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Photoinduced Cycloadditions in the Diversity-Oriented Synthesis Toolbox: Increasing Complexity with Straightforward Postphotochemical Modifications

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Abstract

Rapid growth of complexity and unprecedented molecular architectures are realized via the excited-state intramolecular proton transfer (ESIPT) in *o*-acylamidobenzaldehydes and ketones followed by [4+2] or [4+4] cycloadditions with subsequent postphotochemical modifications. The approach is congruent with Diversity-Oriented Synthesis: photoprecursors are synthesized in a modular fashion allowing for up to four diversity inputs. The complexity of the primary photoproducts is further enhanced using straightforward and high-yielding postphotochemical modification steps such as reactions with nitrile oxides, nitrones, Povarov reaction, and oxa-Diels-Alder reaction.

Despite large investments in pharmaceutical R&D¹ and a massive synthetic effort at the bench as reflected by the number of new compounds synthesized annually,² new drugs – and especially new drugs with the novel mechanism of action – are still rare and the number of untreatable health conditions persists. It can be safely assumed that “well in excess of 10,000 medicinal chemistry compounds are synthesized for each approved drug.”³ Such a moderate degree of success is often associated with lack of structural diversity of compounds in the existing libraries which, in turn, results from the inadequate variety in the synthetic methods employed. Relatively few classes of reactions are utilized to access the majority of the compounds prepared for biological testing⁴, and the range of the used reactions is noticeably biased towards the “easy” chemistry of sp²-sp² carbon coupling.

Photochemical reactions are conspicuously absent from the toolbox of modern combinatorial and medicinal chemists, although one hopes that the visible light photoredox synthetic “revolution” will bring the much needed change of this status quo.^{5,6} Research efforts in our group are aimed at demonstrating the potential of the photochemical methods in the context of diversity-oriented synthesis, leading to complex and topologically novel structures potentially attractive from the medicinal chemistry standpoint. A sample selection of the scaffolds synthesized through the photochemical methods in our group is presented in Figure 1⁷.

The compounds depicted above represent 8 distinct molecular scaffolds, with high content of sp³-hybridized carbons,⁸ relatively low molecular weight and logP, and very small number

of rotatable bonds. All these diverse compounds are accessible through a general and efficient strategy based on intramolecular [4+2] and [4+4] cycloadditions of azaxylylenes. These intermediates can be conveniently generated by the excited-state intramolecular proton transfer (ESIPT) from photoprecursors which are, in turn, readily accessible through standard amide-bond forming reactions (Scheme 1).

Upon irradiation *o*-formyl or *o*-acyl anilides undergo fast and efficient ESIPT into their tautomeric form, azaxylylene, with likely intersystem crossing into the triplet manifold⁹. The involvement of triplet state is supported by (1) heavy atom acceleration of the reaction upon introduction of bromine atom in the azaxylylene precursor and (2) quenching of the cycloaddition reaction by such typical triplet state quenchers as oxygen or *trans*-piperylene. As Scheme 1 illustrates, the reaction is completed via another intersystem crossing and the intramolecular collapse of the singlet radical pair to form the products of formal [4+2] or [4+4] cycloadditions. Intramolecular fluorescence quenching with tethered unsaturated pendants revealed that the cycloaddition reaction is unlikely to occur in the singlet excited state. It was also ruled out for the ground state singlet.⁹

This photochemical reaction is fully congruent with the philosophy of diversity-oriented synthesis. The synthesis of the photoprecursor is straightforward and amenable to modular assembly, allowing for up to four diversity inputs. The photochemical step results in a dramatic growth of complexity, yielding two or more distinct molecular scaffolds, which can be further introduced into a postphotochemical reaction step. We have previously shown that the primary photoproducts lend themselves to various postphotochemical modifications, for example, the Suzuki reaction.^{7d} Further modifications offered by the double bonds in the [4+2] and [4+4] frameworks could allow for the increase in scaffold diversity and complexity via the addition of dipoles or heterodienes. Thus, the aim of the current study was to evaluate the scope of postphotochemical modifications and the opportunities for rapid access to extended polyheterocyclic sheets of unprecedented topology. We also utilized computer-aided property prediction for the synthesized compounds, and assessed their skeletal diversity and other properties. Specifically, we now report the postphotochemical reactions of the primary [4+4] and [4+2] photoproducts with phenylnitrile oxide, N-(phenylmethylene)methanamine N-oxide, 1-oxabutadienes, generated from the 1,3-dicarbonyl compounds and N-phenyl-aryl-2-ylmethanimines (Povarov reaction).

The model system for these studies was prepared via photoinduced cyclization of 2-(3-(fur-2-yl)propanamido)benzaldehyde as shown in Scheme 2. The acylation of TMS-protected *o*-aminobenzyl alcohol **1**, followed by PCC oxidation yielded photoprecursor **2**, which upon irradiation in a Rayonet photoreactor equipped with RPR-3500 UV lamps (a broadband 300–400nm UV source, with $\lambda_{\text{max}} \sim 350\text{nm}$) underwent [4+2] and [4+4] cycloadditions to yield two distinct polyheterocyclic scaffolds in good yields. The reaction occurs diastereospecifically, yielding only *syn*-[4+4] and *anti*-[4+2], where *syn*- and *anti*- refers to the respective arrangement of the benzylic hydroxy group in the quinolinol or benzoazacane ring, and furan's oxygen.

Reactions with dipoles

Both [4+4] and [4+2] cycloadducts react with nitrile oxides¹⁰, generated *in situ* from the corresponding bromooximes (Scheme 3). In both cases the 1,3-dipolar cycloaddition of benzonitrile oxide occurs from the *exo*-face. Similarly to the previously described reaction with bromonitrile oxide, [4+4] cycloadduct produces two regioisomers **6** and **6'** in the ratio of 3:1, while [4+2] reacts regioselectively to give the charged-controlled **5** as the only product. The observed differences can be explained by the stereoelectronic properties of the alkenes: the [4+2] photoproduct possesses a dihydrofuran moiety, and the 1,3-dipolar cycloaddition is expected to proceed through a charge controlled transition state, whereas the double bond in the [4+4] substrate is not as polarized, so both regioisomers are observed. The structure of the adducts was confirmed by the analysis of their NMR spectra and comparison with the previously isolated adducts of bromonitrile oxide^{7g}.

