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Synthesis of spirobarbiturate-pyrrolidinones *via* a domino aza-Michael/S_N2 cyclization of barbiturate-derived alkenes with *N*-alkoxy α-haloamides†

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A highly efficient domino aza-MIRC (Michael Induced Ring Closure) reaction between barbiturate-derived alkenes and *N*-alkoxy α-haloamides has been achieved in moderate to excellent yields. This reaction proceeds smoothly under mild conditions *via* a domino aza-Michael addition/intramolecular S_N2 sequence, providing a practical tool in the synthesis of bioactive molecules spirobarbiturate-3-pyrrolidinones.

Introduction

Barbiturates, namely barbituratic acids derivatives, are remarkable scaffolds since they are prevalent in pharmacologically active compounds. Moreover, spirobarbiturates have continued to gain attention in recent years because of their various pharmacological properties, such as urease inhibitor, HIV-1 inhibitor, anticonvulsant, TACE inhibitor, MMP-13 inhibitor, and anticancer activities (Fig. 1).[1]

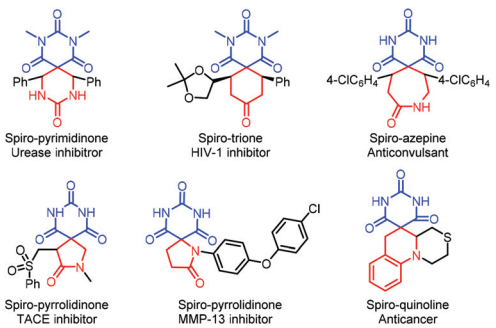

Fig. 1 Biologically active compounds containing the spiro-barbiturates scaffolds.

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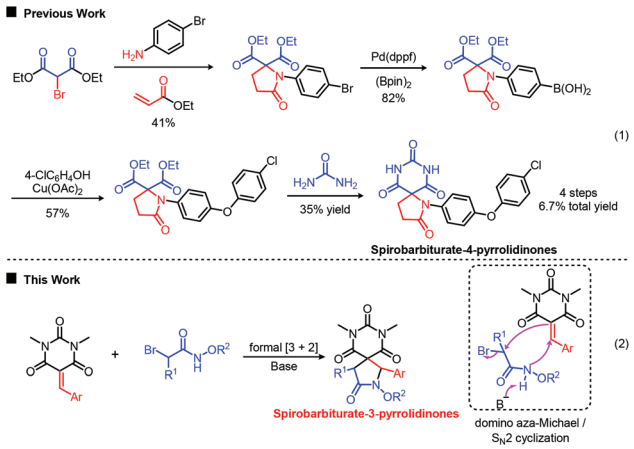
Due to the importance of spirobarbiturate compounds, various synthetic routes to these spiroheterocycles have been explored to achieve bioactive molecules with complex ring frameworks.[2,3] Among them, the [2 + *m*] cycloaddition reactions of barbiturate-derived alkenes were proven to be powerful strategies for the construction of spirobarbiturate compounds.[2] In the last decade, a lot of barbiturate-derived alkenes based cycloaddition reactions have been developed to access various spirobarbiturates scaffolds, such as spirobarbiturate-cyclopentenes,[2a] spirobarbiturate-cyclohexenes,[2b] spirobarbiturate-cyclopentanones,[2c] and spirobarbiturate-cyclopropanes.[2d]

On the other hand, pyrrolidinones are important structural motifs in natural products and medicinally important compounds.[4] Spirobarbiturate-pyrrolidinones with the combination of barbiturates and pyrrolidinones moieties are very appealing in the search for medicinally active compounds.[5] To the best of our knowledge, the only reported method to construct spirobarbiturate-pyrrolidinones is the synthesis of spirobarbiturate-4-pyrrolidinones, relying on time-consuming multistep synthesis in low yields, starting from α-bromo diethyl malonate (Scheme 1, eqn (1)).[5a] However, the synthetic method of spirobarbiturate-3-pyrrolidinones has not been uncovered up to now.[5b] Hence, development of new protocols to construct such scaffolds is highly desirable. As part of our continuing efforts on cyclization reactions,[6] herein, we considered the formal [3 + 2] cycloaddition of barbiturate-derived alkenes with *N*-alkoxy α-haloamides might be an efficient tool to synthesize spirobarbiturate-3-pyrrolidinones (Scheme 1, eqn (2)).

[3 + 2] annulations are highly powerful synthetic strategies for the construction of five-membered rings. Particularly, these annulations have also successfully been applied in the synthesis of pyrrolidinones.[7] Comesse developed the aza-Michael/intramolecular nucleophilic substitution of Michael acceptors



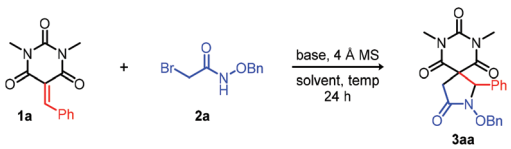
Scheme 1 Synthetic approach to spirobarbiturate-pyrrolidinones.

with α-bromoacetamides to synthesize pyrrolidinones in 49–69% yields.[7a] The strong basic conditions, using NaH in this system limited the application. Moreover, *N*-alkoxy α-haloacetamides are commonly used 3-atom synthons due to their easy availability and high reactivity.[8] Recently, Huang established the [3 + 2] cycloaddition of α-substituted *N*-alkoxy α-haloacetamides with aromatic ethylenes to prepare pyrrolidinones *via* azaoxyallyl cation intermediates in 15–71% yields, performed in HFIP at 50 °C.[7b] It was supposed that substituents on the α-position of *N*-alkoxy α-haloacetamides are necessary to stabilize the formed azaoxyallyl cation species and reactions with α-unsubstituted *N*-alkoxy α-haloacetamides were not reported in this work. We have previously demonstrated the powerful synthetic utility of α-unsubstituted *N*-alkoxy α-haloacetamides with sulfamate-derived cyclic imines to provide 4-imidazolidinones in good to excellent yields under mild conditions.[6] Herein, we present a new formal [3 + 2] cycloaddition of barbiturate-derived alkenes with α-unsubstituted and α-substituted *N*-alkoxy α-haloacetamides to construct spirobarbiturate-3-pyrrolidinones *via* a domino aza-Michael/intramolecular nucleophilic substitution sequence.

