Photogenerated o-Azaxylylenes: Mechanistic Studies and Synthetic Applications

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Photogenerated $\sigma$-Azaxylylenes:
Mechanistic Studies and Synthetic Applications

A Dissertation
Presented to
the Faculty of Natural Sciences and Mathematics
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by
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Abstract

This research sets out to build upon excited state o-azaxylylene cycloaddition. The mechanism behind the excitation and cycloaddition process of photogenerated o-azaxylylenes was determined experimentally. Time-correlated single-photon counting, steady-state spectroscopy, triplet quenching experiments, and quantum yield studies provided evidence suggesting that excited state intramolecular proton transfer is followed by intersystem crossing and stepwise addition to the tethered unsaturated pendant.

In keeping with the principles of diversity oriented synthesis, a modular approach was taken to gain access to a diverse array of N,O,S-Polyheterocycles which were modified postphotochemically via Suzuki coupling to yield fused biaryls. Cycloaddition products, outfitted with halogens in the aromatic ring of the o-azaxylylene, proved to be reactive with a variety of boronic acids resulting in a rapid growth in structural complexity.

A novel procedure was developed that utilized multiple o-azaxylylene cores in a photochemical cascade transformation yielding complex scaffolds of unprecedented topology. The photoprecursors were produced in a one-pot two-step sequence from commercially available starting materials, and upon irradiation yield structures containing up to five fused heterocyclic rings, and showed complete diastereoselectivity.
Acknowledgements

There are many who deserve more than what I have given, and some who I will never be able to repay for what they have given me throughout my life. I will forever be in debt to those who have remained loyal, never gave up, and always believed in me; this is what love should be. Thank you Barb, Bonnie, and Luella, you were always consistent and thanks to you I always had a home, a warm meal, and felt loved.

I am truly blessed, as so many have fought for and supported me throughout my lifetime. The formatting stipulations of this dissertation only allow me one leading page to acknowledge those who have carried me, and I have been so fortunate that this is simply not enough. Please take the time to read Appendix A, which contains the remaining acknowledgements, as those mentioned in this section are the reason I am still breathing and are far more important to me than anything else in this life.
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Chapter One: Introduction

In 2014 $373.9 billion was spent on prescription drugs in the U.S. alone, an increase of 13.1% ($43.4 billion) from the previous year.\(^1\) Per capita spending in 2014 almost tripled since 1995, an increase from $339 to $995 when adjusted to 2005 dollars, and record spending on new brands was observed, totaling $20.2 billion, tripling that in 2013.\(^1\) This recent upward trend in pharmaceutical spending has been driven by an increased emphasis on healthcare in the United States. In 2014 15.7 million people gained health insurance coverage as a result of the Affordable Care Act, and patients filled prescriptions 25.4% more often in states with expanded Medicaid eligibility.\(^1\) Given the growing demand for healthcare, there is a substantial amount of funding that goes into the research and development for the industry. Approximately $30.3 billion in funding is supplied by the National Institute of Health annually to medical research,\(^2\) and R&D spending by the pharmaceutical industry totaled $51.1 billion in 2013.\(^3\) Given the large investment into the pharmaceutical industry, as well as the amount of time and effort spent producing new drugs, it’s staggering to see just how few new active substances are introduced on an annual basis.

At the time this document was written, the CAS registry just reached a 100 million compounds,\(^4\) the majority being small molecules,\(^5\) and annually over 4 million new compounds are submitted; however, only 42 New Active Substances were
introduced in 2014, the most since 2001.¹ The stark contrast between the number of compounds submitted to the CAS registry and the number of new active substances is striking. One possible explanation is the obvious discrepancy between the structure of new active substances and those synthesized in the laboratory. Szychowski et al. emphasize that “despite the prevalence of combinatorially derived libraries in the pharmaceutical industry,” from January 1981 to December 2010, over half of new active drugs were either natural products (NP) or derivatives,⁶ and when compared to compounds prepared by combinatorial approaches, NPs tend to (a) have more stereogenic centers, (b) have a larger fraction of sp³ carbons, (c) be less hydrophobic, (d) have more oxygen atoms, (e) have fewer nitrogens, sulfurs, and halogens, (f) have fewer rotatable bonds, (g) have more fused, bridge, and spiro rings, and (h) have more solvated hydrogen bond donors and acceptors.⁶

Combinatorial chemistry further compounds the problem, as this methodology yields structurally similar products by design, ignoring a vast and unexplored region of chemical space. Half of the compounds submitted to the CAS registry contain one of 143 basic frameworks,⁷ and this lack of structural diversity can partially be attributed to the synthetic cost of developing new molecular architecture,⁷ as modifications to the core framework pose a greater synthetic challenge than modifying the perimeter of an established scaffold.

Given the amount of time and money, as well as the importance of healthcare, it is disturbing to see a trend where many compounds synthesized by combinational methodology lack structural diversity and do not conform to the trends put forth by the body of data which support biological activity. To address this issue, new approaches and a greater amount of structural diversity must be incorporated into scientific
methodology in the future. The research within this dissertation focuses on the photochemical transformations of o-azaxylylenes which yield complex structures of unprecedented topology containing multiple fused rings, chiral centers, a high degree of saturation, and few rotatable bonds, all of which are characteristic of natural products. Below (Scheme 1.1) is a representative example, from the research presented in this dissertation, of the spectacular growth of complexity which can be generated in three steps, from affordable starting materials, and obtained in high purity without column chromatography. This methodology is based on diversity oriented synthesis, an approach that probes a greater region of chemical space when compared to conventional combinatorial methods.

**Scheme 1.1**

**Synthetic Methodology**

Chemical space is an abstract idea that places all possible molecules in a multidimensional coordinate system according to their structure and physical properties. Reymond et al. explains chemical space as a “geographical map to illustrate the
distribution of molecules and their properties,” notes that there are thousands of different descriptors, and as a result many dimensions from which this map can be derived, “including atom and bond types, polar groups, and topological features.” It is the unexplored region of chemical space where new drug discovery takes place, and there are three general approaches to small molecule synthesis, all of which sample a different region of this chemical space: target oriented synthesis (TOS), combinatorial chemistry, and diversity oriented synthesis (DOS). TOS is a process that aims to synthesize a specific compound, usually a natural product, which is known to have a desired biological activity. This approach is (i) based on a retrosynthetic methodology, (ii) only aims to synthesize one specific compound, and as a result (iii) only probes one coordinate of chemical space. Combinatorial chemistry differs from TOS in that it aims to decorate a known biologically active core scaffold with various functional groups leading to a library of new compounds. This methodology probes a greater region of chemical space than TOS, but is somewhat restricted in the region of chemical space that it explores given the conservation of the core scaffold. DOS is a forward-thinking methodology that aims to probe the largest region of chemical space possible, in that multiple modifications are performed throughout the synthesis, including that of the core scaffold, producing a large number of significantly diverse compounds.

A famous example of target oriented synthesis is Taxol® (Figure 1.1), an anticancer drug that was initially isolated as a natural product from the Pacific yew tree (Taxus brevifolia). Harvesting the drug from natural sources was impractical, as 38,000
Taxus *brevifolia* trees would be needed to yield just 25 kg of Taxol®, and three trees would be needed to treat one person.

![Chemical structure of Taxol](image.png)

**Figure 1.1**

It took around two decades for a total synthesis to be accomplished given the complexity of the molecule, as it contains a complex 6:8:6 fused ring system, 11 chiral centers, and is densely populated with various functional groups. One of the first total synthetic pathways, developed by Nicolaou et al., was accomplished in 51 steps with an overall yield of 0.4%. Total synthesis is important, as the process often advances synthetic methodology, and there may be no other way to access these valuable scaffolds. However, when searching for new biologically active drugs, it’s vital to probe the greatest region of chemical space possible. Both combinatorial chemistry and diversity oriented synthesis are valuable tools, as they are capable of producing large libraries of compounds efficiently. A forward thinking DOS philosophy should be implemented in conjunction with combinatorial chemistry to probe the greatest area of chemical space possible in hopes to find new drug candidates.

The principal concept behind diversity oriented synthesis is to efficiently produce a large library of compounds that are significantly different from one another so that a
greater region of chemical space can be explored. To do this, multiple modifications are performed after each step in the sequence resulting in the multiplicative growth of diverse compounds resulting from the synthesis. At each stage stereocenters, appendages, and modifications to the core framework can be introduced. An example of DOS can be seen in Scheme 1.2, which is centered around o-azaxylylene photochemistry and is an excerpt from the research presented in this dissertation.\textsuperscript{12}
Scheme 1.2

Suzuki Products
$X = \text{Ph, 3-Py, 2-Furyl, or 2-Thiophene}$
Peripheral decoration of a core scaffold with functional groups is common place in combinatorial chemistry, as the core scaffold remains the same\(^9\), and there are many examples of this in **Scheme 1.2**, such as the addition of benzylamine or furfuryl amine. However, the most significant transformation can be seen when the overall topology changes in the core framework, the cornerstone of DOS, which occurs upon irradiation yielding significantly different \([4 + 4]\) and \([4 + 2]\) isomers. Not only does this irradiation produce diverse scaffolds, but it also introduces 3 stereocenters, and some of the resultant assemblies contain fragments that are found in active pharmaceuticals, such as a fused 2,5-diketopiperazine ring. This fragment is the core template in many bioactive molecules (**Figure 1.2**), such as PDE-5 inhibitors (Cialis), preterm labor drugs (Retosiban), various cancer inhibitors (Phenylahistin), and “are among the most numerous of all naturally occurring peptide antibiotics.”\(^{13}\)

![Cialis](image1.png)  ![Retosiban](image2.png)  ![Phenylahistin](image3.png)

**Figure 1.2**

In keeping with the principles of DOS, further modifications to the synthetic methodology behind \(\sigma\)-azaxylylene photochemistry have been implemented by various
members of Dr. Kutateladze’s lab yielding structurally diverse scaffolds,\textsuperscript{14-16} and a small subset can be seen in Figure 1.3.

![Figure 1.3](image-url)

All the above examples were synthesized by utilizing intramolecular addition to \textit{o}-azaxylylenes in the excited state, and it should be clear just by looking at Figure 1.3 that this methodology is a powerful technique capable of yielding significantly distinct topologies in keeping with the fundamentals of DOS.

\textit{o}-Azaxylylenes

\textit{o}-Azaxylylenes (1.1a) have been explored for over half a century, and throughout their history have been utilized as unstable heterodiene intermediates in a few [4 + 2] cycloaddition reactions with only a handful of dienophiles (Scheme 1.3).\textsuperscript{17}
Prior to 2011, approaches to the \textit{in situ} generation of \textit{o}-azaxylylenes could be broken down into six categories (Scheme 1.4): nitrene formation followed by a \([1,4]\)-hydrogen shift (1.1b), valence isomerization of strained benzoazetines (1.1c), thermal cheleotropic extrusion of \(\text{SO}_2\) (1.1d) or \(\text{CO}\), \([4 + 2]\) cycloreversions (1.1e), ring-opening of heterocyclic systems (1.1f), and elimination (1.1g).\(^{17}\)
One thing that should be noted when looking at Scheme 1.4 is that the conditions are typically harsh, requiring high temperatures or even flash vacuum thermolysis (FVT), and as a result are not compatible with many substrates. Before 2011 there were few examples of dieneophiles outside of N-phenylmaleimide (NPMI), or basic alkenes and alkynes that were reactive with the o-azaxylylene core.\(^{17}\) Below (Scheme 1.5) is the synthetic sequence used by Burgess and McCullagh to trap an o-azaxylylene intermediate with NPMI, which is also the first experimental proof of o-azaxylylene formation.\(^{18}\)

\[
\begin{align*}
\text{Scheme 1.5}
\end{align*}
\]

Though most of the methods in Scheme 1.4 are harsh, special attention should be paid to the synthesis utilizing substrate 1.1g, which “involves base-induced elimination of hydrogen chloride from amide or sulfonamide derivitives,”\(^{19}\) and was thought at the time to be “the simplest method possible for o-azaxylylene production …” Steinhagen and Corey demonstrated that this methodology can be used for intermolecular and intramolecular [4 + 2] cyclization of electron rich olefins without the need for drastic conditions, allowing access to a handful of unique structures including the core scaffold of virantmycin, an antiviral agent, as a racemic mixture in respectable yields (Scheme 1.6).
On paper this method for generating \( o \)-azaxylylenes looks simple; however, the actual process is not without its difficulties. Synthesis involves the addition of the cholormethylaniline derivative to the base and diene by syringe pump over, and depending on the substrate this can take up to 24 hours while maintaining a temperature as low as \(-78^\circ\text{C}\).\(^{19}\)

**Photogenerated \( o \)-Azaxylylenes**

For ten years Steinhagen and Corey’s\(^{19}\) methodology would stand as the only viable way to utilize azaxylylenes synthetically, until 2011 when Mukhina et al., a fellow group member, reported the first example of \([4 + 2]\) and \([4 + 4]\) cycloadditions stemming from the excited state intramolecular proton transfer (ESIPT) of photogenerated \( o \)-azaxylylenes in the formation of complex N,O,S-Polyheterocycles.\(^{20}\) This novel approach is advantageous over the preceding methodology, as it eliminates the need for harsh conditions or reagents that may not be accommodating to substrates. The irradiation process is about as simple as flipping a switch, and allows access to \([4 + 4]\) cycloaddition products, a process that is forbidden in the ground state, in addition to the \([4 + 2]\) cyclization products. A representative from the work of Mukhina et al. is
depicted in Scheme 1.7. This simple synthetic sequence involves coupling 2’-aminoacetophenone with the acyl chloride produced from 3-(2-furyl)propionic acid, and subsequent irradiation of the photoprecursor (1.2) yielding the [4 + 2] (1.3), and [4 + 4] (1.4) cycloaddition products in only three steps. Given the simplicity of this method it is staggering that it had not been discovered earlier, and the authors note that “it is conceivable that [photochemical generation of azaxylylenes] was attempted but failed due to the back proton transfer successfully competing with bimolecular cycloadditions.”

![Scheme 1.7](image-url)
Multiple diversity inputs can be introduced under these reaction conditions (Scheme 1.8). Tethered alkenes, furan, and thiophene pendants proved to be reactive dienophiles, as o-azaxylylenes act as acceptors in inverse electron demand cycloadditions. The tether could be three to four atoms in length, respectively producing five and six membered rings upon irradiation. Aldehydes, ketones, and cyclic ketones all proved to be reactive.

Scheme 1.8 [Adopted From Angew. Chem. Int. Ed.\textsuperscript{20}]

Photoprecursors showed broad UV absorption, with a maximum between 340-350 nm, and were irradiated using 365 nm Nichia UV LEDs or a Rayonet broadband 300-400 nm UV source yielding [4 + 2] and [4 + 4] isomers in most cases.\textsuperscript{20} An overview of the first series of reactions run by Mukhina et al. can be seen in Scheme 1.9. Not only were the products obtained in high overall yields, ranging from 60-89%, high diastereoselectivity of the hydroxyl group relative to the bridged heteroatom was observed in most cases. The anti diastereomer predominated in the [4 + 2]
cycloadditions while syn predominated in [4 + 4] cycloaddition, and in most cases the diastereomeric ratio was 30:1 for the aldehydes.\textsuperscript{20}

Scheme 1.9 [Adopted From Angew. Chem. Int. Ed.\textsuperscript{20}]

It was postulated that this selectivity was the result of an \textit{endo} transition state for both the [4 + 2] and [4 + 4] cycloadditions (Scheme 1.10), where the resulting isomer is dictated by the direction the hydroxyl group is facing in the transition state.\textsuperscript{20} Tetralone is incapable of rotation at the carbonyl, and ketones are sterically hindered in the out-hydroxy conformer and as a result show exclusive selectivity. Aldehydes show minor
amount of the unfavorable diastereomer, as they are less sterically hindered in the out-hydroxy conformer when compared to the ketones.

Scheme 1.10 [Adopted From Angew. Chem. Int. Ed.20]
The research put forth in the following chapters of this dissertation sets out to build upon the body of research by this initial discovery. In the following chapters, evidence will be presented confirming that these cyclizations occur in the triplet excited state in a stepwise fashion; that these photoproducts, and precursors can be modified in keeping with the principle of diversity oriented synthesis; and build upon the methodology by giving the first example of an excited state cascade reaction involving two consecutively photogenerated o-azaxylylenes.
Chapter Two: Mechanistic Studies

Of all the things that I have accomplished at the University of Denver it is the work in this chapter that I take the most pride in. Many novel compounds and diverse libraries have come out of our lab, but this research was special to me because it was about finding an answer. Understanding the underlying photophysics and photochemistry behind excited state \( o \)-azaaxyylene cycloadditions will optimize future approaches to this methodology. However, this project felt like I was doing science for science’s sake, and there is something special about doing something for its intrinsic value.

Introduction

When Mukhina et al. published their initial work on photogenerated \( o \)-azaaxylenes “a detailed photophysical mechanistic study of these cycloadditions [was] ongoing;”\(^{20}\) however, there were some indications that the reaction occurred in a stepwise fashion. First, concerted \([4 + 2]\) cycloaddition is not allowed in the excited state, but occurs upon coupling photogenerated \( o \)-azaaxylenes with tethered dienophiles, and the only way that this can occur in the excited state is if the addition occurred in a stepwise fashion. This is best demonstrated using frontier molecular orbital theory (Scheme 2.1), where the highest occupied molecular orbital (HOMO) must share the same symmetry
with the lowest unoccupied molecular orbital (LUMO). If this process is concerted an overlap in symmetry must occur for an overall net bonding interaction; however, there is an asymmetrical overlap between the orbitals for [4 + 2] cyclization in the excited state ruling out a concerted process. For clarity, the [4 + 4] cyclization is also depicted, which is allowed in the excited state but forbidden in the ground state according to the frontier molecular orbital theory.
Another piece of evidence suggesting that the mechanism is not concerted was the formation of disproportionation products (Scheme 2.2) that could only occur if the reaction proceeded in a stepwise fashion. If the excited state o-azaxylylene is depicted as a diradical, the mechanism can be initiated with an N-centered radical attack.
on the double bond to form the initial 1,6-diradical, which can (i) rotate its benzylic center and recombine to form the [4 + 2] adducts, or (ii) disproportionate by H-abstraction to form benzylic alcohol with an N-acyl enamine moiety, which undergoes subsequent ground state or photoinduced intramolecular alcohol addition to yield aminal 2.1 (17%).

Scheme 2.2 [Adopted From Angew. Chem. Int. Ed.]

The following study was performed to elucidate the mechanism behind the intramolecular cyclization of photogenerated o-azaxylylenes and was published in the Journal of Physical Chemistry A. Quantum yields, quantum efficiency in the presence of triplet quenchers, steady state spectroscopy, and time-correlated single photon counting were used to provide a significant body of evidence that the excited state intramolecular proton transfer (ESIPT) is followed by intersystem crossing (ISC) to the triplet state, and stepwise addition to the tethered unsaturated pendant.

Results and Discussion

From a mechanistic standpoint, there are several potential pathways that photogenerated o-azaxylylenes can take to yield intramolecular cycloaddition products (Scheme 2.3). This pseudo Jablonski diagram does not depict the relative energies of each species, but instead is designed to be a tool to help envision the possible routes that
can be taken to reach the cyclization products. The possibilities listed in Scheme 2.3 can be ruled out systematically. Pathway 1 and 2 involve cycloaddition in the ground state, and evidence will be presented against this process. Pathway 3 does not undergo intersystem crossing (ISC), and can be eliminated by providing evidence that the reaction proceeds through a triplet state. The final two pathways, 4 and 5, both proceed through a triplet state and only differ where the excited state intramolecular proton transfer (ESIPT) takes place, and this difference can be addressed through phosphorescence studies.\textsuperscript{22}
Scheme 2.3

1) $R \rightarrow {R_{\text{ESIPT}}} \rightarrow P$

2) $R \xrightarrow{hv} {1R} \xrightarrow{EPI} {1R_{\text{ESIPT}}} \rightarrow R_{\text{IPT}} \rightarrow P$

3) $R \xrightarrow{hv} {1R} \xrightarrow{EPI} {1R_{\text{ESIPT}}} \rightarrow P$

4) $R \xrightarrow{hv} {1R} \xrightarrow{EPI} {1R_{\text{ESIPT}}} \xrightarrow{ISC} {3R_{\text{ESIPT}}} \xrightarrow{RA} {3R_{\text{RA}}} \xrightarrow{ISC} R_{\text{RA}} \xrightarrow{RA} P$

5) $R \xrightarrow{hv} {1R} \xrightarrow{ISC} {3R} \xrightarrow{HSIPT} {3R_{\text{ESIPT}}} \xrightarrow{RA} {3R_{\text{RA}}} \xrightarrow{ISC} R_{\text{RA}} \xrightarrow{RA} P$

Key:

$R$ = Reactant  
$P$ = Product  
ESIPT = Excited State Intramolecular Proton Transfer  
IPT = Intramolecular Proton Transfer  
RA = Radical Addition  
ISC = Intersystem Crossing
The first two potential pathways listed involve cycloaddition in the ground state, and both can be addressed simultaneously. Pathway 1, involves a pure ground state reaction leading to the cycloaddition products, and pathway 2 proceeds through excitation to the first singlet excited state ($S_1$), ESIPT, internal conversion to a ground state $o$-azaxylylene, and cycloaddition. According to DFT calculations, there is no energy barrier for the back proton transfer in the ground state (Figure 2.1), indicating that $o$-azaxylylene formation in the ground state is not favorable as the cycloaddition process could not compete with the rate of back proton transfer, ruling out pathway one. There is an energy barrier for the back proton transfer in $S_1$, so the lifetime of the $o$-azaxylylene would be significantly greater in $S_1$ than in the ground state. However, a ground state cycloaddition mechanism after excitation, ESIPT, and internal conversion to the ground state, pathway two, is unfavorable. Internal conversion of an $o$-azaxylylene from $S_1$ to the ground state would result in an immediate back proton transfer, as there is no energy barrier in the ground state, which is significantly faster than the cycloaddition process.
Knowing that the cycloaddition takes place in the excited state, the next question to answer is if the excited state species remains as a singlet, or undergoes intersystem crossing (ISC) to a triplet state. Without ISC to the triplet state, the underlying process could potentially proceed through excitation to $S_1$, followed by ESIPT, cycloaddition, and internal conversion to the ground state yielding the cycloaddition products, Pathway 3. A significant body of evidence has been generated to leave little, if any, doubt that the mechanism proceeds through a triplet state.

To start, the quantum efficiency of cyclization significantly decreases upon the addition of known triplet quenchers, $\textit{trans}$ piperylene$^{23}$ and molecular oxygen (Figure 2.2). Not only does this provide insight to the photochemical process, but allows for the calculation of the excited state species lifetimes using Stern-Volmer analysis ($K_{SV} = 99$
for quenching with O$_2$ in acetonitrile, and K$_{SV} = 57$ for quenching with \textit{trans}-piperylene in benzene). Assuming that the rate of quenching is diffusion controlled (K$_{\text{dif}} = 1.0 \times 10^{10}$ M$^{-1}$ s in benzene, and $1.9 \times 10^{10}$ in acetonitrile$^{24}$), the lifetime of the excited triplet state species for 2.1b was calculated to be approximately 5.2 ns in acetonitrile and 5.7 ns in benzene.

