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Photorearrangement of Quinoline-Protected Dialkylanilines and the Photorelease of Aniline-Containing Biological Effectors

Davide Deodato,[†] Naeem Asad,[†] and Timothy M. Dore*[,†,‡]

[†]New York University Abu Dhabi, PO Box 129188, Abu Dhabi, United Arab Emirates

[‡]Department of Chemistry, University of Georgia, Athens, GA 30602, USA

ABSTRACT

The direct release of dialkylanilines was achieved by controlling the outcome of a photorearrangement reaction promoted by the (8-cyano-7-hydroxyquinolin-2-yl)methyl (CyHQ) photoremovable protecting group (PPG). The substrate scope was investigated to obtain structure-activity relationships and to propose a reaction mechanism. Introducing a methyl substituent at the 2-methyl position of the CyHQ core enabled the bypass of the photorearrangement and significantly improved the aniline release efficiency. We successfully applied the strategy to the photoactivation of mifepristone (RU-486), an antiprogestin drug that is also used to induce the LexPR gene expression system in zebrafish and the gene-switch regulatory system based on the pGL-VP chimeric regulator in mammals.

INTRODUCTION

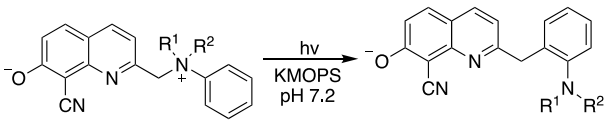
Masking (or "caging") the activity of a biological effector or modulator with a photoremovable protecting group (PPG), represents a powerful and frequently utilized strategy to probe and investigate biological processes.[1-4] Applying an external orthogonal stimulus (light), which does not interfere with the biological function, restores the activity of the modulator enabling the study of the process with spatio-temporal control. Most current PPGs are connected to the biological effector through a covalent bond, which is cleaved upon photoexcitation of the complex resulting in the release of the effector. Many studies have focused on enhancing the photochemical properties of those PPGs (quantum efficiency, wavelength of absorption, two-photon action cross section)[5,6] or other important parameters such as aqueous solubility[7] and kinetics of release.[8] Another crucial aspect to consider is the functional group specificity, since the structural diversity of biologically active molecules limits the application of PPG-mediated light activation to those compounds possessing compatible sites for bond formation.

As a consequence, only biological modulators bearing select functionality (generally good leaving groups) have been protected and successfully used in a biological setting. It is of vital importance to expand the current library of functional groups that can be photoactivated for this strategy to be applied to a broad array of biologically active compounds.[9-13]

A noteworthy case of an unexplored group is the dialkylaniline functionality, for which no photoactivatable constructs have been described thus far. The only examples present in the literature concern primary and secondary anilines, linked to the PPG via a carbamate,[14] sulfonate[15,16] or thiocarbamate.[17] The dialkylanilinyl (and especially the N,N′-dimethylaniline function) represents a recurrent structural motif in biologically active compounds, including anti-cancer[18] and anti-diabetic agents,[19] farnesoid X receptor (FXR) modulators,[20] selective α7 nicotinic receptor agonists,[21] and statin analogues.[22] An interesting example is the progesterone receptor antagonist mifepristone (RU-486), which is also used to activate the pGL-VP chimeric regulator-based gene-switch system[23-25] in mammals and the LexPR gene expression system in zebrafish[26] for selective control of gene function. This technology has been extensively used by molecular biologists in the last 25 years,[26-28] but no photoactivatable version, which would enable the precise spatio-temporal control over gene regulation, has yet been described.

The CyHQ PPG has many desirable properties for in vivo use. It protects and photoreleases a range of biologically relevant functional groups with high sensitivity to 1-photon excitation (1PE) and moderate sensitivity to 2-photon excitation (2PE)[29,30] and kinetics much faster than diffusion in aqueous media.[31] Possessing excellent aqueous solubility and stability in the dark under physiological conditions, CyHQ works well in living organisms.[32] We recently reported a system based on the (8-cyano-7-hydroxyquinolin-2-yl)methyl (CyHQ) PPG that releases tertiary amines under both one and two-photon excitation.[33] The strategy was successfully applied to a broad variety of aliphatic amines including biologically-relevant compounds such as tamoxifen and 4-hydroxytamoxifen, but it failed to release dialkylanilines, instead undergoing a photorearrangement to generate the corresponding *ortho*-substituted dialkylaniline (Scheme 1). The reaction occurred efficiently for substrates **1-3a** furnishing rearranged compounds **6-8a** in good yields (85-95%, uHPLC) and high regioselectivity (no other isomers detected). Under synthetically useful conditions (10 mM in water, 1 h UV irradiation), a 70% isolated yield of compound **6a** was realized.

Scheme 1. Photorearrangement of CyHQ-protected dialkylanilines[33]



1a: R^1, R^2 = Me
2a: R^1, R^2 = Et
3a: R^1, R^2 = $CH_2CH_2CH_2CH_2$

6a: R^1, R^2 = Me
7a: R^1, R^2 = Et
8a: R^1, R^2 = $CH_2CH_2CH_2CH_2$

The rearrangement of N-alkylanilines to ring-alkylated products was first described by Hofmann in the 19th century[34,35] and later investigated by several other groups.[36-38] The reaction requires harsh conditions and furnishes a mixture of *para*- and *ortho*-rearranged products (generally preferring the *para* isomer) in low to moderate yields together with numerous side products. The photochemical equivalent of this rearrangement has also been described; it generates a mixture of regio-isomers, favoring the *ortho* derivative.[39,40] The reaction requires high irradiation power, causing the formation of a complex mixture of by-products and ultimately resulting in low yields. Yoshiro and Katsuhiko investigated the photochemical rearrangement of N-alkylanilines,[41] but the study was limited to *para*-blocked anilines and probed only the electronics of the migrating benzylic group. Little attention was dedicated to the formation of the free aniline.

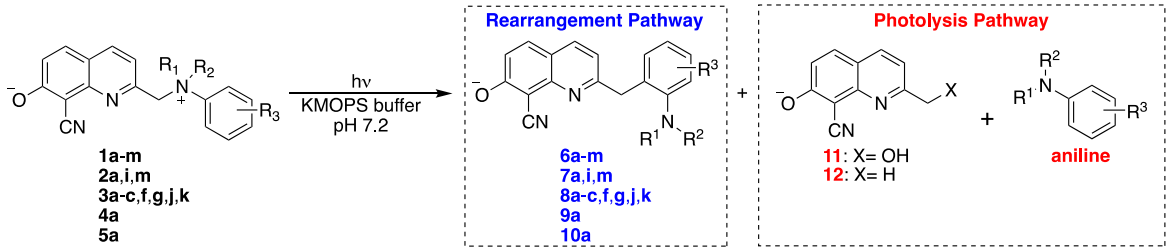
The photorearrangement represents a unique example of efficient and regioselective Hofmann-Martius type rearrangement (similar reactions have been referred to as Claisen-type rearrangements)[33,42]. We investigated the scope and mechanism of the reaction to understand how to modulate and control the outcome (rearrangement vs dialkylaniline release). Considering the occurrence of the dialkylaniline motif in biologically active compounds, our goal was to develop a PPG able to efficiently release biological modulators bearing the dialkylaniline functional group.

RESULTS AND DISCUSSION

CyHQ-protected N,N′-dimethylaniline **1a** (Scheme 2) was chosen as a model compound to study the photorearrangement reaction. Structural modifications to the aniline ring, N,N′-dialkyl groups, and CyHQ were made to study their effect on the reaction outcome. Our first exploration focused on the aniline aromatic ring, aiming to identify the structural features required for productive release. An array of substituents having different electronic and steric properties were introduced on the aniline ring (**1b**-**m**) (Table 1). We also modified the N,N′-dialkyl groups (structures **2**-**5**) with the aim of investigating the role of steric effects on the C-N bond cleavage: ethyl substituents to increase steric bulk and aliphatic cycles to decrease it. CyHQ-protected dialkyl anilines **1a**-**m**; **2a**,**i**,**m**; **3a**-**c**,**f**,**g**,**j**,**k**; **4a**; and **5a** were prepared from the common intermediate MOM-CyHQ-OMs (Scheme 3), whose synthesis has already been described.[33] This latter compound was coupled with the dialkylaniline in

refluxing acetonitrile, affording the corresponding MOM-protected anilinium salts. Final acid-catalyzed deprotection furnished compounds **1a-m**; **2a**,**i**,**m**; **3a-c**,**f**,**g**,**j**,**k**; **4a**; and **5a** in good to high yields.

Scheme 2. Photoreactions of CyHQ-protected dialkylanalines 1-5[a]



[a]Identity of R^3 is given in Table 1.

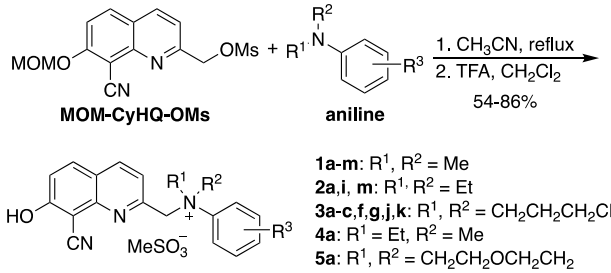
Table 1. Product analysis for the photoreaction of CyHQ-protected dialkylaniline derivatives 1-5

Entry	R^1 R^2 N+	R^3	Conversion: Rearrangement[a] product	yield (%)	Photolysis[b] 11+12 yield (%)	11/12 ratio	aniline (%)
1a		H	**6a**	85[c]	11	2:9	n.d.[d]
1b		2-Me	**6b**	84	16	6:10	n.d.
1c		2-OMe	**6c**	77	23	7:16	n.d.
1d		3-Me	**6d**	82	18	0:18	n.d.
1e		3-F	**6e**	72	28	9:19	n.d.
1f		3-Br	**6f**	56	44	0:44	23
1g	Me, Me	3,5-Me_2	**6g**	73	27	7:20	21
1h		4-Me	**6h**	71	29	6:23	n.d.
1i		4-OMe	**6i**	89	11	3:8	n.d.
1j		4-F	**6j**	75	25	6:19	n.d.
1k		4-Br	**6k**	72	28	7:21	n.d.
1l		4-CF_3	**6l**	75	25	9:16	n.d.
1m		4-*t*-Bu	**6m**	63	37	0:37	23

Entry	R^1 R^2 N+	R^3	Conversion: Rearrangement[a] product	yield (%)	Photolysis[b] 11+12 yield (%)	11/12 ratio	aniline (%)
2a		H	**7a**	89[c]	8	5:3	n.d.
2i	Et, Et	4-OMe	**7i**	92	8	6:2	n.d.
2m		4-*t*-Bu	**7m**	94	6	2:4	n.d.
3a		H	**8a**	95[c]	n.d.	n.d.	n.d.
3b		2-Me	**8b**	84	16	3:13	n.d.
3c		2-OMe	**8c**	76	24	4:20	n.d.
3f		3-Br	**8f**	92	8	1:9	n.d.
3g		3,5-Me_2	**8g**	82	18	2:16	n.d.
3j		4-F	**8j**	85	15	2:13	n.d.
3k		4-Br	**8k**	84	16	2:14	n.d.
4a	Me, Et	H	**9a**	89	11	3:8	n.d.
5a		H	**10a**	87	13	5:8	n.d.

