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Chemoselective synthesis of 5,4′-imidazolinyl spirobarbiturates *via* NBS-promoted cyclization of unsaturated barbiturates and amidines†

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A selective cyclization of unsaturated barbiturates and amidines promoted by *N*-bromosuccinimide has been successfully developed to afford a vast variety of 5,4′-imidazolinyl spirobarbiturates in moderate to good yields. The present protocol features broad substrate scope, facile work-up procedure and mild reaction conditions, providing a novel strategy for the highly selective and efficient construction of structurally diverse spiroimidazolines.

Introduction

Barbiturates are privileged medicinal scaffolds as they are present in more than 5000 pharmacologically active molecules, such as commercially available antiepileptic, anticonvulsant, anxiolytic, sedative, hypnotic and anticancer agents.[1] As a kind of vital barbituric acid derivative, spirobarbiturates also exhibit a broad range of significant bioactivities (Fig. 1). For instance, spirobarbiturate-pyrazoline **I** displays anticonvulsant activity.[2] Spirobarbiturate-pyrrolidone **II** is an inhibitor of MMP-13.[3] Spirobarbiturate **III** shows prominent anticancer activity.[4] Spirobarbiturate-pyrrolidine **IV** was found to be a TACE inhibitor.[5] Therefore, considerable efforts have been devoted to develop novel synthetic methods for the efficient synthesis of structurally diverse spirobarbiturate scaffolds. Among them, organocatalytic [3 + 2] cycloaddition reactions are the generally used approaches.[6,7]

On the other hand, imidazoline motifs are also ubiquitous in bioactive molecules and natural products.[8] In light of the pharmacological activity of spirobarbiturates and the prominent bioactivities of imidazolines, the combination of these two species may be potential drug candidates. To the best of our knowledge, the synthesis of spirobarbiturates embodying an imidazoline segment has not been investigated. Meanwhile, amidines were frequently used as versatile reactants for the synthesis of important nitrogen-containing heterocycles.[9] In this context, our group recently disclosed a novel cyclization reaction of unsaturated barbiturates (**1**) with amidines (**2**) *via* a tandem Michael/electrophilic/nucleophilic sequence under solvent-free ball-milling conditions, and synthesized a series of 5,5′-imidazolinyl spirobarbiturates **4** (Scheme 1, path a).[10] It should be pointed out that the employed amidines **2** possess two nitrogen atoms. We speculated that another constitutional isomers 5,4′-imidazolinyl spirobarbiturates **3** can also be obtained when the Michael addition of **2** to **1** is initiated by the nitrogen atom adjacent to the imino group to generate adducts **3I** (Scheme 1, path b). With our sustained interest in the construction of novel spirocyclic compounds,[10,11] we attempted to synthesize the structurally different 5,4′-imidazolinyl spirobarbiturates by regulating the chemoselectivity of this cyclization reaction.

Results and discussion

The reaction of 5-benzylidene-1,3-dimethylpyrimidine-2,4,6 (1*H*,3*H*,5*H*)-trione (**1a**) with *N*-benzylbenzimidamide (**2a**) was chosen as the model reaction to explore the reaction con-

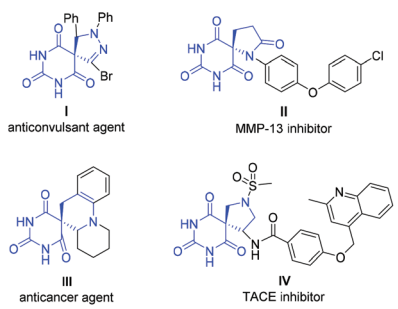

Fig. 1 Representative bioactive spirobarbiturates.

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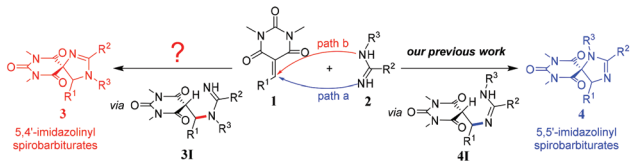
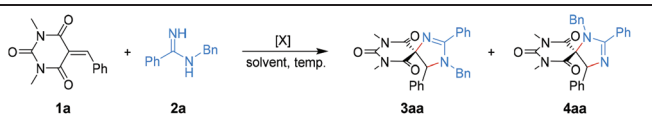


Scheme 1 Synthetic strategies towards 5,4′- and 5,5′-imidazolinyl spirobarbiturates.

ditions favouring the expected 5,4′-imidazolinyl spirobarbiturate **3aa**. Considering that solution-based reactions have more controllable reaction conditions including different kinds of solvents and diverse temperatures, we started probing this model reaction in an organic solvent. Initially, a mixture of **1a** (0.2 mmol), **2a** (0.3 mmol) and NIS (0.2 mmol) in 2 mL of 1,2-dichloroethane (DCE) was stirred at 30 °C, and a new product was isolated in 15% yield along with a significant amount of the known 5,5′-imidazolinyl spirobarbiturate **4aa** after a reaction time of 3 h (Table 1, entry 1). By comparing the NMR spectra of this compound with product **4aa**, we speculated that this newly formed product was the desired 5,4′-imidazolinyl spirobarbiturate, *i.e.*, 3-benzyl-7,9-dimethyl-2,4-diphenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione **3aa**. Although the yield of product **3aa** was very low, this initial result confirmed our assumption and thus prompted us to optimize the reaction conditions for the highly selective synthesis of structurally novel spirobarbiturate-imidazolines. The effect of reaction solvents on the reaction selectivity was first investigated. It was found that the use of tetrahydrofuran (THF), acetonitrile (MeCN), and *N*,*N*-dimethylformamide (DMF) as the reaction solvent could enhance the selectivity favouring 5,4′-imidazolinyl spirobarbiturate **3aa** to some extent (Table 1, entries 2–4). Among them, MeCN exhibited the best effect to deliver product **3aa** as the major product (Table 1, entry 3). Subsequently, several other halogenating agents including I_2 and *N*-bromosuccinimide (NBS) were also examined (Table 1, entries 5 and 6). We were pleasantly surprised to find that the yield of product **3aa** was increased to 66% when NBS was used to replace NIS, and meanwhile, the yield of product **4aa** was significantly decreased to 15% (Table 1, entry 6). Further optimization by increasing the loading amount of NBS demonstrated that 1.2 equiv. of NBS was the optimal choice, and spirocyclic product **3aa** was achieved in 70% yield (Table 1, entry 7 *vs.* entries 6 and 8). Considering that small amounts of starting materials still remained under the reaction conditions of entry 7, we raised the reaction temperature to 50 °C. To our delight, the yield of **3aa** was improved to 80% (Table 1, entry 10). Nevertheless, further elevating the reaction temperature to 70 °C led to a slightly decreased yield due to the increase of an unknown byproduct (Table 1, entry 11). Therefore, the optimal reaction conditions for the highly selective construction of **3aa** from barbiturate-derived alkene **1a** and amidine **2a** were 1.2 equiv. of NBS at 50 °C for 2 h using MeCN as the solvent (Table 1, entry 10).

