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Tricyclic Aza-Andrographolide Derivatives from Late-Stage Hydroamination and Their Anti-human Coronavirus (Anti-HCoV) Activity

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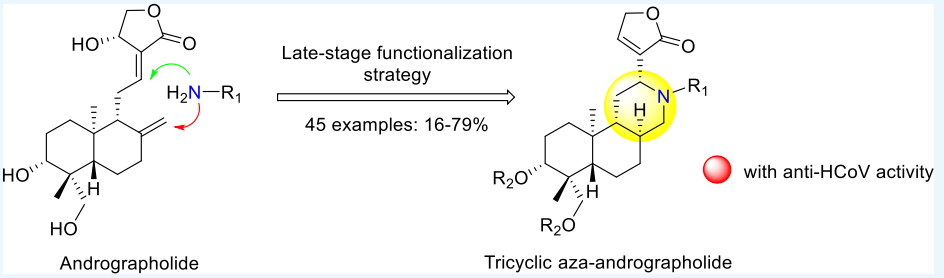

ABSTRACT: A late-stage functionalization (LSF) of the natural product andrographolide for the efficient assembly of a range of structurally interesting and diverse tricyclic-aza derivatives was developed. The key to the diversification is a photo-catalyzed intramolecular hydroamination reaction, and acridinium derivatives were demonstrated to be the optimal catalysts. Additionally, the synthesized tricyclic aza-andrographolide derivatives were found to inhibit human coronavirus with high potency.

INTRODUCTION

Natural products and their derivatives play a highly essential role in combating numerous diseases, especially cancer and infectious diseases.[1] Data have shown that, from 1981 until 2019, 41% of anticancer and 66% of anti-infective small molecule drugs were derived from or inspired by natural sources.[2] Compared with the traditional synthetic compounds, natural products have enormous structural complexity and scaffold diversity, which make them more likely to interact with biological macromolecules in a selective and specific manner.[3] Driven by modern high-throughput drug discovery,[4] there is an urgent and increasing demand for a large collection of bioactive natural-product-derived compounds with significant structural diversity and complexity. Developing facile and practical methods or strategies to construct them, however, remains a considerable interest in the field. Several strategies for the rapid and highly efficient generation of these structurally diverse natural-product-inspired libraries have been developed, including diversity-oriented synthesis from simple starting materials using convergent strategies such as multicomponent reaction,[5] the use of natural products with high abundance as a starting point for the generation of complex natural product analogues,[6] and solid-phase combinatorial synthesis using the above-mentioned strategies.[7]

The diterpene natural product andrographolide, isolated from *Andrographis paniculata*, possesses versatile biological activities, including anti-inflammatory,[8] antimicrobial,[9] immunomodulatory,[10] antidiabetic,[11] cardioprotective,[12] hepatoprotective,[13] and neuroprotective effects.[14] Andrographolide and its derivatives were also found to exert anticancer effects on almost all types of cell lines with varied mechanisms of action.[15] Moreover, it exerts broad-spectrum antivirus properties toward different virus infections.[16]

The outbreak of COVID-19, caused by SARS-CoV-2, has become a global pandemic, which has infected almost 519 million people and claimed over 6.2 million lives worldwide.[17] Searching for effective antivirus treatments for COVID-19 from nature is needed, and thus, we are interested in creating a natural-product-like library with potential antivirus activity.[18] Recent studies revealed that andrographolide is a potential inhibitor of the main protease of SARS-CoV-2 (Mpro) in an *in silico* approach, and it docks successfully in the binding site of SARS-CoV-2 Mpro.[19] Considering its potent antiviral activity and potential interaction with the binding site of SARS-CoV-2, we chose andrographolide with high abundance as a template for analogue generation. Here we present a late-stage functionalization (LSF)[20] approach to tricyclic aza-andrographa-

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pholide derivatives using photo-catalyzed hydroamination as the key reaction, and their anti-HCoV activity.

RESULTS AND DISCUSSION

The structure modifications of andrographolide were mostly focused on the functionalization of the 3,14,19-hydroxyls, 8,17-double bond, C12−C13 double bonds, and α,β-unsaturated γ-butyrolactone moiety (Figure 1a).[21] Modifications at these

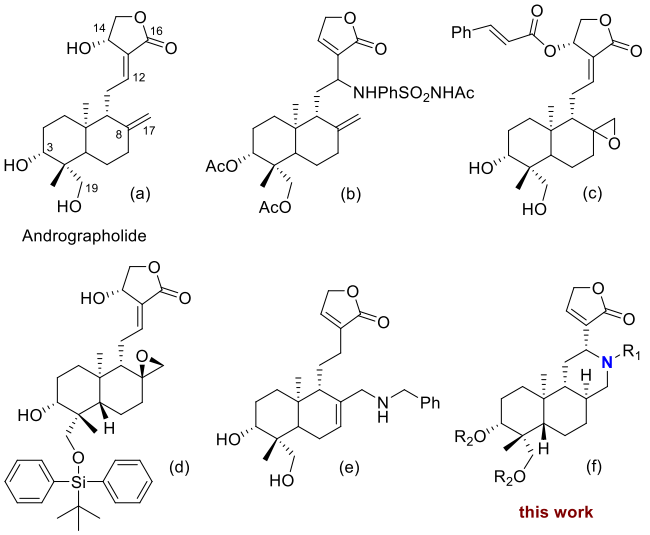

Figure 1. Andrographolide (a), its representative bioactive analogues (b−e), and this work (f).

positions have shown improvement of antivirus or anticancer activity. For example, Golakoti and co-workers found that C-12-substituted amino 14-deoxy-andrographolide derivatives exhibited improved cytotoxic activity compared to andrographolide (Figure 1b).[22] 8,17-Epoxy andrographolide derivatives exhibited significant inhibitory activity toward colon cancer, breast cancer, etc. (Figure 1c,d).[23,24] Andrographolide analogues with 8,17-alkene exo-to-endo isomerization (Figure 1e) displayed a potent anti-influenza virus activity, and it was approximately 1.5-fold more potent than *Lianbizhi*, an andrographolide analogue used clinically in China.[25] Since the N-functionalization plays an important role in the activity and PK profiles of natural products, we proposed to incorporate nitrogen atom into the andrographolide skeleton to further enlarge its chemical space, providing the possibility of a novel structure of tricyclic aza-andrographolides (Figure 1f).

The synthetic pathways toward tricyclic aza-andrographolides mainly include two steps (Scheme 1). The acylated andrographolide **2** was aminated through a base-promoted Michael addition and elimination process, generating C-12-aminated-14-deoxy andrographolides **3**,[22] followed by photo-promoted intramolecular hydroamination of the 8,17-terminal double bond to yield the tricyclic aza-andrographolide derivatives. Based on previous reports,[26] we initially conducted the intramolecular hydroamination of C-12-aminated-14-deoxy andrographolides with the catalysis of the Ir(III) photocatalyst (**I**), which was indicated to be effective for both intermolecular and intramolecular hydroamination of simple unactivated alkenes. However, the reaction proceeded with quite low yield, and some of the C-12-aminated-14-deoxy andrographolides failed to undergo Ir(III)-catalyzed hydroamination. To address this limitation, we then devoted ourselves to search for more effective catalysts.

Toward this end, C-12-benzylamino-14-deoxy andrographolide **3a** was used as a model substrate for the photocatalyst screening. The reaction was carried out using 2−6% photocatalyst and 50% 2,4,6-triisopropylbenzenethiol (TRIP thiol) in toluene under blue light irradiation for 12 h at room temperature. In the presence of $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$, the intramolecular hydroamination reaction produced the desired amination product **4a** in 53% isolated yield (Table 1, entry 1). The related photocatalysts, such as $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, $Ir(ppy)_2(dtbbpy)PF_6$, and $Ir(dFppy)_2(dtbbpy)PF_6$, proved less efficient, providing **4a** in lower yields (entries 2−4). When using $Ir(ppy)_3$, **4a** was obtained in only a trace yield (entry 5). To our delight, the replacement of Ir catalysts with organic dye acridinium

Scheme 1. Synthetic Pathway of Tricyclic Aza-Andrographolide Derivatives

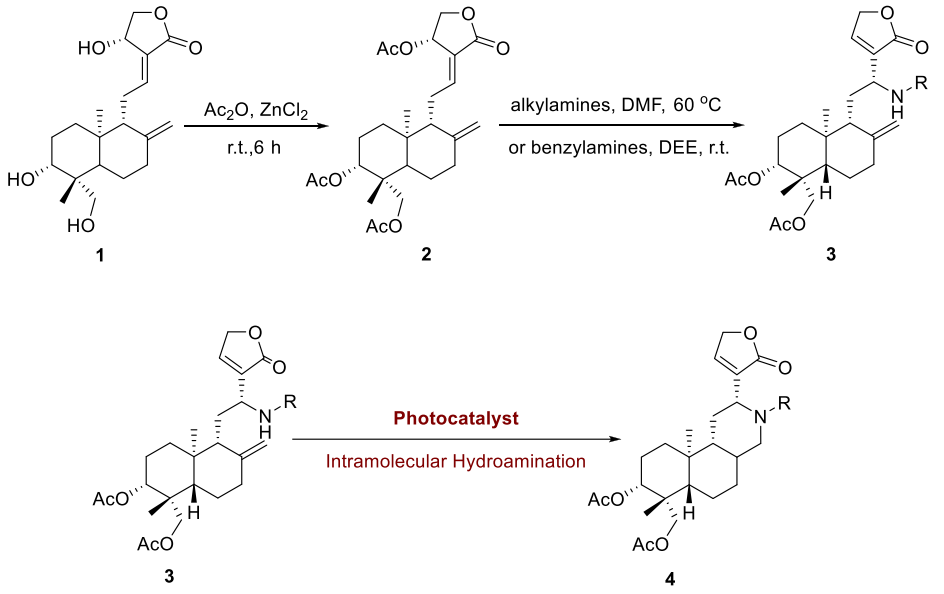

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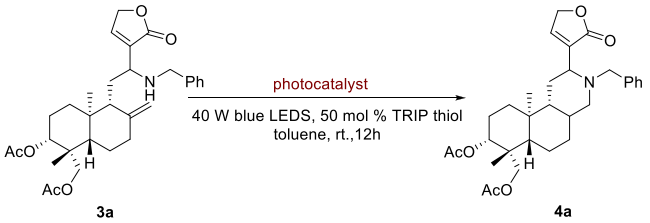
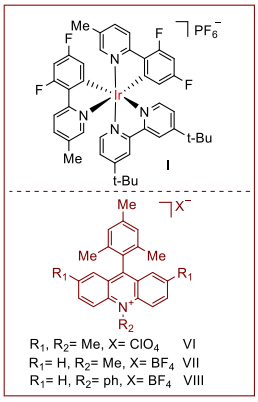
Table 1. Photo-catalyzed Intramolecular Hydroamination: Catalyst Evaluation



entry	photocatalyst	% yield
1	$Ir[dF(Me)ppy]_2(dtbbpy)PF_6$ (I)	53
2	$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (II)	52
3	$[Ir(ppy)_2(dtbbpy)]PF_6$ (III)	50
4	$[Ir(dFppy)_2(dtbbpy)]PF_6$ (IV)	23
5	$Ir(ppy)_3$ (V)	trace
6	VI	79
7	VII	52
8	VIII	26



catalysts led to significantly improved yields. Three acridinium catalysts were evaluated, and catalyst VI proved superior, providing **4a** in 79% yield (entries 6−8). These investigations indicated that acridinium catalyst VI was a better choice for the intramolecular hydroamination of C-12-aminated-14-deoxy andrographolides.

We subsequently set out to explore the scope and potential of the photocatalyst-promoted intramolecular hydroamination. As shown in Table 2, a wide range of substrates **3** were surveyed, including those with arylmethyl, alkyl, and cycloalkyl groups. Pleasingly, most of the substrates examined underwent the cyclization smoothly to give the diverse tricyclic aza-andrographolides **4** in moderate to good yields. Electronic variation on the aryl ring, including electron-withdrawing, neutral, and electron-donating effects, did not obviously affect the efficiency of the reactions. Among these, some functional groups were well tolerated, such as nitro and hydroxyl, which could serve as handles for further synthetic manipulations. In addition, heterocycles including furan and thiophene were also compatible with the current reaction, providing the desired products in moderate yields. Lastly, a series of substrates bearing aliphatic substituents were investigated, and it was found that acyclic and cyclic amines gave diminished yields. The structures of synthesized compounds **4** were all characterized by ^{1}H NMR, ^{13}C NMR, and HRMS, and the stereochemistry was further confirmed by single crystal X-ray diffraction analysis of **4u** (see the Supporting Information).

