

Conformationally Constrained Penta(hetero)cyclic Molecular Architectures by Photoassisted Diversity-Oriented Synthesis

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Intramolecular cycloadditions of photogenerated azaxylylenes provide access to unprecedented polyheterocyclic scaffolds, which are suitable for subsequent postphotochemical modifications to further grow molecular complexity. Here, we explore approaches to the rapid "assembly" of new photoprecursors with nitrogen- or oxygen-rich tethers capable of producing potential pharmacophores and also compatible with subsequent 1,3-dipolar cycloadditions to furnish penta-

Introduction

To date, the Chemical Abstracts Service (CAS) registry contains more than 85 million substances.^[11] In 1965, a little over 200 thousand new substances were added to the CAS. In stark contrast, 2007 saw this number exceed 4 million, of which over 3 million were small molecules.^[2] This awe-inspiring growth is in sharp contrast with the number of new molecular entities approved by the U.S. Food and Drug Administration (FDA): a total of 1513 as of 2011.^[3] The annual approval rate has not changed significantly with the explosive developments in organic synthesis and has only fluctuated between 20–40 entities annually during the last decade.

As the search for new drug candidates is the most common motive to rationalize the expansion of modern combinatorial methods of synthesis, it is not surprising that the apparent gap between the huge number of new synthetic compounds and the tiny trickle of new molecular entities that actually get approved by the FDA has worried many in the field. Some lamented that combinatorial chemists have been perhaps synthesizing mostly the *wrong stuff*, "this apparent lack of productivity ... may in part reflect significant deficiencies in the types of chemical structures generated using combinatorial approaches."^[4] Hence, a vast number of studies have focused on inspecting the differences between the structures of approved drugs and combinatorial libraries or libraries of natural products. Notably, cyclic heterocycles with new structural cores, a minimal number of rotatable bonds, and a high content of sp³-hybridized carbon atoms. The modular assembly of the photoprecursors and the potential variety of postphotochemical modifications of the primary photoproducts provide a framework for the combinatorial implementation of this synthetic strategy.

it has been pointed out that it is the limited diversity of scaffolds that may be one of the underlying reasons. Only 143 framework shapes account for approximately half of the compounds in the CAS registry,^[5] and half of the 836708 known frameworks are only present in one compound. This limited diversity is also reflected in the structures of drugs, and the top 50 frameworks cover 48–52% of approved and experimental drugs,^[6–8]

There are additional problems associated with the structures generated by combinatorial synthesis.^[4] First, according to several studies,^[9,10] the distributions of heteroatoms in drugs, natural products, and compounds in combinatorial libraries differ significantly. On average, drugs and natural products have more oxygen atoms and fewer nitrogen atoms per molecule than compounds in combinatorial libraries. Second, there are generally fewer rotatable bonds in natural products and drugs than there are in compounds in combinatorial libraries. Conformationally constrained molecules are less vulnerable to entropic losses and often possess tighter K_D values compared with those of flexible ligands that can form similar arrays of hydrogen bonds and hydrophobic interactions with proteins.

The extended 3D architectures of the molecules (as opposed to the "flat land" of polyaromatic beads) were also scrutinized in the context of drug design and discovery. Lovering and coauthors,^[11] who proposed a simple saturation parameter, fsp³, demonstrated with convincing statistics that increasing the saturation improves the clinical success of drug candidates. They point out, "Advances over the last 10–15 years in the coupling of sp²–sp² carbons, as well as other sp² couplings, have made the preparation of molecules with greater unsaturation particularly amenable to parallel synthesis. While these advances have contributed to drug discovery, they have also biased efforts at the bench."

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How do we unbias the effort at the bench without throwing out the baby with the water? Our approach has been to employ the modular "assembly" of photoprecursors from simple starting blocks through straightforward and highyielding coupling reactions, including the abovementioned efficient sp²-sp² carbon coupling reactions or other highyielding reactions such as amide bond formation. Subsequent irradiation then triggers intramolecular photocyclizations in these unsaturated photoprecursors. Typically, the photochemical step imparts a spectacular increase in molecular complexity and yields new polyheterocyclic molecular architectures with extended three-dimensional topologies, a reduced number of rotatable bonds, and elevated saturation. As the selection rules for photoinduced cyclizations are very different from those for ground-state cycloadditions, one gains access to polycyclic cores that are not available by conventional methodologies. In this context, photochemistry is a unique tool to overcome the limited diversity of structural frameworks. Coupled with postphotochemical modifications of the reactive unsaturated moieties in the primary photoproducts, it becomes an even more powerful tool in chemical and biological space exploration. The aim of this article is to show how photochemical methods with postphotochemical modifications can be applied to the synthesis of a library of diverse heteroatom-rich polyheterocycles with a limited number of rotatable bonds and relatively high saturation, that is, the Lovering fsp³ parameter.

The main focus of the research efforts in our laboratory in recent years has been the utilization of azaxylylenes, generated by excited-state intramolecular proton transfer (ESIPT) in aromatic *o*-amino ketones, in intramolecular [4+4] or [4+2] cycloaddition reactions to tethered unsaturated moieties, namely, alkenes, furans, thiophenes, and pyrroles,^[12,13] to yield new N,O,S polyheterocycles (Scheme 1).^[14]

The essential aspect of this general methodology is the high availability of simple linear photoprecursors, which are "pre-assembled" in facile and high-yielding chemical coupling reactions that are generally compatible with roboticassisted combinatorial chemistry methods, for example, amide bond formation. These photoprecursors then undergo efficient photoinduced intramolecular cycloadditions with quantum yields of up to $\Phi = 0.75$ to provide access to new molecular architectures.^[15] The primary photoproducts necessarily possess higher saturation and semirigid threedimensional architectures but also contain reactive unsaturated moieties, which make them amenable to postphotochemical modifications for further growth of the complexity, increased saturation, and access to even more elaborate 3D frameworks.^[15,16] For example, for pyrrole-tethered unsaturated pendant moieties, the primary photoproduct possesses a pyrroline ring, that is, a reactive enamine moiety, which is captured in high-yielding reactions with sulfonyl azides or activated in the presence of protic acids or carbon electrophiles to form iminium intermediates and further trapped with appropriate external or internal nucleophiles.^[13]

Although pyrrolines offered a ready postphotochemical modification opportunity owing to the high reactivity of the enamine moiety, another series of primary photoproducts based on furan pendant arms proved more difficult to modify. The [4+4] adducts, that is, azacanes, which contain an alkenyl moiety as a part of an oxabicyclo[4.2.1] core, proved unreactive under classical electrophilic addition reactions. The [4+2] primary photoproducts, which contain a very reactive dihydrofuran moiety, were extremely labile and did not survive even mildly acidic conditions. In this paper, we engage the primary photoproducts in postphotochemical cycloaddition reactions to gain access to new



Scheme 1. Intramolecular cycloadditions of photogenerated azaxylylenes.

polyheterocyclic molecular architectures and assess the applicability and appeal of these transformations in the context of photoassisted diversity-oriented synthesis.^[17]

The other issue is the nature of the tether linking the photoactive amino ketone moiety with the unsaturated pendant arm. As a result of the photoinduced intramolecular cyclization of the photogenerated azaxylylene, a polyheterocyclic scaffold is generated, in which the tether forms additional ring(s) that could be decorated with diverse functional groups or heterocyclic pendants. As we searched for simple and efficient coupling reactions to assemble the photoprecursors, we explored the reactions of o-ketoanilines with isocyanates, including acyl isocyanates, to form urea-based linkers, which upon irradiation introduce additional heterocyclic moieties such as hydantoins fused to the quinolinole or benzazocane cores. Again, this supplementary diversity input allows increased complexity of the polyheterocyclic targets and enhances the systematic exploration of the chemical space in the context of photoassisted diversity-oriented synthesis.