[a]Estimated. [b]Calculated from HPLC by comparison with calibration curves of authentic samples. [c]Data from literature.[33] [d]Not determined. See Table S1 for photophysical data.

Scheme 3. Synthesis of CyHQ-protected diakylanilines 1-5[a]



[a]Identity of R^3 is given in Table 1.

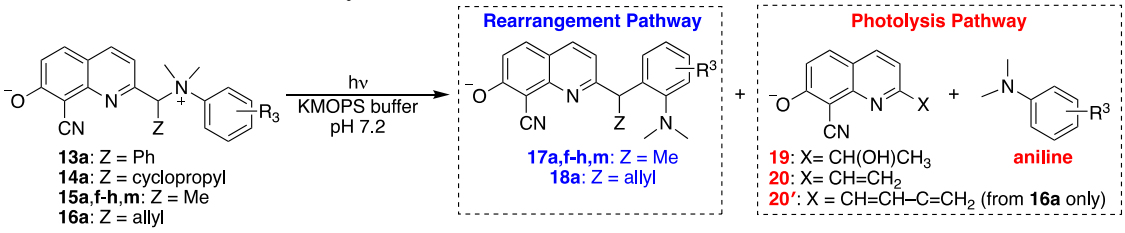
The photochemical reactions of the CyHQ-protected aniline derivatives were investigated to define structure-activity relationships (Scheme 2). In a typical experiment, substrates were dissolved in KMOPS buffer

(pH 7.2, 0.1 mM final concentration) and irradiated with a 365-nm LED lamp (value close to the average λ_{max} of all derivatives) until the starting material was consumed, typically less than one minute, monitoring the course of the reaction by uHPLC. Four different sets of photoproducts were identified, resulting from two different reaction pathways (Scheme 2). The most abundant set of photoproducts were the *ortho*-CyHQ-substituted anilines **6a**-**m**; **7a**,**i**,**m**; **8a**-**c**,**f**,**g**,**j**,**k**; **1a**; and **10a**, resulting from the rearrangement pathway. No formation of the *para*-derivative was observed for any of the substrates. The photolysis pathway generated three different photoproducts: the two CyHQ remnants **11** and **12**, plus the deprotected dialkylanilines. The identification and quantification of the released aniline by uHPLC was in most cases impaired by the low extinction coefficient at the wavelength monitored. The few cases of UV-active anilines gave a final release of 21-23% (Table 1). For this reason, the extent of photolysis versus rearrangement was determined from the more easily detected formation of **11** and **12**. The yields of **11** and **12** were quantified through uHPLC by comparison with calibration curves of authentic samples (Scheme S1). The reaction outcomes favored rearrangement over photolysis, although up to 44% of productive photolysis was observed in some cases.

An interesting result was obtained when analyzing the ratios of the CyHQ remnants **11** and **12**, where a strong preponderance of the dehydroxylated derivative **12** was observed, especially for the constructs showing good release. The photolysis mechanism of the (7-hydroxyquinolin-2-yl)methyl PPGs is well documented and generally proceeds to the formation of the benzylic alcohol derivative **11** by water quenching of the carbocation intermediate after it escapes from the solvent cage.[33,43-45] No formation of **12**, which could form from homolytic cleavage and rapid recombination in non-protic solvents, has ever been reported in aqueous media. The unusual prevalence of **12** in the photolysis pathway of CyHQ-protected dialkylanilines gives important insights into the mechanism of the rearrangement reaction, suggesting the presence of radical species in the excited-state intermediates. Altering the electronics of the aniline ring did not furnish a general trend since neither electron-rich (e.g., **1i**) nor electron-poor (e.g., **1l**) anilines produced a coherent effect on enhancing the release. The yield of photolysis products was increased when bulky substituents were introduced in the *meta* or *para* position (**1f**, **1m**), and surprisingly no effect on product distribution was observed by blocking the *ortho* position (**1b**, **1c** and **3b**, **3c**). Unfortunately, we could not test the reaction on a 2,6-disubstituted derivative because the increased steric hindrance prevented its synthesis. Varying the N,N′-dialkyl substituents (**2-5**) had no significant impact on the rearrangement to photolysis product ratios, hence we decided to maintain the methyl groups at R^1 and R^2 during the next exploration.

We modified CyHQ at the 2-methyl position, inserting different functional groups to check the effect on the photorearrangement (Scheme 4) and probe the nature of the CyHQ excited state intermediate after C-N bond cleavage (carbocation vs radical). A phenyl substituent was introduced (**13a**, Scheme 4 and Table 2) with the aim of increasing the lifetime of the putative benzylic carbocation intermediate and allowing its escape from the solvent cage before rearrangement occurs. A cyclopropyl derivative (**14a**) was added to scavenge for the presence of radical species in the excited state by radical clock experiment.[46] Finally, a methyl group was inserted (**15a**), which resulted in a marked enhancement of the photolysis pathway. Different anilines (specifically those showing increased release in the previous series) were conjugated to the new methyl-substituted CyHQ-based PPG (**15f-h**,**m**).

Scheme 4. Photoreactions of CyHQ derivatives 13-16[a]



[a]Identity of R^3 is given in Table 2.

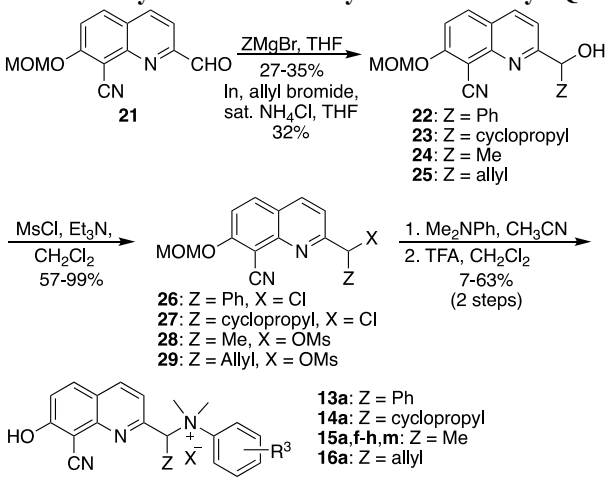
Table 2. Product analysis for the photoreactions of CyHQ derivatives 13-16

Entry	Z	R^3	Conversion: Rearrangement[a] product	Rearrangement[a] yield (%)	Photolysis[b] 19+20 yield (%)	Photolysis[b] 19/20 ratio	Photolysis[b] aniline (%)
13a	Ph	H	*no photoreaction*[c]				
14a	cyclopropyl	H	*no photoreaction*[c]				
15a	Me	H	**17a**	31	69	15:54	n.d.[d]
15f	Me	3-Br	**17f**	33	67	12:55	47
15g	Me	3,5-Me_2	**17g**	32	68	13:53	20
15h	Me	4-Me	**17h**	42	58	15:43	19
15m	Me	4-*t*-Bu	**17m**	42	58	12:46	12
16a	Allyl	H	**18a**[e]	n.d.	n.d.	n.d.	n.d.

[a]Estimated. [b]Calculated from uHPLC by comparison with calibration curves of authentic samples. [c]Only starting material detected even after prolonged irradiation. [d]Not determined. [e]Major product detected. See Table S2 for photophysical data.

We prepared CyHQ-protected dimethylaniline derivatives, bearing different groups on the 2-methyl position (**13a**, **14a**, **15a**,**f-h**,**m**, and **16a**, Scheme 5). Aldehyde **21**[33] was converted to the corresponding secondary alcohols **22-25** with the appropriate Grignard reagent, or in the case of the allyl derivative **25**, by indium-mediated allylation. Alcohols **22-25** were then activated for nucleophilic substitution by reaction with methanesulfonyl chloride in dichloromethane, obtaining the corresponding benzylic chlorides **26-27** or mesylates **28-29**. The target compounds **13a**, **14a**, **15a**,**f-h**,**m**, and **16a** were obtained after coupling with the desired anilines and acid-catalyzed deprotection.

Scheme 5. Synthesis of 2-methyl substituted CyHQ derivatives[a]



[a]Identity of R^3 is listed in Table 2.

The photoreaction of compounds **13a**, **14a**, **15a**,**f-h**,**m**, and **16a** produced different reaction outcomes (Scheme 4), depending on the substituent Z (Table 2). The phenyl- and cyclopropyl-substituted derivatives **13a** and **14a**, respectively, resulted in complete shutdown of the photochemical reaction. Only starting material was detected in both cases even after prolonged irradiation. When Z was a methyl group, dialkylaniline release was increased compared to when Z was hydrogen, yielding from **15a** a high percentage of photolysis products **19** and **20** (69% compared to 11% of **11** and **12** from **1a**). The yields of **19** and **20** were quantified through uHPLC by comparison with calibration curves of authentic samples (Scheme S1). This trend was replicated with all the aniline substitution patterns tested (**15f-h**,**m**). The best result was obtained with the *meta*-bromo derivative **15f**, which yielded 47% of the aniline.

The diversion from rearrangement toward photolysis might be explained by the existence of a new reaction pathway facilitated by the methyl substituent on CyHQ adjacent to the C-N bond. An α-elimination can also occur after C-N bond cleavage, resulting in the formation of the vinyl derivative **20**, which is further stabilized by conjugation with the quinoline ring. All the methyl-substituted derivatives produced greater yields of **20** than **19** in the photolysis (43-55%, Table 2). We also prepared allyl derivative **16a** to enhance the photolysis pathway through α-elimination to form the more conjugated 1,3-butadiene derivative **20′**, but no increase in the photolysis products yield was observed compared to methyl substitution.

Our ultimate goal is to develop a PPG capable of releasing biological effectors bearing the dialkylaniline functionality to be used as tools in chemical biology. In this regard, an interesting compound is the steroid mifepristone (RU-486), a progesterone receptor antagonist used as an abortifacient, that also activates any gene of interest encoded into a mifepristone-inducible pGL-VP[23,24] or LexPR regulator.[26] No photoactivatable form of mifepristone has yet been described to place these conditional gene systems under light control. Light-activated

gene expression is a powerful technique;[47,48] adding a new tool to the current repertoire will be an important contribution to the emerging field of optogenetics.

We conjugated mifepristone to both CyHQ and methyl-substituted CyHQ to generate **30** and **31** (Scheme 6) and evaluated their photochemical properties (Table 3). The rearrangement reaction was completely blocked (no detectable rearranged product by uHPLC or MS analysis) in the case of **31**; only photolysis products were observed. A 55% yield of mifepristone was obtained after 90 s of light exposure (Figure 1, right panel). The appearance of another uHPLC peak was observed during the time course of the photolysis reaction. MS analysis identified it as the N-demethylated mifepristone analogue metapristone (RU-42633). The result was confirmed by comparison with a sample of metapristone synthesized from mifepristone (see Experimental Section). The quantum yield for the photolysis was 0.14 (Table 3). No decomposition of **31** in KMOPS buffer in the dark was observed during one week.

