.6, 28.5; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{11}NO_4$ 270.0761, found 270.0737; [M + Na]$^+$ calcd for $C_{15}H_{11}NO_4Na$ 292.0580, found 292.0580.

*Hydroxy-4-methylacridin-9(10H)-one (**5a**).* To a solution of enol **4a** (11 mg, 0.04 mmol) in toluene (10 mL) was added DBU (12 mg, 0.08 mmol) dropwise at an ambient temperature. The reaction mixture was heated under reflux for 5 h. After cooling, the mixture was diluted with EtOAc (10 mL), quenched by 1 N HCl (10 mL), and then extracted with EtOAc (2 × 10 mL). The organic layer was combined and washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was purified by prep TLC to provide **5a** (9 mg, 0.04 mmol, quant. yield) as a yellow solid: mp = 290−295 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.02 (s, 1H), 10.88 (br s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.82 (ddd, J = 8.4, 7.1, 1.3 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.35 (t, J = 7.6 Hz, 1H), 6.51 (d, J = 8.1 Hz, 1H), 2.49 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 182.9, 160.9, 142.0, 140.6, 137.4, 135.0, 125.8, 122.7, 119.9, 119.0, 114.1, 109.4, 106.3, 18.0; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{11}NO_2$ 226.0863, found 226.0861.

*1-Hydroxy-4,10-dimethylacridin-9(10H)-one (**5a′**).* To a solution of **5a** (30 mg, 0.13 mmol) and methyl iodide (38 mg, 0.27 mmol) in acetone (15 mL) at 0 °C was added potassium carbonate (44 mg, 0.32 mmol) in small portions; the reaction mixture was heated at reflux for 10 h. After cooling, the mixture was concentrated *in vacuo*, then diluted with EtOAc (10 mL), quenched by saturated aq NH_4Cl (10 mL), and then extracted with EtOAc (2 × 10 mL). The organic layer was combined and washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and then concentrated *in vacuo* to provide *N*-methyl acridone **5a′** (30 mg, 0.12 mmol, 92%) as a yellow solid without further purification: R_f = 0.5 (THF/hexane = 1:2); mp = 114.5−117 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 14.19 (s, 1H), 8.36 (dd, J = 8.0, 1.5 Hz, 1H), 7.74−7.72 (m, 1H), 7.45 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 8.3 Hz, 1H), 7.29−7.26 (m, 1H), 6.67 (d, J = 8.3 Hz, 1H), 3.89 (s, 3H), 2.56 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 183.5, 161.6, 146.4, 146.0, 140.5, 134.7, 126.7, 122.0, 121.96, 116.6, 114.6, 112.3, 109.1, 43.3, 22.9; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{13}NO_2$ 240.1019, found 240.1022.

*General Procedure for the Preparation of 1-Hydroxyacridones **5a**−**5t**, **4m**, **4u**, and **4v** (Method C).* A Fisherbrand 6 dr. screw thread vial with a pulp/polyvinyl lined cap was used as the sealed tube. The use of safety shields and/or other safety equipment is recommended. To a mixture of *p*-quinol **1** (1 equiv) and methyl 2-isocyanatobenzoate **2a** (1.1 equiv) in 3 mL of toluene was added 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (2.2 equiv) dropwise at an ambient temperature; the reaction mixture was allowed to stir until the complete consumption of the *p*-quinol **1**, monitored by TLC, usually within 1 h, after which the reaction vial was heated in an oil bath to 130 °C for 6 h, or specified otherwise. The product 1-hydroxyacridone **5** can be monitored by TLC under UV light and as a yellow spot under visible light. After the time required, the reaction mixture was diluted with EtOAc (5 mL) and quenched with 1 M HCl (10 mL), and layers were separated. The aqueous layer was extracted with EtOAc (2 × 10 mL). The organic layers were combined and washed with brine (15 mL) and water (15 mL), dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was added to 1 mL of CH_2Cl_2; sonication was applied, and then the residue was filtered out through a Büchner funnel. After washing with CH_2Cl_2 (3 × 1 mL), the yellow solid residue was collected from the filter paper to afford the desired product without further purification. The filtrate was transferred into a round-bottom flask and concentrated under reduced pressure. The residue was purified by prep TLC to afford additional acridones. A combined total yield was reported, unless otherwise stated.

*1-Hydroxy-4-methylacridin-9(10H)-one (**5a**):* 96 mg, 96% yield, yellow solid. Spectroscopic data were in agreement with those made through the stepwise synthesis (reported in the previous section).

*4-Ethyl-1-hydroxyacridin-9(10H)-one (**5b**):* 82 mg, 95% yield, yellow solid; mp = 267−270 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.10 (s, 1H), 10.85 (br s, 1H), 8.24 (d, J = 7.9 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 6.54 (d, J = 8.1 Hz, 1H), 2.89 (q, J = 7.4 Hz, 2H), 1.27 (t, J = 7.4 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 183.0, 161.0, 142.0, 140.0, 135.7, 135.0, 125.8, 122.7, 120.0, 119.8, 119.0, 109.5, 106.6, 23.5, 15.1; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{13}NO_2$ [M + H]$^+$ 240.1019, found 240.1019.