Results and Discussion

The first objective of this study was to diversify the tether linking the photoactive aromatic amino ketone core with the unsaturated furan-based pendant arm by introducing heteroatoms into it and then to evaluate the scope of intramolecular [4+4] and [4+2] cycloaddition reactions of such photogenerated azaxylylenes. Therefore, the tether is set to introduce an additional heterocyclic ring in the photoproduct. We focused on reactive carbonyl derivatives such as isocyanates or chloroformates, which are capable of straightforward coupling with aromatic amino ketones (Scheme 2). The *o*-amino ketones **1a–1c** were treated with furfuryl isocyanate (**2**), furoyl isocyanate [**3**', formed in situ from furoyl chloride (**3**)],^[18] or furfuryl chloroformate [**4**', formed in situ from furfuryl alcohol (**4**)].^[19]

The yields ranged from moderate to good. Benzaldehyde derivatives, such as **7d**, were obtained in two steps from amino alcohol **1d**, which was first coupled to the furanyl moiety and subsequently oxidized by pyridinium chlorochromate (PCC) into the photoactive amidobenzaldehyde. With the exception of this case, the photoprecursor synthesis proceeds in just one simple step from readily available starting materials; therefore, this modular assembly of photoprecursors is amenable to robotic automation.

The photoprecursors obtained in these reactions were subsequently irradiated in a Rayonet photoreactor equipped with RPR-3500 UV lamps to furnish quinolinols or benzazacanes with fused cyclic ureas, hydantoins, and cyclic carbamates (Scheme 3, isolated yields are shown). Solvent optimization revealed that methanol is the best solvent for irradiation. After irradiation, the reaction mixtures were chromatographed to obtain pure products.

The ratio of the [4+4] to [4+2] products is noticeably affected by the nature of the linker. In the hydantoin and imidazolidinone cases, the [4+4] product is formed prefer-

COCl₂ NaOCN 1a, R = Me 1b, R = -(CH₂)₃-SnCl юн (tetralone-based 1c, R= -(CH₂)₂· (indanone-based) ŇСО 2 \cap C NH 6a, R = Me, 59% 7b, 30% 6b, R = -(CH₂)₃-, 88% 0″ **5b**, R = -(CH₂)₃-, 68% 5c, R = -(CH₂)₂-, 77% C PCC OH ОH 4' Ò $\rm NH_2$ ΝН 1d O² 7d, 83% 7d', 29%

Scheme 2. Modular assembly of photoprecursors containing urea, acylurea, and urethane linkers.





Scheme 3. Products of photoinduced cycloadditions.

entially, whereas the [4+2] cycloaddition product is predominant for oxazolidinone. This trend is most pronounced for tetralone-based photoprecursors **5b** and **7b**, each of which gives only one product upon irradiation: the [4+4] cycloadduct for **5b** or the [4+2] cycloadduct for **7b**. Notably, both the [4+2] and the [4+4] photoproduct are formed as single diastereomers, *syn*-[4+4] and *anti*-[4+2]; *syn* and *anti* refer to the respective arrangement of the benzylic hydroxy group in the quinolinol or benzoazacane ring and the furan oxygen atom. The structures and stereochemistries of the products were determined by NMR spectroscopy and were consistent with our previous findings.^[12] Additionally, for **11a**, **11b**, and **13d**, (and also **16** and **21**, see below) X-ray structures were obtained.

Two of the photoproducts underwent further transformations upon chromatography. The indanone-based [4+2] photoproduct **8c** was subjected to an eliminative opening of the *N*,*O*-ketal to afford product **8c**' upon chromatography (Scheme 4), and the [4+4] adduct **9b** underwent the [4.2.1] \rightarrow [3.3.1] rearrangement of its 2,5-epoxyazacane core to yield the oxabicyclo[3.3.1]nonene scaffold.^[20]

The second objective of this study was to explore the feasibility of facile postphotochemical modifications of the newly generated cyclic alkenes in ground-state cycloaddition reactions. In this context, further elaboration of the molecular architectures was achieved by reacting the [4+4] and [4+2] photoproducts with bromonitrile oxide generated in situ from dibromoformaldoxime.^[21] This reaction was



Scheme 4. Silica-gel-induced transformations in photoproducts 8c and 9b.

initially explored and optimized with model compounds 14 and 15, which were synthesized according to the previously published procedures (Scheme 5).^[12] In both cases, the 1,3dipolar cycloaddition of bromonitrile oxide occurs from the *exo* face. The [4+2] primary photoproduct reacted with bromonitrile oxide in a regiospecific fashion to afford 16 (structure determined by X-ray crystallography), whereas the [4+4] photoproduct produced both regioisomers, 17 and 18, in a 1:4 ratio. The observed differences can be explained by the stereoelectronic properties of the alkenes: the [4+2] photoproduct is a vinyl ether, and the 1,3-dipolar cyclo-



Scheme 5. Postphotochemical 1,3-dipolar cycloadditions to the primary photoproducts. [a] Minor regioisomer **17** was observed by NMR spectroscopy.





Scheme 6. 1,3-Dipolar cycloadditions to hydantoins 10a and 11a. [a] Minor regioisomer 23 was observed by NMR spectroscopy.

addition is expected to proceed through a charge-controlled transition state, whereas the double bond in the [4+4] substrate is not as polarized, so both regioisomers are observed.

The regiochemistry of the major product was determined by the analysis of spin–spin coupling constants and a NOE experiment. Proton H_a is characterized by a doublet at δ = 4.71 ppm with ³J = 8.7 Hz, whereas H_b is represented by a doublet of doublets at δ = 3.75 ppm with ³J = 8.7 and 1.0 Hz; the second constant reflects the interaction with H_c. Upon irradiation of the proton at δ = 3.75 ppm, a NOE of 4.6% is observed for the doublet of doublets at δ = 4.64 ppm belonging to H_d. Instructively, according to DFT calculations, the major isomer, **17**, is 2 kcal/mol higher in energy than **18**, possibly owing to the unfavorable steric interaction of the Br atom with the methylene group in the dimethylene linker.

When α,β -unsaturated ketone **19**, derived from the [4+4] photoproduct **15** through the [4.2.1] \rightarrow [3.3.1] rearrangement and Swern oxidation, was used as a substrate in the postphotochemical 1,3-dipolar cycloaddition, we obtained dibromoisoxazoline **20**' (Scheme 5). Clearly, the initially formed isoxazoline **20** underwent additional bromination under the reaction conditions. We hypothesize that the 1,3-dipole precursor, dibromoformaldoxime, used in excess can brominate the relatively stable conjugated enolate moiety of **20**.

