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

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Abstract

Intramolecular cycloadditions of photogenerated azaxylylenes provide access to unprecedented polyheterocyclic scaffolds, suitable for subsequent postphotochemical modifications to further grow molecular complexity. Here we explore approaches to rapid “assembly” of novel photoprecursors with nitrogen/oxygen-rich tethers capable of producing potential pharmacophores and also compatible with subsequent 1,3-dipolar cycloadditions to furnish pentacyclic heterocycles with new structural cores, minimal number of rotatable bonds, and a high content of sp^3 hybridized carbons. The modular “assembly” of the photoprecursors and potential variety of postphotochemical modifications of primary photoproducts provide framework for combinatorial implementation of this synthetic strategy.

Keywords

azaxylylene; photocycloaddition; 1,3-dipolar; nitrogen heterocycles

Introduction

To date, CAS registry contains more than 85 million substances¹. In 1965, little over 200K new substances were added to CAS. In stark contrast, 2007 saw this number exceed 4 million, of which over 3 million were small molecules². This awe-inspiring growth is in sharp contrast with the number of new molecular entities approved by FDA – a total of 1513 as of 2011³. In fact, the annual approval rate has not changed significantly with the explosive developments in organic synthesis, only fluctuating 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 the New Molecular Entities which actually get approved by the FDA worried many in the field. Some lamented that perhaps combinatorial chemists have been synthesizing mostly the *wrong stuff*: “this apparent lack of productivity [...] may in part reflect significant

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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, 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 about a half of the compounds in CAS registry⁵, while half of 836708 known frameworks are only present in one compound. The limited diversity is also reflected in the structure of drugs. Thus, the top 50 frameworks cover 48–52% of approved and experimental drugs^{6,7,8}.

There are additional problems associated with the structures generated by combinatorial synthesis⁴. First, according to several studies^{9, 10} the distribution of heteroatoms in drugs, natural products, and combinatorial libraries compounds differs significantly. On average, drugs and natural products have more oxygen atoms and fewer nitrogen atoms per molecule than combinatorial libraries compounds do. Second, the number of rotatable bonds in natural products and drugs is lower than in the combinatorial libraries. Conformationally constrained molecules are less vulnerable to entropic losses and often possess tighter K_D 's, compared with flexible ligands that can form similar arrays of hydrogen bonds and hydrophobic interactions with protein.

The extended 3D architecture of the molecules (as opposed to the “flat land” of polyaromatic beads) was also scrutinized in the context of drug design and discovery. Lovering and co-authors,¹¹ who proposed a simple saturation parameter, fsp^3 , demonstrated with convincing statistics that increasing the saturation improves clinical success of drug candidates. They point out: “Advances over the last 10–15 years in the coupling of sp^2 - sp^2 carbons, as well as other sp^2 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.”

How do we un-bias the effort at the bench without throwing the baby with the water? Our approach has been to employ modular “assembly” of photoprecursors from simple starting blocks via straightforward and high yielding coupling reactions, including the abovementioned efficient sp^2 - sp^2 carbon coupling reactions or other high yielding reactions such as amide bond formation etc. Subsequent irradiation then triggers intramolecular photocyclizations in these unsaturated photoprecursors. Typically, the photochemical step imparts a spectacular increase in molecular complexity, yielding new polyheterocyclic molecular architectures with extended three-dimensional topology, reduced number of rotatable bonds, and elevated saturation. As the selection rules for photoinduced cyclizations are very different from the ground state cycloadditions, one gains access to polycyclic cores not available via the conventional methodology. 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 even more powerful a 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 polyheterocycles, rich in heteroatoms, possessing a limited number of rotatable bonds, and relatively high in saturation, i.e. Lovering's fsp^3 parameter.

The main focus of the research efforts in our laboratory in recent years has been the utilization of azaxylylenes generated via excited state intramolecular proton transfer (ESIPT) in aromatic *o*-aminoketones in intramolecular [4+4] or [4+2] cycloaddition reactions to tethered unsaturated moieties – alkenes, furans, thiophenes, and pyrroles^{12, 13} – to yield novel N,O,S-polyheterocycles¹⁴, Scheme 1.

The essential aspect of this general methodology is the high availability of simple *linear* photoprecursors, which are “pre-assembled” via facile and high yielding chemical coupling reactions, generally compatible with robotic-assisted combinatorial chemistry methods, for example, amide bond formation. These photoprecursors then undergo efficient photoinduced intramolecular cycloadditions, with quantum yields of up to $\phi = 0.75$,¹⁵ providing access to novel molecular architectures. The primary photoproducts necessarily possess higher saturation and semi-rigid three-dimensional 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, in the case of pyrrole-tethered unsaturated pendants, the primary photoproduct possesses pyrroline, i.e. 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, further trapped with appropriate external or internal nucleophiles.¹³

While pyrrolines offered a ready postphotochemical modification opportunity due to high reactivity of the enamine moiety, another series of the primary photoproducts *based on the furan pendants* proved more difficult to modify. The [4+4] adducts, i.e. azacanes – containing an alkenyl moiety as a part of a oxabicyclo[4.2.1] core – proved unreactive under classical electrophilic addition reactions. The [4+2] primary photoproducts – containing a very reactive dihydrofuran moiety – proved extremely labile and did not survive even mildly acidic conditions. In this paper we engage the primary photoproducts in postphotochemical cycloaddition reactions with the goal of gaining access to novel polyheterocyclic molecular architectures, while assessing the applicability and appeal of these transformations in the context of photoassisted diversity-oriented synthesis¹⁷.