*4-Cyclohexyl-1-hydroxyacridin-9(10H)-one (**5c**):* 71 mg, 92% yield, yellow solid; mp > 300 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.23 (s, 1H), 10.83 (br s, 1H), 8.25 (dd, J = 8.1, 1.2 Hz, 1H), 8.06 (d, J = 8.5 Hz, 1H), 7.83 (ddd, J = 8.5, 7.0, 1.5 Hz, 1H), 7.56 (d, J = 8.4 Hz, 1H), 7.35 (t, J = 7.5 Hz, 1H), 6.59 (d, J = 8.4 Hz, 1H), 3.31 (looks like a triplet, J = 11.7 Hz, 1H), 1.85−1.79 (m, 5H), 1.67−1.60 (m, 2H), 1.49−1.42 (m, 2H), 1.35−1.28 (m, 1H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 183.1, 160.9, 142.0, 139.3, 135.1, 133.8, 125.8, 124.1, 122.7, 119.6, 119.1, 109.5, 106.9, 35.7, 34.3, 27.2, 26.6; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{19}NO_2$ 294.1489, found 294.1487.

https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524

1-Hydroxy-4-propylacridin-9(10H)-one (**5d**): 58 mg, 72% yield, yellow solid; mp = 237−243 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.13 (s, 1H), 10.83 (br s, 1H), 8.25 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.4 Hz, 1H), 7.82 (t, J = 7.4 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 2.88 (t, J = 7.4 Hz, 2H), 1.67 (sext, J = 7.3 Hz, 2H), 1.00 (t, J = 7.1 Hz, 3H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 183.0, 161.0, 142.0, 140.1, 136.8, 135.1, 125.8, 122.7, 119.7, 119.0, 118.5, 109.6, 106.6, 32.1, 23.4, 14.6; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{15}NO_2$ 254.1176, found 254.1175.

1-Hydroxy-4-phenylacridin-9(10H)-one (**5e**): 69 mg, 88% yield, yellow solid; mp = 215−217 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.45 (s, 1H), 10.78 (br s, 1H), 8.28 (d, J = 7.9 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.77 (t, J = 7.5 Hz, 1H), 7.60−7.55 (m, 4H), 7.52−7.50 (m, 2H), 7.36 (t, J = 7.5 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 183.0, 162.5, 142.0, 139.5, 138.34, 138.25, 135.1, 130.6, 130.1, 128.6, 125.8, 122.9, 120.3, 119.8, 119.5, 109.6, 107.2; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{13}NO_2$ 288.1019, found 288.1019.

4-(1-Hydroxy-9-oxo-9,10-dihydroacridin-4-yl)benzonitrile (**5f**): 50 mg, 68% yield, yellow solid; mp = 296−298 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.54 (s, 1H), 10.89 (br s, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.1 Hz, 1H), 7.85−7.77 (m, 4H), 7.55 (d, J = 8.2 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 6.72 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 183.0, 163.3, 143.5, 142.0, 139.5, 138.4, 135.3, 133.9, 131.7, 125.8, 123.1, 119.9, 119.4, 118.6, 111.1, 109.5, 107.4; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{20}H_{12}N_2O_2$ 313.0972, found 313.0971.

4-(4-Bromophenyl)-1-hydroxyacridin-9(10H)-one (**5g**): 50 mg, 89% yield, yellow solid; mp = 285−288 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.49 (s, 1H), 10.81 (br s, 1H), 8.28 (d, J = 8.1 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.79−7.75 (m, 3H), 7.52−7.50 (m, 3H), 7.36 (t, J = 7.6 Hz, 1H), 6.69 (d, J = 8.2 Hz, 1H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 182.9, 162.8, 142.2, 139.7, 138.2, 137.6, 135.1, 132.94, 132.93, 125.8, 122.9, 122.0, 119.9, 119.5, 119.1, 109.6, 107.1; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{19}H_{12}BrNO_2$ 366.0124, found 366.0125.

1-Hydroxy-2,4-dimethylacridin-9(10H)-one (**5h**): 151 mg, 87% yield, yellow solid; mp = 283.7−286.2 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 14.23 (s, 1H), 10.79 (br s, 1H), 8.24 (d, J = 8.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.78 (t, J = 7.4 Hz, 1H), 7.36 (s, 1H), 7.31 (t, J = 7.5 Hz, 1H), 2.45 (s, 3H), 2.17 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2SO$) δ 182.7, 158.0, 142.0, 139.3, 138.7, 134.8, 125.8, 122.3, 119.7, 118.9, 114.2, 113.2, 109.2, 17.9, 15.2; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{13}NO_2$ 240.1019, found 240.1018.

1-Hydroxy-3,4-dimethylacridin-9(10H)-one (**5i**): 111 mg, 94% yield, yellow solid; mp = 279−281 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.00 (s, 1H), 10.75 (br s, 1H), 8.23 (d, J = 8.0 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 7.2 Hz, 1H), 7.34 (t, J = 7.4 Hz, 1H), 6.51 (s, 1H), 2.39 (s, 6H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 182.6, 160.2, 145.8, 142.2, 140.6, 134.96, 125.8, 122.6, 119.6, 119.1, 112.1, 109.2, 108.2, 22.2, 13.5; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{13}NO_2$ 240.1019, found 240.1020.

1-Hydroxy-4-isopropylacridin-9(10H)-one (**5j**). Method C was applied where the reaction was refluxed in toluene for 6 h after complete consumption of *p*-quinol: 47 mg, 55% yield, yellow solid; mp = 233−234 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.21 (s, 1H), 10.90 (br s, 1H), 8.26 (dd, J = 8.2, 1.4 Hz, 1H), 8.04 (d, J = 8.2 Hz, 1H), 7.83 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 7.36 (t, J = 7.4, 0.8 Hz, 1H), 6.61 (d, J = 8.3 Hz, 1H), 3.64 (septet, J = 6.7 Hz, 1H), 1.32 (d, J = 6.7 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 183.1, 160.9, 142.1, 139.3, 135.1, 133.0, 125.8, 124.6, 122.7, 119.6, 119.1, 109.5, 106.9, 26.3, 24.1; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{16}H_{15}NO_2$ [M + H]$^+$ 254.1176, found 254.1177.