![Graph showing conversion vs time for different quenchers](image)

**Figure 2.2 [Adopted From \textit{J. Phys. Chem. A}$^{21}$]**

Further evidence supporting a triplet state mechanism was provided by time correlated single photon counting (TCSPC) experiments (\textit{Figure 2.3}), which were performed on \textit{o}-azaxylylene photoprecursors bearing furan pendants (2.1a and 2.1b), and their acetylated counterparts (2.11a and 2.11b). It is difficult to determine the identity of each species. However, the results indicate that the addition of a furan pendant does not have an effect on the rate of decay of fluorescence. If the mechanism proceeded through
a singlet state, the fluorescence lifetime of the ESIPT singlet state species would decrease upon substituting the acetyl group with the furan pendant, as there would be an alternative pathway taking away from the quantum yield (QY) of fluorescence. We do not see this when comparing the furanpropanoylated and acetylated pairs, leading to the conclusion that the reaction likely proceeds through a triplet state.
Additional evidence supporting a triplet state mechanism can be seen when comparing the fluorescence spectrum of \( o \)-azaxylylene photoprecursors with differing
pendants and substitutions. o-Azaxylylenes produce two distinct bands, usually between 350 and 650 nm, where the blue shifted band represents the fluorescence of the excited ketone or aldehyde where no ESIPT has taken place, and the red shifted band representing that of the ESIPT species\textsuperscript{25}. When comparing the fluorescence spectrum of the aminotetralone derivative bearing a reactive furan pendant, 2.4a, to that of the acylated species incapable of cycloaddition, 2.12a one can see that there is little difference in the relative intensities between the two bands in the fluorescence spectra (Figure 2.4). The rationale is similar to that in the TCSPC experiment: if there were a cycloaddition channel in the singlet excited state then a decrease in fluorescence emission of the red-shifted band should be observed for the species capable of cycloaddition, 2.4a, when compared to that of the species incapable of cycloaddition, 2.12a. Solutions of 2.4a or 2.12a (1x10\textsuperscript{-5} M in DCM) were irradiated at 325 nm.
Halogen substitution in the aromatic ring produces a significant change in the ratio between the fluorescence intensity of the two bands. This can be seen when comparing the tetralone derivative bearing a reactive furan pendant (2.4a) to the same species with a bromo substitution in the para position (2.2b, Figure 2.5). Heavy atoms, in this case bromine, have a high nuclear charge and cause electrons to accelerate as they pass by the nucleus increasing the rate of spin-orbit coupling-induced transitions, which is necessary for intersystem crossing (ISC) from a singlet to a triplet state. This phenomenon, dubbed the “heavy atom effect,” manifests itself in Figure 2.5 as a decrease in the fluorescence intensity of the ESIPT band upon bromo substitution that results from an increased quantum yield of ISC.
An absolute quantum yield study was performed on a library of o-azaxylylene photoprecursors using a benzophenone-benzhydrol actinometer\textsuperscript{26} (\textbf{Figure 2.6}). Solutions of the photoprecursor (1x10\textsuperscript{-2} M) in acetonitrile were thoroughly degassed with N\textsubscript{2}, irradiated on a carrousel using 365 nm Nichia UV LEDs along with the actinometer, and the formation of the [4 + 2] and [4 + 4] cycloaddition products in the samples being tested, as well as the formation of pinacol in the actinometer were monitored by \textsuperscript{1}H NMR. In keeping with the heavy atom effect, photoprecursors containing halogen substituents had significantly greater quantum yields than their non-halogenated counterparts. Substitution at the carbonyl impeded the cycloaddition process, which can be attributed to the stabilized hydroxybenzylic radical being less reactive.
The greatest quantum yield in the series was the aminobenzaldehyde derivative containing a bromo substitution at the 5 position ($\Phi_r = 0.75$), which showed greater efficiency than that of 5-iodo ($\Phi_r = 0.54$) and 5-chloro ($\Phi_r = 0.32$) substitutions. This series illustrates that there is an interplay between the heavy atom effect on spin-orbit coupling (SOC) and the effect of electron withdrawing substituents enhancing the reactivity of the N-centered radical towards the electron rich diene of the furan pendant.
Pauling electronegativities, atomic SOC values, and the quantum yield ($\Phi_r$) of cycloaddition are compiled in Table 2.1 for this series. Iodo substitution provides sufficient SOC but shows low electronegativity, while chloro substitution displays the inverse. Bromine lies in the middle when it comes to SOC and electronegativity, which may explain the higher $\Phi_r$s compared to the other compounds in the series.

<table>
<thead>
<tr>
<th></th>
<th>Cl</th>
<th>Br</th>
<th>I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronegativity</td>
<td>3.16</td>
<td>2.96</td>
<td>2.66</td>
</tr>
<tr>
<td>Atomic SOC cm$^{-1}$</td>
<td>587</td>
<td>2460</td>
<td>5069</td>
</tr>
<tr>
<td>QY, cycloaddition</td>
<td>0.32</td>
<td>0.75</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Table 2.1 [Adopted From *J. Phys. Chem. A* $^{21}$]

The preceding body of evidence shows that the cycloaddition of $o$-azaxylylenes proceeds through a triplet state, eliminating pathways 1-3; however, this leaves two possible scenarios. ESIPT could potentially occur in the singlet (Pathway 4) or triplet state (Pathway 5). It has been established that ESIPT does not occur in the triplet state, as the two phosphorescence bands of the triplet 2-aminobenzophenone conformers, one being the EISPT species and the other being the ketone, decay independently of one another$^{22}$ leaving pathway 4 as the only remaining excited state pathway. To conclude, the mechanism proceeds through excitation to the singlet state, where ESIPT takes place, followed by ISC, radical addition of the N-centered radical resulting in a ground state species where the final radical recombination occurs yielding the cycloaddition products (Scheme 2.4).
*The spectra and synthetic procedures for the materials presented in this Chapter are given in the experimental section of Chapter 3, as the materials used in this study are a subset of those synthesized in the following chapter.*
Chapter 3: Postphotochemical Modifications

The mechanistic studies in the previous chapter have provided insight into the process of \(\pi\)-azaxylylene cycloaddition and allow those utilizing this chemistry to do so optimally. Moving forward, the next topic to address would be whether these novel scaffolds are amenable to postphotochemical modifications to the overall topology and probe unexplored regions of chemical space. The research in this chapter was published in the Journal of Organic Chemistry.\(^\text{12}\)

Introduction

Combinatorial chemistry and diversity oriented synthesis are valuable tools, as they are capable of producing large libraries of compounds efficiently.\(^\text{9}\) It has been shown that \(\pi\)-azaxylylene cycloadditions are capable of producing significantly diverse frameworks and adhere to the fundamentals of diversity oriented synthesis.\(^\text{20}\) Further modification of the scaffold can yield structures reminiscent of natural products, and expands the area of chemical space explored.\(^\text{9}\) According to an extensive study by Roughley and Jordan,\(^\text{27}\) Suzuki coupling accounts for 40\% of all C-C bond forming reactions, and sp\(^2\)-sp\(^2\) coupling is one of the most commonly used reactions by medicinal chemists in the pursuit of drug candidates. Suzuki coupling holds other advantages that serve as a good starting point for postphotochemical modification, in that there are many
boronic acids commercially available, and the procedures are well documented. This study sets out to explore the modification of these cycloaddition adducts using Suzuki coupling.

**Results and Discussion**

To incorporate Suzuki coupling into the synthesis of the cycloaddition scaffolds two coupling approaches were explored (Scheme 3.1): pre-photochemical coupling of the heteroboronic acid with the halogen-substituted photoprecursor (path a), and post-photochemical coupling of the cycloaddition products (path b). This was the first goal of the study, as extended conjugation could potentially affect the photoefficiency.
Scheme 3.1 [Adopted From J. Org. Chem\textsuperscript{12}]
Synthesis of 3.1a was accomplished by acylating the 5-bromophenylmethanol with 2-furanpropanoyl chloride, and the product was then either subjected to Suzuki coupling followed by PCC oxidation, and irradiation (path a) or oxidized by PCC then irradiated and coupled to the aryl boronic acid (path b). Both the halogen (3.3a), and hetroaryl (3.3b) photoprecursors were irradiated with a Rayonet broadband 300-400 nm UV source, and the optimal solvent for irradiation was determined to be 5% aqueous acetonitrile. Irradiation of both photoprecursors yielded one diastereomer of the [4 + 2] (syn) and [4 + 4] (anti) cycloaddition products in an approximate ratio of 1:1, where syn and anti refer to the relative position of the bridged oxygen and the hydroxyl group. Suzuki coupling of the photoproducts resulted in some degradation of the [4 + 2] product. The yields were comparable for both pathway a and b, 44% and 35% respectively. However, the quantum efficiency differed considerably between photoprecursors 3.3a and 3.3b, being 3.7 times greater for the halogen substituted precursor (3.3a) utilized in pathway b, the reasoning being explained in Chapter 2. Given the similar overall yields, it was decided to follow path b to probe the scope of the reaction due to the increased quantum efficiency.

In keeping with the principles of DOS, a modular approach was implemented to gain access to a diverse array of photoprecursors. Modifications to the halogen and its position in the aromatic ring, the linker connecting the 2-acylaniline to the furan pendant, and the substituent on the carbonyl were employed yielding the compounds seen in Table 3.1.
<table>
<thead>
<tr>
<th>$o$-Formyl- or $o$-acyl-aniline</th>
<th>Linker</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Chemical Structure" /></td>
<td><img src="image2" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><img src="image3" alt="Chemical Structure" /></td>
<td><img src="image4" alt="Chemical Structure" /></td>
</tr>
<tr>
<td><img src="image5" alt="Chemical Structure" /></td>
<td><img src="image6" alt="Chemical Structure" /></td>
</tr>
</tbody>
</table>

Isolated yields of photoprecursors are given

Table 3.1 [Adopted From *J. Org. Chem*]$^{12}$]
Photoprecursors 3.3a-e, 3.9, and 3.12-16 were synthesized according to Scheme 3.2 and 3.3. Halogen substituted alcohols 3.7a, c-e, 3.8 and ketones 3.10, 3.11 were acylated with furanpropanoyl chloride 3.6. After acylation, ketones 3.12 and 3.13 were irradiated, while alcohols were oxidized using PCC to yield photoprecursors 3.3a, c-e. Halogen-substituted methyl anthranilates were coupled in the same fashion, reduced with LiAlH₄, and oxidized using PCC.

![Scheme 3.2](image)

**Scheme 3.2 [Adopted From J. Org. Chem]^{12}**

Diversification of the linker was achieved using a peptoid synthesis-inspired^{28,29} approach with bromoacetyl bromide (Scheme 3.3). Bromoacylation of alcohol 3.7a or ketone 3.11 was followed by the addition of furfuryl or benzyl amine, and subsequent acylation with either pivaloyl or furoyl chloride, respectively. The alcohol was then oxidized using PCC.
The products synthesized from photochemical cyclization and subsequent Suzuki coupling are presented in Scheme 3.4, and the yields can be found in Table 3.2. In all cases irradiation produced both the [4 +2] in [4 + 4] cycloaddition products with good diastereoselectivity, and on average the irradiations were complete in less than 5 hours. The mixture of cycloaddition products were subjected to Suzuki coupling to yield the fused biaryls and purified by column chromatography. Palladium-catalyzed cross coupling proved to be sensitive to the addition of heteroatoms in the linker, as demonstrated in two of the three cases where the peptoid-inspired methodology was employed. In these instances, Suzuki coupling resulted in the complete degradation of [4 + 2] cycloaddition products bringing the yield below 40%.
Scheme 3.4 [Adopted From J. Org. Chem]
**Table 3.2 [Adopted From J. Org. Chem^{12}]**

<table>
<thead>
<tr>
<th>Photoprecursor</th>
<th>Photoproducts ratio [4+2]:[4+4]&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Suzuki coupling product from [4+2]&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Suzuki coupling product from [4+4]&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3a</td>
<td>3.4a:3.5a = 1:1</td>
<td>3.4f, 30%</td>
<td>3.5f, 44%</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.4b, 7%</td>
<td>3.5b, 28%</td>
</tr>
<tr>
<td>3.3d</td>
<td>3.4d:3.5d = 1:1</td>
<td>3.4g, 17%</td>
<td>3.5g, 26%&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.4h, 27%</td>
<td>3.5h, 39%</td>
</tr>
<tr>
<td>3.9</td>
<td>3.17a:3.18a = 1:0.8</td>
<td>3.17b, 30%</td>
<td>3.18b, 24%</td>
</tr>
<tr>
<td>3.12</td>
<td>3.19a:3.20a = 1:1.1</td>
<td>3.19b, 28%</td>
<td>3.20b, 30%</td>
</tr>
<tr>
<td>3.13</td>
<td>3.21a:3.22a = 1:1.9</td>
<td>3.21b, 36%</td>
<td>3.22b, 16%</td>
</tr>
<tr>
<td>3.14</td>
<td>3.23a:3.24a = 1:1.4</td>
<td>3.23b 19%</td>
<td>3.24b, 12%</td>
</tr>
<tr>
<td>3.15</td>
<td>3.25a:3.26a = 1:1.5</td>
<td>3.25b, --</td>
<td>3.26b, 20%</td>
</tr>
<tr>
<td>3.16</td>
<td>3.27a:3.28a = 1:16</td>
<td>3.27b, --</td>
<td>3.28b, 36%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Determined by NMR of the reaction mixture after completion of irradiation. For [4 + 4] the double bond proton at approximately 6.4 ppm (dd, J = 6.0, 2.0 Hz, 1H), and for [4 + 2] the double bond proton at approximately 6.3 ppm (t, 2.8 Hz, 1H); <sup>b</sup>isolated yields; <sup>c</sup>the primary [4+4] photoproduct rearranges from the bicyclo[4.2.1] to bicyclo[3.3.1] framework.

Coupling conditions were dependent on the boronic acid being used. The catalyst of choice for coupling with 3-pyridine boronic acid was Pd<sub>2</sub>(dba)<sub>3</sub> (0.9 mol %) using PCy<sub>3</sub> as a ligand, while 2-furyl and 2-thienyl boronic acids were coupled with Pd(PPh<sub>3</sub>)<sub>4</sub> (5 mol %). Bromine substituted substrates were reactive with 3-pyridine boronic acids; however, thienyl and furyl boronic acids required iodine substituted substrates. All attempts using MIDA<sup>30</sup> boronates failed. X-Ray analysis was performed on crystalline products unambiguously proving their structure and stereochemistry (see experimental).

Additionally, a rearrangement from the bicyclo [4.2.1] to a bicyclo [3.3.1] skeletal structure was observed when 3.5g was subjected to silica during chromatography (Scheme 3.5), which results from ring opening and closure of the [4 + 4] photo product.
It was found that heating the [4 + 4] cycloaddition in DMSO also produces the [3.3.1] rearrangement product.

![Scheme 3.5](image)

**Scheme 3.5 [Adopted From J. Org. Chem][12]**

Since this research was published back in 2014, other novel post photochemical modifications have been implemented demonstrating the synthetic utility of these cycloaddition products. For example, Umstead et al. illustrated that the alkene generated from photochemical cycloaddition was reactive to 1,3-dipoles, and N-phenyl-aryl-2-ylmethanimines\textsuperscript{15} (**Scheme 3.6**), yielding an array of products with significantly diverse core scaffolds.
Given the growing body of data regarding the synthetic utility of photogenerated $\sigma$-azaxylylenes it is clear that this methodology of producing fused ring systems is
aligned with the principles of DOS. These reactions show a high degree of
diastereoselectivity, produce unprecedented fused ring systems, and are amenable to
postphotochemical modifications.

**Experimental**

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 or TCI America and used without
additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C
on a Bruker Avance III 500 MHz in CDCl$_3$ with TMS as an internal standard (unless
noted otherwise) 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.
Shuji Kato and Dr. Dan Gu at 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 Rf using Hexanes/EtOAc or DCM/Methanol as an eluent.

**2-Furanpropanoyl chloride**$^{31}$ (3.6): To a stirred solution of 3-(2-
furyl)propanoic acid (1 eq, 1.15 g, 8.2 mmol) in 15 mL of DCM was
added SOCl$_2$ (1.3 eq, 0.79 mL, 11 mmol). The solution was refluxed for 4 hours, allowed
to cool to room temperature, and concentrated, yielding 1.28 g (99%) of the product. 1H
NMR (500 MHz, CDCl$_3$) δ 7.35 (dd, $J = 1.9$, 0.9 Hz, 1H), 6.32 (dd, $J = 3.2$, 1.9 Hz, 1H),
6.10 (m, 1H), 3.27 (t, $J = 7.3$ Hz, 2H), 3.07 (t, $J = 7.3$ Hz, 2H).
Synthesis of halogen-substituted o-hydroxymethylanilines and o-acetylanilines

**Methyl 2-amino-4-bromobenzoate**$^{32}$ (S1): To an ice cooled solution of 4-bromo-2-nitrobenzoic acid (1.50 g, 6.10 mmol) in DMF (15 mL) was added DBU (8.3 mL, 55 mmol), followed by the addition of MeI (3.4 mL, 54.9 mmol). The reaction was allowed to stir overnight, poured into water (30 mL), extracted with EtOAc (4 x 75 mL), dried over Na$_2$SO$_4$, filtered and concentrated yielding 1.54 g (97%) of methyl 4-bromo-2-nitrobenzoate. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.03 (d, $J$ = 1.9 Hz, 1H), 7.83 (dd, $J$ = 8.2, 1.9 Hz, 1H), 7.67 (d, $J$ = 8.2 Hz, 1H), 3.93 (s, 3H). To a solution of methyl 4-bromo-2-nitrobenzoate (1.52 g, 5.85 mmol) in a 1:1 mixture of EtOAc and DCM (12 mL) was added SnCl$_2$$\cdot$2H$_2$O (6.18 g, 27.4 mmol). After 24 hours the mixture was concentrated, diluted with a solution of sat. aq. NaHCO$_3$, extracted with DCM, and concentrated yielding 1.15g (82%) of the title compound over two steps. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 7.72 (d, $J$ = 8.6 Hz, 1H), 6.87 (d, $J$ = 1.9 Hz, 1H), 6.78 (dd, $J$ = 8.6, 1.9 Hz, 1H), 5.81 (s, 2H), 3.88 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 168.1, 151.2, 132.6, 128.7, 119.5, 119.0, 109.6, 51.7.

**2-Amino-5-bromobenzyl alcohol**$^{33}$ (S2): Methyl 2-amino-5-bromobenzoate (3.00 g, 13.0 mmol) in THF (9 mL) under nitrogen atmosphere was cooled to -41 °C using a acetonitrile/CO$_2$ (s) cooling bath, and DIBAL-H (39.1 mL of a 1.0 M solution in hexanes, 43.0 mmol) was slowly
added to the stirred solution. After maintaining at -41 °C for 1.5 hours, the solution was allowed to reach room temperature and left to stir overnight. The solution was cooled in an ice water bath, quenched by the addition of methanol, a solution of sat. aq. sodium potassium tartrate was added, and the mixture was allowed to stir for 30 min. The organic phase was extracted with Et₂O (3 x 100 mL), and concentrated yielding 2.41 g (92%) of the product. ¹H NMR (500 MHz, CDCl₃) δ 7.24 (m, 2H), 6.61 (d, J = 8.3 Hz, 1H), 4.66 (d, J = 4.5 Hz, 2H), 4.22 (s, 2H).

4-Bromo-2-((trimethylsilyl)methyl)aniline (S3):

Chlorotrimethylsilane (1.16 mL, 9.14 mmol) was added to a stirred solution of 2-amino-5-bromobenzyl alcohol (1.68 g, 8.33 mmol) and triethylamine (2.32 mL, 16.6 mmol) in DCM (70 mL). The reaction mixture was stirred at room temperature overnight. The mixture was quenched with a solution of sat. aq. NH₄Cl (50 mL), the organic layer was separated, and the aqueous phase was extracted with DCM (3 x 100 mL). The organic fractions were combined, dried over Na₂SO₄, filtered, and concentrated yielding 2.35 g (94%) of the product. ¹H NMR (500 MHz, CDCl₃) δ 7.19 (m, 2H), 6.57 (d, J = 8.2 Hz, 1H), 4.61 (s, 2H), 4.18 (s, 2H), 0.16 (s, 9H).

2-Amino-4-bromobenzyl alcohol³⁴ (S4): Methyl 2-amino-4-bromobenzoate (1.14 g, 4.95 mmol) in THF (5.5 mL) under nitrogen atmosphere was cooled to -41 °C. DIBAL-H (16.35 mL of a 1.0 M solution in hexanes, 16.35 mmol) was slowly added to the stirred solution. After
remaining at -41 °C for 1.5 hours, the solution was allowed to reach room temperature and left to stir overnight. The solution was cooled in an ice water bath, quenched by the addition of methanol (35 mL), a solution of sat. aq. sodium potassium tartrate was added (70 mL), and the mixture was allowed to stir for 6 hours. The organic phase was extracted with Et$_2$O (3 x 125 mL), and concentrated yielding 0.98 g of (2-amino-4-bromophenyl)methanol which was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.95 (d, $J$ = 7.9 Hz, 1H), 6.88 (d, $J$ = 1.9 Hz, 1H), 6.85 (dd, $J$ = 7.9, 1.9 Hz, 1H), 4.66 (d, $J$ = 5.1 Hz, 2H), 4.29 (s, 2H), 1.54 (m, 1H).

5-Bromo-2-((trimethylsilyloxy)methyl)aniline (S5):

Chlorotrimethylsilane (0.69 mL, 5.4 mmol) was added to a stirred solution of (2-amino-4-bromophenyl)methanol (0.98 g 4.9 mmol) and triethylamine (1.36 mL, 9.75 mmol) in DCM (43 mL). The reaction mixture was stirred at room temperature overnight. The mixture was quenched with a solution of sat. aq. NH$_4$Cl (70 mL), the organic layer was separated, and the aqueous phase was extracted with DCM (3 x 100 mL). The organic fractions were combined, dried over Na$_2$SO$_4$, filtered, and concentrated yielding 1.11 g of 5-bromo-2-((trimethylsilyloxy)methyl)aniline which was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 6.90 (d, $J$ = 7.8 Hz, 1H), 6.84 (d, $J$ = 1.8 Hz, 1H), 6.82 (dd, $J$ = 7.8, 1.9 Hz, 1H), 4.61 (s, 2H), 4.26 (s, 2H), 0.14 (s, 9H).
2-Amino-5-iodobenzyl alcohol\textsuperscript{(S6)}: Methyl 5-idoanthranilate

(3.00 g, 10.8 mmol) in THF (7.5 mL) under nitrogen atmosphere was cooled to -41 °C. DIBAL-H (32.7 mL of a 1.1 M solution in cyclohexane, 36 mmol) was slowly added to the stirred solution. After remaining at -41 °C for 1.5 hours, the solution was allowed to reach room temperature and left to stir overnight. The solution was cooled in an ice water bath, quenched by the addition of methanol, a solution of sat. aq. sodium potassium tartrate was added, and the mixture was allowed to stir for 30 min. The organic phase was extracted with Et\textsubscript{2}O (3 x 100 mL), and concentrated yielding 2.48 g (92%) of the product. \textsuperscript{1}H NMR (500 MHz, CDCl\subscript{3}) \( \delta \) 7.41 (dd, \( J = 8.3, 2.2 \) Hz, 1H), 7.39 (d, \( J = 2.1 \) Hz, 1H), 6.51 (d, \( J = 8.3 \) Hz, 1H), 4.64 (d, \( J = 5.3 \) Hz, 2H), 4.24 (s, 2H).

4-Iodo-2-((trimethylsilyloxy)methyl)aniline (S7):

Chlorotrimethylsilane (0.49 mL, 3.8 mmol) was added to a stirred solution of 2-amino-5-iodobenzyl alcohol (0.87 g, 3.5 mmol) and triethylamine (0.98 mL, 7.0 mmol) in DCM (32 mL). The reaction mixture was stirred at room temperature overnight. The mixture was quenched with a solution of sat. aq. NH\textsubscript{4}Cl (50 mL), the organic layer was separated, and the aqueous phase was extracted with DCM (3 x 100 mL). The organic fractions were combined, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated yielding 0.94 g (83%) of the product. \textsuperscript{1}H NMR (500 MHz, CDCl\subscript{3}) \( \delta \) 7.37 (dd, \( J = 8.2, 2.2 \) Hz, 1H), 7.35 (d, \( J = 2.1 \) Hz, 1H), 6.47 (d, \( J = 8.3 \) Hz, 1H), 4.59 (s, 2H), 4.21 (s, 2H), 0.15 (s, 9H).
Aminoacetophenone (10 g, 73.96 mmol) was dissolved in Ac₂O, stirred for 2 hours and concentrated. The residue was then dissolved in DCM, treated with Br₂ (6 mL), allowed to stir for 3 hours, quenched with water, filtered, and the collected solid was washed with water. The solid residue was transferred to a round bottomed flask, dissolved in 2 M HCl (200 mL), and the solution was heated at 90 °C for 4 hours. The solution was allowed to reach room temperature, basified to pH 12, extracted with EtOAc (3 x 50 mL), dried over Na₂SO₄, and concentrated yielding 13.5 g (85%) of the product. ¹H NMR (500 MHz, CDCl₃) δ 7.82 (s, 1H), 7.35 (d, J = 8.8 Hz, 1H), 6.58 (d, J = 8.8, 0.9 Hz, 1H), 6.32 (s, 2H), 2.58 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 199.6, 149.1, 137.0, 134.1, 119.4, 119.0, 106.6, 27.8.