The other issue is the nature of the tether linking the photoactive aminoketone moiety with the unsaturated pendant. As the result of photoinduced intramolecular cyclization of photogenerated azaxylylene, a polyheterocyclic scaffold is generated, in which the tether forms additional ring(s) conceivably decorated with diverse functional groups or heterocyclic pendants. As we search for simple and efficient coupling reactions to assemble the photoprecursors, in this paper we explored reactions of *o*-ketoanilines with isocyanates, including acyl isocyanates, which result in 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 for further increase of complexity of the polyheterocyclic targets, enhancing the systematic exploration of 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 aminoketone core with the unsaturated furan-based pendant by introducing heteroatoms into it, and then to evaluate the scope of intramolecular [4+4] and [4+2] cycloaddition reactions of such photogenerated azaxylylenes. This, therefore, is set to introduce an additional heterocyclic ring in the photoproduct. We focused on reactive carbonyl derivatives such as isocyanates or chloroformates, capable of straightforward coupling with aromatic aminoketones, Scheme 2. The *o*-aminoketones **1a–c** were reacted with furfuryl isocyanate **2**, or with furoyl isocyanate **3'** (formed *in situ* from furoyl chloride¹⁸ **3**) or furfuryl chloroformate **4'** (formed *in situ* from furfuryl alcohol¹⁹ **4**).

The yields ranged from moderate to good. Benzaldehyde derivatives, such as **7d**, were obtained in two steps from aminoalcohol **1d** first coupled to the furanyl moiety and subsequently oxidized by PCC into photoactive *amidobenzaldehyde*. With the exception of this case, the photoprecursor synthesis proceeds in just one simple step from readily available starting materials, making this modular assembly of photoprecursors 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, hydantoin, and cyclic carbamates, Scheme 3 (isolated yields are shown). Solvent optimization gave methanol as 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 hydantoin and imidazolidinone cases it is the [4+4] product that is formed preferentially, whereas the [4+2] cycloaddition product is predominant in the case of oxazolidinone. This trend is the most pronounced for *tetralone*-based photoprecursors **5b** and **7b**: each of them upon irradiation gives only one product – the [4+4] cycloadduct in case of **5b**, or [4+2] for **7b**. It is of note that both [4+2] and [4+4] photoproducts are formed as single diastereomers: *syn*-[4+4] and *anti*-[4+2], where *syn*- and *anti*- refers to the respective arrangement of the benzylic hydroxy group in the quinolinol or benzoazacane ring, and furan's oxygen. The structure and stereochemistry of the products was determined by NMR and was consistent with our previous findings.¹² Additionally, for compounds **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. Indanone-based [4+2] photoproduct **8c** upon chromatographing is subjected to an eliminative opening of N,O- ketal affording product **8c'**, Scheme 4, and [4+4] adduct **9b** underwent the [4.2.1] → [3.3.1] rearrangement²⁰ of its 2,5-epoxyazacane core yielding the oxabicyclo[3.3.1]nonene scaffold.

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 dibromoformaldoxime²¹. This reaction was initially explored and optimized on model compounds **14** and **15**, synthesized according to the previously published procedures¹², Scheme 5. In both cases the 1,3-dipolar cycloaddition of bromonitrile oxide occurs from the *exo*-face. The [4+2] primary photoproduct reacted with bromonitrile oxide in a regiospecific fashion resulting in **16** (structure determined by X-ray crystallography) whereas the [4+4] photoproduct produced both regioisomers **17** and **18** in the 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 cycloaddition 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 NOE experiment. Proton H_a is characterized by a doublet at 4.71 ppm with ³J = 8.7 Hz, whereas the proton H_b is represented by a doublet of doublets at 3.75 with ³J = 8.7 Hz and ³J = 1.0 Hz, the second constant reflecting the interaction with H_c. Upon irradiation of the proton at 3.75 ppm a NOE of 4.6% is observed on the doublet of doublets at 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 due to the unfavorable steric interaction of Br with the methylene group in the dimethylene linker.

Scheme 5 also shows that when α,β-unsaturated ketone **19** – derived from the [4+4] photoproduct **15** via the [4.2.1] → [3.3.1] rearrangement and Swern oxidation – is used as a substrate in the postphotochemical 1,3-dipolar cycloaddition, we obtained dibromoisoxazoline **20'**. Clearly, the initially formed isoxazoline **20** underwent additional bromination under the reaction conditions. We hypothesize that the 1,3-dipole precursor, i.e. dibromoformaldoxime, taken in excess is capable of brominating the relatively stable conjugated enolate of **20**.