1-Hydroxy-4-isopropyl-3-methylacridin-9(10H)-one (**5k**): 60 mg, 42% yield, yellow solid; mp = 135−140 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.24 (s, 1H), 10.52 (br s, 1H), 8.22 (d, J = 8.1 Hz, 1H), 8.08 (d, J = 8.4 Hz, 1H), 7.80 (t, J = 7.0 Hz, 1H), 7.34 (t, J = 7.3 Hz, 1H), 6.46 (s, 1H), 3.64 (septet (looks like a triplet), J = 6.7 Hz, 1H), 2.52 (s, 3H); 1.32 (d, J = 6.7 Hz, 6H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 183.1, 160.9, 142.1, 139.3, 135.1, 133.0, 125.8, 124.6, 122.7, 119.6, 119.1, 109.5, 106.9, 26.3, 24.1; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{17}NO_2$ 268.1332, found 268.1333.

6-Hydroxy-1,3,4,12-tetrahydrobenzo[c]acridin-7(2H)-one (**5l**): 83 mg, 83% yield, yellow solid; mp = 298−300 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 13.90 (s, 1H), 10.67 (br s, 1H), 8.21 (dd, J = 8.1, 1.1 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.77 (ddd, J = 8.5, 6.9, 1.5 Hz, 1H), 7.32 (t, J = 7.5 Hz, 1H), 6.29 (s, 1H), 2.79−2.76 (m, 4H), 1.91−1.87 (m, 2H), 1.79−1.76 (m, 2H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 182.3, 159.7, 146.2, 141.8, 140.5, 134.7, 125.7, 122.6, 119.95, 119.1, 113.1, 108.1, 107.4, 31.3, 24.4, 23.0, 22.8; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{15}NO_2$ [M + H]$^+$ 266.1176, found 266.1176.

6-Hydroxy-2,3-dihydro-1H,7H-3a,12-(epoxymethano)-cyclopenta[d]acridine-7,13-dione (**4m**). Method C was applied where the reaction ran at room temperature in toluene for 6 h after complete consumption of *p*-quinol. Also, silica gel flash column chromatography was applied to provide the titled product: 99 mg, 84% yield, white solid; mp = 165−172 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 13.49 (br s, 1H), 8.02 (dd, J = 7.8, 1.3 Hz, 1H), 7.82 (d, J = 8.1 Hz, 1H), 7.61 (t, J = 7.9 Hz, 1H), 7.33 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 10.2 Hz, 1H), 6.24 (d, J = 10.2 Hz, 1H), 2.63−2.58 (m, 1H), 2.34−2.30 (m, 1H), 1.93−1.84 (m, 1H), 1.77- 1.63 (m, 2H), 1.58−1.50 (m, 1H); ^{13}C{^{1}H} NMR (100 MHz, $CDCl_3$) δ 175.1, 173.1, 152.9, 138.9, 136.5, 134.3, 127.0, 126.3, 125.6, 122.99, 122.58, 104.3, 84.0, 67.5, 41.8, 40.8, 19.0; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{17}H_{13}NO_4$ 296.0923, found 296.0919.

1-Hydroxy-2-methoxy-4-methylacridin-9(10H)-one (**5n**): 40 mg, 87% yield, yellow solid; mp decomposed at 143 °C; ^{1}H NMR (600 MHz, $(CD_3)_2SO$) δ 14.13 (s, 1H), 10.82 (br s, 1H), 8.22 (d, J = 8.1 Hz, 1H), 7.94 (d, J = 8.5 Hz, 1H), 7.78 (t, J = 7.5 Hz, 1H), 7.45 (s, 1H), 7.30 (t, J = 7.5 Hz, 1H), 3.85 (s, 3H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR (150 MHz, $(CD_3)_2SO$) δ 183.2, 149.4, 142.1, 139.6, 134.9, 134.8, 125.8, 125.5, 122.2, 118.89, 118.87, 113.4, 110.1, 58.1, 18.1; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{15}H_{13}NO_3$ 256.0968, found 256.0969.

2-Fluoro-1-hydroxy-4-methylacridin-9(10H)-one (**5o**): 95 mg, 79% yield, orange solid; mp decomposed at 298 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 14.20 (s, 1H), 11.01 (br s, 1H), 8.23 (d, J = 8.1 Hz, 1H), 7.99 (d, J = 8.6 Hz, 1H), 7.83 (t, J = 7.2 Hz, 1H), 7.61 (d, J = 12.0 Hz, 1H), 7.37 (t, J = 7.4 Hz, 1H), 2.51 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2SO$) δ 182.7 (d, J = 3.4 Hz), 149.1 (d, J = 12.9 Hz), 142.3 (d, J = 234.4 Hz), 141.6, 136.4, 134.8, 125.2, 124.9 (d, J = 20.2 Hz), 122.5, 118.7, 118.6, 114.1 (d, J = 6.3 Hz), 109.9 (d, J = 4.2 Hz), 17.3; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{10}FNO_2$ 244.0768, found 244.0770.

2-Chloro-1-hydroxy-4-methylacridin-9(10H)-one (**5p**): 79 mg, 75% yield, yellow solid; mp decomposed at 226 °C; ^{1}H NMR (400 MHz, $(CD_3)_2SO$) δ 14.82 (s, 1H), 11.09 (br s, 1H), 8.26 (d, J = 8.0 Hz, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.83 (t, J = 6.9 Hz, 1H), 7.65 (s, 1H), 7.39 (t, J = 7.3 Hz, 1H), 2.50 (s, 3H); ^{13}C{^{1}H} NMR (100 MHz, $(CD_3)_2SO$) δ 182.4, 155.9, 142.0, 139.6, 136.9, 135.4, 125.8, 123.2, 119.7, 119.2, 115.9, 109.8, 108.8, 17.8; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{10}ClNO_2$ 260.0473, found 260.0474.