Scheme 6. Synthesis and photoreactions of CyHQ-mifepristone analogs 30 and 31

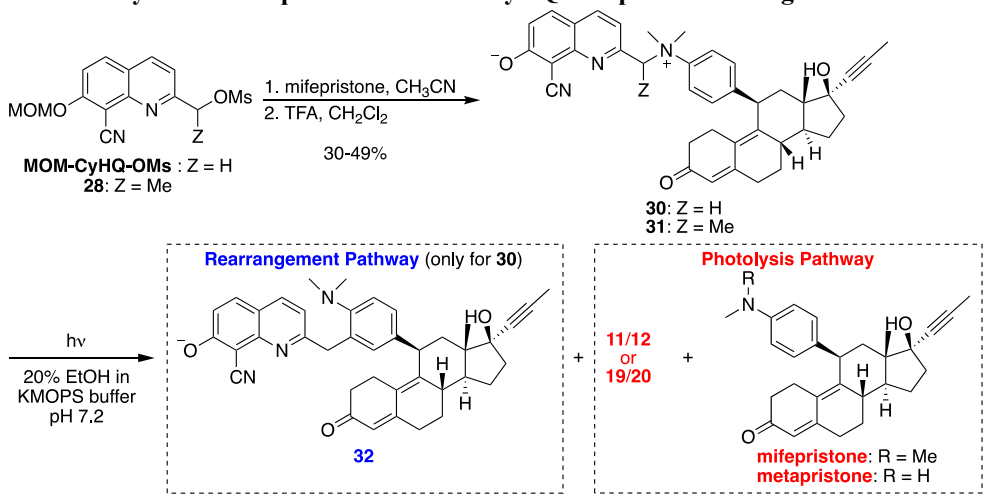


Table 3. Photochemistry of CyHQ-mifepristone analogs 30 and 31.

Entry	Conversion			Quantum yield
	32	mifepristone[a]	metapristone[a]	ϕ
30	49%[b]	6%	45%	0.22[c]
31	-[d]	55%	34%	0.14[e]

[a]Calculated from uHPLC by comparison with calibration curves of authentic samples. [b]Estimated. [c]Sum of quantum yields of rearrangement and uncaging. [d]Not detected. [e]Quantum yield of photolysis. See Table S3 for photophysical data on **30** and **31**.

Metapristone is a well-known metabolite of mifepristone and shares a similar anti-glucocorticoid activity.[49] Additionally, N-demethylation of the dimethylanilinyl group during the photochemistry corroborates the presence of radical species in the reaction mechanism. UV irradiation of **30** produced a 1:1 ratio of rearranged product **32** and released anilines favoring metapristone formation (Table 3), supporting the importance of the α-elimination pathway for successful photolysis.

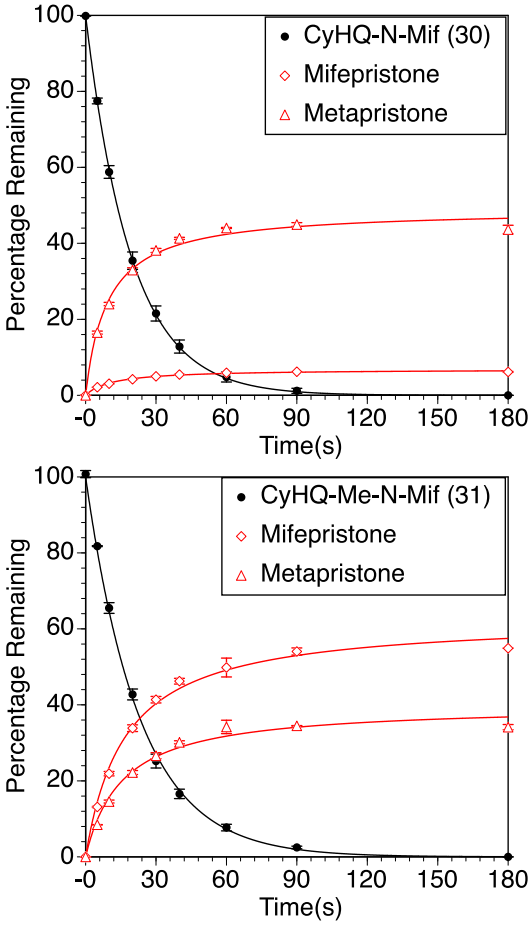
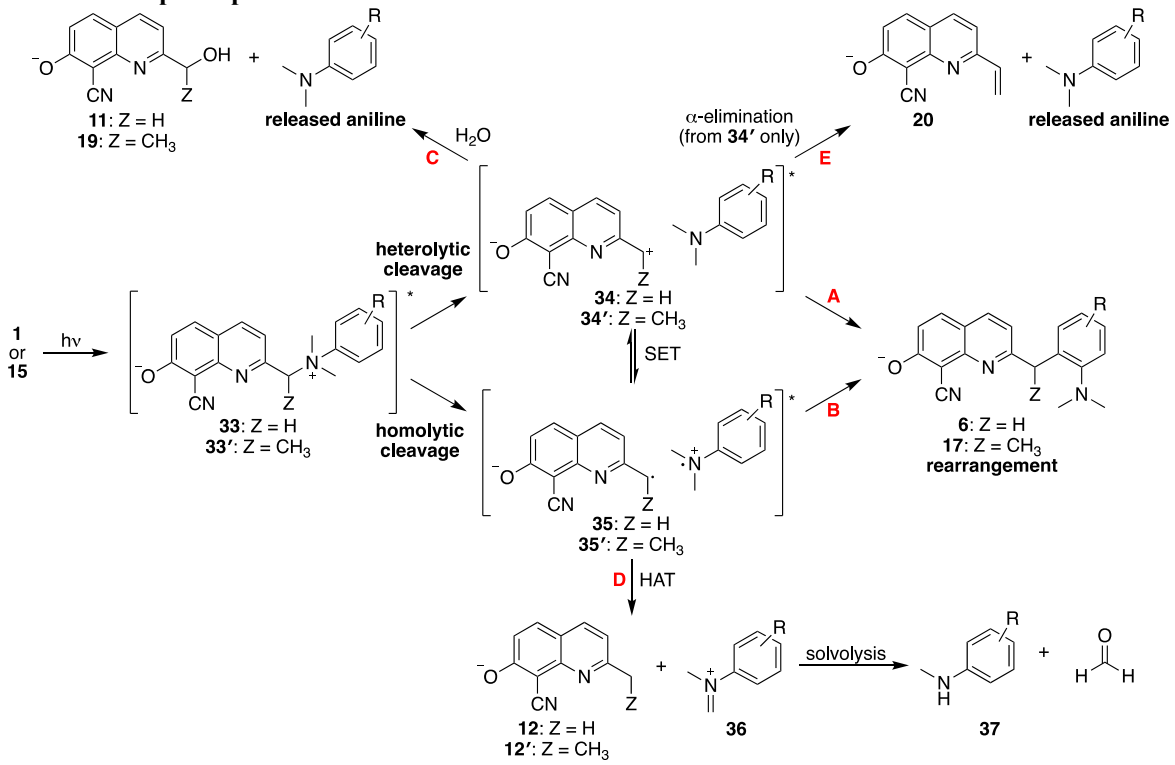


Figure 1. Time courses for the photolysis reactions of **30** (top) and **31** (bottom). Time constant (τ) for the decay curves are 19.3 s for **30** and 22.9 s for **31**. Shown is the appearance of released mifepristone and metapristone. Concentrations were measured by uHPLC and error bars represent standard deviations (three runs). Lines are least-squares fits of a simple exponential decay (black) and of an exponential rise to max (red).

We propose a mechanism for the photoreaction of CyHQ-protected dialkylanilines (Scheme 7). Under the photoreaction conditions, the CyHQ-protected anilines **1** exist in the phenolate form[33] and after photoexcitation they can undergo heterolytic or homolytic C-N bond cleavage furnishing intermediates **34** or **35**, respectively. The product analysis indicates that both **34** and **35** are present during the reaction. Both excited state intermediates can lead to the rearrangement product **6** via cationic (A) or radical (B) pathways,[41] whereas only intermediate **34** can lead to dialkylaniline release and CyHQ-OH (**11**) formation by water quenching (pathway C).[33] The presence of radical pair **35** is supported by the formation of photolysis remnant **12** through hydrogen atom transfer (HAT) from one of the N-methyl groups (pathway D). The reaction mechanism is the same for the methyl-substituted derivatives **15** (Z = CH_3), except that an α-elimination pathway is available from **34′**, leading to **20** (pathway E). A similar reaction outcome was described by Wang et al.[50] in the case of 3-(diethylamino)benzyl-protected tertiary amines. The N-demethylation reaction observed in the case of CyHQ-

protected mifepristone could be explained by the formation of the iminium intermediate **36**, which is known to undergo solvolysis in the ground state,[50] furnishing the corresponding N-demethylated aniline **37**.

Scheme 7. Proposed photoreaction mechanism



[a]Abbreviations: SET, single electron transfer; HAT, hydrogen atom transfer.

CONCLUSION

We report a detailed study regarding the substrate scope of the photorearrangement and photolysis of CyHQ-protected dialkylanilines and propose a mechanism involving either cationic, radical, or both intermediates for each reaction outcome. Photoactivation of dialkylanilines mediated by the 2-methyl-CyHQ derivative of CyHQ is an excellent light-driven method for use in biochemical experiments since the compounds are water soluble, stable in the dark, and release the biological effector efficiently, presumably with the same rapid photolysis kinetics as CyHQ-protected tertiary amines,[33] although this would be the subject of future investigations. The photolysis of methyl-substituted CyHQ-protected mifepristone **31** efficiently produced mifepristone and its equipotent metabolite metapristone. We envision the use of **31** in spatio-temporally resolved studies on the complexity of progesterone-mediated signaling.

EXPERIMENTAL SECTION

General Methods and Materials. Reagents and solvents were purchased from commercial sources and were used without purification. The UV spectra were recorded on a Cary 5000 UV-Vis-NIR spectrophotometer

(Agilent). An Agilent Infinity series system with an autosampler and diode array detector using Zorbax eclipse C-18 reverse phase columns was used for uHPLC and HPLC (analytical and preparative). Agilent 6540 HD Accurate Mass QTOF/LC/MS with electrospray ionization (ESI) or a Micromass QTOF-Ultima with ESI was used for HRMS. KMOPS buffer is 100 mM KCl and 10 mM MOPS titrated to pH 7.2 with KOH. Flash chromatography was carried out on an Isolera Spektra 4 with Biotage SNAP cartridges packed with KPSIL silica.

General procedure for the preparation of 1a-m; **2a**,**i**,**m**; **3a-c**,**f**,**g**,**j**,**k**; **4a**; **5a**; **13a**; **14a**; **15a**,**f-h**,**m**; and **16a**. To a 20-mL vial, **MOM-CyHQ-OMs**, **26**, **27**, **28**, **or 29** (1 equiv) and acetonitrile (5 mL) were added followed by the dialkyl aniline (2 equiv), and the reaction was stirred for about 5 h under refluxing conditions. The reaction was monitored by uHPLC, and upon completion, the reaction mixture was dried in vacuo and dichloromethane was added to the remaining residue followed by the addition of triflouroacetic acid (10 equiv). The reaction was stirred for up to 5 h until the uHPLC showed complete consumption of the starting material. The product was purified either by trituration with tetrahydrofuran or by column chromatography with methanol/dichloromethane (20:80).