We then moved from the model compounds **14** and **15** to photoproducts **10a** and **11a** containing hydantoin moiety (i.e. derived from photoprecursor **6a**), Scheme 6. Similarly to the model system, we observed *exo*-stereochemistry of 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. However, their 5:1 ratio is now reversed, with **22** being the major product. Compound **22** is characterized by two doublets with the common spin-spin coupling constant of 8.8 Hz at 4.92 ppm and 3.85 ppm. It is assumed that the one with the greater chemical shift would belong to H_b, geminal to oxygen of the oxazoline ring. Upon irradiation of the methyl group, which is a singlet at 1.71 ppm, only the proton at 4.92 ppm is affected with NOE enhancement of 2.4%. Thus, in this case electrostatic effect of lone pair repulsion from carbonyl oxygen overrides the stereochemical preferences. The observed relative stability trend is again in keeping with our DFT calculations. According to B3LYP/6-31G(d), 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 developed a method for photochemically assisted assembly of fused hydantoins, imidazolines and oxazolidinones by means of diversifying the tether linking the photoactive aromatic aminoketone core with the unsaturated furan-based pendant. The primary photoproducts were found to be amenable to postphotochemical transformation yielding complex penta(hetero)cyclic molecular architectures characterized by minimal number of rotatable bonds, and a high content of sp^3 hybridized carbons ($f_{sp^3} \sim 0.4$). The resulting molecular polycyclic cores could be further decorated with functional groups or additional heterocyclic pendants, given that 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 THF, which was refluxed over and distilled from potassium benzophenone ketyl prior to use. Common reagents were purchased from Aldrich and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz in DMSO (unless noted otherwise). 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 on the *MDS SCIEX/Applied Biosystems API QSTARTM Pulsar i Hybrid LC/MS/MS System* mass spectrometer by Dr. Jeremy Balsbaugh from the University of Colorado at Boulder. Flash column chromatography was performed using Teledyne Ultra Pure Silica Gel (230 – 400 mesh) on a Teledyne Isco Combiflash R_f using Hexanes/EtOAc as an eluent.

Synthesis of photoprecursors

General procedure A for the synthesis of compounds 6¹⁸—1.3 eq. of sodium cyanate was suspended in 2 mL of 1,2-dichlorobenzene. Under a nitrogen atmosphere 1 eq. of 2-furoyl chloride and 0.05–0.15 eq of tin (IV) chloride were added. Upon complete addition the reaction mixture was refluxed for 3 hours, and then cooled to ambient temperature. 0.3–1.0 eq. of the corresponding amine was then added. The reaction mixture was allowed to stir overnight, then filtered through a pad of Celite®. 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 1.68 g of NaOCN (26.0 mmol, 1.3 eq) 2.0 mL of 2-furoyl chloride (20.0 mmol, 1 eq), 0.23 mL of SnCl₄ (2.0 mmol, 0.1 eq) and 2.0 mL of 2'-aminoacetophenone (16.5 mmol, 0.8 eq) 2.62 g (59%) of the title compound was obtained. ¹H NMR (500 MHz, DMSO) δ 12.35 (s, 1H), 10.86 (s, 1H), 8.40 (dd, J = 8.5, 1.2 Hz, 1H), 8.06 (dd, J = 1.8, 0.8 Hz, 1H), 8.03 (dd, J = 8.0, 1.6 Hz, 1H), 7.73 (dd, J = 3.6, 0.8 Hz, 1H), 7.62 (ddd, J = 8.5, 7.5, 1.6 Hz, 1H), 7.25 (ddd, J = 7.9, 7.5, 1.2 Hz, 1H), 6.75 (dd, J = 3.6, 1.7 Hz, 1H), 2.64 (s, 3H). 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. HRMS (ESI) calcd for C₁₄H₁₂N₂NaO₄⁺ (MNa⁺) 295.0695, found 295.0705

N-[(4-oxotetralin-5-yl)carbamoyl]furan-2-carboxamide (6b): General procedure **A** was followed. From 1.68 g of NaOCN (26.0 mmol, 1.3 eq), 2.0 mL of 2-furoyl chloride (20.0 mmol, 1 eq), 0.35 mL of SnCl₄ (3.0 mmol, 0.15 eq) and 0.60 g of 8-amino-tetralone (4.1 mmol, 0.3 eq) 0.98 g (88%) of the title compound was obtained. ¹H NMR (500 MHz, CDCl₃) δ 13.28 (s, 1H), 8.56 (d, *J*=8.4 Hz, 1H), 8.30 (s, 1H), 7.59 (dd, *J* = 1.8, 0.8 Hz, 1H), 7.49 (t, *J*=7.9 Hz, 1H), 7.46 (dd, *J* = 3.6, 0.8 Hz, 1H), 7.01 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.63 (dd, *J* = 3.6, 1.7 Hz, 1H), 3.02 (t, *J* = 6.1 Hz, 2H), 2.77 (m, 2H), 2.12 (m, 2H). 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 HRMS (ESI) calcd for C₁₆H₁₄N₂NaO₄⁺ (MNa⁺) 321.0851, found 321.0859

General procedure B for the synthesis of compounds 5—1 eq of corresponding amine was dissolved in 20 mL of anh. DCM. To this was added dropwise 1 eq of furfuryl isocyanate dissolved in 5 mL of anh. DCM. The mixture was allowed to stir at ambient temperature for 8 hrs. The resulting mixture was diluted with DCM, washed with water, and then brine. The organic layer was dried over Na₂SO₄ before concentrating *in vacuo* to yield the product which was used in the next step without further purification.

1-(2-furylmethyl)-3-(4-oxotetralin-5-yl)urea (5b): General procedure **B** was followed. From 0.65 g of 8-amino-tetralone (4.1 mmol, 1 eq) and 0.5g of furfuryl isocyanate (4.1 mmol, 1 eq), 0.79 g (68%) of the title compound was obtained. ¹H NMR (500 MHz, CDCl₃) δ 11.68 (s, 1H), 8.46 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.41 (dd, *J* = 8.6, 7.5 Hz, 1H), 7.37 (dd, *J* = 1.9, 0.8 Hz, 1H), 6.82 (dd, *J* = 7.5, 1.1 Hz, 1H), 6.33 (dd, *J* = 3.3, 1.9 Hz, 1H), 6.29 (m, 1H), 5.30 (t, *J* = 5.8 Hz, 1H), 4.49 (d, *J* = 5.7 Hz, 2H), 2.95 (t, *J* = 6.1 Hz, 2H), 2.66 (m, 2H), 2.07 (m, 2H). 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 HRMS (ESI) calcd for C₁₆H₁₆N₂O₃⁺ (MH⁺) 285.1239, found 285.1248