Results and discussion

We commenced our work by examining the reaction between barbiturate-derived alkene **1a** and *N*-OBn α-Br acetamide **2a** (Table 1). Firstly, we conducted the reaction at 25 °C for 24 h with the use of K_2CO_3 and 4 Å MS in CH_3CN under air atmosphere, providing the desired product in 83% yield (entry 1). Other solvents (DCM, THF, Toluene and HFIP) were screened and DCM displayed the best result, giving **3aa** in 92% yield (entries 2–5). It's worth noting that the reaction did not give any product by using HFIP as the solvent (entry 5). Replacement of K_2CO_3 with other bases (Et_3N, Cs_2CO_3, Na_2CO_3 or KOH), the cyclization products could be also successfully obtained, albeit in decreased yields (51–90%, entries 6–9). Most gratifyingly, almost quantitative yield (>99%) was

Table 1 Optimization of the reaction conditions[a]



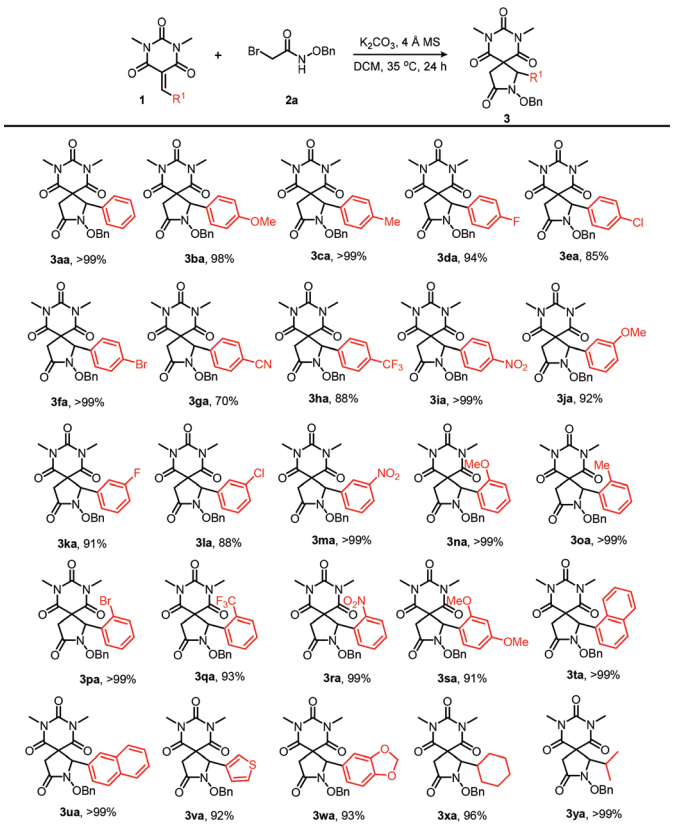
Entry	Base	Solvent	Temp. (°C)	Yield[b] (%)
1	K_2CO_3	CH_3CN	25	83
2	K_2CO_3	DCM	25	92
3	K_2CO_3	THF	25	84
4	K_2CO_3	Toluene	25	59
5	K_2CO_3	HFIP	25	NR
6	Et_3N	DCM	25	78
7	Cs_2CO_3	DCM	25	90
8	Na_2CO_3	DCM	25	51
9	KOH	DCM	25	84
10	**K_2CO_3**	**DCM**	**35**	**>99**
11[c,d]	K_2CO_3	DCM	35	>99
12[c]	K_2CO_3	DCM	35	96

[a] Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), **2a** (0.24 mmol), base (0.24 mmol) and 4 Å MS (100 mg) in 2 mL of solvent under air atmosphere. [b] Isolated yields. [c] Without 4 Å MS. [d] N_2 atmosphere.

obtained when the reaction was carried out at 35 °C for 24 h (entry 10). Controlled experiment conducted without 4 Å MS under N_2 atmosphere also could provide **3aa** in >99% yield (entry 11). However, a slightly decreased yield (96%) was observed under air atmosphere without 4 Å MS. Considering the convenience of operation, the optimized conditions are as follows: **1a** reacts with **2a** in DCM at 35 °C using K_2CO_3 as the base in the presence of 4 Å MS under air atmosphere.

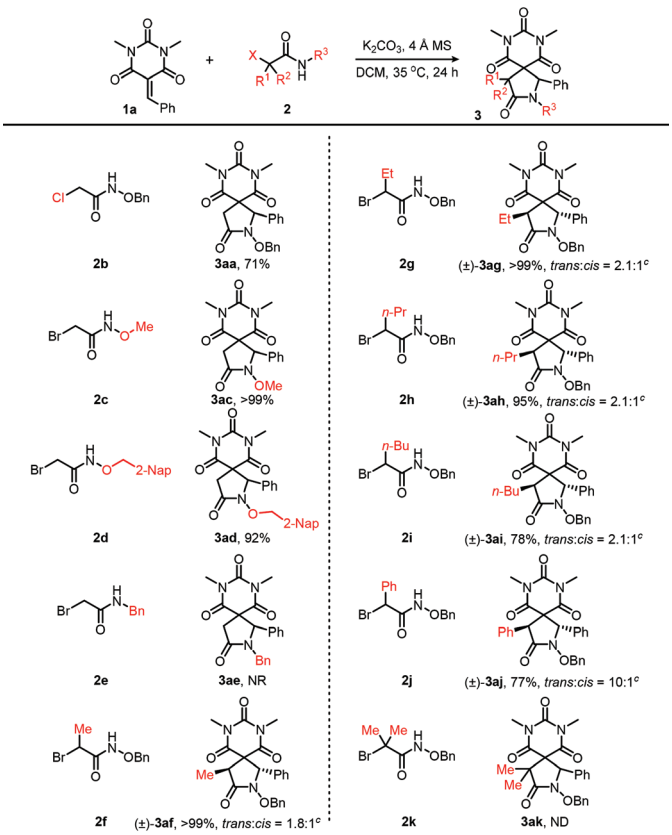
With the optimized conditions in hand, we then explored the scope and functional group tolerance of barbiturate-derived alkenes **1**. As shown in Table 2, a series of barbiturate-derived alkenes **1** were allowed to react with *N*-OBn α-Br acetamide **2a** under optimized conditions, providing the desired products in good to excellent yields. The position of the substituents and the electronic effect seemed to have no remarkable influence on the reaction. Notably, barbiturate-derived alkenes **1** substituted by –OMe (**1b**, **1j**, **1n**) or –NO_2 (**1i**, **1m**, **1r**) groups on different positions of phenyl ring all reacted efficiently with *N*-OBn α-Br acetamide **2a**, affording the corresponding spirocyclic products in excellent yields. Moreover, whether using electron-rich (**1b–1c**, **1j**, **1n–1o**) or electron-deficient (**1d–1i**, **1k–1m**, **1p–1r**) aryl-substituted barbiturate-derived alkenes **1**, the spirobarbiturate-pyrrolidinone products were all obtained in good to excellent yields (**3ba–3ra**). 2,4-Dimethoxyl substituted alkene **1s** also led to the desired product **3sa** in 91% yield. Substrates with a naphthyl (**1t–1u**), thienyl (**1v**) or benzodioxolyl (**1w**) were all applicable in this reaction, affording the desired products (**3ta–3wa**) in excellent yields. Barbiturate-derived alkenes bearing an alkyl group (**1x–1y**) were also compatible with the current system, affording the desired spirobarbiturate-pyrrolidinone products **3xa** and **3ya** in 96% and >99% yield, respectively.