Table 1 Optimization of the reaction conditions[a]

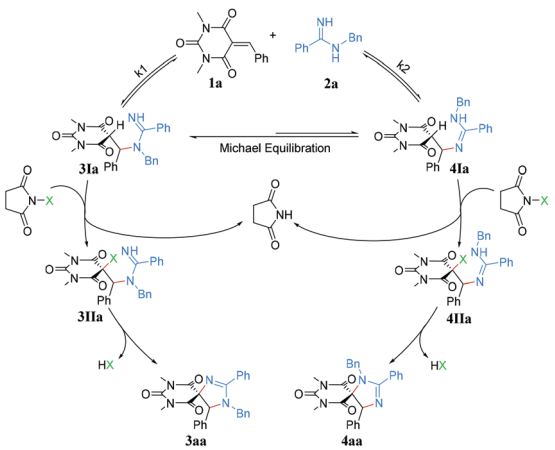


Entry	[X] (equiv.)	Solvent	Temp. (°C)	Time (h)	Yield[b] (%) 3aa	4aa
1	NIS (1.0)	DCE	30	3	15	58
2	NIS (1.0)	THF	30	3	19	52
3	NIS (1.0)	MeCN	30	3	40	35
4	NIS (1.0)	DMF	30	3	33	39
5	I_2 (1.0)	MeCN	30	3	12	32
6	NBS (1.0)	MeCN	30	3	66	15
7	NBS (1.2)	MeCN	30	3	70	10
8	NBS (1.5)	MeCN	30	3	70	12
9[c]	NBS (1.2)	MeCN	30	3	67	15
10	NBS (1.2)	MeCN	50	2	80	8
11	NBS (1.2)	MeCN	70	2	75	7

[a] Reaction conditions: a mixture of **1a** (0.2 mmol), **2a** (0.3 mmol), halogenating agent and solvent (2 mL) was stirred at the given temperature. [b] Isolated yield by flash column chromatography based on **1a**. [c] 0.4 mL of MeCN was used.

These novel and interesting results prompted us to explore the reason for the difference of the chemoselectivity between the present NBS-promoted solution-based reaction and the previously reported NIS-promoted ball-milling reaction. After comprehensive consideration of the fact that reactions performed under solvent-free ball-milling conditions are favourable to access kinetically controlled products due to the high local concentration of the reactants,[12] the experimental results, and some related literature,[13] a tentative mechanism is proposed by using **1a** and **2a** as the typical substrates (Scheme 2).

The formation of **3aa** or **4aa** involves three steps: (1) Michael addition of **1a** with **2a** to generate adduct **3Ia** or **4Ia**; (2) halogenation to give intermediate **3IIa** or **4IIa**; and (3) intra-

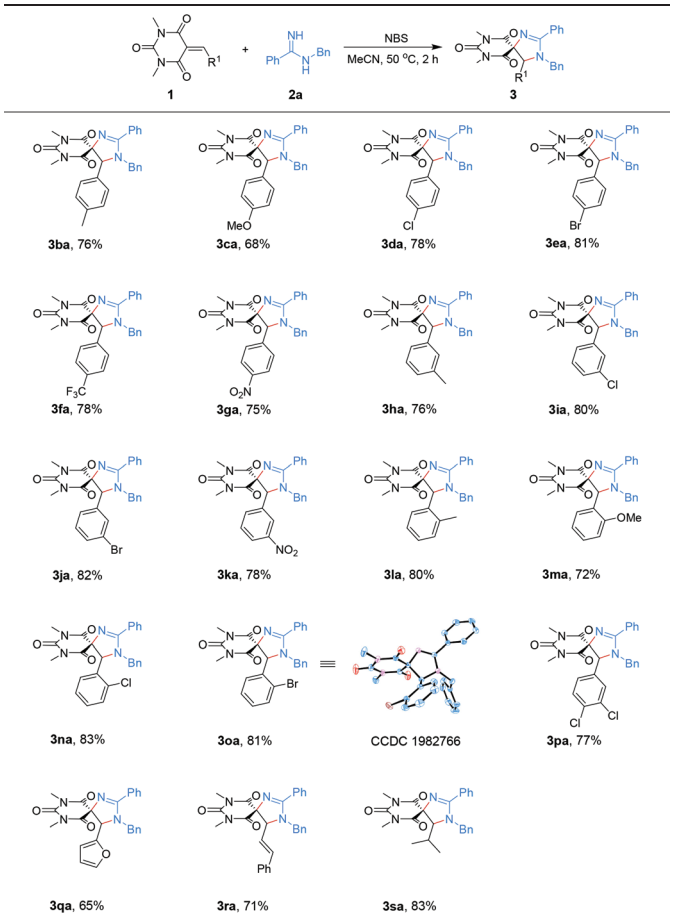


Scheme 2 Proposed mechanism for the selective synthesis of imidazolinyl spirobarbiturates.