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N-dimethylbenzenaminium methanesulfonate (1a). The published procedure[33] was used to prepare **1a**.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N,2-trimethylbenzenaminium methanesulfonate (1b). (11 mg, 54% yield).^{1}H NMR (500 MHz, methanol-d_4, δ): 8.26 (d, J = 8.3 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.73 – 7.59 (m, 1H), 7.47 – 7.37 (m, 2H), 7.37 – 7.23 (m, 3H), 5.55 (s, 2H), 4.11 (s, 6H), 2.92 (s, 3H), 2.72 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.5, 151.7, 148.5, 142.9, 137.9, 135.8, 133.8, 130.7, 130.1, 127.6, 122.1, 121.7, 120.8, 119.3, 114.5, 94.1, 69.5, 56.3, 38.1, 22.3; HRMS (ESI/Q-TOF) m/z: [M – CH_3SO_3]$^+$ calcd for $C_{20}H_{20}N_3O$ 318.1601; found 318.1602.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-2-methoxy-N,N-dimethylbenzenaminium methanesulfonate (1c). (15 mg, 71% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 7.88 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 9.2 Hz, 1H), 7.54 (dd, J = 8.5, 1.4 Hz, 1H), 7.41 (ddd, J = 8.6, 7.4, 1.4 Hz, 1H), 7.26 (dd, J = 8.4, 1.4 Hz, 1H), 7.01 – 6.89 (m, 3H), 5.42 (s, 2H), 4.16 (s, 3H), 4.04 (s, 6H), 2.73 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 174.8, 152.0, 151.2, 149.8, 136.4, 131.9, 131.8, 131.1, 126.0, 122.5, 120.9, 119.7, 118.7, 117.8, 114.1, 92.2, 69.3, 55.6, 54.8, 38.1; HRMS (ESI/Q-TOF) m/z: [M – CH_3SO_3]$^+$ calcd for $C_{20}H_{20}N_3O_2$ 334.1550; found 334.1552.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N,3-trimethylbenzenaminium methanesulfonate (1d). (15.5 mg, 75% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.20 (d, J = 8.3 Hz, 1H), 7.98 (d, J = 9.1 Hz, 1H), 7.78 – 7.71 (m, 1H), 7.60 (dd, J = 8.4, 2.8 Hz, 1H), 7.36 (q, J = 8.0 Hz, 1H), 7.29 (dd, J = 13.7, 8.4 Hz, 2H), 7.23 (d, J

= 8.3 Hz, 1H), 5.45 (s, 2H), 4.02 (s, 6H), 2.73 (s, 3H), 2.40 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.7, 151.8, 148.5, 144.8, 140.8, 137.7, 133.8, 130.6, 129.6, 121.7, 121.4, 121.1, 119.3, 117.7, 114.76, 99.1, 71.4, 55.1, 38.1, 20.1; HRMS (ESI/Q-TOF) *m*/*z*: $[M - CH_3SO_3]^+$ calcd for $C_{20}H_{20}N_3O$ 318.1601; found 318.1606.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-3-fluoro-N,N-dimethylbenzenaminium 2,2,2-trifluoroacetate (1e). (14 mg, 64% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.27 (d, *J* = 8.3 Hz, 1H), 8.03 (d, *J* = 9.1 Hz, 1H), 7.81 (dt, *J* = 10.2, 2.4 Hz, 1H), 7.70 (dd, *J* = 8.5, 2.6 Hz, 1H), 7.56 (td, *J* = 8.5, 6.2 Hz, 1H), 7.37 – 7.25 (m, 3H), 5.48 (s, 2H), 4.04 (s, 6H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 162.8 ($^{1}J_{C-F}$ = 250.32 Hz), 151.4, 148.5 ($^{1}J_{C-F}$ = 4.01 Hz), 137.9, 133.8, 131.3 ($^{3}J_{C-F}$ = 9.01 Hz), 121.7, 120.9, 120.0, 119.4, 117.2 ($^{2}J_{C-F}$ = 21.16 Hz), 117.0 ($^{4}J_{C-F}$ = 3.19 Hz), 114.6, 109.5 ($^{6}J_{C-F}$ = 27.57 Hz), 101.2, 101.0, 94.2, 71.4, 55.3; HRMS (ESI/Q-TOF) *m*/*z*: $[M - CF_3CO_2]^+$ calcd for $C_{19}H_{17}FN_3O$ 322.1350; found 322.1353.

3-bromo-N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N-dimethylbenzenaminium 2,2,2-trifluoroacetate (1f). (18 mg, 74% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.27 (d, *J* = 8.4 Hz, 1H), 8.14 (dd, *J* = 2.7, 1.7 Hz, 1H), 8.02 (d, *J* = 9.1 Hz, 1H), 7.87 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.66 (dd, *J* = 7.9, 1.5 Hz, 1H), 7.45 (t, *J* = 8.3 Hz, 1H), 7.36 – 7.31 (m, 1H), 7.27 (d, *J* = 8.3 Hz, 1H), 5.48 (s, 2H), 4.04 (s, 6H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 161.5, 151.4, 148.5, 145.9, 141.5, 137.9, 133.8, 133.4, 131.3, 124.5, 123.2, 121.7, 120.9, 120.0, 119.4, 114.6, 94.2, 71.4, 55.3; HRMS (ESI/Q-TOF) *m*/*z*: $[M - CF_3CO_2]^+$ calcd for $C_{19}H_{17}BrN_3O$ 382.0550; found 382.0553.

N-((8-cy ano-7-hydroxyquinolin-2-yl)methyl)-N,N,3,5-tetramethylbenzenaminium 2,2,2-trifluoroacetate (1g). (13 mg, 61% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.23 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 9.1 Hz, 1H), 7.48 (s, 2H), 7.32 (d, *J* = 9.1 Hz, 1H), 7.21 (d, *J* = 8.3 Hz, 1H), 7.12 (s, 1H), 5.41 (s, 2H), 3.98 (s, 6H), 2.34 (s, 6H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.5, 151.8, 148.5, 144.8, 140.4, 137.6, 133.8, 131.3, 121.7, 121.0, 119.2, 118.2, 114.6, 94.2, 71.3, 55.0, 47.9, 22.8, 20.0; HRMS (ESI/Q-TOF) *m*/*z*: $[M - CF_3CO_2]^+$ calcd for $C_{21}H_{22}N_3O$ 332.1757; found 332.1754.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N,4-trimethylbenzenaminium 2,2,2-trifluoroacetate (1h). (12 mg, 56% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ) 8.21 (d, *J* = 8.3 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.75 – 7.68 (m, 2H), 7.32 (dd, *J* = 8.9, 2.8 Hz, 3H), 7.20 (d, *J* = 8.4 Hz, 1H), 5.41 (s, 2H), 4.00 (s, 6H), 2.33 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 151.7, 148.5, 140.8, 137.7, 133.8, 130.3, 121.7, 121.3, 120.5, 119.3, 114.7, 94.1, 71.6, 67.5, 55.0, 29.3, 25.1, 19.3. HRMS (ESI/Q-TOF) *m*/*z*: $[M - CF_3CO_2]^+$ calcd for $C_{20}H_{20}N_3O$ 318.1601; found 318.1605.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-4-methoxy-N,N-dimethylbenzenaminium 2,2,2-trifluoroacetate (1i). (15 mg, 67% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.22 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 9.1 Hz, 1H), 7.78 – 7.71 (m, 2H), 7.32 (d, J = 9.1 Hz, 1H), 7.19 (d, J = 8.3 Hz, 1H), 7.04 – 6.97 (m, 2H), 5.38 (s, 2H), 3.98 (s, 6H), 3.80 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 160.5, 151.7, 148.5, 137.7, 137.2, 133.8, 122.2, 121.8, 121.4, 119.3, 115.2, 114.7, 114.6, 94.3, 71.87, 55.1, 54.8, 47.8; HRMS (ESI/Q-TOF) m/z: $[M - CF_3CO_2]^+$ calcd for $C_{20}H_{20}N_3O_2$ 334.1550; found 334.1552.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-4-fluoro-N,N-dimethylbenzenaminium 2,2,2-trifluoroacetate (1j). (17 mg, 80% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ) 7.92 – 7.84 (m, 3H), 7.57 (d, J = 9.3 Hz, 1H), 7.29 – 7.21 (m, 2H), 6.91 (d, J = 9.3 Hz, 1H), 6.81 (d, J = 8.0 Hz, 1H), 5.25 (s, 2H), 3.99 (s, 6H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 176.9, 162.6 ($^1J_{C-F}$ = 253.59 Hz), 151.9, 148.7, 141.8, 140.9, 136.3, 131.6, 131.1, 127.4, 123.6 ($^4J_{C-F}$ = 3.81 Hz), 119.3 ($^3J_{C-F}$ = 7.63 Hz), 117.4, 116.5 ($^2J_{C-F}$ = 23.44 Hz), 91.9, 72.5, 66.7, 55.1; HRMS (ESI/Q-TOF) m/z: $[M - CF_3CO_2]^+$ calcd for $C_{19}H_{17}FN_3O$ 322.1350; found 322.1350.

4-bromo-N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N-dimethylbenzenaminium 2,2,2-trifluoroacetate (1k). (19 mg, 77% yield). ^{1}H NMR (500 MHz, methanol-d_4,δ): 8.26 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 9.2 Hz, 1H), 7.83 – 7.77 (m, 2H), 7.72 – 7.65 (m, 2H), 7.33 (dd, J = 9.0, 4.0 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 5.46 (s, 2H), 4.02 (s, 6H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 151.4, 148.5, 144.0, 137.9, 133.8, 133.0, 131.7, 124.0, 123.0, 121.8, 121.1, 119.4, 116.1, 114.6, 94.2, 71.5, 55.2; HRMS (ESI/Q-TOF) m/z: $[M - CF_3CO_2]^+$ calcd for $C_{19}H_{17}BrN_3O$ 382.0550; found 382.0552.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N-dimethyl-4-(trifluoromethyl)benzenaminium 2,2,2-trifluoroacetate (1l). (14 mg, 59% yield). ^{1}H NMR (500 MHz, methanol-d_4,δ): 8.26 (d, J = 8.3 Hz, 1H), 8.11 (d, J = 8.8 Hz, 2H), 8.00 (d, J = 9.2 Hz, 1H), 7.87 (d, J = 8.7 Hz, 2H), 7.29 (dd, J = 8.7, 6.7 Hz, 2H), 5.54 (s, 2H), 4.07 (s, 6H); ^{13}C NMR{^{1}H} (126 MHz,methanol-d_4, δ): 165.3, 151.1, 148.7, 147.8, 137.9, 133.7, 132.0, 131.8, 127.2, 127.1, 124.2, 122.2, 121.6, 120.6, 119.8, 114.8, 94.0, 71.3, 55.2; HRMS (ESI/Q-TOF) m/z: $[M - CF_3CO_2]^+$ calcd for $C_{20}H_{17}F_3N_3O$ 372.1318; found 372.1320.