2-Bromo-1-hydroxy-4-methylacridin-9(10H)-one (**5q**): 43 mg, 41% yield, yellow solid, 11% of **5a** was also isolated; mp decomposed at 224 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.95 (s, 1H), 11.12 (br s, 1H), 8.28 (d, J = 7.9 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.87 (t, J = 7.5 Hz, 1H), 7.79 (s, 1H), 7.41 (t, J = 7.5 Hz, 1H), 2.52 (s, 3H); ^{13}C{^{1}H} NMR (125 MHz, $(CD_3)_2SO$) δ 182.2, 157.1, 141.95, 140.1, 139.4, 135.5, 125.9, 123.3, 119.7, 119.3, 116.5, 109.9, 97.7, 17.7; HRMS (ESI/Q-TOF) m/z [M + H]$^+$ calcd for $C_{14}H_{10}BrNO_2$ 303.9968, found 303.9966.

1-Hydroxy-4-(2-hydroxyethyl)acridin-9(10H)-one (**5r**): 64 mg, 70% yield, yellow solid; mp = 205−209 °C; ^{1}H NMR (500 MHz, $(CD_3)_2SO$) δ 14.16 (s, 1H), 11.04 (br s, 1H), 8.25 (d, J = 7.9 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.84−7.81 (m, 1H), 7.51 (d, J = 8.0

https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524

Hz, 1H), 7.35 (t, J = 7.4 Hz, 1H), 6.56 (d, J = 8.1 Hz, 1H), 4.94 (br s, 1H), 3.75 (t, J = 6.0 Hz, 2H), 3.08 (t, J = 6.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$) δ 183.0, 161.3, 142.0, 140.7, 137.8, 135.1, 125.9, 122.7, 119.7, 119.0, 116.4, 109.6, 106.6, 61.9, 34.1; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{13}NO_3$ 256.0968, found 256.0969.

*5-Hydroxy-3-tosyl-1,2,3,3a,4,5a1-hexahydro-6H,12H-oxazolo-[5,4,3-de]pyrrolo[2,3-c]acridine-6,12-dione (**4s**).* Method C was applied where the reaction ran at room temperature in toluene for 1 h; also, recrystallization with EtOAc/hexane (10:1) was applied to afford the titled compound: 40 mg, 94% yield, white solid; mp = 261−268 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 14.31 (br s, 1H), 7.99 (dd, J = 7.9, 1.4 Hz, 1H), 7.75−7.73 (m, 3H), 7.59 (t, J = 7.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 2H), 7.30 (t, J = 7.4 Hz, 1H), 4.86 (s, 1H), 3.92−3.88 (m, 1H), 3.81−3.78 (m, 1H), 3.33−3.25 (m, 2H), 2.48−2.40 (m, 5H), 2.28−2.21 (m, 1H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 181.0, 178.1, 152.3, 144.8, 137.5, 135.1, 133.2, 130.3, 128.0, 127.5, 126.0, 123.4, 121.6, 101.6, 86.2, 62.4, 56.4, 46.7, 39.3, 36.2, 22.0; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{23}H_{20}N_2O_6S$ 453.1115, found 453.111; $[M + Na]^+$ calcd for $C_{23}H_{20}N_2O_6SNa$ 475.0934, found 475.0930.

*N-(2-(1-Hydroxy-9-oxo-9,10-dihydroacridin-4-yl)ethyl)-4-methyl-benzenesulfonamide (**5s**):* 48 mg, 57% yield, yellow solid; mp = 234−242 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.17 (s, 1H), 10.75 (br s, 1H), 8.25 (d, J = 8.1 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.85−7.82 (m, 1H), 7.61−7.59 (m, 1H), 7.54 (d, J = 8.1 Hz, 2H), 7.43 (d, J = 8.2 Hz, 1H), 7.38−7.35 (m, 1H), 7.23 (d, J = 8.0 Hz, 2H), 6.53 (d, J = 8.2 Hz, 1H), 3.13−3.09 (m, 2H), 3.06−3.03 (m, 2H), 2.32 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$) δ 182.9, 161.6, 143.3, 141.9, 140.2, 138.1, 137.9, 135.2, 130.3, 127.3, 125.8, 122.8, 119.8, 118.9, 114.9, 109.6, 106.6, 43.0, 30.5, 21.8; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{22}H_{20}N_2O_4S$ 409.1217, found 409.1214.

*11-Hydroxy-4-methyl-1,2,3,5-tetrahydro-10H-cyclopenta[b]-acridin-10-one (**5t**):* 90 mg, 80% yield, yellow solid; mp > 300 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 14.13 (s, 1H), 10.71 (br s, 1H), 8.22 (dd, J = 8.1 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.77 (t, J = 7.7 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 2.96 (t, J = 7.2 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.39 (s, 3H), 2.06 (quint, J = 7.2 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$) δ 182.6, 155.6, 153.6, 141.9, 139.8, 134.6, 125.8, 122.2, 120.4, 119.5, 118.9, 109.1, 108.7, 33.7, 29.3, 25.0, 14.4; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}NO_2$ 266.1176, found 266.1177.

*2a,4,5a-Trimethyl-2a^1,5a-dihydro-1H,5H-oxazolo[5,4,3-de]-acridine-1,5,6(2aH)-trione (**4u**).* Method C was applied where the reaction was refluxed in toluene for 6 h. Also, the residue was purified by silica gel flash column chromatography to provide the titled compound: 71 mg, 44% yield, white solid; mp = 188−192 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.46 (d, J = 8.4 Hz, 1H), 8.06 (dd, J = 7.8, 1.4 Hz, 1H), 7.59−7.56 (m, 1H), 7.19 (t, J = 7.3 Hz, 1H), 6.41 (s, 1H), 1.85 (d, J = 1.1 Hz, 3H), 1.82 (s, 3H), 1.58 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 194.1, 188.7, 151.7, 139.5, 138.1, 136.2, 135.9, 129.1, 124.5, 120.2, 117.3, 76.5, 67.7, 55.3, 24.6, 18.3, 16.6; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}NO_4$ 298.1074, found 298.1067; $[M + Na]^+$ calcd for $C_{17}H_{15}NO_4Na$ 320.0893, found 320.0889.

