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# Synthesis of Large Ring Macrocycles (12–18) by Recyclable Palladium-Complexed Dendrimers on Silica Gel Catalyzed Intramolecular Cyclocarbonylation Reactions

**Shui-Ming Lu and Howard Alper*[a]**

**Abstract:** Intramolecular cyclocarbonylation reactions with palladium-complexed dendrimers on silica gel as catalysts are very effective for the synthesis of twelve- to eighteen-membered ring macrocycles. This process can tolerate a wide variety of functional groups, including halide, ether, ketone, and ester. The heterogeneous dendritic catalysts facilitate excellent substrate reactivity, affording oxygen-, nitrogen-, or sulfur-containing tricyclic heterocycles in 70–92% yields. Importantly, these systems are easily recovered by simple filtration and reused several times with only a slight loss of activity.

**Keywords:** carbonylation · dendrimers · heterocycles · heterogeneous catalysis · palladium

## Introduction

Heterocycles are of great synthetic interest since they constitute important structural motifs in biologically active natural products, as well as for pharmaceuticals and agrochemicals.[1] As a result, much effort has been devoted to the development of novel and efficient strategies for the preparation of cyclic compounds. Among the various options, transition-metal catalysis has attracted increasing attention. In particular, carbonylation reactions provide a powerful tool for the construction of complex polycyclic systems that are generally not accessible by classical methods.[2] However, the synthesis of large ring-fused heterocycles still poses a significant challenge. Furthermore, while homogeneous catalytic processes often display excellent activity, a major drawback is the tedious separation of the catalysts from the reaction products that in turn may lead to economical or ecological problems especially in the case of expensive and/or toxic metal complexes.[3] Therefore, it is highly desirable to develop innovative approaches for the design of recoverable and reusable catalysts.

Dendrimers are regular hyperbranched and well-defined macromolecules with a number of potential applications in chemistry, biology, and materials science.[4] One of the most interesting applications of dendrimers is the use of their transition-metal complexes for catalysis.[5] As an interface between homogeneous and heterogeneous catalysts, metallodendrimers represent a fascinating field of research because they allow the facilitated recovery and reuse of the catalysts, a beneficial feature for reaction efficiency, economy, and environmental concern. Soluble dendritic catalysts are widely applied to a variety of organic reactions, including hydrogenation,[6] oxidation,[7] hydrovinylation,[8] hydrolysis,[9] the Heck,[10] Sonogashira,[11] Suzuki,[12] and Henry reactions,[13] Kharash addition,[14] Stille coupling,[15,16] Knoevenagel condensation, Michael addition,[16] and the asymmetric addition of diethylzinc to aldehydes.[17] However, relatively few examples involve dendritic catalysts on a solid support.[18] Recently, we found that dendrimer complexes on silica gel or a resin show high activity for carbonylation and hydroformylation reactions.[19] These systems can be easily recovered by simple filtration in air and reused without loss of activity. To our knowledge, there are no reports on intramolecular cyclocarbonylation reactions with recyclable palladium-complexed dendrimers on silica gel to form oxygen-, nitrogen-, or sulfur-containing large ring-fused heterocycles. It is anticipated that this protocol could have considerable potential for assembling the desired cyclic compounds. We now demonstrate that heterogeneous dendrimer–palladium complexes are very effective catalysts for the synthesis of

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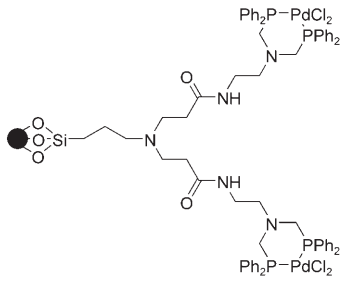
twelve- to eighteen-membered ring macrocycles in good to excellent yields.

## Results and Discussion

Palladium-complexed dendrimers on silica gel, up to the third generation, were prepared according to our recently published procedure.[19a] Briefly, Michael-type addition and amidation reactions were used to construct dendrimers immobilized on silica gel, followed by phosphonation of the dendrimers with diphenylphosphinomethanol. The resulting phosphonated dendrimers were then complexed with dichlorobis(benzonitrile)palladium(II) to give the dendritic catalysts **G0**-Pd–**G3**-Pd (Figure 1).[20] The induced coupled plasma (ICP) results showed that the palladium contents of **G0**-Pd, **G1**-Pd, **G2**-Pd, and **G3**-Pd are 0.57, 0.80, 0.52, and 0.29 mmol $g^{-1}$, respectively.




**G1**-Pd

Figure 1. Structure of palladium-complexed dendrimer on silica **G1**-Pd.

The intramolecular cyclocarbonylation of various iodinated arylamines **1**[20] was used for the synthesis of twelve-membered ring fused heterocycles **2** with **G1**-Pd as the catalyst. Typically, a mixture of 1 mmol of iodinated arylamine **1** in 25 mL of toluene, in the presence of 1.5 mmol of diisopropylethylamine (DIPEA) and 15 mg of **G1**-Pd, was treated with 100 psi of carbon monoxide at 80 °C for 22 h, and the results are listed in Table 1. The dendritic catalyst **G1**-Pd was found to be highly active, irrespective of the electronic nature of the substituents on the aromatic rings. Thus, iodinated arylamines **1** bearing either electron-donating or electron-withdrawing groups on the aromatic rings were readily converted to the corresponding tricyclic heterocycles **2** in good to excellent yields. For example, the reaction of substrate **1a** gave 92% yield of the desired twelve-membered ring **2a** (Table 1, entry 1). The iodinated arylamines **1b** and **c**, which contain methyl and chloro substituents, underwent the intramolecular cyclocarbonylation reactions, and the corresponding products **2b** and **2c** were obtained in 88 and 90% yield, respectively (Table 1, entries 2 and 3). In the realm of drug design, introduction of a fluoride atom into molecules is a widely employed tactic to circumvent metabolism issues arising from the oxidation of the aromatic rings.[21] In this regard, the fluoro-containing substrate **1d** was allowed to react with carbon monoxide in the presence of **G1**-Pd. As expected, this process occurred smoothly and gave the desired tricyclic heterocycle **2d** in 87% yield (Table 1, entry 4). The presence of a strongly electron-donating methoxy group on the aromatic ring, the iodinated arylamine

Table 1. Synthesis of twelve-membered ring fused heterocycles by **G1**-Pd-catalyzed intramolecular cyclocarbonylation of iodinated arylamines **1**.[a]