4-(tert-butyl)-N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N-dimethylbenzenaminium chloride (1m). (13.6 mg, 69% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.22 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 9.1 Hz, 1H), 7.75 (d, J = 8.6 Hz, 2H), 7.56 (d, J = 8.8 Hz, 2H), 7.33 (d, J = 9.1 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 5.40 (s, 2H), 3.99 (s, 6H), 1.29 (s, 9H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 153.7, 151.5, 148.6, 142.3, 137.7, 133.8, 126.9, 121.8, 121.4, 120.4, 119.4, 114.6, 94.3, 71.7, 54.8, 34.2, 29.9; HRMS (ESI/Q-TOF) m/z: $[M - Cl]^+$ calcd for $C_{23}H_{26}N_3O$ 360.2070; found 360.2073.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N-diethylbenzenaminium methanesulfonate (2a). The published procedure[33] was used to prepare **2a**.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N-diethyl-4-methoxybenzenaminium 2,2,2-trifluoroacetate (2i). (18 mg, 77% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.33 – 8.25 (m, 1H), 8.10 – 8.03 (m, 1H), 7.53 (t, J = 8.4 Hz, 1H), 7.45 – 7.26 (m, 4H), 7.20 – 7.12 (m, 1H), 5.34 (s, 2H), 4.40 – 4.27 (m, 2H), 4.19 (dq, J = 13.9, 7.0 Hz, 2H), 3.88 (s, 3H), 1.44 (t, J = 7.0 Hz, 6H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 169.9, 161.3, 159.8, 151.5, 148.8, 137.9, 133.8, 131.1, 121.6, 119.5, 115.0, 114.5, 113.7, 108.9, 94.4, 79.8, 62.0, 57.6, 55.1, 7.3; HRMS (ESI/Q-TOF) m/z: [M – CF_3CO_2]$^+$ calcd for $C_{22}H_{24}N_3O_2$ 362.1863; found 362.1865.

4-(tert-butyl)-N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N,N-diethylbenzenaminium 2,2,2-trifluoroacetate (2m). (16 mg, 64% yield). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 7.91 – 7.82 (m, 2H), 7.77 (d, J = 7.9 Hz, 1H), 7.65 – 7.57 (m, 2H), 7.41 (d, J = 9.3 Hz, 1H), 6.73 (d, J = 7.9 Hz, 1H), 6.58 (d, J = 9.3 Hz, 1H), 5.11 (s, 2H), 4.19 – 3.99 (m, 4H), 1.31 (s, 9H), 1.20 (t, J = 7.0 Hz, 6H); ^{13}C NMR{^{1}H} (126 MHz, DMSO-d_6, δ): 183.6, 177.8, 154.2, 153.0, 148.6, 147.4, 140.0, 136.1, 131.0, 130.3, 127.3, 122.4, 121.4, 118.3, 116.1, 90.5, 61.7, 58.2, 34.9, 31.3, 8.7; HRMS (ESI/Q-TOF) m/z: [M – CF_3CO_2]$^+$ calcd for $C_{25}H_{30}N_3O$ 388.2383; found 388.2385.

1-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-1-phenylpyrrolidin-1-ium methanesulfonate (3a). The published procedure[33] was used to prepare **3a**.

1-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-1-(o-tolyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3b). (17.6 mg, 77% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.12 (d, J = 8.1 Hz, 1H), 8.00 (d, J = 9.1 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H), 7.37 – 7.27 (m, 3H), 7.11 (t, J = 7.9 Hz, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.19 (s, 2H), 5.07 (dd, J = 12.3, 7.0 Hz, 2H), 4.21 (dt, J = 13.4, 7.8 Hz, 2H), 2.77 (s, 3H), 2.69 – 2.62 (m, 2H), 2.48 (t, J = 7.6 Hz, 2H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.7, 161.7, 151.6, 148.6, 142.9, 137.6, 135.3, 133.8, 131.3, 130.2, 127.2, 123.7, 121.9, 121.6, 119.5, 118.0, 114.5, 94.3, 66.2, 64.8, 21.9, 20.4; HRMS (ESI/Q-TOF) m/z: [M – CF_3CO_2]$^+$ calcd for $C_{22}H_{22}N_3O$ 344.1757; found 344.1760.

1-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-1-(2-methoxyphenyl)pyrrolidin-1-ium methanesulfonate (3c). (19.6 mg, 86% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 7.85 (d, J = 8.1 Hz, 1H), 7.66 (d, J = 9.2 Hz, 1H), 7.42 (ddd, J = 8.6, 7.3, 1.4 Hz, 1H), 7.30 (ddd, J = 10.1, 8.4, 1.4 Hz, 2H), 7.02 (d, J = 9.2 Hz, 1H), 6.83 (ddd, J = 8.6, 7.4, 1.4 Hz, 1H), 6.74 (d, J = 8.0 Hz, 1H), 5.20 (s, 2H), 4.91 – 4.85 (m, 2H), 4.32 (qd, J = 8.2, 5.3, 3.1 Hz, 2H), 4.15 (s, 3H), 2.72 (s, 3H), 2.56 (dtt, J = 8.5, 6.2, 2.9 Hz, 2H), 2.33 (td, J = 10.1, 9.1, 5.1 Hz, 2H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 173.2, 152.2, 150.8, 150.3, 136.5, 132.2, 131.8, 130.4, 124.9, 123.7, 120.6,

120.0, 118.4, 118.0, 114.1, 92.5, 65.3, 64.2, 55.6, 38.1, 20.3; HRMS (ESI/Q-TOF) *m*/*z*: $[M - CH_3SO_3]^+$ calcd for $C_{22}H_{22}N_3O_2$ 360.1707; found 360.1709.

1-(3-bromophenyl)-1-((8-cyano-7-hydroxyquinolin-2-yl)methyl)pyrrolidin-1-ium methanesulfonate (3f). (22 mg, 85% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 7.91 (dd, J = 2.6, 1.7 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 7.68 – 7.60 (m, 2H), 7.58 (ddd, J = 8.5, 2.6, 0.8 Hz, 1H), 7.35 (t, J = 8.2 Hz, 1H), 6.99 (d, J = 9.3 Hz, 1H), 6.62 (d, J = 8.0 Hz, 1H), 5.10 (s, 2H), 4.91 – 4.84 (m, 2H), 4.33 – 4.24 (m, 2H), 2.72 (s, 3H), 2.60 (s, 2H), 2.42 – 2.35 (m, 2H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 151.5, 149.2 144.8, 136.4, 133.3, 132.0, 131.0, 126.4, 125.6, 122.9, 121.3, 119.7, 118.7, 118.0, 92.2, 68.1, 66.7, 65.2, 38.0, 20.2; HRMS (ESI/Q-TOF) *m*/*z*: $[M - CH_3SO_3]^+$ calcd for $C_{21}H_{19}BrN_3O$ 408.0706; found 408.0702.

1-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-1-(3,5-dimethylphenyl)pyrrolidin-1-ium chloride (3g). (15 mg, 77% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.15 (d, J = 8.3 Hz, 1H), 8.01 (d, J = 9.1 Hz, 1H), 7.34 (d, J = 9.1 Hz, 1H), 7.27 (s, 2H), 7.09 (s, 1H), 6.92 (d, J = 8.3 Hz, 1H), 5.22 (s, 2H), 4.78 – 4.67 (m, 2H), 4.35 (tdd, J = 8.1, 5.3, 2.4 Hz, 2H), 2.59 (ddq, J = 8.9, 6.5, 3.7, 3.1 Hz, 2H), 2.44 – 2.29 (m, 2H), 2.27 (s, 6H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.5, 151.9, 148.6, 143.3, 140.3, 137.4, 133.8, 131.3, 121.7, 121.2, 119.4, 119.3, 114.7, 94.2, 67.8, 65.1, 20.2, 19.8; HRMS (ESI/Q-TOF) *m*/*z*: $[M - Cl]^+$ calcd for $C_{23}H_{24}N_3O$ 358.1914; found 358.1917.

1-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-1-(4-fluorophenyl)pyrrolidin-1-ium methanesulfonate (3j). (17 mg, 77% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 7.83 (d, J = 8.0 Hz, 1H), 7.70 – 7.60 (m, 3H), 7.22 – 7.13 (m, 2H), 6.98 (d, J = 9.2 Hz, 1H), 6.61 (d, J = 8.0 Hz, 1H), 5.08 (s, 2H), 4.95 – 4.85 (m, 2H), 4.26 (dddd, J = 11.5, 8.4, 5.6, 2.5 Hz, 2H), 2.73 (s, 3H), 2.60 (tdd, J = 8.6, 6.3, 3.0 Hz, 2H), 2.43 – 2.32 (m, 2H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 175.1, 162.6 ($^1J_{C–F}$ = 248.55 Hz), 151.4, 149.4, 139.7 ($^4J_{C–F}$ = 3.17 Hz), 136.4, 132.0, 126.3, 124.7 ($^3J_{C–F}$ = 7.97 Hz), 119.1, 118.8, 118.2, 116.4 ($^2J_{C–F}$ = 22.39 Hz), 92.1, 68.2, 65.3, 38.1, 20.3; HRMS (ESI/Q-TOF) *m*/*z*: $[M - CH_3SO_3]^+$ calcd for $C_{21}H_{19}FN_3O$ 348.1507; found 348.1509.

1-(4-bromophenyl)-1-((8-cyano-7-hydroxyquinolin-2-yl)methyl)pyrrolidin-1-ium 2,2,2-trifluoroacetate (3k). (19.3 mg, 77% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 7.89 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 9.2 Hz, 1H), 7.65 – 7.53 (m, 4H), 7.03 (d, J = 9.2 Hz, 1H), 6.68 (d, J = 8.1 Hz, 1H), 5.12 (s, 2H), 4.87 – 4.82 (m, 2H), 4.37 – 4.22 (m, 2H), 2.66 – 2.55 (m, 2H), 2.38 (td, J = 9.1, 7.8, 5.4 Hz, 2H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 174.0, 151.2, 149.5, 142.8, 136.6, 132.7, 132.2, 129.0, 128.2, 125.6, 124.2, 123.9, 119.9, 118.4, 92.4, 68.0, 65.2, 38.1, 20.2; HRMS (ESI/Q-TOF) *m*/*z*: $[M - CF_3CO_2]^+$ calcd for $C_{21}H_{19}BrN_3O$ 408.0706; found 408.0709.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-N-ethyl-N-methylbenzenaminium methanesulfonate (4a). (16 mg, 79% yield). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 12.28 (s, 1H), 8.30 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 9.1 Hz, 1H), 7.87 – 7.83 (m, 2H), 7.54 – 7.48 (m, 2H), 7.47 – 7.43 (m, 1H), 7.40 (d, J = 9.1 Hz, 1H), 7.21 (d, J = 8.3 Hz, 1H), 5.57 (d, J = 13.7 Hz, 1H), 5.37 (d, J = 13.8 Hz, 1H), 4.31 (dq, J = 14.3, 7.1 Hz, 1H), 4.18 (dq, J = 13.9, 7.1 Hz, 1H), 3.92 (s, 3H), 2.36 (s, 3H), 1.12 (t, J = 7.1 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, DMSO-d_6, δ) 164.9, 152.4, 148.4, 142.3, 138.3, 134.6, 130.4, 130.3, 122.6, 122.5, 121.6, 120.1, 115.5, 94.2, 70.6, 64.8, 48.3, 10.7, 8.7; HRMS (ESI/Q-TOF) m/z: [M – CH_3SO_3]$^+$ calcd for $C_{20}H_{20}N_3O$ 318.1601; found 318.1602.