The [4+2] photoproduct does not tolerate the conditions for the addition of the nitrones¹¹, degrading in the process, while the [4+4] photoproduct reacts cleanly to give two stereoisomers **7** and **7'** in the 3:1 ratio (Scheme 3). Both isomers result from the attack of the nitron from the least hindered- *exo*-face and differ in the relative position of the phenyl ring with the phenyl group pointing away from the pyrrolidinone moiety. We were able to obtain an Xray structure for the major isomer **7**, and based stereochemical assignment of the minor isomer on the results of NOE experiments. The aliphatic regions of the ¹H NMR spectra of both stereoisomers **7** and **7'** possess two separate spin systems: H_a-H_b and H_c-H_d-H_e. The spin-spin coupling constant H_b-H_e is not observed experimentally. In both cases H_e signal is a triplet at 2.73 (**7**) or 2.82 (**7'**) ppm. To unambiguously prove the structure of the products, we conducted NOE differences experiments for both isomers. In **7** upon irradiating the triplet H_e at 2.73 ppm, we see NOE of 3% with H_a, which is indicative of the regiochemistry shown, as well as NOE of 13% on H_b and H_c, but no signal from H_d, which implies that protons H_d and H_e reside on the opposite faces of the isoxazoline ring. Similarly, in **7'** upon irradiating the triplet H_e at 2.82 ppm, we see NOE of 8% with protons H_a and H_b, which again indicated that phenyl group is located on the “northern” side of the molecule, *syn* to the benzylic OH group and anti to pyrrolidone moiety. Additionally we see NOE on both H_c and H_d (13% and 11%, respectively), suggesting that all three protons are *syn* to each other.

Reaction with dichlorocarbene

One observation that we made during this study is that the general reactivity of the remaining double bond in primary [4+4] photoproduct **3** was very low. Product **3** was then modified through the sequence of acid-induced bicyclo[4.2.1] → bicyclo[3.3.1] rearrangement and oxidation as shown in Scheme 4^{7g}. Dichlorocarbene was generated *in situ* from chloroform and sodium hydroxide, but the reaction yielded α-chloroester **8**, which is presumably formed as a result of Jovic-Reeve reaction of the carbene with the ketone functionality¹⁴.

We hypothesized that the carbene attacked from *exo*-side of the bicyclic benzoazacane ring, and the initially formed epoxide is ring-opened by the nucleophile (Cl^-) from the sterically accessible *exo*-side.

Hetero-Diels-Alder reactions

Expectedly the [4+4] adduct was neither reactive in the Povarov nor in the oxa-Diels-Alder reaction. However, the [4+2] product possessing a much more reactive vinyl ether moiety proved to react smoothly, yielding a single regio- and stereoisomer as a result of the Povarov reaction and the reactions with both Meldrum's acid and barbituric acid-based *s-cis* oxabutadienes as shown in Scheme 5.

Povarov reaction^{15,16} was conducted in 2,2,2-trifluoroethanol as a solvent at 40°C. Again, the 2-azadiene expectedly attacks from the less hindered *exo*-face, with the pyridine ring winding up in the thermodynamically favored equatorial position. The structure of the product was supported by the NMR data. Among the aliphatic protons H_c has the highest chemical shift, being observed at 5.25 ppm as a doublet, $J = 7.7$ Hz. H_b is characterized by ddd at 2.54 ppm with the spin-spin coupling constants of 10.4 Hz (with H_a), 7.8 Hz (with H_c) and 2.9 Hz (with H_d). The value of the biggest constants corresponds to axial-axial interaction, which puts the pyridine ring in equatorial position.

Next we attempted oxa-Diels-Alder reactions using oxabutadienes¹⁷, generated *in situ* from 1,3-dicarbonyl compounds (Meldrum's acid and dimethyl barbituric acid). The reaction with dimethyl barbituric acid proceeds smoothly giving one stable product of *exo*-addition of the diene, the Meldrum's acid adduct was unstable, undergoing ketal hydrolysis followed by decarboxylation. The structure of the product was unambiguously proven by X-ray analysis. Structures of both products are supported by ^1H NMR analysis.

These postphotochemical modifications are not limited to furan-based photoproducts and can be carried out with thiophene- and pyrrole-based systems as well. Thiophene-based [4+2] photoproduct **13**, obtained in a manner similar to furanyl adduct **11**, was introduced into the reaction with dimethyl barbituric acid (Scheme 6). The reaction yielded a single product of a charged-controlled cycloaddition of the *in situ* generated oxabutadiene to the dihydrothiophene moiety of **13**.

Similarly to furan-based compounds **11** and **12''**, its structure was determined by NMR analysis, which was augmented by the prediction of proton spin-spin coupling constants (SSCCs). For this we used a DFT *relativistic force field* method which we have recently developed and which is based on fast and accurate scaling of Fermi contacts.¹⁸ As Figure 4 shows, for all three postphotochemical cycloadducts experimental SSCCs matched the computed constants very well, leaving no doubt that our stereochemical assignment is accurate.

Pyrrolines, such as **16**, accessed via intramolecular cycloadditions of azaxylylenes photogenerated from amino acid-based pyrroles, such as **15**, are also well-suited for postphotochemical modifications, although in this case an unexpected *double addition* occurred. For example, when phenylalanine-based *enantiopure* photoprecursor **15** was

irradiated in DMSO and, without further purification, subjected to hetero-Diels-Alder reaction with methylenearbituric acid generated *in situ*, the reaction yielded a product incorporating two pyrimidinetrione moieties (Scheme 7). We believe that the first equivalent of the diene adds to the enamine moiety, forming transient intermediate **17** similar to **11** and **14**. However, due to additional stability of the iminium ion, intermediate **17** exists in equilibrium with its zwitterionic form **17**^{+/-}, which captures the second equivalent of methylenearbituric acid, effectively resulting in a [2+2+2] product (**18**). We have found only one example of a somewhat related cycloaddition in the literature¹⁹.