After exploring the scope of the substrates based on the 3,19-diacetate andrographolide, we next investigated other 3,19-substituted substrates, such as 3,19-ketal andrographolides, which were found to have interesting biological activity.[27] To this end, two types of substrates, **7** and **8** (Scheme 2), were synthesized and subjected to the intramolecular hydroamination, leading to the rapid generation of structurally diverse aza-andrographolide derivatives **9a−p** and **10a−d**, as listed in Table 3.

When compounds **7** and **8** bearing arylmethyl groups served as substrates for cyclization, the desired cyclized products were produced in moderate to good yields (**9a−m** and **10a−d**), while the substrates with branched aliphatic chains furnished the products in low yields (**9o** and **9p**). Considering the aqueous solubility of the cyclized products, we intended to make 3,19-diol derivatives. Accordingly, the selected compound **9** was treated with acetic acid in THF and water to yield the desired product **11** in good yield (Table 3, **11a−e**).

The collection of synthesized aza-andrographolide derivatives **4**, **9**, **10**, and **11** was evaluated in the cytopathic effect (CPE) assays for their antiviral activity against the human coronavirus (HCoV) 229E. All the tested compounds were assayed at 25 μM in the MRC5 cells, and their antiviral activity was calculated based on the protection of the virus-induced CPE normalized by the virus-only control. Additionally, the cytotoxicity of compounds toward MRC5 cells was also assessed under the same conditions, but without virus infection, in parallel. The antiviral activity of compounds is expressed as % inhibition normalized by the cytotoxicity, and selected examples are depicted in Table 4 (entries 1−20). From these assessments, four types of compounds displayed a distinct inhibition profile toward HCoV 229E, with compounds **4a−y** and **9a−p** being potent and compounds **10a−d** and **11a−e** being weak. This result indicated that structural moiety at the 3,19-position is also important for activity. We found that compounds **4d**, **4h**, and **4l−n** with halo- or CF_3-substituted benzyl exhibited good inhibitory activity (~100% inhibition) at 25 μM, whereas **4o** and **4p** with *N*-furylmethyl or *N*-thiophenylmethyl showed a weak inhibition effect. Bulky N-substituents (**4q**, **4v**, and **4y**) gave more favorable results compared to compounds **4r** and **4w**. As for compounds **9**, only substituents at the benzyl-4-position with methyl (**9f**), *tert*-butyl (**9 g**), and nitro (**9 h**) demonstrated good inhibition. Noteworthily, all the tested compounds demonstrated little toxicity against the MRC5 cells (see the Supporting Information for details).

Four compounds—**4l**, **4m**, **4y**, and **9f**—were then chosen to assess the anti-HCoV 229E activity through full dose−response curves. These compounds exhibited great potency with a half-maximal effective concentration (EC_{50}) ranging from 10.1 to 23.1 μM (Table 4, entries 21−24), and compound **4y** was identified as the most promising one, with an EC_{50} of 10.1 μM. The four tested compounds displayed no signs of cytotoxicity, with a half-maximal cytotoxic concentration (CC_{50}) of >100 μM. This result indicated that our synthesized compounds have a potential as anti-HCoV hits for further development.

CONCLUSIONS

In conclusion, we have developed a concise approach to the structurally diverse and bioactive tricyclic aza-andrographolide derivatives through photo-redox catalyzed intramolecular hydroamination, in which the acridinium catalyst VI was proven to be the most effective. We anticipate that this method or strategy will find a variety of applications in the late-stage functionalization of natural products and drugs. Preliminary screening of the generated library of aza-andrographolide derivatives led to the identification of small molecules with anti-HCoV activity, and they can serve as promising anti-HCoV hits for further drug development.

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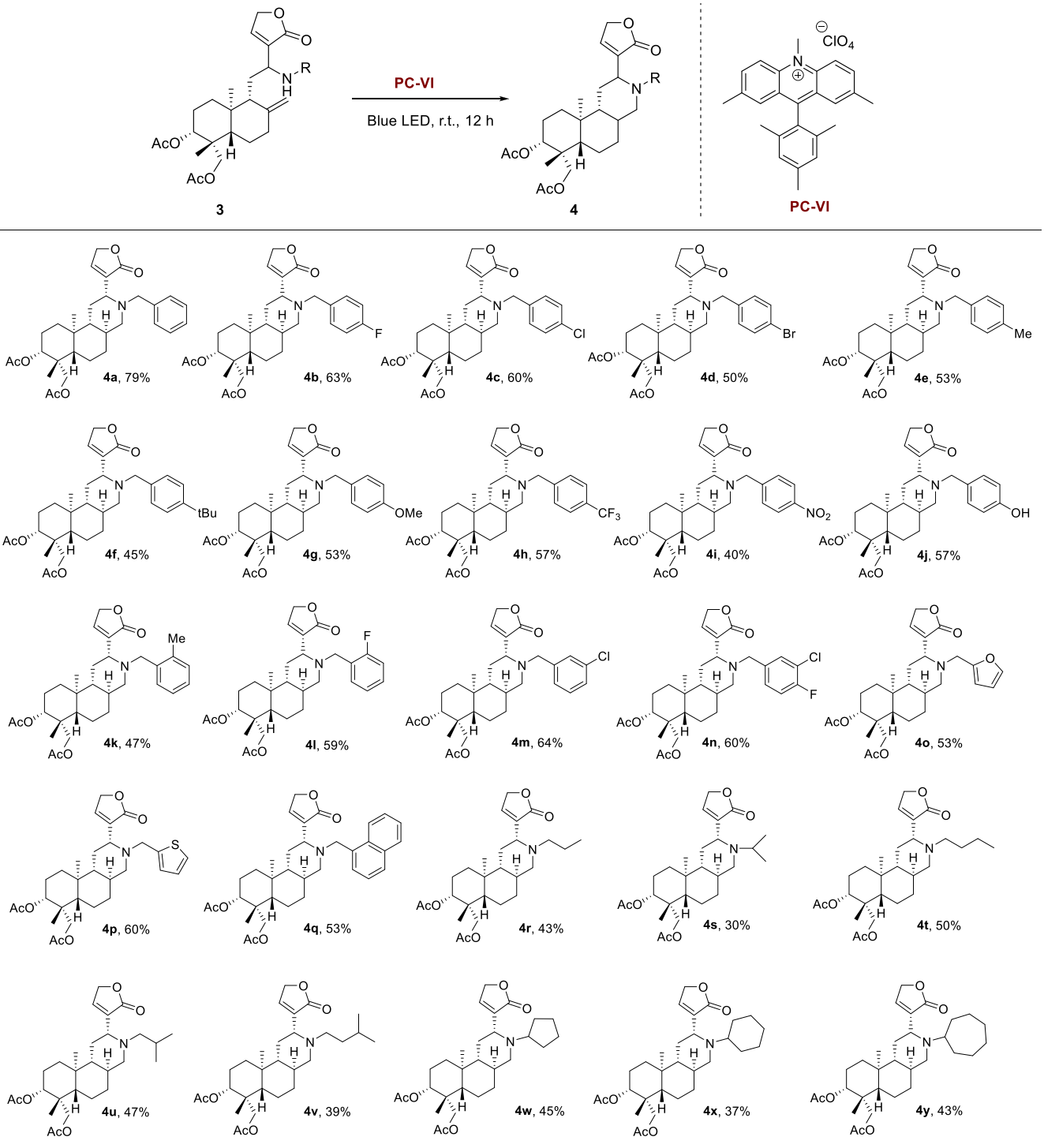
Table 2. Tricyclic Aza-Andrographolide Analogues Synthesized through Intramolecular Hydroamination[a]



[a]Reaction conditions: 3 (0.05 mmol, 1 equiv), PC-VI (6 mol %), 2,4,6-triisopropylbenzene-1-thiol (TRIP thiol) (0.5 equiv), toluene (2 mL), blue LED (40 W), under N_2, room temperature, 12 h. Yields shown are the yields of the isolated product.

EXPERIMENTAL SECTION

General Information. Unless noted otherwise, all reactions were performed under a nitrogen atmosphere, and materials obtained from commercial suppliers were used without further purification. The purification of products was conducted by flash column chromatography on a silica gel (200−300 mesh). ^{1}H NMR spectra were recorded on 300−500 MHz spectrometers using the residual solvent (δ ($CDCl_3$) = 7.26) as internal standard. All the coupling constants are reported in hertz. ^{13}C NMR spectra were recorded on the same instruments, and chemical shifts were measured relative to solvent resonances (δ ($CDCl_3$) = 77.0). High-resolution mass spectra were obtained on a quadrupole time-of-flight (QqTOF) mass spectrometer utilizing the electrospray ionization (ESI) method.

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Scheme 2. Synthetic Route for the Substrates of Intramolecular Hydroamination

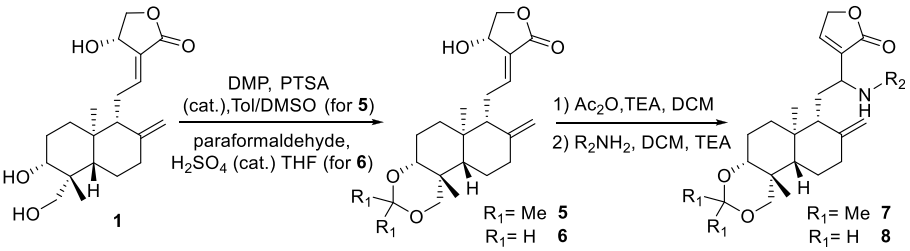
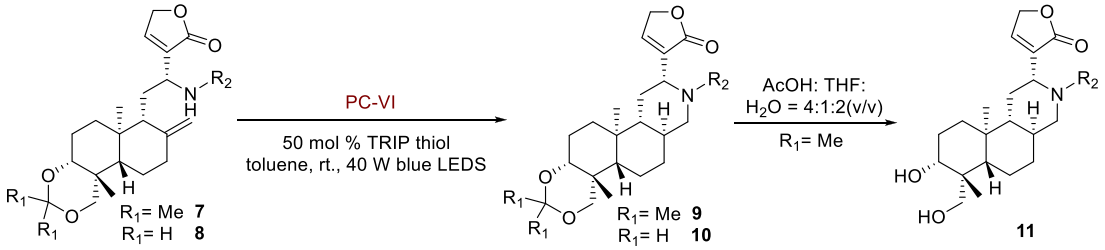


Table 3. Tricyclic Aza-Andrographolide Analogues Synthesized through Intramolecular Hydroamination