We then moved from the model compounds 14 and 15 to photoproducts 10a and 11a, which contain hydantoin moieties (derived from photoprecursor 6a; Scheme 6). Similarly to the model system, we observed *exo* stereochemistry for the nitrile oxide addition. The [4+2] photoproduct again gave only one regioisomer, 21 (structure determined by X-ray crystallography), whereas the [4+4] photoproduct gave two regioisomers. However, their 5:1 ratio is now reversed, and 22 is the major product. Compound 22 is characterized by two doublets with the common spin–spin coupling constant of 8.8 Hz at $\delta = 4.92$ and 3.85 ppm. It is assumed that

the one with the greater chemical shift would belong to H_b , geminal to the oxygen atom of the oxazoline ring. Upon irradiation of the methyl group, which is a singlet at $\delta = 1.71$ ppm, only the proton at $\delta = 4.92$ ppm is affected with a NOE enhancement of 2.4%. Thus, in this case, the electrostatic effect of lone-pair repulsion from the carbonyl oxygen atom overrides the stereochemical preferences. The observed relative stability trend is again consistent with our DFT calculations. According to B3LYP/6-31G(d) calculations, regioisomer **22** is 0.75 kcal/mol lower in energy than regioisomer **23**. Provided that the transition state in these 1,3-dipolar cycloadditions is late, the relative product stability tracks the relative height of the activation barrier.

Conclusions

We have developed a method for the photochemically assisted assembly of fused hydantoins, imidazolines, and oxazolidinones by diversifying the tether that links the photoactive aromatic amino ketone core to the unsaturated furan-based pendant group. The primary photoproducts were amenable to postphotochemical transformations to yield complex penta(hetero)cyclic molecular architectures characterized by a minimal number of rotatable bonds and a high content of sp³-hybridized carbon atoms (fsp³ \approx 0.4). The resulting molecular polycyclic cores could be further decorated with functional groups or additional heterocyclic pendants, as the bromine atom in the 3-bromoisoxazoline moiety is readily replaced with carbon nucleophiles.^[22]

Experimental Section

Common solvents were purchased from Pharmco and used as is, except for tetrahydrofuran (THF), which was heated under reflux over potassium benzophenone ketyl and distilled before use. Common reagents were purchased from Aldrich and used without additional purification, unless indicated otherwise. NMR spectra

were recorded at 25 °C with a Bruker Avance III 500 MHz spectrometer with samples in dimethyl sulfoxide (DMSO), unless noted otherwise. The X-ray structures were obtained with a Bruker APEX II instrument (for details see Supporting Information and included cif files). High resolution mass spectra were obtained with a MDS SCIEX/Applied Biosystems API QSTARTM Pulsar i Hybrid LC/MS/MS system by Dr. Jeremy Balsbaugh from the University of Colorado at Boulder. Flash column chromatography was performed with a Teledyne Isco Combiflash $R_{\rm f}$ system with Teledyne Ultra Pure Silica Gel (230–400 mesh) and hexanes/EtOAc as the eluent.

CCDC-1039241 (for **11a**), -1039242 (for **11b**), -1039243 (for **13d**), -1039244 (for **16**), and -1039245 (for **21**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

General Procedure A for the Synthesis of Compounds 6^[18] Sodium cyanate (1.3 equiv.) was suspended in 1,2-dichlorobenzene (2 mL). Under nitrogen, 2-furoyl chloride (1 equiv.) and tin(IV) chloride (0.05–0.15 equiv.) were added. Upon complete addition, the reaction mixture was heated under reflux for 3 h and then cooled to ambient temperature. The corresponding amine (0.3–1.0 equiv.) was then added. The reaction mixture was stirred overnight and then filtered through a pad of Celite®. The filter cake was washed with chloroform. The solvent was evaporated in vacuo, and the crude material was purified by flash chromatography.

N-[(2-Acetylphenyl)carbamoyl]furan-2-carboxamide (6a): General procedure A was followed. From NaOCN (1.68 g, 26.0 mmol, 1.3 equiv.) 2-furoyl chloride (2.0 mL, 20.0 mmol, 1 equiv.), SnCl₄ (0.23 mL, 2.0 mmol, 0.1 equiv.), and 2'-aminoacetophenone (2.0 mL, 16.5 mmol, 0.8 equiv.), the title compound was obtained (2.62 g, 59%). ¹H NMR (500 MHz, DMSO): δ = 12.35 (s, 1 H), 10.86 (s, 1 H), 8.40 (dd, *J* = 8.5, 1.2 Hz, 1 H), 8.06 (dd, *J* = 1.8, 0.8 Hz, 1 H), 8.03 (dd, *J* = 8.5, 7.5, 1.6 Hz, 1 H), 7.73 (dd, *J* = 3.6, 0.8 Hz, 1 H), 7.62 (ddd, *J* = 8.5, 7.5, 1.6 Hz, 1 H), 7.25 (ddd, *J* = 7.9, 7.5, 1.2 Hz, 1 H), 6.75 (dd, *J* = 3.6, 1.7 Hz, 1 H), 2.64 (s, 3 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 201.3, 158.0, 151.7, 148.3, 145.8, 138.2, 134.0, 131.8, 125.9, 123.5, 122.5, 118.0, 112.9, 29.2 ppm. HRMS (ESI): calcd. for C₁₄H₁₂N₂NaO₄ [M + Na]⁺ 295.0695; found 295.0705.

N-[(4-Oxotetralin-5-yl)carbamoyl]furan-2-carboxamide (6b): General procedure A was followed. From NaOCN (1.68 g, 26.0 mmol, 1.3 equiv.), 2-furoyl chloride (2.0 mL, 20.0 mmol, 1 equiv.), SnCl₄ (0.35 mL, 3.0 mmol, 0.15 equiv.), and 8-aminotetralone (0.60 g, 4.1 mmol, 0.3 equiv.), the title compound was obtained (0.98 g, 88%). ¹H NMR (500 MHz, CDCl₃): δ = 13.28 (s, 1 H), 8.56 (d, *J* = 8.4 Hz, 1 H), 8.30 (s, 1 H), 7.59 (dd, *J* = 1.8, 0.8 Hz, 1 H), 7.49 (t, *J* = 7.9 Hz, 1 H), 7.46 (dd, *J* = 3.6, 0.8 Hz, 1 H), 7.01 (dd, *J* = 7.5, 1.1 Hz, 1 H), 6.63 (dd, *J* = 3.6, 1.7 Hz, 1 H), 3.02 (t, *J* = 6.1 Hz, 2 H), 2.77 (m, 2 H), 2.12 (m, 2 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 201.4, 156.4, 150.6, 145.9, 145.9, 145.6, 140.1, 134.2, 123.7, 120.3, 119.6, 118.2, 113.2, 40.4, 31.1, 22.7 ppm. HRMS (ESI): calcd. for C₁₆H₁₄N₂NaO₄ [M + Na]⁺ 321.0851; found 321.0859.

General Procedure B for the Synthesis of Compounds 5: The corresponding amine (1 equiv.) was dissolved in anhydrous DCM (20 mL). To this solution was added dropwise furfuryl isocyanate (1 equiv.) dissolved in anhydrous DCM (5 mL). The mixture was stirred at ambient temperature for 8 h. The resulting mixture was diluted with DCM and washed with water and then brine. The organic layer was dried with Na₂SO₄ and then concentrated in

vacuo to yield the product, which was used in the next step without further purification.