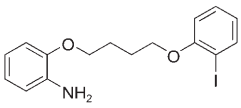
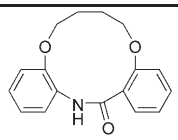
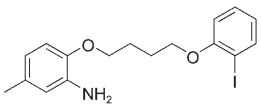
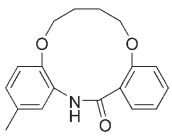
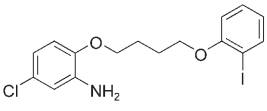
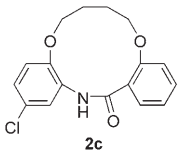
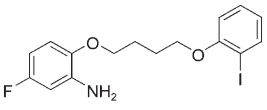
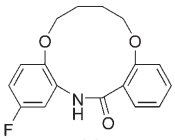
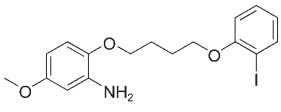
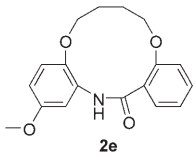
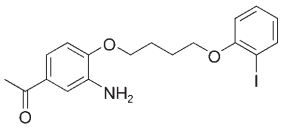
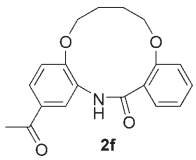
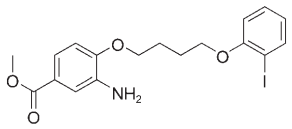
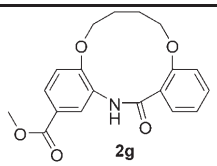
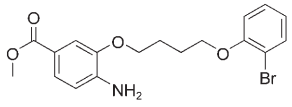
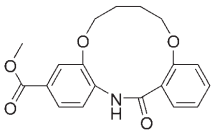
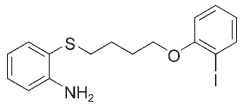
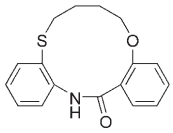
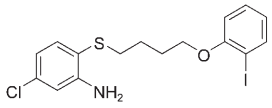
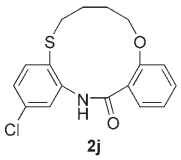
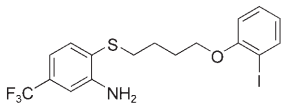
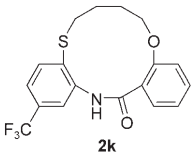
| Entry | Substrate | Product | Yield [%][b] |
|---|---|---|---|
| 1 |  **1a** |  **2a** | 92 |
| 2 |  **1b** |  **2b** | 88 |
| 3 |  **1c** |  **2c** | 90 |
| 4 |  **1d** |  **2d** | 87 |
| 5 |  **1e** |  **2e** | 83 |
| 6 |  **1f** |  **2f** | 76 |

Table 1. (Continued)

| Entry | Substrate | Product | Yield [%][b] |
|---|---|---|---|
| 7 |  1g |  2g | 81 |
| 8[c] |  1h |  2h | 83 |
| 9 |  1i |  2i | 86 |
| 10 |  1j |  2j | 91 |
| 11 |  1k |  2k | 82 |

[a] 1 mmol **1**, 15 mg **G1**-Pd, 1.5 mmol DIPEA, 25 mL toluene, 100 psi CO, 80 °C and 22 h. [b] Isolated yield. [c] Run at 120 °C.

**1e**, also resulted in the intramolecular cyclocarbonylation reaction, affording the corresponding twelve-membered ring **2e** in 83% yield (Table 1, entry 5). It is noteworthy that strongly electron-withdrawing substituents such as acetyl and methoxycarbonyl groups on the aromatic rings, which act as useful handles for further functional transformation, can tolerate this process under the same reaction conditions, although a slightly lower yield was obtained in the case of **1f** (Table 1, entries 6 and 7).

In comparison with iodinated arylamines, brominated arylamines are less reactive for the intramolecular cyclocarbonylation reaction, but they are very attractive due to lower cost and more readily available. We were interested in determining whether the brominated arylamine **1h** could be utilized as a substrate for this transformation. The intramolecular cyclocarbonylation of **1h** was thus carried out under the reaction conditions established for iodinated arylamines, and 65% conversion was achieved at 80 °C. Gratifyingly, increasing the reaction temperature to 120 °C gave full conversion to the desired tricyclic heterocycle **2h** in 83% isolated yield (Table 1, entry 8), and its X-ray crystal structure is shown in Figure 2.[22] Sulfur-containing compounds have long been known to act as a poison for transition-metal catalysts because of their strong coordinating and absorptive properties. Nevertheless, the iodinated arylamines **1i–k** facilitate the intramolecular cyclocarbonylation reactions with **G1**-Pd as the catalyst. The sulfur atom did not have any influence on this process, affording the corresponding twelve-membered rings **2i–k** in 86, 91, and 82% yields, respectively (Table 1, entries 9–11).

Encouraged by these exciting results, we then expanded the scope of the intramolecular cyclocarbonylation reactions to the preparation of larger ring (13–18) fused heterocycles in the presence of **G1**-Pd. As can be seen from Table 2, the dendritic catalyst was very efficient in all cases. Again, the reactions of iodinated arylamines **3**[20] bearing electron-donating or electron-withdrawing substituents on the aromatic rings gave the desired tricyclic heterocycles **4** in good to excellent yields. Importantly, a broad array of functional groups, such as methyl, fluoro, chloro, trifluoromethyl, methoxy, and methoxycarbonyl, are compatible with this process. For instance, treatment of the iodinated arylamines **3g** and **j** with

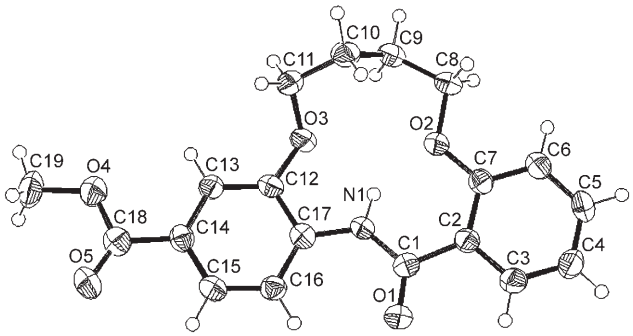
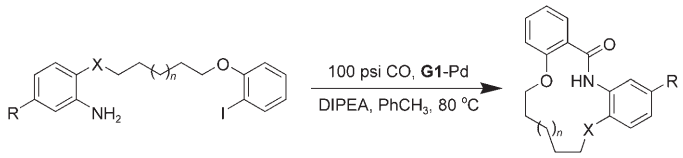


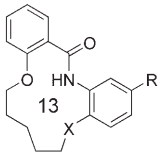
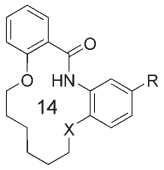
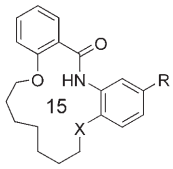
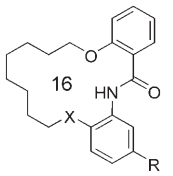
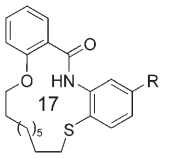
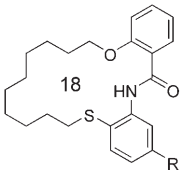

Figure 2. X-ray crystal structure of **2h**.

carbon monoxide furnished the corresponding fifteen-membered ring **4g** and sixteen-membered ring **4j** in 80 and 75% yields, respectively (Table 2, entries 7 and 10). Sulfur-containing substrates are also viable partners, and one can isolate the desired tricyclic heterocycles in good yields. Specifically, the iodinated arylamine **3p** was subjected to the standard reaction conditions, and **G1**-Pd catalyzed cyclocarbonylation gave the corresponding eighteen-membered ring **4p** in 72% yield (Table 2, entry 16), whose structure was unambiguously confirmed by its X-ray diffraction analysis (Figure 3).[23] The above examples further illustrate the effi-

Table 2. Synthesis of thirteen- to eighteen-membered ring fused heterocycles by **G1**-Pd-catalyzed intramolecular cyclocarbonylation of iodinated arylamines **3**.[a]




| Entry | Substrate | Product | | Yield [%][b] |
|---|---|---|---|---|
| 1 | **3a** $n=1$, X=O, R=$CH_3$ |  | **4a** | 83 |
| 2 | **3b** $n=1$, X=S, R=H | | **4b** | 87 |
| 3 | **3c** $n=1$, X=S, R=Cl | | **4c** | 91 |
| 4 | **3d** $n=2$, X=O, R=F |  | **4d** | 88 |
| 5 | **3e** $n=2$, X=S, R=H | | **4e** | 85 |
| 6 | **3f** $n=2$, X=S, R=$CF_3$ | | **4f** | 82 |
| 7 | **3g** $n=3$, X=O, R=$CH_3O$ |  | **4g** | 80 |
| 8 | **3h** $n=3$, X=S, R=Cl | | **4h** | 87 |
| 9 | **3i** $n=3$, X=S, R=$CF_3$ | | **4i** | 83 |
| 10 | **3j** $n=4$, X=O, R=$CO_2CH_3$ |  | **4j** | 75 |
| 11 | **3k** $n=4$, X=S, R=H | | **4k** | 83 |
| 12 | **3l** $n=4$, X=S, R=$CF_3$ | | **4l** | 79 |
| 13 | **3m** $n=5$, X=S, R=Cl |  | **4m** | 83 |
| 14 | **3n** $n=5$, X=S, R=$CF_3$ | | **4n** | 78 |
| 15 | **3o** $n=6$, X=S, R=H |  | **4o** | 70 |
| 16 | **3p** $n=6$, X=S, R=Cl | | **4p** | 72 |

[a] 1 mmol **3**, 15 mg **G1**-Pd, 1.5 mmol DIPEA, 25 mL toluene, 100 psi CO, 80 °C and 22 h. [b] Isolated yield.

ciency and generality of this protocol for the construction of large ring fused heterocycles.