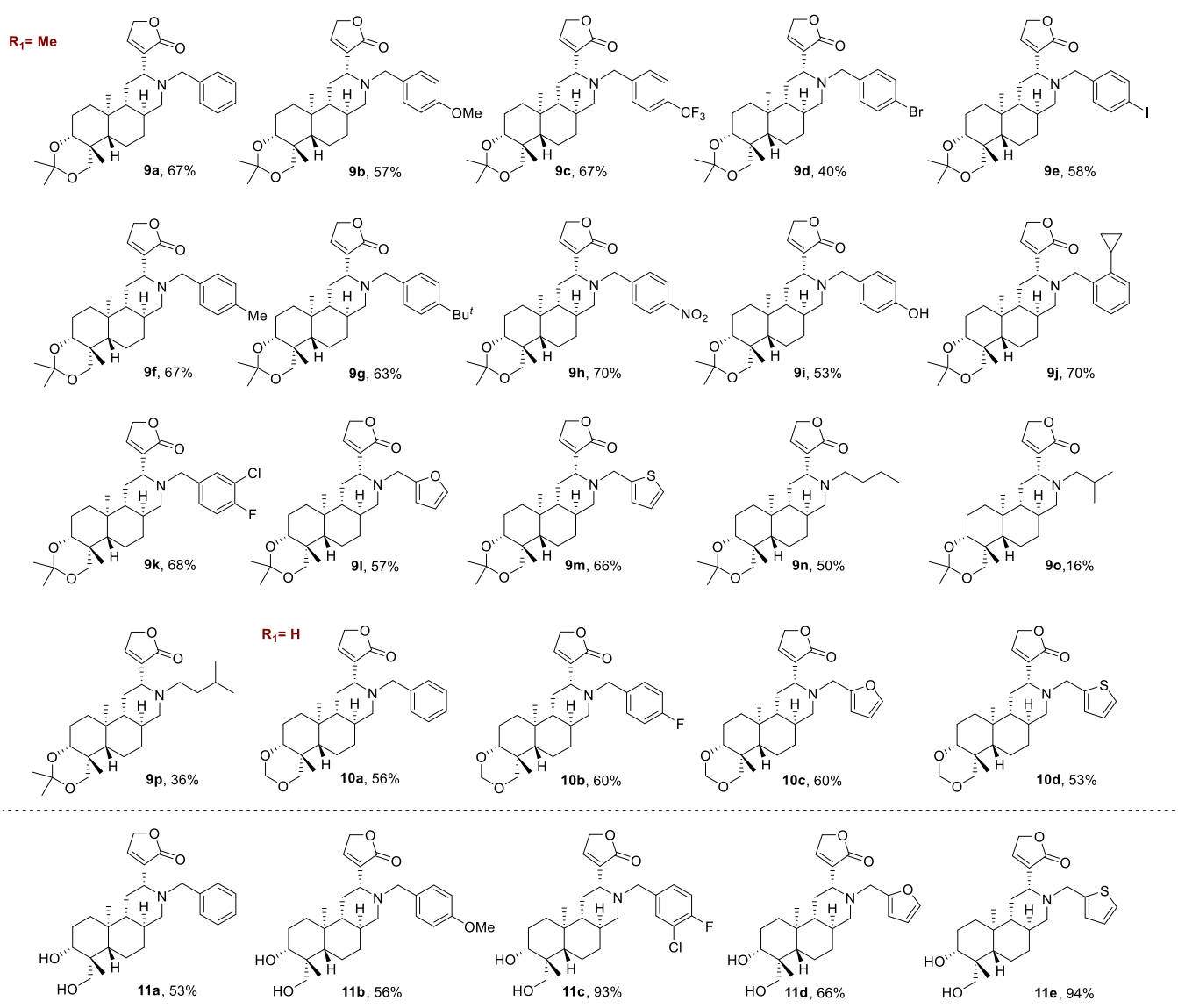


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Table 4. Evaluation of the *In Vitro* Inhibitory Activity of Test Compounds against Human Coronavirus 229E

entry	CPD no.	inhibition % (25 μM)	cytotoxicity % (25 μM)	normalized inhibition % (25 μM)
1	4a	82.4	15.5	66.8
2	4d	106.9	−3.0	110.0
3	4h	113.5	−5.4	118.9
4	4j	50.4	−5.2	55.6
5	4l	128.4	−19.5	148.0
6	4m	116.5	−13.2	129.8
7	4n	96.6	−4.9	101.5
8	4o	53.9	−4.5	58.4
9	4p	31.2	4.2	26.9
10	4q	106.4	−14.7	121.2
11	4r	45.8	−5.6	51.4
12	4v	104.9	3.2	101.7
13	4w	6.8	−4.5	11.3
14	4y	116.8	−18.2	135.0
15	9f	98.8	−1.6	100.5
16	9g	103.1	−0.2	103.3
17	9h	97.5	−4.7	102.3
18	10d	45.1	−13.4	58.6
19	11a	34.9	−4.8	39.7
20	andrographolide 1	58.4	23.6	34.8
		EC_{50} (μM)		CC_{50} (μM)
21	4l	18.7		>100
22	4m	15.7		>100
23	4y	10.1		>100
24	9f	23.1		>100

General Procedure for Photocatalytic Intramolecular Hydroamination. A 16 × 125 mm screw cap culture tube with a Teflon septum was equipped with a Teflon stir bar and charged with the secondary amine (0.05 mmol), 9-mesityl-2,7,10-trimethylacridinium perchlorate (1.5 mg, 0.0030 mmol, 6 mol %), and 2,4,6-triisopropylbezene-1-thiol (6 mg, 0.025 mmol, 0.5 equiv).The reaction vessel was placed under a vacuum and backfilled with argon three times. Dry toluene (2 mL, 0.05 M) was then added. The resulting pale green solution was then irradiated by two 40 W Kessil KSH150B blue LED lamps and stirred vigorously until starting material consumption was observed by TLC. Throughout the reaction, a fan was positioned to keep the culture tube at room temperature. Upon completion as determined by GC analysis, the reaction mixture was concentrated and then purified by silica gel column chromatography to obtain the desired product.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-benzyl-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4a**). 79% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.37−7.18 (m, 5H), 4.78 (s, 2H), 4.57 (dd, *J* = 10.2, 5.6 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.10 (d, *J* = 12.0 Hz, 1H), 3.82 (s, 1H), 3.15 (d, *J* = 9.9 Hz, 1H), 2.96 (d, *J* = 13.9 Hz, 1H), 2.87−2.73 (m, 1H), 2.02 (d, *J* = 2.3 Hz, 6H), 1.60 (qdd, *J* = 26.7, 12.8, 2.8 Hz, 10H), 1.11 (dd, *J* = 27.1, 7.5 Hz, 2H), 0.98 (s, 3H), 0.88−0.74 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.65, 171.15, 170.68, 146.01, 139.28, 137.42, 130.11, 128.50, 127.09, 80.21, 77.58, 77.26, 76.94, 70.59, 65.18, 60.47, 59.48, 59.41, 55.37, 53.89, 41.34, 36.79, 36.11, 35.06, 33.23, 31.99, 29.96, 29.88, 29.51, 27.40, 23.97, 22.79, 21.92, 21.38, 21.28, 21.24, 14.63; HRMS (*m*/*z*) calcd for $C_{31}H_{42}NO_6$ (+) 524.3012, found 524.3004.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(4-fluorobenzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4b**). 63% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.22 (dd, *J* = 8.4, 5.6 Hz, 2H), 6.97 (t, *J* = 8.7 Hz, 2H), 4.79 (s, 2H), 4.56 (dd, *J* = 11.1, 4.8 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.12−4.07 (m, 1H), 3.77 (d, *J* = 13.8 Hz, 1H), 3.14 (d, *J* = 9.3 Hz, 1H), 2.92 (d, *J* = 13.8 Hz, 1H), 2.77 (dd, *J* = 11.1, 3.2 Hz, 1H), 2.02 (d, *J* = 3.8 Hz, 6H), 1.80−1.42 (m, 10H), 1.16−1.04 (m, 2H), 0.98 (s, 3H), 0.85−0.76 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.26, 170.87, 170.42, 162.85, 160.90, 145.78, 137.22, 134.71, 134.68, 129.78, 129.72, 115.15, 114.98, 80.02, 70.30, 64.96, 60.18, 59.24, 58.51, 55.22, 53.77, 41.18, 36.63, 35.93, 34.90, 32.97, 31.82, 23.78, 22.58, 21.74, 21.12, 21.02, 14.43; HRMS (*m*/*z*) calcd for $C_{31}H_{41}FNO_6$ (+) 542.2918, found 542.2918.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(4-chlorobenzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4c**). 60% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 (s, 1H), 7.28−7.26 (m, 1H), 7.22 (t, *J* = 7.8 Hz, 2H), 7.17 (d, *J* = 7.0 Hz, 1H), 4.79 (s, 2H), 4.57 (dd, *J* = 11.1, 4.6 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.11 (d, *J* = 11.8 Hz, 1H), 3.78 (d, *J* = 14.0 Hz, 1H), 3.15 (d, *J* = 9.6 Hz, 1H), 2.93 (d, *J* = 14.0 Hz, 1H), 2.76 (dd, *J* = 11.1, 3.2 Hz, 1H), 2.03 (d, *J* = 4.3 Hz, 6H), 1.78−1.38 (m, 10H), 1.17−1.03 (m, 2H), 0.99 (s, 3H), 0.85 (s, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.36, 170.99, 170.53, 145.91, 137.17, 132.59, 129.65, 129.07, 128.48, 128.26, 125.33, 80.05, 77.33, 77.07, 76.82, 70.40, 65.02, 60.27, 59.25, 58.61, 55.22, 53.74, 41.19, 36.64, 35.96, 34.91, 32.99, 31.82, 23.80, 22.63, 21.76, 21.21, 21.11, 14.47; HRMS (*m*/*z*) calcd for $C_{31}H_{41}ClNO_6$ (+) 558.2622, found 558.2620.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(4-bromobenzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4d**). 50% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (d, *J* = 8.2 Hz, 3H), 7.16 (d, *J* = 8.2 Hz, 2H), 4.79 (s, 2H), 4.57 (dd, *J* = 10.1, 5.6 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.14−4.07 (m, 1H), 3.76 (d, *J* = 14.0 Hz, 1H), 3.15 (d, *J* = 10.1 Hz, 1H), 2.92 (d, *J* = 14.0 Hz, 1H), 2.76 (d, *J* = 8.3 Hz, 1H), 2.03 (d, *J* = 2.8 Hz, 6H), 1.82−1.36 (m, 10H), 1.17−1.02 (m, 2H), 0.98 (s, 3H), 0.88−0.71 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.56, 171.21, 170.74, 146.14, 138.34, 137.31, 131.63, 130.24, 120.86, 80.22, 77.58, 77.26, 76.94, 70.62, 65.22, 60.44, 59.42, 58.82, 55.39, 53.90, 41.37, 36.82, 36.15, 35.07, 33.16, 31.99, 23.98, 22.82, 21.94, 21.41, 21.32, 14.66; HRMS (*m*/*z*) calcd for $C_{31}H_{41}BrNO_6$ (+) 602.2117, found 602.2110.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-7,10a-dimethyl-3-(4-methylbenzyl)-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4e**). 53% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.15 (d, *J* = 7.9 Hz, 2H), 7.10 (d, *J* = 7.8 Hz, 2H), 4.79 (s, 2H), 4.57 (dd, *J* = 11.2, 4.8 Hz, 1H), 4.37 (d, *J* = 11.7 Hz, 1H), 4.11 (d, *J* = 11.7 Hz, 1H), 3.80 (d, *J* = 13.7 Hz, 1H), 3.14 (d, *J* = 10.3 Hz, 1H), 2.94 (d, *J* = 13.8 Hz, 1H), 2.83 (dd, *J* = 11.1, 2.7 Hz, 1H), 2.32 (s, 3H), 2.02 (d, *J* = 3.7 Hz, 6H), 1.80−1.40 (m, 10H), 1.09 (dd, *J* = 21.0, 19.2 Hz, 2H), 0.98 (s, 3H), 0.85−0.76 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.64, 171.14, 170.68, 145.93, 137.53, 136.73, 136.06, 129.22, 128.54, 80.29, 77.51, 77.26, 77.01, 70.59,