1-(2-FuryImethyl)-3-(4-oxotetralin-5-yl)urea (5b): General procedure B was followed. From 8-aminotetralone (0.65 g, 4.1 mmol, 1 equiv.) and furfuryl isocyanate (0.5 g, 4.1 mmol, 1 equiv.), the title compound was obtained (0.79 g, 68%). ¹H NMR (500 MHz, CDCl₃): δ = 11.68 (s, 1 H), 8.46 (dd, J = 8.6, 1.1 Hz, 1 H), 7.41 (dd, J = 8.6, 7.5 Hz, 1 H), 7.37 (dd, J = 1.9, 0.8 Hz, 1 H), 6.82 (dd, J = 7.5, 1.1 Hz, 1 H), 6.33 (dd, J = 3.3, 1.9 Hz, 1 H), 6.29 (m, 1 H), 5.30 (t, J = 5.8 Hz, 1 H), 4.49 (d, J = 5.7 Hz, 2 H), 2.95 (t, J = 6.1 Hz, 2 H), 2.66 (m, 2 H), 2.07 (m, 2 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 203.5, 154.7, 151.8, 145.8, 143.8, 142.2, 135.1, 121.1, 117.5, 117.2, 110.4, 107.3, 40.7, 37.3, 31.0, 22.8 ppm. HRMS (ESI): calcd. for C₁₆H₁₆N₂O₃ [M + H]⁺ 285.1239; found 285.1248.

1-(2-Furylmethyl)-3-(3-oxoindan-4-yl)urea (5c): General procedure B was followed. From 7-amino-2,3-dihydro-1*H*-inden-1-one (0.50 g, 3.4 mmol, 1 equiv.) and furfuryl isocyanate (0.42 g, 3.4 mmol, 1 equiv.), the title compound (0.71 g, 77%) was obtained. ¹H NMR (500 MHz, DMSO): $\delta = 9.51$ (s, 1 H), 8.19 (t, 1 H), 8.16 (d, J = 8.3 Hz, 1 H), 7.60 (dd, J = 1.9, 0.9 Hz, 1 H), 7.52 (t, J = 7.8 Hz, 1 H), 7.04 (dd, J = 7.5, 0.9 Hz, 1 H), 6.41 (dd, J = 3.2, 1.8 Hz, 1 H), 6.28 (dd, J = 3.2, 0.9 Hz, 1 H), 4.28 (d, J = 5.5 Hz, 2 H), 3.04 (m, 2 H), 2.66 (m, 2 H) ppm. ¹³C NMR (126 MHz, DMSO): $\delta = 208.5$, 156.5, 154.8, 153.2, 142.6, 140.4, 136.7, 122.1, 118.7, 115.3, 110.9, 107.2, 36.6, 36.4, 25.4 ppm. HRMS (ESI): calcd. for C₁₅H₁₄N₂NaO₃ [M + Na]⁺ 293.0902; found 293.0909.

General Procedure C for the Synthesis of Compounds 7:^[19] A 15 wt.-% phosgene (2 equiv.) solution in toluene was cooled to -78 °C under nitrogen. To this solution was added dropwise furfuryl alcohol (1 equiv.) dissolved in anhydrous diethyl ether (3 mL). Upon complete addition, the mixture was warmed to -15 °C and stirred for 3 h, followed by an additional 30 min at 0 °C. The chlorocarbamate solution was added to a stirring solution of the corresponding amine (0.5–1.0 equiv.) and dry pyridine (1.1–2.0 equiv.) dissolved in anhydrous DCM (10 mL). The mixture was stirred at ambient temperature overnight. The mixture was washed with water and extracted with DCM. The organic layer was washed with brine, dried with Na₂SO₄, and concentrated in vacuo. The crude product was further purified by flash chromatography.

2-Furylmethyl-N-(2-formylphenyl)carbamate (7d): General procedure C was followed. From 15 wt.-% phosgene solution in toluene (6.42 mL, 9.0 mmol, 2 equiv.), furfuryl alcohol (0.44 g, 4.5 mmol, 1 equiv.), 2-aminobenzyl alcohol (0.55 g, 4.5 mmol, 1 equiv.), and dry pyridine (0.41 mL, 5.1 mmol, 1.1 equiv.), 2-furylmethyl N-[2-(hydroxymethyl)phenyl]carbamate (7d', 0.33 g, 29%) was obtained. ¹H NMR (500 MHz, CDCl₃): δ = 7.96 (s, 2 H), 7.47 (dd, J = 1.9, 0.9 Hz, 1 H), 7.35 (td, J = 7.8, 1.6 Hz, 1 H), 7.18 (dd, J = 7.5, 1.6 Hz, 1 H), 7.06 (td, J = 7.5, 1.2 Hz, 1 H), 6.49 (dd, J =3.2, 0.8 Hz, 1 H), 6.41 (dd, J = 3.3, 1.8 Hz, 1 H), 5.18 (s, 2 H), 4.70(s, 2 H), 2.14 (s, 1 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 153.7, 149.7, 143.3, 137.4, 129.2, 129.1, 128.8, 123.6, 121.1, 110.8, 110.6, 64.0, 58.7 ppm. To 7d' (0.33 g, 1.3 mmol, 1 equiv.) dissolved in anhydrous DCM (20 mL) was added PCC (0.43 g, 2.0 mmol, 1.5 equiv.). The mixture was stirred at ambient temperature overnight. The solution was filtered through a pad of silica gel and washed thoroughly with DCM. The resulting organic layer was concentrated in vacuo to yield pale yellow solid 7d (0.27 g, 83%). ¹H NMR (500 MHz, CDCl₃): δ = 10.66 (s, 1 H), 9.92 (d, J = 0.7 Hz, 1 H), 8.50 (d, J = 8.5 Hz, 1 H), 7.67 (dd, J = 7.7, 1.7 Hz, 1 H), 7.63 (ddd, J = 8.8, 7.3, 1.7 Hz, 1 H), 7.48 (dd, J = 1.9, 0.8 Hz,



1 H), 7.21 (td, J = 7.5, 1.0 Hz, 1 H), 6.50 (dd, J = 3.3, 0.7 Hz, 1 H), 6.41 (dd, J = 3.3, 1.9 Hz, 1 H), 5.21 (s, 2 H) ppm. ¹³C NMR (126 MHz, CDCl₃): $\delta = 195.0$, 153.2, 149.4, 143.4, 141.1, 136.0, 122.1, 121.4, 118.4, 110.9, 110.6, 77.2, 58.8 ppm. HRMS (ESI): calcd. for C₁₃H₁₁NNaO₄ [M + Na]⁺ 268.0586; found 268.0594.

2-FuryImethyl-*N***-(4-oxotetralin-5-yl)carbamate (7b):** General procedure C was followed. From 15 wt.-% phosgene solution in toluene (6.42 mL, 9.0 mmol, 2 equiv.), furfuryl alcohol (0.44 g, 4.5 mmol, 1 equiv.), tetralone (0.38 g, 2.3 mmol, 0.5 equiv.), and dry pyridine (0.9 mL, 5.1 mmol, 2.0 equiv.), the title compound (0.35 g, 30%) was obtained. ¹H NMR (500 MHz, CDCl₃): δ = 11.70 (s, 1 H), 8.34 (dd, *J* = 8.6, 1.1 Hz, 1 H), 7.45 (m, 1 H), 7.43 (d, *J* = 8.0 Hz, 1 H), 6.89 (dt, *J* = 7.4, 1.0 Hz, 1 H), 6.48 (dd, *J* = 3.3, 0.8 Hz, 1 H), 6.39 (dd, *J* = 3.2, 1.9 Hz, 1 H), 5.17 (s, 2 H), 2.96 (t, *J* = 6.1 Hz, 2 H), 2.68 (dd, *J* = 7.3, 5.8 Hz, 2 H), 2.07 (p, *J* = 6.4 Hz, 2 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 202.7, 153.5, 149.8, 146.0, 143.2, 142.1, 134.9, 122.2, 118.2, 116.7, 110.6, 110.5, 58.6, 40.6, 31.0, 22.7 ppm. HRMS (ESI): calcd. for C₁₆H₁₅NO₄ [M + H]⁺ 286.1074; found 286.1079.