molecular cyclization *via* nucleophilic substitution to generate the final product **3aa** or **4aa**. The following reaction results were obtained: (a) the solvent-free ball-milling reaction only gave **4aa**, while thermal heating in a solvent resulted in the dominant formation of **3aa**, which was accompanied by a small amount of **4aa**, thus demonstrating that the selectivity at lower temperature and higher concentration is higher than that at higher temperature; (b) under thermal heating in a solvent, the selectivity towards **3aa** was improved as we increased the reaction temperature (Table 1, entries 7, 10 and 11); and (c) the reaction carried out with a higher concentration could slightly improve the ratio of **4aa** (Table 1, entry 9). Thus, we think that **4Ia** is a kinetically controlled adduct, while **3Ia** is a thermodynamically controlled adduct. This means that the reaction rate for the generation of **3Ia** is lower than that of **4Ia**, whereas adduct **3Ia** is more stable than adduct **4Ia**. Under solvent-free ball-milling conditions, adduct **4Ia** is dominantly generated, and it can transform rapidly to iodide **4IIa** in the presence of the stronger halogenating agent NIS, followed by an intramolecular cyclization to give 5,5′-imidazolinyl spirobarbiturate **4aa**. When this cyclization reaction is carried out by thermal heating in MeCN, the thermodynamical adduct **3Ia** is mainly formed. Moreover, the use of NBS delivers higher chemoselectivity towards product **3aa** because NBS is a relatively weaker halogenating agent and can provide more time for the shifting of **4Ia** into more stable **3Ia** before halogenation. Then, bromide **3IIa** is dominantly formed, which further undergoes an intramolecular nucleophilic substitution with the elimination of HBr to provide 5,4′-imidazolinyl spirobarbiturate **3aa**. In addition, several factors including the formed HBr may also affect the chemoselectivity of this reaction.[14]

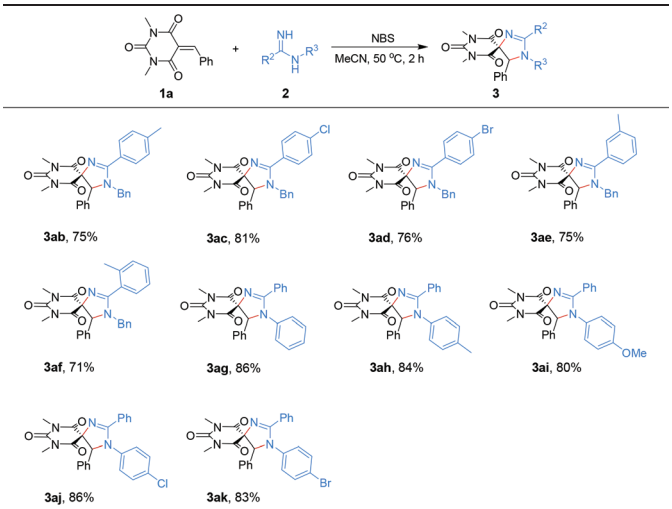
With the optimized thermodynamic conditions in hand, we then investigated the substrate scope of this intermolecular cyclization reaction. Firstly, a vast variety of barbiturate-derived alkenes **1** were examined, and the results are presented in Table 2. Barbiturates with either electron-donating groups (–Me and –OMe) or electron-withdrawing groups (–Cl, –Br, $–CF_3$ and $–NO_2$) at the *para*-position of the benzene ring in R^1 reacted smoothly with *N*-benzylbenzimidamide **2a** under the standard reaction conditions, providing a series of 5,4′-imidazolinyl spirobarbiturates **3ba–ga** in 68–81% yields. To our delight, barbiturates with the benzene ring in R^1 bearing both *meta*- and *ortho*-substituents still showed excellent reactivity and selectivity to give spirocyclic products **3ha–oa** in good yields (72–83%). Furthermore, 3,4-dichloro-substituted barbiturate **1p** reacted well in the present transformation, and the corresponding product **3pa** was delivered in 77% yield. It should be noted that the barbiturate containing a heterocyclic group was also compatible in this protocol, affording product **3qa** in a moderate yield of 65%. In addition, both alkenyl- and alkyl-derived barbiturates reacted efficiently with **2a** to con-

Table 2 NBS-promoted synthesis of 5,4′-imidazolinyl spirobarbiturates **3ba–sa** from unsaturated barbiturates **1** and amidine **2a** [a,b]



[a] Reaction conditions: a mixture of **1** (0.2 mmol), **2a** (0.3 mmol), NBS (0.24 mmol) and MeCN (2 mL) was stirred at 50 °C for 2 h. [b] Isolated yield based on **1**.

Table 3 NBS-promoted synthesis of 5,4′-imidazolinyl spirobarbiturates **3ab–ak** from unsaturated barbiturate **1a** and amidines **2** [a,b]



[a] Reaction conditions: a mixture of **1a** (0.2 mmol), **2** (0.3 mmol), NBS (0.24 mmol) and MeCN (2 mL) was stirred at 50 °C for 2 h. [b] Isolated yield based on **1a**.

struct products **3ra** and **3sa** in 71% and 83% yields, respectively. The structure of products **3** was clearly confirmed by single-crystal X-ray diffraction analysis using **3oa** as an example (see the ESI† for details).

To further explore the substrate scope of this methodology, various amidine derivatives were allowed to reacted with **1a** under the optimized reaction conditions (Table 3), and a series of 5,4′-imidazolinyl spirobarbiturates **3ab–ak** were obtained in good to excellent yields. Amidines with the benzene ring in R^2 bearing different functional groups (–Me, –Cl and –Br) reacted smoothly to provide products **3ab–af** in 71–81% yields. Moreover, *N*-aryl-substituted amidines were also examined, and the results demonstrated that all the used *N*-aryl amidines exhibited high reactivity towards various spirobarbiturates **3ag–ak**.

Conclusions

In summary, we have successfully developed a novel cyclization pattern for the efficient synthesis of structurally different 5,4′-imidazolinyl spirobarbiturates *via* an *N*-bromosuccinimide-promoted selective reaction of unsaturated barbiturates with amidines. In addition to the advantages of high selectivity and good product yields, this protocol also features excellent functional group tolerance, high atom economy and mild reaction conditions. These merits make the present method a new strategy for the selective and efficient construction of structurally diverse spirocyclic imidazolines. Efforts towards thoroughly understanding the reaction selectivity are ongoing in our laboratory.

Experimental

General information

All reagents were obtained from commercial sources and used without further purification. NMR spectra were recorded on a 400, 500 or 600 MHz NMR spectrometer (400, 500 or 600 MHz for ^{1}H NMR; 100, 125 or 150 MHz for ^{13}C NMR). ^{1}H NMR chemical shifts were determined relative to internal TMS at δ 0.0 ppm. ^{13}C NMR chemical shifts were determined relative to $CDCl_3$ at δ 77.16 ppm. The data for ^{1}H NMR and ^{13}C NMR are reported as follows: chemical shift (δ, ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet). High-resolution mass spectra (HRMS) were measured with ESI-TOF in a positive mode.