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65.22, 60.41, 59.41, 59.19, 55.47, 53.99, 41.43, 36.87, 36.17, 35.13, 33.29, 32.06, 29.91, 24.03, 22.83, 21.99, 21.38, 21.29, 14.67, 14.31; HRMS (*m/z*) calcd for $C_{32}H_{44}NO_6$ (+) 538.3169, found 538.3159.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(4-(tert-butyl)benzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4f**). 45% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.32 (d, J = 8.2 Hz, 2H), 7.20 (d, J = 8.1 Hz, 2H), 4.77 (d, J = 4.4 Hz, 2H), 4.57 (dd, J = 11.3, 4.7 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.12 (d, J = 11.7 Hz, 1H), 3.81 (d, J = 13.9 Hz, 1H), 3.15 (d, J = 10.1 Hz, 1H), 2.96 (d, J = 13.9 Hz, 1H), 2.87 (dd, J = 11.1, 2.8 Hz, 1H), 2.03 (d, J = 2.9 Hz, 6H), 1.82−1.50 (m, 10H), 1.31 (s, 9H), 1.08 (d, J = 11.1 Hz, 2H), 0.99 (s, 3H), 0.86−0.78 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.66, 171.14, 170.68, 150.08, 145.91, 137.60, 136.19, 128.21, 125.44, 77.52, 77.26, 77.01, 60.56, 59.43, 59.13, 55.50, 54.00, 41.46, 36.90, 36.21, 35.18, 34.70, 33.34, 32.10, 31.64, 24.06, 22.86, 22.02, 21.39, 21.28, 14.69; HRMS (*m/z*) calcd for $C_{35}H_{50}NO_6$ (+) 580.3638 found 580.3629.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(4-methoxybenzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4g**). 53% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.16 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 4.80 (s, 2H), 4.56 (dd, J = 10.0, 5.6 Hz, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.09 (d, J = 11.8 Hz, 1H), 3.78 (s, 4H), 3.12 (d, J = 9.7 Hz, 1H), 2.92 (d, J = 13.6 Hz, 1H), 2.81 (d, J = 8.3 Hz, 1H), 2.02 (d, J = 2.5 Hz, 6H), 1.80−1.37 (m, 10H), 1.17−1.03 (m, 2H), 0.97 (s, 3H), 0.86−0.71 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.85, 171.21, 170.73, 158.81, 146.14, 137.33, 130.79, 129.81, 113.86, 77.68, 77.26, 76.83, 65.18, 60.13, 59.26, 58.74, 55.47, 55.34, 53.85, 41.32, 36.77, 36.09, 34.98, 33.19, 32.01, 23.96, 22.78, 21.92, 21.41, 21.31, 14.63; HRMS (*m/z*) calcd for $C_{32}H_{44}FNO_7$ (+) 554.3118, found 554.3110.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-3-(4-(trifluoromethyl)-benzyl)tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4h**). 57% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.55 (d, J = 8.1 Hz, 2H), 7.41 (d, J = 7.4 Hz, 3H), 4.79 (s, 2H), 4.57 (dd, J = 10.2, 5.6 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.11 (d, J = 11.6 Hz, 1H), 3.86 (d, J = 14.3 Hz, 1H), 3.19 (d, J = 9.7 Hz, 1H), 3.03 (d, J = 14.4 Hz, 1H), 2.76 (dd, J = 10.7, 2.5 Hz, 1H), 2.03 (d, J = 2.2 Hz, 6H), 1.87−1.34 (m, 10H), 1.21−1.12 (m, 1H), 1.12−1.04 (m, 1H), 0.99 (s, 3H), 0.91−0.75 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.53, 171.21, 170.75, 146.17, 143.71, 137.31, 129.64, 129.26, 128.63, 128.45, 125.50, 125.46, 80.22, 77.58, 77.26, 76.94, 70.60, 65.22, 60.61, 59.44, 59.03, 55.40, 53.90, 41.37, 36.82, 36.16, 35.10, 33.15, 31.98, 23.98, 22.82, 21.94, 21.41, 21.31, 14.66; HRMS (*m/z*) calcd for $C_{32}H_{41}F_3NO_6$ (+) 592.2886, found 592.2880.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-7,10a-dimethyl-3-(4-nitrobenzyl)-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4i**). 40% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.16 (d, J = 8.6 Hz, 2H), 7.48 (d, J = 8.5 Hz, 2H), 7.40 (s, 1H), 4.80 (s, 2H), 4.57 (dd, J = 10.0, 5.5 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.12 (d, J = 11.7 Hz, 1H), 3.89 (d, J = 14.7 Hz, 1H), 3.22 (d, J = 9.4 Hz, 1H), 3.09 (d, J = 14.9 Hz, 1H), 2.77−2.64 (m, 1H), 2.03 (d, J = 1.9 Hz, 6H), 1.74−1.57 (m, 10H), 1.08 (d, J = 11.0 Hz, 2H), 0.99 (s, 3H), 0.87 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.41, 171.23, 170.78, 147.51, 147.33, 146.34, 137.22, 129.01, 123.87, 80.22, 77.59, 77.27, 76.95, 70.60, 65.23, 60.78, 59.50, 58.92, 55.41, 53.92, 41.39, 36.84, 36.19, 35.14, 33.07, 31.98, 23.99, 22.84, 21.94, 21.44, 21.34, 14.69; HRMS (*m/z*) calcd for $C_{31}H_{41}N_2O_8$ (+) 569.2863, found 569.2857.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(4-hydroxybenzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4j**). 57% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.11 (d, J = 8.1 Hz, 2H), 6.75 (d, J = 8.4 Hz, 2H), 4.84 (s, 2H), 4.56 (dd, J = 10.0, 5.8 Hz, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.13−4.07 (m, 1H), 3.79 (s, 1H), 3.00 (m, 4H), 2.03 (d, J = 2.6 Hz, 6H), 1.84−1.38 (m, 10H), 1.15−1.02 (m, 2H), 0.98 (s, 3H), 0.86−0.76 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.92, 171.04, 170.59, 152.64, 135.92, 125.06, 124.16, 115.29, 105.83, 80.05, 67.11, 66.68, 65.03, 60.41, 59.10, 58.54, 55.18, 41.18, 36.62, 35.96, 33.63, 31.85, 29.73, 23.78, 22.62, 21.74, 21.21, 21.11, 14.43; HRMS (*m/z*) calcd for $C_{31}H_{43}NO_7$ (+) 540.2961, found 540.2956.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-7,10a-dimethyl-3-(2-methylbenzyl)-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4k**). 47% yield, yellow solid; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, J = 7.1 Hz, 1H), 7.36 (s, 1H), 7.14 (dt, J = 16.7, 7.1 Hz, 3H), 4.75 (d, J = 8.5 Hz, 2H), 4.59 (dd, J = 11.3, 4.9 Hz, 1H), 4.38 (d, J = 11.7 Hz, 1H), 4.16−4.11 (m, 1H), 3.68 (d, J = 14.5 Hz, 1H), 3.19 (d, J = 10.3 Hz, 1H), 3.07−2.98 (m, 1H), 2.83 (d, J = 9.6 Hz, 1H), 2.24 (s, 3H), 2.03 (d, J = 3.5 Hz, 6H), 1.79−1.58 (m, 10H), 1.09 (d, J = 10.7 Hz, 2H), 1.00 (s, 3H), 0.91−0.85 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.83, 171.22, 170.75, 145.98, 137.46, 136.64, 130.35, 128.41, 126.82, 126.07, 77.58, 77.26, 76.94, 70.61, 65.28, 60.82, 59.83, 57.26, 55.44, 54.00, 41.39, 36.85, 36.17, 35.18, 33.42, 32.04, 24.02, 22.84, 21.98, 21.43, 21.33, 19.60, 14.68; HRMS (*m/z*) calcd for $C_{32}H_{44}NO_6$ (+) 538.3169, found 538.3176.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(2-fluorobenzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4l**). 59% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.34 (t, J = 7.4 Hz, 1H), 7.24 7.15 (m, 1H), 7.09 (t, J = 7.1 Hz, 1H), 7.0−6.94 (m, 1H), 4.83 (s, 2H), 4.57 (dd, J = 10.3, 5.4 Hz, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.10 (d, J = 11.8 Hz, 1H), 3.81 (d, J = 13.8 Hz, 1H), 3.12 (dd, J = 22.3, 12.2 Hz, 2H), 2.85 (dd, J = 11.0, 2.8 Hz, 1H), 2.02 (d, J = 1.8 Hz, 6H), 1.83−1.37 (m, 10H), 1.11 (d, J = 11.4 Hz, 2H), 0.98 (s, 3H), 0.86−0.75 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.59, 171.11, 170.65, 162.54, 160.58, 146.14, 137.15, 131.26, 128.88, 124.12, 115.61, 115.44, 80.25, 77.51, 77.26, 77.01, 70.63, 65.20, 60.37, 59.58, 55.44, 53.86, 52.68, 41.42, 36.85, 36.16, 35.06, 33.31, 32.07, 24.02, 22.83, 21.97, 21.37, 21.27, 14.65; HRMS (*m/z*) calcd for $C_{31}H_{41}FNO_6$ (+) 542.2918, found 542.2910.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(3-chlorobenzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4m**). 64% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.30 (s, 1H), 7.21 (d, J = 5.7 Hz, 2H), 7.17−7.10 (m, 1H), 4.80 (s, 2H), 4.58 (d, J = 9.6 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.11 (d, J = 11.6 Hz, 1H), 3.80 (d, J = 14.1 Hz, 1H), 3.16 (d, J = 10.1 Hz, 1H), 2.93 (d, J = 14.1 Hz, 1H), 2.78 (d, J = 8.2 Hz, 1H), 2.03 (d, J = 3.0 Hz, 6H), 1.84−1.34 (m, 10H), 1.10 (dd, J = 17.6, 16.0 Hz, 2H), 0.99 (s, 3H),

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0.90−0.76 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.61, 171.21, 170.74, 146.13, 141.65, 137.31, 134.51, 129.81, 128.35, 127.34, 126.66, 80.23, 77.58, 77.26, 76.94, 70.64, 65.25, 60.56, 59.38, 58.96, 55.39, 53.90, 41.36, 36.82, 36.16, 35.04, 33.20, 32.00, 23.98, 22.83, 21.95, 21.41, 21.32, 14.66; HRMS (m/z) calcd for $C_{31}H_{41}ClNO_6$ (+) 558.2622, found 558.2618.

*((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(3-chloro-4-fluorobenzyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4n**).* 60% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.34 (d, J = 6.7 Hz, 1H), 7.09 (dd, J = 13.6, 6.6 Hz, 2H), 4.81 (s, 2H), 4.58 (d, J = 9.2 Hz, 1H), 4.37 (d, J = 11.6 Hz, 1H), 4.11 (d, J = 11.5 Hz, 1H), 3.75 (d, J = 13.9 Hz, 1H), 3.15 (d, J = 10.1 Hz, 1H), 2.89 (d, J = 14.0 Hz, 1H), 2.74 (d, J = 9.0 Hz, 1H), 2.03 (s, 6H), 1.64 (m, J = 48.5, 31.1, 19.0 Hz, 10H), 1.08 (d, J = 12.1 Hz, 2H), 0.99 (s, 3H), 0.86 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.52, 171.21, 170.75, 158.51, 156.05, 146.15, 137.29, 136.50, 130.26, 128.10, 128.03, 121.12, 120.95, 116.65, 116.44, 80.22, 77.58, 77.27, 76.95, 70.62, 65.23, 60.42, 59.39, 58.34, 55.39, 53.92, 41.36, 36.82, 36.16, 35.05, 33.14, 32.00, 23.98, 22.83, 21.94, 21.41, 21.32, 14.66; HRMS (m/z) calcd for $C_{31}H_{40}ClFNO_6$ (+) 576.2528, found 576.2525.

*((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-(furan-2-ylmethyl)-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4o**).* 53% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.35 (d, J = 1.1 Hz, 1H), 6.28 (dd, J = 3.1, 1.9 Hz, 1H), 6.13 (d, J = 3.0 Hz, 1H), 4.82 (s, 2H), 4.57 (s, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.10 (d, J = 11.6 Hz, 1H), 3.69 (d, J = 14.5 Hz, 1H), 3.28 (d, J = 14.5 Hz, 1H), 3.09 (d, J = 9.7 Hz, 1H), 2.92 (dd, J = 11.3, 3.4 Hz, 1H), 2.02 (d, J = 6.3 Hz, 6H), 1.77−1.38 (m, 10H), 1.06 (d, J = 12.6 Hz, 2H), 0.98 (s, 3H), 0.83 (s, 3H), 0.80−0.67 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.60, 171.20, 170.74, 146.44, 142.38, 130.34, 110.38, 108.92, 80.23, 77.51, 77.26, 77.01, 60.65, 58.65, 55.40, 53.74, 51.81, 41.40, 36.82, 36.15, 35.08, 33.07, 32.06, 24.00, 22.83, 21.97, 21.42, 21.33, 14.66; HRMS (m/z) calcd for $C_{29}H_{40}NO_7$ (+) 514.2805, found 514.2800.

*((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-3-(thiophen-2-ylmethyl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4p**).* 60% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.20 (d, J = 4.9 Hz, 1H), 6.93 (dd, J = 5.0, 3.5 Hz, 1H), 6.84 (d, J = 3.2 Hz, 1H), 4.82 (s, 2H), 4.56 (dd, J = 10.1, 5.7 Hz, 1H), 4.36 (d, J = 11.7 Hz, 1H), 4.14−4.08 (m, 1H), 3.89 (d, J = 14.5 Hz, 1H), 3.36 (d, J = 14.5 Hz, 1H), 3.17 (d, J = 9.6 Hz, 1H), 2.95 (dd, J = 11.1, 3.3 Hz, 1H), 2.03 (d, J = 3.5 Hz, 6H), 1.83−1.42 (m, 10H), 1.09 (s, 2H), 0.98 (s, 3H), 0.87−0.73 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.65, 171.21, 170.73, 146.09, 142.71, 137.10, 126.91, 125.65, 124.84, 80.23, 77.58, 77.47, 77.26, 76.94, 70.74, 65.23, 60.42, 58.72, 55.39, 53.93, 53.82, 41.38, 36.82, 36.15, 35.13, 33.33, 32.02, 23.99, 22.83, 21.95, 21.42, 21.32, 14.65; HRMS (m/z) calcd for $C_{29}H_{40}NO_6S$ (+) 530.2576, found 530.2574.