General Procedure D for Irradiation: Solutions of the photoprecursors (ca. 3.0 mM) in methanol (except where noted) were degassed and irradiated in Pyrex or borosilicate glass reaction vessels in a Rayonet reactor equipped with RPR-3500 UV lamps (broadband 300–400 nm UV source with peak emission at 350 nm) until the reaction was complete, as determined by ¹H NMR spectroscopy. The solution was concentrated, and the mixture was purified by flash chromatography.

Compound **6a** (0.20 g, 0.74 mmol) was irradiated by general procedure D with acetonitrile as the solvent. Flash chromatography yielded 12-hydroxy-12-methyl-16-oxa-3,5-diazatetracyclo-[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6(11),7,9,14-tetraene-2,4-dione (**11a**, 0.13 g, 63%) and 11-hydroxy-11-methyl-7-oxa-2,4-diazatetracyclo-[10.4.0.0^{2,6}.0^{6,10}]hexadeca-1(12),8,13,15-tetraene-3,5-dione (**10a**, 0.039 g, 19%).

Compound 11a: ¹H NMR (500 MHz, DMSO): δ = 11.58 (s, 1 H), 7.58 (dd, J = 8.2, 1.5 Hz, 1 H), 7.57 (dd, J = 8.1, 1.6 Hz, 1 H), 7.28 (ddd, J = 8.3, 7.1, 1.5 Hz, 1 H), 7.17 (ddd, J = 8.4, 7.2, 1.5 Hz, 1 H), 6.65 (dd, J = 5.9, 1.7 Hz, 1 H), 5.93 (dd, J = 5.9, 1.3 Hz, 1 H), 5.53 (s, 1 H), 4.78 (t, J = 1.5 Hz, 1 H), 1.59 (s, 3 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 169.4, 153.0, 137.7, 135.8, 132.2, 129.0, 127.81, 126.01, 125.61, 124.51, 97.31, 90.31, 78.51, 26.3 ppm. HRMS (ESI): calcd. for C₁₄H₁₂N₂NaO₄ [M + Na]⁺ 295.0695; found 295.0709.

Compound 10a: ¹H NMR (500 MHz, DMSO): $\delta = 11.59$ (s, 1 H), 7.37 (m, 3 H), 7.28 (td, J = 7.2, 2.0 Hz, 1 H), 6.52 (t, J = 2.8 Hz, 1 H), 5.47 (s, 1 H), 4.87 (dd, J = 2.9, 2.2 Hz, 1 H), 3.88 (t, J =2.5 Hz, 1 H), 1.66 (s, 3 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 171.6, 154. 5, 146.9, 136.4, 133.5, 128.0, 126.2, 125.5, 125.1, 100.3, 94.0, 69.0, 58.7, 24.2 ppm. HRMS (ESI): calcd. for C₁₄H₁₂N₂NaO₄ [M+ Na]⁺ 295.0695; found 295.0703.

Compound **6b** (0.36 g, 1.2 mmol) was irradiated by general procedure D. Flash chromatography yielded 1-hydroxyl-19-oxa-7,9-diazapentacyclo[$8.7.1.1^{2.5}.0^{5,9}.0^{14,18}$]nonadeca-3,10(18),11,13-tetraene-6,8-dione (**11b**, 0.150 g, 43%) and 11-hydroxy-7-oxa-2,4-diazapentacyclo[$9.7.1.0^{2.6}.0^{6,10}.0^{15,19}$]nonadeca-1(19),8,15,17-tetraene-3,5-dione (**10b**, 0.072 g, 19%).

Compound 11b: ¹H NMR (500 MHz, DMSO): $\delta = 11.52$ (s, 1 H), 7.33 (dd, J = 7.9, 1.2 Hz, 1 H), 7.14 (t, J = 7.8 Hz, 1 H), 6.95 (dd, J = 7.5, 1.4 Hz, 1 H), 6.68 (dd, J = 5.9, 1.7 Hz, 1 H), 5.90 (dd, J = 5.9, 1.2 Hz, 1 H), 5.39 (d, J = 1.3 Hz, 1 H), 4.62 (t, J = 1.5 Hz, 1 H), 2.81 (m, 1 H), 2.70 (ddd, J = 17.2, 12.9, 5.6 Hz, 1 H), 2.01

(m, 1 H), 1.87 (m, 1 H), 1.69 (m, 2 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 169.4, 153.0, 138.9, 137.9, 133.4, 132.3, 127.6, 127.3, 124.7, 124.3, 97.3, 89.0, 75.5, 35.7, 31.5, 17.4 ppm. HRMS (ESI): calcd. for C₁₆H₁₄N₂NaO₄ [M + Na]⁺ 321.0851; found 321.0856.

Compound 10b: ¹H NMR (500 MHz, DMSO): δ = 11.59 (s, 1 H), 7.25 (t, *J* = 7.7 Hz, 1 H), 7.17 (dd, *J* = 7.6, 1.1 Hz, 1 H), 7.05 (d, *J* = 8.0 Hz, 1 H), 6.54 (t, *J* = 2.8 Hz, 1 H), 5.45 (s, 1 H), 4.95 (dd, *J* = 3.0, 2.2 Hz, 1 H), 3.90 (t, *J* = 2.4 Hz, 1 H), 2.72 (m, 1 H), 2.60 (m, 1 H), 1.90 (m, 3 H), 1.72 (m, 1 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 172.1, 155.0, 147.2, 138.4, 133.9, 131.4, 127.8, 127.2, 123.4, 101.1, 94.5, 67.9, 57.9, 35.4, 29.5, 18.4 ppm. HRMS (ESI): calcd. for C₁₆H₁₄N₂O₄ [M - H]⁻ 297.0875, found 297.0886.

Compound **5b** (0.50 g, 1.8 mmol) was irradiated by general procedure D. Flash chromatography yielded 1-hydroxy-19-oxa-7,9-diazapentacyclo[$8.7.1.1^{2.5}.0^{5.9}.0^{14,18}$]nonadeca-3,10,12,14(18)-tetraen-8-one (**9b**, 0.270 g, 54%) and 2-hydroxy-19-oxa-7,9-diazapentacyclo[$8.7.1.1^{1.5}.0^{5.9}.0^{14,18}$]nonadeca-3,10,12,14(18)tetraen-8-one (**9b**', 0.077 g, 15%).

Compound 9b: ¹H NMR (500 MHz, DMSO): δ = 7.21 (s, 1 H), 7.09 (m, 2 H), 6.87 (m, 1 H), 6.53 (dd, J = 5.7, 1.8 Hz, 1 H), 5.77 (dd, J = 5.7, 1.1 Hz, 1 H), 4.46 (m, 1 H), 3.80 (dd, J = 10.8, 1.1 Hz, 1 H), 3.48 (dd, J = 10.7, 1.4 Hz, 1 H), 2.79 (m, 1 H), 2.68 (ddd, J = 17.4, 12.9 Hz, 5.5 1 H), 2.00 (m, 1 H), 1.84 (m, 1 H), 1.68 (m, 3 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 157.0, 138.3, 136.2, 135.1, 133.1, 128.1, 126.9, 126.6, 126.0, 99.6, 87.6, 75.5, 46.4, 36.0, 31.5, 17.7 ppm. HRMS (ESI): calcd. for C₁₆H₁₆N₂O₃ [M – H]⁻ 283.1083; found 283.1087.