4-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-4-phenylmorpholin-4-ium methanesulfonate (5a). (15 mg, 69% yield). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 12.28 (s, 1H), 8.21 (d, J = 8.3 Hz, 1H), 8.08 (d, J = 9.2 Hz, 1H), 7.73 – 7.68 (m, 2H), 7.51 – 7.46 (m, 3H), 7.41 (d, J = 9.1 Hz, 1H), 6.80 (d, J = 8.2 Hz, 1H), 5.42 (s, 2H), 4.67 – 4.59 (m, 2H), 4.50 (ddd, J = 13.0, 8.8, 2.8 Hz, 2H), 4.25 (dt, J = 14.2, 3.4 Hz, 2H), 3.84 – 3.70 (m, 2H), 2.33 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, DMSO-d_6, δ): 164.9, 151.4, 148.4, 140.7, 139.3, 138.5, 138.1, 134.6, 130.8, 130.6, 123.1, 122.7, 121.7, 120.3, 115.5, 94.4, 61.5, 61.0; HRMS (ESI/Q-TOF) m/z: [M – CH_3SO_3]$^+$ calcd for $C_{21}H_{20}N_3O_2$ 346.1550; found 346.1552.

N-((8-cyano-7-hydroxyquinolin-2-yl)(phenyl)methyl)-N,N-dimethylbenzenaminium chloride (13a). (11 mg, 54% yield). *Atropisomer 1:* ^{1}H NMR (500 MHz, methanol-d_4, δ): 9.04 (d, J = 8.3 Hz, 1H), 8.82 (d, J = 9.1 Hz, 1H), 8.18 (d, J = 7.8 Hz, 4H), 8.16 – 7.97 (m, 8H), 6.61 (s, 1H), 3.83 (s, 6H); ^{13}C NMR (126 MHz, MeOD, δ): 164.5, 163.9, 148.8, 142.9, 142.2, 136.9, 133.7, 131.1, 129.0, 128.5, 128.2, 126.5, 120.9, 120.7, 117.5, 94.5, 69.7, 58.5, 44.5, 38.1. *Atropisomer 2*: ^{1}H NMR (500 MHz, methanol-d_4, δ): 9.10 (d, J = 8.4 Hz, 1H), 8.85 (d, J = 9.0 Hz, 1H), 8.27 (d, J = 8.2 Hz, 4H), 8.16 – 7.97 (m, 8H), 7.27 (s, 1H), 3.95 (s, 6H); ^{13}C NMR{^{1}H} (126 MHz, MeOD, δ): 164.4, 163.9, 148.8, 142.9, 142.2, 136.9, 133.7, 131.1, 129.0, 128.5, 128.2, 126.5, 121.1, 120.7, 117.5, 94.5, 69.7, 58.5, 44.5, 38.1; HRMS (ESI/Q-TOF) m/z: [M - Cl]$^+$ calcd for $C_{25}H_{22}N_3O$ 380.1757; found 380.1784.

N-((8-cyano-7-hydroxyquinolin-2-yl)(cyclopropyl)methyl)-N,N-dimethylbenzenaminium chloride (14a). (1.3 mg, 7% yield). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 11.92 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 9.0 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.38 – 7.06 (m, 3H), 7.09 – 6.87 (m, 1H), 6.76 (s, 1H), 6.65 (d, J = 7.7 Hz, 1H), 2.58 (s, 6H), 1.76 (s, 1H), 1.24 (s, 2H), 0.86 (s, 1H), 0.56 (d, J = 41.2 Hz, 1H), 0.28 (d, J = 10.4 Hz, 1H); ^{13}C NMR{^{1}H} (126 MHz, DMSO-d_6, δ): 164.3, 158.8, 148.7, 137.3, 134.4, 129.9, 129.0, 122.4, 120.8, 120.0, 118.4, 117.9, 116.1, 116.0, 115.5, 94.6, 70.2, 58.0, 16.5, 5.4; HRMS (ESI/Q-TOF) m/z: [M - Cl]$^+$ calcd for $C_{22}H_{22}N_3O$ 344.1757; found 344.1786.

N-(1-(8-cyano-7-hydroxyquinolin-2-yl)ethyl)-N,N-dimethylbenzenaminium methanesulfonate (15a). (8 mg, 34% yield). ^{1}H NMR (500 MHz, methanol-d_4 δ): ^{1}H NMR (500 MHz, Methanol-d_4 δ): 8.20 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 9.1 Hz, 1H), 7.87 – 7.81 (m, 2H), 7.55 – 7.44 (m, 3H), 7.35 (d, J = 9.1 Hz, 1H), 7.23 (d, J = 8.2 Hz, 1H), 5.63 (q, J = 6.7 Hz, 1H), 3.97 (s, 3H), 3.92 (s, 3H), 3.13 (s, 3H), 1.94 (d, J = 6.8 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 155.8, 148.5, 146.3, 137.9, 133.8, 130.0, 129.9, 122.0, 121.1, 121.0, 119.4, 114.7, 95.4, 77.3, 52.3, 49.1, 15.0; HRMS (ESI/Q-TOF) m/z: [M – CH_3SO_3]$^+$ calcd for $C_{20}H_{20}N_3O$ 318.1601; found 318.1599

3-bromo-N-(1-(8-cyano-7-hydroxyquinolin-2-yl)ethyl)-N,N-dimethylbenzenaminium methanesulfonate (15f). (3.4 mg, 14% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.12 (dd, J = 2.6, 1.7 Hz, 1H), 7.93 – 7.84 (m, 1H), 7.80 (dd, J = 8.4, 2.8 Hz, 1H), 7.68 – 7.56 (m, 2H), 7.40 (t, J = 8.3 Hz, 1H), 6.99 – 6.90 (m, 1H), 6.87 (d, J = 8.0 Hz, 1H), 5.43 (q, J = 6.7 Hz, 1H), 4.11 – 3.80 (m, 6H), 2.99 – 2.90 (m, 1H), 2.72 (s, 3H), 1.95 – 1.82 (m, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 166.9, 165.9, 151.8, 147.4, 136.4, 133.1, 131.6, 131.1, 127.5, 126.4, 124.9, 123.0, 120.2, 117.0, 108.7, 97.4, 78.1, 52.0, 38.0, 36.7, 15.1; HRMS (ESI/Q-TOF) m/z: [M - CH_3SO_3]$^+$ calcd for $C_{20}H_{19}BrN_3O$ 396.0706; found 396.0704.

N-(1-(8-cyano-7-hydroxyquinolin-2-yl)ethyl)-N,N,3,5-tetramethylbenzenaminium methanesulfonate (15g). (13 mg, 60% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.23 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.46 (s, 2H), 7.35 (d, J = 9.1 Hz, 1H), 7.32 – 7.22 (m, 2H), 7.10 (s, 1H), 5.59 (q, J = 6.8 Hz, 1H), 3.87 (d, J = 11.1 Hz, 6H), 3.33 (s, 3H), 2.31 (s, 6H), 1.90 (d, J = 6.8 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 156.0, 148.5, 140.4, 137.8, 133.8, 131.2, 122.0, 119.4, 118.6, 114.7, 94.2, 77.0, 69.8, 51.8, 45.5, 29.3, 19.8, 15.0; HRMS (ESI/Q-TOF) m/z: [M - CH_3SO_3]$^+$ calcd for $C_{22}H_{24}N_3O$ 346.1914; found 346.1913.

N-(1-(8-cyano-7-hydroxyquinolin-2-yl)ethyl)-N,N,4-trimethylbenzenaminium methanesulfonate (15h). (4.7 mg, 22 % yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.21 (d, J = 8.3 Hz, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.75 – 7.63 (m, 2H), 7.33 (dd, J = 19.0, 8.8 Hz, 3H), 7.24 (d, J = 8.2 Hz, 1H), 5.58 (q, J = 6.8 Hz, 1H), 3.90 (d, J = 21.0 Hz, 6H), 2.33 (s, 3H), 1.92 (d, J = 6.7 Hz, 3H), 1.31 (d, J = 2.6 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 155.9, 148.6, 143.9, 140.8, 137.9, 133.8, 130.3, 122.0, 121.2, 120.8, 119.4, 114.6, 94.3, 77.2, 52.2, 29.3, 19.2, 15.0; HRMS (ESI/Q-TOF) m/z: [M - CH_3SO_3]$^+$ calcd for $C_{21}H_{22}N_3O$ 332.1757; found 332.1760.

4-(tert-butyl)-N-(1-(8-cyano-7-hydroxyquinolin-2-yl)ethyl)-N,N-dimethylbenzenaminium methanesulfonate (15m). (13.4 mg, 57% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.21 (d, J = 8.2 Hz, 1H), 8.03 (d, J = 9.1 Hz, 1H), 7.78 – 7.69 (m, 2H), 7.58 – 7.49 (m, 2H), 7.35 (d, J = 9.1 Hz, 1H), 7.29 (d, J = 8.3 Hz, 1H), 5.60 (q, J = 6.8 Hz, 1H), 3.89 (d, J = 5.3 Hz, 6H), 2.73 (s, 3H), 1.92 (d, J = 6.7 Hz, 3H), 1.28 (s, 9H); ^{13}C

NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.6, 155.7, 153.7, 148.5, 143.7, 137.8, 133.8, 126.8, 122.1, 121.4, 120.7, 119.4, 114.6, 94.3, 77.4, 51.8, 38.1, 34.2, 29.9, 14.8; HRMS (ESI/Q-TOF) *m*/*z*: [M - CH_3SO_3]$^+$ calcd for $C_{24}H_{28}N_3O$ 374.2227; found 374.3047.

N-(1-(8-cyano-7-hydroxyquinolin-2-yl)but-3-en-1-yl)-N,N-dimethylbenzenaminium methanesulfonate (16a). (14 mg, 63% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 7.88 – 7.78 (m, 3H), 7.59 (d, *J* = 9.3 Hz, 1H), 7.52 (dd, *J* = 8.6, 6.4 Hz, 2H), 7.47 (d, *J* = 7.1 Hz, 1H), 6.94 (d, *J* = 9.2 Hz, 1H), 6.83 (d, *J* = 8.0 Hz, 1H), 5.52 – 5.40 (m, 1H), 5.24 (dd, *J* = 11.5, 3.1 Hz, 1H), 5.04 – 4.91 (m, 2H), 3.95 (s, 3H), 3.88 (s, 3H), 3.47 – 3.36 (m, 1H), 2.99 – 2.87 (m, 1H), 2.72 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 176.7, 151.9, 151.2, 146.5, 135.8, 131.6, 130.9, 129.9, 127.4, 121.1, 119.7, 119.1, 119.0, 80.8, 54.8, 51.6, 50.2, 48.1, 38.0, 33.5; HRMS (ESI/Q-TOF) *m*/*z*: [M - CH_3SO_3]$^+$ calcd for $C_{22}H_{22}N_3O$ 344.1757; found 344.1760.