*((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-7,10a-dimethyl-3-(naphthalen-1-ylmethyl)-2-(2-oxo-2,5-dihydrofuran-3-yl)tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4q**).* 53% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14−8.06 (m, 1H), 7.88−7.80 (m, 1H), 7.74 (d, J = 8.1 Hz, 1H), 7.61 (d, J = 6.9 Hz, 1H), 7.52−7.39 (m, 3H), 7.37 (s, 1H), 4.64 (dt, J = 16.0, 11.9 Hz, 3H), 4.38 (d, J = 11.7 Hz, 1H), 4.12 (dd, J = 13.3, 5.6 Hz, 2H), 3.55 (d, J = 14.6 Hz, 1H), 3.28 (d, J = 9.9 Hz, 1H), 2.87 (dd, J = 11.1, 2.6 Hz, 1H), 2.03 (s, 6H), 1.86−1.42 (m, 10H), 1.11 (s, 2H), 0.99 (s, 3H), 0.87 (s, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.82, 171.22, 170.75, 146.02, 137.38, 135.01, 133.90, 132.13, 128.80, 127.65, 126.01, 125.97, 125.83, 125.73, 123.98, 80.27, 77.58, 77.26, 76.94, 70.57, 65.27, 61.21, 60.10, 57.76, 55.42, 54.01, 41.38, 36.85, 36.17, 35.20, 33.41, 32.01, 24.01, 22.83, 21.96, 21.42, 21.32, 14.70; HRMS (m/z) calcd for $C_{35}H_{44}NO_6$ (+) 574.3169, found 574.3138.

*((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-3-propyltetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4r**).* 43% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 4.87−4.78 (m, 2H), 4.57 (dd, J = 10.8, 5.3 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.12 (d, J = 11.7 Hz, 1H), 3.16−3.02 (m, 2H), 2.51 (dd, J = 11.6, 5.4 Hz, 1H), 2.03 (d, J = 8.3 Hz, 8H), 1.71−1.42 (m, 10H), 1.13−1.04 (m, 2H), 0.99 (s, 3H), 0.83 (d, J = 16.0 Hz, 10H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.66, 171.18, 170.73, 139.16, 114.38, 80.20, 77.51, 77.26, 77.00, 70.71, 65.20, 59.95, 59.12, 57.07, 55.38, 53.79, 41.38, 36.79, 36.15, 34.80, 32.73, 32.11, 23.97, 22.82, 21.99, 21.41, 21.33, 19.26, 14.61, 12.04; HRMS (m/z) calcd for $C_{27}H_{42}NO_{66}$ (+) 476.3012, found 476.3005.

*((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-isopropyl-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4s**).* 30% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.66 (s, 1H), 4.95−4.76 (m, 2H), 4.65−4.48 (m, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.12 (d, J = 11.6 Hz, 1H), 3.51 (d, J = 10.2 Hz, 1H), 3.02 (dd, J = 39.3, 8.4 Hz, 2H), 2.04 (d, J = 6.4 Hz, 7H), 1.71 (ddd, J = 16.5, 10.0, 4.6 Hz, 10H), 1.16 (d, J = 6.6 Hz, 3H), 1.10 (s, 2H), 1.00 (s, 3H), 0.98−0.93 (m, 3H), 0.91−0.77 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.16, 171.13, 170.77, 149.90, 139.99, 80.11, 77.51, 77.26, 77.01, 70.86, 65.24, 56.39, 55.36, 53.91, 51.02, 41.37, 36.80, 36.27, 32.05, 29.94, 29.52, 27.51, 23.94, 22.91, 21.97, 21.41, 21.33, 14.58; HRMS (m/z) calcd for $C_{27}H_{42}NO_6$ (+) 476.3012, found 476.3012.

*((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-butyl-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4t**).* 50% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41 (s, 1H), 4.93−4.78 (m, 2H), 4.56 (dd, J = 10.1, 5.9 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.11 (dd, J = 9.5, 2.2 Hz, 1H), 3.11−2.99 (m, 2H), 2.59−2.46 (m, 1H), 2.03 (d, J = 6.4 Hz, 8H), 1.80−1.32 (m, 13H), 1.14−1.04 (m, 2H), 0.99 (s, 3H), 0.86 (d, J = 7.3 Hz, 4H), 0.85−0.74 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.70, 171.19, 170.73, 146.57, 136.77, 77.58, 77.26, 76.94, 70.64, 65.18, 60.12, 59.24, 55.39, 55.06, 53.85, 41.38, 36.79, 36.13, 35.01, 32.93, 32.15, 28.53, 23.98, 22.81, 22.00, 21.41, 21.33, 20.87, 14.62, 14.21; HRMS (m/z) calc. For $C_{28}H_{44}NO_6$ (+) 490.3169, found 490. 3164.

*((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-isobutyl-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (**4u**).* 47% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.32 (s, 1H), 4.91−4.71 (m, 2H), 4.57 (dd, J = 10.7, 5.3 Hz, 1H), 4.37 (d, J = 11.7 Hz, 1H), 4.12 (d, J = 11.7 Hz, 1H), 2.97 (dd, J = 18.2, 8.9 Hz, 2H), 2.10 (t, J = 12.0 Hz, 1H), 2.03 (d, J = 7.6 Hz, 6H), 1.81−1.43 (m, 12H), 1.12−1.04 (m, 2H), 0.99 (s, 3H), 0.85 (d, J = 8.7 Hz, 8H), 0.78 (d, J = 6.3 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.92, 171.22, 170.73, 146.18, 137.79, 80.28, 77.58, 77.26, 76.94, 70.54, 65.24, 63.57, 60.65,

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59.84, 55.43, 53.81, 41.40, 36.80, 36.11, 35.10, 33.46, 32.24, 25.92, 24.00, 22.83, 22.03, 21.51, 21.43, 21.34, 20.80, 14.66; HRMS (*m/z*) calcd for $C_{28}H_{44}NO_6$ (+) 490.3169, found 490.3164.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-isopentyl-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (***4v***). 39% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 (s, 1H), 4.91−4.75 (m, 2H), 4.56 (dd, *J* = 10.7, 5.4 Hz, 1H), 4.36 (d, *J* = 11.7 Hz, 1H), 4.17−4.09 (m, 1H), 3.16−3.01 (m, 2H), 2.62−2.52 (m, 1H), 2.10−1.97 (m, 8H), 1.77−1.39 (m, 11H), 1.38−1.28 (m, 2H), 1.16−1.05 (m, 2H), 0.99 (s, 3H), 0.88−0.72 (m, 11H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.55, 171.07, 170.64, 146.42, 136.39, 80.24, 77.51, 77.26, 77.01, 70.62, 65.17, 60.56, 60.11, 59.27, 55.46, 53.90, 53.55, 41.45, 36.85, 36.18, 35.21, 34.99, 32.83, 32.15, 29.90, 26.72, 24.01, 23.06, 22.83, 22.59, 22.03, 21.35, 21.27, 14.63; HRMS (*m/z*) calcd for $C_{29}H_{46}NO_6$ (+) 504.3325, found 504.3323.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-cyclopentyl-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (***4w***). 45% yield, yellow solid; ^{1}H NMR (500 MHz, MeOD) δ 7.73 (s, 1H), 4.94 (dd, *J* = 3.6, 1.4 Hz, 2H), 4.57 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.14 (d, *J* = 11.7 Hz, 1H), 3.55 (d, *J* = 10.5 Hz, 1H), 3.44−3.33 (m, 1H), 3.03 (dd, *J* = 11.5, 3.4 Hz, 1H), 2.27−2.10 (m, 1H), 2.03 (d, *J* = 8.8 Hz, 6H), 1.83−1.47 (m, 18H), 1.21 (d, *J* = 13.8 Hz, 2H), 1.03 (s, 3H), 0.98−0.85 (m, 5H); ^{13}C NMR (125 MHz, MeOD) δ 173.83, 171.37, 170.93, 151.14, 139.40, 80.12, 71.09, 64.53, 62.01, 58.10, 54.80, 53.11, 51.59, 48.11, 47.94, 47.77, 47.60, 47.43, 47.26, 47.09, 41.01, 36.10, 35.61, 34.02, 31.32, 28.22, 24.27, 23.96, 23.36, 22.18, 21.55, 21.47, 19.68, 19.59, 13.28; HRMS (*m/z*) calcd for $C_{29}H_{44}NO_6$ (+) 502.3169, found 502.3163.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-cyclohexyl-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (***4x***). 37% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1H), 4.85 (d, *J* = 6.2 Hz, 2H), 4.66−4.49 (m, 1H), 4.38 (d, *J* = 11.7 Hz, 1H), 4.11 (d, *J* = 11.7 Hz, 1H), 3.47 (d, *J* = 9.5 Hz, 1H), 2.88 (d, *J* = 10.3 Hz, 1H), 2.42 (s, 1H), 2.04 (d, *J* = 5.9 Hz, 6H), 1.75−1.46 (m, 21H), 1.11−1.05 (m, 2H), 1.00 (s, 4H), 0.86 (s, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.54, 171.10, 170.79, 146.49, 133.32, 80.01, 77.56, 77.25, 76.93, 75.48, 65.32, 63.69, 55.26, 54.67, 54.01, 52.72, 41.29, 36.79, 36.28, 34.40, 32.17, 31.88, 29.93, 29.55, 24.40, 23.86, 22.93, 21.92, 21.41, 21.32, 14.53, 14.30; HRMS (*m/z*) calcd for $C_{30}H_{46}NO_6$ (+) 516.3325, found 516.3326.

((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Acetoxy-3-cycloheptyl-7,10a-dimethyl-2-(2-oxo-2,5-dihydrofuran-3-yl)-tetradecahydrobenzo[f]isoquinolin-7-yl)methyl Acetate (***4y***). 43% yield, yellow solid; ^{1}H NMR (500 MHz, MeOD) δ 7.73 (s, 1H), 5.01−4.90 (m, 2H), 4.57 (dd, *J* = 11.6, 4.6 Hz, 1H), 4.46 (d, *J* = 11.7 Hz, 1H), 4.14 (d, *J* = 11.7 Hz, 1H), 3.66 (s, 1H), 3.03 (d, *J* = 9.1 Hz, 1H), 2.81 (s, 1H), 2.31−2.09 (m, 1H), 2.03 (d, *J* = 8.5 Hz, 6H), 1.91−1.37 (m, 20H), 1.28−1.08 (m, 4H), 1.02 (s, 3H), 0.98−0.82 (m, 5H); ^{13}C NMR (125 MHz, MeOD) δ 173.78, 171.39, 170.94, 148.73, 143.94, 80.13, 75.62, 71.16, 64.52, 55.97, 54.82, 53.23, 51.88, 41.01, 36.09, 35.63, 34.22, 32.57, 31.30, 27.45, 27.27, 25.10, 24.47, 23.36, 21.54, 21.45, 19.67, 19.59, 13.32; HRMS (*m/z*) calcd for $C_{31}H_{49}NO_6$ (+) 530.3482, found 530.3474.

3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-Benzyl-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino[5′,4′:3,4]benzo-[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (***9a***). 67% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44 (*s*, 1H), 7.7−7.32 (*m*, 5H), 4.82(*s*, 2H), 3.99(d, *J* = 11.7 Hz, 1H), 3.84 (d, J = 13.8 Hz,1H), 3.44−3.50 (m, 1H), 3.17−3.21 (m, 2H), 3.95 (d, J = 14.1 Hz, 1H), 2.83 (d, J = 8.4 Hz, 1H), 1.93−2.02 (m, 2H), 1.59−1.86 (m, 7H), 1.43 (s, 3H), 1.37 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H), 0.76−1.03 (m, 4H); ^{13}CNMR (75 MHz, $CDCl_3$) δ 173.52, 145.67, 137.22, 130.10, 128.31, 126.90, 98.91, 70.44, 63.94, 60.40, 59.36, 59.26, 53.63, 52.34, 37.53, 35.21, 34.09, 33.24, 31.37, 29.29, 27.32, 26.10, 25.49, 24.73, 20.39, 15.93, 14.10; HRMS (*m/z*) calcd for $C_{30}H_{42}NO_4$ (+) 480.3108, found 480.3111.