1-(2-furylmethyl)-3-(3-oxoindan-4-yl)urea (5c): General procedure **B** was followed. From 0.50 g of 7-amino-2,3-dihydro-1H-inden-1-one (3.4 mmol, 1 eq) and 0.42 g of furfuryl isocyanate (3.4 mmol, 1 eq), 0.71 g (77%) of the title compound was obtained. ¹H NMR (500 MHz, DMSO) δ 9.51 (s, 1H), 8.19 (t, 1H), 8.16 (d, *J*=8.3 Hz, 1H), 7.60 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.52 (t, *J*=7.8 Hz, 1H), 7.04 (dd, *J* = 7.5, 0.9 Hz, 1H), 6.41 (dd, *J* = 3.2, 1.8 Hz, 1H), 6.28 (dd, *J* = 3.2, 0.9 Hz, 1H), 4.28 (d, *J* = 5.5 Hz, 2H), 3.04 (m, 2H), 2.66 (m, 2H). ¹³C NMR (126 MHz, DMSO) δ 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 HRMS (ESI) calcd for C₁₅H₁₄N₂NaO₃⁺ (MNa⁺) 293.0902, found 293.0909

General procedure C for the synthesis of compounds 7¹⁹—2 eq. of a 15% wt phosgene solution in toluene was cooled to -78°C under a N₂ atmosphere. To this was added dropwise 1 eq. of furfuryl alcohol dissolved in 3 mL of anh. diethyl ether. Upon complete addition, the mixture was warmed to -15°C and stirred for 3 hrs, followed by an additional 30 mins at 0°C. The chlorocarbamate solution was added to a stirring solution of 0.5–1.0 eq. of corresponding amine and 1.1–2.0 eq. of dry pyridine, dissolved in 10 mL of anh. DCM. The mixture was allowed to stir at ambient temperature overnight. The mixture

was quenched with water and extracted with DCM. The organic layer was washed with brine and dried over Na₂SO₄ before concentrating *in vacuo*. The crude product was further purified by flash chromatography.

2-furymethyl N-(2-formylphenyl)carbamate (7d): General procedure C was followed. From 6.42 mL of 15% wt phosgene solution in toluene (9.0 mmol, 2 eq), 0.44 g of furfuryl alcohol (4.5 mmol, 1 eq), 0.55 g of 2-aminobenzyl alcohol (4.5 mmol, 1 eq), and 0.41 mL of dry pyridine (5.1 mmol, 1.1 eq), 0.33 g (29%) of **2-furymethyl N-(2-(hydroxymethyl)phenyl)carbamate (7d')** was obtained. ¹H NMR (500 MHz, CDCl₃) δ 7.96 (s, 2H), 7.47 (dd, *J* = 1.9, 0.9 Hz, 1H), 7.35 (td, *J* = 7.8, 1.6 Hz, 1H), 7.18 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.06 (td, *J* = 7.5, 1.2 Hz, 1H), 6.49 (dd, *J* = 3.2, 0.8 Hz, 1H), 6.41 (dd, *J* = 3.3, 1.8 Hz, 1H), 5.18 (s, 2H), 4.70 (s, 2H), 2.14 (s, 1H). 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. To 0.33 g of **7d'** (1.3 mmol, 1 eq) dissolved in 20 mL of anhydrous DCM was added 0.43 g of PCC (2.0 mmol, 1.5 eq). 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 0.27 g (83%) of pale yellow solid **7d**. ¹H NMR (500 MHz, CDCl₃) δ 10.66 (s, 1H), 9.92 (d, *J* = 0.7 Hz, 1H), 8.50 (d, *J* = 8.5 Hz, 1H), 7.67 (dd, *J* = 7.7, 1.7 Hz, 1H), 7.63 (ddd, *J* = 8.8, 7.3, 1.7 Hz, 1H), 7.48 (dd, *J* = 1.9, 0.8 Hz, 1H), 7.21 (td, *J* = 7.5, 1.0 Hz, 1H), 6.50 (dd, *J* = 3.3, 0.7 Hz, 1H), 6.41 (dd, *J* = 3.3, 1.9 Hz, 1H), 5.21 (s, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 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 HRMS (ESI) calcd for C₁₃H₁₁NNaO₄⁺ (MNa⁺) 268.0586, found 268.0594

2-furymethyl N-(4-oxotetralin-5-yl)carbamate (7b): General procedure C was followed. From 6.42 mL of 15% wt phosgene solution in toluene (9.0 mmol, 2 eq), 0.44 g of furfuryl alcohol (4.5 mmol, 1 eq), .38 g of tetralone (4.5 mmol, 0.5 eq), and 0.9 mL of dry pyridine (5.1 mmol, 2.0 eq), 0.35 g (30%) of the title compound was obtained. ¹H NMR (500 MHz, CDCl₃) δ 11.70 (s, 1H), 8.34 (dd, *J* = 8.6, 1.1 Hz, 1H), 7.45 (m, 1H), 7.43 (d, *J* = 8.0 Hz, 1H), 6.89 (dt, *J* = 7.4, 1.0 Hz, 1H), 6.48 (dd, *J* = 3.3, 0.8 Hz, 1H), 6.39 (dd, *J* = 3.2, 1.9 Hz, 1H), 5.17 (s, 2H), 2.96 (t, *J* = 6.1 Hz, 2H), 2.68 (dd, *J* = 7.3, 5.8 Hz, 2H), 2.07 (p, *J* = 6.4 Hz, 2H). 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. HRMS (ESI) calcd for C₁₆H₁₅NO₄⁺ (MH⁺) 286.1074, found 286.1079

Photochemical cycloadditions

General procedure D for irradiation—Solutions with ca. 3.0 mM of the photo-precursors 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. The solution was concentrated and the mixture was purified by flash chromatography.