Compound 9b': ¹H NMR (500 MHz, CDCl₃): δ = 7.64 (d, *J* = 8.1 Hz, 1 H), 7.25 (t, *J* = 7.8 Hz, 1 H), 6.92 (d, *J* = 7.6 Hz, 1 H), 6.22 (dd, *J* = 9.7, 5.4 Hz, 1 H), 5.93 (d, *J* = 9.7 Hz, 1 H), 5.69 (s, 1 H), 3.84 (d, *J* = 5.4 Hz, 1 H), 3.68 (d, *J* = 1.1 Hz, 2 H), 2.93 (ddd, *J* = 17.5, 10.0, 5.5 Hz, 1 H), 2.87 (ddd, *J* = 17.5, 9.6, 5.8 Hz, 1 H), 2.49 (ddd, *J* = 12.2, 6.8, 2.4 Hz, 1 H), 2.11 (m, 2 H), 1.96 (m, 1 H), 1.56 (td, *J* = 12.3, 7.7 Hz, 1 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 157.55, 136.1, 131.2, 130.0, 128.8, 127.9, 125.5, 123.8, 118.0, 84.3, 77.1, 64.3, 49.4, 29.1, 26.1, 15.9 ppm. HRMS (ESI): calcd. for C₁₆H₁₆N₂LiO₃ [M + Li]⁺ 291.1321; found 291.1328.

Compound **5c** (0.30 g, 1.1 mmol) was irradiated by general procedure D. Flash chromatography yielded 1-hydroxy-18-oxa-7,9-diazapentacyclo[$8.6.1.1^{2.5}.0^{5.9}.0^{14,17}$]octadeca-3,10,12,14(17)-tetraen-8-one (**9c**, 0.15 g, 52%) and 2-[8-hydroxy-3-oxo-2,4-diaza-tertacyclo[$6.6.1.0^{2.6}.0^{11,15}$]pentadeca-1(14),5,11(15),12-tetraen-7-yl]acetaldehyde (**8c**', 0.077 g, 26%).

Compound 9c: ¹H NMR (500 MHz, DMSO): δ = 7.33 (d, *J* = 8.1 Hz, 1 H), 7.23 (s, 1 H), 7.15 (dd, *J* = 8.1, 7.3 Hz, 1 H), 6.96 (d, *J* = 7.3 Hz, 1 H), 6.53 (dd, *J* = 5.8, 1.9 Hz, 1 H), 5.80 (dd, *J* = 5.8, 1.2 Hz, 1 H), 5.09 (s, 1 H), 4.77 (t, *J* = 1.5 Hz, 1 H), 3.80 (d, *J* = 10.6 Hz, 1 H), 3.48 (dd, *J* = 10.7, 1.4 Hz, 1 H), 3.11 (m, 1 H), 2.75 (m, 1 H), 1.93 (m, 2 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 156.7, 145.4, 136.8, 136.4, 132.6, 128.5, 128.24, 122.6, 120.7, 100.3, 89.0, 85.9, 47.2, 41.0, 30.4 ppm. HRMS (ESI): calcd. for C₁₅H₁₄N₂O₃ [M + H]⁺ 271.1083; found 271.1091.

Compound 8'c: ¹H NMR (500 MHz, DMSO): δ = 10.03 (d, J = 2.4 Hz, 1 H), 9.56 (d, J = 2.7 Hz, 1 H), 7.90 (d, J = 8.0 Hz, 1 H), 7.30 (t, J = 7.8 Hz, 1 H), 7.03 (d, J = 7.5 Hz, 1 H), 6.36 (d, J = 2.3 Hz, 1 H), 5.24 (s, 1 H), 3.67 (dd, J = 8.9, 5.7 Hz, 1 H), 3.19 (m, 1 H), 2.82 (dd, J = 15.8, 8.4 Hz, 1 H), 2.59 (dd, J = 16.8, 5.7 Hz, 1 H), 2.11 (m, 1 H), 1.97 (m, 2 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 202.2, 151.9, 144.3, 132.1, 132.0, 130.3, 121.4, 120.3, 113.6, 107.2, 78.7, 46.2, 40.9, 39.5, 30.8 ppm. HRMS

(ESI): calcd. for $C_{15}H_{14}N_2O_3 [M - H]^-$ 269.0926; found 269.0928.

Compound **7d** (0.26 g, 1.1 mmol) was irradiated by general procedure D. Flash chromatography yielded 12-hydroxy-3,16-dioxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tertaen-4-one (**13d**, 0.076 g, 29%) and 11-hydroxy-4,7-dioxa-2-azatetracyclo-[10.4.0.0^{2,6}. 0^{6,10}]hexadeca-1(16),8,12,14-tertaen-3-one (**12d**, 0.15 g, 58%).

Compound 13d: ¹H NMR (500 MHz, DMSO): δ = 7.71 (dt, *J* = 8.0, 1.4 Hz, 1 H), 7.34 (m, 1 H), 7.30 (tdd, *J* = 7.8, 1.8, 0.7 Hz, 1 H), 7.25 (td, *J* = 7.5, 1.7 Hz, 1 H), 6.55 (dd, *J* = 5.8, 1.8 Hz, 1 H), 6.18 (d, *J* = 6.4 Hz, 1 H), 5.95 (dd, *J* = 5.8, 1.0 Hz, 1 H), 4.91 (dd, *J* = 6.4, 3.3 Hz, 1 H), 4.85 (ddd, *J* = 3.2, 1.8, 1.0 Hz, 1 H), 4.75 (d, *J* = 10.2 Hz, 1 H), 4.49 (d, *J* = 10.2 Hz, 1 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 158.6, 142.0, 140.4, 136.2, 132.7, 132.3, 131.9, 131.3, 130.8, 104.2, 88.5, 79.4, 73.9 ppm. HRMS (ESI): calcd. for C₁₃H₁₁NNaO₄ [M + Na]⁺ 268.0586; found 268.0596.

Compound 12d: ¹H NMR (500 MHz, DMSO): δ = 7.50 (dd, J = 7.8, 1.3 Hz, 1 H), 7.44 (dt, J = 7.4, 1.4 Hz, 1 H), 7.31 (tdd, J = 7.7, 1.7, 0.9 Hz, 1 H), 7.25 (td, J = 7.5, 1.3 Hz, 1 H), 6.43 (t, J = 2.7 Hz, 1 H), 5.97 (d, J = 5.5 Hz, 1 H), 4.95 (t, J = 5.9 Hz, 1 H), 4.84 (dd, J = 3.1, 2.2 Hz, 1 H), 4.76 (d, J = 10.1 Hz, 1 H), 4.62 (d, J = 10.1 Hz, 1 H), 3.96 (dt, J = 6.2, 2.3 Hz, 1 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 153.5, 146.6, 134.4, 131.9, 127.4, 125.9, 125.3, 120.9, 99.6, 98.0, 73.4, 65.8, 54.1 ppm. HRMS (ESI): calcd. for C₁₃H₁₁NNaO₄ [M + Na]⁺ 268.0586; found 268.0594.

