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Facile access to novel 1,2,4-oxadiazinan-5-ones *via* [3 + 3] cycloaddition of *in situ* generated azaoxyallyl cations with nitrones†

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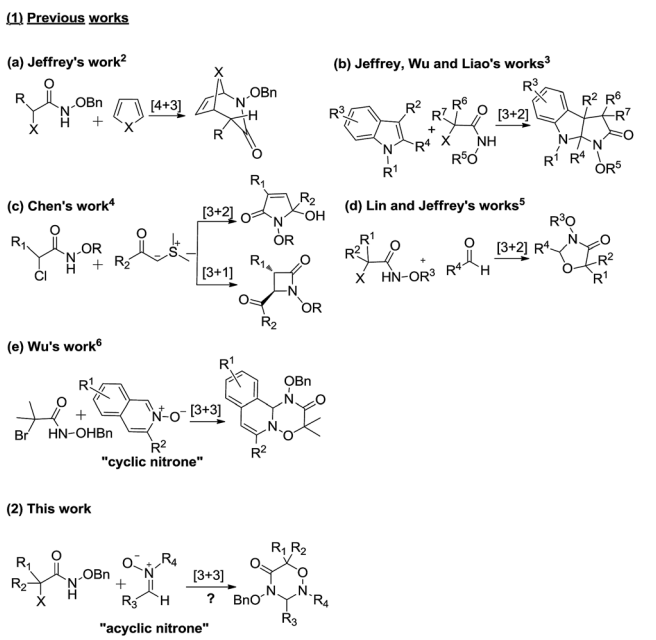
In the presence of Na_2CO_3, azaoxyallyl cations *in situ* generated from α-halohydroxamates with nitrones readily underwent [3 + 3] cycloaddition, and gave rise to 1,2,4-oxadiazinan-5-one derivatives in 56–99% chemical yields. The chemical structure of the title compounds was unambiguously identified by X-ray single crystal structure analysis.

1. Introduction

Azaoxyallyl cations represent a family of versatile and powerful synthetic synthons, which are generally *in situ* generated from α-halohydroxamates in the presence of organic or inorganic bases.[1] Owing to the unique structural features and reactivities of azaoxyallyl cations, some various efforts have been made to enrich the synthetic methodology of azaoxyallyl cations (Scheme 1, **1**). In 2011, Jeffrey and co-workers pioneeringly reported the [4 + 3] cycloaddition between azaoxyallyl cations and cyclic dienes (Scheme 1, **1a**).[2] Since then, the research groups of Jeffrey, Wu and Liao independently devised similar [3 + 2] cycloadditions of azaoxyallyl cations with differently substituted indoles for the preparation of pyrroloindolines (Scheme 1, **1b**).[3] Moreover, Chen's group discovered the [3 + 1] and [3 + 2] cycloadditions of azaoxyallyl cations with sulfur ylides delivering β- and γ-lactams (Scheme 1, **1c**).[4] In 2016, Lin and Jeffrey's groups individually successfully applied the [3 + 2] cycloaddition of azaoxyallyl cations with aldehydes in the synthesis of oxazolidin-4-ones (Scheme 1, **1d**).[5] Additionally, in the same year, Wu and co-workers established the [3 + 3] cycloaddition of isoquinoline N-oxides as cyclic nitrones with azaoxyallyl cations (Scheme 1, **1e**).[6] Even though the important and elegant advances in the synthetic methodology of azaoxyallyl cations, it remains highly demanded to develop novel and efficient synthetic methodologies of azaoxyallyl cations for the synthesis of structurally diverse heterocycles.

Encouraged by the previous works on the synthetic methodology of azaoxyallyl cations, we designed the novel [3 + 3] cycloaddition of the azaoxyallyl cations *in situ* generated from α-halohydroxamates with acyclic nitrones as 1,3-dipoles with a purpose to prepare potentially bioactive 1,2,4-oxadiazine-5-ones (Scheme 1, **2**).[7] Pleasantly, the [3 + 3] cycloaddition between azaoxyallyl cations and acyclic nitrones proceeded readily under mild reaction conditions, and gave the title target molecules in the desirable chemical yields. To the best of our knowledge, no such a work has been reported in the literature to date.