The structure of the product **18** was supported by additional NMR experiments (¹³C APT, HMBC and HMQC), as well as by comparison of the experimental and calculated NMR spectra, Figure 5. HMBC spectrum of the initial photoproduct skeleton revealed an expected pattern of C-H cross-peaks, indicating that the pyrrolo-quinolinone skeleton remains unchanged. Characteristic are the protons C_d-H and C_d-H', which are represented by two doublets at 2.14 and 2.48 ppm with ²J = 15.3 Hz. In HMBC spectrum these doublets exhibit cross-peaks with quaternary carbons C_c and C_e at 51.5 and 56.1 ppm. The peak at 56.1 ppm is attributed to carbon C_e judging by the cross-peaks with C_f-H and C_a-H in HMBC spectrum; whereas the peak at 51.5 ppm, which has a cross-peak with C_b-H, - to carbon C_d. The calculated spin-spin coupling constants for the proposed structure are in an excellent agreement with the experiment (rmsd = 0.36 Hz and the maximum unsigned error of 0.81 Hz).

It is clear that a combination of the [4+4] and [4+2] scaffolds generated via the photochemical step and further modified in simple postphotochemical steps involving mostly 1,3-dipolar, or [4+2], or [2+2+2] cycloadditions, produced complex polyheterocyclic sheets with “visibly” diverse frameworks. Out of 10 compounds synthesized, 9 distinct molecular scaffolds were prepared in a total of 19 steps. Although compared to a typical combinatorial chemistry libraries the number of compounds in this library is very small, we believe that the “steps per scaffold efficiency”²⁰ (2.11 steps per scaffold) is very appealing, as is the rapid growth of complexity from the readily available photoprecursors to the postphotochemical final products.

To quantify the diversity of the combined mini-library of the compounds **5–18** synthesized in this work and augmented with previously synthesized compounds **A–H** we employed computed Tanimoto similarity coefficients²¹. As Table 1 illustrates, the off-diagonal elements are in the 0.2–0.5 range for the majority of compounds, which amounts to significant scaffold diversity.

Table 2 shows comparison of additional properties of our compounds with the mean properties of compounds appearing in the Journal of Medicinal Chemistry publications in 2005–2009.³

Instructively, our mini-library has compounds with higher fsp3, lower logP values, and a very small number of rotatable bonds, which makes the synthesized molecules attractive candidates for fragment-based drug discovery approach that is gaining momentum²². Synthesized polyheterocyclic sheets **11**, **12**, **14** have a “belt” of polyacetal moieties a

structural feature somewhat similar to oxatriquinane motif found in biologically active gracilins J, K, H,²³ paracaseolide A,²⁴ and novel nonpeptide HIV-1 protease inhibitors from the Ghosh lab.²⁵

In conclusion, we have demonstrated that significant structural diversity can be generated with a high *steps per scaffold efficiency* via a combination of intramolecular cycloadditions of photogenerated azaxylylenes and experimentally simple and straightforward postphotochemical modifications of the primary photoproducts.

Experimental part

Common solvents were purchased from Pharmco and used as is, except for THF, which was refluxed over and distilled from sodium benzophenone ketyl prior to use. Common reagents were purchased from Aldrich and used without additional purification, unless indicated otherwise. NMR spectra were recorded at 25°C on a Bruker Avance III 500 MHz in CDCl₃ (unless noted otherwise). X-Ray structures were obtained with a Bruker APEX II instrument (for details see S₁ and included cif files). High resolution mass spectra were obtained on the *MDS SCIEX/Applied Biosystems API QSTARTM Pulsar i Hybrid LC/MS/MS System* mass spectrometer from the University of Colorado at Boulder. Flash column chromatography was performed using Teledyne Ultra Pure Silica Gel (230–400 mesh) on a Teledyne Isco Combiflash R_f using Hexanes/EtOAc as an eluent.

Synthesis of Photoprecursor and Photoproducts

The compounds **3**, **4** and **13** were synthesized as previously described by our group. **N-hydroxy-benzenecarboximidoyl bromide**,¹⁰ **(1E)-N-phenyl-1-pyridin-2-ylmethanimine**,¹⁵ **N-oxide-N-(phenylmethylene)-methanamine**¹¹ were prepared according to the existing procedures.

Postphotochemical Modifications

Addition of nitile oxide, general procedure I

1 eq of photoproduct was dissolved in EtOAc. To this was added 3 eq of N-hydroxy-benzenecarboximidoyl bromide and 6 eq of KHCO₃. An additional 3 eq of N-hydroxy-benzenecarboximidoyl bromide and 6 eq of KHCO₃ were added after stirring for 12 h. The reaction was monitored by NMR until the starting photoproduct was consumed. The resulting mixture was diluted with water, extracted with 3x20 mL of EtOAc, washed with brine, dried over Na₂SO₄, and concentrated *in vacuo*. The mixture was then purified by flash chromatography.