6a (0.20 g, 0.74 mmol) was irradiated following general procedure D with acetonitrile as a solvent. Flash chromatography yielded 0.13 g (63%) of **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) and 0.039 g (19%) of **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)**.

11a: ¹H NMR (500 MHz, DMSO) δ 11.58 (s, 1H), 7.58 (dd, *J* = 8.2, 1.5 Hz, 1H), 7.57 (dd, *J* = 8.1, 1.6 Hz, 1H), 7.28 (ddd, *J* = 8.3, 7.1, 1.5 Hz, 1H), 7.17 (ddd, *J* = 8.4, 7.2, 1.5 Hz, 1H), 6.65 (dd, *J* = 5.9, 1.7 Hz, 1H), 5.93 (dd, *J* = 5.9, 1.3 Hz, 1H), 5.53 (s, 1H), 4.78 (t, *J* = 1.5 Hz, 1H), 1.59 (s, 3H). 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. HRMS (ESI) calcd for C₁₄H₁₂N₂NaO₄⁺ (MNa⁺) 295.0695, found 295.0709

10a: ¹H NMR (500 MHz, DMSO) δ 11.59 (s, 1H), 7.37 (m, 3H), 7.28 (td, *J* = 7.2, 2.0 Hz, 1H), 6.52 (t, *J* = 2.8 Hz, 1H), 5.47 (s, 1H), 4.87 (dd, *J* = 2.9, 2.2 Hz, 1H), 3.88 (t, *J* = 2.5 Hz, 1H), 1.66 (s, 3H). 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. HRMS (ESI) calcd for C₁₄H₁₂N₂NaO₄⁺ (MNa⁺) 295.0695, found 295.0703

6b (0.36 g, 1.2 mmol) was irradiated following general procedure **D**. Flash chromatography yielded 0.150 g (43%) **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)** and 0.072 g (19%) of **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)**

11b: ¹H NMR (500 MHz, DMSO) δ 11.52 (s, 1H), 7.33 (dd, *J* = 7.9, 1.2 Hz, 1H), 7.14 (t, *J* = 7.8 Hz, 1H), 6.95 (dd, *J* = 7.5, 1.4 Hz, 1H), 6.68 (dd, *J* = 5.9, 1.7 Hz, 1H), 5.90 (dd, *J* = 5.9, 1.2 Hz, 1H), 5.39 (d, *J* = 1.3 Hz, 1H), 4.62 (t, *J* = 1.5 Hz, 1H), 2.81 (m, 1H), 2.70 (ddd, *J* = 17.2, 12.9, 5.6 Hz, 1H), 2.01 (m, 1H), 1.87 (m, 1H), 1.69 (m, 2H). 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. HRMS (ESI) calcd for C₁₆H₁₄N₂NaO₄⁺ (MNa⁺) 321.0851, found 321.0856

10b: ¹H NMR (500 MHz, DMSO) δ 11.59 (s, 1H), 7.25 (t, *J* = 7.7 Hz, 1H), 7.17 (dd, *J* = 7.6, 1.1 Hz, 1H), 7.05 (d, *J* = 8.0 Hz, 1H), 6.54 (t, *J* = 2.8 Hz, 1H), 5.45 (s, 1H), 4.95 (dd, *J* = 3.0, 2.2 Hz, 1H), 3.90 (t, *J* = 2.4 Hz, 1H), 2.72 (m, 1H), 2.60 (m, 1H), 1.90 (m, 3H), 1.72 (m, 1H). 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. HRMS (ESI) calcd for C₁₆H₁₄N₂O₄⁻ (MH⁻) 297.0875, found 297.0886

5b (0.50 g, 1.8 mmol) was irradiated following general procedure **D**. Flash chromatography yielded 0.270 g (54%) of **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)** and 0.077 g (15%) of **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')**.

9b: ¹H NMR (500 MHz, DMSO) δ 7.21 (s, 1H), 7.09 (m, 2H), 6.87 (m, 1H), 6.53 (dd, *J* = 5.7, 1.8 Hz, 1H), 5.77 (dd, *J* = 5.7, 1.1 Hz, 1H), 4.46 (m, 1H), 3.80 (dd, *J* = 10.8, 1.1 Hz, 1H), 3.48 (dd, *J* = 10.7, 1.4 Hz, 1H), 2.79 (m, 1H), 2.68 (ddd, *J* = 17.4, 12.9, 5.5 Hz, 1H), 2.00

(m, 1H), 1.84 (m, 1H), 1.68 (m, 3H). ^{13}C 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 HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{O}_3^-$ (M-H^-) 283.1083, found 283.1087