N-(4-bromo-5,6,7,8-tetrahydro-1-naphthalen-1-yl)acetamide (S8):

5,6,7,8-Tetrahydro-1- naphthylamine (3.0 mL, 21.6 mmol) in EtOH (10 mL) was added dropwise to an ice-cooled solution of acetic anhydride (4.08 mL, 43.2 mmol) in EtOH (40 mL). The mixture was stirred for 16 hours at room temperature. Subsequently, the solvent was removed under reduced pressure to yield N-(5,6,7,8- tetrahydro-1-naphthyl)-acetamide as a white solid which was used without further purification ¹H NMR (500 MHz, CDCl₃) δ = 7.63 (d, J=7.9, 1H), 7.15 (t, J=7.8, 1H), 6.95 (d, J=7.5, 1H), 6.89 (s, 1H), 2.81 (m, 2H), 2.62 (m, 2H), 2.23 (s, 3H), 1.87 (m, 2H), 1.80 (m, 2H). To a cooled solution of N-(5,6,7,8-
tetrahydro-1-naphthyl)-acetamide in AcOH (55 mL) was slowly added a solution of Br₂ (3.36 mL, 65.2 mmol) in AcOH (4 mL) so that the temperature remained below 17 °C. The reaction mixture was then allowed to stir at room temperature for 24 hours. The mixture was poured over ice water, the resulting suspension was filtered, and the collected solid was washed with water. The solid was dissolved in DCM (200 mL) and H₂O (50 mL), the organic phase was separated, and the aqueous phase was extracted with DCM (3 x 100 mL). The organic phases were combined, dried over Na₂SO₄, filtered, and concentrated yielding 6.98 g (99.6%) of the product. ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, J = 8.6 Hz, 1H), 7.43 (d, J = 8.6 Hz, 1H), 6.89 (s, 1H), 2.77 (m, 2H), 2.61 (m, 2H), 2.24 (s, 3H), 1.81 (m, 4H).

N-(4-Bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (S9):
N-(4-bromo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (3.09 g, 11.5 mmol) in acetone (80 mL) and 15% aqueous MgSO₄ (1.90 g, 15.8 mmol in 11 mL of H₂O) was treated with KMnO₄ (5.47 g, 34.6 mmol) in portions. The mixture was allowed to stir for 12 hours, filtered through Celite®, and the solids were washed with CHCl₃ (100 mL) and H₂O (100 mL). The aqueous layer was extracted with CHCl₃ (4 x 100 mL). The organic fractions were combined, washed with brine, and dried over Na₂SO₄, and concentrated yielding 1.90 g (58.6%) of the desired product. ¹H NMR (500 MHz, CDCl₃) δ 12.16 (s, 1H), 8.58 (d, J = 9.1 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 3.06 (t, J = 6.2 Hz, 2H), 2.72 (m, 2H), 2.25 (s, 3H), 2.14 (m, 2H).
**8-Amino-5-bromo-3,4-dihydronaphthalen-1(2H)-one (3.8):** A stirred solution of N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (1.90 g, 6.74 mmol) in 6M HCl (100 mL) was heated at 90 °C for 8 hours. The mixture was cooled to room temperature and the volatiles were removed under vacuum. Ice was added to the mixture, followed by 2M NaOH until pH of 8 was reached. The aqueous layer was extracted with EtOAc, the organic fractions were combined, washed with brine, dried, filtered, and the concentrated to give 1.26 g of the product (77.9%). $^1$H NMR (500 MHz, CDCl$_3$) δ 7.39 (d, $J = 8.9$ Hz, 1H), 6.55 (s, 2H), 6.43 (d, $J = 8.8$ Hz, 1H), 2.96 (t, $J = 6.2$ Hz, 2H), 2.65 (m, 2H), 2.08 (m, 2H).

**Photoprecursors synthesis**

![Diagram of photoprecursors synthesis](image)

**General procedure for the reaction of 2-furanpropanoyl chloride with amines (FC):** A crude solution of 2-furanpropanoyl chloride (1.2 -1.5 eq) in dry THF (25 mL) was added dropwise to an ice-cooled stirred solution of substituted anilines (1 eq) and anhydrous pyridine (1.1 eq) in THF (50 mL). The solution was allowed to reach room temperature and left to stir overnight. The reaction mixture was then diluted with water (100 mL), extracted with EtOAc (4 x100 mL), the combined organic fractions were
washed with 10% NaOH (100 mL), dried over Na₂SO₄, filtered, and concentrated. The product was purified when necessary using flash chromatography.

**General procedure for the synthesis of and N-(2-acetylphenyl)-2-bromoacetamides (BB):** Bromoacetyl bromide (1.1 eq) in dry DCM (10 mL) was slowly added to a stirred solution of amine (1 eq), pyridine (1.1 eq) in dry DCM (20 mL) at 0°C under nitrogen atmosphere. The reaction mixture was left stirring overnight, then it was quenched with water (10 mL) and the aqueous phase was extracted with DCM (2x75 mL). Combined organic layers were dried over Na₂SO₄ and concentrated, giving the crude product, which was used further without purification.

**N-(4-chloro-2-formylphenyl)-3-(furan-2-yl)propanamide (3.3c):** General procedure FC was followed using 2-furanpropanoyl chloride (6) (0.51 g, 3.2 mmol, 1 eq), 2-amino-5-chlorobenzyl alcohol (0.50 g, 3.2 mmol, 1 eq) and anhydrous pyridine (0.28 mL, 3.5 mmol) in THF (10 mL). The workup and purification by flash chromatography yielded 0.67 g (2.4 mmol, 75%) of N-(4-chloro-2-(hydroxymethyl)phenyl)-3-(furan-2-yl)propanamide. ¹H NMR (500 MHz, CDCl₃) δ 8.45 (s, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.36 (m, 1H), 7.31 (dd, J = 8.7, 2.4 Hz, 1H), 7.20 (d, J = 2.4 Hz, 1H), 6.32 (t, J = 2.4 Hz, 1H), 6.11 (d, J = 3.2 Hz, 1H), 4.62 (d, J = 4.5 Hz, 2H), 3.11 (t, J = 7.4 Hz, 2H), 2.77 (t, J = 7.4 Hz, 2H), 2.07 (s, 1H). To a stirred solution of N-(4-chloro-2-(hydroxymethyl)phenyl)-3-(furan-2-yl)propanamide (0.67 g, 2.4
mmol) in dry DCM (100 mL) was added PCC (0.78 g, 3.6 mmol). The reaction mixture was left stirring overnight, filtered through a layer of silica gel, and evaporated yielding 0.64 g (2.3 mmol, 54% over two steps) of the title compound. $^1$H NMR (500 MHz, CDCl$_3$) δ 11.08 (s, 1H), 9.88 (d, $J = 0.7$ Hz, 1H), 8.77 (d, $J = 9.0$ Hz, 1H), 7.66 (d, $J = 2.5$ Hz, 1H), 7.58 (dd, $J = 9.1$, 2.5 Hz, 1H), 7.34 (dd, $J = 1.9$, 0.9 Hz, 1H), 6.30 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.09 (m, 1H), 3.11 (m, 2H), 2.84 (m, 2H).

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 194.3, 171.2, 153.8, 141.3, 139.3, 136.0, 135.0, 128.0, 122.5, 121.6, 110.2, 105.6, 36.5, 23.6.

**Methyl 5-bromo-2-(3-(furan-2-yl)propanamido)benzoate**

(S10): General procedure FC was followed using 2-furanpropanoyl chloride (1.2 eq, 1.67 g, 10.5 mmol), **methyl 2-amino-5-bromobenzoate** (1 eq, 2.00 g, 8.6 mmol) and anhydrous pyridine (1.1 eq, 0.76mL, 9.5mmol). The workup yielded 3.00 g (99%) of the product. $^1$H NMR (500 MHz, CDCl$_3$) δ 11.05 (s, 1H), 8.68 (d, $J = 9.1$ Hz, 1H), 8.17 (d, $J = 2.5$ Hz, 1H), 7.65 (dd, $J = 9.1$, 2.5 Hz, 1H), 7.33 (dd, $J = 1.9$, 0.8 Hz, 1H), 6.29 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.09 (m, 1H), 3.96 (s, 3H), 3.11 (m, 2H), 2.81 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.7, 167.6, 154.0, 141.3, 140.5, 137.4, 133.3, 122.1, 116.4, 114.8, 110.2, 105.5, 52.7, 36.7, 23.7.
N-(4-Bromo-2-formylphenyl)-3-(furan-2-yl)propanamide (3.3a): To a suspension of LiAlH₄ (0.88 g, 23 mmol) in THF (12 mL) at -78 °C under nitrogen atmosphere was added methyl 5-bromo-2-(3-(furan-2-yl)propanamido)benzoate (4.29 g, 12.2 mmol) dissolved in THF (24 mL). The mixture was allowed to stir overnight, treated with water (1 mL), 10% NaOH (1 mL), followed by an additional allotment of water (3 mL), and dried over Na₂SO₄. The solvent was filtered and concentrated yielding 3.52 g of N-(4-bromo-2-(hydroxymethyl)phenyl)-3-(furan-2-yl)propanamide which was used without further purification. ¹H NMR (500 MHz, CDCl₃) δ 8.50 (s, 1H), 7.98 (d, J = 8.7 Hz, 1H), 7.45 (dd, J = 8.7, 2.4 Hz, 1H), 7.35 (m, 2H), 6.32 (dd, J = 3.1, 1.9 Hz, 1H), 6.11 (m, 1H), 4.61 (s, 2H), 3.10 (t, J = 7.4 Hz, 2H), 2.76 (t, J = 7.4 Hz, 2H), 2.21 (s, 1H). ¹³C NMR (126 MHz, CDCl₃) δ 170.4, 154.0, 141.3, 136.4, 131.9, 131.5, 131.4, 124.2, 116.9, 110.4, 105.8, 63.8, 36.2, 24.0. To the alcohol (3.52 g) in dry DCM (250 mL) was added PCC (2.63 g, 12.2 mmol). The reaction mixture was left stirring overnight, filtered through a layer of silica gel, and evaporated yielding 2.11 g (53%) of the product over two steps. ¹H NMR (500 MHz, CDCl₃) δ 11.08 (s, 1H), 9.87 (s, 1H), 8.72 (d, J = 8.9 Hz, 1H), 7.80 (d, J = 2.4 Hz, 1H), 7.72 (dd, J = 9.0, 2.4 Hz, 1H), 7.34 (dd, J = 1.9, 0.9 Hz, 1H), 6.30 (dd, J = 3.2, 1.9 Hz, 1H), 6.09 (m, 1H), 3.11 (m, 2H), 2.84 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 194.2, 171.2, 153.8, 141.3, 136.4, 131.9, 138.9, 138.0, 122.9, 121.9, 115.0, 110.2, 105.6, 36.5, 23.6. HRMS (ESI) calcd for C₁₄H₁₃BrNO₃⁺ (MH⁺) 322.0073, found 322.0067.
N-(5-bromo-2-formylphenyl)-3-(furan-2-yl)propanamide (3.9): General procedure FC was followed using 2-furanpropanoyl chloride (0.90 g, 5.7 mmol), 5-bromo-2-((trimethylsilyloxy)methyl)aniline (1.11 g, 4.05 mmol) and anhydrous pyridine (0.49 mL, 6.1 mmol). Upon workup 1.27 g of N-(5-bromo-2-(hydroxymethyl)phenyl)-3-(furan-2-yl)propanamide was isolated, which was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.68 (s, 1H), 8.31 (d, $J = 1.2$ Hz, 1H), 7.35 (dd, $J = 1.9$, 0.9 Hz, 1H), 7.20 (dd, $J = 8.1$, 2.2 Hz, 1H), 7.02 (d, $J = 8.1$ Hz, 1H), 6.32 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.10 (m, 1H), 4.60 (s, 2H), 3.08 (m, 2H). To N-(5-bromo-2-(hydroxymethyl)phenyl)-3-(furan-2-yl)propanamide (1.27 g, 3.71 mmol) in DCM (90 mL) was added PCC (4.80 g, 22.3 mmol). The reaction mixture was left stirring for 12 h, filtered through a layer of silica gel using EtOAc, concentrated, and the mixture was subjected to flash chromatography yielding 0.40 g (24%) of the product over four steps. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.22 (s, 1H), 9.89 (s, 1H), 9.05 (d, 1H), 7.53 (d, $J = 8.2$ Hz, 1H), 7.39 (dd, $J = 8.2$, 1.8 Hz, 1H), 7.34 (dd, $J = 1.9$, 0.9 Hz, 1H), 6.30 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.10 (m, 1H), 3.11 (m, 2H), 2.84 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 194.6, 171.3, 153.8, 141.4, 141.3, 136.8, 131.9, 126.3, 123.0, 120.2, 110.2, 105.6, 36.4, 23.5. HRMS (ESI) calcd for C$_{14}$H$_{13}$BrNO$_3^+$ (MH$^+$) 322.0073, found 322.0080.
N-(2-Formyl-4-iodophenyl)-3-(furan-2-yl)propanamide

(3.3d): General procedure FC was followed using 2-furanpropanoyl chloride (0.79 g, 5.0 mmol), 4-iodo-2-((trimethylsilyloxy)methyl)aniline (0.94 g, 2.9 mmol) and dry pyridine (0.40 mL, 5.0 mmol) in THF (10 mL). Upon workup 0.90 g of N-(4-iodo-2-(hydroxymethyl)phenyl)-3-(furan-2-yl)propanamide was isolated which was used without further purification. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.50 (s, 1H), 7.89 (d, \(J = 8.5\) Hz, 1H), 7.65 (dd, \(J = 8.6, 2.1\) Hz, 1H), 7.53 (d, \(J = 2.2\) Hz, 1H), 7.36 (dd, \(J = 1.9, 0.9\) Hz, 1H), 6.32 (dd, \(J = 3.2, 1.9\) Hz, 1H), 6.10 (m, 1H), 4.60 (d, \(J = 5.7\) Hz, 2H), 3.10 (t, \(J = 7.4\) Hz, 2H), 2.76 (t, \(J = 7.4\) Hz, 2H), 2.10 (s, 1H). To N-(4-iodo-2-(hydroxymethyl)phenyl)-3-(furan-2-yl)propanamide (0.90 g) in DCM (60 mL) was added PCC (3.15 g, 14.6 mmol). The reaction mixture was left stirring for 8 hours, filtered through a layer of silica gel using EtOAc, concentrated, and the mixture was subjected to flash chromatography yielding 0.37 g (34%) of the product over two steps. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 11.08 (s, 1H), 9.85 (s, 1H), 8.58 (d, \(J = 8.9\) Hz, 1H), 7.97 (d, \(J = 2.2\) Hz, 1H), 7.89 (dd, \(J = 8.9, 2.2\) Hz, 1H), 7.33 (dd, \(J = 1.8, 0.9\) Hz, 1H), 6.29 (dd, \(J = 3.2, 1.9\) Hz, 1H), 6.09 (m, 1H), 3.11 (m, 2H), 2.83 (m, 2H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 194.2, 171.2, 153.8, 144.6, 144.1, 141.4, 140.4, 123.3, 122.0, 110.2, 105.6, 84.7, 36.6, 23.6. HRMS (ESI) calcd for C\(_{14}\)H\(_{13}\)INO\(_3\)^+ (MH\(^+\)) 369.9935, found 369.9945.
N-(2-acetyl-4-bromophenyl)-3-(furan-2-yl)propanamide (3.12): General procedure FC was followed using 2-furanpropanoyl chloride (2 eq, 0.72 g, 2.8 mmol), 1-(2-amino-5-bromophenyl)ethanone (1 eq, 0.30 g, 1.4 mmol) and anhydrous pyridine (1.5 eq, 0.17 mL, 2.1 mmol). The concentration yielded 0.45 g (93%) of the product. $^1$H NMR (500 MHz, CDCl$_3$) δ 11.66 (s, 1H), 8.73 (d, $J = 9.0$ Hz, 1H), 8.01 (d, $J = 2.4$ Hz, 1H), 7.66 (dd, $J = 9.1$, 2.4 Hz, 1H), 7.33 (dd, $J = 1.9$, 0.8 Hz, 1H), 6.29 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.08 (m, 1H), 3.10 (m, 2H), 2.81 (m, 2H), 2.68 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 201.6, 171.1, 154.0, 141.3, 139.9, 137.8, 134.0, 123.2, 122.6, 114.6, 110.2, 105.5, 36.7, 28.6, 23.7. HRMS (ESI) calcd for C$_{15}$H$_{15}$BrN$_2$O$_3$ (MH$^+$) 336.0230, found 336.0235.

N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)-3-(furan-2-yl)propanamide (3.13): General procedure FC was followed using 2-furanpropanoyl chloride (3.8 mmol), 8-amino-5-bromo-3,4-dihydronaphthalen-1(2H)-one (0.48 g, 2.0 mmol) and dry pyridine (0.18 mL, 2.2 mmol). Purification by flash chromatography yielded 0.38 g of the title compound (50%). $^1$H NMR (500 MHz, CDCl$_3$) δ 12.23 (s, 1H), 8.61 (d, $J = 9.1$ Hz, 1H), 7.72 (d, $J = 9.1$ Hz, 1H), 7.33 (dd, $J = 1.9$, 0.8 Hz, 1H), 6.29 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.08 (m, 1H), 3.10 (m, 2H), 3.06 (t, $J = 6.2$ Hz, 2H), 2.82 (m, 2H), 2.72 (m, 2H), 2.14 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 203.0, 171.2, 154.1,
HRMS (ESI) calcd for C_{17}H_{17}BrNO_{3}^{+} (MH^{+}) 362.0386, found 362.0382.

N-(2-(4-bromo-2-formylphenylamino)-2-oxoethyl)-N-(furan-2-ylmethyl)pivalamide (S11): General procedure BB was followed using 4-bromo-2-((trimethylsilyl)methyl)aniline (2.28 g, 8.32 mmol), DIPEA (1.65 mL, 9.98 mmol) and bromoacetyl bromide (0.86 mL, 9.9 mmol). The workup yielded 2-bromo-N-(4-bromo-2-(hydroxymethyl)phenyl)acetamide (3.07 g) which was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.51 (s, 1H), 8.02 (d, $J$ = 8.7 Hz, 1H), 7.50 (dd, $J$ = 8.7, 2.4 Hz, 1H), 7.39 (d, $J$ = 2.3 Hz, 1H), 4.75 (s, 2H), 4.06 (s, 2H). To N-(4-bromo-2-(hydroxymethyl)phenyl)acetamide (1.20 g) and DIPEA (0.71 mL, 4.1 mmol) in DCM (30 mL) was added furfuryl amine (0.49 mL, 5.5 mmol). The mixture was allowed to stir overnight, quenched with water (100 mL), the organic phase was separated, and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic fractions were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated yielding N-(4-bromo-2-(hydroxymethyl)phenyl)-2-(furan-2-ylmethy lamino)acetamide (1.53 g crude) which was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 10.07 (s, 1H), 8.02 (d, $J$ = 8.6 Hz, 1H), 7.45 (dd, $J$ = 8.6, 2.4 Hz, 1H), 7.41 (d, $J$ = 2.4 Hz, 1H), 7.39 (dd, $J$ = 1.9, 0.8 Hz, 1H), 6.36 – 6.34 (m, 1H), 6.28 – 6.27 (m, 1H), 4.66 (s, 2H), 3.88 (s, 2H), 3.47 (s, 2H). To N-(4-bromo-2-(hydroxymethyl)phenyl)-2-(furan-2-ylmethy lamino)acetamide (1.08 g) and DIPEA...
(0.30 mL, 1.8 mmol) in DCM (100 mL) was added pivaloyl chloride (0.19 mL, 1.5 mmol). The mixture was allowed to stir overnight, quenched with water (100 mL), the organic phase was separated, and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by flash chromatography yielded 0.40 g (29%) of the product over three steps. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.11 (s, 1H), 7.88 (d, $J = 8.7$ Hz, 1H), 7.39 (dd, $J = 8.7$, 2.4 Hz, 1H), 7.37 (dd, $J = 1.8$, 0.8 Hz, 1H), 7.32 (d, $J = 2.4$ Hz, 1H), 6.36 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.32 (m, 1H), 4.79 (s, 2H), 4.60 (d, $J = 4.8$ Hz, 2H), 4.10 (s, 2H), 3.48 (s, 1H), 1.39 (s, 9H).

**N-(2-(4-bromo-2-formylphenylamino)-2-oxoethyl)-N-(furan-2-ylmethyl)pivalamide (3.14):** To a stirred solution of **N-(2-(4-bromo-2-formylphenylamino)-2-oxoethyl)-N-(furan-2-ylmethyl)pivalamide** (0.35 g, 0.83 mmol) in 40 mL of DCM was added MnO$_2$ (1.02 g, 11.7 mmol). After stirring for 24 hours the solution was filtered through Celite® and concentrated yielding the product (0.28 g, 0.67 mmol, 23% over four steps). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.19 (s, 1H), 9.85 (d, $J = 0.7$ Hz, 1H), 8.68 (d, $J = 9.0$ Hz, 1H), 7.79 (d, $J = 2.4$ Hz, 1H), 7.70 (dd, $J = 9.0$, 2.4 Hz, 1H), 7.34 (dd, $J = 1.8$, 0.9 Hz, 1H), 6.33 (dd, $J = 3.3$, 1.8 Hz, 1H), 6.31 (dd, $J = 3.3$, 0.9 Hz, 1H), 4.87 (s, 2H), 4.17 (s, 2H), 1.45 (s, 9H). HRMS (ESI) calcd for C$_{19}$H$_{22}$BrN$_2$O$_4$ $^+$ (MH$^+$) 421.0757, found 421.0757.
N-(2-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-ylamino)-2-oxoethyl)-N-(furan-2-ylmethyl)pivalamide (3.15):

General procedure BB was followed using 8-amino-5-bromo-3,4-dihydronaphthalen-1(2H)-one (1.15 g, 4.79 mmol), pyridine (0.77 mL, 9.56 mmol), bromoacetyl bromide (0.50 mL, 5.7 mmol). The workup yielded 2-bromo-N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (1.67 g) which was used without further purification. $^1$H NMR (500 MHz, CDCl3) $\delta$ 12.80 (s, 1H), 8.56 (d, $J = 9.1$ Hz, 1H), 7.76 (d, $J = 9.1$ Hz, 1H), 4.04 (s, 2H), 3.08 (t, $J = 6.2$ Hz, 2H), 2.76 (m, 2H), 2.16 (m, 2H). To 2-bromo-N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (1.67 g) and DIPEA (1.21 mL, 6.95 mmol) in DCM (75 mL) was added furfuryl amine (0.61 mL, 0.67 mmol). The mixture was allowed to stir overnight, quenched with water (50 mL), the organic phase was separated, and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic fractions were washed with brine, dried over Na$_2$SO$_4$, filtered, and concentrated yielding N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)-2-(furan-2-ylmethlamino)acetamide (1.60 g) which was used without further purification. $^1$H NMR (500 MHz, CDCl3) $\delta$ 12.85 (s, 1H), 8.66 (d, $J = 9.1$ Hz, 1H), 7.73 (d, $J = 9.1$ Hz, 1H), 7.38 (dd, $J = 1.9$, 0.9 Hz, 1H), 6.34 (dd, $J = 3.2$, 1.7 Hz, 1H), 6.29 (dd, $J = 3.2$, 0.8 Hz, 1H), 3.92 (s, 2H), 3.48 (s, 2H), 3.07 (t, $J = 6.2$ Hz, 2H), 2.73 (m, 2H), 2.14 (m, 2H). To N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)-2-(furan-2-ylmethlamino)acetamide (1.60 g) and DIPEA (0.96 mL, 5.5 mmol) in DCM (75 mL) was added pivaloyl chloride (0.68 mL, 5.5 mmol). The mixture was allowed to
stir overnight, quenched with water (75 mL), the organic phase was separated, and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered, and concentrated. Purification by flash chromatography yielded 0.43 g (19%) of the product over three steps. $^1$H NMR (500 MHz, CDCl$_3$) δ 12.35 (s, 1H), 8.57 (d, $J = 9.1$ Hz, 1H), 7.71 (d, $J = 9.1$ Hz, 1H), 7.36 (dd, $J = 1.8$, 0.9 Hz, 1H), 6.34 (dd, $J = 3.2$, 1.8 Hz, 1H), 6.29 (dd, $J = 3.3$, 0.9 Hz, 1H), 4.85 (s, 2H), 4.18 (s, 2H), 3.05 (t, $J = 6.2$ Hz, 2H), 2.70 (m, 2H), 2.12 (m, 2H), 1.42 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.6, 178.2, 168.5, 150.1, 144.1, 142.6, 140.8, 138.7, 120.2, 119.9, 117.9, 110.4, 109.0, 52.0, 46.2, 40.0, 39.2, 31.4, 28.6, 21.7. HRMS (ESI) calcd for C$_{22}$H$_{26}$BrN$_2$O$_4$ $^+$ (MH$^+$) 461.1070, found 461.1073.