12-hydroxy-15-phenyl-17,19-dioxa-5,16-diazapentacyclo[11.5.1.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6,8,10,15-tetraen-4-one (6)—

General procedure **I** was followed. From 0.25 g of **1** (1.0 mmol), 1.2 g of **N-hydroxy-benzenecarboximidoyl bromide** (6.2 mmol), and 1.2 g of KHCO₃ (12.3 mmol), 0.15 g (61%) of the title compound was obtained. ¹H NMR (500 MHz, CDCl₃) δ 7.65 (m, 2H), 7.57 (dd, *J* = 8.4, 1.3 Hz, 1H), 7.48 (m, 5H), 7.35 (m, 1H), 4.86 (d, *J* = 8.8 Hz, 1H), 4.78 (m, 2H), 3.87 (dd, *J* = 8.8, 1.0 Hz, 1H), 2.88 (m, 2H), 2.77 (dt, *J* = 14.1, 9.9 Hz, 1H), 2.66 (ddd,

$J = 16.7, 9.5, 0.9$ Hz, 1H), 2.46 (ddd, $J = 14.1, 8.8, 1.0$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.8, 156.3, 133.4, 133.1, 132.6, 130.7, 129.9, 129.2, 128.5, 127.6, 127.5, 126.7, 104.9, 88.1, 82.2, 77.6, 56.3, 29.4, 27.2. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4\text{Li}^+$ (MLi) $^+$ 369.1427 found 369.1405

12-hydroxy-15-phenyl-17,19-dioxo-5,16-diazapentacyclo[11.6.0.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6(11),7,9,15-tetraen-4-one (5)

—General procedure **I** was followed. From 0.25 g of **2** (1.0 mmol), 1.2 g of **N-hydroxy-benzenecarboximidoyl bromide** (6.1 mmol) and 1.2 g of KHCO_3 (12.4 mmol), 0.14 g (59%) of the title compound was obtained. ^1H NMR (500 MHz, CDCl_3) δ 7.98 (d, $J = 8.0$ Hz, 1H), 7.73 (m, 2H), 7.54 (m, 3H), 7.49 (td, $J = 7.9, 1.5$ Hz, 1H), 7.46 (dd, $J = 7.5, 1.3$ Hz, 1H), 7.27 (td, $J = 7.5, 1.2$ Hz, 1H), 5.81 (d, $J = 6.2$ Hz, 1H), 4.97 (d, $J = 3.0$ Hz, 1H), 3.84 (dd, $J = 6.2, 3.3$ Hz, 1H), 3.29 (t, $J = 3.1$ Hz, 1H), 2.84 (m, 1H), 2.40 (m, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.3, 158.7, 134.5, 130.8, 130.0, 129.8, 129.2, 128.7, 127.7, 127.1, 125.5, 122.9, 107.0, 101.4, 70.7, 57.1, 55.1, 34.1, 30.1. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{18}\text{N}_2\text{O}_4\text{Li}^+$ (MLi) $^+$ 369.1427 found 369.1407

Nitrone Cycloadditions

1 eq of photoproduct was dissolved in 1 mL of anhyd. toluene along with 4 eq of **N-oxide-N-(phenylmethylene)-methanamine**. The reaction was sealed in a high pressure reaction vessel and heated to completion as shown by ^1H NMR. The toluene was removed *in vacuo* and the residue purified by flash chromatography.

anti-12-hydroxy-16-methyl-15-phenyl-17,19-dioxo-5,16-diazapentacyclo[11.5.1.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6,8,10-trien-4-one (7)—From 100 mg of **1** (0.41 mmol) and 0.22 g of **N-oxide-N-(phenylmethylene)-methanamine** (1.6 mmol), 98.0 mg (63%) of title compound was isolated. ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, $J = 8.0$ Hz, 1H), 7.39 (m, 4H), 7.32 (m, 2H), 7.24 (m, 2H), 4.59 (d, $J = 4.4$ Hz, 1H), 4.38 (m, 2H), 3.32 (d, $J = 8.6$ Hz, 1H), 2.87 (m, 1H), 2.74 (t, $J = 7.5$ Hz, 1H), 2.58 (m, 2H), 2.43 (m, 1H), 2.20 (s, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.9, 134.0, 133.6, 132.5, 129.5, 129.1, 128.7, 128.2, 127.8, 127.8, 127.1, 102.6, 84.2, 81.4, 79.5, 77.4, 61.2, 29.6, 27.1. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4\text{Li}^+$ (MLi) $^+$ 385.1740 found 385.1724

syn-12-hydroxy-16-methyl-15-phenyl-17,19-dioxo-5,16-diazapentacyclo[11.5.1.0^{1,5}.0^{6,11}.0^{14,18}]nonadeca-6,8,10-trien-4-one (7')—General procedure **IV** was followed. From 0.10 g of **1** (0.41 mmol) and 0.22 g of **N-oxide-N-(phenylmethylene)-methanamine** (1.6 mmol), 33.0 mg (21%) of title compound was isolated. ^1H NMR (500 MHz, CDCl_3) δ 7.55 (dd, $J = 8.0, 0.9$ Hz, 1H), 7.39 (m, 6H), 7.25 (m, 2H), 4.33 (d, $J = 7.0$ Hz, 1H), 4.19 (m, 2H), 3.61 (d, $J = 7.7$ Hz, 1H), 2.92 (m, 1H), 2.81 (t, $J = 7.4$ Hz, 1H), 2.68 (m, 1H), 2.58 (s, 3H), 2.54 (m, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.9, 135.8, 133.9, 133.8, 132.5, 129.4, 128.9, 128.3, 128.2, 128.0, 126.8, 103.6, 83.9, 78.7, 77.7, 75.4, 55.9, 43.6, 29.9, 26.7. HRMS (ESI) calcd for $\text{C}_{22}\text{H}_{22}\text{N}_2\text{O}_4\text{Li}^+$ (MLi) $^+$ 385.1740 found 385.1724