N-((8-cyano-7-hydroxyquinolin-2-yl)methyl)-4-((8S,11R,13S,14S,17S)-17-hydroxy-13-methyl-3-oxo-17-(prop-1-yn-1-yl)-2,3,6,7,8,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-11-yl)-N,N-dimethylbenzenaminium methanesulfonate (30). (17 mg, 49% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.15 (d, *J* = 8.3 Hz, 1H), 7.96 (d, *J* = 9.1 Hz, 1H), 7.79 – 7.71 (m, 2H), 7.35 (s, 1H), 7.33 – 7.25 (m, 2H), 7.19 (d, *J* = 8.3 Hz, 1H), 5.74 (s, 1H), 5.45 (s, 2H), 4.47 (d, *J* = 7.6 Hz, 1H), 4.04 (d, *J* = 20.8 Hz, 6H), 3.53 (s, 1H), 2.77 – 2.68 (m, 2H), 2.67 – 2.54 (m, 2H), 2.50 – 2.30 (m, 3H), 2.25 – 2.11 (m, 3H), 2.09 – 2.03 (m, 2H), 2.01 – 1.91 (m, 2H), 1.86 (d, *J* = 16.0 Hz, 4H), 1.71 (td, *J* = 9.2, 7.8, 4.7 Hz, 2H), 1.49 – 1.24 (m, 4H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 200.8, 171.6, 164.5, 151.8, 148.4, 145.8, 142.0, 137.6, 133.9, 129.6, 128.7, 122.0, 121.1, 119.2, 114.7, 94.2, 81.9, 81.3, 79.0, 71.7, 60.1, 56.9, 55.3, 55.0, 49.4, 46.7, 39.8, 39.0, 38.7, 38.1, 30.6, 27.3, 25.2, 22.7, 19.5, 17.0, 13.1, 1.8; HRMS (ESI/Q-TOF) *m*/*z*: [M - CH_3SO_3]$^+$ calcd for $C_{40}H_{42}N_3O_3$ 612.3221; found 612.3262.

N-(1-(8-cyano-7-hydroxyquinolin-2-yl)ethyl)-4-((8S,11R,13S,14S,17S)-17-hydroxy-13-methyl-3-oxo-17-(prop-1-yn-1-yl)-2,3,6,7,8,11,12,13,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-11-yl)-N,N-dimethylbenzenaminium methanesulfonate (31). (10.8 mg, 30% yield). ^{1}H NMR (500 MHz, DMSO-d_6, δ): 8.54 (s, 1H), 7.67 (dd, *J* = 19.2, 8.5 Hz, 2H), 7.48 (t, *J* = 7.4 Hz, 1H), 7.24 (dt, *J* = 16.4, 9.0 Hz, 2H), 6.46 (dd, *J* = 23.6, 9.3 Hz, 1H), 6.38 (dd, *J* = 11.8, 7.8 Hz, 1H), 5.65 (d, *J* = 10.8 Hz, 1H), 5.27 (dt, *J* = 18.8, 6.8 Hz, 1H), 5.14 (s, 1H), 4.44 (t, *J* = 6.0 Hz, 1H), 3.78 (t, *J* = 4.7 Hz, 6H), 2.64 (td, *J* = 15.2, 13.1, 7.5 Hz, 3H), 2.31 (d, *J* = 12.0 Hz, 3H), 2.19 – 2.06 (m, 3H), 2.00 (s, 1H), 1.93 (d, *J* = 4.3 Hz, 2H), 1.72 (d, *J* = 6.7 Hz, 4H), 1.59 (s, 5H), 1.34 – 1.17 (m, 3H), 0.89 – 0.78 (m, 1H), 0.24 (d, *J* = 25.8 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 164.5, 156.7, 148.9, 148.7, 148.4, 146.3, 137.7, 137.6, 133.7, 132.6, 128.9, 122.0, 121.7, 121.3, 121.2, 121.0,

120.9, 119.4, 119.3, 114.8, 94.1, 88.8, 88.7, 77.4, 77.3, 73.8, 54.3, 48.1, 42.1, 40.2, 38.1, 37.9, 31.2, 30.7, 29.3, 27.7, 16.3, 15.3, 2.5; HRMS (ESI/Q-TOF) *m/z*: $[M - CH_3SO_3]^+$ calcd for $C_{41}H_{44}N_3O_3$ 626.3377; found 626.3428.

General procedure for the Grignard reaction to prepare compounds 22-24. To a 50-mL flask containing 15 mL of dry THF, **21** was added (1.24 mmol, 1 equiv) under argon. The temperature was taken to 0 °C in an ice bath and then the appropriate alkyl or aryl magnesium bromide solution in 1 M THF (1.5 equiv) was added. The mixture was stirred at 0 °C until consumption of starting material was complete (0.5-2 h). The reaction was quenched with ammonium chloride and then extracted with ethyl acetate. The remaining residue after evaporation of the solvent was purified by column chromatography.

2-(hydroxy(phenyl)methyl)-7-(methoxymethoxy)quinoline-8-carbonitrile (22). (107 mg, 27% yield). ^{1}H NMR (500 MHz, chloroform-*d*, δ): 8.07 – 7.98 (m, 1H), 7.93 (d, *J* = 9.1 Hz, 1H), 7.54 (dd, *J* = 15.2, 8.4 Hz, 1H), 7.44 (d, *J* = 7.4 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.28 (t, *J* = 7.3 Hz, 1H), 7.21 (d, *J* = 8.4 Hz, 1H), 5.90 (s, 1H), 5.81 (s, 1H), 5.52 – 5.39 (m, 2H), 3.57 (d, *J* = 15.2 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, chloroform-*d*, δ): 163.7, 162.3, 146.7, 142.3, 137.2, 133.7, 128.7, 128.1, 127.3, 122.6, 119.0, 115.7, 114.3, 99.4, 95.1, 75.4, 56.9; HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{19}H_{17}N_2O_3$ 321.1234; found 321.1246.

2-(cyclopropyl(hydroxy)methyl)-7-(methoxymethoxy)quinoline-8-carbonitrile (23). (106 mg, 30% yield). ^{1}H NMR (500 MHz, chloroform-*d*, δ): 8.17 (dd, *J* = 8.5, 1.4 Hz, 1H), 8.01 (dd, *J* = 9.0, 1.6 Hz, 1H), 7.58 – 7.51 (m, 2H), 5.47 (s, 2H), 4.89 (s, 1H), 4.37 (d, *J* = 7.7 Hz, 1H), 3.59 (d, *J* = 1.6 Hz, 3H), 1.20 – 1.13 (m, 1H), 0.65 (td, *J* = 15.6, 14.8, 6.1 Hz, 4H); ^{13}C NMR{^{1}H} (126 MHz, chloroform-*d*, δ): 164.9, 162.6, 147.0, 137.0, 133.6, 122.8, 118.5, 115.5, 114.3, 99.5, 95.1, 75.7, 56.9, 17.9, 2.8, 2.4; HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3$ 285.1234; found 285.1246.

2-(1-hydroxyethyl)-7-(methoxymethoxy)quinoline-8-carbonitrile (24). (112 mg, 35% yield). ^{1}H NMR (500 MHz, chloroform-*d*, δ): 8.14 (d, *J* = 8.4 Hz, 1H), 7.97 (d, *J* = 9.2 Hz, 1H), 7.52 (d, *J* = 9.2 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 5.44 (s, 2H), 5.05 (q, *J* = 6.7 Hz, 1H), 4.85 (s, 1H), 3.57 (s, 3H), 1.57 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, chloroform-*d*, δ): 166.1, 162.2, 147.0, 137.2, 133.6, 122.5, 117.8, 115.4, 114.4, 99.3, 95.1, 69.0, 56.9, 24.0; HRMS (ESI/Q-TOF) *m/z*: $[M + H]^+$ calcd for $C_{14}H_{15}N_2O_3$ 259.1077; found 259.1088.

2-(1-hydroxybut-3-en-1-yl)-7-(methoxymethoxy)quinoline-8-carbonitrile (25). To a 100-mL flask containing 10 mL of THF, **21** was added (0.98 mmol, 1 equiv) under argon. Indium powder (0.98 mmol, 1 equiv), allyl bromide (9.83 mmol, 10 equiv), and 10 mL of a saturated aqueous solution of ammonium chloride were added. The mixture was placed in an ultrasound bath at 55 °C for 1.5 h. The mixture was diluted with ethyl acetate and filtered through a Celite pad. The organic phase was washed with saturated ammonium chloride solution and

brine. The resulting crude residue after evaporation of the solvent was purified by column chromatography. (89 mg, 32% yield). ^{1}H NMR (500 MHz, chloroform-*d*, δ): 8.15 (d, *J* = 8.5 Hz, 1H), 7.99 (d, *J* = 9.2 Hz, 1H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.40 (d, *J* = 8.4 Hz, 1H), 5.88 (ddt, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.49 – 5.42 (m, 2H), 5.15 – 5.05 (m, 2H), 5.01 (dt, *J* = 7.3, 4.4 Hz, 1H), 4.66 (d, *J* = 5.3 Hz, 1H), 3.59 (s, 3H), 2.75 (ddd, *J* = 11.6, 8.9, 5.2 Hz, 1H), 2.58 (dt, *J* = 14.2, 7.1 Hz, 1H); ^{13}C NMR{^{1}H} (126 MHz, chloroform-*d*, δ): 164.6, 162.2, 147.1, 136.9, 133.8, 133.6, 122.6, 118.4, 118.1, 115.5, 114.4, 99.4, 95.1, 72.4, 56.9, 42.5; HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{17}N_2O_3$ 285.1234; found 285.1236.

General procedure for the preparation of 26-29. To a 25-mL flask containing 5 mL of CH_2Cl_2 the secondary alcohol **22-25** was added (0.156 mmol, 1 equiv). The temperature was taken to 0 °C by keeping the flask in an ice bath. Triethyl amine (2.34 mmol, 15 equiv) was added followed by subsequent addition of mesyl chloride (1.56 mmol, 10 equiv) in a dropwise manner. The mixture was stirred at room temperature for 12 h. The reaction was diluted with CH_2Cl_2 and then washed with water and brine. The oil obtained was carried to the next step without further purification. Compounds were isolated as the mesylates or chlorides.

2-(chloro(phenyl)methyl)-7-(methoxymethoxy)quinoline-8-carbonitrile (26). (30 mg, 57% yield). ^{1}H NMR (500 MHz, chloroform-*d*, δ): 8.13 (d, *J* = 8.5 Hz, 1H), 7.94 (d, *J* = 9.1 Hz, 1H), 7.68 (d, *J* = 8.6 Hz, 1H), 7.62 (dd, *J* = 7.4, 1.8 Hz, 2H), 7.54 (d, *J* = 9.2 Hz, 1H), 7.41 – 7.35 (m, 2H), 7.35 – 7.28 (m, 1H), 6.42 (s, 1H), 5.46 (d, J = 1.2 Hz, 2H), 3.59 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, chloroform-*d*, δ): 162.6, 162.3, 147.7, 139.0, 137.4, 133.39, 128.7, 128.4, 127.6, 122.6, 119.5, 116.07, 114.5, 100.0, 95.1, 64.9, 56.9; HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{19}H_{16}ClN_2O_2$ 339.0895; found 339.0901.