*5-Hydroxy-2a,2a^1,3-trimethyl-2a,2a^1-dihydro-1H,6H-oxazolo-[5,4,3-de]acridine-1,6-dione (**4v**).* Method C was applied where the reaction was refluxed in toluene for 6 h. The sealed tube condition led to 1-hydroxy-3,4-dimethylacridin-9(10*H*)-one (**5i**) as the side product. Also, the residue was purified by silica gel flash column chromatography to provide the titled compound: 54 mg, 54% yield, white solid; mp = 202−206 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 14.06 (br s, 1H), 8.00 (dd, J = 7.8, 1.4 Hz, 1H), 7.65−7.62 (m, 1H), 7.57 (dd, J = 8.0, 0.9 Hz, 1H), 7.43−7.40 (m, 1H), 2.17 (d, J = 1.5 Hz, 3H), 1.74 (s, 3H), 1.35 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 179.2, 170.8, 154.7, 150.1, 136.9, 133.9, 127.9, 127.1, 126.4, 125.8, 124.2, 105.7, 81.0, 62.1, 22.6, 20.9, 20.6; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}NO_4$ 298.1074, found 298.1069; $[M + Na]^+$ calcd for $C_{17}H_{15}NO_4Na$ 320.0893, found 320.0892.

*General Procedure for the Preparation of Aryl Isocyanates **2b**−**2d**[33] and 1-Hydroxyacridones **5x**−**5z** (Method D).* To a solution of commercial aniline (1 equiv) in a 1:1 mixture of methylene chloride (10 mL) and saturated aqueous $NaHCO_3$ (10 mL) at 0 °C was added triphosgene (0.4 equiv). The reaction mixture was stirred at 0 °C for 1 h. After the layers were separated, the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The organic layers were combined and washed with water (20 mL) and brine (20 mL), dried over Na_2SO_4, and then concentrated *in vacuo*. The residue was used directly in the next step without further purification. Method C was then applied to deliver the desired acridones.

*Methyl 5-Bromo-2-isocyanatobenzoate (**2b**):* 0.3 g, quant. yield, white solid; mp decomposed at 121.1 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.14 (d, J = 2.4 Hz, 1H), 7.58 (dd, J = 8.5, 2.4 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 3.97 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 165.4, 137.0, 134.6, 133.9, 128.3, 125.7, 125.3, 118.7, 53.1; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_9H_6BrNO_3$ 255.9604, found 255.9604.

*Dimethyl 2-Isocyanatoterephthalate (**2c**):* 0.4 g, quant. yield, white solid; mp decomposed at 126 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 8.06 (d, J = 8.2 Hz, 1H), 7.87 (dd, J = 8.2, 1.7 Hz, 1H), 7.76 (d, J = 1.7 Hz, 1H), 3.98 (s, 3H), 3.94 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 166.0, 165.6, 135.2, 134.8, 132.0, 127.8, 127.4, 126.4, 125.5, 53.1, 53.0; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{11}H_9NO_5$ 236.0553, found 236.0553.

*Methyl 2-Isocyanato-3-methylbenzoate (**2d**):* 1.7 g, quant. yield, white solid; mp = 124−126 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 7.8 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.15−7.12 (m, 1H), 3.95 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.0, 136.2, 135.2, 134.9, 133.2, 129.4, 125.1, 124.1, 52.7, 19.2; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{10}H_9NO_3$ 192.0655, found 192.0653.

*7-Bromo-4-ethyl-1-hydroxyacridin-9(10H)-one (**5x**):* 93 mg, 82% yield, yellow solid; mp = 257−260 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 13.80 (s, 1H), 11.02 (br s, 1H), 8.31 (d, J = 2.3 Hz, 1H), 7.99 (d, J = 9.0 Hz, 1H), 7.95 (dd, J = 9.0, 2.3 Hz, 1H), 7.53 (d, J = 8.2 Hz, 1H), 6.60 (d, J = 8.2 Hz, 1H), 2.90 (q, J = 7.4 Hz, 2H), 1.29 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$) δ 181.8, 160.8, 140.9, 139.8, 137.6, 136.2, 127.7, 121.7, 121.1, 120.4, 114.9, 109.6, 107.1, 23.5, 15.1; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{15}H_{12}BrNO_2$ 318.0124, found 318.0121.

*Methyl 5-Ethyl-8-hydroxy-9-oxo-9,10-dihydroacridine-3-carboxylate (**5y**):* 90 mg, 73% yield, yellow solid; mp = 254−257 °C; ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 13.81 (s, 1H), 11.00 (br s, 1H), 8.63 (d, J = 1.3 Hz, 1H), 8.25 (d, J = 8.5 Hz, 1H), 7.71 (dd, J = 8.4, 1.5 Hz, 1H), 7.47 (d, J = 8.2 Hz, 1H), 6.55 (d, J = 8.1 Hz, 1H), 3.96 (s, 3H), 2.85 (q, J = 7.5 Hz, 2H), 1.26 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $(CD_3)_2SO$) δ 182.6, 166.4, 160.8, 141.5, 140.1, 136.2, 134.7, 126.5, 122.0, 121.6, 121.0, 120.3, 109.9, 107.0, 53.5, 23.5, 15.2; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{17}H_{15}NO_4$ 298.1074, found 298.1076.