Ethyl 13-chloro-4-oxo-16-oxa-5-azatetracyclo[10.3.1.0^{1,5}.0^{6,11}]hexadeca-6,8,10,14-tetraene-13-carboxylate (9)—0.14 g of **5** (0.58 mmol) was

dissolved in 50 mL of chloroform. To this was added 30 mg of tetrabutylammonium hydrogen sulfate (0.084 mmol) and 10 mL of a 50% w/w solution of NaOH. The mixture was vigorously stirred at ambient temperature for 20 h, then poured into 200 mL of water and extracted with CHCl_3 . The organic layer was separated, dried over anhydrous Na_2SO_4 , and concentrated *in vacuo*. The mixture was purified by flash chromatography to yield 0.12 g (66%) of the title compound. ^1H NMR (500 MHz, CDCl_3) δ 8.42 (dd, J = 8.3, 1.0 Hz, 1H), 7.38 (ddd, J = 8.7, 7.5, 1.6 Hz, 1H), 7.19 (dd, J = 8.0, 1.4 Hz, 1H), 7.09 (td, J = 7.7, 1.3 Hz, 1H), 6.38 (dd, J = 9.9, 1.2 Hz, 1H), 5.83 (d, J = 9.9 Hz, 1H), 5.47 (s, 1H), 4.27 (m, 2H), 2.74 (m, 2H), 2.42 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR (126 MHz, CDCl_3) δ 170.8, 167.3, 133.1, 129.7, 126.9, 126.8, 126.4, 123.8, 120.4, 119.9, 85.9, 77.3, 64.2, 62.9, 30.3, 29.9, 13.8. HRMS (ESI) calcd for $\text{C}_{17}\text{H}_{16}\text{NO}_4\text{Li}^+$ (MLi) $^+$ 340.0928 found 340.0920

14-hydroxy-11-(pyridin-2-yl)-2-oxa-10,21-diazahexacyclo[11.11.0.0^{1,21}.0^{3,12}.0^{4,9}.0^{15,20}] tetracos-4(9),5,7,15,17,19-hexaen-22-one (10)—0.22 g of (1E)-N-phenyl-1-pyridin-2-ylmethanimine (1.2 mmol) and 0.15 g of **4** (0.61 mmol) were dissolved in 1.5 mL of 2,2,2-trifluoroethanol and warmed to 40°C until the reaction was complete as observed by ^1H NMR. The resulting mixture was concentrated *in vacuo* and purified by flash chromatography, yielding 80 mg (31%) of the title compound. ^1H NMR (500 MHz, CDCl_3) δ 8.74 (ddd, J = 4.9, 1.8, 0.9 Hz, 1H), 7.88 (td, J = 7.7, 1.8 Hz, 1H), 7.85 (d, J = 8.1 Hz, 1H), 7.57 (d, J = 7.9 Hz, 1H), 7.39 (m, 3H), 7.17 (td, J = 7.6, 1.0 Hz, 3H), 7.11 (td, J = 7.5, 1.1 Hz, 2H), 6.85 (td, J = 7.5, 1.2 Hz, 1H), 6.77 (dd, J = 7.4, 1.1 Hz, 2H), 5.25 (d, J = 7.7 Hz, 1H), 4.82 (d, J = 1.4 Hz, 1H), 4.65 (s, 1H), 3.38 (dd, J = 10.4, 2.5 Hz, 1H), 3.10 (d, J = 2.5 Hz, 1H), 2.69 (ddd, J = 16.3, 10.9, 8.2 Hz, 1H), 2.54 (ddd, J = 10.4, 7.9, 2.5 Hz, 1H), 2.18 (dd, J = 16.6, 8.6 Hz, 1H), 2.06 (ddd, J = 12.4, 10.9, 8.8 Hz, 1H), 1.68 (dd, J = 12.6, 8.0 Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.7, 159.2, 149.5, 143.4, 137.1, 134.0, 130.6, 130.0, 129.9, 128.9, 128.6, 125.5, 123.8, 123.1, 121.6, 120.8, 119.3, 115.6, 100.2, 77.2, 74.7, 70.2, 56.6, 50.5, 45.9, 36.0, 29.9. HRMS (ESI) calcd for $\text{C}_{26}\text{H}_{23}\text{N}_3\text{O}_3\text{Li}^+$ (MLi) $^+$ 432.1900 found 432.1889

General Procedure II for oxa-Diels-Alder Reactions

1 eq of photoproduct and 1 eq of 1,3-dicarbonyl compound were dissolved in 0.7 mL of dry acetonitrile. To this was added 0.08 eq of L-proline and 1.3 eq of 37% aq. formaldehyde solution. The reaction stirred at ambient temperature until full consumption of the photoproduct, as determined by ^1H NMR. The reaction was diluted with water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 , and concentrated *in vacuo*. The mixture was then purified by flash chromatography.

12-hydroxy-16-methylidene-18,20-dioxa-5-azapentacyclo[11.7.0.0^{1,5}.0^{6,11}.0^{14,19}]jicosa-6,8,10-triene-4,17-dione (12'')—General procedure II was followed. From 0.10 g of **2** (0.41 mmol), 0.06 g of Meldrum's acid (0.41 mmol), 3.8 mg of L-proline (0.033 mmol), and 0.04 mL of 37% w/w formaldehyde solution in water (0.53 mmol), was obtained 52 mg (35%) of the title compound. ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, J = 8.0 Hz, 1H), 7.42 (td, J = 7.7, 1.5 Hz, 1H), 7.33 (d, J = 7.3 Hz, 1H), 7.21 (td, J = 7.7, 1.2 Hz, 1H), 6.59 (s, 1H), 5.77 (s, 1H), 5.66 (d, J = 4.8 Hz, 1H), 4.64 (d, J = 2.4 Hz, 1H), 2.89 (dd, J = 11.0, 2.5 Hz, 1H), 2.75 (m,

3H), 2.47 (dd, $J = 12.6, 8.4$ Hz, 1H), 2.35 (tdd, $J = 12.7, 9.8, 1.7$ Hz, 1H), 2.23 (dt, $J = 16.4, 8.1$ Hz, 1H), 2.16 (dtd, $J = 11.3, 4.7, 2.6$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.7, 173.7, 163.5, 133.4, 130.9, 130.0, 130.0, 129.8, 129.3, 125.9, 123.8, 102.9, 102.0, 68.8, 51.7, 40.4, 35.8, 29.6, 27.3. HRMS (ESI) calcd for $\text{C}_{18}\text{H}_{17}\text{NO}_5\text{Li}^+$ (MLi^+)⁺ 334.1267 found 334.1253