General procedures for the NBS-promoted synthesis of 5,4′-imidazolinyl spirobarbiturates

In a 25 mL sealed tube, a mixture of unsaturated barbiturates **1** (0.2 mmol), amidines **2** (0.3 mmol), NBS (0.24 mmol) and MeCN (2 mL) was stirred at 50 °C for 2 h. After completion of the reaction (detected by TLC), the reaction mixture was concentrated under reduced pressure. Then, the residue was separated by column chromatography on silica gel with acetone/petroleum ether as the eluent to afford 5,4′-imidazolinyl spirobarbiturates **3**.

3-Benzyl-7,9-dimethyl-2,4-diphenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3aa). The general procedure was followed to afford **3aa** as a white solid. 72.5 mg, 80% yield; mp 70–72 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.87–7.83 (m, 2H), 7.54–7.48 (m, 3H), 7.38–7.32 (m, 3H), 7.27–7.21 (m, 3H), 7.20–7.15 (m, 2H), 6.95 (d, J = 6.7 Hz, 2H), 4.96 (s, 1H), 4.85 (d, J = 15.9 Hz, 1H), 3.98 (d, J = 15.9 Hz, 1H), 3.33 (s, 3H), 2.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.9, 166.5, 150.8, 134.9, 133.6, 131.0, 130.1, 129.3, 128.94 (2C), 128.92 (2C), 128.89 (2C), 128.86 (2C), 128.0, 127.8 (2C), 127.7 (2C), 80.8, 73.5, 49.3, 29.3, 28.3; HRMS (ESI-TOF) calcd for $C_{27}H_{25}N_4O_3$ $[M + H]^+$ 453.1927, found 453.1930.

3-Benzyl-7,9-dimethyl-2-phenyl-4-(*p*-tolyl)-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ba). The general procedure was followed to afford **3ba** as a white solid. 71.3 mg, 76% yield; mp 185–187 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86 (d, J = 7.1 Hz, 2H), 7.61–7.51 (m, 3H), 7.29–7.23 (m, 3H), 7.18 (d, J = 7.5 Hz, 2H), 7.06–7.00 (m, 2H), 6.95–6.89 (m, 2H), 4.97 (s, 1H), 4.89 (d, J = 15.8 Hz, 1H), 4.01 (d, J = 15.8 Hz, 1H), 3.33 (s, 3H), 2.71 (s, 3H), 2.36 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 170.0, 166.5, 150.9, 139.2, 135.0, 130.9, 130.5, 130.2, 129.6 (2C), 128.9 (2C), 128.82 (2C), 128.81 (2C), 127.9, 127.8 (2C), 127.7 (2C), 80.8, 73.5, 49.2, 29.2, 28.3, 21.3; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_4O_3$ $[M + H]^+$ 467.2083, found 467.2078.

3-Benzyl-4-(4-methoxyphenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ca). The general procedure was followed to afford **3ca** as a white solid. 65.4 mg, 68% yield; mp 150–152 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86–7.82 (m, 2H), 7.54–7.48 (m, 3H), 7.28–7.21 (m, 3H), 7.09 (d, J = 8.0 Hz, 2H), 6.94 (d, J = 6.8 Hz, 2H), 6.87 (d, J = 8.7 Hz, 2H), 4.91 (s, 1H), 4.83 (d, J = 15.9 Hz, 1H), 3.94 (d, J = 15.9 Hz, 1H), 3.81 (s, 3H), 3.33 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 170.0, 166.7, 160.3, 150.9, 135.0, 130.9, 130.2, 129.1 (2C), 128.93 (2C), 128.87 (2C), 128.86 (2C), 128.0, 127.8 (2C), 125.2, 114.3 (2C), 80.7, 73.2, 55.5, 49.2, 29.3, 28.5; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_4O_4$ $[M + H]^+$ 483.2032, found 483.2037.

3-Benzyl-4-(4-chlorophenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3da). The general procedure was followed to afford **3da** as a white solid. 75.6 mg, 78% yield; mp 101–103 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85–7.80 (m, 2H), 7.55–7.49 (m, 3H), 7.33 (d, J = 8.5 Hz, 2H), 7.28–7.22 (m, 3H), 7.14 (d, J = 7.9 Hz, 2H), 6.94 (d, J = 6.4 Hz, 2H), 4.99 (s, 1H), 4.84 (d, J = 15.8 Hz, 1H), 3.94 (d, J = 15.8 Hz, 1H), 3.33 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 169.7, 166.3, 150.7, 135.1, 134.6, 132.3, 131.1, 129.8, 129.2 (2C), 129.1 (2C), 129.0 (2C), 128.91 (2C), 128.89 (2C), 128.2, 127.9 (2C), 80.3, 72.3, 49.6, 29.4, 28.5; HRMS (ESI-TOF) calcd for $C_{27}H_{24}ClN_4O_3$ $[M + H]^+$ 487.1537, found 487.1529.

3-Benzyl-4-(4-bromophenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ea). The general procedure was followed to afford **3ea** as a white solid. 86.2 mg, 81% yield; mp 106–108 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2H), 7.55–7.47 (m, 5H), 7.29–7.22 (m, 3H), 7.08

(d, J = 8.0 Hz, 2H), 6.97–6.91 (m, 2H), 5.00 (s, 1H), 4.84 (d, J = 15.8 Hz, 1H), 3.95 (d, J = 15.8 Hz, 1H), 3.34 (s, 3H), 2.79 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.7, 166.3, 150.7, 134.6, 132.8, 132.1 (2C), 131.1, 129.8, 129.5 (2C), 129.0 (2C), 128.92 (2C), 128.88 (2C), 128.2, 127.9 (2C), 123.2, 80.2, 72.3, 49.6, 29.4, 28.5; HRMS (ESI-TOF) calcd for $C_{27}H_{24}BrN_4O_3$ $[M + H]^+$ 531.1032, found 531.1036.

3-Benzyl-7,9-dimethyl-2-phenyl-4-(4-(trifluoromethyl)phenyl)-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3fa). The general procedure was followed to afford **3fa** as a white solid. 81.2 mg, 78% yield; mp 67–69 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (m, 2H), 7.64–7.59 (d, J = 8.2 Hz, 2H), 7.55–7.49 (m, 3H), 7.35 (d, J = 7.9 Hz, 2H), 7.29–7.23 (m, 3H), 6.97–6.92 (m, 2H), 5.14 (s, 1H), 4.87 (d, J = 15.8 Hz, 1H), 3.98 (d, J = 15.8 Hz, 1H), 3.35 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.5, 166.1, 150.5, 138.2, 134.4, 131.20 (q, J = 32.9 Hz), 131.17, 129.6, 129.0 (2C), 128.91 (2C), 128.85 (2C), 128.3 (2C), 128.2, 127.9 (2C), 125.7 (q, J = 3.7 Hz, 2C), 123.8 (q, J = 273.4 Hz), 80.2, 72.0, 49.8, 29.4, 28.4; ^{19}F NMR (470 MHz, $CDCl_3$) δ −62.70 (s, 3F); HRMS (ESI-TOF) calcd for $C_{28}H_{24}F_3N_4O_3$ $[M + H]^+$ 521.1801, found 521.1800.