9b': ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 8.1$ Hz, 1H), 7.25 (t, $J = 7.8$ Hz, 1H), 6.92 (d, $J = 7.6$ Hz, 1H), 6.22 (dd, $J = 9.7, 5.4$ Hz, 1H), 5.93 (d, $J = 9.7$ Hz, 1H), 5.69 (s, 1H), 3.84 (d, $J = 5.4$ Hz, 1H), 3.68 (d, $J = 1.1$ Hz, 2H), 2.93 (ddd, $J = 17.5, 10.0, 5.5$ Hz, 1H), 2.87 (ddd, $J = 17.5, 9.6, 5.8$ Hz, 1H), 2.49 (ddd, $J = 12.2, 6.8, 2.4$ Hz, 1H), 2.11 (m, 2H), 1.96 (m, 1H), 1.56 (td, $J = 12.3, 7.7$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) 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. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{16}\text{N}_2\text{LiO}_3^+$ (MLi^+) 291.1321, found 291.1328

5c (0.30 g, 1.1 mmol) was irradiated following general procedure **D**. Flash chromatography yielded 0.15 g (52%) **1-hydroxyl-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)** and 0.077 g (26%) **2-(8-hydroxy-3-oxo-2,4-diazatertacyclo[6.6.1.0^{2,6}.0^{11,15}]pentadeca-1(14), 5,11(15),12-tetraen-7-yl)acetaldehyde (8c')**.

9c: ^1H NMR (500 MHz, DMSO) δ 7.33 (d, $J = 8.1$ Hz, 1H), 7.23 (s, 1H), 7.15 (dd, $J = 8.1, 7.3$ Hz, 1H), 6.96 (d, $J = 7.3$ Hz, 1H), 6.53 (dd, $J = 5.8, 1.9$ Hz, 1H), 5.80 (dd, $J = 5.8, 1.2$ Hz, 1H), 5.09 (s, 1H), 4.77 (t, $J = 1.5$ Hz, 1H), 3.80 (d, $J = 10.6$ Hz, 1H), 3.48 (dd, $J = 10.7, 1.4$ Hz, 1H), 3.11 (m, 1H), 2.75 (m, 1H), 1.93 (m, 2H). ^{13}C 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. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3^+$ (MH^+) 271.1083, found 271.1091

8'c: ^1H NMR (500 MHz, DMSO) δ 10.03 (d, $J = 2.4$ Hz, 1H), 9.56 (d, $J = 2.7$ Hz, 1H), 7.90 (d, $J = 8.0$ Hz, 1H), 7.30 (t, $J = 7.8$ Hz, 1H), 7.03 (d, $J = 7.5$ Hz, 1H), 6.36 (d, $J = 2.3$ Hz, 1H), 5.24 (s, 1H), 3.67 (dd, $J = 8.9, 5.7$ Hz, 1H), 3.19 (m, 1H), 2.82 (dd, $J = 15.8, 8.4$ Hz, 1H), 2.59 (dd, $J = 16.8, 5.7$ Hz, 1H), 2.11 (m, 1H), 1.97 (m, 2H). ^{13}C 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 HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{14}\text{N}_2\text{O}_3^-$ (M-H^-) 269.0926, found 269.0928

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

13d: ^1H NMR (500 MHz, DMSO) δ 7.71 (dt, $J = 8.0, 1.4$ Hz, 1H), 7.34 (m, 1H), 7.30 (tdd, $J = 7.8, 1.8, 0.7$ Hz, 1H), 7.25 (td, $J = 7.5, 1.7$ Hz, 1H), 6.55 (dd, $J = 5.8, 1.8$ Hz, 1H), 6.18 (d, $J = 6.4$ Hz, 1H), 5.95 (dd, $J = 5.8, 1.0$ Hz, 1H), 4.91 (dd, $J = 6.4, 3.3$ Hz, 1H), 4.85 (ddd, $J = 3.2, 1.8, 1.0$ Hz, 1H), 4.75 (d, $J = 10.2$ Hz, 1H), 4.49 (d, $J = 10.2$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) 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 HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{NNaO}_4^+$ (MNa^+) 268.0586, found 268.0596

12d: ^1H NMR (500 MHz, DMSO) δ 7.50 (dd, $J = 7.8, 1.3$ Hz, 1H), 7.44 (dt, $J = 7.4, 1.4$ Hz, 1H), 7.31 (tdd, $J = 7.7, 1.7, 0.9$ Hz, 1H), 7.25 (td, $J = 7.5, 1.3$ Hz, 1H), 6.43 (t, $J = 2.7$ Hz,

1H), 5.97 (d, $J = 5.5$ Hz, 1H), 4.95 (t, $J = 5.9$ Hz, 1H), 4.84 (dd, $J = 3.1, 2.2$ Hz, 1H), 4.76 (d, $J = 10.1$ Hz, 1H), 4.62 (d, $J = 10.1$ Hz, 1H), 3.96 (dt, $J = 6.2, 2.3$ Hz, 1H). ^{13}C 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 HRMS (ESI) calcd for $\text{C}_{13}\text{H}_{11}\text{NNaO}_4^+$ (MNa^+) 268.0586, found 268.0594

7b (0.10 g, 0.35 mmol) was irradiated following general procedure **D**. Flash chromatography yielded 0.063 g (63%) **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)**.