2-(chloro(cyclopropyl)methyl)-7-(methoxymethoxy)quinoline-8-carbonitrile (27). (27 mg, 57% yield). ^{1}H NMR (500 MHz, chloroform-*d*, δ): 8.19 (d, *J* = 8.5 Hz, 1H), 7.98 (d, *J* = 9.2 Hz, 1H), 7.70 (d, *J* = 8.5 Hz, 1H), 7.55 (d, *J* = 9.1 Hz, 1H), 5.46 (s, 2H), 4.61 (d, *J* = 9.5 Hz, 1H), 3.59 (s, 3H), 1.72 (ddd, *J* = 14.6, 8.1, 4.8 Hz, 1H), 0.86 (ddt, *J* = 13.4, 10.0, 4.5 Hz, 1H), 0.74 – 0.61 (m, 3H); ^{13}C NMR{^{1}H} (126 MHz, chloroform-*d*, δ): 162.8, 162.2, 147.7, 137.2, 133.4, 122.8, 119.2, 115.9, 114.5, 100.0, 95.1, 69.2, 56.9, 18.7, 6.2, 5.9; HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{16}H_{16}ClN_2O_2$ 303.0895; found 303.0877.

1-(8-cyano-7-(methoxymethoxy)quinolin-2-yl)ethyl methanesulfonate (28). (52 mg, 99% yield). ^{1}H NMR (500 MHz, chloroform-*d*, δ): 8.23 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.59 (dd, *J* = 16.2, 8.8 Hz, 2H), 5.98 (q, *J* = 6.7 Hz, 1H), 5.46 (s, 2H), 3.58 (s, 3H), 3.14 (s, 3H), 1.87 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, chloroform-*d*, δ): 162.5, 161.2, 147.9, 137.7, 133.7, 122.9, 117.8, 116.3, 99.6, 95.1, 80.5, 56.9, 52.6, 38.9, 21.5; HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{15}H_{17}N_2O_5S$ 337.0853; found 337.0860.

1-(8-cyano-7-(methoxymethoxy)quinolin-2-yl)but-3-en-1-yl methanesulfonate (29). (56 mg, 99% yield). ^{1}H NMR (500 MHz, chloroform-*d*, δ): 8.22 (d, *J* = 8.5 Hz, 1H), 8.01 (d, *J* = 9.2 Hz, 1H), 7.59 (dd, *J* = 15.8, 8.8 Hz, 2H), 5.96 – 5.81 (m, 2H), 5.46 (s, 2H), 5.26 – 5.13 (m, 2H), 3.70 (s, 3H), 3.58 (s, 3H), 3.04 – 2.82 (m, 2H); ^{13}C NMR{^{1}H} (126 MHz, chloroform-*d*, δ): 162.5, 160.4, 147.9, 137.5, 133.7, 131.9, 122.9, 119.7, 118.3, 116.2, 114.6, 95.1, 83.0, 56.9, 52.6, 39.6, 38.9; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{17}H_{19}N_2O_5S$ 363.1009; found 363.1019.

General procedure for the preparation of 11, 12, 19, and 20. The MOM protected precursor **38**, **39**, **40**, or **41** (Scheme S1) (0.05 mmol, 1 equiv) was dissolved in dichloromethane (3 mL) and trifluoroacetic acid (10 equiv) was added dropwise. The reaction was stirred until the uHPLC showed complete consumption of the starting material (2-5 h). The solvent was evaporated, and the product was purified by trituration with tetrahydrofuran.

7-hydroxy-2-(hydroxymethyl)quinoline-8-carbonitrile (11). The published procedure[33] was used to prepare **11**.

7-hydroxy-2-methylquinoline-8-carbonitrile (12). (95% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.36 (d, *J* = 8.3 Hz, 1H), 8.08 (d, *J* = 9.1 Hz, 1H), 7.47 (d, *J* = 8.3 Hz, 1H), 7.30 (d, *J* = 9.1 Hz, 1H), 2.82 (s, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 165.3, 161.2, 146.3, 139.3, 134.2, 121.0, 120.8, 117.7, 113.9, 92.2, 22.5; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{11}H_9N_2O$ 185.0709; found 185.0716.

7-hydroxy-2-(1-hydroxyethyl)quinoline-8-carbonitrile (19). (98% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.32 (d, *J* = 8.5 Hz, 1H), 8.04 (d, *J* = 9.0 Hz, 1H), 7.64 (d, *J* = 8.4 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 5.08 (q, *J* = 6.7 Hz, 1H), 1.59 (d, *J* = 6.7 Hz, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 166.9, 164.4, 147.1, 138.2, 133.9, 121.6, 117.6, 116.4, 114.5, 93.7, 69.8, 22.6; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{12}H_{11}N_2O_2$ 215.0815; found 215.0821.

7-hydroxy-2-vinylquinoline-8-carbonitrile (20). (96% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.23 (d, *J* = 8.4 Hz, 1H), 7.99 (d, *J* = 9.0 Hz, 1H), 7.75 – 7.49 (m, 2H), 7.24 (d, *J* = 9.0 Hz, 1H), 7.05 (dd, *J* = 17.6, 10.9 Hz, 1H), 6.50 (dd, *J* = 17.6, 1.2 Hz, 1H), 5.71 (dd, *J* = 10.8, 1.2 Hz, 1H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 157.7, 148.9, 137.0, 136.8, 133.6, 131.6, 128.6, 128.5, 121.6, 120.2, 117.3, 29.3; HRMS (ESI/Q-TOF) *m*/*z*: [M + H]$^+$ calcd for $C_{12}H_9N_2O$ 197.0709; found 197.0715.

Preparation of metapristone.[51] To a 25-mL flask containing 1 mL of THF, mifepristone was added (0.07 mmol, 1 equiv) and the temperature was taken to 0 °C by keeping the flask in an ice bath. A solution of iodine in methanol (100 mg/mL, 0.21 mmol, 3 equiv) and potassium acetate (0.70 mmol, 10 equiv) were added. The temperature was raised to 25 °C by removing the ice bath, and the mixture was stirred for 12 h. The mixture was diluted with ethyl acetate and washed with water and a 5% solution of sodium thiosulfate. The crude material remaining after

evaporation of the ethyl acetate was purified by column chromatography (62% yield). ^{1}H NMR (500 MHz, methanol-d_4, δ): 8.33 – 7.92 (m, 1H), 7.50 (td, J = 7.9, 2.2 Hz, 1H), 7.04 – 6.94 (m, 2H), 6.65 – 6.53 (m, 2H), 5.74 (s, 1H), 4.43 – 4.29 (m, 2H), 2.76 (s, 3H), 2.68 – 2.49 (m, 2H), 2.49 – 2.36 (m, 2H), 2.36 – 2.26 (m, 4H), 2.17 (ddd, J = 13.2, 9.2, 5.3 Hz, 2H), 2.07 (dq, J = 12.9, 4.3 Hz, 2H), 1.99 – 1.75 (m, 4H), 1.57 – 1.34 (m, 3H), 1.08 – 0.83 (m, 3H); ^{13}C NMR{^{1}H} (126 MHz, methanol-d_4, δ): 201.1, 159.1, 148.6, 147.7, 133.1, 129.0, 128.7, 128.2, 127.4, 121.4, 112.7, 82.3, 81.1, 79.3, 49.8, 46.7, 39.8, 39.4, 38.8, 38.2, 36.3, 30.8, 29.7, 27.4, 25.4, 22.8, 13.0, 1.9; HRMS (ESI/Q-TOF) *m*/*z*: $[M + H]^+$ calcd for $C_{28}H_{34}NO_2$ 416.2584; found 416.2537. See Supporting Information for HPLC chromatogram showing purity of metapristone.

Determination of the molar extinction coefficient (ε). A 0.1 mM solution of substrate in KMOPS buffer was used to acquire the UV-vis spectrum using a blank solution of KMOPS buffer as baseline. Spectra were obtained with an Agilent Cary UV-vis-NIR spectrophotometer with a spectral window measuring from 200 to 800 nm. The measurement was repeated in triplicate and the absorbance values averaged. Final ε values at λ = 365 nm were obtained from the Beer-Lambert law: $\varepsilon = A(cl)^{-1}$.

Assessment of the stability in the dark of 30 and 31. Solutions or **30** and **31** (0.1 mM) in KMOPS buffer were stored in the dark at room temperature and sampled periodically to determine the extent of degradation by uHPLC as described for the photolysis reactions. Less than 1% of **30** or **31** degraded during a period of one week.

Photochemistry experiments and analysis of photolysis products. A solution of CyHQ-protected anilines (2 mL, 0.1 mM) in KMOPS buffer (KCl 100 mM, MOPS 10 mM, pH 7.2) was placed in a 3 mL quartz cuvette together with a stirring bar. For the mifepristone analogues **30** and **31**, ethanol (20% final concentration) was added for solubilization. The samples were irradiated with an LED lamp (OptoLED, Cairn Research Ltd) at 365 nm (average power 8-12 mW) with stirring, sampling (70 µL) at different time points and analyzing by reverse-phase uHPLC. Each experiment was repeated three times. Separations were obtained with a gradient elution (flux rate of 0.3 mL/min) using a mobile phase composed of A = 0.1% trifuoroacetic acid in water and B = acetonitrile (starting from 5% B to 30% over 6 min, followed by ramping to 100% B in 11 min and re-equilibrating to 5% B before the next run). Chromatograms were obtained by scanning at 254 or 320 nm, depending on the extinction coefficient of the compound monitored. The quantification of the concentration remaining was obtained by comparison of the area under the curve measured to an external standard calibration curve generated from different concentrations of the starting material. The percentages remaining were plotted against the time of irradiation and the decay curve obtained was fitted to a simple exponential decay using DeltaGraph software (Red Rock Software Inc). Quantum yields (ϕ) for the photoreaction were calculated as previously described,[33,43] using the following

equation: $\phi = 1/(I\sigma t_{90\%})$ where I is the irradiation intensity of the lamp in Einstein cm^{-2} s^{-1} calculated by ferrioxalate actinometry,[33] σ is the decadic extinction coefficient (1000 times ε, the molar extinction coefficient), and $t_{90\%}$ is the time for 90% consumption of the starting material calculated from the exponential decay curve equation. The quantification of the appearance of CyHQ remnants **11**, **12**, **19**, and **20** and of the released aniline was also obtained by external standard calibration method and plotted to fit an exponential rise to max.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website.

Scheme S1, HPLC chromatograms (Figures S1-S5), photophysical and photochemical data (Tables S1-S3), time-courses of the photoreactions, ^{1}H and ^{13}C NMR spectra, and HPLC chromatogram of metapristone (PDF)

AUTHOR INFORMATION

Corresponding Author

* E-mail: timothy.dore@nyu.edu

ORCID

Davide Deodato: 0000-0001-6715-0503

Naeem Asad: 0000-0001-6871-5270

Timothy M. Dore: 0000-0002-3876-5012

Author Contributions

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ABBREVIATIONS

PPG, photoremovable protecting group; CyHQ, (8-cyano-7-hydroxyquinolin-2-yl)methyl; MOPS, 3-morpholinopropane-1-sulfonic acid; TFA, trifluoroacetic acid; TEA, triethylamine; MsCl, methanesulfonyl chloride

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