The key property of metallodendrimers is their recovery and reuse, an essential perspective for green chemistry involving both ecological and economical considerations. We chose the intramolecular cyclocarbonylation of 2-[4-(2-iodophenoxy)butoxy]aniline (**1a**) as the model reaction for the evaluation of the activity and recyclability of different dendritic catalysts **G0**-Pd–**G3**-Pd under the standard conditions, and the results are presented in Table 3. The dendritic species **G0**-Pd–**G3**-Pd were found to be highly active catalysts for this transformation. All of the first cycles afforded complete conversions of the iodinated arylamine to the tricyclic heterocycle. For example, **G0**-Pd exhibited good recyclability, and the intramolecular cyclocarbonylation reaction was conducted for five consecutive runs in 100–95% conversions (Table 3, entries 1–5). As seen from Table 1, the recyclability of **G1**-Pd proved to be best. The dendritic catalyst could be recovered by simple filtration in air and reused up to the eighth cycle with only a slight loss of activity (Table 3, entries 6–13). There were 100–91% conversions from the first cycle to the fifth cycle when **G2**-Pd was examined as the catalyst under the same reaction conditions (Table 3, entries 14–18). **G3**-Pd showed low recyclability, and the fifth cycle gave 43% conversion (Table 3, entries 19–23). This was attributed to steric crowding at the higher generation. In order to relieve steric crowding and allow for increased catalyst loading, **G3**(C6)-Pd was prepared by the use of 1,6-diaminohexane in place of the ethylenediamine linker, with 0.57 mmol $g^{-1}$ palladium.[20] Indeed, the recyclability of **G3**(C6)-Pd was comparable to that observed employing **G0**-Pd as the catalyst (Table 3, entries 1–5 and entries 24–28), and substantially superior to that of **G3**-Pd. Note that these dendritic catalysts are very stable in a chemical sense since they can be stored in air at room temperature for months.

## Conclusion

In summary, the intramolecular cyclocarbonylation reaction with recyclable palladium-complexed dendrimers on silica gel is a powerful method for the synthesis of oxygen-, nitrogen-, or sulfur-containing macrocycles. The heterogeneous dendritic catalysts display high activity in these transformations, affording the desired tricyclic heterocycles with twelve to eighteen members in good to excellent yields. Moreover, these dendritic catalysts have competitive advantages in that they can be easily recovered by simple filtration in air and reused for up to eight cycles with only a slight loss of activity.

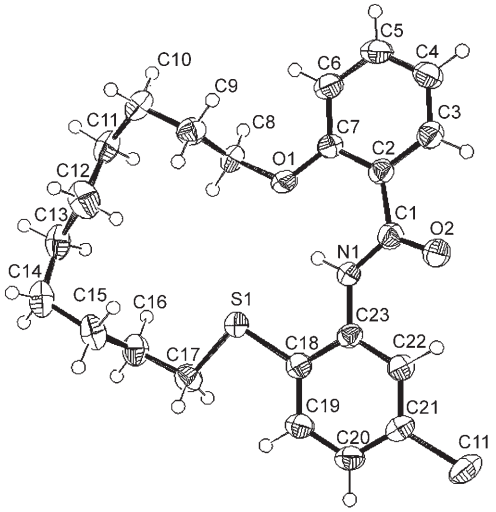
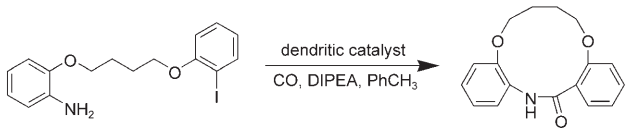



Figure 3. X-ray crystal structure of **4p**.

Table 3. Intramolecular cyclocarbonylation of 2-[4-(2-iodophenoxy)butoxy)]aniline with different palladium-complexed dendrimers on silica gel.[a]




| Entry | Catalyst | Cycle | Conversion[b] [%] |
|---|---|---|---|
| 1 | **G0**-Pd | 1 | 100 |
| 2 | **G0**-Pd | 2 | 100 |
| 3 | **G0**-Pd | 3 | 98 |
| 4 | **G0**-Pd | 4 | 97 |
| 5 | **G0**-Pd | 5 | 95 |
| 6 | **G1**-Pd | 1 | 100 |
| 7 | **G1**-Pd | 2 | 100 |
| 8 | **G1**-Pd | 3 | 99 |
| 9 | **G1**-Pd | 4 | 98 |
| 10 | **G1**-Pd | 5 | 98 |
| 11 | **G1**-Pd | 6 | 96 |
| 12 | **G1**-Pd | 7 | 96 |
| 13 | **G1**-Pd | 8 | 95 |
| 14 | **G2**-Pd | 1 | 100 |
| 15 | **G2**-Pd | 2 | 98 |
| 16 | **G2**-Pd | 3 | 96 |
| 17 | **G2**-Pd | 4 | 93 |
| 18 | **G2**-Pd | 5 | 91 |
| 19 | **G3**-Pd | 1 | 100 |
| 20 | **G3**-Pd | 2 | 85 |
| 21 | **G3**-Pd | 3 | 73 |
| 22 | **G3**-Pd | 4 | 62 |
| 23 | **G3**-Pd | 5 | 43 |
| 24 | **G3**(C6)-Pd | 1 | 100 |
| 25 | **G3**(C6)-Pd | 2 | 100 |
| 26 | **G3**(C6)-Pd | 3 | 97 |
| 27 | **G3**(C6)-Pd | 4 | 97 |
| 28 | **G3**(C6)-Pd | 5 | 96 |

[a] 1 mmol 2-[4-(2-iodophenoxy)butoxy]aniline, 15 mg catalyst, 1.5 mmol DIPEA, 25 mL toluene, 100 psi CO, 80 °C and 22 h. [b] Determined by GC and $^1$H NMR.

## Experimental Section

**General methods**: All solvents were dried and distilled under nitrogen prior to use, other chemicals were used as received without further purification. Analytical thin-layer chromatography (TLC) was performed on E. Merck silica gel 60 $F_{254}$ precoated plates (0.25 mm) and visualized with a 254 nm ultraviolet lamp. Flash column chromatography was undertaken with silica gel (60, 230–400 mesh) supplied by Silicycle (Quebec, Canada). GC analyses were carried out using an Agilent 6850 series chromatograph. IR spectra were obtained with a Shimadzu FTIR-8400S spectrometer. Mass spectra were determined using a VG 7070E spectrometer. Solution $^1$H NMR and $^{13}$C NMR spectra were recorded in $CDCl_3$ or [$D_6$]DMSO on a Varian Inova 500 MHz spectrometer. Chemical shifts ($\delta$) were reported in ppm with the solvent signals as reference, and coupling constants ($J$) were given in Hertz (Hz). Solid-state $^{13}$C NMR and $^{13}$P NMR spectra were measured with a Bruker ASX-200 spectrometer. ICP analyses were done by Galbraith Laboratories, Knoxville, TN. Melting points are uncorrected.