3-Benzyl-7,9-dimethyl-4-(4-nitrophenyl)-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ga). The general procedure was followed to afford **3ga** as a white solid. 74.6 mg, 75% yield; mp 199–201 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.19 (d, J = 8.5 Hz, 2H), 7.84–7.79 (m, 2H), 7.57–7.50 (m, 3H), 7.42 (d, J = 7.5 Hz, 2H), 7.28–7.22 (m, 3H), 6.96–6.91 (m, 2H), 5.32 (s, 1H), 4.85 (d, J = 15.7 Hz, 1H), 4.04 (d, J = 15.7 Hz, 1H), 3.37 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.4, 169.3, 165.9, 150.5, 148.2, 141.9, 134.2, 131.3, 129.6, 129.1 (2C), 129.02 (2C), 128.99 (2C), 128.88 (2C), 128.4, 128.1 (2C), 123.8 (2C), 80.1, 71.1, 50.5, 29.6, 28.6; HRMS (ESI-TOF) calcd for $C_{27}H_{24}N_5O_5$ $[M + H]^+$ 498.1777, found 498.1772.

3-Benzyl-7,9-dimethyl-2-phenyl-4-(*m*-tolyl)-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ha). The general procedure was followed to afford **3ha** as a white solid. 70.7 mg, 76% yield; mp 176–178 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88–7.83 (m, 2H), 7.54–7.48 (m, 3H), 7.27–7.20 (m, 4H), 7.15 (d, J = 7.5 Hz, 1H), 6.99–6.92 (m, 4H), 4.93 (s, 1H), 4.83 (d, J = 16.0 Hz, 1H), 3.99 (d, J = 16.0 Hz, 1H), 3.33 (s, 3H), 2.68 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 169.8, 166.4, 150.8, 138.8, 134.9, 133.4, 131.0, 130.1, 129.9, 128.92 (2C), 128.87 (2C), 128.8 (3C), 128.1, 128.0, 127.8 (2C), 124.8, 80.7, 73.6, 49.3, 29.3, 28.3, 21.5; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_4O_3$ $[M + H]^+$ 467.2083, found 467.2084.

3-Benzyl-4-(3-chlorophenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ia). The general procedure was followed to afford **3ia** as a white solid. 78.4 mg, 80% yield; mp 127–129 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (m, 2H), 7.54–7.47 (m, 3H), 7.33–7.20 (m, 6H), 7.04 (d, J = 7.1 Hz, 1H), 6.95 (d, J = 7.4 Hz, 2H), 5.01 (s, 1H), 4.84 (d, J = 15.8 Hz, 1H), 3.99 (d, J = 15.8 Hz, 1H), 3.33 (s, 3H), 2.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 169.4, 166.0, 150.5, 135.9, 134.8, 134.4, 131.0, 130.0, 129.6, 129.2, 128.83 (2C), 128.77 (4C), 128.0, 127.8 (2C), 127.7, 125.9, 80.2, 72.2, 49.6, 29.3, 28.33; HRMS (ESI-TOF) calcd for $C_{27}H_{24}ClN_4O_3$ $[M + H]^+$ 487.1537, found 487.1532.

3-Benzyl-4-(3-bromophenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ja). The general procedure was followed to afford **3ja** as a white solid. 86.9 mg, 82% yield; mp 139–141 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.80 (m, 2H), 7.54–7.48 (m, 3H), 7.46 (d, J = 8.3 Hz, 1H), 7.38 (s, 1H), 7.30–7.17 (m, 4H), 7.10 (d, J = 7.5 Hz, 1H), 6.98–6.92 (m, 2H), 5.00 (s, 1H), 4.83 (d, J = 15.8 Hz, 1H), 3.99 (d, J = 15.8 Hz, 1H), 3.33 (s, 3H), 2.78 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.4, 169.4, 166.0, 150.5, 136.2, 134.5, 132.2, 131.0, 130.6, 130.3, 129.7, 128.85 (2C), 128.79 (4C), 128.1, 127.8 (2C), 126.4, 122.9, 80.3, 72.2, 49.7, 29.3, 28.4; HRMS (ESI-TOF) calcd for $C_{27}H_{24}BrN_4O_3$ $[M + H]^+$ 531.1032, found 531.1033.

3-Benzyl-7,9-dimethyl-4-(3-nitrophenyl)-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ka). The general procedure was followed to afford **3ka** as a white solid. 77.5 mg, 78% yield; mp 207–209 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, J = 7.8 Hz, 1H), 8.11 (s, 1H), 7.86–7.80 (m, 2H), 7.59–7.49 (m, 5H), 7.29–7.22 (m, 3H), 6.99–6.93 (m, 2H), 5.35 (s, 1H), 4.83 (d, J = 15.7 Hz, 1H), 4.08 (d, J = 15.7 Hz, 1H), 3.38 (s, 3H), 2.84 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 169.3, 165.9, 150.5, 148.4, 136.8, 134.3, 134.0, 131.3, 129.6, 129.5, 129.1 (2C), 129.0 (2C), 128.9 (2C), 128.4, 128.1 (2C), 123.8, 123.1, 79.8, 70.9, 50.5, 29.62, 28.61; HRMS (ESI-TOF) calcd for $C_{27}H_{24}N_5O_5$ $[M + H]^+$ 498.1777, found 498.1775.