14-hydroxy-6,8-dimethyl-2,4-dioxo-6,8,21-

triazahexacyclo[11.11.0.0^{1,21}.0^{3,12}.0^{5,10}.0^{15,20}]tetracos-5(10),15,17,19-

tetraene-7,9,22-trione (11)—General procedure **II** was followed. From 100 mg of **2** (0.41 mmol), 0.064 g of 1,3-dimethylbarbituric acid (0.41 mmol), 3.8 mg of L-proline (0.033 mmol), and 0.04 mL of 37% w/w formaldehyde solution in water (0.53 mmol), was obtained 76 mg (45%) of the title compound. ^1H NMR (500 MHz, CDCl_3) δ 7.89 (d, $J = 8.0$ Hz, 1H), 7.48 (td, $J = 7.8, 1.6$ Hz, 1H), 7.36 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.26 (td, $J = 7.4, 1.2$ Hz, 1H), 5.57 (d, $J = 4.0$ Hz, 1H), 4.79 (d, $J = 2.6$ Hz, 1H), 3.42 (s, 3H), 3.39 (s, 3H), 2.90 (m, 1H), 2.85 (dd, $J = 11.6, 2.6$ Hz, 1H), 2.77 (d, $J = 17.1$ Hz, 1H), 2.56 (dd, $J = 17.1, 6.5$, 1H), 2.42 (m, 4H), 2.16 (dddd, $J = 11.6, 6.5, 4.0, 1.4$ Hz, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 173.4, 163.0, 154.0, 151.0, 133.2, 130.3, 129.8, 129.1, 126.1, 124.0, 102.1, 100.0, 82.5, 69.2, 51.6, 39.6, 36.5, 29.6, 28.7, 28.1, 18.1. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_6\text{Li}^+$ (MLi^+)⁺ 418.1591 found 418.1571

14-hydroxy-6,8-dimethyl-4-oxa-2-thia-6,8,21-

triazahexacyclo[11.11.0.0^{1,21}.0^{3,12}.0^{5,10}.0^{15,20}]tetracos-5(10),15,17,19-

tetraene-7,9,22-trione (14)—General procedure **II** was followed with DMSO as a solvent. From 70.0 mg of **13** (0.27 mmol), 0.13 g of 1,3-dimethylbarbituric acid (0.81 mmol), 7.5 mg of L-proline (0.065 mmol), and 0.08 mL of 37% formaldehyde in water (1.1 mmol), was obtained 36 mg (31%) of the title compound. ^1H NMR (500 MHz, CDCl_3) δ 7.78 (d, $J = 7.9$ Hz, 1H), 7.49 (td, $J = 7.7, 1.2$ Hz, 1H), 7.35 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.27 (dd, $J = 7.5, 1.0$ Hz, 1H), 5.55 (d, $J = 3.1$ Hz, 1H), 4.84 (d, $J = 3.1$ Hz, 1H), 3.40 (s, 3H), 3.38 (s, 3H), 2.86 (dd, $J = 12.1, 2.3$ Hz, 1H), 2.78 (dd, $J = 17.0, 0.8$ Hz, 1H), 2.65 (m, 2H), 2.60 (dd, $J = 17.0, 6.5$ Hz, 1H), 2.50 (m, 2H), 2.39 (dddd, $J = 12.05, 6.5, 3.2, 0.8$ Hz, 1H), 2.30 (s, 1H). ^{13}C NMR (126 MHz, CDCl_3) δ 171.8, 163.1, 154.5, 150.9, 133.5, 130.9, 130.4, 128.9, 126.4, 124.4, 88.8, 85.0, 82.9, 70.4, 56.2, 45.4, 42.4, 30.7, 28.7, 28.1, 20.3. HRMS (ESI) calcd for $\text{C}_{21}\text{H}_{21}\text{N}_3\text{O}_5\text{SLi}^+$ (MLi^+)⁺ 434.1362 found 434.1353

14-benzyl-5-hydroxy-5,21,23,28,30-pentamethyl-17,19-dioxo-12,15,21,23,28,30-hexaazaoctacyclo[16.8.4.1^{4,12}.0^{1,18}.0^{3,16}.0^{6,11}.0^{20,25}.0^{15,31}]

hentriaconta-6,8,10,20(25)-tetraene-13,22,24,27,29-pentone (18)—0.10 g of (*S*)-*N*-(2-acetylphenyl)-3-phenyl-2-(1*H*-pyrrol-1-yl)propanamide (**15**) (0.3 mmol) was dissolved in 1.5 mL of DMSO. This was degassed and irradiated in Pyrex reaction vessel in LED-365 until the reaction was complete, as determined by ^1H NMR. The solution was then added directly to 0.05 g of 1,3-dimethylbarbituric acid (0.3 mmol). To this was added 3.0 mg of L-proline (0.024 mmol), and 0.03 mL of 37% w/w formaldehyde solution in water (0.39 mmol). The reaction was heated to 70°C until full consumption of the photoproduct, as determined by ^1H NMR. The reaction was diluted with water and extracted with EtOAc. The organic layer was separated, dried over Na_2SO_4 , and concentrated *in vacuo*. The mixture