**CAUTION**: Carbon monoxide, a powerful asphyxiant, should be used with care. To use and work with carbon monoxide safely, reactions must be carried out in a properly working fumehood with carbon monoxide detectors installed nearby.

**General procedure for the intramolecular cyclocarbonylation reaction**: A glass liner containing the substrate (1 mmol), dendritic catalyst (15 mg), diisopropylethylamine (1.5 mmol) and toluene (25 mL) was placed in a 45 mL autoclave equipped with a magnetic stirring bar. The autoclave was flushed three times with carbon monoxide and pressurized to 100 psi. The autoclave was then placed in an oil bath preset to the desired temperature on a stirring hot plate (80 °C for iodides and 120 °C for bromides). After 22 h, the autoclave was removed from the oil bath and cooled to room temperature prior to the release of excess carbon monoxide. The reaction mixture was filtered and washed with dichloromethane. The combined solvent was evaporated in vacuo, and the residue was purified by silica gel chromatography with a mixture of hexane and ethyl acetate as the eluant to afford the product. The recovered catalyst was reused for subsequent cycles.

**6,7,8,9-Tetrahydro-15*H*-5,10-dioxa-15-azadibenzo[*a*,*e*]cyclododecen-16-one (2a)**: 92 % yield; $^1$H NMR (500 MHz, [$D_6$]DMSO): $\delta$ = 11.34 (s, 1H), 8.30 (dd, $J$ = 1.5, 8.0 Hz, 1H), 8.08 (dd, $J$ = 1.5, 7.5 Hz, 1H), 7.55 (dt, $J$ = 1.5, 8.0 Hz, 1H), 7.20 (d, $J$ = 8.5 Hz, 1H), 7.14–7.03 (m, 4H), 4.30 (t, $J$ = 5.0 Hz, 2H), 4.05 (t, $J$ = 5.5 Hz, 2H), 2.15–2.13 (m, 2H), 2.01–1.99 ppm (m, 2H); $^{13}$C NMR (125 MHz, [$D_6$]DMSO): $\delta$ = 162.52, 157.54, 148.85, 134.45, 132.02, 131.95, 124.41, 124.25, 121.78, 121.49, 119.69, 119.56, 113.48, 72.37, 70.91, 28.59, 25.13 ppm; IR (neat): $\tilde{\nu}$ = 1660 cm$^{-1}$; MS (70 eV, EI): $m/z$: 283 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{17}H_{17}NO_3$: 283.1208; found: 283.1189.

**13-Methyl-6,7,8,9-tetrahydro-15*H*-5,10-dioxa-15-azadibenzo[*a*,*e*]cyclododecen-16-one (2b)**: 88 % yield; m.p. 89–90 °C; $^1$H NMR (500 MHz, [$D_6$]DMSO): $\delta$ = 11.23 (s, 1H), 8.17 (d, $J$ = 1.0 Hz, 1H), 8.08 (dd, $J$ = 1.5, 8.0 Hz, 1H), 7.54 (dt, $J$ = 2.0, 8.0 Hz, 1H), 7.18 (d, $J$ = 8.0 Hz, 1H), 7.12 (t, $J$ = 7.5 Hz, 1H), 7.00 (d, $J$ = 8.0 Hz, 1H), 6.82 (dd, $J$ = 1.5, 8.0 Hz, 1H), 4.28 (t, $J$ = 5.0 Hz, 2H), 3.98 (t, $J$ = 5.5 Hz, 2H), 2.27 (s, 3H), 2.13–2.11 (m, 2H), 1.99–1.97 ppm (m, 2H); $^{13}$C NMR (125 MHz, [$D_6$]DMSO): $\delta$ = 162.43, 157.49, 146.69, 134.41, 133.50, 131.95, 131.89, 124.68, 121.77, 121.48, 120.31, 119.89, 113.40, 72.48, 70.79, 28.66, 24.88, 21.66 ppm; IR (neat): $\tilde{\nu}$ = 1665 cm$^{-1}$; MS (70 eV, EI): $m/z$: 297 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{18}H_{19}NO_3$: 297.1365; found: 297.1343.

**13-Chloro-6,7,8,9-tetrahydro-15*H*-5,10-dioxa-15-azadibenzo[*a*,*e*]cyclododecen-16-one (2c)**: 90 % yield; m.p. 144–145 °C; $^1$H NMR (500 MHz, [$D_6$]DMSO): $\delta$ = 11.40 (s, 1H), 8.32 (d, $J$ = 2.5 Hz, 1H), 8.06 (dd, $J$ = 2.0, 7.5 Hz, 1H), 7.56 (dt, $J$ = 1.5, 8.0 Hz, 1H), 7.20–7.06 (m, 4H), 4.28 (t, $J$ = 5.0 Hz, 2H), 4.04 (t, $J$ = 5.5 Hz, 2H), 2.13–2.10 (m, 2H), 2.01–1.96 ppm (m, 2H); $^{13}$C NMR (125 MHz, [$D_6$]DMSO): $\delta$ = 162.79, 157.61, 147.66, 134.78, 133.09, 131.95, 127.86, 123.79, 121.85, 120.98, 120.93, 119.03, 113.55, 72.75, 70.96, 28.46, 25.06 ppm; IR (neat): $\tilde{\nu}$ = 1662 cm$^{-1}$; MS (70 eV, EI): $m/z$: 317 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{17}H_{16}ClNO_3$: 317.0819; found: 317.0801.

**13-Fluoro-6,7,8,9-tetrahydro-15*H*-5,10-dioxa-15-azadibenzo[*a*,*e*]cyclododecen-16-one (2d)**: 87% yield; m.p. 122–123°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=11.39 (s, 1H), 8.12–8.07 (m, 2H), 7.58 (dt, $J$=1.5, 8.0 Hz, 1H), 7.25–7.12 (m, 3H), 6.86 (dt, $J$=3.0, 8.5 Hz, 1H), 4.31 (t, $J$=5.0 Hz, 2H), 4.03 (t, $J$=5.5 Hz, 2H), 2.15–2.13 (m, 2H), 2.00–1.98 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=162.82, 158.58 (d, $J$=235.6 Hz), 157.61, 145.10 (d, $J$=1.9 Hz), 134.79, 133.18 (d, $J$=12.5 Hz), 131.98, 121.86, 121.37 (d, $J$=9.5 Hz), 120.91, 113.49, 110.06 (d, $J$=23.9 Hz), 106.76 (d, $J$=28.6 Hz), 72.93, 70.84, 28.58, 24.79 ppm; IR (neat): $\tilde{\nu}$=1658 cm$^{-1}$; MS (70 eV, EI): $m/z$: 301 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{17}H_{16}FNO_3$: 301.1114; found: 301.1102.

**13-Methoxy-6,7,8,9-tetrahydro-15*H*-5,10-dioxa-15-azadibenzo[*a*,*e*]cyclododecen-16-one (2e)**: 83% yield; m.p. 108–109°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=11.23 (s, 1H), 8.09 (dd, $J$=1.5, 8.0 Hz, 1H), 7.99 (d, $J$=3.0 Hz, 1H), 7.55 (dt, $J$=1.5, 8.5 Hz, 1H), 7.19 (d, $J$=8.5 Hz, 1H), 7.12 (t, $J$=7.5 Hz, 1H), 7.05 (d, $J$=8.5 Hz, 1H), 6.58 (dd, $J$=3.0, 8.5 Hz, 1H), 4.30 (t, $J$=5.0 Hz, 2H), 3.96 (t, $J$=5.5 Hz, 2H), 3.72 (s, 3H), 2.14–2.12 (m, 2H), 1.98–1.95 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=162.62, 157.53, 156.19, 142.57, 134.57, 132.98, 131.99, 121.80, 121.40, 121.20, 113.38, 108.71, 106.03, 72.81, 70.71, 55.99, 28.73, 24.60 ppm; IR (neat): $\tilde{\nu}$=1661 cm$^{-1}$; MS (70 eV, EI): $m/z$: 313 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{18}H_{19}NO_4$: 313.1314; found: 313.1305.