Table 2 Substrate scope for alkenyl compounds **1**[a,b]



[a] Unless otherwise noted, all reactions were carried out with **1** (0.2 mmol), **2a** (0.24 mmol), K_2CO_3 (0.24 mmol) and 4 Å MS (100 mg) in 2 mL of DCM at 35 °C for 24 h under air atmosphere. [b] Isolated yields.

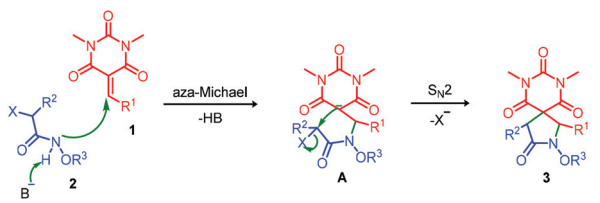
Table 3 Substrate scope for α-haloamides **2**[a,b]



[a] Unless otherwise noted, all reactions were carried out with **1a** (0.2 mmol), **2** (0.24 mmol), K_2CO_3 (0.24 mmol) and 4 Å MS (100 mg) in 2 mL of DCM at 35 °C for 24 h under air atmosphere. [b] Isolated yields. [c] The *trans* : *cis* value is determined by ^{1}H NMR spectroscopy.

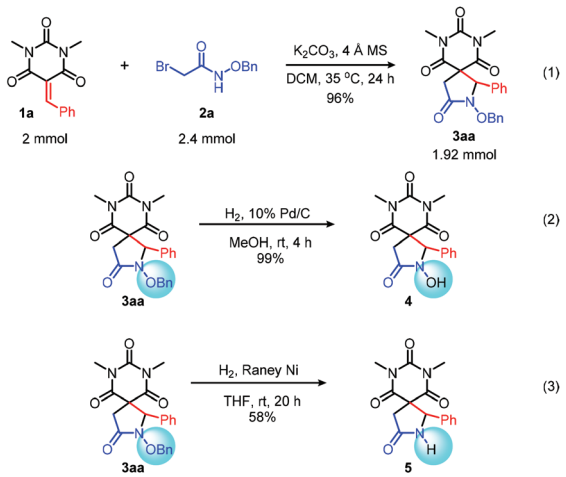
Encouraged by the feasibility of this domino sequence, we next explored the scope of α-haloamides **2**. As summarized in Table 3, when *N*-OBn α-Cl acetamide **2b** was applied to this formal [3 + 2] cycloaddition procedure, the expected product **3aa** also could be obtained in 71% yield. Unsubstituted *N*-alkoxy α-Br acetamides **2c** and **2d** with different substituents (methyl, 2-naphthylmethylene) on oxygen atom, both produced the desired products spirobarbiturate-pyrrolidinones (**3ac–3ad**) in excellent yields. When *N*-Bn α-Br acetamide **2e** was used as the material, the reaction failed to give the corresponding product **3ae** under standard conditions, perhaps owing to the weaker acidity of **2e** than **2a**. When using *N*-OBn α-Br amides **2f–2j** with different substituents (Me, Et, *n*-Pr, *n*-Bu or Ph) on α-position, the spirobarbiturate-pyrrolidinones were all readily obtained in excellent yields. The *trans* configuration of the major isomer (**3af**) was confirmed by ^{1}H-NMR NOE analysis. As expected, the steric hindrance on α-position of the α-substituted *N*-alkoxy α-bromo amides **2** plays a crucial role in the reaction and α,α-dimethyl substituted *N*-OBn α-Br amide **2k** did not work under standard conditions.

On the basis of previous report[6] and the observed results, we speculate that the reaction might occur through a cascade aza-Michael addition/intramolecular S_N2 pathway. As depicted in Scheme 2, under the promotion of base, the deprotonation on the nitrogen atom of *N*-alkoxy α-haloamides **2** and the concomitant aza-Michael addition to imines **1** leading to intermediate **A** could occur. Next the following intramolecular S_N2 substitution reaction will generate the desired spirobarbiturate-pyrrolidinones.



Scheme 2 Putative aza-Michael addition/intramolecular S_N2 reaction pathway.

To further illustrate the preparative utility of this [3 + 2] cyclization, a 2 mmol scale reaction was carried out under the standard conditions, giving the desired product **3aa** in a comparable yield (Scheme 3, eqn (1)). Furthermore, deprotection of the *N*-OBn of **3aa** was also realized, generating *N*-OH compound **4** and *N*-H compound **5** in 99% yield and 58% yield respectively (Scheme 3, eqn (2) and (3)).



Scheme 3 2 mmol scale synthesis of **3aa** and deprotections of **3aa**.

Conclusions

In conclusion, barbiturate-derived alkenes and *N*-alkoxy α-haloamides can undergo cascade aza-Michael/intramolecular nucleophilic substitution reaction to afford spirobarbiturate-pyrrolidinones in good to excellent yields. This cascade [3 + 2] cyclization was successfully performed under air atmosphere and mild conditions with excellent tolerance of a wide range of functional groups. This system does not require strong bases or fluorinated solvents for successful cycloaddition, perhaps owing to the high acidity of *N*-alkoxy α-haloamides. This method not only further expands the synthetic utility of *N*-alkoxy α-haloamides, but also provides a practical strategy for the synthesis of spirobarbiturate-pyrrolidinones. Futher synthetic application investigation of this method is in progress.

Experimental

General information

All reactions were performed in oven-dried glassware with magnetic stirring under air atmosphere. Unless otherwise stated, all reagents were purchased from commercial suppliers and used without further purification. All solvents were purified and dried according to standard methods prior to use. Organic solutions were concentrated under reduced pressure on a rotary evaporator or an oil pump. Reactions were monitored through thin layer chromatography (TLC) on silica gel-precoated glass plates. Subsequent to elution, plates were visualized using UV radiation at 254 nm and by staining with aqueous potassium permanganate or ethanolic phosphomolybdic acid solution. Flash column chromatography was performed using silica gel (300–400 mesh). Nuclear Magnetic Resonance (NMR) spectras were acquired on a Varian Mercury 400 operating at 400, 100 and 376 MHz for ^{1}H, ^{13}C and ^{19}F, respectively. Chemical shifts are reported in δ ppm referenced to an internal $SiMe_4$ standard for ^{1}H NMR, chloroform-d (δ 77.16) for ^{13}C NMR. Datas for ^{1}H NMR are recorded as follows: chemical shift (δ ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br s, broad), coupling constant (Hz) and integration. Datas for ^{13}C NMR and ^{19}F NMR are reported in terms of chemical shift (δ, ppm). High-resolution mass spectra (HRMS) were recorded on a Thermo Q-Exactive Spectrometer (ESI).