3-Benzyl-7,9-dimethyl-2-phenyl-4-(*o*-tolyl)-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3la). The general procedure was followed to afford **3la** as a white solid. 74.3 mg, 80% yield; mp 194–196 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.88–7.84 (m, 2H), 7.57 (d, J = 7.7 Hz, 1H), 7.54–7.50 (m, 3H), 7.30 (d, J = 7.4 Hz, 1H), 7.28–7.20 (m, 4H), 7.08 (d, J = 7.5 Hz, 1H), 6.90 (d, J = 6.5 Hz, 2H), 5.22 (s, 1H), 4.84 (d, J = 15.5 Hz, 1H), 3.86 (d, J = 15.5 Hz, 1H), 3.28 (s, 3H), 2.72 (s, 3H), 1.75 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.3, 170.1, 166.7, 150.8, 135.9, 134.8, 131.2, 130.9, 130.7, 130.2, 129.0 (2C), 128.93 (2C), 128.88 (2C), 128.76 (2C), 128.14, 128.13 (2C), 126.5, 79.8, 69.1, 49.5, 29.1, 28.5, 18.5; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_4O_3$ $[M + H]^+$ 467.2083, found 467.2089.

3-Benzyl-4-(2-methoxyphenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ma). The general procedure was followed to afford **3ma** as a white solid. 69.2 mg, 72% yield; mp 163–165 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.85–7.81 (m, 2H), 7.53–7.45 (m, 4H), 7.30–7.24 (m, 3H), 7.22 (t, J = 7.2 Hz, 1H), 7.09–7.03 (m, 3H), 6.77 (d, J = 8.2 Hz, 1H), 5.46 (s, 1H), 4.88 (d, J = 16.1 Hz, 1H), 4.09 (d, J = 16.1 Hz, 1H), 3.58 (s, 3H), 3.36 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.5, 170.4, 166.9, 156.4, 151.3, 135.3, 130.8, 130.2, 129.5, 128.9 (2C), 128.8 (2C), 128.7 (2C), 128.3, 127.78, 127.77 (2C), 123.2, 121.1, 109.7, 79.5, 67.3, 55.4, 49.9, 29.0, 28.2; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_4O_4$ $[M + H]^+$ 483.2032, found 483.2028.

3-Benzyl-4-(2-chlorophenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3na). The general procedure was followed to afford **3na** as a white solid. 80.6 mg,

83% yield; mp 153–155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87–7.81 (m, 2H), 7.65 (d, J = 7.7 Hz, 1H), 7.56–7.48 (m, 3H), 7.37 (t, J = 7.1 Hz, 1H), 7.31–7.21 (m, 5H), 6.99 (d, J = 6.5 Hz, 2H), 5.52 (s, 1H), 4.82 (d, J = 15.5 Hz, 1H), 4.01 (d, J = 15.5 Hz, 1H), 3.32 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.2, 169.8, 166.6, 150.9, 134.5, 132.8, 132.7, 131.1, 130.2, 129.8 (2C), 129.4, 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.2 (3C), 127.2, 79.3, 69.1, 50.4, 29.2, 28.4; HRMS (ESI-TOF) calcd for $C_{27}H_{24}ClN_4O_3$ $[M + H]^+$ 487.1537, found 487.1549.

3-Benzyl-4-(2-bromophenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3oa). The general procedure was followed to afford **3oa** as a white solid. 86.0 mg, 81% yield; mp 161–163 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.86–7.81 (m, 2H), 7.63 (d, J = 7.8 Hz, 1H), 7.55–7.48 (m, 3H), 7.48–7.44 (m, 1H), 7.43–7.38 (m, 1H), 7.29–7.16 (m, 4H), 6.99 (d, J = 7.0 Hz, 2H), 5.49 (s, 1H), 4.80 (dd, J = 15.5, 3.3 Hz, 1H), 4.00 (dd, J = 15.5, 2.1 Hz, 1H), 3.31 (s, 3H), 2.82 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.9, 169.6, 166.4, 150.8, 134.4, 134.1, 132.7, 131.1, 130.6, 130.2, 129.6, 129.0 (2C), 128.9 (2C), 128.8 (2C), 128.21 (2C), 128.15, 127.7, 122.9, 79.1, 71.3, 50.3, 29.1, 28.4; HRMS (ESI-TOF) calcd for $C_{27}H_{24}BrN_4O_3$ $[M + H]^+$ 531.1032, found 531.1025.

3-Benzyl-4-(3,4-dichlorophenyl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3pa). The general procedure was followed to afford **3pa** as a white solid. 80.4 mg, 77% yield; mp 159–161 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.79 (m, 2H), 7.54–7.49 (m, 3H), 7.42 (d, J = 8.3 Hz, 1H), 7.34 (s, 1H), 7.28–7.24 (m, 3H), 7.05 (d, J = 7.4 Hz, 1H), 6.97–6.93 (m, 2H), 5.08 (s, 1H), 4.83 (d, J = 15.8 Hz, 1H), 3.99 (d, J = 15.8 Hz, 1H), 3.34 (s, 3H), 2.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.3, 169.3, 166.0, 150.5, 134.30, 134.28, 133.08, 133.06, 131.2, 130.7, 129.8, 129.5, 128.94 (2C), 128.87 (2C), 128.79 (2C), 128.2, 127.9 (2C), 127.2, 79.8, 71.0, 49.9, 29.4, 28.5; HRMS (ESI-TOF) calcd for $C_{27}H_{23}Cl_2N_4O_3$ $[M + H]^+$ 521.1147, found 521.1150.

3-Benzyl-4-(furan-2-yl)-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3qa). The general procedure was followed to afford **3qa** as a pink oil. 57.6 mg, 65% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 7.7 Hz, 2H), 7.54–7.45 (m, 3H), 7.34–7.22 (m, 4H), 7.05 (d, J = 7.0 Hz, 2H), 6.39 (d, J = 3.3 Hz, 1H), 6.28 (d, J = 3.3 Hz, 1H), 5.17 (s, 1H), 4.73 (d, J = 15.9 Hz, 1H), 4.18 (d, J = 15.9 Hz, 1H), 3.34 (s, 3H), 3.09 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.7, 169.0, 166.0, 150.7, 149.6, 134.7, 131.3, 129.1, 128.93 (2C), 128.89 (2C), 128.84 (2C), 128.2, 127.7 (2C), 122.8, 113.4, 112.8, 78.3, 66.5, 50.2, 29.4, 28.9; HRMS (ESI-TOF) calcd for $C_{25}H_{23}N_4O_4$ $[M + H]^+$ 443.1719, found 443.1720.