Scheme 1 Representative cycloadditions involving azaoxyallyl cations.

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† Electronic supplementary information (ESI) available: Copies of NMR spectra for all products related to this article; X-ray single crystal structure analysis data for **3ad**. CCDC 1504786. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c6ra27440d

2. Results and discussion

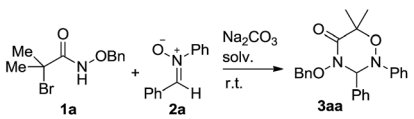
Initially, we screened the solvent effects on the [3 + 3] cycloaddition of α-halohydroxamate **1a** with nitrone **2a** as outlined in Table 1. Noticeably, the use of the different solvents significantly affected the chemical yield of the [3 + 3] cycloaddition. When EtOH was tested as polar protonic solvent, product **3aa** was produced in a trace amount in 48 h (entry 6). Compared with the former case, the use of TFE, toluene and DCM as solvents differently increased the chemical yield of the [3 + 3] cycloaddition (entries 2 and 4–5 *vs.* 6). Moreover, the significant increase in the chemical yield of product **3aa** was observed by using CH_3CN as a polar aprotonic solvent (entry 3). Finally, the [3 + 3] cycloaddition underwent more efficiently in HFIP as a polar fluorinated solvent, and provided product **3aa** in the highest chemical yield (entry 1).

Then, we examined a variety of bases bearing the various basic strength to clarify their effects on the [3 + 3] cycloaddition of α-halohydroxamate **1a** with nitrone **2a** using HFIP as solvent as summarized in Table 2. Remarkably, the chemical yield of the [3 + 3] cycloaddition highly depended on the used bases. As for $NaHCO_3$ as base, it provided **3aa** in 13% chemical yield (entry 6). By comparison, the use of K_2CO_3, Cs_2CO_3 and MeONa bases enhanced the chemical yield of the [3 + 3] cycloaddition differently (entries 2–3 & 7 *vs.* 6). As far as other examined bases such as Na_2CO_3, Et_3N, KOH and DBU were concerned, they could promote the [3 + 3] cycloaddition efficiently, and delivered product **3aa** in excellent chemical yields (entries 1, 4–5 & 8). Accordingly, in the presence of by Na_2CO_3 as an inorganic base, the [3 + 3] cycloaddition proceeded most efficiently, and produced product **3aa** in the highest chemical yield (98%, entry 1).

Meanwhile, we also investigated the effect of the equivalent ratio of **1a**/**2a**/Na_2CO_3 on the [3 + 3] cycloaddition of α-halohydroxamate **1a** with nitrone **2a** as shown in Table 3. Apparently, the used equivalent ratio of **1a**/**2a**/Na_2CO_3 dramatically influenced the chemical yield of the [3 + 3] cycloaddition. The application of the ratio of 1 : 1 : 1 in the [3 + 3] cycloaddition formed product **3aa** in 59% chemical yield (entry 1). In regard to the ratios such as 1.5 : 1 : 1.5, 1 : 1.5 : 1 and 1 : 2 : 1, they provided product **3aa** in the increased chemical yields (entries 1 *vs.* 2 & 4–5). Moreover, it was found that product **3aa** was obtained in excellent chemical yields with the use of ratios of 2 : 1 : 2 and 2 : 1 : 1 in the [3 + 3] cycloaddition (entries 3 & 6). Noticeably, among all the screened ratios of **1a**/**2a**/Na_2CO_3, the ratio of 2 : 1 : 2 should be the most optimal for the [3 + 3] cycloaddition, and furnished product **3aa** in 98% chemical yield (entry 3).