**13-Acetyl-6,7,8,9-tetrahydro-15*H*-5,10-dioxa-15-azadibenzo[*a*,*e*]cyclododecen-16-one (2f)**: 76% yield; m.p. 171–172°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=11.56 (s, 1H), 8.80 (d, $J$=2.0 Hz, 1H), 8.08 (dd, $J$=1.5, 7.5 Hz, 1H), 7.72 (dd, $J$=2.0, 8.0 Hz, 1H), 7.57 (dt, $J$=2.0, 8.5 Hz, 1H), 7.23–7.18 (m, 2H), 7.14 (t, $J$=7.5 Hz, 1H), 4.30 (t, $J$=5.0 Hz, 2H), 4.16 (t, $J$=5.5 Hz, 2H), 2.54 (s, 3H), 2.15–2.13 (m, 2H), 2.06–2.02 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=197.29, 162.64, 157.66, 152.67, 134.58, 132.19, 131.87, 131.15, 125.74, 121.83, 121.45, 118.46, 116.49, 113.67, 72.07, 71.31, 28.24, 27.25, 25.81 ppm; IR (neat): $\tilde{\nu}$=1685, 1660 cm$^{-1}$; MS (70 eV, EI): $m/z$: 325 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{19}H_{19}NO_4$: 325.1314; found: 325.1296.

**16-Oxo-6,7,8,9,15,16-hexahydro-5,10-dioxa-15-azadibenzo[*a*,*e*]cyclododecene-13-carboxylic methyl ester (2g)**: 81% yield; m.p. 169–170°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=11.56 (s, 1H), 8.82 (d, $J$=2.0 Hz, 1H), 8.06 (dd, $J$=1.5, 8.0 Hz, 1H), 7.66 (dd, $J$=2.0, 8.0 Hz, 1H), 7.56 (dt, $J$=1.5, 8.0 Hz, 1H), 7.20–7.12 (m, 3H), 4.28 (t, $J$=5.0 Hz, 2H), 4.14 (t, $J$=5.5 Hz, 2H), 3.83 (s, 3H), 2.13–2.11 (m, 2H), 2.04–2.01 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=166.60, 162.60, 157.65, 152.58, 134.58, 131.86, 131.06, 126.09, 124.34, 121.80, 121.38, 119.67, 116.58, 113.63, 71.97, 71.31, 52.73, 28.22, 25.80 ppm; IR (neat): $\tilde{\nu}$=1680, 1663 cm$^{-1}$; MS (70 eV, EI): $m/z$: 341 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{19}H_{19}NO_5$: 341.1263; found: 341.1248.

**16-Oxo-6,7,8,9,15,16-hexahydro-5,10-dioxa-15-azadibenzo[*a*,*e*]cyclododecene-12-carboxylic methyl ester (2h)**: 83% yield; m.p. 163–164°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=11.64 (s, 1H), 8.39 (d, $J$=8.5 Hz, 1H), 8.08 (dd, $J$=1.5, 8.0 Hz, 1H), 7.72 (dd, $J$=1.0, 8.5 Hz, 1H), 7.61–7.56 (m, 2H), 7.22 (d, $J$=8.5 Hz, 1H), 7.14 (t, $J$=7.5 Hz, 1H), 4.30 (t, $J$=5.0 Hz, 2H), 4.12 (t, $J$=5.5 Hz, 2H), 3.81 (s, 3H), 2.15–2.13 (m, 2H), 2.04–2.01 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=166.27, 162.81, 157.69, 148.44, 136.12, 134.85, 132.01, 125.84, 125.03, 121.86, 121.01, 119.02, 118.68, 113.62, 72.52, 71.12, 52.72, 28.40, 25.32 ppm; IR (neat): $\tilde{\nu}$=1683, 1665 cm$^{-1}$; MS (70 eV, EI): $m/z$: 341 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{19}H_{19}NO_5$: 341.1263; found: 341.1251.

**6,7,8,9-Tetrahydro-15*H*-5-oxa-10-thia-15-azadibenzo[*a*,*e*]cyclododecen-16-one (2i)**: 86% yield; m.p. 111–112°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.65 (s, 1H), 8.66 (d, $J$=8.0 Hz, 1H), 8.11 (dd, $J$=1.0, 7.5 Hz, 1H), 7.62 (d, $J$=7.5 Hz, 1H), 7.55 (dt, $J$=1.5, 8.0 Hz, 1H), 7.40 (t, $J$=7.5 Hz, 1H), 7.24 (d, $J$=8.0 Hz, 1H), 7.12 (t, $J$=7.5 Hz, 1H), 7.07 (d, $J$=7.5 Hz, 1H), 4.29 (t, $J$=5.0 Hz, 2H), 3.03 (t, $J$=6.0 Hz, 2H), 2.14–2.12 (m, 2H), 1.91–1.86 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.25, 157.48, 141.57, 137.16, 134.63, 132.68, 130.82, 124.42, 122.59, 121.80, 121.57, 120.48, 113.51, 70.90, 35.60, 26.52, 25.32 ppm; IR (neat): $\tilde{\nu}$=1660 cm$^{-1}$; MS (70 eV, EI): $m/z$: 299 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{17}H_{17}NO_2S$: 299.0980; found: 299.0965.

**13-Chloro-6,7,8,9-tetrahydro-15*H*-5-oxa-10-thia-15-azadibenzo[*a*,*e*]cyclododecen-16-one (2j)**: 91% yield; m.p. 118–119°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.71 (s, 1H), 8.74 (d, $J$=8.0 Hz, 1H), 8.11 (dd, $J$=1.5, 8.0 Hz, 1H), 7.64–7.57 (m, 2H), 7.26 (d, $J$=8.5 Hz, 1H), 7.15–7.12 (m, 2H), 4.30 (t, $J$=5.0 Hz, 2H), 3.04 (t, $J$=6.0 Hz, 2H), 2.15–2.12 (m, 2H), 1.93–1.87 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.54, 157.61, 142.51, 138.37, 135.20, 135.00, 132.70, 124.08, 121.90, 121.52, 121.01, 119.91, 113.61, 71.00, 35.58, 26.45, 25.46 ppm; IR (neat): $\tilde{\nu}$=1666 cm$^{-1}$; MS (70 eV, EI): $m/z$: 333 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{17}H_{16}ClNO_2S$: 333.0590; found: 333.0568.

**13-Trifluoromethyl-6,7,8,9-tetrahydro-15*H*-5-oxa-10-thia-15-azadibenzo-[*a*,*e*]cyclododecen-16-one (2k)**: 82% yield; m.p. 137–138°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.76 (s, 1H), 9.03 (s, 1H), 8.11 (dd, $J$=1.5, 7.5 Hz, 1H), 7.82 (d, $J$=8.0 Hz, 1H), 7.58 (dt, $J$=2.0, 7.5 Hz, 1H), 7.38 (d, $J$=8.0 Hz, 1H), 7.25 (d, $J$=8.0 Hz, 1H), 7.14 (d, $J$=7.5 Hz, 1H), 4.30 (t, $J$=5.0 Hz, 2H), 3.10 (t, $J$=6.0 Hz, 2H), 2.15–2.12 (m, 2H), 1.94–1.90 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.76, 157.64, 142.02, 137.92, 135.05, 132.70, 130.86 (q, $J$=32.5 Hz), 127.56, 124.57 (q, $J$=270.9 Hz), 121.91, 120.93, 120.54 (q, $J$=3.8 Hz), 116.40 (q, $J$=3.9 Hz), 113.58, 71.07, 35.21, 26.47, 25.16 ppm; IR (neat): $\tilde{\nu}$=1663 cm$^{-1}$; MS (70 eV, EI): $m/z$: 367 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{18}H_{16}F_3NO_2S$: 367.0854; found: 367.0848.