(*E*)-3-Benzyl-7,9-dimethyl-2-phenyl-4-styryl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ra). The general procedure was followed to afford **3ra** as a white solid. 68.3 mg, 71% yield; mp 88–90 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67–7.64 (m, 2H), 7.46 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.2 Hz, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.31–7.24 (m, 6H), 7.20 (d, J = 7.3 Hz, 2H), 6.47 (dd, J = 15.9, 9.3 Hz, 1H), 6.39 (d, J = 15.9 Hz, 1H), 5.02 (d, J = 9.3 Hz, 1H), 4.60 (d, J = 16.4 Hz, 1H), 4.34 (d, J = 16.4 Hz, 1H), 3.35 (s, 3H), 3.24 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.7, 167.1, 150.9, 136.7, 136.1, 135.6, 130.8, 129.8, 128.82 (2C), 128.80 (2C), 128.7 (2C), 128.6, 128.5 (2C), 127.7, 127.4 (2C), 126.9 (2C), 123.5, 78.3, 70.6, 49.4, 29.4, 28.8; HRMS (ESI-TOF) calcd for $C_{29}H_{27}N_4O_3$ $[M + H]^+$ 479.2083, found 479.2083.

3-Benzyl-4-isopropyl-7,9-dimethyl-2-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3sa). The general procedure was followed to afford **3sa** as a colorless oil. 69.3 mg, 83% yield; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70–7.64 (m, 2H), 7.46–7.42 (m, 3H), 7.29–7.22 (m, 3H), 7.14–7.10 (m, 2H), 4.43 (d, J = 14.3 Hz, 1H), 4.29 (d, J = 9.7 Hz, 1H), 3.98 (d, J = 14.3 Hz, 1H), 3.22 (s, 3H), 2.93 (s, 3H), 1.98–1.88 (m, 1H), 1.18 (d, J = 6.6 Hz, 3H), 0.70 (d, J = 6.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.9, 167.0, 164.3, 150.0, 134.6, 130.5, 130.1, 129.7 (2C), 128.8 (2C), 128.65 (2C), 128.57, 128.5 (2C), 87.8, 74.9, 50.8, 30.5, 29.0, 28.4, 21.2, 20.4; HRMS (ESI-TOF) calcd for $C_{24}H_{27}N_4O_3$ $[M + H]^+$ 419.2083, found 419.2089.

3-Benzyl-7,9-dimethyl-4-phenyl-2-(*p*-tolyl)-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ab). The general procedure was followed to afford **3ab** as a colorless oil. 69.8 mg, 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.74 (d, J = 8.0 Hz, 2H), 7.37–7.32 (m, 3H), 7.31 (d, J = 7.9 Hz, 2H), 7.26–7.20 (m, 3H), 7.19–7.14 (m, 2H), 6.95 (d, J = 6.9 Hz, 2H), 4.93 (s, 1H), 4.86 (d, J = 15.9 Hz, 1H), 3.96 (d, J = 15.9 Hz, 1H), 3.32 (s, 3H), 2.66 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.6, 170.0, 166.5, 150.8, 141.2, 135.0, 133.8, 129.5 (2C), 129.2, 128.9 (4C), 128.8 (2C), 128.0, 127.9 (2C), 127.7 (2C), 127.2, 80.8, 73.5, 49.5, 29.3, 28.3, 21.6; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_4O_3$ $[M + H]^+$ 453.1927, found 453.1940.

3-Benzyl-2-(4-chlorophenyl)-7,9-dimethyl-4-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ac). The general procedure was followed to afford **3ac** as a white solid. 78.5 mg, 81% yield; mp 178–180 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.80 (d, J = 8.4 Hz, 2H), 7.49 (d, J = 8.4 Hz, 2H), 7.38–7.33 (m, 3H), 7.28–7.22 (m, 3H), 7.18–7.13 (m, 2H), 6.93 (d, J = 6.7 Hz, 2H), 4.95 (s, 1H), 4.78 (d, J = 16.0 Hz, 1H), 3.98 (d, J = 16.0 Hz, 1H), 3.33 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 169.8, 166.4, 150.8, 137.2, 134.7, 133.5, 130.3 (2C), 129.4, 129.3 (2C), 129.01 (2C), 128.97 (2C), 128.6, 128.2, 127.8 (2C), 127.7 (2C), 80.8, 73.8, 49.5, 29.3, 28.4; HRMS (ESI-TOF) calcd for $C_{27}H_{24}ClN_4O_3$ $[M + H]^+$ 487.1537, found 453.1941.

3-Benzyl-2-(4-bromophenyl)-7,9-dimethyl-4-phenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ad). The general procedure was followed to afford **3ad** as a white solid. 81.0 mg, 76% yield; mp 183–185 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, J = 8.2 Hz, 2H), 7.66 (d, J = 8.2 Hz, 2H), 7.38–7.34 (m, 3H), 7.29–7.23 (m, 3H), 7.17–7.12 (m, 2H), 6.93 (d, J = 7.0 Hz, 2H), 4.92 (s, 1H), 4.77 (d, J = 16.0 Hz, 1H), 3.97 (d, J = 16.0 Hz, 1H), 3.33 (s, 3H), 2.65 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.5, 169.7, 166.3, 150.7, 134.7, 133.4, 132.1 (2C), 130.5 (2C), 129.4, 129.0, 128.96 (2C), 128.92 (2C), 128.1, 127.73 (2C), 127.66 (2C), 125.4, 80.8, 73.8, 49.4, 29.3, 28.3; HRMS (ESI-TOF) calcd for $C_{27}H_{24}BrN_4O_3$ $[M + H]^+$ 531.1032, found 453.1939.

3-Benzyl-7,9-dimethyl-4-phenyl-2-(*m*-tolyl)-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ae). The general procedure was followed to afford **3ae** as a colorless oil. 69.8 mg, 75% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.68 (s, 1H), 7.62 (d, J =

7.6 Hz, 1H), 7.40–7.31 (m, 5H), 7.28–7.21 (m, 3H), 7.19–7.15 (m, 2H), 6.95 (d, J = 6.7 Hz, 2H), 4.94 (s, 1H), 4.87 (d, J = 15.9 Hz, 1H), 3.96 (d, J = 15.9 Hz, 1H), 3.33 (s, 3H), 2.67 (s, 3H), 2.43 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.7, 170.0, 166.5, 150.9, 138.9, 135.0, 133.8, 131.7, 130.0, 129.6, 129.3, 128.94 (2C), 128.86 (2C), 128.7, 128.02, 127.98 (2C), 127.8 (2C), 125.9, 80.8, 73.5, 49.5, 29.3, 28.4, 21.5; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_4O_3$ $[M + H]^+$ 467.2083, found 467.2077.