Finally, we broadened the reaction scope of the [3 + 3] cycloaddition under the optimal reaction conditions by employing structurally different α-halohydroxamates **1** and nitrones **2** as summarized in Table 4. Obviously, the variations of R_1–R_4 groups of substrates **1** and **2** significantly affected the chemical yield of the [3 + 3] cycloaddition. Nitrones **2a–2l** reacted easily with **1a** bearing two methyl groups at the α-position, and gave products **3aa–3al** in 76–99% chemical yields

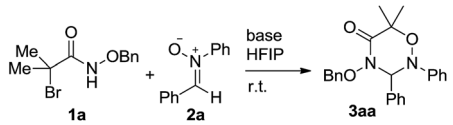
Table 1 Screening of solvents[a]



Entry	Solvent	Time (h)	Yield[b] (%)
1	HFIP	1	98
2	TFE	1.5	40
3	CH_3CN	4	90
4	Toluene	48	30
5	DCM	48	26
6	EtOH	48	Trace

[a] Reactions were carried out with 0.2 mmol of **1a** (54.2 mg) and 0.1 mmol of **2a** (19.7 mg) in the presence of 0.2 mmol of Na_2CO_3 (21.2 mg) in 0.5 mL of the indicated solvents at room temperature. [b] Isolated yield.

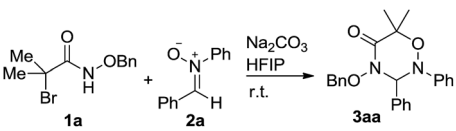
Table 2 Screening of bases[a]



Entry	Base	Time (h)	Yield[b] (%)
1	Na_2CO_3	1	98
2	K_2CO_3	1	78
3	Cs_2CO_3	1	82
4	Et_3N	1	98
5	KOH	1	92
6	$NaHCO_3$	1	13
7	MeONa	1	48
8	DBU	1	98

[a] Reactions were carried out with 0.2 mmol of **1a** (54.2 mg) and 0.1 mmol of **2a** (19.7 mg) in the presence of 0.2 mmol of the indicated bases in 0.5 mL of HFIP at room temperature. [b] Isolated yield.

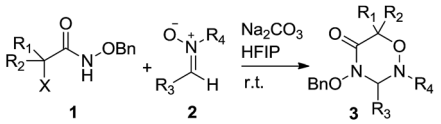
Table 3 Screening of ratios of **1a**/**2a**/Na_2CO_3[a]

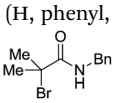


Entry	Equivalentratio (**1a**/**2a**/Na_2CO_3)	Time (h)	Yield[b] (%)
1	1 : 1 : 1	1	59
2	1.5 : 1 : 1.5	1	85
3	2 : 1 : 2	1	98
4	1 : 1.5 : 1	1	68
5	1 : 2 : 1	1	78
6	2 : 1 : 1	1	92

[a] Reactions were carried out with **1a** and **2a** in the presence of Na_2CO_3 in 0.5 mL of HFIP at the indicated equivalent ratios of **1a**/**2a**/Na_2CO_3 at room temperature. [b] Isolated yield.

Table 4 Extension of reaction scope[a]