N-benzyl-N-(2-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-ylamino)-2-oxoethyl)furan-2-carboxamide (3.16): General procedure BB was followed using 8-amino-5-bromo-3,4-dihydronaphthalen-1(2H)-one (0.42 g, 1.7 mmol), DIPEA (0.36 mL, 2.1 mmol) and bromoacetyl bromide (0.18 mL, 2.1 mmol). The workup yielded 2-bromo-N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (0.70 g) which was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 12.80 (s, 1H), 8.56 (d, $J = 9.1$ Hz, 1H), 7.76 (d, $J = 9.1$ Hz, 1H), 4.04 (s, 2H), 3.08 (t, $J = 6.2$ Hz, 2H), 2.76 (m, 2H), 2.16 (m, 2H). To 2-bromo-N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (0.70 g) and DIPEA (0.34 mL, 2.0 mmol) in DCM (40 mL) was added
benzyl amine (0.29 mL, 2.7 mmol). The mixture was allowed to stir overnight, quenched with water (50 mL), the organic phase was separated, and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic fractions were dried over Na₂SO₄, filtered, and concentrated yielding 2-(benzylamino)-N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (0.88 g) ¹H NMR (500 MHz, CDCl₃) δ 12.92 (s, 1H), 8.67 (d, J = 9.1, 0.7 Hz, 1H), 7.72 (d, J = 9.1 Hz, 1H), 7.47 (m, 2H), 7.37 (m, 3H), 3.93 (s, 2H), 3.50 (s, 2H), 3.07 (t, J = 6.2 Hz, 2H), 2.75 (m, 2H), 2.15 (m, 2H). To 2-(benzylamino)-N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)acetamide (0.88 g) and DIPEA (0.44 mL, 2.5 mmol) in DCM (45 mL) was added 2-furoyl chloride (0.27 mL, 2.7 mmol). The mixture was allowed to stir overnight, quenched with water (50 mL), the organic phase was separated, and the aqueous layer was extracted with DCM (3 x 100 mL). The combined organic fractions were dried over Na₂SO₄, filtered, and concentrated. Purification by flash chromatography yielded 0.32 g (39%) of the product over three steps. ¹H NMR (500 MHz, CDCl₃) ¹H NMR (500 MHz, CDCl₃) δ 12.68 (m, 1H), 8.63 (d, J = 8.8 Hz, 1H), 7.74 (d, J = 9.1 Hz, 1H), 7.50 (m, 1H), 7.36 (m, 5H), 7.21 (m, 1H), 6.51 (m, 1H), 5.04 (m, 2H), 4.28 (m, 2H), 3.05 (m, 2H), 2.69 (m, 2H), 2.12 (m, 2H). ¹³C NMR (126 MHz, CDCl₃) δ 202.8, 163.5, 144.6, 144.3, 140.7, 138.8, 136.5, 136.2, 135.0, 129.1, 128.9, 128.9, 128.4, 127.8, 127.8, 120.3, 119.7, 118.1, 111.6, 52.2, 46.6, 40.0, 31.4, 21.7. HRMS (ESI) calcd for C₂₄H₂₂BrN₂O₄⁺ (MH⁺) 481.0757, found 481.0758.
N-(2-formyl-4-(pyridin-3-yl)phenyl)-3-(furan-2-yl)propanamide (3.3b): General procedure for Suzuki coupling SPy with pyridine boronic acid using pyridine-3-boronic acid (0.39 g, 3.2 mmol), Pd$_2$(dba)$_3$ (0.035 g, 0.038 mmol), PCy$_3$ (0.027 g, 0.096 mmol), and N-(4-bromo-2-(hydroxymethyl)phenyl)-3-(furan-2-yl)propanamide (0.61 g, 1.9 mmol), dioxane (5.0 mL), and aqueous K$_3$PO$_4$ (5.0 mmol, 3.9 mL of a 1.27 M solution) was followed. The crude 3-(furan-2-yl)-N-(2-(hydroxymethyl)-4-(pyridin-3-yl)phenyl)propanamide (0.60 g) was used without further purification. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.81 (s, 1H), 8.63 (s, 1H), 8.56 (dd, $J = 4.8, 1.1$ Hz, 1H), 8.25 (d, $J = 8.4$ Hz, 1H), 7.84 (ddd, $J = 7.9, 2.4, 1.6$ Hz, 1H), 7.52 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.37 (m, 3H), 6.33 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.13 (dd, $J = 3.1, 0.6$ Hz, 1H), 4.75 (s, 2H), 3.14 (t, $J = 7.5$ Hz, 2H), 2.81 (t, $J = 7.5$ Hz, 2H), 1.41 (s, 1H). To a stirred solution of 3-(furan-2-yl)-N-(2-(hydroxymethyl)-4-(pyridin-3-yl)phenyl)propanamide (0.60 g, 1.9 mmol) in DCM (45 mL) was added MnO$_2$ (2.28 g, 26.2 mmol). After 24 hours, the solution was filtered through Celite®, concentrated, and purified by flash chromatography yielding 0.31g (51%) of the product over two steps. $^1$H NMR (500 MHz, CDCl$_3$) δ 11.22 (s, 1H), 10.05 (s, 1H), 8.92 (d, $J = 8.7$ Hz, 1H), 8.90 (dd, $J = 2.4, 0.9$ Hz, 1H), 8.66 (dd, $J = 4.8, 1.6$ Hz, 1H), 7.91 (m, 2H), 7.86 (dd, $J = 8.7, 2.3$ Hz, 1H), 7.43 (ddd, $J = 7.9, 4.8, 0.9$ Hz, 1H), 7.35 (dd, $J = 1.9, 0.9$ Hz, 1H), 6.31 (dd, $J = 3.2, 1.9$ Hz, 1H), 6.11 (m, 1H), 3.14 (m, 2H), 2.88 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 195.3, 171.3, 153.9, 149.0, 147.9, 141.3, 140.6, 134.6, 134.5, 134.2, 133.9,
132.6, 123.7, 122.0, 120.8, 110.2, 105.6, 36.6, 23.6. HRMS (ESI) calcd for C$_{19}$H$_{17}$N$_2$O$_3^+$ (MH$^+$) 321.1234, found 321.1241.

**Irradiation and Suzuki coupling of the photoproducts**

*General Scheme and Procedure for the Irradiation and Subsequent Coupling of Bromo-Substituted Aromatic Compounds with Pyridine-3-Boronic Acid*

**General procedure for irradiation (I):** Solutions with ca. 6.0 mM of the photoprecursors 3.3a-3.3e, 3.9, 3.12-3.16 in 5% aq. acetonitrile were degassed by sparging with N$_2$ 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 $^1$H NMR. The solution was concentrated and the cycloaddition products were used without further purification.
General procedure for Suzuki coupling with pyridine-3-boronic acid (SPy): Aqueous K$_3$PO$_4$ (1.70 mmol, 1.33 mL of a 1.27 M solution), degassed by sparging with N$_2$ for 30 min, was added to the reaction mixture containing pyridine-3-boronic acid (1.1 mmol, 1.1 eq), Pd$_2$(dba)$_3$ (0.01 mmol, 0.9 mol%), PCy$_3$ (0.024 mmol, 2.2 mol%), and the heteroaryl bromide (1.0 mmol, 1.0 eq) in dioxane (2.67 mL) under nitrogen atmosphere. The mixture was refluxed for 36 hours with vigorous stirring, cooled to room temperature, filtered through a layer of silica gel using extra allotments of EtOAc, concentrated, diluted with water (40 mL) and extracted with EtOAc (3 x 75 mL). The combined organic fractions were dried over Na$_2$SO$_4$, filtered, concentrated, and the product(s) were purified using flash chromatography yielding the isolated coupling products.

General procedure for Suzuki coupling with phenylboronic acid (SPh): The heteroaryl halide (0.94 mmol, 1 eq) and Pd(PPh$_3$)$_4$ (5.3 mol%, 0.050 mmol), were suspended in dimethoxyethane (4 mL) the mixture was allowed to stir under nitrogen atmosphere for 10 min. Phenylboronic acid (1.17 eq, 1.1 mmol) followed by aq. Na$_2$CO$_3$ (1.06 mL, 2 M solution, 2.12 mmol) were added to the mixture, and the resulting solution was refluxed under nitrogen atmosphere for 24 hours. The mixture was allowed to cool to room temperature, extracted with Et$_2$O (6 x 40 mL), and the combined organic fractions were washed with water, dried over Na$_2$SO$_4$, concentrated, and subjected to flash chromatography.
General procedure for Suzuki coupling with thiophene-2- and furan-2-boronic acids (STF): To a stirred mixture of the heteroaryl iodide (0.20 g, 0.54 mmol) and Pd(PPh$_3$)$_4$ (5.2-5.8 mol%, 0.032 g, 0.028 mmol) in DME (16 mL) was added thiophene-2- or furan-2-boronic acid (0.077 g, 0.60 mmol). The mixture was placed under nitrogen atmosphere, and NaHCO$_3$ (0.095 g, 1.1 mmol) in H$_2$O (16 mL) was added. The reaction mixture was heated under reflux with vigorous stirring for 12 hours. Subsequently, the organic solvent was removed under reduced pressure, an extraction was performed on the remaining aqueous layer using EtOAc (5 x 25 mL), the combined organic fractions were dried using MgSO$_4$, filtered, concentrated, and subjected to flash chromatography.

**8-Hydroxy-5-phenyl-12-oxa-1-azatetracyclo[11.3.0.0$^{2,7}$.0$^{9,13}$]hexadeca-2,4,6,10-tetraen-16-one (3.4f):** General procedure I was followed. From N-(4-bromo-2-formylphenyl)-3-(furan-2-yl)propanamide (3.3a) (1.0 g, 3.1 mmol) a mixture 5-bromo-8-hydroxy-12-oxa-1-azatetracyclo[11.3.0.0$^{2,7}$.0$^{9,13}$]hexadeca-2,4,6,10-tetraen-16-one (3.4a) and 5-bromo-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0$^{3,8}$,0$^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (3.5a) in the ratio of 1:1 was formed, which was introduced into Suzuki coupling following the general procedure SPh. From 0.3 g of that mixture (0.94 mmol), phenylboronic acid (0.13 g, 1.1 mmol), Pd(PPh$_3$)$_4$ (0.058 g, 0.05 mmol) Na$_2$CO$_3$ (1.06 mL of a 2 M solution, 2.12 mmol) 0.089 g (30%) of the title compound and 0.13 g (44%)
of 2-hydroxy-5-phenyl-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.5f) were isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.98 (d, $J$ = 8.3 Hz, 1H), 7.64 (dd, $J$ = 8.3, 2.1 Hz, 1H), 7.59 (m, 2H), 7.46 (m, 3H), 7.38 (m, 1H), 6.27 (t, $J$ = 2.8 Hz, 1H), 4.84 (d, $J$ = 2.1 Hz, 1H), 4.70 (dd, $J$ = 3.1, 2.2 Hz, 1H), 3.89 (q, $J$ = 2.3 Hz, 1H), 2.86 (m, 1H), 2.59 (m, 1H), 2.47 (m, 2H), 2.19 (s, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.4, 146.7, 146.1, 138.8, 133.3, 131.3, 128.9, 128.2, 127.5, 127.4, 126.9, 123.5, 101.4, 99.4, 70.5, 56.1, 35.2, 29.8. HRMS (ESI) calcd for C$_{20}$H$_{18}$NO$_3$+ (MH$^+$) 320.1281, found 320.1281.

2-Hydroxy-5-phenyl-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.5f): General procedure I was followed. From N-(4-bromo-2-formylphenyl)-3-(furan-2-yl)propanamide (3.3a) (1.0 g, 3.1 mmol) a 5-bromo-8-hydroxy-12-oxa-1-azatetracyclo[11.2.0.0^{2,7}.0^{9,13}]hexadeca-2,4,6,10-tetraen-16-one (4a) and 5-bromo-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.5a) in the ratio of 1:1 was formed, which was introduced into Suzuki coupling following the general procedure SPh From 0.3 g of the mixture (0.94 mmol), phenylboronic acid (0.13 g, 1.1 mmol), Pd(PPh$_3$)$_4$ (0.058g, 0.05 mmol) Na$_2$CO$_3$ (1.06 mL of a 2 M solution, 2.12 mmol) 0.13 g (44%) of the title compound and 0.089 g (30%) of 8-hydroxy-5-phenyl-12-oxa-1-azatetracyclo[11.3.0.0^{2,7}.0^{9,13}]hexadeca-2,4,6,10-tetraen-16-one (3.4f) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.60 (m, 4H), 7.54 (m, 1H), 7.45 (m, 2H), 7.38 (m, 1H), 6.36 (dd, $J$ = 5.9, 1.9 Hz, 1H), 5.70 (dd, $J$ =
5.8, 1.1 Hz, 1H), 5.09 (m, 1H), 4.75 (d, $J = 7.0$ Hz, 1H), 3.15 (s, 1H), 2.89 (m, 1H), 2.65 (m, 1H), 2.57 (dt, $J = 13.8, 9.8$, 1H), 2.48 (ddd, $J = 13.9, 9.5, 1.7$, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.2, 139.9, 139.5, 134.8, 133.5, 131.6, 131.2, 129.3, 128.8, 128.0, 127.5, 127.2, 127.0, 103.6, 83.7, 79.5, 30.0, 28.9. HRMS (ESI) calcd for C$_{20}$H$_{18}$NO$_3$+ (MH$^+$) 320.1281, found 320.1283.

8-Hydroxy-5-pyridin-3-yl-12-oxa-1-azatetracyclo[11.3.0.0$^{2,7}$,0$^{9,13}$]hexadeca-2,4,6,10-tetraen-16-one (3.4b): Pathway A: 0.25 g (0.78 mmol) of N-(2-formyl-4-(pyridin-3-yl)phenyl)-3-(furan-2-yl)propanamide (3.3b) was irradiated following the general procedure I. Flash chromatography resulted in an isolated yield of 0.12 g (47%) of the title compound and 0.10 g (40%) of 2-Hydroxy-5-pyridin-2-yl-16-oxa-9-azatetracyclo[11.2.1.0$^{3,8}$,0$^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (3.5b).

Pathway B: 0.34 g (1.1 mmol) of N-(4-bromo-2-formylphenyl)-3-(furan-2-yl)propanamide (3.3a) was irradiated following general procedure I yielding a mixture of a 5-bromo-8-hydroxy-12-oxa-1-azatetracyclo[11.3.0.0$^{2,7}$,0$^{9,13}$]hexadeca-2,4,6,10-tetraen-16-one (3.4a) and 5-bromo-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0$^{3,8}$,0$^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (3.5a) in the ratio of 1:1. 0.34 g of the mixture was then introduced into Suzuki coupling following general procedure SPy using pyridine-3-boronic acid (0.23 g, 1.9 mmol), Pd$_2$(dba)$_3$ (0.021 g,
0.023 mmol), PCy$_3$ (0.016 g, 0.057 mmol), dioxane (3.1 mL), and aqueous K$_3$PO$_4$ (2.86 mmol, 2.3 mL of a 1.27 M solution) resulting in an isolated yield of 0.024 g, (6.8%) of the title compound and 0.10 g (28%) of 2-Hydroxy-5-pyridin-2-yl-16-oxa-9-azatetracyclo[11.2.1.0$^{3,8}$,0$^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (3.5b) ¹H NMR (500 MHz, CDCl$_3$) δ 8.64 (d, $J = 2.4$ Hz, 1H), 8.56 (dd, $J = 4.8$, 1.6 Hz, 1H), 8.05 (d, $J = 8.3$ Hz, 1H), 7.83 (ddd, $J = 8.0$, 2.4, 1.6 Hz, 1H), 7.57 (dd, $J = 8.3$, 2.1 Hz, 1H), 7.41 (d, $J = 2.1$ Hz, 1H), 7.36 (ddd, $J = 8.0$, 4.8, 0.9 Hz, 1H), 6.29 (t, $J = 2.8$ Hz, 1H), 4.88 (d, $J = 2.2$ Hz, 1H), 4.71 (dd, $J = 3.1$, 2.3 Hz, 1H), 3.93 (q, $J = 2.3$ Hz, 1H), 2.90 (ddd, $J = 16.1$, 10.3, 8.2 Hz, 1H), 2.56 (m, 3H), 1.64 (s, 1H). ¹³C NMR (126 MHz, CDCl$_3$) δ 173.3, 148.4, 148.0, 146.8, 135.7, 135.1,134.4, 134.2, 131.8, 128.2, 127.4, 123.8, 123.6, 101.4, 99.4, 70.3, 56.1, 35.2, 29.8 HRMS (ESI) calcd for C$_{19}$H$_{17}$N$_2$O$_3^+$ (MH$^+$) 321.1234, found 321.1241.

2-Hydroxy-5-pyridin-2-yl-16-oxa-9-
azatetracyclo[11.2.1.0$^{3,8}$,0$^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (3.5b): Pathway A: 0.25 g (0.78 mmol) of N-(2-formyl-4-(pyridin-3-yl)phenyl)-3-(furan-2-yl)propanamide was irradiated following the general procedure I. Flash chromatography resulted in an isolated yield of 0.12 g (47%) of 8-hydroxy-5-(pyridin-3-yl)-12-oxa-1-
azatetracyclo[11.3.0.0$^{2,7}$,0$^{9,13}$]hexadeca-2,4,6,10-tetraen-16-one (3.4b) and 0.10 g (40%) of the title compound.
Pathway B: 0.34 g (1.1 mmol) of N-(4-Bromo-2-formylphenyl)-3-(furan-2-yl)propanamide (3.3a) was irradiated following general procedure for irradiation yielding a mixture of a 5-bromo-8-hydroxy-12-oxa-1-azatetracyclo[11.3.0.0^2,7.0^9,13]hexadeca-2,4,6,10-tetraen-16-one (4a) and 5-bromo-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0^3,8.0^5,9]hexadeca-3,5,7,14-tetraen-10-one (3.5a) in the ratio of 1:1. 0.34 g of the mixture was then subjected to general procedure SPy using pyridine-3-boronic acid (0.23 g, 1.9 mmol), Pd\(_2\)(dba)\(_3\) (0.021 g, 0.023 mmol), PCy\(_3\) (0.016 g, 0.057 mmol), dioxane (3.1 mL), and aqueous K\(_3\)PO\(_4\) (2.86 mmol, 2.3 mL, 1.27 M solution) resulting in an isolated yield of 0.024 g (6.8%) of 8-hydroxy-5-pyridin-3-yl-12-oxa-1-azatetracyclo[11.3.0.0^2,7.0^9,13]hexadeca-2,4,6,10-tetraen-16-one (3.4b) and 0.10 g (28%) of the title compound. \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.83 (d, \(J = 2.1\) Hz, 1H), 8.61 (dd, \(J = 4.8, 1.6\) Hz, 1H), 7.88 (dt, \(J = 8.0, 1.9\) Hz, 1H), 7.65 (d, \(J = 8.3\) Hz, 1H), 7.58 (dd, \(J = 8.4, 2.2\) Hz, 1H), 7.53 (d, \(J = 2.2\) Hz, 1H), 7.39 (ddd, \(J = 7.9, 4.8, 0.9\) Hz, 1H), 6.38 (dd, \(J = 5.8, 1.8\) Hz, 1H), 5.71 (dd, \(J = 5.8, 1.2\) Hz, 1H), 5.10 (m, 1H), 4.76 (d, \(J = 3.3\) Hz, 1H), 2.91 (dt, \(J = 17.2, 9.7\) Hz, 1H), 2.67 (ddd, \(J = 17.2, 9.8, 1.8\) Hz, 1H), 2.58 (dt, \(J = 13.8, 9.8\) Hz, 1H), 2.50 (ddd, \(J = 13.8, 9.5, 1.8\) Hz, 1H). \(^1^3\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 173.3, 148.7, 148.1, 136.0, 135.4, 134.8, 134.2, 133.9, 132.5, 131.2, 129.3, 128.4, 127.2, 123.6, 103.6, 83.6, 79.4, 30.0, 28.9. HRMS (ESI) calcd for C\(_{19}\)H\(_{17}\)N\(_2\)O\(_3\)\(^+\) (MH\(^+\)) 321.1234, found 321.1241.
8-Hydroxy-6-(pyridin-3-yl)-12-oxa-1-azatetracyclo[11.3.0.0^{2.7}.0^{9,13}] hexadeca-2,4,6,10-tetraen-16-one (3.17b): General procedure I was followed using 0.25 g (0.78 mmol) of N-(5-bromo-2-formylphenyl)-3-(furan-2-yl)propanamide (3.9) yielding a mixture of 6-bromo-8-hydroxy-12-oxa-1-azatetracyclo[11.3.0.0^{2.7}.0^{9,13}]hexadeca-2,4,6,10-tetraen-16-one (3.17a) and 6-bromo-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0^{3.8}.0^{5.9}]hexadeca-3,5,7,14-tetraen-10-one (3.18a) in the ratio of 1:0.8. 0.25 g of the mixture was then subjected to general procedure for Suzuki coupling using pyridine-3-boronic acid (0.14 g, 1.1 mmol), Pd$_2$(dba)$_3$ (0.014 g, 0.015 mmol), PCy$_3$ (0.012 g, 0.043 mmol), dioxane (2.25 mL), and aqueous K$_3$PO$_4$ (0.73 mmol, 0.97 mL of a 1.27 M solution) resulting in an isolated yield of 0.072 g (28%) of the title compound and 0.059 g (23%) of 2-hydroxy-6-(pyridin-3-yl)-16-oxa-9-azatetracyclo[11.2.1.0^{3.8}.0^{5.9}]hexadeca-3,5,7,14-tetraen-10-one (3.18b)

$^1$H NMR (500 MHz, CDCl$_3$) δ 8.53 (d, $J = 4.8$ Hz, 1H), 8.41 (s, 1H), 8.12 (d, $J = 1.7$ Hz, 1H), 7.89 (ddd, $J = 7.9, 2.4, 1.6$ Hz, 1H), 7.33 (m, 2H), 6.28 (t, $J = 2.8$ Hz, 1H), 4.86 (d, $J = 2.2$ Hz, 1H), 4.71 (dd, $J = 3.0, 2.2$ Hz, 1H), 3.93 (q, $J = 2.4$ Hz, 1H), 2.88 (m, 1H), 2.56 (m, 4H), 1.64 (s, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.3, 148.3, 148.0, 146.7, 139.1, 135.0, 134.7, 131.0, 129.5, 124.3, 123.6, 121.9, 101.5, 99.5, 69.8, 56.2, 35.2, 29.9.