Compound **7b** (0.10 g, 0.35 mmol) was irradiated by general procedure D. Flash chromatography yielded 11-hydroxy-4,7-dioxa-2-azapentacyclo[$9.7.1.0^{2.5}.0^{6,10}.0^{15,19}$]nonadeca-1(18),8,15(19),16-tetraen-3-one (**12b**, 0.063 g, 63%).

Compound 12b: ¹H NMR (500 MHz, CDCl₃): δ = 7.56 (dt, J = 7.9, 1.1 Hz, 1 H), 7.31 (t, J = 7.8 Hz, 1 H), 7.02 (dq, J = 7.7, 1.0 Hz, 1 H), 6.31 (t, J = 2.9 Hz, 1 H), 4.73 (dd, J = 3.2, 2.3 Hz, 1 H), 4.71 (d, J = 9.4 Hz, 1 H), 4.60 (d, J = 9.5 Hz, 1 H), 3.75 (t, J = 2.4 Hz, 1 H), 2.82 (m, 1 H), 2.72 (m, 1 H), 2.07 (m, 1 H), 1.92 (m, 3 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 146.9, 138.0, 133.2, 128.8, 128.5, 126.7, 121.2, 99.1, 97.4, 77.2, 75.4, 69.3, 58.3, 35.4, 29.5, 18.5 ppm. HRMS (ESI): calcd. for C₁₆H₁₅NLiO₄ [M + L]i⁺ 292.1161; found 292.1169.

Postphotochemical Cycloadditions: For the model system, an equimolar mixture of 4-hydroxy-2,3-benzo-8-oxa-1-azatricyclo- $[7.3.0.0^{5,9}]$ dodeca-2,6-dien-12-one (**14**) and 2-hydroxy-3,4-benzo-12-oxa-5-azatricyclo $[7.2.1.0^{5,9}]$ dodec-3,10-dien-6-one (**15**) was synthesized as described previously.¹²

16-Oxa-5-azatetracyclo[10.3.1.0^{1,5}.0^{6,11}]hexadeca-6(11),7,9,14tetraen-4,13-dione (19): To 15 (0.40 g, 1.6 mmol, 1 equiv.) was added CHCl₃ (40 mL), followed by trifluoroacetic acid (TFA, 5 mL). The mixture was stirred at room temperature overnight. The reaction was quenched with satd. NaHCO3 solution, and the organic layer was washed with brine, dried over Na₂SO₄, and concentrated in vacuo. The resulting residue was purified by flash chromatography to yield 13-hydroxy-16-oxa-5-azatetracyclo-[10.3.1.0^{1,5}.0^{6,11}]hexadeca-6(11),7,9,14-tetraen-4-one (0.30 g, 78%). ¹H NMR (500 MHz, CDCl₃): δ = 8.38 (dd, J = 8.3, 1.2 Hz, 1 H), 7.41 (dddd, J = 8.1, 7.4, 1.7, 0.5 Hz, 1 H), 7.30 (m, 2 H), 7.22 (td, *J* = 7.5, 1.2 Hz, 1 H), 6.13 (d, *J* = 9.9 Hz, 1 H), 6.07 (ddd, *J* = 9.8, 5.0, 1.2 Hz, 1 H), 5.31 (s, 1 H), 5.17 (dd, J = 5.0, 1.2 Hz, 1 H), 2.77 (m, 2 H), 2.45 (m, 2 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 171.4, 133.6, 132.6, 129.3, 125.5, 124.6, 121.3, 120.9, 120.3, 85.8, 73.8, 71.0, 30.2, 29.7 ppm. Oxalyl chloride (0.07 mL, 0.84 mmol, 1.1 equiv.) was dissolved in anhydrous DCM (0.9 mL), and the solution was cooled to -78 °C before dry DMSO (0.12 mL,

1.7 mmol, 2.2 equiv.) was slowly added. Upon complete addition, the mixture was stirred for 2 min until the evolution of gas stopped. Then, the alcohol (0.19 g, 0.77 mmol, 1 equiv.) dissolved in anhydrous DCM (1.5 mL) was added dropwise. Upon complete addition, the mixture was stirred for 15 min, and NEt₃ (0.54 mL, 3.9 mmol, 5 equiv.) was slowly added. Upon complete addition, the mixture was slowly warmed to room temp. and then stirred overnight. The reaction mixture was quenched with water and extracted with DCM. The resulting organic layer was washed with brine, dried with Na₂SO₄, and concentrated in vacuo to yield **19** (0.11 g, 60%). The resulting solid was used in the next step without further purification. ¹H NMR (500 MHz, CDCl₃): δ = 8.46 (dd, J = 8.4, 1.2 Hz, 1 H), 7.41 (ddd, J = 8.6, 7.3, 1.6 Hz, 1 H), 7.27 (dd, J = 7.8, 1.7 Hz, 1 H), 7.19 (td, J = 7.5, 1.2 Hz, 1 H), 6.79 (d, J =10.0 Hz, 1 H), 6.19 (dd, J = 10.1, 0.7 Hz, 1 H), 5.22 (s, 1 H), 2.79 (m, 2 H), 2.55 (ddd, J = 13.5, 7.1, 4.5 Hz, 1 H), 2.41 (dt, J = 13.5, 10.4 Hz, 1 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 192.5, 170.9, 143.2, 132.3, 129.5, 126.3, 125.8, 125.0, 119.9, 119.3, 86.3, 78.7, 31.0, 29.7 ppm. HRMS (ESI): calcd. for $C_{14}H_{11}NO_3 [M + H]^+$ 242.0812; found 242.0816.

Synthesis of Dibromoformaldoxime:^[21] To a solution of glyoxylic acid monohydrate (20.3 g, 0.22 mol, 1 equiv.) in water (160 mL, 1.4 M) was added hydroxylamine hydrochloride (19.4 g, 0.28 mol, 1.3 equiv.). The mixture was stirred at ambient temperature for 24 h. NaHCO₃ (47.7 g, 0.57 mol, 2.58 equiv.) was slowly added, followed by DCM (70 mL). The resulting mixture was cooled in an ice bath, and Br₂ (19.5 mL, 0.38 mol, 1.7 equiv.) in DCM (100 mL) was slowly added with the temperature maintained at or below 10 °C. Upon complete addition, the mixture was stirred at room temperature for 3 h. The resulting mixture was diluted with water (100 mL), extracted with DCM (3 × 30 mL), dried with Na₂SO₄, and concentrated in vacuo. The resulting solid was recrystallized from hexanes to yield a white crystalline solid (12.5 g, 28%); m.p. 65–66 °C (ref.^[21] 65–66 °C).

General Procedure E for Nitrile Oxide Addition:^[21] The photoproduct (1 equiv.) was dissolved in EtOAc or EtOAc/DCM. To this solution was added dibromoformaldoxime (3 equiv.) and KHCO₃ (6 equiv.). Additional dibromoformaldoxime (3 equiv.) and KHCO₃ (6 equiv.) were usually added after 12 h. The reaction was monitored by NMR spectroscopy until the starting materials were consumed. The resulting mixture was diluted with water, extracted with EtOAc or DCM (3×20 mL), washed with brine, dried with Na₂SO₄, and concentrated in vacuo. The mixture was then purified by flash chromatography.