was then purified by flash chromatography, yielding 46 mg (23%) of the title compound. ¹H NMR (500 MHz, CDCl₃) δ 8.63 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.58 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.37 (ddd, *J* = 8.5, 7.3, 1.6 Hz, 1H), 7.19 (m, 6H), 5.04 (d, *J* = 4.5 Hz, 1H), 4.34 (d, *J* = 11.1 Hz, 1H), 3.76 (dd, *J* = 11.2, 3.4 Hz, 1H), 3.40 (s, 3H), 3.27 (s, 3H), 3.22 (s, 3H), 3.17 (dd, *J* = 10.6, 4.5 Hz, 1H), 2.99 (s, 3H), 2.96 (dd, *J* = 13.6, 3.4 Hz, 1H), 2.78 (dd, *J* = 13.5, 11.3 Hz, 1H), 2.75 (dd, *J* = 13.5, 11.3 Hz, 1H), 2.53 (qd, *J* = 11.2, 7.2 Hz, 1H), 2.52 (d, *J* = 14.8 Hz, 1H), 2.45 (dd, *J* = 13.6, 7.1 Hz, 1H), 2.32 (d, *J* = 14.8 Hz, 1H), 2.04 (s, 1H), 1.65 (s, 3H). ¹³C NMR (126 MHz, CDCl₃) δ 173.6, 172.1, 171.3, 170.7, 170.6, 150.7, 150.3, 138.2, 132.4, 130.4, 129.7, 128.8, 127.8, 126.6, 126.1, 124.7, 117.9, 78.3, 71.9, 71.5, 66.7, 56.0, 53.3, 51.4, 39.1, 37.1, 36.5, 36.0, 34.6, 29.4, 29.4, 29.3, 29.1. HRMS (ESI) calcd for C₃₅H₃₆N₆O₈Li⁺ (MLi)⁺ 675.2755 found 675.2742

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References

1. In 2013 the R&D spending in the US pharmaceutical industry totaled \$51.1 billion, the financial support for the medical research by NIH made another \$30.3 billion. <http://www.nih.gov/about/budget.htm>, <http://www.statista.com/study/10708/us-pharmaceutical-industry-statista-dossier/>
2. CAS statistical summary 1907–2007
3. Walters WP, Green J, Weiss JR, Murcko MA. J Med Chem. 2011; 54:6405–6416. [PubMed: 21755928]
4. Cooper TWJ, Campbell IB, Macdonald SJF. Angew Chem Int Ed. 2010; 49:8082–8091. Roughley SD, Jordan AM. J Med Chem. 2011; 54:3451. [PubMed: 21504168]
5. Prier CK, Rankic DA, MacMillan DWC. Chem Rev. 2013; 113:5322. [PubMed: 23509883]
6. for recent examples of significant increase of complexity as a result of a photochemical step followed by postphotochemical transformations see: Finn PB, Kulyk S, Mc Sieburth SN. Tetrahedron Lett. 2015; 56:3567. Chen P, Carroll PJ, Mc Sieburth SN. Org Lett. 2010; 12:4510. [PubMed: 20857951]
7. (a) Mukhina OA, Kumar NNB, Arisco TM, Valiulin RA, Metzel GA, Kutateladze AG. Angew Chem, Int Ed. 2011; 50:9423. (b) Nandurkar NS, Kumar NNB, Mukhina OA, Kutateladze AG. ACS Comb Sci. 2013; 15:73. [PubMed: 23157463] (c) Kumar NNB, Mukhina OA, Kutateladze AG. J Am Chem Soc. 2013; 135:9608. [PubMed: 23789841] (d) Cronk WC, Mukhina OA, Kutateladze AG. J Org Chem. 2014; 79:1235. [PubMed: 24397435] (e) Kumar NNB, Kuznetsov DM, Kutateladze AG. Org Lett. 2015; 17(3):438–441. [PubMed: 25587772] (f) Mukhina OA, Kumar NNB, Cowger TM, Kutateladze AG. J Org Chem. 2014; 79(22):10956–10971. [PubMed: 25370821] (g) Umstead WJ, Mukhina OA, Kutateladze AG. Eur J Org Chem. 2015; (10):2205–2213.
8. for Lovering's fsp3 parameter see: Lovering F, Bikker H, Humblet C. J Med Chem. 2009; 52:6752. [PubMed: 19827778]
9. Mukhina OA, Cronk WC, Kumar NNB, Sekhar M, Samanta A, Kutateladze AG. J Phys Chem A. 2014; 118(45):10487–10496. [PubMed: 24958234]
10. Liu, Ying. TIANJIN INST PHARM RESEARCH, assignee. Oxime Derivatives Containing Thienopyridine, Preparation Method and Application Thereof. Patent. CN101402641. Apr 8. 2009 Print
11. Canterbury DP, Herrick IR, Um J, Houk KN, Frontier AJ. Tetrahedron. 2009; 65:3165–3179. [PubMed: 20161228]
12. Signals for protons Hb and Hc overlap; we assign Ha signal to the doublet in the lowest field
13. Signals for protons Ha and Hb overlap

14. Snowden TS. ARKIVOC. 2012:24–40.
15. Borrione E, Prato M, Scorrano G, Stivanello M, Lucchini V. J Heterocyclic Chem. 1988; 25:1831–1835.
16. Spanedda MV, Hoang VD, Croisse B, Bonnet-Delpon D, Bégué J-P. Tetrahedron Lett. 2003; 44:217–219.
17. Stevenson R, Weber JV. Heterocycles. 1988; 27:1929–1933.
18. Kutateladze AG, Mukhina OA. J Org Chem. 2015; doi: 10.1021/acs.joc.5b00619 for the previous version of *rff* see Kutateladze AG, Mukhina OA. J Org Chem. 2014; 79:8397. [PubMed: 25158224]
19. Kuan H-H, Chien C-H, Chen K. Org Lett. 2013; 15:2880–2883. [PubMed: 23718287]
20. For examples of steps-per-scaffold concept use in the description of combinatorial libraries, see Sen S, Kamma SR, Gundla R, Adepally U, Kuncha S, Thirunathi S, Prasad UV. RSC Adv. 2013; 3:2404–2411. Diaz-Gavilan M, Galloway WRJD, O'Connell KMG, Hodgkinson JT, Spring DR. Chem Commun. 2010; 46:776–778.
21. (a) Rogers DJ, Tanimoto TT. Science. 1960; 132:1115–1118. [PubMed: 17790723] (b) Open Babel software package. <http://openbabel.org>
22. Baker M. Nature Rev Drug Discov. 2013; 12:5–7. [PubMed: 23274457]
23. (a) Leiros M, Sanchez JA, Alonso E, Rateb ME, Houssen WE, Ebel R, Jaspars M, Alfonso A, Botana LM. Marine Drugs. 2014; 12:700. [PubMed: 24473170] (b) Leiros M, Sanchez JA, Alonso E, Rateb ME, Houssen WE, Ebel R, Jaspars M, Alfonso A, Botana LM. Neuropharmacology. 2015; 93:285. [PubMed: 25724081]
24. (a) Noutsias D, Vassilikogiannakis G. Org Lett. 2012; 14:3565. [PubMed: 22734450] (b) Vasamsetty L, Sahu D, Ganguly B, Khan FA, Mehta G. Tetrahedron. 2014; 70:8488.
25. (a) Ghosh AK, Xu CX, Rao KV, Baldrige A, Agniswamy J, Wang YF, Weber IT, Aoki M, Miguel SGP, Amano M, Mitsuya H. ChemMedChem. 2010; 5:1850. [PubMed: 20827746] (b) Ghosh AK, Xu CX, Oswald HL. Tetrahedron Lett. 2015; 56:3314. [PubMed: 26185337]