General procedures for [3 + 2] annulation reaction

In a 10 mL test tube was sequentially added barbiturate-derived alkenes **1** (0.2 mmol, 1.0 equiv.), K_2CO_3 (0.24 mmol, 1.2 equiv.), *N*-Alkoxy α-haloamides **2** (0.24 mmol, 1.2 equiv.), 4 Å MS (100 mg) and DCM (2.0 mL) under air atmosphere. Then the tube was sealed and stirred at 35 °C. Once the barbiturate-derived alkenes **1** was completed consumption (24 h), the reaction mixture was concentrated under reduced pressure and the resulting residue was purified by flash column chromatography on silica gel to afford the pure products **3**. (PE/EA = 3/2 for **3aa–3fa**, **3ha**, **3ja–3ka**, **3na–3ra**, **3ta–3wa**, **3ab**, **3ad**; PE/EA = 1/1 for **3ga**, **3ia**, **3ma**, **3sa**; PE/EA = 2/1 for **3la**, **3xa**, **3af**; PE/EA = 4/3 for **3ac**; PE/EA = 3/1 for **3ag–3ai**).

2-(Benzyloxy)-7,9-dimethyl-1-phenyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3aa). Purification by column chromatography on silica gel afforded the title compound as colorless oil. 81 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.27 (m, 6H), 7.22–7.20 (m, 2H), 6.99–6.98 (m, 2H), 5.14 (d, J = 10.8 Hz, 1H), 4.88 (d, J = 10.4 Hz, 1H), 4.39 (s, 1H), 3.29 (s, 3H), 3.23 (d, J = 16.8 Hz, 1H), 3.13 (d, J = 16.8 Hz, 1H), 2.66 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 168.5, 166.7, 150.2, 134.9, 132.3, 130.2, 129.8, 129.1, 129.0, 128.6, 127.3, 77.6, 71.1, 55.4, 32.7, 29.5, 28.7 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{22}H_{22}N_3O_5$ $[M + H]^+$: 408.1554, found 408.1548.

2-(Benzyloxy)-1-(4-methoxyphenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraon (3ba). Purification by column chromatography on silica gel afforded the title compound as colorless oil. 85 mg, 98% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 3H), 7.22–7.20 (m, 2H), 6.91–6.84 (m, 4H), 5.10 (d, J = 10.8 Hz, 1H), 4.85 (d, J = 10.4 Hz, 1H), 4.33 (s, 1H), 3.80 (s, 3H), 3.28 (s, 3H), 3.19 (d, J = 17.2 Hz, 1H), 3.11 (d, J = 17.2 Hz, 1H), 2.72 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.7, 166.8, 161.0, 150.4, 135.0, 129.9, 129.1, 128.7, 128.6, 123.9, 114.3, 77.6, 70.9, 55.5 (2C), 32.5, 29.5, 28.9 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{23}H_{24}N_3O_6$ $[M + H]^+$: 438.1660, found 438.1657.

2-(Benzyloxy)-7,9-dimethyl-1-(*p*-tolyl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ca). Purification by column chromatography on silica gel afforded the title compound as colorless oil. 84 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.27 (m, 3H), 7.23–7.20 (m, 2H), 7.16–7.14 (m, 2H), 6.87–6.85 (m, 2H), 5.12 (d, J = 10.8 Hz, 1H), 4.87 (d, J = 10.4 Hz, 1H), 4.33 (s, 1H), 3.28 (s, 3H), 3.20 (d, J = 16.8 Hz, 1H), 3.13 (d, J = 16.8 Hz, 1H), 2.69 (s, 3H), 2.35 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.6, 166.8, 150.3, 140.3, 134.9, 129.9, 129.6, 129.2, 129.1, 128.6, 127.2, 77.6, 71.0, 55.4,

32.5, 29.5, 28.8, 21.4 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{23}H_{24}N_3O_5$ $[M + H]^+$: 422.1710, found 422.1702.

2-(Benzyloxy)-1-(4-fluorophenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3da). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 157–159 °C. 80 mg, 94% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 3H), 7.22–7.20 (m, 2H), 7.06–7.02 (m, 2H), 6.96–6.92 (m, 2H), 5.11 (d, J = 10.8 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.32 (s, 1H), 3.29 (s, 3H), 3.20 (d, J = 16.8 Hz, 1H), 3.12 (d, J = 16.8 Hz, 1H), 2.72 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.5, 166.6, 163.7 (d, J = 249.0 Hz, 1C), 150.2, 134.9, 129.9, 129.3, 129.2 (d, J = 4.0 Hz, 1C), 128.7, 128.2 (d, J = 4.0 Hz, 1C), 116.1 (d, J = 22.0 Hz, 1C), 77.6, 70.4, 55.2, 32.7, 29.5, 28.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.0 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{22}H_{21}FN_3O_5$ $[M + H]^+$: 426.1460, found 426.1449.

2-(Benzyloxy)-1-(4-chlorophenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ea). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 130–132 °C. 75 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37–7.28 (m, 5H), 7.22–7.20 (m, 2H), 6.89–6.87 (m, 2H), 5.11 (d, J = 10.8 Hz, 1H), 4.87 (d, J = 10.8 Hz, 1H), 4.29 (s, 1H), 3.29 (s, 3H), 3.19 (d, J = 16.8 Hz, 1H), 3.12 (d, J = 16.8 Hz, 1H), 2.72 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.4, 166.5, 150.2, 136.2, 134.8, 130.9, 129.9, 129.21, 129.19, 128.71, 128.69, 77.6, 70.3, 55.1, 32.6, 29.5, 28.8 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{22}H_{21}ClN_3O_5$ $[M + H]^+$: 442.1164, found 442.1157.

2-(Benzyloxy)-1-(4-bromophenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3fa). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 138–140 °C. 97 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.46 (m, 2H), 7.35–7.28 (m, 3H), 7.23–7.20 (m, 2H), 6.83–6.81 (m, 2H), 5.11 (d, J = 10.8 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 4.26 (s, 1H), 3.29 (s, 3H), 3.19 (d, J = 16.8 Hz, 1H), 3.12 (d, J = 16.8 Hz, 1H), 2.72 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.4, 166.5, 150.2, 134.8, 132.2, 131.5, 129.9, 129.2, 129.0, 128.7, 124.4, 77.6, 70.4, 55.0, 32.6, 29.6, 28.8 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{22}H_{21}BrN_3O_5$ $[M + H]^+$: 486.0659, found 486.0655.

4-(2-(Benzyloxy)-7,9-dimethyl-3,6,8,10-tetraoxo-2,7,9-triazaspiro[4.5]decan-1-yl)benzonitrile (3ga). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 130–132 °C. 60 mg, 70% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63–7.61 (m, 2H), 7.39–7.29 (m, 3H), 7.21–7.20 (m, 2H), 7.04–7.02 (m, 2H), 5.11 (d, J = 11.2 Hz, 1H), 4.90 (d, J = 11.2 Hz, 1H), 4.28 (s, 1H), 3.30 (s, 3H), 3.19 (d, J = 16.8 Hz, 1H), 3.13 (d, J = 16.8 Hz, 1H), 2.70 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.0, 168.2, 166.2, 150.0, 137.8, 134.8, 132.5, 130.0, 129.4, 128.8, 128.2, 117.8, 114.1, 77.7, 70.1, 54.8, 32.8, 29.6, 28.8 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{23}H_{21}N_4O_5$ $[M + H]^+$: 433.1506, found. 433.1498.