HRMS (ESI) calcd for C$_{19}$H$_{17}$N$_2$O$_3$ (MH$^+$) 321.1234, found 321.1237.
2-Hydroxy-6-(pyridin-3-yl)-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.18b): General procedure I was followed using 0.25 g (0.78 mmol) of N-(5-bromo-2-formylphenyl)-3-(furan-2-yl)propanamide (3.9) yielding a mixture of 6-bromo-8-hydroxy-12-oxa-1-azatetracyclo[11.3.0.0^{2,7},0^{9,13}]hexadeca-2,4,6,10-tetraen-16-one (3.17a) and 6-bromo-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.18a) in the ratio of 1:0.8. 0.25 g of the mixture was then subjected to general procedure for Suzuki coupling SPy using pyridine-3-boronic acid (0.14 g, 1.1 mmol), Pd$_2$(dba)$_3$ (0.014 g, 0.015 mmol), PCy$_3$ (0.012 g, 0.043 mmol), dioxane (2.25 mL), and aqueous K$_3$PO$_4$ (0.73 mmol, 0.97 mL of a 1.27 M solution) resulting in an isolated yield of 0.072 g (28%) of 8-hydroxy-6-(pyridin-3-yl)-12-oxa-1-azatetracyclo[11.3.0.0^{2,7},0^{9,13}]hexadeca-2,4,6,10-tetraen-16-one (3.17b) and 0.059 g (23%) of the title compound. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.84 (s, 1H), 8.61 (s, 1H), 7.91 (dt, $J$ = 8.0, 2.0 Hz, 1H), 7.76 (d, $J$ = 1.8 Hz, 1H), 7.43 (m, 2H), 7.38 (t, $J$ = 7.5, 4.8 Hz, 1H), 6.37 (dd, $J$ = 5.9, 1.9 Hz, 1H), 5.71 (dd, $J$ = 5.9, 1.2 Hz, 1H), 5.08 (m, 1H), 4.73 (s, 1H), 3.17 (s, 1H), 2.94 (m, 1H), 2.68 (ddd, $J$ = 17.3, 9.8, 1.8 Hz, 1H), 2.58 (dt, $J$=13.9, 9.8, 1H), 2.50 (ddd, $J$=13.9, 9.5, 1.8, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.1, 148.8, 148.2, 138.2, 134.8, 138.4, 134.5, 133.4, 133.2, 132.8, 129.3, 126.4, 125.1, 123.6, 103.7, 83.6, 79.0, 30.1, 28.9. HRMS (ESI) calcd for C$_{19}$H$_{17}$N$_2$O$_3^+$ (MH$^+$) 321.1234, found 321.1240.
8-Hydroxy-8-methyl-5-(pyridin-3-yl)-12-oxa-1-azatetracyclo[11.3.0.0^2,7.0^9,13]hexadeca-2,4,6,10-tetraen-16-one (3.19b): General procedure I was followed using 0.50 g (1.5 mmol) of N-(2-acetyl-4-bromophenyl)-3-(furan-2-yl)propanamide (3.10) yielding 0.50 g of a mixture of 5-bromo-8-hydroxy-8-methyl-12-oxa-1-azatetracyclo[11.3.0.0^2,7.0^9,13]hexadeca-2,4,6,10-tetraen-16-one (3.19a) and 5-bromo-2-hydroxy-2-methyl-16-oxa-9-azatetracyclo[11.2.1.0^3,8.0^5,9]hexadeca-3,5,7,14-tetraen-10-one (3.20a) in the ratio of 1:1. 0.25 g of the mixture was then subjected to general procedure for Suzuki coupling SPy using pyridine-3-boronic acid (0.14 g, 1.1 mmol), Pd$_2$(dba)$_3$ (0.014 g, 0.015 mmol), PCy$_3$ (0.012 g, 0.043 mmol), dioxane (2.25 mL), and aqueous K$_3$PO$_4$ (0.73 mmol, 0.97 mL of a 1.27 M solution) resulting in an isolated yield of 0.071 g, (28%) of the title compound and 0.072 g (30%) of 2-Hydroxy-2-methyl-3,4-(4'-pyridin-3-yl)benzo-12-oxa-5-azatricyclo[7.2.1.0^5,9]dodec-3,10-dien-6-one (3.20b). $^1$H NMR (500 MHz, CDCl$_3$) δ 8.43 (dd, $J = 4.8, 1.7$ Hz, 1H), 8.22 (d, $J = 2.4$ Hz, 1H), 7.94 (d, $J = 8.2$ Hz, 1H), 7.73 (ddd, $J = 7.9, 2.4, 1.6$ Hz, 1H), 7.43 (dd, $J = 8.2, 2.0$ Hz, 1H), 7.38 (d, $J = 2.1$ Hz, 1H), 7.28 (dd, $J = 7.8, 4.8$ Hz, 1H), 6.25 (t, $J = 2.8$ Hz, 1H), 4.65 (dd, $J = 3.1, 2.2$ Hz, 1H), 4.18 (s, 1H), 3.74 (t, $J = 2.4$ Hz, 1H), 2.85 (m, 1H), 2.52 (m, 3H), 1.79 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.3, 147.9, 147.8, 146.9, 136.1, 134.9, 134.5, 134.3, 134.3, 127.4, 124.1, 123.7, 123.5, 101.6, 99.1, 70.5, 61.3, 35.1, 29.8, 25.4. HRMS (ESI) calcd for C$_{20}$H$_{19}$N$_2$O$_5^+$ (MH$^+$) 335.1390, found 335.1396.
2-Hydroxy-2-methyl-5-(pyridin-3-yl)-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}] hexadeca-3,5,7,14-tetraen-10-one (3.20b): General procedure I was performed using 0.50 g (1.5 mmol) of N-(2-acetyl-4-bromophenyl)-3-(furan-2-yl)propanamide (3.10) yielding 0.50 g of a mixture of 5-bromo-8-hydroxy-8-methyl-12-oxa-1-azatetracyclo[11.3.0.0^{2,7}.0^{9,13}]hexadeca-2,4,6,10-tetraen-16-one (3.19a) and 5-bromo-2-hydroxy-2-methyl-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.20a) in the ratio of 1:1. 0.25 g of the mixture was then subjected to general procedure for Suzuki coupling SPy using pyridine-3-boronic acid (0.14 g, 1.1 mmol), Pd$_2$(dba)$_3$ (0.014 g, 0.015 mmol), PCy$_3$ (0.012 g, 0.043 mmol), dioxane (2.25 mL), and aqueous K$_3$PO$_4$ (0.73 mmol, 0.97 mL of a 1.27 M solution) resulting in an isolated yield of 0.071 g, (28%) of 8-hydroxy-8-methyl-5-(pyridin-3-yl)-12-oxa-1-azatetracyclo[11.3.0.0^{2,7}.0^{9,13}]hexadeca-2,4,6,10-tetraen-16-one (3.19b) and 0.072 g (30%) of the title compound. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.84 (s, 1H), 8.63 (s, 1H), 7.87 (dt, $J$ = 8.1, 1.8 Hz, 1H), 7.72 (d, $J$ = 1.9 Hz, 1H), 7.56 (m, 2H), 7.40 (dd, $J$ = 8.0, 4.7 Hz, 1H), 6.37 (dd, $J$ = 5.9, 1.9 Hz, 1H), 5.72 (dd, $J$ = 5.8, 1.1 Hz, 1H), 4.78 (t, $J$ = 1.4 Hz, 1H), 3.57 (s, 1H), 2.95 (dt, $J$ = 17.4, 9.8 Hz, 1H), 2.69 (ddd, $J$ = 17.4, 9.7, 1.8 Hz, 1H), 2.57 (dt, $J$=13.9, 9.9, 1H), 2.49 (ddd, $J$=13.9, 9.5, 1.8, 1H), 1.80 (s, 3H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 173.0, 148.6, 148.2, 137.1, 136.0, 136.0, 134.8, 134.3, 132.6, 129.3, 129.0, 126.9, 126.4, 123.6, 103.4, 89.2, 78.0, 30.2, 28.5, 24.7. HRMS (ESI) calcd for C$_{20}$H$_{19}$N$_2$O$_3^+$ (MH$^+$) 335.1390, found 335.1398.
11-Hydroxy-16-(pyridine-3-yl)-7-oxa-2-azapentacyclo[9.7.1.0^2.6.0^6.10.0^15.19]nonadeca-1(19),8,15(16),17-tetraen-3-one (3.21b): General procedure I was performed using 0.36 g (0.99 mmol) of \textit{N}-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)-3-(furan-2-yl)propanamide (3.11) yielding a mixture of 11-hydroxy-16-bromo-7-oxa-2-azapentacyclo[9.7.1.0^2.6.0^6.10.0^15.19]nonadeca-1(19),8,15(16),17-tetraen-3-one (3.21a) and 10-hydroxy-15-bromo-9-oxa-2-azapentacyclo[8.7.1.1^6.9.0^2.6.0^14.18]nonadeca-1(18),7,14(15),16(17)tetraen-3-one (3.22a) in the ratio of 1:1.9. 0.36 g of the mixture was then subjected to general procedure SPy using pyridine-3-boronic acid (0.14 g, 1.1 mmol), Pd\textsubscript{2}(dba)\textsubscript{3} (0.011 g, 0.012 mmol), PCy\textsubscript{3} (0.078 g, 0.028 mmol), dioxane (3.1 mL), and aqueous K\textsubscript{3}PO\textsubscript{4} (1.70 mmol, 1.34 mL of a 1.27 M solution) resulting in an isolated yield of 0.13 g, (36%) of the title compound and 0.057 g (16%) of 10-Hydroxy-15-(pyridine-3-yl)-9-oxa-2-azapentacyclo[8.7.1.1^6.9.0^2.6.0^14.18]nonadeca-1(18),7,14(15),16(17)tetraen-3-one (3.22b). \textit{H} NMR (500 MHz, CDCl\textsubscript{3}) δ 8.52 (dd, \textit{J} = 4.8, 1.6 Hz, 1H), 8.04 (s, 1H), 7.81 (d, \textit{J} = 8.2 Hz, 1H), 7.62 (ddd, \textit{J} = 7.8, 2.3, 1.6 Hz, 1H), 7.32 (ddd, \textit{J} = 7.8, 4.8, 0.9 Hz, 1H), 7.21 (d, \textit{J} = 8.2 Hz, 1H), 6.33 (t, \textit{J} = 2.8 Hz, 1H), 4.76 (dd, \textit{J} = 3.2, 2.2 Hz, 1H), 3.78 (t, \textit{J} = 2.4 Hz, 1H), 2.90 (m, 1H), 2.58 (m, 6H), 2.05 (m, 1H), 1.92 (td, \textit{J} = 13.0, 3.4 Hz, 1H), 1.84 (m, 1H), 1.67 (s, 1H). \textit{C} NMR (126 MHz, CDCl\textsubscript{3}) δ 173.4, 149.6, 147.9, 146.8, 136.7, 136.6, 135.7, 135.1, 134.2, 130.0, 129.6, 122.9, 121.5, 101.5, 99.4, 69.5, 60.0, 41.0, 35.2, 29.8, 28.7, 18.4. HRMS (ESI) calcd for C\textsubscript{22}H\textsubscript{21}N\textsubscript{2}O\textsubscript{3}\textsuperscript{+} (MH\textsuperscript{+}) 361.1547, found 361.1550.
10-Hydroxy-15-(pyridine-3-yl)-9-oxa-2-azapentacyclo[8.7.1.1^6.9.0^2.6.0^14.18]nonadeca-1(18),7,14(15),16(17)tetraen-3-one (3.22b): General procedure I was followed using 0.36 g (0.99 mmol) of N-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)-3-(furan-2-yl)propanamide (3.11) yielding a mixture of 11-hydroxy-16-bromo-7-oxa-2-azapentacyclo[9.7.1.0^2.6.0^6.10.0^15.19]nonadeca-1(19),8,15(16),17-tetraen-3-one (3.21a) and 10-hydroxy-15-bromo-9-oxa-2-azapentacyclo[8.7.1.1^6.9.0^2.6.0^14.18]nonadeca-1(18),7,14(15),16(17)tetraen-3-one (3.22a) in the ratio of 1:1.9. 0.36 g of the mixture was then subjected to general procedure SPy using pyridine-3-boronic acid (0.14 g, 1.1 mmol), Pd_2(dba)_3 (0.011 g, 0.012 mmol), PCy_3 (0.078 g, 0.028 mmol), dioxane (3.1 mL), and aqueous K_3PO_4 (1.70 mmol, 1.34 mL of a 1.27M solution) resulting in an isolated yield of 0.13 g, (36%) of 11-hydroxy-16-(pyridine-3-yl)-7-oxa-2-azapentacyclo[9.7.1.0^2.6.0^6.10.0^15.19]nonadeca-1(19),8,15(16),17-tetraen-3-one (3.21b) and 0.057 g (16%) of the title compound. \^H NMR (500 MHz, CDCl_3) δ 8.61 (dd, \(J=4.9, 1.7, 1H\)), 8.55 (dd, \(J=2.3, 0.9, 1H\)), 7.61 (dt, \(J=7.8, 2.0, 1H\)), 7.36 (dd, \(J=7.8, 4.9, 0.9, 1H\)), 7.28 (m, 1H), 7.15 (d, \(J=8.1, 1H\)), 6.43 (dd, \(J=5.8, 1.9, 1H\)), 5.76 (dd, \(J=5.9, 1.1, 1H\)), 4.62 (m, 1H), 3.51 (s, 1H), 3.03 (ddd, \(J=17.4, 10.3, 9.2, 1H\)), 2.71 (ddd, \(J=17.5, 9.6, 1.7, 1H\)), 2.56 (m, 4H), 2.09 (m, 1H), 1.99 (m, 1H), 1.77 (m, 1H), 1.69 (td, \(J=13.5, 3.1, 1H\)). \(^{13}C\) NMR (126 MHz, CDCl_3) δ 173.1, 149.9, 148.3, 137.5, 137.3, 136.5, 136.2, 135.3, 133.8, 129.6, 129.3, 126.4, 123.1, 103.2, 88.0, 75.4, 35.8, 30.4, 30.3, 29.7, 28.6, 17.8. HRMS (ESI) calcd for C_{22}H_{21}N_{2}O_3^+ (MH^+) 361.1547, found 361.1553.
8-Hydroxy-5-pyridin-3-yl-15-pivaloyl-12-oxa-1,15-diazatetracyclo[11.3.0.0^{27}.0^{9,13}]heptadeca-2,4,6,10-tetraen-17-one (3.23b): General procedure I was followed using 0.26 g (0.62 mmol) of N-(2-(4-bromo-2-formylphenylamino)-2-oxoethyl)-N-(furan-2-ylmethyl)pivalamide (3.14) yielding a mixture of 5-bromo-8-hydroxy-15-pivaloyl-12-oxa-1,15-diazatetracyclo[11.3.0.0^{27}.0^{9,13}]heptadeca-2,4,6,10-tetraen-17-one (3.23a) and 5-bromo-2-hydroxy-12-pivaloyl-17-oxa-9,12-diazatetracyclo[11.2.1.0^{3,8}.0^{5,9}]heptadeca-3,5,7,15-tetraen-10-one (3.24a) in the ratio of 1:1.4. 0.26 g of the mixture was then subjected to general procedure SPy using pyridine-3-boronic acid (0.086 g, 0.70 mmol), Pd$_2$(dba)$_3$ (0.0063 g, 0.0069 mmol), PCy$_3$ (0.0046 g, 0.016 mmol), dioxane (2.0 mL), and aqueous K$_3$PO$_4$ (1.1 mmol, 0.84 mL of a 1.27 M solution) resulting in an isolated yield of 0.050 g, (19%) of the title compound and 0.030 g (12%) of 2-hydroxy-12-pivaloyl-5-(pyridin-3-yl)-17-oxa-9,12-diazatetracyclo[11.2.1.0^{3,8}.0^{5,9}]heptadeca-3,5,7,15-tetraen-10-one (3.24b). $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.53 (d, $J = 4.3$ Hz, 1H), 8.44 (s, 1H), 7.81 (ddd, $J = 7.9, 2.4, 1.6$ Hz, 1H), 7.75 (d, $J = 8.3$ Hz, 1H), 7.54 (dd, $J = 8.3, 2.2$ Hz, 1H), 7.34 (t, $J = 7.8, 4.9$ Hz, 1H), 7.32 (d, $J = 2.2$ Hz, 1H), 6.22 (t, $J = 2.7$ Hz, 1H), 5.09 (d, $J = 18.7$ Hz, 1H), 4.76 (dd, $J = 3.1, 2.3$ Hz, 1H), 4.75 (d, $J = 2.2$ Hz, 1H), 4.67 (dd, $J = 13.9, 1.9$ Hz, 1H), 4.14 (d, $J = 18.7$ Hz, 1H), 3.81 (d, $J = 13.9$ Hz, 1H), 3.70 (q, $J = 2.3$ Hz, 1H), 1.66 (s, 1H), 1.36 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 176.5, 164.9, 148.4, 147.9, 146.9, 135.9, 135.5,
134.6, 134.3, 133.9, 127.9, 127.8, 127.2, 123.6, 99.8, 94.9, 68.9, 55.1, 51.7, 50.2, 38.9, 28.3. HRMS (ESI) calcd for C\textsubscript{24}H\textsubscript{26}N\textsubscript{3}O\textsubscript{4} (MH\textsuperscript{+}) 420.1918, found 420.1921.

2-Hydroxy-12-pivaloyl-5-(pyridin-3-yl)-17-oxa-9,12-diazatetracyclo[11.2.1.0\textsuperscript{3,8}.0\textsuperscript{5,9}]heptadeca-3,5,7,15-tetraen-10-one (3.24b): General procedure I was performed using 0.26 g (0.62 mmol) of N-(2-(4-bromo-2-formylphenylamino)-2-oxoethyl)-N-(furan-2-ylmethyl)pivalamide (3.14) yielding a mixture of 5-bromo-8-hydroxy-15-pivaloyl-12-oxa-1,15-diazatetracyclo[11.3.0.0\textsuperscript{2,7}.0\textsuperscript{9,13}]heptadeca-2,4,6,10-tetraen-17-one (3.23a) and 5-bromo-2-hydroxy-12-pivaloyl-17-oxa-9,12-diazatetracyclo[11.2.1.0\textsuperscript{3,8}.0\textsuperscript{5,9}]heptadeca-3,5,7,15-tetraen-10-one (3.24a) in the ratio of 1:1.4. 0.26 g of the mixture was then subjected to general procedure SPy using pyridine-3-boronic acid (0.086 g, 0.70 mmol), Pd\textsubscript{2}(dba)\textsubscript{3} (0.0063 g, 0.0069 mmol), PCy\textsubscript{3} (0.0046 g, 0.016 mmol), dioxane (2.0 mL), and aqueous K\textsubscript{3}PO\textsubscript{4} (1.1 mmol, 0.84 mL of a 1.27 M solution) resulting in an isolated yield of 0.050 g (19%) of 8-hydroxy-5-(pyridin-3-yl)-15-pivaloyl-12-oxa-1,15-diazatetracyclo[11.3.0.0\textsuperscript{2,7}.0\textsuperscript{9,13}]heptadeca-2,4,6,10-tetraen-17-one (3.23b) and 0.030 g (12%) of the title compound. \textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}) \(\delta\) 8.79 (s, 1H), 8.61 (s, 1H), 7.86 (ddd, \(J = 8.0, 2.4, 1.5\) Hz, 1H), 7.52 (dd, \(J = 8.3, 2.2\) Hz, 1H), 7.43 (d, \(J = 2.2\) Hz, 1H), 7.38 (m, 2H), 6.31 (dd, \(J = 6.0, 1.8\) Hz, 1H), 5.75 (dd, \(J = 5.9, 1.0\) Hz, 1H), 5.16 (m, 1H), 4.92 (dd, \(J = 18.2, 1.6\) Hz, 1H), 4.76 (d, \(J = 3.6\) Hz, 1H), 4.68 (dd, \(J = 14.0, 1.6\) Hz, 1H), 4.26 (d, \(J = 18.4\) Hz, 1H), 3.96 (d, \(J = 14.0\) Hz, 1H).
Hz, 1H), 1.37 (s, 9H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 176.8, 166.1, 148.8, 148.1, 137.3, 136.3, 135.7, 135.2, 134.3, 134.1, 131.1, 130.3, 128.0, 126.9, 123.6, 96.9, 83.9, 79.1, 49.9, 49.7, 38.9, 28.3. HRMS (ESI) calcd for C$_{24}$H$_{26}$N$_3$O$_4$ ($\text{MH}^+$) 420.1918, found 420.1920.

10-Hydroxy-5-pivaloyl-16-(pyridine-3-yl)-20-oxa-2,5-
diazapentacyclo[9.7.1.1$^7$.0$^2$.7.0$^{15}$.0$^{19}$]icosa-
1(19),8,15(16),17(18)tetraen-3,5-dione: General procedure I was performed using 0.43 g (0.93 mmol) of N-(2-(4-oxo-5,6,7,8-tetrahydronaphthalen-1-
ylamino)-2-oxoethyl)-N-(furan-2-ylmethyl)pivalamide (3.15) yielding a mixture containing 12-hydroxy-17-bromo-6-pivaloyl-8-oxa-2,5-
diazapentacyclo[10.7.1.0$^2$.7.0$^7$.11.0$^{16}$.0$^{20}$]icosa-1(20),9,16(17),18-tetraen-3,6-dione (25a) and 10-hydroxy-5-pivaloyl-16-bromo-20-oxa-2,5-diazapentacyclo
[9.7.1.1$^7$.0$^2$.7.0$^{15}$.0$^{19}$]icosa-1(19),8,15(16),17(18)tetraen-3,5-dione (3.26a) in the ratio of 1:1.5. 0.43 g of the mixture was then subjected to general procedure SPy using pyridine-3-boronic acid (0.21 g, 1.7 mmol), Pd$_2$(dba)$_3$ (0.020 g, 0.022 mmol), PCy$_3$ (0.015 g, 0.053 mmol), dioxane (3 mL), and aqueous K$_3$PO$_4$ (2.7 mmol, 2.1 mL of a 1.27 M solution) resulting in an isolated yield of 0.086 g (20%) of the title compound. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.62 (d, $J = 3.8$ Hz, 1H), 8.54 (s, 1H), 7.62 (dt, $J = 7.9$, 1.9 Hz, 1H), 7.37 (dd, $J = 7.8$, 4.8 Hz, 1H), 7.09 (m, 2H), 6.36 (dd, $J = 5.9$, 1.8 Hz, 1H), 5.80 (dd, $J = 5.9$, 0.9 Hz, 1H), 4.97 (d, $J = 18.5$ Hz, 1H), 4.73 (m, 2H), 4.30 (d, $J = 18.3$ Hz, 1H), 3.93
(d, J = 13.9 Hz, 1H), 3.48 (s, 1H), 2.59 (m, 1H), 2.47 (ddd, J = 17.4, 12.6, 5.5 Hz, 1H), 2.10 (m, 1H), 1.96 (m, 1H), 1.76 (m, 1H), 1.60 (dt, J = 13.5, 2.9 Hz, 1H), 1.39 (s, 9H).

13C NMR (126 MHz, CDCl3) δ 176.8, 166.2, 149.8, 148.8, 148.4, 137.1, 136.9, 136.5, 136.2, 135.6, 135.2, 129.2, 128.6, 128.2, 123.2, 96.3, 88.4, 75.3, 49.9, 49.1, 38.9, 36.2, 30.4, 28.3, 17.8. HRMS (ESI) calcd for C27H30N3O4+ (MH+) 460.2231, found 460.2234.