15-Bromo-12-hydroxy-17,19-dioxa-5,16-diazapentacyclo[**11.5.1.0**^{1.5}. **0**^{6,11}.**0**^{14,18}]**nonadeca-6(11),7,9,15-tetraen-4-one (18):** General procedure E was followed with EtOAc. From **15** (0.19 g, 0.76 mmol, 1 equiv.), dibromoformaldoxime (0.46 g, 2.3 mmol, 3 equiv.), and KHCO₃ (0.46 g, 4.6 mmol, 6 equiv.), the formation of a 4:1 mixture of two regioisomers of the title compound was observed. Upon purification, the title compound (major isomer) was isolated (0.17 g, 63%). ¹H NMR (500 MHz, DMSO): δ = 7.39 (m, 3 H), 7.27 (m, 1 H), 5.53 (d, *J* = 5.8 Hz, 1 H), 4.71 (d, *J* = 8.6 Hz, 1 H), 4.64 (dd, *J* = 5.8, 4.3 Hz, 1 H), 4.53 (d, *J* = 4.2 Hz, 1 H), 3.75 (dd, *J* = 8.6, 1.1 Hz, 1 H), 2.68 (ddd, *J* = 16.1, 9.9, 8.8 Hz, 1 H), 2.55 (m, 1 H), 2.46 (m, 1 H), 2.07 (m, 1 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 173.3, 140.0, 134.3, 134.2, 133.4, 128.9, 128.4, 126.9, 104.1, 88.1, 81.7, 76.4, 61.0, 29.5, 27.3 ppm. HRMS (ESI): calcd. for C₁₅H₁₃N₂LiO₄Br [M + Li]⁺ 371.0219; found 371.0219.

15-Bromo-12-hydroxy-17,19-dioxa-5,16-diazapentacyclo[**11.6.0.0**^{1,5}. **0**^{6,11}.**0**^{14,18}]**nonadeca-6**(**11**),**7,9,15-tetraen-4-one** (**16**): General procedure E was followed. From **14** (0.20 g, 0.82 mmol, 1 equiv.), di-

bromoformaldoxime (1.0 g, 4.9 mmol, 6 equiv.), and KHCO₃ (1.0 g, 9.8 mmol, 12 equiv.), the title compound was obtained (0.19 g, 65%). ¹H NMR (500 MHz, CDCl₃): δ = 7.92 (d, *J* = 7.9 Hz, 1 H), 7.49 (td, *J* = 7.8, 1.5 Hz, 1 H), 7.37 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.25 (td, *J* = 7.5, 1.2 Hz, 1 H), 5.65 (d, *J* = 6.0 Hz, 1 H), 4.79 (t, *J* = 2.9 Hz, 1 H), 3.51 (s, 1 H), 3.45 (dd, *J* = 6.0, 3.6 Hz, 1 H), 3.37 (dd, *J* = 3.5, 2.9 Hz, 1 H), 2.85 (ddd, *J* = 16.6, 9.9, 8.7 Hz, 1 H), 2.48 (m, 3 H) ppm. ¹³C NMR (126 MHz, CDCl₃): δ = 173.2, 140.8, 134.2, 130.8, 129.0, 128.7, 126.1, 123.7, 106.8, 101.2, 71.0, 61.6, 41.0, 34.2, 29.9 ppm. HRMS (ESI): calcd. for C₁₅H₁₃N₂O₄Br [M + H]⁺ 366.0168; found 366.0181.

14,15-Dibromo-17,19-dioxa-5,16-diazapentacyclo[10.6.1.0^{1,5}.0^{6,11}. **0**^{14,18}**]nonadeca-6(11),7,9,15-tetraene-4,13-dione (20'):** General procedure E was followed with an EtOAc/DCM mixture. From **19** (0.11 g), the title compound was obtained after flash chromatography (0.13 g, 62%). ¹H NMR (500 MHz, CD₂Cl₂): δ = 8.44 (m, 1 H), 7.49 (ddd, *J* = 8.4, 7.4, 1.8 Hz, 1 H), 7.28 (m, 2 H), 5.41 (s, 1 H), 5.15 (s, 1 H), 3.04 (ddd, *J* = 13.8, 8.1, 3.7 Hz, 1 H), 2.74 (m, 2 H), 2.30 (dt, *J* = 13.8, 10.1 Hz, 1 H) ppm. ¹³C NMR (126 MHz, CD₂Cl₂): δ = 191.8, 172.6, 141.4, 134.1, 131.0, 126.4, 126.0, 120.8, 118.1, 92.7, 90.1, 78.2, 57.7, 30.1, 28.8 ppm. HRMS (ESI): calcd. for C₁₅H₁₀Br₂N₂O₄Li [M + Li]⁺ 448.9148; found 449.1726.

17-Bromo-12-hydroxy-12-methyl-15,19-dioxa-3,5,16-triazapenta-cyclo[11.5.1.0^{1,5}.0^{6,11}.0^{14,18}]nondeca-6(11),7,9,16-tetraene-2,4-dione (22): General procedure E was followed. From **11a** (0.16 g, 0.58 mmol, 1 equiv.), dibromoformaldoxime (0.70 g, 3.4 mmol, 6 equiv.), and KHCO₃ (0.70 g, 6.8 mmol, 12 equiv.), the formation of a 5:1 mixture of two regioisomers was observed. After purification, the major isomer was isolated (0.12 g, 53 %). ¹H NMR (500 MHz, DMSO): δ = 11.89 (s, 1 H), 7.66 (dd, J = 8.1, 1.4 Hz, 1 H), 7.54 (dd, J = 8.1, 1.5 Hz, 1 H), 7.37 (m, 1 H), 7.25 (ddd, J = 8.7, 7.3, 1.4 Hz, 1 H), 5.44 (s, 1 H), 4.92 (d, J = 8.7 Hz, 1 H), 4.54 (d, J = 0.7 Hz, 1 H), 3.85 (dd, J = 8.7, 0.7 Hz, 1 H), 1.71 (s, 3 H) ppm. ¹³C NMR (126 MHz, DMSO): δ = 166.5, 152.8, 136.2, 135.2, 133.4, 128.8, 128.3, 127.1, 126.5, 94.9, 91.3, 88.5, 73.6, 63.5, 26.0 ppm. HRMS (ESI): calcd. for C₁₅H₁₂BrN₃LiO₅ [M+ Li]⁺ 401.0132; found 401.0136.

15-Bromo-12-hydroxy-12-methyl-17,19-dioxa-3,5,16-triazapentacyclo[11.6.0.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6(11),7,9,15-tetraene-2,4-dione (21): General procedure E was followed. From **10a** (0.15 g, 0.55 mmol, 1 equiv.), dibromoformaldoxime (0.66 g, 3.2 mmol, 6 equiv.), and KHCO₃ (0.66 g, 6.6 mmol, 12 equiv.), the title compound was obtained (0.14 g, 65%). ¹H NMR (500 MHz, DMSO): $\delta = 11.68$ (s, 1 H), 7.49 (m, 2 H), 7.38 (m, 2 H), 5.73 (s, 1 H), 5.71 (d, J = 6.0 Hz, 1 H), 4.02 (dd, J = 6.0, 4.2 Hz, 1 H), 3.20 (d, J = 4.2 Hz, 1 H), 1.77 (s, 3 H) ppm. ¹³C NMR (126 MHz, DMSO): $\delta = 170.5$, 154.7, 142.9, 135.0, 133.4, 129.0, 126.6, 126.0, 107.7, 93.9, 69.0, 59.6, 57.5, 30.6, 24.2 ppm. HRMS (ESI): calcd. for C₁₅H₁₂N₃LiO₅ [M + Li]⁺ 402.0102; found 402.0110.

Supporting Information (see footnote on the first page of this article): ¹H and ¹³C NMR spectra.

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