12b: ^1H NMR (500 MHz, CDCl_3) δ 7.56 (dt, $J = 7.9, 1.1$ Hz, 1H), 7.31 (t, $J = 7.8$ Hz, 1H), 7.02 (dq, $J = 7.7, 1.0$ Hz, 1H), 6.31 (t, $J = 2.9$ Hz, 1H), 4.73 (dd, $J = 3.2, 2.3$ Hz, 1H), 4.71 (d, $J = 9.4$ Hz, 1H), 4.60 (d, $J = 9.5$ Hz, 1H), 3.75 (t, $J = 2.4$ Hz, 1H), 2.82 (m, 1H), 2.72 (m, 1H), 2.07 (m, 1H), 1.92 (m, 3H). ^{13}C NMR (126 MHz, CDCl_3) 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. HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{15}\text{NLiO}_4^+$ (MLi^+) 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 previously described.¹²

16-oxa-5-azatetracyclo[10.3.1.0^{1,5}.0^{6,11}]hexadeca-6(11),7,9,14-tetraen-4,13-dione (19):

To 0.40 g of **15** (1.6 mmol, 1 eq) was added 40 mL of CHCl_3 . To this was added 5 mL of TFA. The mixture stirred at room temperature overnight. The reaction was quenched with sat. NaHCO_3 solution, followed by washing of the organic layer with brine, drying over Na_2SO_4 , and concentration *in vacuo*. The resulting residue was purified by flash chromatography to yield 0.30 g of **13-hydroxy-16-oxa-5-azatetracyclo[10.3.1.0^{1,5}.0^{6,11}]hexadeca-6(11),7,9,14-tetraen-4-one (78%)**. ^1H NMR (500 MHz, CDCl_3) δ 8.38 (dd, $J = 8.3, 1.2$ Hz, 1H), 7.41 (dddd, $J = 8.1, 7.4, 1.7, 0.5$ Hz, 1H), 7.30 (m, 2H), 7.22 (td, $J = 7.5, 1.2$ Hz, 1H), 6.13 (d, $J = 9.9$ Hz, 1H), 6.07 (ddd, $J = 9.8, 5.0, 1.2$ Hz, 1H), 5.31 (s, 1H), 5.17 (dd, $J = 5.0, 1.2$ Hz, 1H), 2.77 (m, 2H), 2.45 (m, 2H). ^{13}C NMR (126 MHz, CDCl_3) 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. 0.07 mL of oxalyl chloride (0.84 mmol, 1.1 eq) was dissolved in 0.9 mL of anhydrous DCM and cooled to -78°C before 0.12 mL of dry DMSO (1.7 mmol, 2.2 eq) was slowly added. Upon complete addition, the mixture stirred for 2 mins while the evolution of gas stopped. Then, 0.19 g of the alcohol (0.77 mmol, 1 eq) dissolved in 1.5 mL of anhydrous DCM was added dropwise. Upon complete addition. After stirring for 15 mins, 0.54 mL of NEt_3 (3.9 mmol, 5 eq) was slowly added. Upon complete addition, the mixture was slowly warmed to RT at which it was stirred overnight. The reaction mixture was quenched with water, and extracted with DCM. The resulting organic layer was washed with brine, dried over Na_2SO_4 , and concentrated *in vacuo* to yield 0.11 g of **19** (60%). The resulting solid was used in the next step without further purification. ^1H NMR (500 MHz, CDCl_3) δ 8.46 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.41 (ddd, $J = 8.6, 7.3, 1.6$ Hz, 1H), 7.27 (dd, $J = 7.8, 1.7$ Hz, 1H), 7.19 (td, $J = 7.5, 1.2$ Hz, 1H), 6.79 (d, $J = 10.0$ Hz, 1H), 6.19 (dd, $J = 10.1,$

0.7 Hz, 1H), 5.22 (s, 1H), 2.79 (m, 2H), 2.55 (ddd, $J = 13.5, 7.1, 4.5$ Hz, 1H), 2.41 (dt, $J = 13.5, 10.4$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) 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. HRMS (ESI) calcd for $\text{C}_{14}\text{H}_{11}\text{NO}_3^+$ (MH) $^+$ 242.0812 found 242.0816

Synthesis of dibromoformaldoxime²¹: To a solution of 20.3 g of glyoxylic acid monohydrate (0.22 mol, 1 eq.) in 160 mL of water (1.4M) was added 19.4 g of hydroxylamine hydrochloride (0.28 mol, 1.3 eq.). The mixture was stirred at ambient temperature for 24 hrs. 47.7 g of NaHCO_3 (0.57 mol, 2.58 eq.) was slowly added, followed by 70 mL of DCM. Upon cooling the resulting mixture in the ice bath, 19.5 mL of Br_2 (0.38 mol, 1.7 eq.) in 100 mL of DCM was slowly added maintaining the temperature at or below 10°C. Upon complete addition, the mixture was stirred at room temperature for 3 hrs. The resulting mixture was diluted with 100 mL of water, extracted with 3×30 mL of DCM, dried over Na_2SO_4 , and concentrated *in vacuo*. The resulting solid was recrystallized from hexanes to yield 12.5 g (28%) of a white crystalline solid. mp 65–66°C (lit. 65–66°C)

General procedure E for nitrile oxide addition²¹—1 eq. of photoproduct was dissolved in EtOAc or EtOAc/DCM mixture. To this was added 3 eq. of dibromoformaldoxime and 6 eq of KHCO_3 . An additional 3 eq. of dibromoformaldoxime and 6 eq. of KHCO_3 were usually added after stirring for 12 hrs. The reaction was monitored by NMR until the starting materials were consumed. The resulting mixture was diluted with water, extracted with 3×20 mL of EtOAc or DCM, washed with brine, dried over Na_2SO_4 , 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 using EtOAc. From 0.19 g of **15** (0.76 mmol, 1 eq), 0.46 g of dibromoformaldoxime (2.3 mmol, 3 eq), and 0.46 g of KHCO_3 (4.6 mmol, 6 eq), 0.17 g (63%) of formation of 4:1 mixture of two regioisomers of the title compound was observed. Upon purification 0.17 g (63%) of the title compound (major isomer) was isolated. ^1H NMR (500 MHz, DMSO) δ 7.39 (m, 3H), 7.27 (m, 1H), 5.53 (d, $J = 5.8$ Hz, 1H), 4.71 (d, $J = 8.6$ Hz, 1H), 4.64 (dd, $J = 5.8, 4.3$ Hz, 1H), 4.53 (d, $J = 4.2$ Hz, 1H), 3.75 (dd, $J = 8.6, 1.1$ Hz, 1H), 2.68 (ddd, $J = 16.1, 9.9, 8.8$ Hz, 1H), 2.55 (m, 1H), 2.46 (m, 1H), 2.07 (m, 1H). ^{13}C 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. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{LiO}_4\text{Br}^+$ (MLi) $^+$ 371.0219, found 371.0219