10-Hydroxy-5-benzyl-16-(pyridine-3-yl)-20-oxa-2,5-diazapentacyclo [9.7.1.17.10.02.7.015.19]icosa-1(19),8,15(16),17(18)tetraen-3,5-dione (3.28b): General procedure I was followed using 0.81 g (1.7 mmol) of N-benzyl-N-(2-(4-bromo-8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl- amino)-2-oxoethyl)furan-2-carboxamide (3.16) forming mixture of 12-hydroxy-17-bromo-6-benzyl-8-oxa-2,5-diazapentacyclo[10.7.1.02.7.07.11.016.20]icosa-1(20),9,16(17),18-tetraen-3,6-dione (3.27a) and 10-hydroxy-5-benzyl-16-bromo-20-oxa-2,5-diazapentacyclo[9.7.1.17.10.02.7.015.19]icosa-1(19),8,15(16),17(18)tetraen-3,5-dione (3.28a) in the ratio of 1:16. 0.20 g of the crude photoproduct was then subjected to general procedure SPy using pyridine-3-boronic acid (0.081 g, 0.66 mmol), Pd2(dba)3 (0.0090 g, 0.022 mmol), PCy3 (0.0066 g, 0.024 mmol), dioxane (1.2 mL), and aqueous K3PO4 (0.42 mmol, 0.56 mL of a 1.27 M solution) resulting in an isolated yield of 0.072 g, (36%) of the title compound. 1H NMR (500 MHz, CDCl3) δ 8.62 (dd, J = 5.0, 1.7 Hz, 1H), 8.51 (m, 1H), 7.62 (dt, J = 7.8, 2.0 Hz, 1H), 7.40 (m, 6H), 7.13 (d, J = 8.0 Hz, 1H), 7.04 (d, J = 7.9 Hz, 1H), 6.40 (dd, J = 6.0,
1.8 Hz, 1H), 6.10 (d, J = 5.9 Hz, 1H), 4.96 (d, J = 14.5 Hz, 1H), 4.87 (m, 1H), 4.57 (d, J = 14.5 Hz, 1H), 4.40 (d, J = 18.2 Hz, 1H), 4.11 (d, J = 18.2 Hz, 1H), 3.16 (s, 1H), 2.59 (m, 1H), 2.47 (ddd, J = 17.5, 12.6, 5.4 Hz, 1H), 2.11 (m, 1H), 1.96 (qdd, J = 13.2, 4.9, 2.5 Hz, 1H), 1.79 (m, 1H), 1.64 (td, J = 13.4, 3.0 Hz, 1H). 13C NMR (126 MHz, CDCl$_3$) δ 167.1, 162.5, 149.8, 148.6, 139.2, 136.9, 136.8, 136.4, 136.1, 135.8, 135.7, 134.6, 129.8, 129.1, 128.5, 128.5, 128.4, 123.1, 96.5, 89.6, 75.8, 49.9, 49.8, 36.3, 30.2, 17.7. HRMS (ESI) calcd for C$_{29}$H$_{26}$N$_3$O$_4$+ (MH$^+$) 480.1918, found 480.1927.

8-Hydroxy-5-(thiophen-2-yl)-12-oxa-1-
azatetracyclo[11.3.0.0$^{2,7}$.0$^{9,13}$]hexadeca-2,4,6,10-tetraen-12-one (4h): N-(2-Formyl-4-iodophenyl)-3-(furan-2-yl)propanamide (3.3d) (0.42 g, 1.1 mmol) was irradiated following the general procedure for irradiation yielding 0.42 g of a mixture of 8-hydroxy-5-iodo-2-yl-12-oxa-1-azatetracyclo[11.3.0.0$^{2,7}$.0$^{9,13}$]hexadeca-2,4,6,10-tetraen-12-one (4d) and 2-hydroxy-5-iodo-16-oxa-9-
azatetracyclo[11.2.1.0$^{3,8}$.0$^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (3.5d) in the ratio 1:1 which was used without further purification. Following the general procedure for Suzuki coupling STF from 0.20 g (0.54 mmol) of the photoproducts, Pd(PPh$_3$)$_4$ (0.032 g, 0.028 mmol), thiophene-2-boronic acid (0.077 g, 0.60 mmol), NaHCO$_3$ (0.095 g, 1.1 mmol) in H$_2$O (16 mL) upon flash chromatography 0.030 g (17%) of the title compound and 0.044 g (26%) of 2-hydroxy-5-(thiophen-2-yl)-16-oxa-9-
azatetracyclo[11.2.1.0$^{3,8}$.0$^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (3.5h) was isolated. 1H
NMR (500 MHz, CDCl$_3$) δ 7.95 (d, $J = 8.3$ Hz, 1H), 7.66 (dd, $J = 8.3$, 2.2 Hz, 1H), 7.48 (d, $J = 2.2$ Hz, 1H), 7.31 (s, 1H), 7.30 (m, 1H), 7.10 (dd, $J = 5.0$, 3.7 Hz, 1H), 6.28 (t, $J = 2.8$ Hz, 1H), 4.83 (t, $J = 2.5$ Hz, 1H), 4.70 (dd, $J = 3.1$, 2.2 Hz, 1H), 3.89 (q, $J = 2.3$ Hz, 1H), 2.88 (ddd, $J = 16.5$, 10.6, 8.9 Hz, 1H), 2.60 (m, 1H), 2.45 (ddd, $J = 12.7$, 10.6, 8.9 Hz, 1H), 1.90 (m, 1H).  

$^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.2, 146.7, 143.3, 133.4, 132.0, 131.3, 128.1, 127.0, 126.2, 125.0, 123.6, 123.3, 101.3, 99.3, 70.4, 55.9, 35.1, 29.8. HRMS (ESI) calcd for C$_{18}$H$_{15}$LiNO$_3$S$^+$ (MLi$^+$) 332.0927, found 332.0935.

2-Hydroxy-5-(thiophen-2-yl)-16-oxa-9-azatetracyclo[11.2.1.0$_3$3,8.0$_5$9]hexadeca-3,5,7,14-tetraen-10-one (3.5h): N-(2-Formyl-4-iodophenyl)-3-(furan-2-yl)propan-amide (3.3d) (0.42 g, 1.1 mmol) was irradiated following the general procedure for irradiation yielding 0.42 g of a mixture containing 8-hydroxy-5-iodo-12-oxa-1-azatetracyclo[11.3.0.0$_2$2,7.0$_9$13]hexadeca-2,4,6,10-tetraen-12-one (3.4d) and 2-hydroxy-5-iodo-16-oxa-9-azatetracyclo[11.2.1.0$_3$3,8.0$_5$9]hexadeca-3,5,7,14-tetraen-10-one (3.5d) in the ratio 1:1 which was used without further purification. Following the general procedure for Suzuki coupling STF from 0.20 g (0.54 mmol) of the photoproducts, Pd(PPh$_3$)$_4$ (0.032 g, 0.028 mmol), thiophene-2-boronic acid (0.077 g, 0.60 mmol), NaHCO$_3$ (0.095 g, 1.1 mmol) in H$_2$O (16 mL) upon flash chromatography 0.030 g (17%) of 8-hydroxy-5-(thiophen-2-yl)-12-oxa-1-azatetracyclo[11.3.0.0$_2$2,7.0$_9$13]hexadeca-2,4,6,10-tetraen-12-one (3.4h) and 0.044 g
(26%) of the title compound was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.60 (dd, $J = 8.4, 2.2$ Hz, 1H), 7.55 (m, 2H), 7.31 (m, 2H), 7.10 (dd, $J = 5.1, 3.6$ Hz, 1H), 6.36 (dd, $J = 5.8, 1.9$ Hz, 1H), 5.70 (dd, $J = 5.9, 1.1$ Hz, 1H), 5.07 (m, 1H), 4.72 (dd, $J = 10.8, 3.3$ Hz, 1H), 2.93 (m, 2H), 2.69 (ddd, $J = 17.4, 9.8, 1.9$ Hz, 1H), 2.58 (m, 1H), 2.49 (ddd, $J = 13.9, 9.5, 1.9$ Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.1, 143.0, 134.7, 133.6, 132.9, 131.9, 131.6, 129.9, 129.3, 128.1, 126.0, 125.2, 123.4, 103.6, 83.6, 79.3, 30.1, 28.9.

HRMS (ESI) calcd for C$_{18}$H$_{15}$LiNO$_3$S$^+$ (MLi$^+$) 332.0927, found 332.0931.

5-(Furan-2-yl)-8-hydroxy-12-oxa-1-
azatetracyclo[11.3.0.0$^{2,7}$.0$^{9,13}$]hexadeca-2,4,6,10-tetraen-12-one (3.4g): N-(2-Formyl-4-iodophenyl)-3-(furan-2-yl)propanamide (3.3d) (0.31 g, 0.84 mmol) was irradiated following the general procedure for irradiation yielding 0.31 g of a mixture containing 8-hydroxy-5-iodo-12-oxa-1-azatetracyclo[11.3.0.0$^{2,7}.0^{9,13}$]hexadeca-2,4,6,10-tetraen-12-one (3.4d) and 2-hydroxy-5-iodo-16-oxa-9-azatetracyclo[11.2.1.0$^{3,8}.0^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (3.5d) in the ratio of 2.9:1 which was used without further purification. From 0.31 g (0.83 mmol) of that mixture following the general procedure for Suzuki coupling STF, using Pd(PPh$_3$)$_4$ (0.056 g, 0.048 mmol), furan-2-boronic acid (0.11 g, 0.98 mmol), NaHCO$_3$ (0.16 g, 1.9 mmol) in water (27 mL) upon flash chromatography 0.068 g (27%) of the title compound and 0.10 g (39%) of an inseparable mixture of 5-(furan-2-yl)-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0$^{3,8}.0^{5,9}$]hexadeca-3,5,7,14-tetraen-10-one (5g) and 4-(furan-2-yl)-15-hydroxy-16-oxa-8-
azatetracyclo[10.3.1.0^{2,7}.0^{8,12}]hexadeca-2,4,6,13-tetraen-9-one (3.29) was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ 7.94 (d, $J = 8.4$ Hz, 1H), 7.70 (dd, $J = 8.4$, 2.0 Hz, 1H), 7.57 (d, $J = 2.0$ Hz, 1H), 7.48 (dd, $J = 1.8$, 0.7 Hz, 1H), 6.66 (dd, $J = 3.3$, 0.8 Hz, 1H), 6.50 (dd, $J = 3.4$, 1.8 Hz, 1H), 6.26 (t, $J = 2.8$ Hz, 1H), 4.83 (d, $J = 2.2$ Hz, 1H), 4.68 (dd, $J = 3.0$, 2.2 Hz, 1H), 3.88 (m, 1H), 2.87 (ddd, $J = 16.3$, 10.4, 8.2 Hz, 1H), 2.52 (m, 4H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 173.2, 153.1, 146.7, 142.2, 133.2, 131.2, 128.5, 125.0, 124.0, 123.5, 111.8, 105.2, 101.4, 99.3, 70.4, 55.9, 35.1, 29.8. HRMS (ESI) calcd for C$_{18}$H$_{16}$NO$_4^+$ (MH$^+$) 310.1074, found 310.1081.

4-(Furan-2-yl)-15-hydroxy-16-oxa-8-azatetracyclo[10.3.1.0^{2,7}.0^{8,12}]hexadeca-2,4,6,13-tetraen-9-one (3.29): N-(2-Formyl-4-iodophenyl)-3-(furan-2-yl)propanamide (3.3d) (0.31 g, 0.84 mmol) was irradiated following the general procedure for irradiation yielding 0.31 g of a mixture containing 8-hydroxy-5-iodo-12-oxa-1-azatetracyclo[11.3.0.0^{2,7}.0^{9,13}]hexadeca-2,4,6,10-tetraen-12-one (4d) and 2-hydroxy-5-iodo-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.5d) in the ratio of 2.9:1 which was used without further purification. From 0.31 g (0.83 mmol) of that mixture following the general procedure for Suzuki coupling, using Pd(PPh$_3$)$_4$ (0.056 g, 0.048 mmol), furan-2-boronic acid (0.11 g, 0.98 mmol), NaHCO$_3$ (0.16 g, 1.9 mmol) in water (27 mL) upon flash chromatography 0.068 g (27%) of 5-(furan-2-yl)-8-hydroxy-12-oxa-1-azatetracyclo[11.3.0.0^{2,7}.0^{9,13}]hexadeca-2,4,6,10-tetraen-12-one (3.4g) and 0.10 g
(39%) of an inseparable mixture of 5-(furan-2-yl)-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.5g) and 4-(furan-2-yl)-15-hydroxy-16-oxa-8-azatetracyclo[10.3.1.0^{2,7}.0^{8,12}]hexadeca-2,4,6,13-tetraen-9-one (3.29). A mixture of 5-(furan-2-yl)-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.5g) and 4-(furan-2-yl)-15-hydroxy-16-oxa-8-azatetracyclo[10.3.1.0^{2,7}.0^{8,12}]hexadeca-2,4,6,13-tetraen-9-one (3.29) (0.093 g, 0.30 mmol) in 4 nmL of DMSO was placed in a glycerol bath at 160 °C for 60 min. The solution was allowed to cool, concentrated, and the remaining mixture subjected to flash chromatography resulting in an isolated yield of 0.043 g of the title compound. $^1$H NMR (500 MHz, CDCl$_3$) δ 8.38 (d, $J = 8.7$ Hz, 1H), 7.63 (dd, $J = 8.6$, 2.0 Hz, 1H), 7.51 (d, $J = 2.0$ Hz, 1H), 7.48 (dd, $J = 1.9$, 0.8 Hz, 1H), 6.64 (dd, $J = 3.4$, 0.8 Hz, 1H), 6.50 (dd, $J = 3.4$, 1.8 Hz, 1H), 6.11 (ddd, $J = 9.7$, 5.3, 1.2 Hz, 1H), 5.86 (m, 1H), 5.23 (s, 1H), 4.03 (d, $J = 5.2$ Hz, 1H), 2.74 (m, 2H), 2.40 (m, 2H), 2.28 (s, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 170.9, 153.1, 142.2, 131.6, 129.5, 127.1, 127.0, 124.1, 123.5, 120.6, 120.2, 111.8, 105.0, 86.1, 78.1, 66.8, 30.3, 29.9. HRMS (ESI) calcd for C$_{18}$H$_{15}$LiNO$_4^+$ (MLi$^+$) 316.1156, found 316.1164.
X-Ray Structures

X-Ray structures were obtained with a Bruker APEX II instrument and the structure was refined using XShell software. The goodness of fit “S” is listed after each entry.

1. 8-Hydroxy-5-phenyl-12-oxa-1-azatetracyclo[11.3.0.0²,7.0⁹,13]hexadeca-2,4,6,10-tetraen-16-one (3.4f) \( S = 0.891 \)

![Chemical structure 1](image)

2. 11-Hydroxy-16-(pyridine-3-yl)-7-oxa-2-azapentacyclo[9.7.1.0²,6.0⁶,10.0¹⁵,19]nonadeca-1(19),8,15(16),17-tetraen-3-one (3.21b) \( S = 0.907 \)

![Chemical structure 2](image)
3. 10-Hydroxy-15-(pyridine-3-yl)-9-oxa-2-
azapentacyclo[8.7.1.1{6,9}.0{2,6}.0{14,18}]nonadeca-1(18),7,14(15),16(17)tetraen-3-one
(3.22b) $S = 0.747$

4. 8-Hydroxy-6-(pyridin-3-yl)-12-oxa-1-azatetracyclo[11.3.0.0{2,7}.0{9,13}]hexadeca-
2,4,6,10-tetraen-16-one (3.17b) $S = 1.109$

5. 5-(Furan-2-yl)-8-hydroxy-12-oxa-1-azatetracyclo[11.3.0.0{2,7}.0{9,13}]hexadeca-
2,4,6,10-tetraen-12-one (3.4g) $S = 0.876$
6. 5-(furan-2-yl)-2-hydroxy-16-oxa-9-azatetracyclo[11.2.1.0^{3,8}.0^{5,9}]hexadeca-3,5,7,14-tetraen-10-one (3.5g) $S = 0.859$
Chapter 4: *o*-Azaxylylene Cascade Reactions

Diversity oriented synthesis aims to probe the greatest region of chemical space possible\(^9\), and this is best accomplished through modifications to the core framework which significantly change the overall topology of a molecule. This chapter focuses on the first reported case of \(o\)-azaxylylene cascade reactions in the excited state. Not only does this approach yield a significantly unique topology in keeping with DOS, but also forms multiple fused \(sp^3\) ring systems, which can be synthesized in a one-pot two-step fashion, from affordable starting materials, and obtained without column chromatography. These products contain many stereogenic centers, have a large fraction of \(sp^3\) carbons, few rotatable bonds, and multiple fused bridges which are all characteristics of active pharmaceuticals derived from natural products.\(^6\)

Introduction

Cascade reactions have been shown to be a prominent method from which nature generates this selectivity.\(^38\) Polycyclic structures with multiple stereocenters generated from linear achiral precursors are a stunning example of this phenomena, and is demonstrated in the electrophilic cascade leading to the formation of terpenes,\(^39\) such as the steroid precursor lanosterol illustrated in Figure 4.1.
Cascade reactions are often regarded as an “environmentally friendly means to generate molecular complexity”\(^{40}\) in the formation of natural or designed products. However, implementation of this methodology on the bench top does pose some challenges, as cascade reactions by their very nature rely on the formation of highly reactive, short-lived intermediates in minute quantities without any spatial compartmentalization of sequential processes making the control over the reaction difficult, if not impossible. These reactions are not only attractive from the standpoint of synthesizing natural or designed products, but also have the potential to serve as powerful tools in the exploration of chemical space.

Herein we set out to utilize two photochemically generated \(o\)-azaxylylene intermediates, resulting from the excited state intramolecular proton transfer of \(o\)-amido aldehydes and ketones, in a cascade reaction that results in a rapid growth in complexity to yield novel fused ring systems.

**Results and Discussion**

Photoprecursors were equipped with two reactive \(o\)-acylanilid moieties, each of which can form \(o\)-azaxylylenes upon irradiation and potentially react with a dieneophile.
The system was designed so that the first o-azaxylylene addition to the tethered furan pendant would bring the second tethered o-azaxylylene into close spatial proximity so that it could react with the newly formed 2,5- or 3,4-dihydrofuran moiety generated from the first addition (Scheme 4.1)

![Scheme 4.1](image_url)

In order to introduce two azaxylylene pendants into one framework, a two-step one-pot procedure was developed (Scheme 4.2): (i) acetylation of isatin (4.1) with furanproanoic acids 4.2 or 4.3 followed by (ii) ring opening with anilines 4.6a-d. Photoprecursors 4.7b-d were obtained after workup, while photoprecursors 4.7a and 4.8a required an additional oxidation step with PCC to yield the aldehyde products.
Photoprecursors (4.7a-d, 4.8a) are characterized by the maximum UV absorption between 350-365 nm, and were irradiated using a Rayonet broadband 300-400 nm UV source yielding photoproducts 4.9-14 in moderate to good yields. The reaction was found to be substantially slower for photoprecursors bearing one reactive o-azaxylylene core, with an absolute quantum yield of cyclization for the irradiation of 4.7b being < 0.02.

Irradiation of photoprecursors 4.7a-d yielded three products (Scheme 4.3): (i) [4 + 4] or “single click” cyclization products 4.9a-d, (ii) [4 + 2]/[4 + 2] or “double click” cascade products 4.10a-d, and (iii) [4 + 2]/disproportion or “1.5 click” cascade products.
4.11a-d. Irradiation of photoprecursor 4.8a yielded only the single click [4 + 4] (4.12) and [4 + 2]/[4 + 2] double click (4.13) products. The photoproduct of [4 + 4] cyclization likely does not undergo a cascade reaction because of the unfavorable spatial arrangement between the \( o \)-azaxylyene core and the double bond resulting from the initial cycloaddition.
It is likely that the double click and disproportionation products are derived from an initial [4 + 2] cyclization. When monitoring the reaction by $^1$H NMR, the
accumulation and subsequent disappearance of a single click [4 + 2] cyclization is observed, and this disappearance is likely the result of the [4 + 2] cycloaddition product being consumed through the double click and disproportionation channels. Given these observations and the previous work on the mechanism of o-azaxylylene cycloaddition\textsuperscript{21}, the double click and disproportionation process is postulated to proceed through excitation to S\textsubscript{1}, followed by excited state intramolecular proton transfer, intersystem crossing to the triplet state, and a step-wise addition to the furan pendant starting with the N-centered attack and finishing with radical recombination to reach the single click [4 + 2] product. At this point, the same process occurs with the second pendant; however, after the initial attack on the double bond the second radical can do one of two things: (a) radical recombination forming the double click product, or (b) hydrogen abstraction from the OH group reforming the o-amido ketone or aldehyde leading to the 1.5 click product (Scheme 4.4).
In all cases only one diastereomer was observed, and the stereochemistry was assigned using NOE experiments (Figure 4.2). For compound 4.10b irradiation of the methyl group results in the enhancement of Hb (2.2%) and Ha (0.8%) signals. Irradiation of OH-b does not result in the enhancement of any proton signals, and the irradiation of OH-a results in the enhancement of Hc (3%). This suggests that Ha, Hb, and Hc, and OH-a are on the same face. Compound 4.11b showed signal enhancement of He (12%) upon irradiation of Hd, implying that these protons are on the same face. The ¹H NMR spectra are in agreement with calculations using a relativistic force field method developed by Kutateladze et al.⁴¹
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 or TCI America and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25 °C on a Bruker Avance III 500 MHz in CDCl₃ with TMS as an internal standard (unless noted otherwise). 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 at the University of Colorado at Boulder. Flash column chromatography was performed using Teledyne Ultra Pure Silica Gel (230 – 400 mesh) on a Teledyne Isco Combiblack Rf using Hexanes/EtOAc or DCM/Methanol as eluents. 8-Amino-1-tetralone⁴² and 1-(2-amino-5-bromophenyl)ethanone³⁶ were synthesized according to the published procedures.
Synthesis of photoprecursors

**General procedure for isatin coupling** (A): Isatin (1 mmol) was added to the solution of carboxylic acid (1.2 mmol) in DCM (4 mL) at 0 °C, followed by EDC (1.2 mmol) and DMAP (0.10 mmol). The reaction mixture was allowed to stir at room temperature for three hours, followed by the addition of the amine (1.2 mmol) and left stirring overnight. The mixture was diluted with DCM (14 mL), and washed with 5% aq. HCl, water, a solution of sat. aq. NaHCO₃, and water (6 mL each). The organic layer was dried over anh. Na₂SO₄, filtered, concentrated, and purified by flash chromatography (Hex/EtOAc) yielding the desired product.

**General procedure for the oxidation of alcohols to aldehydes** (B): To a stirred mixture of the alcohol (1 mmol) in dry DCM (8 mL) was added PCC (1.6 mmol). The reaction mixture was left stirring overnight, filtered through a layer of silica gel using CH₂Cl₂/3% MeOH, (100 mL) as an eluent, concentrated, and purified by flash chromatography (Hex/EtOAc) yielding the isolated desired product.
N-(2-(((2-Formylphenyl)carbamoyl)carbonyl)phenyl)-3-(furan-2-yl)propanamide (4.7a): Following general procedure A, from furanpropanoic acid (0.34 g, 2.4 mmol), isatin (0.30 g, 2.0 mmol), EDC (0.47 g, 2.5 mmol), DMAP (0.025 g, 0.20 mmol), and 2-aminobenzyl alcohol (0.30 g, 2.4 mmol) in DCM (12 mL) upon workup 3-(furan-2-yl)-N-[2-(((2-(hydroxymethyl)phenyl)carbamoyl)carbonyl)phenyl]propanamide (0.78 g, crude) was obtained, and used in the next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.01 (s, 1H), 10.12 (s, 1H), 8.74 (dd, $J = 8.6$, 1.2 Hz, 1H), 8.54 (dd, $J = 8.1$, 1.5 Hz, 1H), 8.32 (dd, $J = 8.1$, 1.1 Hz, 1H), 7.67 (ddd, $J = 8.8$, 7.5, 1.6 Hz, 1H), 7.45 (td, $J = 7.8$, 1.6 Hz, 1H), 7.34 (dd, $J = 1.9$, 0.9 Hz, 1H), 7.27 (d, $J = 1.4$ Hz, 1H), 7.20 (m, 2H), 6.30 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.10 (dd, $J = 3.3$, 0.8 Hz, 1H), 4.86 (d, $J = 5.5$ Hz, 2H), 3.12 (t, $J = 7.6$ Hz, 2H), 2.84 (dd, $J = 7.8$, 6.4 Hz, 2H), 2.28 (t, $J = 5.6$ Hz, 1H).