3-Benzyl-7,9-dimethyl-4-phenyl-2-(*o*-tolyl)-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3af). The general procedure was followed to afford **3af** as a colorless oil. 66.5 mg, 71% yield; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.64 (d, J = 7.3 Hz, 1H), 7.40–7.28 (m, 6H), 7.26–7.21 (m, 3H), 7.19–7.14 (m, 2H), 6.89 (d, J = 6.0 Hz, 2H), 5.00 (s, 1H), 4.43 (d, J = 15.6 Hz, 1H), 3.91 (d, J = 15.6 Hz, 1H), 3.35 (s, 3H), 2.70 (s, 3H), 2.68 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.0, 170.1, 166.5, 150.8, 137.2, 134.7, 133.6, 130.9, 130.3, 129.9, 129.4, 129.3, 128.0 (2C), 128.8 (2C), 128.1 (2C), 128.0, 127.9 (2C), 126.1, 81.0, 73.1, 48.7, 29.3, 28.3, 19.9; HRMS (ESI-TOF) calcd for $C_{28}H_{27}N_4O_3$ $[M + H]^+$ 467.2083, found 467.2081.

7,9-Dimethyl-2,3,4-triphenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ag). The general procedure was followed to afford **3ag** as a white solid. 75.4 mg, 86% yield; mp 167–169 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (d, J = 7.4 Hz, 2H), 7.39 (t, J = 7.5 Hz, 1H), 7.36–7.32 (m, 3H), 7.31–7.26 (m, 4H), 7.10 (t, J = 7.5 Hz, 2H), 7.05 (t, J = 7.3 Hz, 1H), 6.89 (d, J = 7.6 Hz, 2H), 5.36 (s, 1H), 3.41 (s, 3H), 2.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 169.7, 169.5, 166.3, 150.7, 141.8, 134.8, 131.1, 129.8 (2C), 129.6, 129.3, 129.2 (2C), 128.8 (2C), 128.2 (2C), 127.8 (2C), 126.4, 125.8 (2C), 81.5, 79.3, 29.4, 28.5; HRMS (ESI-TOF) calcd for $C_{26}H_{23}N_4O_3$ $[M + H]^+$ 439.1770, found 439.1775.

7,9-Dimethyl-2,4-diphenyl-3-(*p*-tolyl)-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ah). The general procedure was followed to afford **3ah** as a white solid. 76.0 mg, 84% yield; mp 218–220 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 7.2 Hz, 2H), 7.38 (t, J = 7.4 Hz, 1H), 7.36–7.26 (m, 7H), 6.90 (d, J = 8.2 Hz, 2H), 6.80 (d, J = 8.2 Hz, 2H), 5.30 (s, 1H), 3.41 (s, 3H), 2.72 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.9, 169.8, 166.4, 150.8, 139.4, 136.4, 135.0, 131.0, 130.0 (2C), 129.84, 129.81 (2C), 129.3, 128.8 (2C), 128.2 (2C), 127.9 (2C), 126.0 (2C), 81.7, 79.7, 29.4, 28.5, 21.0; HRMS (ESI-TOF) calcd for $C_{27}H_{25}N_4O_3$ $[M + H]^+$ 453.1927, found 453.1936.

3-(4-Methoxyphenyl)-7,9-dimethyl-2,4-diphenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ai). The general procedure was followed to afford **3ai** as a white solid. 75.1 mg, 80% yield; mp 224–226 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.69 (d, J = 7.3 Hz, 2H), 7.39–7.26 (m, 8H), 6.89 (d, J = 8.8 Hz, 2H), 6.63 (d, J = 8.8 Hz, 2H), 5.25 (s, 1H), 3.66 (s, 3H), 3.41 (s, 3H), 2.72 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.1, 170.0, 166.5, 158.2, 150.8, 135.0 (2C), 130.9, 129.80 (2C), 129.77, 129.3, 128.8 (2C), 128.2 (2C), 127.93 (2C), 127.85 (2C), 114.6 (2C), 81.6, 80.1, 55.4, 29.4, 28.4; HRMS (ESI-TOF) calcd for $C_{27}H_{25}N_4O_4$ $[M + H]^+$ 469.1876, found 468.1881.

3-(4-Chlorophenyl)-7,9-dimethyl-2,4-diphenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3aj). The general procedure was followed to afford **3aj** as a white solid. 81.6 mg, 86% yield; mp 222–224 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 6.3 Hz, 2H), 7.43 (m, 1H), 7.39–7.30 (m, 5H), 7.28–7.22 (m, 2H), 7.07 (d, J = 7.1 Hz, 2H), 6.81 (d, J = 7.2 Hz, 2H), 5.34 (s, 1H), 3.41 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.7, 169.2, 166.2, 150.7, 140.4, 134.5, 132.0, 131.3, 129.8 (2C), 129.52, 129.49 (2C), 129.4, 129.0 (2C), 128.4 (2C), 127.8 (2C), 127.0 (2C), 81.6, 79.2, 29.4, 28.5; HRMS (ESI-TOF) calcd for $C_{26}H_{22}ClN_4O_3$ $[M + H]^+$ 473.1380, found 473.1378.

3-(4-Bromophenyl)-7,9-dimethyl-2,4-diphenyl-1,3,7,9-tetraazaspiro[4.5]dec-1-ene-6,8,10-trione (3ak). The general procedure was followed to afford **3ak** as a white solid. 86.1 mg, 83% yield; mp 255–257 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.67 (d, J = 7.2 Hz, 2H), 7.44 (t, J = 7.3 Hz, 1H), 7.37–7.31 (m, 5H), 7.26–7.20 (m, 4H), 6.75 (d, J = 8.7 Hz, 2H), 5.35 (s, 1H), 3.41 (s, 3H), 2.74 (s, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 169.6, 169.0, 166.1, 150.7, 140.9, 134.5, 132.4 (2C), 131.3, 129.7 (2C), 129.5, 129.4, 128.9 (2C), 128.4 (2C), 127.8 (2C), 127.2 (2C), 119.7, 81.5, 79.0, 29.4, 28.5; HRMS (ESI-TOF) calcd for $C_{26}H_{22}BrN_4O_3$ $[M + H]^+$ 517.0875, found 517.0881.

Conflicts of interest

There are no conflicts to declare.

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