3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(4-Methoxybenzyl)-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (***9b***). 57% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.19 (d, *J* = 8.3 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.83 (s, 2H), 4.02 (d, *J* = 11.5 Hz, 1H), 3.80 (s, 3H), 3.77 (s, 1H), 3.46 (dd, *J* = 9.1, 4.1 Hz, 1H), 3.19 (d, *J* = 11.6 Hz, 1H), 3.13 (d, *J* = 11.7 Hz, 1H), 2.93 (d, *J* = 14.5 Hz, 1H), 2.83 (d, *J* = 9.5 Hz, 1H), 2.10−1.88 (m, 2H), 1.82 (d, *J* = 12.8 Hz, 1H), 1.78−1.61 (m, 7H), 1.43 (s, 3H), 1.37 (s, 3H), 1.18 (s, 3H), 1.03 (s, 3H), 0.98−1.01 (m, 1H), 0.96−0.68 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.52, 159.05, 145.78, 129.89, 129.86, 129.61, 129.59, 113.70, 98.91, 70.47, 60.23, 59.26, 58.59, 55.25, 53.63, 52.34, 37.53, 35.21, 34.10, 33.37, 32.46, 31.39, 29.67, 29.30, 27.33, 27.21, 26.10, 25.49, 24.73, 22.93, 20.39, 15.93, 14.34; HRMS (*m/z*) calcd for $C_{31}H_{44}NO_5$ (+) 510.3214, found 510.3209.

3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-2,2,4a,10b-Tetramethyl-8-(4-(trifluoromethyl)benzyl) tetradecahydro-4H-[1,3]dioxino[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (***9c***). 67% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (t, *J* = 8.8 Hz, 2H), 7.42 (d, *J* = 8.8 Hz, 3H), 4.94−4.66 (m, 2H), 4.01 (d, *J* = 11.6 Hz, 1H), 3.88 (d, *J* = 14.4 Hz, 1H), 3.47 (dd, *J* = 9.0, 4.1 Hz, 1H), 3.19 (d, *J* = 11.5 Hz, 1H), 3.05 (d, *J* = 14.4 Hz, 1H), 2.77 (d, *J* = 8.6 Hz, 1H), 2.09−1.90 (m, 1H), 1.84 (d, *J* = 12.8 Hz, 1H), 1.78−1.49 (m, 6H), 1.43 (s, 3H), 1.37 (s, 3H), 1.18 (s, 3H), 1.04 (s, 3H), 1.03−0.97 (m, 1H), 0.96−0.70 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 177.47, 173.39, 145.73, 144.06, 137.14, 128.39, 125.22, 98.95, 70.39, 63.96, 60.58, 59.38, 58.82, 53.64, 52.32, 37.56, 35.29, 35.22, 34.07, 33.20, 31.34, 29.77, 27.27, 26.11, 25.50, 24.71, 20.38, 15.94; HRMS (*m/z*) calc. For $C_{31}H_{41}F_3NO_4$ (+) 548.2982, found 548.2982.

3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(4-Bromobenzyl)-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (***9d***). 40% yield, yellow solid; 1H NMR (400 MHz, $CDCl_3$) δ 7.50−7.35 (m, 3H), 7.17 (d, *J* = 8.0 Hz, 2H), 4.83 (d, *J* = 9.7 Hz, 2H), 4.01 (d, *J* = 11.7 Hz, 1H), 3.78 (d, *J* = 13.7 Hz, 1H), 3.46 (dd, *J* = 9.0, 4.1 Hz, 1H), 3.30−3.04 (m, 1H), 2.93 (d, *J* = 14.2 Hz, 1H), 2.77 (d, *J* = 8.8 Hz, 1H), 2.06−1.89 (m, 2H), 1.82 (d, *J* = 13.0 Hz, 1H), 1.70 (dd, *J* = 11.2, 6.8 Hz, 3H), 1.65−1.49 (m, 6H), 1.43 (s, 3H), 1.37 (s, 3H), 1.17 (s, 3H), 1.03 (s, 3H), 0.97 (dd, *J* = 8.2, 4.8 Hz, 2H), 0.93−0.73 (m, 4H); ^{13}C NMR(100 MHz, $CDCl_3$) δ 173.32, 145.97, 137.16, 131.48, 131.28, 129.89, 98.83, 70.30, 63.85, 60.30, 59.26, 58.52, 53.55, 52.24, 37.45, 35.11, 33.98, 33.09, 31.80, 31.26, 29.57, 29.19, 27.19, 26.01, 25.40, 24.62, 22.57, 20.29, 15.83, 14.00; HRMS (*m/z*) calcd for $C_{30}H_{41}BrNO_4$ (+) 558.2213, found 558.2213.

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*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(4-Iodobenzyl)-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9e**).* 58% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (d, J = 8.2 Hz, 2H), 7.39 (s, 1H), 7.05 (d, J = 8.2 Hz, 2H), 4.87−4.73 (m, 2H), 4.01 (d, J = 11.6 Hz, 1H), 3.77 (d, J = 14.2 Hz, 1H), 3.46 (dd, J = 9.0, 4.2 Hz, 1H), 3.17 (dd, J = 16.1, 10.7 Hz, 2H), 2.92 (d, J = 14.1 Hz, 1H), 2.77 (d, J = 8.1 Hz, 1H), 2.09−1.89 (m, 2H), 1.82 (d, J = 12.8 Hz, 1H), 1.71 (dd, J = 13.3, 5.0 Hz, 2H), 1.67−1.61 (m, 6H), 1.43 (s, 3H), 1.37 (s, 3H), 1.22 (dd, J = 11.6, 4.4 Hz, 2H), 1.18 (s, 3H), 1.13 (dd, J = 8.5, 5.4 Hz, 1H), 1.03 (s, 3H), 1.00 (d, J = 13.0 Hz, 1H), 0.9−0.71 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.42, 145.65, 138.85, 137.36, 137.19, 130.28, 98.93, 92.05, 70.40, 63.95, 60.45, 59.35, 58.71, 53.65, 52.33, 37.55, 35.29, 35.21, 34.08, 33.21, 31.35, 29.68, 27.30, 26.11, 25.50, 24.72, 20.39, 15.94; HRMS (m/z) calcd for $C_{30}H_{41}INO_4$ (+) 606.2075, found 606.2076.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-2,2,4a,10b-Tetramethyl-8-(4-methylbenzyl)tetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9f**).* 67% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.17 (d, J = 7.9 Hz, 2H), 7.12 (d, J = 7.9 Hz, 2H), 4.82 (s, 2H), 4.02 (d, J = 11.6 Hz, 1H), 3.82 (d, J = 13.6 Hz, 1H), 3.46 (dd, J = 9.1, 4.1 Hz, 1H), 3.19 (d, J = 8.9 Hz, 1H), 3.14 (d, J = 10.2 Hz, 1H), 2.94 (d, J = 13.7 Hz, 1H), 2.84 (d, J = 8.2 Hz, 1H), 2.34 (s, 3H), 2.08−1.90 (m, 2H), 1.78−1.67 (m, 2H), 1.66−1.60 (m, 5H), 1.43 (s, 3H), 1.37 (s, 3H), 1.17 (s, 3H), 1.02 (s, 3H), 0.82−0.98 (m, 5H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.45, 145.49, 137.80, 136.59, 136.00, 128.89, 128.22, 98.80, 70.35, 63.84, 60.28, 59.21, 58.84, 53.53, 52.26, 37.43, 35.11, 34.00, 33.13, 31.27, 29.57, 29.37, 27.24, 26.00, 25.39, 24.64, 20.97, 20.30, 15.83; HRMS (m/z) calcd for $C_{31}H_{44}NO_4$ (+) 494.3265, found 494.3270.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(4-(tert-Butyl)-benzyl)-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]-dioxino[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9g**).* 63% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 (s, 1H), 7.33 (d, J = 8.2 Hz, 2H), 7.21 (d, J = 8.0 Hz, 2H), 4.92−4.68 (m, 2H), 4.02 (d, J = 11.6 Hz, 1H), 3.82 (d, J = 13.9 Hz, 1H), 3.46 (dd, J = 9.1, 4.1 Hz, 1H), 3.24−3.08 (m, 2H), 2.97 (d, J = 14.0 Hz, 1H), 2.88 (d, J = 8.2 Hz, 1H), 2.11−1.91 (m, 2H), 1.84 (d, J = 13.2 Hz, 1H), 1.78−1.63 (m, 6H), 1.43 (s, 3H), 1.36 (s, 3H), 1.32 (s, 9H), 1.18 (s, 3H), 1.03 (s, 3H), 0.99 (s, 1H), 0.95−0.65 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.92, 145.84, 137.54, 136.08, 127.97, 125.20, 98.91, 70.43, 63.96, 60.42, 59.29, 58.92, 55.57, 53.63, 52.36, 37.54, 35.22, 34.44, 34.10, 33.37, 31.36, 29.68, 29.39, 27.34, 26.11, 25.50, 24.74, 22.74, 20.40, 15.94; HRMS (m/z) calcd for $C_{34}H_{50}NO_4$ (+) 536.3734, found 536.3735.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-2,2,4a,10b-Tetramethyl-8-(4-nitrobenzyl)tetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9h**).* 70% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 8.7 Hz, 2H), 7.49 (d, J = 8.6 Hz, 2H), 7.41 (s, 1H), 4.91−4.71 (m, 2H), 4.02 (d, J = 11.6 Hz, 1H), 3.90 (d, J = 14.9 Hz, 1H), 3.47 (dd, J = 9.1, 4.1 Hz, 1H), 3.21 (t, J = 10.1 Hz, 1H), 3.10 (d, J = 14.9 Hz, 1H), 2.76−2.65 (m, 1H), 2.07−1.89 (m, 2H), 1.84 (d, J = 13.0 Hz, 1H), 1.58−1.72 (m, 6H), 1.43 (s, 3H), 1.37 (s, 3H), 1.18 (s, 3H), 1.05 (s, 3H), 1.01 (d, J = 10.9 Hz, 1H), 0.95−0.74 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.34, 147.31, 147.02, 145.95, 137.03, 128.77, 123.62, 114.06, 98.98, 70.43, 63.96, 60.73, 59.42, 58.71, 53.65, 53.46, 52.30, 37.57, 35.31, 35.23, 34.07, 33.12, 31.32, 29.70, 27.30, 26.12, 25.51, 24.71, 20.37, 15.97; HRMS (m/z) calcd for $C_{30}H_{41}N_2O_6$ (+) 525.2959, found 525.2951.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(4-Hydroxybenzyl)-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9i**).* 53% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (s, 1H), 7.14 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 7.8 Hz, 2H), 4.87 (s, 2H), 4.00 (d, J = 11.7 Hz, 1H), 3.82−3.92 (m, 1H), 3.35−3.58 (m, 2H), 3.22−3.32 (m, 1H), 3.17 (d, J = 11.6 Hz, 2H), 2.90 (d, J = 7.8 Hz, 1H), 1.86−2.05 (m, 2H), 1.83 (d, J = 13.2 Hz, 1H), 1.79−1.47 (m, 7H), 1.42 (s, 3H), 1.37 (s, 3H), 1.17 (s, 3H), 1.04 (s, 3H), 0.59−1.02 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.59, 155.70, 130.40, 129.75, 115.35, 98.92, 70.74, 65.75, 63.80, 59.23, 58.52, 53.21, 52.13, 37.42, 35.09, 34.61, 33.92, 31.13, 29.57, 29.19, 27.19, 25.98, 25.38, 22.56, 20.22, 15.76, 15.11, 14.00; HRMS (m/z) calcd for $C_{30}H_{42}NO_5$ (+) 496.3057, found 496.3058.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(2-Cyclopropyl-benzyl)-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]-dioxino[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9j**).* 70% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (d, J = 6.7 Hz, 1H), 7.35 (s, 1H), 7.21−7.12 (m, 2H), 7.03−6.96 (m, 1H), 4.83−4.69 (m, 2H), 4.03 (d, J = 11.7 Hz, 1H), 3.82 (d, J = 14.8 Hz, 1H), 3.47 (dd, J = 9.1, 4.1 Hz, 1H), 3.36 (d, J = 14.7 Hz, 1H), 3.22 (t, J = 12.4 Hz, 2H), 2.90−2.85 (m, 1H), 2.08−1.81 (m, 3H), 1.80−1.61 (m, 8H), 1.44 (s, 3H), 1.38 (s, 3H), 1.19 (s, 3H), 1.04 (s, 3H), 1.02 (d, J = 12.8 Hz, 1H), 0.93−0.78 (m, 6H), 0.70−0.59 (m, 1H), 0.57−0.47 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.67, 145.42, 141.00, 138.73, 137.35, 127.64, 126.54, 125.79, 125.62, 98.89, 70.41, 63.95, 60.94, 59.85, 56.37, 53.75, 52.44, 37.54, 35.36, 35.25, 34.16, 33.39, 31.40, 29.68, 27.38, 26.14, 25.54, 24.80, 20.42, 15.93, 12.69, 7.44, 6.60; HRMS (m/z) calcd for $C_{33}H_{46}NO_4$ (+) 520.3421, found 520.3414.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(3-Chloro-4-fluorobenzyl)-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]-dioxino[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9k**).* 68% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.35 (d, J = 5.3 Hz, 1H), 7.16−7.10 (m, 1H), 7.07 (t, J = 8.6 Hz, 1H), 4.95−4.73 (m, 2H), 4.02 (d, J = 11.6 Hz, 1H), 3.77 (d, J = 14.3 Hz, 1H), 3.47 (dd, J = 9.0, 4.0 Hz, 1H), 3.24−3.12 (m, 2H), 2.91 (d, J = 14.1 Hz, 1H), 2.76 (d, J = 7.7 Hz, 1H), 2.06−1.88 (m, 2H), 1.82 (d, J = 12.8 Hz, 1H), 1.57−1.72 (m, 6H), 1.43 (s, 3H), 1.37 (s, 3H), 1.18 (s, 3H), 1.04 (s, 3H), 1.00 (d, J = 10.8 Hz, 1H), 0.82−0.88 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.38, 145.70, 137.15, 136.60, 130.02, 127.85, 122.61, 116.41, 98.94, 70.41, 63.95, 60.40, 59.34, 58.14, 53.66, 52.32, 37.55, 35.22, 34.08, 33.18, 31.36, 29.67, 27.29, 26.12, 25.50, 24.72, 20.38, 15.94; HRMS (m/z) calc. For $C_{30}H_{40}ClFNO_4$ (+) 532.2624, found 532.2624.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(Furan-2-ylmethyl)-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9l**).* 57% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.36 (s, 1H), 6.29 (s, 1H), 6.14 (s, 1H), 4.85 (s, 2H), 4.01 (d, J = 11.7 Hz, 1H), 3.71 (d, J = 14.7 Hz, 1H), 3.45 (dd, J = 8.8, 4.1 Hz, 1H), 3.27 (d, J = 14.2 Hz, 1H), 3.18 (d, J = 11.6 Hz, 1H), 3.09 (d, J = 11.4 Hz, 1H), 2.92 (d, J = 10.3 Hz, 1H), 2.12−1.98 (m, 1H), 1.94 (dd, J = 13.8, 5.1 Hz, 1H), 1.86−1.75 (m, 2H), 1.62−1.57 (m, 4H), 1.42 (s, 3H), 1.36 (s, 3H), 1.17 (s, 3H), 1.13−1.10 (m, 2H), 1.01 (s, 3H), 0.97−