General procedure B was followed using 3-(furan-2-yl)-N-[2-(((2-(hydroxymethyl)phenyl)carbamoyl)carbonyl)phenyl]propanamide (0.78 g), and PCC (0.64 g, 3.0 mmol) in DCM (50 mL). Upon purification by flash chromatography 0.31 g (40% over two steps) of the title compound was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.35 (s, 1H), 11.06 (s, 1H), 10.05 (d, $J = 0.8$ Hz, 1H), 8.87 (d, $J = 8.4$ Hz, 1H), 8.79 (dd, $J = 8.6$, 1.1 Hz, 1H), 8.45 (dd, $J = 8.1$, 1.6 Hz, 1H), 7.82 (dd, $J = 7.6$, 1.7 Hz, 1H), 7.74 (m, 1H), 7.68 (ddd, $J = 8.8$, 7.2, 1.6 Hz, 1H), 7.41 (td, $J = 7.5$, 1.0 Hz, 1H), 7.36 (dd, $J = 1.9$, 0.9 Hz, 1H), 7.19 (ddd, $J = 8.2$, 7.3, 1.2 Hz, 1H), 6.30 (dd, $J = 3.2$, 1.9 Hz, 1H), 6.12 (m, 1H), 3.14 (t, $J = 7.6$ Hz, 2H), 2.88 (dd, $J = 8.3$, 6.8 Hz, 2H). $^{13}$C NMR (126 MHz,
CDCl$_3$ $\delta$ 195.2, 190.4, 171.0, 161.3, 153.9, 142.5, 141.3, 139.2, 136.8, 136.2, 136.1, 134.3, 124.8, 122.5, 121.0, 120.3, 118.4, 110.2, 105.6, 36.8, 23.7. HRMS (ESI) calcd for C$_{22}$H$_{19}$BrN$_2$O$_5$ $^+$ (MH$^+$) 391.1288, found 391.1299.

N-((2-Formylphenyl)carbamoyl)carbonyl)phenyl)-3-(5-(2-(trifluoromethyl)phenyl)furan-2-yl)propanamide (4.8a): Following general procedure A, from 3-(5-(2-(trifluoromethyl)phenyl)furan-2-yl)propionic acid (0.90 g, 3.2 mmol), isatin (0.39 g, 2.7 mmol), EDC (0.61 g, 3.2 mmol), DMAP (0.032 g, 0.26 mmol), and 2-aminobenzyl alcohol (0.39 g, 3.2 mmol) in DCM (40 mL) N-((2-(hydroxymethyl)phenyl)carbamoyl)carbonyl)phenyl)-3-(5-(2-(trifluoromethyl)phenyl)furan-2-yl)propanamide (1.72 g, crude) was obtained, and used in the next step without further purification. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 11.06 (s, 1H), 10.15 (s, 1H), 8.75 (dd, $J = 8.5, 1.1$ Hz, 1H), 8.53 (dd, $J = 8.2, 1.6$ Hz, 1H), 8.30 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.73 (m, 2H), 7.67 (ddd, $J = 8.8, 7.3, 1.6$ Hz, 1H), 7.53 (m, 1H), 7.43 (td, $J = 8.0, 1.5$ Hz, 1H), 7.38 (m, 1H), 7.26 (dd, $J = 8.2, 1.2$ Hz, 1H), 7.20 (m, 2H), 6.64 (d, $J = 3.4$ Hz, 1H), 6.23 (d, $J = 3.4$ Hz, 1H), 4.83 (s, 2H), 3.20 (t, $J = 7.5$ Hz, 2H), 2.90 (dd, $J = 8.4, 6.8$ Hz, 2H).

General procedure B was followed using N-((2-(hydroxymethyl)phenyl)carbamoyl)carbonyl)phenyl)-3-(5-(2-(trifluoromethyl)phenyl)furan-2-yl)propanamide (1.72 g), and PCC (1.04 g, 4.82
mmol) in DCM (50 mL). Upon purification by flash chromatography 0.36 g (25 % over
two steps) of the title compound was obtained. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.33 (s,
1H), 11.10 (s, 1H), 10.03 (d, $J = 0.7$ Hz, 1H), 8.86 (d, $J = 8.4$ Hz, 1H), 8.79 (dd, $J = 8.7$,
1.1 Hz, 1H), 8.45 (dd, $J = 8.1$, 1.6 Hz, 1H), 7.81 (dd, $J = 7.6$, 1.6 Hz, 1H), 7.74 (m, 3H),
7.68 (ddd, $J = 8.7$, 7.4, 1.6 Hz, 1H), 7.54 (m, 1H), 7.40 (td, $J = 7.5$, 1.0 Hz, 1H), 7.37 (m,
1H), 7.20 (ddd, $J = 8.2$, 7.3, 1.2 Hz, 1H), 6.65 (d, $J = 3.3$ Hz, 1H), 6.25 (dt, $J = 3.3$, 0.9
Hz, 1H), 3.22 (t, $J = 7.5$ Hz, 2H), 2.94 (dd, $J = 8.3$, 6.8 Hz, 2H). $^{13}$C NMR (126 MHz,
CDCl$_3$) $\delta$ 195.2, 190.4, 170.9, 161.2, 154.7, 149.2, 142.4, 139.2, 136.8, 136.2, 136.1,
134.3, 131.6, 129.8 (q, $J = 1.9$ Hz, 1C), 129.5, 127.2, 126.6 (q, $J = 6.0$ Hz, 1C), 126.0 (q,
$J = 31.2$ Hz, 1C), 124.5, 124.1 (q, $J = 273.8$ Hz, 1C), 122.8, 122.5, 121.1, 120.2, 118.4,
111.0 (q, $J = 3.6$ Hz, 1C), 108.0, 36.6, 23.8. HRMS (ESI) calcd for C$_{29}$H$_{22}$F$_3$N$_2$O$_5$\(^+\)
(MH$^+$) 535.1475, found 535.1496.

N-(2-(((2-Acetylphenyl)carbamoyl)carbonyl)phenyl)-3-
(furan-2-yl)propanamide (4.7b): Following general procedure
A, from furanpropanoic acid (1.71 g, 12.2 mmol), isatin (1.50 g,
12.2 mmol), EDC (2.35 g, 12.3 mmol), DMAP (0.12 g, 0.98
mmol), and 2'-aminoacetophenone (1.65 g, 12.2 mmol) in DCM
(45 mL) upon purification by flash chromatography 2.08 g (50 %) of the title compound
was isolated. $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.93 (s, 1H), 11.10 (s, 1H), 8.87 (dd, $J =$
8.4, 1.2 Hz, 1H), 8.78 (dd, $J = 8.5$, 1.2 Hz, 1H), 8.43 (dd, $J = 8.1$, 1.6 Hz, 1H), 8.02 (dd, $J$
= 8.0, 1.6 Hz, 1H), 7.67 (m, 2H), 7.35 (dd, $J = 1.9$, 0.9 Hz, 1H), 7.29 (m, 1H), 7.18 (ddd,
$J = 8.3, 7.2, 1.2 \text{ Hz, } 1H), 6.30 (dd, J = 3.2, 1.8 \text{ Hz, } 1H), 6.10 (m, 1H), 3.13 (t, J = 7.5 \text{ Hz, } 2H), 2.86 (dd, J = 8.4, 6.6 \text{ Hz, } 2H), 2.74 (s, 3H). \ ^{13}C \text{ NMR (126 MHz, CDCl}_3) \delta 202.8, 191.0, 171.0, 161.4, 154.0, 142.4, 141.3, 139.4, 136.7, 135.2, 134.3, 131.9, 123.9, 122.9, 122.5, 121.0, 118.4, 110.2, 105.6, 36.7, 28.5, 23.7. \text{ HRMS (ESI) calcd for } C_{23}H_{21}N_2O_5^+ (MH^+) 405.1445, \text{ found 405.1454.}

N-((2-(Acetyl-4-bromophenyl)carbamoyl)carbonyl)phenyl)-3-(furan-2-yl)propanamide (4.7c): Following general procedure A, from furanpropanoic acid (1.14 g, 8.13 mmol), isatin (1.00 g, 6.80 mmol), EDC (1.56 g, 8.14 mmol), DMAP (0.083 g, 0.68 mmol), and 1-(2-amino-5-bromophenyl)ethanone (1.75 g, 8.18 mmol) in DCM (30 mL) upon purification by flash chromatography 0.81 g (25%) of the title compound was isolated. \[^1H \text{ NMR (500 MHz, CDCl}_3) \delta 12.83 (s, 1H), 11.05 (s, 1H), 8.81 (d, J = 9.0 \text{ Hz, } 1H), 8.78 (dd, J = 8.6, 1.1 \text{ Hz, } 1H), 8.43 (dd, J = 8.1, 1.6 \text{ Hz, } 1H), 8.11 (d, J = 2.3 \text{ Hz, } 1H), 7.77 (dd, J = 8.9, 2.3 \text{ Hz, } 1H), 7.67 (dd, J = 8.7, 7.2, 1.7 \text{ Hz, } 1H), 7.35 (dd, J = 1.9, 0.9 \text{ Hz, } 1H), 7.19 (dd, J = 8.2, 7.2, 1.2 \text{ Hz, } 1H), 6.30 (dd, J = 3.2, 1.9 \text{ Hz, } 1H), 6.11 (m, 1H), 3.13 (t, J = 7.5 \text{ Hz, } 2H), 2.86 (dd, J = 8.3, 6.8 \text{ Hz, } 2H), 2.74 (s, 3H). \ ^{13}C \text{ NMR (126 MHz, CDCl}_3) \delta 201.6, 190.5, 171.0, 161.2, 153.9, 142.5, 141.3, 138.3, 137.8, 136.8, 134.5, 134.3, 124.3, 122.6, 122.5, 121.0, 118.3, 116.5, 110.2, 105.6, 36.7, 28.6, 23.7. \text{ HRMS (ESI) calcd for } C_{23}H_{20}BrN_2O_5^+ (MH^+) 483.0550, \text{ found 483.0557.}
3-(Furan-2-yl)-N-(2-(((8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamoyl)carbonyl)phenyl)propanamide (4.7d): Following general procedure A, from furanpropanoic acid (0.62 g, 4.4 mmol), isatin (0.55 g, 3.7 mmol), EDC (0.85 g, 4.4 mmol), DMAP (0.045 g, 0.37 mmol), and 8-aminotetralone (0.72 g, 4.5 mmol) in DCM (50 mL) upon purification by flash chromatography 0.57 g (35%) of the title compound was isolated. $^1$H NMR (500 MHz, CDCl$_3$) δ 13.35 (s, 1H), 11.14 (s, 1H), 8.79 (dd, $J$ = 8.5, 1.2 Hz, 1H), 8.73 (d, $J$ = 8.4 Hz, 1H), 8.42 (dd, $J$ = 8.1, 1.6 Hz, 1H), 7.66 (ddd, $J$ = 8.7, 7.3, 1.6 Hz, 1H), 7.57 (d, $J$ = 8.0 Hz, 1H), 7.35 (dd, $J$ = 2.0, 0.9 Hz, 1H), 7.18 (ddd, $J$ = 8.3, 7.2, 1.2 Hz, 1H), 7.10 (m, 1H), 6.30 (dd, $J$ = 3.2, 1.9 Hz, 1H), 6.10 (m, 1H), 3.14 (t, $J$ = 7.6 Hz, 2H), 3.06 (t, $J$ = 6.1 Hz, 2H), 2.86 (dd, $J$ = 8.4, 6.8 Hz, 2H), 2.78 (dd, $J$ = 7.1, 6.2 Hz, 2H), 2.16 (p, $J$ = 6.4 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 203.4, 191.2, 171.0, 161.5, 154.0, 146.5, 142.4, 141.3, 140.3, 136.6, 135.1, 134.3, 124.7, 122.4, 120.9, 119.4, 118.6, 118.4, 110.2, 105.5, 40.6, 36.7, 30.9, 23.7, 22.7. HRMS (ESI) calcd for C$_{25}$H$_{23}$N$_2$O$_5$ (MH$^+$) 431.1601, found 431.1612.

Photochemical reactions

General procedure for irradiation (C): Solutions with ca. 4 mM of the photoprecursors in DCM were degassed with N$_2$ 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 consumption of the starting material and [4 + 2] cycloaddition products was observed, as determined by
\(^1\)H NMR. Specific purification procedures are listed below the compound of interest. When purification by chromatography was necessary compounds were separated using silica gel with DCM and MeOH as an eluent.

Irradiation of N-(2-(((2-formylphenyl)carbonyl)phenyl)-3-(furan-2-yl)propanamide (4.7a): General procedure C was followed using 0.28 g of 4.7a (0.72 mmol) in DCM (250 mL). Irradiation of N-(2-(((2-formylphenyl)carbonyl)phenyl)-3-(furan-2-yl)propanamide (4.7a) The mixture was purified by flash chromatography yielding pure 14,23-dihydroxy-2-oxa-7,16-diazahexacyclo[11.9.2.0\(^{3,7}\).0\(^{3,25}\).0\(^{8,13}\).0\(^{16,24}\).0\(^{17,22}\)]pentacos-17(18),19(20),21(22)-hexaene-6,15-dione (4.10a) (0.093 g, 33%), 5-(2-formylphenyl)-2-oxa,5,14-diaza-pentacyclo[10.5.1.0\(^{1,14}\).0\(^{4,8}\).0\(^{8,13}\)]octadec-8(9),10(11),12(13)-triene-6,15-dione (4.11a) (0.021 g, 8%), and N-(2-formylphenyl)-12-hydroxy-4-oxo-16-oxa-5-azatetracyclo[11.2.1.0\(^{1,5}\).0\(^{6}\).11]hexadeca-6,8,10,14-tetraene-12-carboxamide (4.9a) (0.036 g, 13%).

![image]

4.10a: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.35 (m, 2H), 7.69 (dd, \(J = 7.9, 1.2\) Hz, 1H), 7.50 (td, \(J = 7.7, 1.5\) Hz, 1H), 7.40 (m, 2H), 7.31 (m, 1H), 7.20 (ddd, \(J = 8.6, 7.4, 1.3\) Hz, 1H), 4.83 (d, \(J = 5.6\) Hz, 1H), 4.63 (dd, \(J = 9.0, 6.8\) Hz, 1H), 4.40 (dd, \(J = 6.8, 5.7\) Hz, 1H), 3.48 (d, \(J = 9.0\) Hz, 1H), 3.35 (s, 1H), 2.89 (dt, \(J = 17.1, 9.6\) Hz, 1H), 2.54 (m, 2H), 2.34 (m, 2H). \(^{13}\)C NMR (126 MHz, DMSO) \(\delta\) 174.3,
171.2, 136.0, 133.3, 133.2, 129.9, 129.5, 128.8, 128.6, 127.0, 126.3, 124.1, 122.8, 119.2, 98.9, 74.2, 71.8, 65.0, 61.0, 51.3, 31.8, 30.3. HRMS (ESI) calcd for C$_{22}$H$_{19}$N$_2$O$_5^+$ (MH$^+$) 391.1288, found 391.1293.

**4.11a:** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 9.91 (s, 1H), 8.33 (dd, $J$ = 8.2, 1.3 Hz, 1H), 8.15 (dd, $J$ = 8.0, 1.6 Hz, 1H), 8.00 (dd, $J$ = 7.7, 1.6 Hz, 1H), 7.72 (td, $J$ = 7.7, 1.6 Hz, 1H), 7.61 (td, $J$ = 7.6, 1.1 Hz, 1H), 7.48 (m, 1H), 7.27 (m, 2H), 4.89 (ddd, $J$ = 9.4, 6.0, 3.9 Hz, 1H), 3.88 (dd, $J$ = 10.3, 6.0 Hz, 1H), 3.78 (dd, $J$ = 10.3, 3.8 Hz, 1H), 3.71 (d, $J$ = 9.0 Hz, 1H), 3.43 (s, 1H), 2.83 (dt, $J$ = 17.1, 9.5 Hz, 1H), 2.51 (ddd, $J$ = 17.2, 9.6, 2.2 Hz, 1H), 2.45 (ddd, $J$ = 13.2, 9.3, 2.3 Hz, 1H), 2.32 (dt, $J$ = 13.2, 9.6 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 189.4, 174.2, 173.0, 137.5, 135.1, 133.6, 132.8, 132.1, 130.3, 128.6, 127.9, 127.1, 126.6, 125.7, 121.6, 98.3, 71.8, 69.2, 62.8, 54.5, 31.2, 29.7. HRMS (ESI) calcd for C$_{22}$H$_{19}$N$_2$O$_5^+$ (MH$^+$) 391.1288, found 391.1301.

**4.9a:** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.56 (s, 1H), 10.02 (s, 1H), 8.96 (d, $J$ = 8.4 Hz, 1H), 7.80 (dd, $J$ = 7.7, 1.7 Hz, 1H), 7.72 (ddd, $J$ = 8.8, 7.7, 1.7), 7.48 (dd, $J$ = 7.8, 1.1 Hz, 1H), 7.37 (m, 2H), 7.18 (m, 2H), 6.74 (dd, $J$ = 5.8, 2.0 Hz, 1H), 5.72 (dd, $J$ = 5.8, 1.1 Hz, 1H), 4.90 (dd, $J$ = 2.0, 1.1 Hz, 1H), 4.61 (s, 1H), 2.85 (dt, $J$ = 17.3, 9.7 Hz, 1H), 2.66 (ddd, $J$ = 17.3, 9.6, 1.6 Hz, 1H), 2.56 (dt, $J$ = 13.9, 9.9 Hz, 1H), 2.47 (ddd, $J$ = 13.8, 9.4, 1.6 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 194.6,
173.2, 171.3, 139.3, 136.9, 136.1, 135.9, 133.2, 129.4, 128.7, 128.5, 128.0, 126.8, 123.9, 123.0, 120.0, 104.1, 85.4, 85.0, 30.0, 28.8. HRMS (ESI) calcd for C_{22}H_{18}LiN_{2}O_{5}^{+} (MH^{+}) 397.1370, found 397.1380.

Irradiation of N-((2-formylphenyl)carbamoyl)carbonylphenyl)-3-(5-(2-(trifluoromethyl)phenyl)furan-2-yl)propanamide (4.8a): General procedure C was followed using 0.32 g of 4.8a (0.60 mmol) in DCM (250 mL). The mixture was purified by flash chromatography yielding pure 14,23-Dihydroxy-1-(2-(trifluoromethyl)phenyl)-2-oxa-7,16-diazahptacyclo[11.9.2.0^{3,7}.0^{3,25}.0^{8,13}.0^{16,24}.0^{17,22}]pentacos-17(18),19(20),21(22)-hexaene-6,15-dione (4.13) (0.042 g, 13%), and N-(2-formylphenyl)-12-hydroxy-4-oxo-13-[2-(trifluoromethyl)phenyl]-16-oxa-5-azatetracyclo[11.2.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tetraene-12-carboxamide (4.12) (0.030 g, 9%).

4.13: $^1$H NMR (500 MHz, DMSO) δ 8.20 (dd, J = 8.0, 1.6 Hz, 1H), 8.16 (dd, J = 8.3, 1.3 Hz, 1H), 7.88 (dd, J = 7.9, 1.5 Hz, 1H), 7.55 (dd, J = 7.8, 1.3 Hz, 1H), 7.49 (m, 2H), 7.44 (td, J = 7.9, 1.2 Hz, 1H), 7.35 (ddd, J = 8.8, 7.3, 1.6 Hz, 1H), 7.16 (td, J = 7.5, 1.3 Hz, 1H), 7.12 (ddd, J = 8.5, 7.3, 1.3 Hz, 1H), 7.01 (dd, J = 7.4, 1.4 Hz, 1H), 6.95 (d, J = 8.0 Hz, 1H), 6.56 (s, 1H), 5.47 (d, J = 9.5 Hz, 1H), 4.39 (d, J = 2.3 Hz, 1H), 3.86 (d, J = 2.3 Hz, 1H), 3.53 (d, J = 9.3 Hz, 1H), 2.59 (dt, J = 18.7, 9.5 Hz, 1H), 2.43 (dd, J = 17.2, 9.5 Hz, 1H), 2.22 (dt, J = 13.5, 9.9 Hz, 1H), 1.79
(ddd, $J = 13.7, 9.7, 1.7$ Hz, 1H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 173.4, 172.6, 141.6, 137.2, 133.8, 133.0, 132.0, 130.2, 129.9, 129.4, 129.1, 128.9, 128.7, 127.4, 125.8, 124.9, 121.0, 101.7, 88.8, 74.6, 70.8, 66.5, 54.4, 40.1, 32.8, 29.4. HRMS (ESI) calcd for C$_{29}$H$_{21}$F$_3$LiN$_2$O$_5^+$ (MH$^+$) 541.1557, found 541.1539.

4.12: $^1$H NMR (500 MHz, DMSO) $\delta$ 11.82 (s, 1H), 9.70 (s, 1H), 8.56 (d, $J = 8.3$ Hz, 1H), 7.85 (d, $J = 7.7, 1.7$ Hz, 1H), 7.74 (m, 3H), 7.48 (dd, $J = 8.1$, 1.5 Hz, 1H), 7.44 (s, 1H), 7.36 (dd, $J = 7.5, 1.1$ Hz, 1H), 7.33 (m, 2H), 7.27 (td, $J = 7.8, 1.5$ Hz, 1H), 7.15 (ddd, $J = 8.5, 7.0, 1.5$ Hz, 1H), 7.11 (dd, $J = 8.1, 1.6$ Hz, 1H), 7.09 (d, $J = 5.7$ Hz, 1H), 5.95 (d, $J = 5.7$ Hz, 1H), 2.77 (m, 1H), 2.59 (m, 2H), 2.27 (m, 1H).

$^{13}$C NMR (126 MHz, DMSO) $\delta$ 195.2, 173.0, 172.8, 139.8, 138.5, 137.6, 136.1, 135.8, 135.0, 134.1, 132.2, 131.4, 130.9, 128.4, 128.1, 127.8, 127.5, 125.9, 124.4, 123.6, 120.3, 104.1, 95.1, 91.8, 30.4, 28.3. HRMS (ESI) calcd for C$_{29}$H$_{21}$F$_3$LiN$_2$O$_5^+$ (MH$^+$) 541.1557, found 541.1578.

Irradiation of N-(2-(((2-acetylphenyl)carbamoyl)carbonyl)phenyl)-3-(furan-2-yl)propanamide (4.7b): General procedure C was followed using 0.35 g of 4.7b (0.87 mmol) in DCM (250 mL). Following the irradiation, the solution was concentrated to 40 mL, the mixture was centrifuged, the precipitate formed was filtered, washed with cold DCM (3 x 10 mL) followed by water (3 x 10 mL), and dried in a desiccator yielding pure 4,23-dihydroxy-23-methyl-2-oxa-7,16-
diazahexacyclo[11.9.2.0\(^{3,7}0^{3,25}0^{8,13}0^{16,24}0^{17,22}\)pentacos-17(18),19(20),21(22)-hexaene-6,15-dione (4.10) (0.12 g, 34%). The filtrate was purified by flash chromatography (DCM/MeOH) yielding pure 5-(2-acetylphenyl)-2-oxa,5,14-diazahexacyclo[10.5.1.0\(^{1,14}0^{4,8}0^{8,13}\)octadec-8(9),10(11),12(13)-triene-6,15-dione (4.11b) (0.049 g, 14%) and N-(2-acetylphenyl)-12-hydroxy-4-oxo-16-oxa-5-aza-tetracyclo[11.2.1.0\(^{5}0^{6,11}\)hexadeca-6,8,10,14-tetraene-12-carboxamide (4.9b) (0.084 g, 24%).