2-(Benzyloxy)-7,9-dimethyl-1-(4-(trifluoromethyl)phenyl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ha). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 158–160 °C. 84 mg, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.58 (m, 2H), 7.36–7.29 (m, 3H), 7.22–7.20 (m, 2H), 7.07–7.05 (m, 2H), 5.12 (d, J = 10.8 Hz, 1H), 4.90 (d, J = 10.8 Hz, 1H), 4.32 (s, 1H), 3.30 (s, 3H), 3.21 (d, J = 16.8 Hz, 1H), 3.14 (d, J = 16.8 Hz, 1H), 2.65 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 168.3, 166.4, 150.1, 136.6, 134.8, 132.3 (q, J = 33.0 Hz, 1C), 129.9, 129.3, 128.8, 127.9, 125.8 (q, J = 3.3 Hz, 1C), 123.7 (q, J = 272.0 Hz, 1C), 77.6, 70.3, 55.0, 32.8, 29.6, 28.7 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −62.9 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{23}H_{21}F_3N_3O_5$ $[M + H]^+$: 476.1428, found 476.1417.

2-(Benzyloxy)-7,9-dimethyl-1-(4-nitrophenyl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ia). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 192–194 °C. 90 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25–8.22 (m, 1H), 7.73–7.72 (m, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.37–7.29 (m, 4H), 7.22–7.20 (m, 2H), 5.14 (d, J = 10.8 Hz, 1H), 4.92 (d, J = 11.2 Hz, 1H), 4.38 (s, 1H), 3.31 (s, 3H), 3.21 (d, J = 16.8 Hz, 1H), 3.14 (d, J = 17.2 Hz, 1H), 2.71 (s, 3H) ppm. ^{13}C NMR (100 MHz, DMSO-d_6) δ 168.5, 168.3, 166.7, 150.5, 147.6, 136.0, 134.4, 133.8, 130.2, 129.2, 128.7, 128.3, 124.2, 122.0, 76.0, 65.7, 54.3, 32.5, 29.0, 28.1 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{22}H_{21}N_4O_7$ $[M + H]^+$: 453.1405, found 453.1365.

2-(Benzyloxy)-1-(3-methoxyphenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ja). Purification by column chromatography on silica gel afforded the title compound as colorless oil. 80 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35–7.23 (m, 6H), 7.95–6.92 (m, 1H), 6.57–6.55 (m, 2H), 5.17 (d, J = 10.4 Hz, 1H), 4.91 (d, J = 10.8 Hz, 1H), 4.37 (s, 1H), 3.79 (s, 3H), 3.30 (s, 3H), 3.24 (d, J = 16.8 Hz, 1H), 3.13 (d, J = 16.8 Hz, 1H), 2.73 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 168.5, 166.7, 160.1, 150.3, 134.9, 133.9, 130.1, 129.8, 129.1, 128.7, 119.4, 115.9, 112.6, 77.6, 71.1, 55.5, 55.4, 32.8, 29.5, 28.8 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{23}H_{24}N_3O_6$ $[M + H]^+$: 438.1660, found 438.1654.

2-(Benzyloxy)-1-(3-fluorophenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ka). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 168–170 °C. 77 mg, 91% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 4H), 7.29–7.21 (m, 2H), 7.11–7.07 (m, 1H), 6.74–6.70 (m, 2H), 5.14 (d, J = 10.4 Hz, 1H), 4.89 (d, J = 10.8 Hz, 1H), 4.33 (s, 1H), 3.29 (s, 3H), 3.20 (d, J = 16.8 Hz, 1H), 3.12 (d, J = 16.8 Hz, 1H), 2.74 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.4, 166.5, 162.9 (d, J = 248.0 Hz, 1C), 150.2, 135.1 (d, J = 7.0 Hz, 1C), 134.8, 130.7 (d, J = 9.0 Hz, 1C), 129.9, 129.2, 128.7, 123.0 (d, J = 3.0 Hz, 1C), 117.3 (d, J = 21.0 Hz, 1C), 114.4 (d, J = 23.0 Hz, 1C), 77.7, 70.4, 55.1, 32.8, 29.5, 28.8 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −110.8 ppm. HRMS (ESI) *m*/*z* Exact mass calcd for $C_{22}H_{21}FN_3O_5$ $[M + H]^+$: 426.1460, found 426.1450.

2-(Benzyloxy)-1-(3-chlorophenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3la). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 162–164 °C. 77 mg, 88% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.28 (m, 5H), 7.24–7.22 (m, 2H), 6.96–6.95 (m, 1H), 6.84–6.82 (m, 1H), 5.14 (d, J = 10.8 Hz, 1H),

4.89 (d, J = 10.8 Hz, 1H), 4.28 (s, 1H), 3.29 (s, 3H), 3.19 (d, J = 16.8 Hz, 1H), 3.12 (d, J = 16.8 Hz, 1H), 2.75 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.3, 166.4, 150.1, 135.2, 134.8, 134.6, 130.4, 130.2, 129.9, 129.2, 128.7, 127.4, 125.5, 77.7, 70.4, 55.2, 32.7, 29.5, 28.8 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{22}H_{21}ClN_3O_5$ $[M + H]^+$: 442.1164, found 442.1154.

2-(Benzyloxy)-7,9-dimethyl-1-(3-nitrophenyl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ma). Purification by column chromatography on silica gel afforded the title compound as colorless oil. 90 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18–8.16 (m, 2H), 7.37–7.29 (m, 3H), 7.22–7.19 (m, 2H), 7.13–7.11 (m, 2H), 5.09 (d, J = 11.2 Hz, 1H), 4.90 (d, J = 11.2 Hz, 1H), 4.38 (s, 1H), 3.31 (s, 3H), 3.19 (d, J = 17.2 Hz, 1H), 3.14 (d, J = 16.8 Hz, 1H), 2.71 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.2, 166.1, 150.0, 148.9, 139.7, 134.8, 130.0, 129.4, 128.8, 128.5 (2C), 124.0 (2C), 77.7, 69.8, 54.7, 32.9, 29.7, 28.9 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{22}H_{21}N_4O_7$ $[M + H]^+$: 453.1405, found 453.1366.

2-(Benzyloxy)-1-(2-methoxyphenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3na). Purification by column chromatography on silica gel afforded the title compound as colorless oil. 87 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.31–7.23 (m, 6H), 7.13–7.12 (m, 1H), 7.00–6.96 (m, 1H), 6.83–6.81 (m, 1H), 5.07 (d, J = 10.8 Hz, 1H), 5.02 (s, 1H), 4.94 (d, J = 10.8 Hz, 1H), 3.66 (s, 3H), 3.28 (s, 3H), 3.19 (d, J = 16.8 Hz, 1H), 3.11 (d, J = 16.8 Hz, 1H), 2.65 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 168.9, 167.0, 156.9, 150.8, 135.0, 130.8, 129.7, 128.90, 128.86, 128.6, 121.0, 120.6, 110.2, 77.3, 63.5, 55.7, 54.2, 32.9, 29.4, 28.6 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{23}H_{24}N_3O_6$ $[M + H]^+$: 438.1660, found 438.1654.