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0.91 (m, 1H), 0.91−0.82 (m, 2H), 0.78 (t, J = 10.1 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.44, 145.99, 142.15, 129.89, 110.12, 108.98, 98.93, 70.54, 63.94, 60.55, 58.60, 53.46, 52.27, 51.53, 37.55, 35.18, 34.03, 33.02, 31.40, 29.68, 27.29, 26.08, 25.43, 24.66, 20.41, 15.97; HRMS (m/z) calcd for $C_{28}H_{40}NO_5$ (+) 470.2901, found 470.2906.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-2,2,4a,10b-Tetramethyl-8-(thiophen-2-ylmethyl)tetradecahydro-4H-[1,3]dioxino[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9m**).* 66% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.47 (s, 1H), 7.21 (d, J = 4.8 Hz, 1H), 6.97−6.89 (m, 1H), 6.85 (s, 1H), 4.84 (s, 2H), 4.02 (d, J = 11.6 Hz, 1H), 3.90 (d, J = 14.4 Hz, 1H), 3.46 (dd, J = 9.1, 4.1 Hz, 1H), 3.37 (d, J = 14.5 Hz, 1H), 3.18 (t, J = 9.7 Hz, 2H), 2.96 (dd, J = 11.0, 2.8 Hz, 1H), 2.04−1.87 (m, 1H), 1.84 (d, J = 12.8 Hz, 1H), 1.78−1.51 (m, 7H), 1.43 (s, 3H), 1.37 (s, 3H), 1.18 (s, 3H), 1.02 (s, 3H), 0.95−0.64 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.49, 145.66, 142.53, 137.92, 126.67, 125.37, 124.57, 98.92, 70.53, 63.95, 60.40, 58.68, 53.72, 53.64, 52.34, 37.54, 35.31, 35.26, 34.10, 33.32, 31.38, 29.68, 27.33, 26.11, 25.50, 24.73, 20.39, 15.93; HRMS (m/z) calcd for $C_{28}H_{40}NO_4S$ (+) 486.2673, found 486.2673.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-Butyl-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino[5′,4′:3,4]benzo-[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9n**).* 50% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26 (s, 1H), 4.99−4.76 (m, 2H), 4.01 (d, J = 11.6 Hz, 1H), 3.47 (dd, J = 8.7, 3.7 Hz, 2H), 3.34−3.23 (m, 1H), 3.20 (d, J = 11.6 Hz, 1H), 2.89−2.65 (m, 1H), 2.44 (dd, J = 27.2, 7.9 Hz, 2H), 2.12−1.91 (m, 4H), 1.88−1.67 (m, 5H), 1.65−1.49 (m, 4H), 1.42 (s, 3H), 1.37 (s, 3H), 1.19 (s, 3H), 1.09 (s, 3H), 0.90 (dd, J = 14.3, 7.1 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.11, 129.86, 129.12, 99.08, 76.43, 70.98, 63.87, 59.01, 54.40, 53.03, 52.07, 37.60, 35.90, 35.25, 33.95, 31.49, 30.13, 29.68, 29.29, 27.16, 26.08, 25.40, 24.51, 22.66, 20.26, 15.93, 14.10, 13.68; HRMS (m/z) calcd for $C_{27}H_{44}NO_4$ (+) 446.3265, found 446.3269.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-Isobutyl-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9o**).* 16% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33 (s, 1H), 4.91−4.76 (m, 2H), 4.03 (d, J = 11.6 Hz, 1H), 3.46 (dd, J = 8.9, 4.0 Hz, 1H), 3.20 (d, J = 11.6 Hz, 1H), 2.98 (dd, J = 20.1, 9.3 Hz, 2H), 2.12 (s, 1H), 2.06−1.89 (m, 3H), 1.85−1.66 (m, 6H), 1.65−1.47 (m, 4H), 1.43 (s, 3H), 1.37 (s, 3H), 1.19 (s, 3H), 1.15−1.08 (m, 2H), 1.02 (s, 3H), 0.99−0.93 (m, 2H), 0.87 (d, J = 6.8 Hz, 6H), 0.79 (d, J = 5.1 Hz, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.74, 145.82, 129.86, 98.90, 70.34, 63.95, 63.42, 60.61, 59.78, 53.70, 52.96, 37.54, 35.55, 34.09, 31.90, 31.59, 29.67, 29.30, 27.28, 26.12, 25.57, 24.76, 21.98, 20.53, 15.91, 14.10; HRMS (m/z) calcd for $C_{27}H_{44}NO_4$ (+) 446.3265, found 446.3268.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-Isopentyl-2,2,4a,10b-tetramethyltetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**9p**).* 36% yield, yellow solid; ^{1}H NMR (300 MHz, MeOD) δ 7.84 (s, 1H), 5.00 (s, 2H), 4.06 (d, J = 11.6 Hz, 1H), 3.82 (d, J = 7.4 Hz, 1H), 3.50 (dd, J = 8.6, 3.9 Hz, 1H), 3.22 (d, J = 11.7 Hz, 1H), 2.94 (d, J = 12.3 Hz, 1H), 2.68 (t, J = 12.1 Hz, 1H), 2.58−2.29 (m, 2H), 2.00 (dd, J = 13.1, 5.1 Hz, 2H), 1.94−1.75 (m, 5H), 1.75−1.60 (m, 5H), 1.58−1.48 (m, 3H), 1.41 (s, 3H), 1.33 (s, 3H), 1.19 (s, 3H), 1.13 (s, 3H), 0.91 (dd, J = 12.4, 5.8 Hz, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.95, 129.60, 128.49, 99.90, 99.11, 76.36, 71.09, 63.83, 58.75, 52.91, 52.05, 37.60, 35.27, 33.95, 33.47, 30.98, 29.47, 29.24, 27.08, 26.23, 26.05, 25.40, 24.48, 22.57, 22.03, 20.14, 15.91; HRMS (m/z) calcd for $C_{28}H_{46}NO_4$ (+) 460.3421, found 460.3422.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-Benzyl-4a,10b-dimethyltetradecahydro-4H-[1,3]dioxino[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**10a**).* 56% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.31 (dd, J = 11.7, 4.7 Hz, 4H), 7.23 (d, J = 6.5 Hz, 1H), 4.93 (d, J = 6.3 Hz, 1H), 4.83 (d, J = 6.5 Hz, 1H), 4.80 (s, 2H), 4.03 (d, J = 11.4 Hz, 1H), 3.86 (d, J = 13.9 Hz, 1H), 3.51−3.36 (m, 2H), 3.16 (d, J = 10.1 Hz, 1H), 2.97 (d, J = 13.9 Hz, 1H), 2.84 (dd, J = 10.7, 2.7 Hz, 1H), 2.30−2.17 (m, 1H), 1.91−1.80 (m, 1H), 1.79−1.72 (m, 1H), 1.63 (d, J = 10.5 Hz, 4H), 1.37 (s, 3H), 1.22−1.14 (m, 2H), 1.05 (td, J = 13.3, 2.8 Hz, 1H), 0.95 (d, J = 12.8 Hz, 1H), 0.91 (d, J = 4.7 Hz, 3H), 0.89−0.68 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.47, 145.64, 139.01, 137.27, 128.30, 126.90, 87.66, 79.62, 70.41, 69.28, 60.40, 59.27, 54.79, 53.41, 37.48, 35.82, 35.44, 34.79, 33.05, 31.40, 29.68, 25.75, 20.42, 19.92, 15.10; HRMS (m/z) calcd for $C_{28}H_{38}NO_4$ (+) 452.2795, found 452.2792.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(4-Fluorobenzyl)-4a,10b-dimethyltetradecahydro-4H-[1,3]dioxino[5′,4′:3,4]-benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**10b**).* 60% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41 (s, 1H), 7.24 (dd, J = 8.3, 5.6 Hz, 2H), 6.99 (t, J = 8.7 Hz, 2H), 4.93 (d, J = 6.3 Hz, 1H), 4.82 (s, 2H), 4.80 (s, 1H), 4.03 (d, J = 11.4 Hz, 1H), 3.79 (d, J = 13.8 Hz, 1H), 3.49−3.39 (m, 2H), 3.15 (d, J = 9.4 Hz, 1H), 2.94 (d, J = 13.8 Hz, 1H), 2.78 (dd, J = 10.6, 2.4 Hz, 1H), 2.28−2.19 (m, 1H), 1.85−1.77 (m, 1H), 1.74 (dt, J = 13.3, 3.4 Hz, 1H), 1.62 (t, J = 15.0 Hz, 7H), 1.37 (s, 3H), 1.23−1.10 (m, 3H), 1.08−1.02 (m, 1H), 0.95 (d, J = 11.0 Hz, 1H), 0.91 (d, J = 4.7 Hz, 3H), 0.89−0.67 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.37, 160.63, 145.70, 137.20, 134.54, 129.76, 115.19, 114.98, 87.65, 79.60, 70.38, 69.26, 60.23, 59.23, 58.50, 54.79, 53.42, 37.47, 35.81, 35.44, 34.77, 32.97, 31.40, 29.67, 25.74, 20.41, 19.91, 15.08; HRMS (m/z) calcd for $C_{28}H_{37}FNO_4$ (+) 470.2701, found 470.2701.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-8-(Furan-2-ylmethyl)-4a,10b-dimethyltetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**10c**).* 60% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (s, 1H), 7.36 (d, J = 1.1 Hz, 1H), 6.30 (dd, J = 3.0, 1.9 Hz, 1H), 6.14 (d, J = 2.9 Hz, 1H), 4.93 (d, J = 6.3 Hz, 1H), 4.85 (s, 2H), 4.80 (d, J = 6.1 Hz, 1H), 4.02 (d, J = 11.4 Hz, 1H), 3.71 (d, J = 14.5 Hz, 1H), 3.44 (dd, J = 12.2, 5.5 Hz, 2H), 3.26 (d, J = 14.5 Hz, 1H), 3.09 (d, J = 10.2 Hz, 1H), 2.92 (dd, J = 11.1, 3.2 Hz, 1H), 2.28−2.20 (m, 1H), 2.07−1.92 (m, 1H), 1.80 (dd, J = 12.8, 3.0 Hz, 1H), 1.77−1.69 (m, 3H), 1.61−1.52 (m, 2H), 1.37 (s, 3H), 1.23−1.08 (m, 3H), 1.04 (dd, J = 13.6, 2.8 Hz, 1H), 1.00−0.91 (m, 2H), 0.89 (s, 3H), 0.81−0.65 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.46, 145.91, 142.10, 136.51, 110.10, 87.66, 79.61, 70.51, 69.26, 60.54, 58.46, 54.76, 53.22, 51.59, 37.47, 35.80, 35.43, 34.78, 32.83, 31.42, 29.67, 25.75, 20.39, 19.93, 15.06; HRMS (m/z) calc. For $C_{26}H_{36}NO_5$ (+) 442.2588, found 442.2590.