*4-Ethyl-1-hydroxy-5-methylacridin-9(10H)-one (**5z**).* The crude material was purified by silica gel flash column chromatography to provide the titled compound: 124 mg, 85% yield, yellow solid; mp = 163−170 °C; ^1H NMR (500 MHz, $CDCl_3$) δ 13.73 (br s, 1H), 8.24 (d, J = 8.2 Hz, 1H), 7.93 (br s, 1H), 7.53 (d, J = 7.1 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.18 (t, J = 7.6 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 2.76 (q, J = 7.5 Hz, 2H), 2.55 (s, 3H), 1.40 (t, J = 7.5 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 183.5, 161.2, 138.9, 138.4, 135.0, 134.7, 124.7, 123.5, 121.9, 120.2, 117.5, 109.3, 107.2, 23.1, 16.7, 13.3; HRMS (ESI/Q-TOF) m/z $[M + H]^+$ calcd for $C_{16}H_{15}NO_2$ 254.1176, found 254.1176.

Anti-Human Cytomegalovirus (HCMV) Activity Analysis. *Compound Preparation.* Seven 1-hydroxyacridones (**5a**, **5c**, **5e**, **5f**, **5h**, **5i**, and **5x**) and one tetracyclic compound **4u** were synthesized according to Method C and used in this study. Compound **5a′** was an *N*-methyl derivative of **5a**. Substrates were dissolved in dimethyl sulfoxide (DMSO), and stocks of 10 mM were stored at −80 °C.

HCMV Replication Assay. Human foreskin fibroblasts (HFF) cells (ATCC CRL-2088) were plated at approximately 2 × 10^4 cells/well

https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524

in white-bottom 96-well tissue culture plates and the next day inoculated with the ADCREGFP virus (obtained from Wade Bresnahan, University of Minnesota) in Dulbecco's modified Eagle's medium (DMEM) containing 5% fetal bovine serum for 2 h at a multiplicity of infection of 0.05. The cells were washed with phosphate-buffered saline and incubated with 100 μL of DMEM containing 5% fetal bovine serum, and test compounds were incubated at 37 °C and 5% CO_2 for 7 days. Next, the extent of virus replication was determined by lysing the infected cells and measuring green fluorescent protein (GFP) expression. For lysis, each well-received 200 μL of lysis buffer (25 mM Tris (pH 7.8), 2 mM dithiothreitol (DTT), 2 mM *trans*-1,2-diaminocyclohexane-*N*,*N*,*N*′,*N*′-tetraacetic acid, 1% Triton X-100, 10% glycerol) for 10 min at 37 °C, followed by 30 min of incubation at room temperature on a shaker. GFP relative fluorescence units were determined at excitation/emission = 495/515 nm in a Molecular Devices M5e plate reader.

Compounds were evaluated in triplicate, and mean values of triplicate wells were determined and compared to the mean value for the wells that received DMSO alone.

Cell Viability Assay. HFF cells were plated at approximately 2 × 104 cells/well and the next day incubated in culture medium with testing compounds at 37 °C for 7 days. Cellular viability was determined using the MTS-based tetrazolium reduction assay, CellTiter 96 Aqueous Non-Radioactive cell proliferation assay (Promega), as per manufacturer's instructions. Compounds were evaluated in triplicate, and mean values of triplicate wells were determined and compared to the mean value for the wells that received DMSO alone.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.joc.9b03307.

Additional experimental details and copies of NMR spectra (PDF)

Crystal structure data of **5a** (CIF)

Crystal structure data of **4a** (CIF)

Crystal structure data of **4a″** (CIF)

■ AUTHOR INFORMATION

Corresponding Author

Shengping Zheng − *Department of Chemistry, Hunter College, New York, New York 10065, United States; Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, New York, New York 10016, United States;* orcid.org/0000-0003-0668-8849; Email: szh0007@hunter.cuny.edu

Authors

Jing Wu − *Department of Chemistry, Hunter College, New York, New York 10065, United States; Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, New York, New York 10016, United States*

Jinzhu Zhang − *Department of Chemistry, Hunter College, New York, New York 10065, United States; Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, New York, New York 10016, United States*

Ruben Soto-Acosta − *Center for Drug Design, University of Minnesota, Minneapolis, Minnesota 55455, United States*

Lili Mao − *Center for Drug Design, University of Minnesota, Minneapolis, Minnesota 55455, United States*

Jiahui Lian − *Department of Chemistry, Hunter College, New York, New York 10065, United States*

Kenny Chen − *Department of Chemistry, Hunter College, New York, New York 10065, United States*

Guy Pillon − *Department of Chemistry, Hunter College, New York, New York 10065, United States*

Guoqi Zhang − *Ph.D. Program in Chemistry, The Graduate Center of the City University of New York, New York, New York 10016, United States; Department of Sciences, John Jay College of Criminal Justice, New York, New York 10019, United States;* orcid.org/0000-0001-6071-8469

Robert J. Geraghty − *Center for Drug Design, University of Minnesota, Minneapolis, Minnesota 55455, United States;* orcid.org/0000-0002-0560-6509

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.joc.9b03307

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

We are grateful to Professors Richard Franck and Klaus Grohmann at Hunter College for helpful discussions. We also thank Drs. Barney Yoo, Matthew Devany, Michelle Neary, and Tony Hu for mass spectrometric, NMR spectroscopic, and X-ray crystallographic assistance, respectively. Financial support from the Bertha and Louis Weinstein Research Grant, NIH (SC2GM100783), NSF (CHE-1464543), and PSC−CUNY Research Award is gratefully acknowledged.

■ DEDICATION

This work is dedicated to the memory of Professors Gilbert Stork, Koji Nakanishi, and Ronald Breslow.

■ REFERENCES

(1) Belmont, P.; Bosson, J.; Godet, T.; Tiano, M. Acridine and acrdione derivatives, anticancer properties and synthetic methods: where are we now. *Anti-Cancer Agents Med. Chem.* **2007**, *7*, 139−169.