Entry	1 (R_1, R_2, X)	2 (R_3, R_4)	3	Time (h)	Yield[b] (%)
1	**1a** (Me, Me, Br)	**2a** (Ph, Ph)	**3aa**	1	98
2	**1a** (Me, Me, Br)	**2b** (4-$MeOC_6H_4$, Ph)	**3ab**	1	96
3	**1a** (Me, Me, Br)	**2c** (4-MeC_6H_4, Ph)	**3ac**	1	93
4	**1a** (Me, Me, Br)	**2d** (4-ClC_6H_4, Ph)	**3ad**	1	99
5	**1a** (Me, Me, Br)	**2e** (3-$MeOC_6H_4$, Ph)	**3ae**	1	89
6	**1a** (Me, Me, Br)	**2f** (3-ClC_6H_4, Ph)	**3af**	1	99
7	**1a** (Me, Me, Br)	**2g** (2-$MeOC_6H_4$, Ph)	**3ag**	1	76
8	**1a** (Me, Me, Br)	**2h** (2-ClC_6H_4, Ph)	**3ah**	1	99
9	**1a** (Me, Me, Br)	**2i** (4-BrC_6H_4, Ph)	**3ai**	1	97
10	**1a** (Me, Me, Br)	**2j** (4-FC_6H_4, Ph)	**3aj**	1	87
11	**1a** (Me, Me, Br)	**2k** (4-CNC_6H_4, Ph)	**3ak**	1	99
12	**1a** (Me, Me, Br)	**2l** (4-$NO_2C_6H_4$, Ph)	**3al**	1	97
13	**1a** (Me, Me, Br)	**2m** (Ph, Bn)	**3am**	1	81
14	**1a** (Me, Me, Br)	**2n** (Et, Bn)	**3an**	1	77
15	**1a** (Me, Me, Br)	**2o** (Ph, Me)	**3ao**	1	93
16	**1a** (Me, Me, Br)	**2p** (2-naphthyl, Ph)	**3ap**	1	92
17	**1a** (Me, Me, Br)	**2q** (2-furyl, Ph)	**3aq**	1	99
18	**1b** (H, Et, Br)	**2a** (Ph, Ph)	**3ba**	1	nr[c]
19	**1c** (R_1, R_2 = $-CH_2(CH_2)_3CH_2-$, X = Br)	**2a** (Ph, Ph)	**3ca**	1	92
20	**1d** (H, Cl, Cl)	**2a** (Ph, Ph)	**3da**	12	nr[c]
21	**1e** (H, phenyl, Cl)	**2a** (Ph, Ph)	**3ea**	1	56
22	**1f** 	**2a** (Ph, Ph)	**3fa**	12	nr[c]
23	**1c** (R_1, R_2 = $-CH_2(CH_2)_3CH_2-$, X = Br)	**2m** (Ph, Bn)	**3cm**	1	78
24	**1c** (R_1, R_2 = $-CH_2(CH_2)_3CH_2-$, X = Br)	**2g** (2-$MeOC_6H_4$, Ph)	**3cg**	1	67
25	**1c** (R_1, R_2 = $-CH_2(CH_2)_3CH_2-$, X = Br)	**2h** (2-ClC_6H_4, Ph)	**3ch**	1	86
26	**1c** (R_1, R_2 = $-CH_2(CH_2)_3CH_2-$, X = Br)	**2p** (2-naphthyl, Ph)	**3cp**	1	90
27	**1c** (R_1, R_2 = $-CH_2(CH_2)_3CH_2-$, X = Br)	**2q** (2-furyl, Ph)	**3cq**	1	61

[a] Reactions were carried out with 0.2 mmol of **1** and 0.1 mmol of **2** in the presence of 0.2 mmol of Na_2CO_3 (21.2 mg) in 0.5 mL of HFIP at room temperature. [b] Isolated yield. [c] No reaction.

(entries 1–12). Basically, with respect to the [3 + 3] cycloaddition with **1a**, the nitrones **2** could well tolerate the existence of electron-poor or electron-rich phenyl rings as R_3 group, and furnished products **3** in excellent chemical yields (entries 2–4, 8 and 9, 11 and 12). Moreover, the nitrones **2b**, **2e** and **2g**, involving a 4-, 3- or 2-MeO-substituted phenyl ring as R_3 group respectively, afforded products **3ab**, **3ae** and **3ag** in the quite different chemical yields in [3 + 3] the cycloaddition with **1a** (entries 2, 5 & 7); in contrast, the nitrones **2d**, **2f** and **2h**, including a 4-, 3- or 2-Cl-substituted phenyl ring as R_3 group individually, provide products **3ad**, **3af** and **3ah** in the same chemical yields (entries 4, 6 & 8).