*3-((4aR,4bS,6aS,9R,10aR,10bS,12aR)-4a,10b-Dimethyl-8-(thiophen-2-ylmethyl)tetradecahydro-4H-[1,3]dioxino-[5′,4′:3,4]benzo[1,2-f]isoquinolin-9-yl)furan-2(5H)-one (**10d**).* 53% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.21 (d, J = 4.9 Hz, 1H), 6.94 (dd, J = 5.0, 3.5 Hz, 1H), 6.84 (d, J = 3.2 Hz, 1H), 4.93 (d, J = 6.3 Hz, 1H), 4.84 (s, 2H), 4.81 (d, J = 6.4 Hz, 1H), 4.03 (d, J = 11.4 Hz,

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1H), 3.90 (d, J = 14.4 Hz, 1H), 3.47−3.40 (m, 2H), 3.36 (d, J = 14.5 Hz, 1H), 3.17 (d, J = 9.4 Hz, 1H), 2.96 (dd, J = 11.2, 3.4 Hz, 1H), 2.29−2.19 (m, 1H), 1.88−1.80 (m, 1H), 1.78−1.70 (m, 2H), 1.69−1.63 (m, 3H), 1.58−1.54 (m, 1H), 1.37 (s, 3H), 1.21−1.08 (m, 3H), 1.04 (td, J = 13.4, 3.0 Hz, 1H), 0.97−0.93 (m, 1H), 0.91 (s, 3H), 0.90−0.73 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.43, 145.65, 142.52, 136.95, 126.66, 125.35, 124.55, 87.66, 79.61, 70.51, 69.28, 60.34, 58.53, 54.78, 53.73, 53.32, 37.48, 35.82, 35.44, 34.84, 33.11, 31.40, 29.68, 25.75, 20.40, 19.91, 15.09; HRMS (m/z) calcd for $C_{26}H_{36}NO_4S$ (+) 458.2360, found 458.2357.

*3-((2R,4aS,6aS,7R,8R,10aS,10bR)-3-Benzyl-8-hydroxy-7-(hydroxymethyl)-7,10a-dimethyltetradecahydrobenzo[f]-isoquinolin-2-yl)furan-2(5H)-one (**11a**).* A solution of **9a** (0.03 mmol) in 1 mL of AcOH/THF/H_2O (4:1:2) was stirred at 45 °C for 2 h. The reaction mixture was then concentrated under reduced pressure, and the residue was purified by prep-TLC using MeOH/DCM (1:15) as a developing agent to yield the desired product **11a** as a yellow solid in 53% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (s, 1H), 7.37−7.28 (m, 4H), 7.25−7.24 (m, 1H), 4.80 (s, 2H), 4.21 (d, J = 11.1 Hz, 1H), 3.85 (d, J = 14.0 Hz, 1H), 3.45 (dd, J = 11.8, 3.9 Hz, 1H), 3.32 (d, J = 10.7 Hz, 1H), 3.15 (d, J = 11.0 Hz, 1H), 2.97 (d, J = 13.4 Hz, 1H), 2.84 (d, J = 11.2 Hz, 2H), 2.02 (d, J = 5.3 Hz, 1H), 1.86−1.76 (m, 2H), 1.76−1.64 (m, 4H), 1.21 (s, 3H), 1.19−1.01 (m, 3H), 0.96 (d, J = 10.9 Hz, 1H), 0.87 (dt, J = 7.3, 5.2 Hz, 3H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.54, 131.49, 129.91, 128.55, 128.38, 128.30, 80.76, 70.53, 64.22, 59.22, 55.05, 53.59, 42.77, 36.53, 35.79, 31.57, 29.68, 29.30, 27.69, 27.19, 22.67, 22.51, 20.84, 14.99, 14.10. HRMS (m/z) calcd for $C_{27}H_{38}NO_4$ (+) 440.2795, found 440.2796.

*3-((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Hydroxy-7-(hydroxymethyl)-3-(4-methoxybenzyl)-7,10a-dimethyltetradecahydrobenzo[f]isoquinolin-2-yl)furan-2(5H)-one (**11b**).* The synthetic procedure of **11a** was applied to **11b** using **9b** as substrate. 56% yield, yellow solid; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (s, 1H), 7.23 (d, J = 8.1 Hz, 2H), 6.87 (d, J = 8.4 Hz, 2H), 4.89 (s, 2H), 4.19 (d, J = 11.0 Hz, 1H), 4.10−3.83 (m, 1H), 3.81 (d, J = 3.6 Hz, 3H), 3.7−3.55 (m, 1H), 3.47−3.25 (m, 3H), 2.93 (s, 1H), 2.16−1.94 (m, 2H), 1.88−1.68 (m, 6H), 1.62 (s, 2H), 1.20 (s, 3H), 1.11−1.02 (m, 2H), 0.97 (d, J = 6.8 Hz, 2H), 0.89 (t, J = 8.9 Hz, 4H), 0.80 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.40, 129.94, 114.22, 114.17, 114.07, 114.00, 80.60, 70.82, 64.15, 58.99, 55.28, 54.98, 53.41, 42.70, 36.50, 35.80, 31.90, 31.41, 29.67, 27.61, 22.53, 20.73, 14.97, 14.10; HRMS (m/z) calc. For $C_{28}H_{40}NO_5$ (+) 470.2901, found 470.2903.

*3-((2R,4aS,6aS,7R,8R,10aS,10bR)-3-(3-Chloro-4-fluorobenzyl)-8-hydroxy-7-(hydroxymethyl)-7,10a-dimethyltetradecahydrobenzo[f]isoquinolin-2-yl)furan-2(5H)-one (**11c**).* The synthetic procedure of **11a** was applied to **11c** using **9k** as substrate. 93% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (s, 1H), 7.34 (d, J = 7.3 Hz, 1H), 7.17−7.10 (m, 1H), 7.06 (t, J = 8.6 Hz, 1H), 4.82 (s, 2H), 4.21 (d, J = 11.1 Hz, 1H), 3.76 (d, J = 14.1 Hz, 1H), 3.45 (dd, J = 11.1, 4.6 Hz, 1H), 3.32 (d, J = 11.1 Hz, 1H), 3.14 (d, J = 10.2 Hz, 1H), 2.90 (d, J = 14.0 Hz, 1H), 2.75 (d, J = 8.2 Hz, 1H), 2.07 (d, J = 16.1 Hz, 1H), 1.87−1.76 (m, 2H), 1.76−1.62 (m, 8H), 1.22 (s, 3H), 1.19−1.00 (m, 3H), 0.97 (d, J = 10.6 Hz, 1H), 0.92−0.82 (m, 2H), 0.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.37, 155.72, 145.77, 136.93, 129.96, 127.79, 120.79, 116.32, 116.11, 80.57, 70.38, 65.73, 64.12, 60.15, 59.05, 57.97, 54.95, 53.54, 42.61, 36.41, 35.68, 34.57, 32.94, 31.47, 29.57, 27.54, 22.45, 20.73, 15.13, 14.90; HRMS (m/z) calcd for $C_{27}H_{36}ClFNO_4$ (+) 492.2311, found 492.2321.

*3-((2R,4aS,6aS,7R,8R,10aS,10bR)-3-(Furan-2-ylmethyl)-8-hydroxy-7-(hydroxymethyl)-7,10a-dimethyltetradecahydrobenzo[f]isoquinolin-2-yl)furan-2(5H)-one (**11d**).* The synthetic procedure of **11a** was applied to **11d** using **9l** as substrate. 66% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.50 (s, 1H), 7.36 (s, 1H), 6.30 (s, 1H), 6.15 (s, 1H), 4.91−4.75 (m, 2H), 4.20 (d, J = 11.1 Hz, 1H), 3.71 (d, J = 14.9 Hz, 1H), 3.44 (dd, J = 11.3, 4.4 Hz, 1H), 3.30 (t, J = 14.8 Hz, 2H), 3.08 (d, J = 10.0 Hz, 1H), 2.93 (d, J = 11.5 Hz, 1H), 2.06−1.98 (m, 1H), 1.81−1.64 (m, 9H), 1.22 (s, 3H), 1.05 (ddd, J = 13.0, 10.2, 6.2 Hz, 3H), 0.96 (d, J = 10.6 Hz, 1H), 0.91−0.83 (m, 3H), 0.76 (s, 3H), 0.73 (d, J = 7.6 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.52, 142.19, 129.93, 110.16, 100.82, 80.81, 70.61, 64.25, 60.50, 58.45, 55.06, 53.47, 51.57, 42.80, 36.53, 35.79, 34.73, 31.65, 29.72, 29.34, 27.71, 22.63, 20.89, 15.01, 14.15; HRMS (m/z) calcd for $C_{25}H_{36}NO_5$ (+) 430.2588, found 430.2591.

*3-((2R,4aS,6aS,7R,8R,10aS,10bR)-8-Hydroxy-7-(hydroxymethyl)-7,10a-dimethyl-3-(thiophen-2-ylmethyl)-tetradecahydrobenzo[f]isoquinolin-2-yl)furan-2(5H)-one (**11e**).* The synthetic procedure of **11a** was applied to **11e** using **9m** as substrate. 94% yield, yellow solid; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.21 (t, J = 5.6 Hz, 1H), 6.97−6.91 (m, 1H), 6.85 (s, 1H), 4.84 (s, 2H), 4.21 (d, J = 11.1 Hz, 1H), 3.90 (d, J = 13.1 Hz, 1H), 3.48−3.42 (m, 1H), 3.38 (d, J = 14.2 Hz, 1H), 3.32 (d, J = 11.1 Hz, 1H), 3.16 (d, J = 10.5 Hz, 1H), 2.96 (d, J = 8.4 Hz, 1H), 2.01 (d, J = 5.7 Hz, 1H), 1.80 (dd, J = 16.0, 6.5 Hz, 4H), 1.75−1.62 (m, 7H), 1.21 (s, 3H), 1.14−1.00 (m, 3H), 0.96 (d, J = 12.4 Hz, 1H), 0.91−0.83 (m, 2H), 0.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.51, 145.76, 136.64, 126.65, 125.54, 124.45, 80.71, 70.48, 64.17, 60.12, 58.33, 54.96, 53.45, 42.59, 36.36, 35.67, 34.55, 33.07, 31.42, 29.57, 27.56, 22.44, 20.75, 14.89; HRMS (m/z) calcd for $C_{25}H_{36}NO_4S$ (+) 446.2360, found 446.2351.

Protocol for Evaluation of the *In Vitro* Inhibitory Activity of Test Compounds against Human Coronavirus 229E. MRC5 cells are seeded in 96-well plates, at 100 μL per well of the assay medium, at an appropriate density of 20,000 cells per well and cultured at 37 °C and 5% CO_2 overnight. Next day, the test compound is diluted with the assay medium and then added into the cells at 50 μL per well. Then 50 μL per well of the assay medium diluted virus is added. The final volume of the cell culture is 200 μL per well. The final concentration of DMSO in the cell culture is 0.5%. The resulting cell culture is incubated for an additional 3 days until the virus infection in the virus control (cells infected with virus, without compound treatment) displays significant CPE. The CPEs are measured by CellTiter Glo following the manufacturer's manual. The antiviral activity of compounds is calculated based on the protection of the virus-induced CPE at each concentration normalized by the virus control. The cytotoxicity of compounds is assessed under the same conditions, but without virus infection, in parallel. Cell viability is measured with CellTiter Glo following the manufacturer's manual. EC_{50} and CC_{50} values are calculated using the GraphPad Prism software using the nonlinear regression model of log(inhibitor) vs response-variable slope (four parameters) (see Supporting Information S53−S55 for details).

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■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acsomega.2c02979.

^{1}H and ^{13}C NMR spectra for compounds **4a−4y**, **9a−9p**, **10a−10d**, and **11a−11e** (PDF)

X-ray data for compound **4u** (CIF)

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Notes

The authors declare no competing financial interest.

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