**20-Methyl-10,16-dioxa-2-azatricyclo[15.4.0.0$^{4,9}$]heneicosa-1(17),4(9),5,7,18,20-hexaen-3-one (4a)**: 83% yield; m.p. 80–81°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.65 (s, 1H), 8.40 (d, $J$=1.5 Hz, 1H), 8.11 (dd, $J$=1.5, 7.5 Hz, 1H), 7.52 (dt, $J$=1.5, 8.0 Hz, 1H), 7.16 (d, $J$=8.5 Hz, 1H), 7.12–7.06 (m, 2H), 6.82 (dd, $J$=1.5, 8.0 Hz, 1H), 4.17–4.12 (m, 4H), 2.24 (s, 3H), 1.93–1.90 (m, 2H), 1.82–1.78 ppm (m, 4H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=162.82, 157.58, 146.02, 134.39, 132.31, 131.23, 130.8, 124.47, 121.61, 121.42, 120.64, 115.51, 113.59, 69.57, 68.70, 27.23, 26.79, 21.59, 21.56 ppm; IR (neat): $\tilde{\nu}$=1665 cm$^{-1}$; MS (70 eV, EI): $m/z$: 311 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{19}H_{21}NO_3$: 311.1521; found: 311.1504.

**10-Oxa-16-thia-2-azatricyclo[15.4.0.0$^{4,9}$]heneicosa-1(17),4(9),5,7,18,20-hexaen-3-one (4b)**: 87% yield; m.p. 103–104°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.28 (s, 1H), 8.50 (d, $J$=8.0 Hz, 1H), 7.96 (dd, $J$=1.5, 7.5 Hz, 1H), 7.65 (d, $J$=7.5 Hz, 1H), 7.53 (dt, $J$=1.5, 8.5 Hz, 1H), 7.38 (t, $J$=8.0 Hz, 1H), 7.19 (d, $J$=8.5 Hz, 1H), 7.12–7.08 (m, 2H), 4.15 (t, $J$=5.0 Hz, 2H), 2.90 (t, $J$=6.0 Hz, 2H), 1.85–1.81 (m, 2H), 1.75–1.70 (m, 2H), 1.61–1.57 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.95, 157.26, 141.20, 137.52, 134.25, 132.50, 130.36, 125.00, 124.26, 122.69, 121.63, 121.28, 113.75, 69.92, 38.19, 27.13, 26.46, 23.63 ppm; IR (neat): $\tilde{\nu}$=1660 cm$^{-1}$; MS (70 eV, EI): $m/z$: 313 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{18}H_{19}NO_2S$: 313.1136; found: 313.1119.

**20-Chloro-10-oxa-16-thia-2-azatricycl[15.4.0.0$^{4,9}$]heneicosa-1(17),4(9),5,7,18,20-hexaen-3-one (4c)**: 91% yield; m.p. 133–134°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.37 (s, 1H), 8.62 (d, $J$=2.0 Hz, 1H), 7.95 (dd, $J$=1.5, 7.5 Hz, 1H), 7.69 (d, $J$=8.5 Hz, 1H), 7.57 (dt, $J$=1.5, 8.0 Hz, 1H), 7.24–7.18 (m, 2H), 7.12 (t, $J$=7.5 Hz, 1H), 4.19 (t, $J$=5.0 Hz, 2H), 2.94 (t, $J$=6.0 Hz, 2H), 1.88–1.84 (m, 2H), 1.76–1.71 (m, 2H), 1.64–1.60 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.34, 157.36, 142.24, 138.88, 134.75, 134.62, 132.29, 124.71, 123.09, 122.27, 121.76, 120.55, 113.95, 70.15, 38.18, 26.91, 26.43, 23.68 ppm; IR (neat): $\tilde{\nu}$=1658 cm$^{-1}$; MS (70 eV, EI): $m/z$: 347 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{18}H_{18}ClNO_2S$: 347.0747; found: 347.0728.

**15-Fluoro-6,7,8,9,10,11-hexahydro-17*H*-5,12-dioxa-17-azadibenzo[*a*,*e*]cyclotetradecen-18-one (4d)**: 88% yield; m.p. 147–148°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.08 (s, 1H), 8.50 (dd, $J$=3.0, 7.0 Hz, 1H), 8.13 (dd, $J$=1.5, 7.5 Hz, 1H), 7.55 (dt, $J$=1.5, 8.0 Hz, 1H), 7.21 (d, $J$=8.0 Hz, 1H), 7.12–7.04 (m, 2H), 6.88 (dt, $J$=3.0, 8.5 Hz, 1H), 4.21 (t, $J$=5.0 Hz, 2H), 4.12 (t, $J$=5.0 Hz, 2H), 1.92–1.88 (m, 4H), 1.83–1.77 (m, 2H), 1.69–1.66 ppm (m, 2H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.76, 157.49, 156.23 (d, $J$=231.9 Hz), 145.02 (d, $J$=1.9 Hz), 134.78, 132.82, 128.89 (d, $J$=11.4 Hz), 121.59, 120.68, 113.45, 112.35 (d, $J$=8.5 Hz), 109.91 (d, $J$=23.0 Hz), 108.40 (d, $J$=29.5 Hz), 72.14, 69.73, 27.76, 27.32, 25.36, 25.16 ppm; IR (neat): $\tilde{\nu}$=1663 cm$^{-1}$; MS (70 eV, EI): $m/z$: 329 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{19}H_{20}FNO_3$: 329.1427; found: 329.1411.

**6,7,8,9,10,11-Hexahydro-17*H*-5-oxa-12-thia-17-azadibenzo[*a*,*e*]cyclotetradecen-18-one (4e)**: 85% yield; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=

10.36 (s, 1H), 8.40 (d, $J$=8.5 Hz, 1H), 8.00 (dd, $J$=1.5, 7.5 Hz, 1H), 7.60 (dd, $J$=1.0, 7.5 Hz, 1H), 7.52 (dt, $J$=1.5, 8.5 Hz, 1H), 7.33 (t, $J$=7.5 Hz, 1H), 7.23 (d, $J$=8.5 Hz, 1H), 7.12–7.07 (m, 2H), 4.32 (t, $J$=5.5 Hz, 2H), 2.96 (t, $J$=5.5 Hz, 2H), 1.84–1.81 (m, 2H), 1.57–1.52 ppm (m, 6H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.89, 156.84, 140.37, 135.47, 134.19, 132.37, 129.32, 125.12, 124.98, 122.49, 121.91, 121.53, 113.82, 68.50, 36.79, 27.03, 25.42, 25.26, 23.14 ppm; IR (neat): $\tilde{\nu}$=1665 cm$^{-1}$; MS (70 eV, EI): $m/z$: 327 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{19}H_{21}NO_2S$: 327.1293; found: 327.1275.