4.10b: \(^1\)H NMR (500 MHz, DMSO) \(\delta\) 8.29 (dd, \(J = 8.4, 1.3\) Hz, 1H), 8.12 (dd, \(J = 8.0, 1.6\) Hz, 1H), 7.78 (dd, \(J = 8.0, 1.3\) Hz, 1H), 7.53 (dd, \(J = 7.8, 1.5\) Hz, 1H), 7.31 (m, 2H), 7.22 (td, \(J = 7.5, 1.3\) Hz, 1H), 7.14 (td, \(J = 7.7, 1.3\) Hz, 1H), 6.63 (s, 1H), 4.78 (dd, \(J = 7.6, 4.5\) Hz, 1H), 4.54 (s, 1H), 4.10 (d, \(J = 4.6\) Hz, 1H), 3.26 (d, \(J = 7.5\) Hz, 1H), 2.77 (dt, \(J = 16.8, 9.4\) Hz, 1H), 2.65 (dd, \(J = 13.1, 8.4\) Hz, 1H), 2.20 (m, 1H), 1.49 (s, 3H). \(^{13}\)C NMR (126 MHz, DMSO) \(\delta\) 174.6, 171.6, 135.8, 134.9, 133.3, 129.9, 128.8, 128.1, 126.7, 126.7, 126.0, 124.0, 122.1, 119.0, 98.5, 78.6, 71.9, 68.2, 60.3, 51.3, 32.1, 30.6, 30.4. HRMS (ESI) calcd for C\(_{23}\)H\(_{20}\)LiN\(_{2}\)O\(_{5}\)\(^+\) (MLi\(^+\)) 411.1527, found 411.1547.
**4.11b:** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.30 (dd, $J = 8.3$, 1.2 Hz, 1H), 8.05 (dd, $J = 8.0$, 1.5 Hz, 1H), 7.81 (dd, $J = 7.7$, 1.6 Hz, 1H), 7.57 (td, $J = 7.7$, 1.6 Hz, 1H), 7.50 (td, $J = 7.6$, 1.3 Hz, 1H), 7.45 (ddd, $J = 8.6$, 7.5, 1.6 Hz, 1H), 7.22 (td, $J = 7.7$, 1.3 Hz, 1H), 7.13 (dd, $J = 7.8$, 1.3 Hz, 1H), 4.84 (dt, $J = 9.1$, 5.3 Hz, 1H), 3.91 (m, 2H), 3.69 (d, $J = 9.2$, 1H), 3.49 (s, 1H), 2.81 (dt, $J = 17.1$, 9.4 Hz, 1H), 2.62 (s, 3H), 2.44 (m, 2H), 2.32 (dt, $J = 13.2$, 9.7 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 199.7, 174.0, 173.1, 136.8, 135.0, 133.7, 132.7, 130.0, 129.6, 128.7, 128.2, 127.3, 126.7, 125.5, 121.7, 98.3, 71.6, 69.7, 63.3, 54.9, 31.6, 29.8, 28.7. HRMS (ESI) calcd for C$_{23}$H$_{20}$LiN$_2$O$_5$ $^\pm$ (MLi$^+$) 411.1527, found 411.1530.

**4.9b:** $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 12.97 (s, 1H), 8.96 (dd, $J = 8.4$, 1.2 Hz, 1H), 8.00 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.66 (m, 1H), 7.47 (dd, $J = 8.1$, 1.3 Hz, 1H), 7.35 (ddd, $J = 8.7$, 6.9, 2.0 Hz, 1H), 7.26 (ddd, $J = 8.4$, 7.4, 1.2 Hz, 1H), 7.20 (dd, $J = 8.0$, 1.9 Hz, 1H), 7.17 (ddd, $J = 8.0$, 6.9, 1.4 Hz, 1H), 6.75 (dd, $J = 5.8$, 2.0 Hz, 1H), 5.70 (dd, $J = 5.8$, 1.1 Hz, 1H), 4.89 (dd, $J = 2.0$, 1.2 Hz, 1H), 4.67 (s, 1H), 2.82 (dt, $J = 17.1$, 9.7 Hz, 1H), 2.71 (s, 3H), 2.64 (ddd, $J = 17.4$, 9.6, 1.7 Hz, 1H), 2.54 (dt, $J = 13.8$, 9.8 Hz, 1H), 2.46 (ddd, $J = 13.6$, 9.1, 1.4 Hz, 1H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 201.8, 173.2, 171.1, 139.4, 137.1, 134.8, 134.0, 133.2, 131.7, 129.4, 128.6, 128.4, 127.9, 127.8, 126.7, 123.4, 120.9, 104.1, 85.4, 85.1, 30.1, 28.8, 28.6. C$_{23}$H$_{21}$N$_2$O$_5$ $^\pm$ (MH$^+$) 405.1445, found 405.1461.
Irradiation of N-(2-(((2-acetyl-4-bromophenyl)carbamoyl)carbonyl)phenyl)-3-(furan-2-yl)propanamide (4.7c): General procedure C was followed using 0.25 g of 4.7c (0.52 mmol) in DCM (250 mL). The mixture was purified by flash chromatography yielding pure 20-bromo-14,23-dihydroxy-23-methyl-2-oxa-7,16-diazahexacyclo[11.9.2.0^3,7.0^3,25.0^8,13.0^16,24,0^17,22]pentacos-17(18),19(20),21(22)-hexaene-6,15-dione (4.10c) (0.055 g, 21%), 5-(2-acetyl-4-bromophenyl)-2-oxa,5,14-diaza-pentacyclo[10.5.1.0^1,4.0^8,13]octadec-8(9),10(11),12(13)-triene-6,15-dione (4.11c) (0.033 g, 13%), and N-(2-acetyl-4-bromophenyl)-12-hydroxy-4-oxo-16-oxa-5-aza-tetracyclo[11.2.1.0^1,5.0^6,11]hexadeca-6,8,10,14-tetraene-12-carboxamide (4.9c) (0.035 g, 14%).

\[
\text{4.10c: } ^1H \text{ NMR (500 MHz, DMSO)} \delta 8.31 (dd, J = 8.4, 1.2 Hz, 1H), 8.08 (dd, J = 8.0, 1.6 Hz, 1H), 7.83 (d, J = 8.7 Hz, 1H), 7.65 (d, J = 2.4 Hz, 1H), 7.49 (dd, J = 8.7, 2.4 Hz, 1H), 7.30 (ddd, J = 8.4, 7.3, 1.7 Hz, 1H), 7.15 (ddd, J = 7.9, 7.2, 1.3 Hz, 1H), 6.69 (s, 1H), 5.01 (s, 1H), 4.82 (dd, J = 7.3, 4.0 Hz, 1H), 4.09 (d, J = 4.0 Hz, 1H), 3.26 (d, J = 6.9 Hz, 1H), 2.73 (m, 2H), 2.45 (m, 1H), 2.17 (ddd, J = 13.0, 10.5, 9.0 Hz, 1H), 1.49 (s, 3H). \]

\[
\text{13C NMR (126 MHz, DMSO)} \delta 174.8, 171.8, 138.1, 133.7, 133.3, 130.8, 130.0, 129.6, 128.9, 126.1, 124.0, 123.4, 118.7, 118.1, 98.0, 77.4, 72.0, 68.1, 60.2, 50.9, 32.1, 31.6, 30.4. \]

HRMS (ESI) calcd for C_{23}H_{19}BrLiN_2O_5^+ (MLi^+) 489.0632, found 489.0619.
4.11c: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 8.31 (dd, \(J = 8.2, 1.3\) Hz, 1H), 8.00 (dd, \(J = 8.0, 1.5\) Hz, 1H), 7.88 (d, \(J = 2.3\) Hz, 1H), 7.69 (dd, \(J = 8.4, 2.2\) Hz, 1H), 7.46 (ddd, \(J = 8.2, 7.4, 1.5\) Hz, 1H), 7.22 (td, \(J = 7.7, 1.3\) Hz, 1H), 7.02 (d, \(J = 8.4\) Hz, 1H), 4.82 (ddd, \(J = 9.2, 6.1, 4.6\) Hz, 1H), 3.92 (dd, \(J = 10.0, 6.1\) Hz, 1H), 3.87 (dd, \(J = 10.1, 4.6\) Hz, 1H), 3.66 (d, \(J = 9.1\) Hz, 1H), 3.22 (s, 1H), 2.83 (dt, \(J = 17.2, 9.5\) Hz, 1H), 2.60 (s, 3H), 2.52 (ddd, \(J = 17.2, 9.5, 2.2\) Hz, 1H), 2.45 (ddd, \(J = 13.2, 9.2, 2.2\) Hz, 1H), 2.33 (d, \(J = 13.2, 9.7\) Hz, 1H). \(^{13}\)C NMR (126 MHz, DMSO) \(\delta\) 198.2, 173.5, 173.0, 139.6, 135.0, 133.8, 133.7, 131.3, 129.2, 128.8, 128.2, 127.8, 124.5, 120.5, 120.4, 98.4, 71.5, 68.0, 61.8, 53.7, 31.2, 29.9, 28.7. HRMS (ESI) calcd for C\(_{23}\)H\(_{19}\)BrLiN\(_2\)O\(_5\)\(^{+}\) (MLi\(^{+}\)) 489.0632, found 489.0617.

4.9c: \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta\) 12.88 (s, 1H), 8.90 (d, \(J = 9.0\) Hz, 1H), 8.08 (d, \(J = 2.4\) Hz, 1H), 7.74 (dd, \(J = 9.0, 2.4\) Hz, 1H), 7.47 (dd, \(J = 8.0, 1.2\) Hz, 1H), 7.35 (ddd, \(J = 8.1, 6.8, 2.0\) Hz, 1H), 7.16 (m, 2H), 6.72 (dd, \(J = 5.8, 2.0\) Hz, 1H), 5.70 (dd, \(J = 5.8, 1.1\) Hz, 1H), 4.97 (s, 1H), 4.87 (dd, \(J = 1.9, 1.1\) Hz, 1H), 2.74 (dd, \(J = 17.4, 9.8\) Hz, 1H), 2.70 (s, 3H), 2.58 (m, 1H), 2.52 (dt, \(J = 13.8, 9.7\) Hz, 1H), 2.44 (ddd, \(J = 13.7, 9.3, 1.5\) Hz, 1H). \(^{13}\)C NMR (126 MHz, CDCl\(_3\)) \(\delta\) 200.6, 173.4, 171.3, 138.3, 137.4, 136.9, 134.2, 133.8, 133.2, 129.3, 128.6, 128.5, 127.9, 126.7, 124.8, 122.6,
115.8, 104.1, 85.5, 85.1, 30.0, 28.8, 28.6. HRMS (ESI) calcd for C_{23}H_{19}BrLiN_{2}O_{5}^{+} (MLi^{+}) 489.0632, found 489.0615.

Irradiation of 3-(furan-2-yl)-N-(2-(((8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)carbamoyl)carbonyl)phenyl)propanamide (4.7d): General procedure C was followed using 0.45 g of 4.7d (1.0 mmol) in DCM (200 mL). Following the irradiation, the solution was concentrated to 25 mL, the mixture was centrifuged, the precipitate formed was filtered, washed with cold DCM (3 x 10 mL) followed by water (3 x 10 mL), and dried in a desiccator yielding pure 14,25-Dihydroxy-2-oxa-7,16-diazaoctacyclo[12.11.2.1.0^{1},17,0^{3}.0^{7}.0^{3}.0^{13}.0^{16,26}.0^{25,28}]octacos-8(9),10(11),12(13),17(18),19(20),21(28)-hexaene-6,15-dione (4.10d) (0.15 g, 35%). The filtrate was purified by flash chromatography (DCM/MeOH) yielding pure 5-(8-Oxo-5,6,7,8-tetrahydronaphthalen-1-yl)-2-oxa,5,14-diaza-pentacyclo[10.5.1.0^{1}.0^{14}.0^{4,8}.0^{8,13}]octadec-8(9),10(11),12(13)-triene-6,15-dione (4.11d) (0.10 g, 23%) and 12-Hydroxy-4-oxo-N-(8-oxo-5,6,7,8-tetrahydronaphthalen-1-yl)-16-oxa-5-azatetracyclo[11.2.1.0^{1}.0^{5}.0^{6,11}]hexadeca-6,8,10,14-tetraene-12-carboxamide (4.9d) (0.052 g, 12%).
4.10d: $^1$H NMR (500 MHz, DMSO) $\delta$ 8.22 (dd, $J = 8.0$, 1.6 Hz, 1H), 8.20 (dd, $J = 8.3$, 1.3 Hz, 1H), 7.33 (ddd, $J = 8.6$, 7.4, 1.5 Hz, 1H), 7.28 (m, 2H), 7.12 (ddd, $J = 8.2$, 7.3, 1.3 Hz, 1H), 7.03 (dd, $J = 7.1$, 1.8 Hz, 1H), 6.50 (s, 1H), 4.62 (dd, $J = 9.0$, 6.7 Hz, 1H), 4.13 (d, $J = 6.7$ Hz, 1H), 3.32 (d, $J = 8.9$ Hz, 1H), 3.25 (s, 1H), 2.77 (dt, $J = 17.0$, 9.5 Hz, 1H), 2.67 (s, 2H), 2.55 (m, 1H), 2.46 (m, 1H), 2.33 (dt, $J = 13.2$, 9.7 Hz, 1H), 1.94 (m, 1H), 1.66 (m, 3H). $^{13}$C NMR (126 MHz, DMSO) $\delta$ 173.6, 171.2, 139.2, 137.0, 133.3, 131.7, 129.4, 128.8, 128.2, 128.2, 127.2, 124.5, 122.1, 120.1, 100.6, 81.7, 71.5, 66.6, 60.7, 52.4, 37.7, 32.0, 30.0, 29.2, 18.8. HRMS (ESI) calcld for C$_{25}$H$_{22}$LiN$_2$O$_5^+$ (MLi$^+$) 437.1683, found 437.1710.

4.11d: $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.33 (dd, $J = 8.3$, 1.2 Hz, 1H), 8.14 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.51 (t, $J = 7.8$ Hz, 1H), 7.44 (ddd, $J = 8.4$, 7.4, 1.5 Hz, 1H), 7.38 (dd, $J = 7.8$, 1.2 Hz, 1H), 7.22 (td, $J = 7.7$, 1.3 Hz, 1H), 6.97 (d, $J = 7.7$ Hz, 1H), 4.69 (m, 1H), 3.86 (dd, $J = 10.1$, 4.0 Hz, 1H), 3.82 (dd, $J = 10.1$, 6.0 Hz, 1H), 3.75 (d, $J = 9.2$ Hz, 1H), 3.48 (d, $J = 2.3$ Hz, 1H), 3.06 (m, 2H), 2.82 (dt, $J = 17.2$, 9.5 Hz, 1H), 2.76 (m, 1H), 2.67 (ddd, $J = 16.9$, 7.8, 4.9 Hz, 1H), 2.52 (ddd, $J = 17.2$, 9.5, 2.1 Hz, 1H), 2.43 (ddd, $J = 13.2$, 9.2, 2.2 Hz, 1H), 2.31 (dt, $J = 13.2$, 9.7 Hz, 1H), 2.17 (m, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) $\delta$ 198.0, 174.4, 173.2, 147.6, 137.0, 133.8, 133.6, 130.4, 129.8, 128.5, 128.5, 127.4, 127.1, 125.4, 121.3, 98.4, 71.4, 69.2, 63.0, 54.9, 40.4,
31.2, 30.5, 29.8, 22.7. HRMS (ESI) calcd for C_{25}H_{22}LiN_{2}O_{5}^{+} (MLi^{+}) 437.1683, found 437.1695.

4.9d: $^{1}$H NMR (500 MHz, CDCl$_3$) δ 13.40 (s, 1H), 8.83 (dd, J = 8.4, 1.1 Hz, 1H), 7.54 (t, J = 8.0 Hz, 1H), 7.46 (dd, J = 8.0, 1.3 Hz, 1H), 7.34 (dd, J = 8.0, 1.8 Hz, 1H), 7.20 (dd, J = 8.0, 1.7 Hz, 1H), 7.16 (dd, J = 8.1, 1.4 Hz, 1H), 7.07 (dd, J = 7.6, 1.0 Hz, 1H), 6.75 (dd, J = 5.8, 2.0 Hz, 1H), 5.70 (dd, J = 5.8, 1.1 Hz, 1H), 4.89 (dd, J = 2.0, 1.1 Hz, 1H), 4.75 (s, 1H), 3.04 (t, J = 6.1 Hz, 2H), 2.80 (dt, J = 17.2, 9.7 Hz, 1H), 2.74 (dd, J = 7.4, 5.7 Hz, 2H), 2.62 (dd, J = 17.1, 9.6, 1.6 Hz, 1H), 2.53 (dt, J = 13.9, 9.8 Hz, 1H), 2.45 (ddd, J = 13.8, 9.3, 1.6 Hz, 1H), 2.13 (p, J = 6.5 Hz, 2H). $^{13}$C NMR (126 MHz, CDCl$_3$) δ 202.3, 173.2, 171.2, 146.2, 140.4, 137.2, 134.7, 134.1, 133.2, 129.5, 128.5, 128.3, 127.8, 126.7, 124.1, 119.7, 118.4, 104.1, 85.5, 85.2, 40.7, 31.0, 30.1, 28.8, 22.7. HRMS (ESI) calcd for C_{25}H_{22}LiN_{2}O_{5}^{+} (MLi^{+}) 437.1683, found 437.1670.

One pot procedure for the synthesis of 14,23-dihydroxy-23-methyl-2-oxa-7,16-diazaheptacyclo[11.9.2.0^{3,7}.0^{3,25}.0^{8,13}.0^{16,24}.0^{17,22}]pentacos-17(18),19(20),21(22)-hexaene-6,15-dione (4.10b):

Isatin (0.20 g, 1.4 mmol) was added to 3-(2-furyl)propionic acid (0.23 g, 1.6 mmol) solution in DCM (10 mL) at 0 °C, followed by EDC (0.31 g, 1.6 mmol) and
DMAP (0.017 g, 0.14 mmol). The reaction mixture was allowed to stir at room temperature for three hours. The mixture was then treated with 2’-aminoacetophenone (0.22 g, 1.6 mmol) and stirred overnight. After that, the mixture was diluted with DCM (50 mL) and washed with 5% aq. HCl, water, a solution of sat. aq. NaHCO₃, and water (25 mL each). The organic layer was dried over Na₂SO₄, filtered, and concentrated. The crude product was then dissolved in DCM (250 mL), degassed with N₂ 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 consumption of the starting material and [4 + 2] cycloaddition products was observed, as determined by ¹H NMR. Following the irradiation, the solution was concentrated to 25 mL, the mixture was centrifuged, the precipitate formed was filtered, washed with cold DCM (3 x 10 mL), followed by water (3 x 10 mL), and dried in a desiccator yielding pure 4.10d (0.22, 39% over two steps).
Chapter 5: Conclusion

The synthetic utility of o-azaxylylene cycloadditions in the excited state has grown rapidly since this methodology was introduced in 2011,\textsuperscript{20} and will likely continue to grow at an even greater rate. The excited state reaction pathway is no longer a black box, and has been shown to proceed through excitation to the singlet state, where ESIPT takes place, followed by intersystem crossing, an N-centered radical attack on the dienophile, and radical recombination yielding the [4 + 4] and [4 + 2] cycloaddition products. This information will prove to be invaluable to those who utilize this methodology in the future.

From this work it is clear that these cycloadditions follow the philosophy of diversity oriented synthesis, as they are capable of producing complex, and diverse scaffolds with good diastereoselectivity, and can probe an even greater region of chemical space, as these cycloaddition products are amenable to post-photochemical modifications such as palladium catalyzed cross coupling reactions.

Cascade reactions involving o-azaxylylenes cores have been shown to yield fused sp\textsuperscript{3} cyclic systems containing multiple fused rings, chiral centers, hydrogen bond donors and acceptors, as well as few rotatable bonds keeping in keeping with the general characteristics of approved drug sources.\textsuperscript{6} These complex structures can be synthesized efficiently, as the photoprecursors can be obtained in a one-pot two-step reaction from
commercially available starting materials, and the \([4 + 2]/[4 + 2]\) cascade products precipitate out of solution upon irradiation requiring no chromatographic purification.
References


Appendix A: Further Acknowledgements

I need to acknowledge my father for the long days where most would have turned their back on me. I once just needed someone to listen, and without this I don’t know if I would have been able to continue. Thank you for saving me; for always giving, and never expecting anything in return. You are someone I can always count on.

I want to thank my mother for the long nights spent editing every word I wrote as an undergraduate. Without her contribution, I would not have been able to be where I am today. Thank you for preparing me for the future and giving me the tools that I need to succeed in this world. What you have given me over the past few years is freedom, and that is invaluable to me. Greg, you are such a good man. Thank you for taking care of my mother.

Asher, you have been the best brother a man could ask for. Thank you for taking me with you out that window on those late nights, it meant a lot to me. I will never forget that you didn’t run in that hallway back at the Parkway, and it was at that moment I knew that you were more than just a brother; you are a good man and I love you.

Andrej, you are loyal, consistent, and you can always count on me for what you continue to selflessly give. Thank you for the long philosophical debates, always driving, listening, and most importantly being there when I needed you. You never give up and always forgive those around you. This characteristic alone is enough reason for me to look up to you. You inspire me to be a better man, and I am proud to say that you are my best friend.
Olga, thank you for the patience you have consistently given every day over the past five years, it couldn’t have been easy. Not once when I asked for your help were you too busy, and I am truly blessed to have had the opportunity to study under your guidance. You work so hard, and have such a passion for chemistry that wherever you wind up you will not only succeed, but they will fight to keep you. I don’t know if it has been said, but you have held this group up. You are in the trenches every day, fight for every single one of us in the K-Group, make all of us better, and without you I truly believe that this lab would only be a shadow of what it is today.

Dr. K, thank you for the opportunity that you have given me, your support, and understanding. What you do behind the scenes needs to be acknowledged. I once asked you what you missed most about working in the lab, and you told me that all you had to worry about were chemicals, but now you must worry about those who rely on you to put food on the table. Thank you for the countless hours you have put into supporting me, and funding my education; thank you for the late nights that you have spent writing grants, calculating coupling constants, and guiding me through my research; thank you for always keeping your door open.

Dr. Gareth Eaton, you cheer me up every morning. I will always remember, and truly miss the fist-bumps, jokes, and how you always took the time to have a word with me regardless of how busy you were. When I am in the area you can count on me stopping in from time to time just to visit you.

Benton, Michelle, Glenn, and Weston thank you for making these past five years fun, and most importantly being a friend. If I took nothing else from my stint here at DU
it all would have been worth it just to meet you. I am truly lucky to have been around such great people. Because of you, I will look forward to the 31st of October more than any other day of the year.
Appendix B: List of Abbreviations

Δ  temperature (heat)
Φ  quantum yield
Ac  acetyl
ACN  acetonitrile
aq.  aqueous
Ar  aryl
c.a.  circa
calcd  calculated
cat.  catalyst (or catalytic amount)
DCM  dichloromethane
DFT  density functional theory
DBU  1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAI-H  diisobutylaluminum hydride
DIPEA  N,N-diisopropylethylamine
DMAP  4-(dimethylamino)pyridine
DME  dimethoxyethane
DMF  dimethylformamide
DMSO  dimethyl sulfoxide
DOS  diversity oriented synthesis
EDC  N-(3-dimethylaminopropyl)-N’-ethylcarbodiimide hydrochloride
ESIPT  excited state intramolecular proton transfer
Et  ethyl
eq  equivalent
FVT  flash vacuum thermolysis
h  hour(s)
hex  hexane
HOMO  highest occupied molecular orbital
HPLC  high-performance liquid chromatography
HRMS  high-resolution mass spectrum
hv  light (irradiation)
IPT  intramolecular proton transfer
ISC  intersystem crossing
K_{diff}  rate of diffusion
K_{sv}  Stern-Volymer constant
LED  light emitting diode
LUMO  lowest unoccupied molecular orbital
LC  liquid chromatography
Me  methyl
MIDA  N-methyliminodiacetic acid
min  minute(s)
MS  mass spectroscopy
NMR  nuclear magnetic resonance
NPMI  N-phenylmaleimide
<table>
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<tr>
<td>P</td>
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<tr>
<td>PCC</td>
<td>pyridinium chlorochromate</td>
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<tr>
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<td>tricyclohexylphosphine</td>
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