15-bromo-12-hydroxyl-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 0.20 g of **14** (0.82 mmol, 1 eq), 1.0 g of dibromoformaldoxime (4.9 mmol, 6 eq), and 1.0 g of KHCO_3 (9.8 mmol, 12 eq), 0.19 g (65%) of the title compound was obtained. ^1H NMR (500 MHz, CDCl_3) δ 7.92 (d, $J = 7.9$ Hz, 1H), 7.49 (td, $J = 7.8, 1.5$ Hz, 1H), 7.37 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.25 (td, $J = 7.5, 1.2$ Hz, 1H), 5.65 (d, $J = 6.0$ Hz, 1H), 4.79 (t, $J = 2.9$ Hz, 1H), 3.51 (s, 1H), 3.45 (dd, $J = 6.0, 3.6$ Hz, 1H), 3.37 (dd, $J = 3.5, 2.9$ Hz, 1H), 2.85 (ddd, $J = 16.6, 9.9, 8.7$ Hz, 1H), 2.48 (m,

3H). ^{13}C NMR (126 MHz, CDCl_3) 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. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{13}\text{N}_2\text{O}_4\text{Br}^+$ (MH^+) 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 using EtOAc/DCM mixture. From 0.11 g of **19**, 0.13 g of the title compound was obtained after flash chromatography (62%). ^1H NMR (500 MHz, CD_2Cl_2) δ 8.44 (m, 1H), 7.49 (ddd, $J = 8.4$, 7.4, 1.8 Hz, 1H), 7.28 (m, 2H), 5.41 (s, 1H), 5.15 (s, 1H), 3.04 (ddd, $J = 13.8$, 8.1, 3.7 Hz, 1H), 2.74 (m, 2H), 2.30 (dt, $J = 13.8$, 10.1 Hz, 1H). ^{13}C NMR (126 MHz, CD_2Cl_2) 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. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{10}\text{Br}_2\text{N}_2\text{O}_4\text{Li}^+$ (MLi^+) 448.9148, found 449.1726

17-bromo-12-hydroxy-12-methyl-15,19-dioxa-3,5,16-triazapentacyclo[11.5.1.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6(11),7,9,16-tetraene-2,4-dione (22): General procedure E was followed. From 0.16 g of **11a** (0.58 mmol, 1 eq), 0.70 g of dibromoformaloxime (3.4 mmol, 6 eq), and 0.70 g of KHCO_3 (12.0 mmol, 12 eq), formation of 5:1 mixture of two regioisomers was observed. After purification, 0.12 g (53%) of the major isomer was isolated. ^1H NMR (500 MHz, DMSO) δ 11.89 (s, 1H), 7.66 (dd, $J = 8.1$, 1.4 Hz, 1H), 7.54 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.37 (m, 1H), 7.25 (ddd, $J = 8.7$, 7.3, 1.4 Hz, 1H), 5.44 (s, 1H), 4.92 (d, $J = 8.7$ Hz, 1H), 4.54 (d, $J = 0.7$ Hz, 1H), 3.85 (dd, $J = 8.7$, 0.7 Hz, 1H), 1.71 (s, 3H). ^{13}C 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. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{12}\text{BrN}_3\text{LiO}_5^+$ (MLi^+) 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 0.15 g of **10a** (0.55 mmol, 1 eq), 0.66 g of dibromoformaloxime (3.2 mmol, 6 eq), and 0.66 g of KHCO_3 (6.6 mmol, 12 eq), 0.14 g (65%) of the title compound was obtained. ^1H NMR (500 MHz, DMSO) δ 11.68 (s, 1H), 7.49 (m, 2H), 7.38 (m, 2H), 5.73 (s, 1H), 5.71 (d, $J = 6.0$ Hz, 1H), 4.02 (dd, $J = 6.0$, 4.2 Hz, 1H), 3.20 (d, $J = 4.2$ Hz, 1H), 1.77 (s, 3H). ^{13}C NMR (126 MHz, DMSO) δ 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. HRMS (ESI) calcd for $\text{C}_{15}\text{H}_{12}\text{N}_3\text{LiO}_5^+$ (MLi^+) 402.0102, found 402.0110

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Scheme 1.
Intramolecular Cycloadditions of Photogenerated Azaxylylenes.

Scheme 2.

Modular Assembly of Photoprecursors Containing Urea, Acylurea, and Urethane Linkers.

Scheme 3.
 Products of Photoinduced Cycloadditions.

Scheme 4.
Silica Gel-induced Transformations in Photoproducts **8c** and **9b**.

Scheme 5.

Postphotochemical 1,3-Dipolar Cycloadditions to the Primary Photoproducts.

^aMinor regioisomer **17** was observed by NMR.

Scheme 6.
1,3-Dipolar Cycloadditions to Hydantoins **10a** and **11a**