(2) Zhang, B.; Li, X.; Li, B.; Gao, C.; Jiang, Y. Acridine and its derivatives: a patent review (2009−2013). *Expert Opin. Ther. Pat.* **2014**, *24*, 647−664.

(3) Guo, H.-M.; Mao, R.-Z.; Wang, Q.-T.; Niu, H.-Y.; Xie, M.-S.; Qu, G.-R. Pd(II)-Catalyzed One-Pot, Three-Step Route for the Synthesis of Unsymmetrical Acridines. *Org. Lett.* **2013**, *15*, 5460−5463.

(4) (a) Cholesinski, G.; Dzierzbicka, K.; Kolodziejczyk, A. M. Natural and synthetic acridines/acridones as antitumor agents: their biological activities and methods of synthesis. *Pharmacol. Rep.* **2011**, *63*, 305−336. (b) Gensicka-Kowalewska, M.; Cholewinski, G.; Dzierzbicka, K. Recent developments in the synthesis and biological activity of acridine/acridone analogues. *RSC Adv.* **2017**, *7*, 15776−15804.

(5) Akanitapichat, P.; Bastow, K. F. The antiviral agent 5-chloro-1,3-dihydroxyacridone interferes with assembly and maturation of herpes simplex virus. *Antiviral Res.* **2002**, *53* (2), 113−126.

(6) Lowden, C. T.; Bastow, K. F. Cell culture replication of herpes simplex virus and, or human cytomegalovirus is inhibited by 3,7-dialkoxylated, 1-hydroxyacridone derivatives. *Antiviral Res.* **2003**, *59* (3), 143−154.

(7) Goodell, J. R.; Madhok, A. A.; Hiasa, H.; Ferguson, D. M. Synthesis and evaluation of acridine- and acridone-based anti-herpes agents with topoisomerase activity. *Bioorg. Med. Chem.* **2006**, *14* (16), 5467−5480.

(8) Tabarrini, O.; Manfroni, G.; Fravolini, A.; Cecchetti, V.; Sabatini, S.; De Clercq, E.; Rozenski, J.; Canard, B.; Dutartre, H. N.; Paeshuyse, J.; Neyts, J. Synthesis and anti-BVDV activity of acridones as new potential antiviral agents. *J. Med. Chem.* **2006**, *49* (8), 2621−2627.

(9) Manfroni, G.; Paeshuyse, J.; Massari, S.; Zanoli, S.; Gatto, B.; Maga, G.; Tabarrini, O.; Cecchetti, V.; Fravolini, A.; Neyts, J.