Simultaneously, the nitrones **2** well endured the varying bulky size of R_3 and R_4 groups in the cycloaddition with **1a**, and gave the corresponding products **3** in 77–99% chemical yields (entries 13–17). By comparison, in the cycloaddition with **2a**, the α-halohydroxamates **1** could not widely tolerate the structural change of R_1 and R_2 groups. For example, the [3 + 3] cycloaddition of substrates **1b** or **1d** with **2a** did not take place at all (entries 18 & 20); however, substrates **1c** and **1e** could well react with **2a**, and furnished products **3ca** and **3ea** in 92% and 56% chemical yields, respectively (entries 19 & 21). In addition, we performed the [3 + 3] cycloaddition of α-halohydroxamate **1c** containing a cyclohexyl subunit with the nitrones **2** with different R_3 or R_4 groups, and discovered that all these [3 + 3] cycloadditions proceeded ready to form products **3** in the reasonable chemical yields (entries 23–27). Finally, the chemical structure of **3ad** was unambiguously determined by single crystal X-ray analysis as depicted in Fig. 1.[8]

Finally, we proposed the reaction mechanism for the formation of **3ad** (Scheme 2). In the presence of Na_2CO_3, the elimination reaction of **1a** takes place to give azaoxyallyl cation **4**. Then, two possible transition states TS1 and TS2 will be produced for the [3 + 3] cycloaddition between **4** and **2d**. With the aid of the molecular model, it was found that in TS2 phenyl group at nitrogen atom of **2d** sterically repulses α-methyl group of **4** severely; whereas, this strong destabilizing interaction does not exist in TS1 at all. Therefore, the transition state TS1 is more stable than the transition state TS2, and mainly accounts for the formation of the desired cycloadduct **3ad**.

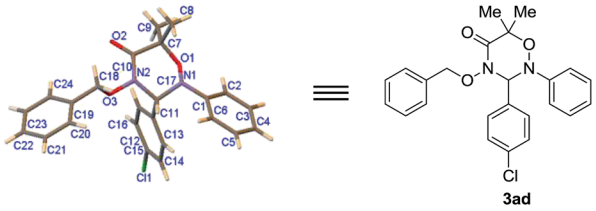
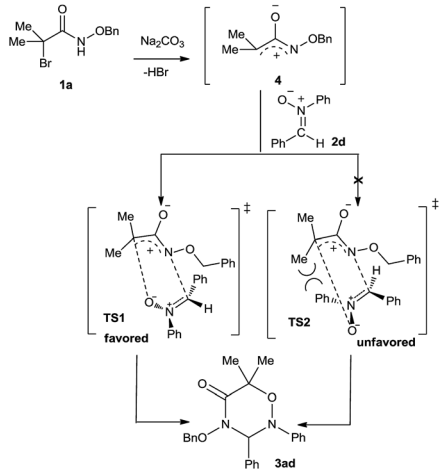


Fig. 1 X-ray single crystal structure of **3ad** (with thermal ellipsoils shown at the 50% probability level).



Scheme 2 Proposed mechanism for the formation of **3ad**.

3. Conclusions

In conclusion, the [3 + 3] cycloadditions of *in situ* generated azaoxyallyl cations with nitrones underwent efficiently, and provided an easy access to the novel potentially bioactive 1,2,4-oxadiazinan-5-ones in reasonable chemical yields. Furthermore, the exploration of other novel cycloadditions of azaoxyallyl cations with various 1,3-, 1,4- and 1,5-dipoles is ongoing in our organic lab, and will be reported in due course.