**15-Trifluoromethyl-6,7,8,9,10,11-hexahydro-17*H*-5-oxa-12-thia-17-azadibenzo[*a*,*e*]cyclotetradecen-18-one (4f)**: 82% yield; m.p. 149–150°C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=10.66 (s, 1H), 8.99 (d, $J$=1.5 Hz, 1H), 8.24 (dd, $J$=1.5, 7.5 Hz, 1H), 7.62 (d, $J$=8.0 Hz, 1H), 7.47 (dt, $J$=1.5, 8.5 Hz, 1H), 7.28 (dd, $J$=1.5, 8.0 Hz, 1H), 7.09 (t, $J$=7.5 Hz, 1H), 7.03 (d, $J$=8.5 Hz, 1H), 4.37 (t, $J$=5.0 Hz, 2H), 3.02 (t, $J$=5.5 Hz, 2H), 1.96–1.92 (m, 2H), 1.75–1.65 ppm (m, 6H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=164.18, 156.40, 140.65, 134.84, 133.35, 132.72, 130.76 (q, $J$=32.5 Hz), 128.43, 123.76 (q, $J$=270.9 Hz), 121.87, 120.10, 120.21 (q, $J$=3.8 Hz), 118.2 (q, $J$=3.9 Hz), 112.10, 67.55, 36.54, 26.73, 25.01, 24.80, 22.18 ppm; IR (neat): $\tilde{\nu}$=1660 cm$^{-1}$; MS (70 eV, EI): $m/z$: 395 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{20}H_{20}F_3NO_2S$: 395.1167; found: 395.1149.

**22-Methoxy-10,18-dioxa-2-azatricyclo[17.4.0.0$^{4,9}$]tricosa-1(19),4(9),5,7,20,22-hexaen-3-one (4g)**: 80% yield; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=9.52 (s, 1H), 7.99–7.96 (m, 2H), 7.51 (dt, $J$=1.5, 8.5 Hz, 1H), 7.18 (d, $J$=8.5 Hz, 1H), 7.08 (t, $J$=7.5 Hz, 1H), 6.92 (d, $J$=9.0 Hz, 1H), 6.62 (dd, $J$=3.0, 8.5 Hz, 1H), 4.20 (t, $J$=5.0 Hz, 2H), 4.02 (t, $J$=5.0 Hz, 2H), 3.69 (s, 3H), 1.78–1.75 (m, 4H), 1.59–1.47 ppm (m, 6H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.70, 157.11, 153.20, 143.12, 134.16, 132.39, 128.03, 122.34, 121.50, 113.65, 112.17, 109.22, 108.92, 69.99, 69.51, 56.03, 28.74, 27.49, 27.43, 26.57, 25.52 ppm; IR (neat): $\tilde{\nu}$=1662 cm$^{-1}$; MS (70 eV, EI): $m/z$: 355 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{21}H_{25}NO_4$: 355.1784; found: 355.1765.

**22-Chloro-10-oxa-18-thia-2-azatricyclo[17.4.0.0$^{4,9}$]tricosa-1(19),4(9),5,7,20,22-hexaen-3-one (4h)**: 87% yield; m.p. 67–68°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.21 (s, 1H), 8.29 (d, $J$=2.5 Hz, 1H), 7.96 (dd, $J$=1.5, 8.0 Hz, 1H), 7.59–7.52 (m, 2H), 7.26–7.19 (m, 2H), 7.09 (d, $J$=7.5 Hz, 1H), 4.36 (t, $J$=5.0 Hz, 2H), 3.03 (t, $J$=5.5 Hz, 2H), 1.81–1.78 (m, 2H), 1.52–1.41 ppm (m, 8H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=164.25, 156.94, 140.16, 134.34, 133.99, 132.26, 132.19, 125.40, 125.15, 122.32, 122.25, 121.53, 114.00, 68.62, 34.70, 28.05, 27.13, 26.03, 25.58, 24.51 ppm; IR (neat): $\tilde{\nu}$=1665 cm$^{-1}$; MS (70 eV, EI): $m/z$: 375 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{20}H_{22}ClNO_2S$: 375.1060; found: 375.1047.

**22-Trifluoromethyl-10-oxa-18-thia-2-azatricyclo[17.4.0.0$^{4,9}$]tricosa-1(19),4(9),5,7,20,22-hexaen-3-one (4i)**: 83% yield; m.p. 87–88°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=10.28 (s, 1H), 8.52 (s, 1H), 8.00 (dd, $J$=1.5, 7.5 Hz, 1H), 7.70 (d, $J$=8.0 Hz, 1H), 7.52 (dt, $J$=1.5, 8.0 Hz, 1H), 7.44 (dd, $J$=1.5, 8.0 Hz, 1H), 7.22 (d, $J$=8.0 Hz, 1H), 7.08 (t, $J$=7.5 Hz, 1H), 4.32 (t, $J$=5.0 Hz, 2H), 3.10 (t, $J$=5.5 Hz, 2H), 1.79–1.74 (m, 2H), 1.56–1.38 ppm (m, 8H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=164.29, 157.17, 138.66, 134.44, 132.70, 132.26, 131.70, 127.58 (q, $J$=31.5 Hz), 124.72 (q, $J$=270.9 Hz), 121.98 (q, $J$=3.9 Hz), 121.58, 121.48, 119.16 (q, $J$=3.8 Hz), 114.01, 68.90, 33.96, 28.29, 27.16, 25.91, 25.75, 24.58 ppm; IR (neat): $\tilde{\nu}$=1660 cm$^{-1}$; MS (70 eV, EI): $m/z$: 409 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{21}H_{22}F_3NO_2S$: 409.1323; found: 409.1301.

**20-Oxo-6,7,8,9,10,11,12,13,19,20-decahydro-5,14-dioxa-19-azadibenzo-[*a*,*e*]cyclohexadecene-17-carboxylic methyl ester (4j)**: 75% yield; m.p. 106–107°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=9.79 (s, 1H), 9.02 (d, $J$=2.0 Hz, 1H), 8.02 (dd, $J$=1.5, 7.5 Hz, 1H), 7.69 (dd, $J$=1.5, 8.0 Hz, 1H), 7.52 (dt, $J$=1.0, 8.0 Hz, 1H), 7.22 (d, $J$=8.0 Hz, 1H), 7.17 (d, $J$=8.5 Hz, 1H), 7.09 (t, $J$=7.5 Hz, 1H), 4.29–4.23 (m, 4H), 3.81 (s, 3H), 1.79–1.73 (m, 4H), 1.46–1.40 ppm (m, 8H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=166.66, 164.08, 156.85, 152.16, 134.16, 132.44, 127.96, 126.71, 122.84, 122.38, 122.03, 121.59, 114.09, 112.24, 69.15, 68.29, 52.60, 27.51, 27.00, 25.73, 25.55, 23.27, 22.78 ppm; IR (neat): $\tilde{\nu}$=1685, 1666 cm$^{-1}$; MS (70 eV, EI): $m/z$: 397 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{23}H_{27}NO_5$: 397.1889; found: 397.1871.

**6,7,8,9,10,11,12,13-Octahydro-19*H*-5-oxa-14-thia-19-azadibenzo[*a*,*e*]cyclohexadecen-20-one (4k)**: 83% yield; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=9.79 (s, 1H), 8.00 (dd, $J$=1.5, 8.0 Hz, 1H), 7.93 (dd, $J$=1.0, 7.0 Hz, 1H), 7.52 (dt, $J$=1.5, 8.0 Hz, 1H), 7.47 (dd, $J$=1.5, 8.0 Hz, 1H), 7.24–7.14 (m, 3H), 7.09 (t, $J$=7.5 Hz, 1H), 4.24 (t, $J$=5.0 Hz, 2H), 3.14 (t, $J$=5.5 Hz, 2H), 1.88–1.83 (m, 2H), 1.53–1.49 (m, 4H), 1.37–1.26 ppm (m, 6H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=164.05, 157.48, 137.35, 134.18, 132.27, 129.78, 127.85, 126.50, 125.78, 124.80, 122.21, 121.53, 113.98, 70.23, 31.98, 27.94, 26.64, 25.19, 24.52, 23.99, 23.42 ppm; IR (neat): $\tilde{\nu}$=1662 cm$^{-1}$; MS (70 eV, EI): $m/z$: 355 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{21}H_{25}NO_2S$: 355.1606; found: 355.1588.