Inhibition of Subgenomic Hepatitis C Virus RNA Replication by Acridone Derivatives: Identification of an NS3 Helicase Inhibitor. *J. Med. Chem.* **2009**, *52* (10), 3354−3365.
(10) Yamamoto, N.; Furukawa, H.; Ito, Y.; Yoshida, S.; Maeno, K.; Nishiyama, Y. Anti-Herpesvirus Activity of Citrusinine-I, a New Acridone Alkaloid, and Related-Compounds. *Antiviral Res.* **1989**, *12* (1), 21−36.
(11) Fujiwara, M.; Okamoto, M.; Okamoto, M.; Watanabe, M.; Machida, H.; Shigeta, S.; Konno, K.; Yokota, T.; Baba, M. Acridone derivatives are selective inhibitors of HIV-1 replication in chronically infected cells. *Antiviral Res.* **1999**, *43* (3), 189−199.
(12) Kankanala, J.; Kirby, K. A.; Liu, F.; Miller, L.; Nagy, E.; Wilson, D. J.; Parniak, M. A.; Sarafianos, S. G.; Wang, Z. Q. Design, Synthesis, and Biological Evaluations of Hydroxypyridonecarboxylic Acids as Inhibitors of HIV Reverse Transcriptase Associated RNase H. *J. Med. Chem.* **2016**, *59* (10), 5051−5062.
(13) (a) Putic, A.; Stecher, L.; Prinz, H.; Muller, K. Structure-activity relationship studies of acridones as potential antipsoriatic agents. 1. Synthesis and antiproliferative activity of simple N-unsubstituted 10H-acridin-9-ones against human keratinocyte growth. *Eur. J. Med. Chem.* **2010**, *45* (8), 3299−3310. (b) Anand, R. C.; Sinha, A. K. A regioselective and flexible synthesis of acronycine. *Heterocycles* **1990**, *31*, 1733−1735. (c) Boutefnouchet, S.; Gaboriaud-Kolar, N.; Minh, N. T.; Depauw, S.; David-Cordonnier, M. H.; Pfeiffer, B.; Leonce, S.; Pierre, A.; Tillequin, F.; Lallemand, M. C.; Michel, S. Synthesis, Cytotoxic Activity, and Mechanism of Action of Furo[2,3-c]acridin-6-one and Benzo[b]furo[3,2-h]acridin-6-one Analogues of Psorospermin and Acronycine. *J. Med. Chem.* **2008**, *51* (22), 7287−7297. (d) Nishihama, Y.; Ishikawa, Y.; Nishiyama, S. Total synthesis of (±)-megistophylline I. *Tetrahedron Lett.* **2009**, *50*, 2801−2804.
(14) For a review, see: Magdziak, D.; Meek, S. J.; Pettus, T. R. R. Cyclohexadienone ketals and quinols: Four building blocks potentially useful for enantioselective synthesis. *Chem. Rev.* **2004**, *104* (3), 1383−1429.
(15) (a) Carreno, M. C.; Gonzalez-Lopez, M.; Urbano, A. Oxidative de-aromatization of para-alkyl phenols into para-peroxyquinols and para-quinols mediated by oxone as a source of singlet oxygen. *Angew. Chem., Int. Ed.* **2006**, *45* (17), 2737−2741. (b) Green, N. J.; Connolly, C. A.; Rietdijk, K. P. W.; Nichol, G. S.; Duarte, F.; Lawrence, A. L. Bio-inspired Domino oxa-Michael/Diels-Alder/oxa-Michael Dimerization of para-Quinols. *Angew. Chem., Int. Ed.* **2018**, *57* (21), 6198−6202.
(16) Zhang, J. Z.; Wu, J.; Yin, Z. W.; Zeng, H. S.; Khanna, K.; Hu, C. H.; Zheng, S. P. An expedient stereoselective and chemoselective synthesis of bicyclic oxazolidinones from quinols and isocyanates. *Org. Biomol. Chem.* **2013**, *11* (18), 2939−2942.
(17) Yin, Z. W.; Zhang, J. Z.; Wu, J.; Liu, C.; Sioson, K.; Devany, M.; Hu, C. H.; Zheng, S. P. Double Hetero-Michael Addition of N-Substituted Hydroxylamines to Quinone Monoketals: Synthesis of Bridged Isoxazolidines. *Org. Lett.* **2013**, *15* (14), 3534−3537.
(18) Zhang, J. Z.; Yin, Z. W.; Leonard, P.; Wu, J.; Sioson, K.; Liu, C.; Lapo, R.; Zheng, S. P. A Variation of the Fischer Indolization Involving Condensation of Quinone Monoketals and Aliphatic Hydrazines. *Angew. Chem., Int. Ed.* **2013**, *52* (6), 1753−1757.
(19) Yin, Z. W.; Zhang, J. Z.; Wu, J.; Green, R.; Li, S. H.; Zheng, S. P. Synthesis of o-chlorophenols via an unexpected nucleophilic chlorination of quinone monoketals mediated by N, N′-dimethylhydrazine dihydrochloride. *Org. Biomol. Chem.* **2014**, *12* (18), 2854−2858.
(20) Zhao, J.; Larock, R. C. Synthesis of xanthones, thioxanthones, and acridones by the coupling of arynes and substituted benzoates. *J. Org. Chem.* **2007**, *72* (2), 583−588.
(21) Pintori, D. G.; Greaney, M. F. Insertion of Benzene Rings into the Amide Bond: One-Step Synthesis of Acridines and Acridones from Aryl Amides. *Org. Lett.* **2010**, *12* (1), 168−171.
(22) Dubrovskiy, A. V.; Larock, R. C. Synthesis of o-(Dimethylamino)aryl Ketones and Acridones by the Reaction of 1,1-Dialkylhydrazones and Arynes. *Org. Lett.* **2011**, *13* (15), 4136−4139.
(23) Fang, Y. S.; Rogness, D. C.; Larock, R. C.; Shi, F. Formation of Acridones by Ethylene Extrusion in the Reaction of Arynes with beta-Lactams and Dihydroquinolinones. *J. Org. Chem.* **2012**, *77* (14), 6262−6270.
(24) Kim, J.; Stoltz, B. M. A C-N insertion of beta-lactam to benzyne: unusual formation of acridone. *Tetrahedron Lett.* **2012**, *53* (37), 4994−4996.
(25) Feng, M. H.; Tang, B. Q.; Wang, N. Z.; Xu, H. X.; Jiang, X. F. Ligand Controlled Regiodivergent C-1 Insertion on Arynes for Construction of Phenanthridinone and Acridone Alkaloids. *Angew. Chem., Int. Ed.* **2015**, *54* (49), 14960−14964.
(26) Himeshima, Y.; Sonoda, T.; Kobayashi, H. Fluoride-Induced 1,2-Elimination of Ortho-Trimethylsilylphenyl Triflate to Benzyne under Mild Conditions. *Chem. Lett.* **1983**, *12* (8), 1211−1214.
(27) (a) Danishefsky, S.; Kahn, M. Regiospecific Michael Reactions to an Enedione. *Tetrahedron Lett.* **1981**, *22* (6), 485−488. (b) For **1t**, if the N adds to the five-membered ring side, the enolate double bond would be an exo-methylene moiety to a five-membered ring, which is still strained.
(28) Aponick, A.; McKinley, J. D.; Raber, J. C.; Wigal, C. T. Quinone alkylation using organocadmium reagents: A gen-eral synthesis of quinols. *J. Org. Chem.* **1998**, *63* (8), 2676−2678.
(29) Yakura, T.; Omoto, M.; Yamauchi, Y.; Tian, Y.; Ozono, A. Hypervalent iodine oxidation of phenol derivatives using a catalytic amount of 4-iodophenoxyacetic acid and Oxone (R) as a co-oxidant. *Tetrahedron* **2010**, *66* (31), 5833−5840.
(30) Hashimoto, T.; Shimazaki, Y.; Omatsu, Y.; Maruoka, K. Indanol-Based Chiral Organoiodine Catalysts for Enantioselective Hydrative Dearomatization. *Angew. Chem., Int. Ed.* **2018**, *57*, 7200−7204.
(31) Tello-Aburto, R.; Kalstabakken, K. A.; Volp, K. A.; Harned, A. M. Regioselective and stereoselective cycliza-tions of cyclohexadienones tethered to active methylene groups. *Org. Biomol. Chem.* **2011**, *9* (22), 7849−7859.
(32) Gu, Q.; You, S. L. Desymmetrization of cyclohexadi-enones via cinchonine derived thiourea-catalyzed enantiose-lective aza-Michael reaction and total synthesis of (−)-Mesembrine. *Chem. Sci.* **2011**, *2* (8), 1519−1522.
(33) Sutherell, C. L.; Thompson, S.; Scott, R. T. W.; Hamil-ton, A. D. Aryl-linked imidazolidin-2-ones as non-peptidic β-strand mimetics. *Chem. Commun.* **2012**, *48*, 9834−9836.

https://dx.doi.org/10.1021/acs.joc.9b03307
J. Org. Chem. 2020, 85, 4515−4524