2-(Benzyloxy)-7,9-dimethyl-1-(*o*-tolyl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3oa). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 162–163 °C. 84 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.28 (m, 3H), 7.25–7.20 (m, 4H), 7.18–7.15 (m, 1H), 7.12–7.10 (m, 1H), 5.16 (d, J = 10.8 Hz, 1H), 4.83 (d, J = 10.8 Hz, 1H), 4.79 (s, 1H), 3.25 (s, 3H), 3.23 (d, J = 16.8 Hz, 1H), 3.16 (d, J = 16.8 Hz, 1H), 2.69 (s, 3H), 1.83 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.4, 168.6, 166.9, 150.3, 136.0, 135.1, 131.2, 129.9, 129.8, 129.6, 129.1, 128.8, 127.8, 126.4, 77.6, 66.4, 55.0, 33.2, 29.5, 28.8, 18.2 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{23}H_{24}N_3O_5$ $[M + H]^+$: 422.1710, found 422.1701.

2-(Benzyloxy)-1-(2-bromophenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3pa). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 169–171 °C. 97 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51–7.49 (m, 1H), 7.37–7.32 (m, 4H), 7.27–7.26 (m, 1H), 7.25–7.24 (m, 1H), 7.22–7.18 (m, 2H), 5.09 (d, J = 11.2 Hz, 1H), 5.05 (s, 1H), 4.90 (d, J = 11.2 Hz, 1H), 3.28 (s, 3H), 3.20 (d, J = 16.4 Hz, 1H), 3.10 (d, J = 16.8 Hz, 1H), 2.75 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.6, 168.4, 166.5, 150.4, 134.7, 133.3, 131.7, 131.3, 130.1, 129.8, 129.2, 128.9, 127.9, 123.2, 77.5, 68.1, 54.1, 33.2, 29.6, 28.8 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{22}H_{21}BrN_3O_5$ $[M + H]^+$: 486.0659, found 486.0652.

2-(Benzyloxy)-7,9-dimethyl-1-(2-(trifluoromethyl)phenyl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3qa). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 109–110 °C. 88 mg, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66–7.58 (m, 2H), 7.51–7.44 (m, 2H), 7.34–7.29 (m, 3H), 7.24–7.22 (m, 2H), 5.17 (s, 1H), 5.03 (d, J = 10.8 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 3.32–3.28 (m, 4H), 3.10 (d, J = 16.8 Hz, 1H), 2.77 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 168.9, 168.2, 166.7, 150.2, 134.2, 132.1, 131.0, 130.6, 130.1, 129.8, 129.1, 128.7 (q, J = 30.3 Hz, 1C), 128.6, 126.5 (q, J = 5.7 Hz, 1C), 123.9 (q, J = 272.7 Hz, 1C), 77.3, 64.5, 54.0, 34.3, 29.4, 28.9 ppm. ^{19}F NMR (376 MHz, $CDCl_3$) δ −57.1 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{23}H_{21}F_3N_3O_5$ $[M + H]^+$: 476.1428, found 476.1422.

2-(Benzyloxy)-7,9-dimethyl-1-(2-nitrophenyl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ra). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 182–183 °C. 89 mg, 99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.87 (m, 1H), 7.64–7.60 (m, 1H), 7.47–7.43 (m, 1H), 7.39–7.37 (m, 1H), 7.27–7.17 (m, 3H), 7.13–7.11 (m, 2H), 4.99 (s, 1H), 4.931–4.930 (m, 2H), 3.28 (s, 3H), 3.08 (d, J = 16.8 Hz, 1H), 2.87 (d, J = 16.8 Hz, 1H), 2.75 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 167.1, 167.0, 150.4, 148.3, 134.7, 133.9, 131.3, 130.3, 129.51, 129.46, 129.3, 128.8, 125.2, 77.7, 64.5, 52.9, 36.0, 29.5, 28.9 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{22}H_{21}N_4O_7$ $[M + H]^+$: 453.1405, found 453.1366.

2-(Benzyloxy)-1-(2,4-dimethoxyphenyl)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3sa). Purification by column chromatography on silica gel afforded the title compound as colorless oil. 79 mg, 85% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.34–7.24 (m, 5H), 7.00 (d, J = 8.4 Hz, 1H), 6.48 (dd, J = 8.4 Hz, J = 2.4 Hz, 1H), 6.36 (d, J = 2.0 Hz, 1H), 5.03 (d, J = 10.8 Hz, 1H), 4.92 (d, J = 10.8 Hz, 1H), 4.89 (s, 1H), 3.80 (s, 3H), 3.63 (s, 3H), 3.27 (s, 3H), 3.18 (d, J = 16.8 Hz, 1H), 3.07 (d, J = 16.8 Hz, 1H), 2.71 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.3, 168.7, 167.0, 161.8, 158.0, 150.9, 135.0, 129.76 (1C), 129.75 (2C), 128.8, 128.5, 112.7, 104.7, 98.2, 77.3, 63.4, 55.7, 55.6, 55.4, 32.5, 29.3, 28.7 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{24}H_{26}N_3O_7$ $[M + H]^+$: 468.1765, found 468.1760.

2-(Benzyloxy)-7,9-dimethyl-1-(naphthalen-1-yl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ta). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 183–185 °C. 91 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90–7.86 (m, 2H), 7.53–7.42 (m, 4H), 7.34–7.31 (m, 1H), 7.24–7.20 (m, 4H), 7.10–7.08 (m, 1H), 5.37 (s, 1H), 5.24 (d, J = 10.8 Hz, 1H), 4.95 (d, J = 10.8 Hz, 1H), 3.26 (d, J = 16.8 Hz, 1H), 3.14 (d, J = 16.8 Hz, 1H), 3.10 (s, 3H), 2.29 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.7, 168.7, 166.8, 149.7, 135.0, 133.8, 130.7, 130.2, 129.9, 129.6, 129.1, 128.8, 127.1, 126.8, 126.2, 126.1, 125.3, 120.7, 77.4, 65.9, 55.4, 33.5, 29.4, 28.3 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{26}H_{24}N_3O_5$ $[M + H]^+$: 458.1710, found 458.1701.