Figure 1.

A subset of diverse molecular scaffolds previously synthesized via intramolecular cycloadditions of photogenerated azaxylenes.

Figure 2.
NOE experiments

$$H_a-H_b = 10.4 \text{ Hz}$$

$$H_b-H_c = 7.8 \text{ Hz}$$

$$H_b-H_d = 2.6 \text{ Hz}$$

Figure 3.
Spin-spin coupling constants in structures **10**

Figure 4.
Comparison of experimental and predicted SSCC for compounds **11**, **12''** and **14**

Figure 5. Selected HMBC relationships between carbon and hydrogen atoms and comparison of calculated and experimental SSCCs for compound **18**

Scheme 1.

Photochemical generation of azaxylylenes via ESIPT and their intramolecular cycloadditions.

Scheme 2.
Synthesis of model compounds

Scheme 3.

Reactions with dipoles (**6'** was observed by NMR but not isolated)

Scheme 4. Addition of dichlorocarbene to α,β -unsaturated ketone **8**

Scheme 5.

Postphotochemical [4+2] cycloadditions of heterodienes to primary photoproducts.

Scheme 6.

Thiophene-based [4+2] adduct in the reaction with dimethyl barbituric acid

Scheme 7.
Reaction with pyrroles

Table 1

Tanimoto coefficients for the library of synthesized compounds

	A	B	C	D	E	F	G	H	5	6	7	9	10	11	12	14	18
A	1	0.37	0.44	0.47	0.27	0.33	0.43	0.38	0.44	0.56	0.6	0.42	0.48	0.43	0.52	0.33	0.42
B	0.37	1	0.41	0.32	0.24	0.34	0.46	0.27	0.34	0.36	0.38	0.63	0.4	0.31	0.37	0.26	0.26
C	0.11	0.41	1	0.31	0.22	0.27	0.33	0.32	0.44	0.42	0.46	0.52	0.55	0.39	0.52	0.28	0.37
D	0.47	0.32	0.31	1	0.33	0.43	0.3	0.46	0.4	0.36	0.4	0.35	0.5	0.4	0.45	0.36	0.4
E	0.27	0.24	0.22	0.33	1	0.37	0.22	0.34	0.29	0.25	0.25	0.21	0.33	0.31	0.3	0.28	0.33
F	0.33	0.34	0.27	0.43	0.37	1	0.4	0.34	0.35	0.34	0.36	0.29	0.37	0.34	0.38	0.32	0.35
G	0.43	0.46	0.33	0.3	0.22	0.4	1	0.25	0.32	0.42	0.46	0.45	0.34	0.32	0.39	0.25	0.26
H	0.38	0.27	0.32	0.46	0.34	0.34	0.25	1	0.39	0.33	0.34	0.3	0.52	0.37	0.44	0.36	0.67
5	0.44	0.34	0.44	0.4	0.29	0.35	0.32	0.39	1	0.7	0.5	0.42	0.58	0.52	0.65	0.37	0.42
6	0.56	0.36	0.42	0.36	0.25	0.34	0.42	0.33	0.7	1	0.7	0.42	0.47	0.42	0.5	0.32	0.33
7	0.6	0.38	0.46	0.4	0.25	0.36	0.46	0.34	0.5	0.7	1	0.44	0.54	0.45	0.53	0.35	0.35
9	0.42	0.63	0.52	0.35	0.21	0.29	0.45	0.3	0.42	0.42	0.44	1	0.48	0.37	0.49	0.28	0.31
10	0.48	0.4	0.55	0.5	0.33	0.37	0.34	0.52	0.58	0.47	0.54	0.48	1	0.53	0.65	0.38	0.46
11	0.43	0.31	0.39	0.4	0.31	0.34	0.32	0.37	0.52	0.42	0.45	0.37	0.53	1	0.57	0.62	0.38
12	0.52	0.37	0.52	0.45	0.3	0.38	0.39	0.44	0.65	0.5	0.53	0.49	0.65	0.57	1	0.38	0.49
14	0.33	0.26	0.28	0.36	0.28	0.32	0.25	0.36	0.37	0.32	0.35	0.28	0.38	0.62	0.38	1	0.38
18	0.42	0.26	0.37	0.4	0.33	0.35	0.26	0.67	0.42	0.33	0.35	0.31	0.46	0.38	0.49	0.38	1

Comparison of the computed properties of the synthesized library and compounds appearing in the Journal of Medicinal Chemistry publications in 2005–2009.

Table 2

	MW	fsp3	clogP	HB donors	HB acceptors	Rotatable bonds	TPSA
Averages for the mini-library.	374.51	0.43	1.89	1.22	5.83	0.94	78.66
J. Med. Chem. average	403.29	0.34	3.1	1.77	4.24	6.33	87.05