**17-Trifluoromethyl-6,7,8,9,10,11,12,13-octahydro-19*H*-5-oxa-14-thia-19-azadibenzo[*a*,*e*]cyclohexadecen-20-one (4l)**: 79% yield; m.p. 116–117°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=9.98 (s, 1H), 8.35 (s, 1H), 8.00 (dd, $J$=1.5, 8.0 Hz, 1H), 7.67 (d, $J$=8.0 Hz, 1H), 7.56 (dt, $J$=1.5, 8.5 Hz, 1H), 7.47 (d, $J$=8.0 Hz, 1H), 7.24 (d, $J$=8.5 Hz, 1H), 7.10 (t, $J$=7.5 Hz, 1H), 4.26 (t, $J$=5.0 Hz, 2H), 3.26 (t, $J$=5.5 Hz, 2H), 1.90–1.82 (m, 2H), 1.61–1.50 (m, 4H), 1.38–1.29 ppm (m, 6H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=164.42, 157.54, 137.30, 134.52, 133.58, 132.33, 129.72, 126.48 (q, $J$=32.5 Hz), 124.80 (q, $J$=270.0 Hz), 121.81 (q, $J$=3.8 Hz), 121.73, 121.59, 120.64 (q, $J$=3.9 Hz), 113.98, 70.40, 31.37, 27.94, 26.71, 24.50, 24.17, 23.90, 23.21 ppm; IR (neat): $\tilde{\nu}$=1665 cm$^{-1}$; MS (70 eV, EI): $m/z$: 423 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{22}H_{24}F_3NO_2S$: 423.1480; found: 423.1465.

**18-Chloro-7,8,9,10,11,12,13,14-octahydro-6*H*,20*H*-5-oxa-15-thia-20-azadibenzo[*a*,*e*]cycloheptadecen-21-one (4m)**: 83% yield; m.p. 127–128°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=9.82 (s, 1H), 7.98–7.95 (m, 2H), 7.55 (dt, $J$=1.5, 8.0 Hz, 1H), 7.43 (d, $J$=8.5 Hz, 1H), 7.24 (dd, $J$=2.0, 8.5 Hz, 2H), 7.09 (t, $J$=7.5 Hz, 1H), 4.29 (t, $J$=5.5 Hz, 2H), 3.08 (t, $J$=6.0 Hz, 2H), 1.84–1.80 (m, 2H), 1.62–1.59 (m, 2H), 1.48–1.44 (m, 2H), 1.37–1.23 ppm (m, 8H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=164.17, 157.33, 137.67, 134.41, 132.24, 130.35, 129.97, 128.80, 125.88, 124.48, 121.76, 121.51, 113.94, 69.80, 31.99, 28.96, 27.08, 26.68, 25.99, 25.56, 25.16, 24.98 ppm; IR (neat): $\tilde{\nu}$=1660 cm$^{-1}$; MS (70 eV, EI): $m/z$: 403 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{22}H_{26}ClNO_2S$: 403.1373; found: 403.1358.

**18-Trifluoromethyl-7,8,9,10,11,12,13,14-octahydro-6*H*,20*H*-5-oxa-15-thia-20-azadibenzo[*a*,*e*]cycloheptadecen-21-one (4n)**: 78% yield; m.p. 137–138°C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=9.78 (s, 1H), 8.39 (s, 1H), 8.24 (dd, $J$=1.5, 8.0 Hz, 1H), 7.47 (dt, $J$=1.5, 8.5 Hz, 1H), 7.36–7.32 (m, 2H), 7.09 (t, $J$=7.5 Hz, 1H), 7.03 (d, $J$=8.0 Hz, 1H), 4.28 (t, $J$=6.0 Hz, 2H), 3.09 (t, $J$=6.0 Hz, 2H), 1.96–1.91 (m, 2H), 1.79–1.74 (m, 2H), 1.59–1.35 ppm (m, 10H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=164.13, 157.04, 135.92, 133.48, 133.37, 132.65, 127.65 (q, $J$=32.5 Hz), 126.51, 123.95 (q, $J$=270.9 Hz), 121.46 (q, $J$=3.8 Hz), 121.38, 121.13, 121.08 (q, $J$=3.8 Hz), 112.38, 69.56, 31.61, 29.04, 26.65, 26.22, 25.44, 24.96, 24.81, 24.72 ppm; IR (neat): $\tilde{\nu}$=1661 cm$^{-1}$; MS (70 eV, EI): $m/z$: 437 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{23}H_{26}F_3NO_2S$: 437.1636; found: 437.1627.

**10-Oxa-21-thia-2-azatricyclo[20.4.0.0$^{4,9}$]hexacosa-1(22),4(9),5,7,23,25-hexaen-3-one (4o)**: 70% yield; m.p. 87–88°C; $^1$H NMR (500 MHz, [D$_6$]DMSO): $\delta$=9.97 (s, 1H), 8.09–8.04 (m, 2H), 7.53 (dt, $J$=2.0, 8.5 Hz, 1H), 7.38 (dd, $J$=1.0, 7.5 Hz, 1H), 7.25–7.07 (m, 4H), 4.30 (t, $J$=5.5 Hz, 2H), 3.05 (t, $J$=6.0 Hz, 2H), 1.91–1.83 (m, 2H), 1.65–1.59 (m, 2H), 1.40–1.27 ppm (m, 12H); $^{13}$C NMR (125 MHz, [D$_6$]DMSO): $\delta$=163.70, 159.95, 136.60, 134.27, 132.42, 128.46, 128.16, 126.19, 125.66, 123.73, 121.94, 121.55, 113.91, 69.40, 32.81, 27.51, 27.01, 26.20, 25.82, 25.69, 25.62, 24.90, 23.74 ppm; IR (neat): $\tilde{\nu}$=1665 cm$^{-1}$; MS (70 eV, EI): $m/z$: 383 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{23}H_{29}NO_2S$: 383.1919; found: 383.1902.

**25-Chloro-10-oxa-21-thia-2-azatricyclo[20.4.0.0$^{4,9}$]hexacosa-1(22),4(9),5,7,23,25-hexaen-3-one (4p)**: 72% yield; m.p. 151–152°C; $^1$H NMR (500 MHz, CDCl$_3$): $\delta$=10.19 (s, 1H), 8.51 (d, $J$=2.5 Hz, 1H), 8.24 (dd, $J$=1.5, 8.0 Hz, 1H), 7.44 (dt, $J$=1.5, 8.0 Hz, 1H), 7.24–7.21 (m, 1H), 7.08–7.00 (m, 3H), 4.29 (t, $J$=7.5 Hz, 2H), 2.97 (t, $J$=6.5 Hz, 2H), 1.99–1.93 (m, 2H), 1.72–1.66 (m, 2H), 1.51–1.35 ppm (m, 12H); $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$=163.86, 156.56, 138.26, 133.26, 132.65, 132.22, 129.61, 124.77, 124.23, 122.36, 121.72, 121.04, 112.38, 69.19, 34.23, 27.00, 26.76, 25.81, 25.46, 25.50, 24.98, 24.24, 23.25 ppm; IR (neat): $\tilde{\nu}$=1660 cm$^{-1}$; MS (70 eV, EI): $m/z$: 417 [$M^+$]; HRMS (70 eV, EI): $m/z$: calcd for $C_{23}H_{28}ClNO_2S$: 417.1529; found: 417.1512.

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[23] CCDC-629029 (**4p**) contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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