2-(Benzyloxy)-7,9-dimethyl-1-(naphthalen-2-yl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ua). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 112–114 °C. 91 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.78 (m, 3H), 7.56–7.51 (m, 2H), 7.44–7.43 (m, 1H), 7.34–7.25 (m, 3H), 7.21–7.19 (m, 2H), 7.05–7.03 (m, 1H), 5.15 (d, J = 10.8 Hz, 1H), 4.90 (d, J = 10.8 Hz, 1H), 4.52 (s, 1H), 3.31 (s, 3H), 3.25 (d, J = 16.8 Hz, 1H), 3.20 (d, J = 16.8 Hz, 1H), 2.51 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.6, 166.7, 150.2, 134.9, 133.9, 133.0, 129.9, 129.7, 129.1, 128.9, 128.6, 128.1, 128.0, 127.4 (2C), 127.2, 123.8, 77.7, 71.3, 55.4, 32.6, 29.5, 28.7 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{26}H_{24}N_3O_5$ $[M + H]^+$: 458.1710, found 458.1701.

2-(Benzyloxy)-7,9-dimethyl-1-(thiophen-3-yl)-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3va). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 135–137 °C. 76 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.27 (m, 4H), 7.22–7.19 (m, 2H), 7.08–7.07 (m, 1H), 6.80–6.79 (m, 1H), 5.12 (d, J = 10.4 Hz, 1H), 4.85 (d, J = 10.4 Hz, 1H), 4.58 (s, 1H), 3.29 (s, 3H), 3.23 (d, J = 16.8 Hz, 1H), 3.10 (d, J = 16.8 Hz, 1H), 2.83 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.5, 167.0, 150.3, 134.8, 133.8, 129.8, 129.1, 128.6, 127.4, 126.0, 125.4, 77.8, 66.9, 55.1, 33.0, 29.5, 29.0 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{20}H_{20}N_3O_5S$ $[M + H]^+$: 414.1118, found 414.1110.

1-(Benzo[*d*][1,3]dioxol-5-yl)-2-(benzyloxy)-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3wa). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 166–168 °C. 84 mg, 93% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.28 (m, 3H), 7.25–7.23 (m, 2H), 6.74 (d, J = 8.0 Hz, 1H), 6.48 (d, J = 1.6 Hz, 1H), 6.38 (dd, J = 8.0 Hz, J = 1.6 Hz, 1H), 5.99 (s, 2H), 5.11 (d, J = 10.8 Hz, 1H), 4.88 (d, J = 10.8 Hz, 1H), 4.26 (s, 1H), 3.27 (s, 3H), 3.17 (d, J = 16.8 Hz, 1H), 3.11 (d, J = 17.2 Hz, 1H), 2.81 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.5, 168.5, 166.7, 150.4, 149.2, 148.4, 134.9, 129.9, 129.1, 128.6, 125.8, 121.4, 108.5, 107.3, 101.8, 77.6, 71.0, 55.4, 32.5, 29.5, 29.0 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{23}H_{22}N_3O_7$ $[M + H]^+$: 452.1452, found 453.1444.

2-(Benzyloxy)-1-cyclohexyl-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3xa). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 168–170 °C. 80 mg, 96% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.34 (m, 5H), 4.98 (d, J = 11.6 Hz, 1H), 4.93 (d, J = 11.6 Hz, 1H), 3.28 (s, 3H), 3.21 (s, 3H), 3.18 (d, J = 16.8 Hz, 1H), 3.12 (d, J = 1.6 Hz, 1H), 2.73 (d, J = 16.8 Hz, 1H), 1.73–1.71 (m, 3H), 1.59–1.56 (m, 3H), 1.25–1.20 (m, 1H), 1.10–1.03 (m, 4H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.1, 167.7, 166.7, 150.8, 135.2, 130.3, 129.0, 128.5, 77.5, 69.7, 53.4, 42.3, 33.0, 32.2, 29.53, 29.49, 27.6, 27.2, 26.1, 25.8 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{22}H_{28}N_3O_5$ $[M + H]^+$: 414.2023, found 414.2018.

2-(Benzyloxy)-1-isopropyl-7,9-dimethyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ya). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 167–170 °C. 75 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.34 (m, 5H), 4.99 (d, J = 11.2 Hz, 1H), 4.94 (d, J = 11.6 Hz, 1H), 3.28 (s, 3H), 3.25 (d, J = 2.4 Hz, 1H), 3.24 (s, 3H), 3.18 (d, J = 16.8 Hz, 1H), 2.74 (d, J = 16.8 Hz, 1H), 1.66–1.59 (m, 1H), 0.98 (d, J = 7.2 Hz, 3H), 0.92 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.2, 167.8, 166.7, 150.8, 135.1, 130.3, 129.1, 128.6, 77.5, 70.0, 53.2, 32.9, 31.8, 29.6, 29.5, 22.1, 16.9 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{19}H_{24}N_3O_5$ $[M + H]^+$: 374.1710, found 374.1699.

2-Methoxy-7,9-dimethyl-1-phenyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ac). Purification by column chromatography on silica gel afforded the title compound as colorless oil. 66 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43–7.37 (m, 3H), 7.17–7.15 (m, 2H), 4.91 (s, 1H), 3.77 (s, 3H), 3.36 (s, 3H), 3.28 (d, J = 17.2 Hz, 1H), 3.09 (d, J = 16.8 Hz, 1H), 2.69 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.5, 167.0, 150.2, 132.0, 130.2, 129.2, 127.0, 72.2, 55.6, 33.6, 29.6, 28.7 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{16}H_{18}N_3O_5$ $[M + H]^+$: 332.1241, found 332.1269.

7,9-Dimethyl-2-(naphthalen-2-ylmethoxy)-1-phenyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (3ad). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 149–150 °C. 84 mg, 92% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85–7.71 (m, 4H), 7.54–7.49 (m, 2H), 7.43–7.31 (m, 4H), 7.00–6.97 (m, 2H), 5.32 (d, J = 10.8 Hz, 1H), 5.07 (d, J = 10.8 Hz, 1H), 4.35 (s, 1H), 3.24 (d, J = 17.2 Hz, 1H), 3.19 (d, J = 16.8 Hz, 1H), 3.05 (s, 3H), 2.66 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 168.4, 166.5, 150.2, 133.5, 133.1, 132.3, 132.2, 130.2, 129.5, 128.9, 128.38, 128.35, 127.8, 127.3, 126.9, 126.8, 126.5, 77.9, 71.0, 55.2, 32.3, 29.2, 28.7 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{26}H_{24}N_3O_5$ $[M + H]^+$: 458.1710, found 458.1701.

2-(Benzyloxy)-4,7,9-trimethyl-1-phenyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (*trans*-3af). Purification by column chromatography on silica gel afforded the title compound as white solid. 54 mg, 64% yield. mp 205–207 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 8H), 6.92–6.90 (m, 2H), 5.03 (d, J = 11.6 Hz, 1H), 4.98 (d, J = 11.6 Hz, 1H), 4.28 (s, 1H), 3.60 (q, J = 7.1 Hz, 1H), 3.29 (s, 3H), 2.89 (s, 3H), 1.25 (d, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 167.0, 165.4, 150.6, 135.4, 132.5, 129.90, 129.88, 129.01, 128.97, 128.5, 127.1, 78.0, 69.0, 60.0, 36.4, 29.1, 9.7, 1.1 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{23}H_{24}N_3O_5$ $[M + H]^+$: 422.1710, found 422.1706.

2-(Benzyloxy)-4,7,9-trimethyl-1-phenyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (*cis*-3af). Purification by column chromatography on silica gel afforded the title compound as white solid. 30 mg, 36% yield. mp 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40–7.25 (m, 6H), 7.20–7.18 (m, 2H), 7.06–7.04 (m, 2H), 5.23 (d, J = 10.0 Hz, 1H), 4.91 (d, J = 10.0 Hz, 1H), 4.64 (s, 1H), 3.55 (q, J = 7.0 Hz, 1H), 3.28 (s, 3H), 2.76 (s, 3H), 1.24 (d, J = 6.8 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 172.7, 167.9, 164.8, 149.9, 134.9, 131.9, 130.1, 129.7, 129.1, 128.9, 128.6, 127.3, 70.9, 61.8, 41.2, 29.4, 28.3, 10.1, 1.2 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{23}H_{24}N_3O_5$ $[M + H]^+$: 422.1710, found 422.1701.

2-(Benzyloxy)-4-ethyl-7,9-dimethyl-1-phenyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (*trans*-3ag). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 155–157 °C. 86 mg, >99% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 8H), 6.91–6.89 (m, 2H), 5.02 (d, J = 11.2 Hz, 1H), 4.98 (d, J = 11.2 Hz, 1H), 4.23 (s, 1H), 3.56–3.52 (m, 1H), 3.31 (s, 3H), 2.88 (s, 3H), 2.17–2.10 (m, 1H), 1.69–1.62 (m, 1H), 0.80 (t, J = 7.6 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 167.1, 165.8, 150.7, 135.4, 132.7, 129.9 (3C), 128.99, 128.95, 128.5, 127.2, 78.0, 69.2, 58.3, 42.9, 29.1, 19.0, 12.5, 1.1 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{24}H_{26}N_3O_5$ $[M + H]^+$: 436.1867, found 436.1842.

2-(Benzyloxy)-7,9-dimethyl-1-phenyl-4-propyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (*trans*-3ah). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 132–135 °C. 85 mg, 95% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36–7.29 (m, 8H), 6.91–6.89 (m, 2H), 5.02 (d, J = 11.2 Hz, 1H), 4.98 (d, J = 11.2 Hz, 1H), 4.22 (s, 1H), 3.61–3.58 (m, 1H), 3.30 (s, 3H), 2.87 (s, 3H), 2.09–2.00 (m, 1H), 1.59–1.51 (m, 1H), 1.35–1.30 (m, 1H), 1.04–0.96 (m, 1H), 0.86 (t, J = 7.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 167.1, 165.9, 150.7, 135.4, 132.7, 129.92, 129.89, 128.98, 128.94, 128.5, 127.2, 78.0, 69.2, 58.6, 41.3, 29.2, 29.1, 27.9, 21.3, 14.1 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{25}H_{28}N_3O_5$ $[M + H]^+$: 450.2023, found 450.1999.

2-(Benzyloxy)-4-butyl-7,9-dimethyl-1-phenyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (*trans*-3ai). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 197–198 °C. 72 mg, 78% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 8H), 6.91–6.89 (m, 2H), 5.02 (d, J = 11.2 Hz, 1H), 4.98 (d, J = 11.6 Hz, 1H), 4.23 (s, 1H), 3.60–3.56 (m, 1H), 3.30 (s, 3H), 2.88 (s, 3H), 2.12–2.03 (m, 1H), 1.62–1.53 (m, 1H), 1.31–1.23 (m, 3H), 0.95–0.90 (m, 1H), 0.82 (t, J = 3.2 Hz, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 167.1, 165.7, 150.7, 135.4, 132.7, 129.91, 129.88, 129.0, 128.9, 128.5, 127.2, 78.0, 69.1, 58.6, 41.4, 30.0, 29.2, 29.1, 25.4, 22.6, 13.8 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{26}H_{30}N_3O_5$ $[M + H]^+$: 464.2180, found 464.2157.

2-(Benzyloxy)-7,9-dimethyl-1,4-diphenyl-2,7,9-triazaspiro[4.5]decane-3,6,8,10-tetraone (*trans*-3aj). Purification by column chromatography on silica gel afforded the title compound as white solid. mp 207–209 °C. 74 mg, 77% yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.27 (m, 11H), 7.25–7.24 (m, 2H), 7.16–7.14 (m, 2H), 5.35 (d, J = 10.0 Hz, 1H), 5.00 (d, J = 10.0 Hz, 1H), 4.93 (s, 1H), 4.88 (s, 1H), 3.31 (s, 3H), 3.56 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.6, 168.2, 164.1, 149.6, 134.8, 132.2, 132.0, 130.0, 129.9, 129.7, 129.1, 128.9, 128.7, 128.4, 127.5, 77.5, 70.0, 63.5, 51.7, 29.5, 28.2 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{28}H_{26}N_3O_5$ $[M + H]^+$: 484.1867, found 484.1861.

General procedures for the synthesis of 4[9]

Compound **3aa** (0.2 mmol, 1.0 equiv.) was dissolved in MeOH (2 mL) and then 10% Pd/C (6 mg) was added. The reaction mixture was stirred under H_2 atmosphere for 4 h at room temperature. After filtration through a Celite pad, the filtrate was concentrated *in vacuo* to yield the pure product **4** as a pale white powder (63 mg, 99% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.36 (s, 1H), 7.42–7.40 (m, 3H), 7.17–7.15 (m, 2H), 5.05 (s, 1H), 3.44 (d, J = 16.8 Hz, 1H), 3.39 (s, 3H), 3.15 (d, J = 16.8 Hz, 1H), 2.64 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 168.5, 167.0, 150.2, 132.0, 130.2, 129.2, 127.0, 72.2, 55.6, 33.6, 29.6, 28.7 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{15}H_{14}N_3O_5$ $[M - H]^-$: 316.0939, found 316.0915.

General procedures for the synthesis of 5

Compound **3aa** (0.2 mmol, 1.0 equiv.) was dissolved in THF (2 mL) and then Ni (6 mg) was added. The reaction mixture was stirred under H_2 atmosphere for 12 h at room temperature. After filtration through a Celite pad, the crude product was purified by flash chromatography to yield the pure product **5** as a white powder (35 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.37 (m, 3H), 7.15–7.14 (m, 2H), 6.66 (s, 1H), 5.04 (s, 1H), 3.40 (d, J = 16.8 Hz, 1H), 3.36 (s, 3H), 2.95 (d, J = 16.8 Hz, 1H), 2.64 (s, 3H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$) δ 175.1, 168.8, 167.5, 150.3, 134.3, 130.3, 129.3, 126.1, 67.9, 60.2, 37.2, 29.4, 28.4 ppm. HRMS (ESI) m/z Exact mass calcd for $C_{15}H_{16}N_3O_4$ $[M + H]^+$: 302.1135, found 302.1129.

Conflicts of interest

There are no conflicts to declare.

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