4. Experimental section

4.1 General information

Proton (^{1}H) and carbon (^{13}C) NMR spectra were recorded on 400 MHz instrument (400 MHz for ^{1}H NMR, 100 MHz for ^{13}C NMR) and calibrated using tetramethylsilane (TMS) as internal reference. High resolution mass spectra (HRMS) were recorded under electrospray ionization (ESI) conditions. The melting point of compounds was determined by a melting point instrument. Flash column chromatography was performed on silica gel (0.035–0.070 mm) using compressed air. Thin layer chromatography (TLC) was carried out on 0.25 mm SDS silica gel coated glass plates (60F254). Eluted plates were visualized using a 254 nm UV lamp. Unless otherwise indicated, all reagents were commercially available and used without further purification. All solvents were distilled from the appropriate drying agents immediately before using. α-halohydroxamates **1a–1e** and α-haloamide **1f** and nitrone **2a–2q** were prepared according to literature procedures.[2,3c,9]

4.2 Procedure for the synthesis of products 3

A mixture of α-halohydroxamate **1** (2.0 equiv., 0.2 mmol), nitrone **2** (1.0 equiv., 0.1 mmol) and Na_2CO_3 (2.0 equiv., 0.2 mmol) in 0.5 mL of HFIP was stirred at room temperature for 1 h. After the reaction was completed as indicated by TLC plate, the solvent was removed by evaporation and the crude product was purified by flash column chromatography on silica gel (petroleum ether/ethyl acetate = 15 : 1) to afford the pure products **3** as white solid (56–99% yields).

4-(Benzyloxy)-6,6-dimethyl-2,3-diphenyl-1,2,4-oxadiazinan-5-one (3aa). White solid, yield: 38.0 mg, 98%; mp = 110.8–111.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.35 (m, 3H), 7.32–7.30 (m, 3H), 7.29–7.23 (m, 4H), 7.20–7.16 (m, 2H), 6.97 (t, J = 7.2 Hz, 1H), 6.81 (d, J = 10.0 Hz, 2H), 5.64 (s, 1H), 5.17 (d, J = 10.0 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 1.73 (s, 3H), 1.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 145.6, 134.9, 133.6, 130.0, 129.3, 129.0, 128.9, 128.6, 128.5, 128.1, 123.8, 118.3, 83.9, 83.5, 77.4, 24.0, 23.5 ppm; HRMS (ESI) calculated for $C_{24}H_{25}N_2O_3$ $[M + H]^+$: 389.18597, found 389.18533.

4-(Benzyloxy)-3-(4-methoxyphenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3ab). White solid, yield: 40.2 mg, 96%; mp = 105.2–105.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38–7.28 (m, 5H), 7.20–7.16 (m, 4H), 6.98–6.95 (m, 1H), 6.83–6.77 (m, 4H), 5.60 (s, 1H), 5.14 (d, J = 10.0 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 3.78 (s, 3H), 1.72 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 145.2, 135.6, 134.7, 134.1, 130.0, 129.4, 129.3, 129.1, 128.9, 128.8, 128.6, 127.0, 124.0, 118.1, 83.7, 83.2, 77.4, 24.0, 23.4 ppm; HRMS (ESI) calculated for $C_{25}H_{27}N_2O_4$ $[M + H]^+$: 419.19653, found 419.19543.

4-(Benzyloxy)-6,6-dimethyl-2-phenyl-3-(*p*-tolyl)-1,2,4-oxadiazinan-5-one (3ac). White solid, yield: 37.4 mg, 93%; mp = 131.3–132.0 °C; ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.38–7.28 (m, 5H), 7.20–7.15 (m, 2H), 7.12 (d, J = 8.0 Hz, 2H), 7.06 (d, J = 8.0 Hz, 2H), 6.98–6.94 (m, 1H), 6.81 (d, J = 8.0 Hz, 2H), 5.61 (s, 1H), 5.15 (d, J = 10.0 Hz, 1H), 4.64 (d, J = 10.0 Hz, 1H), 2.31 (s, 3H), 1.71 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 145.6, 139.1, 134.9, 130.6, 130.0, 128.9, 128.8, 128.7, 128.6, 128.5, 123.6, 118.2, 83.4, 83.2, 77.3, 24.0, 23.5, 21.2 ppm; HRMS (ESI) calculated for $C_{25}H_{27}N_2O_3$ $[M + H]^+$: 403.20162, found 403.20087.

4-(Benzyloxy)-3-(4-chlorophenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3ad). White solid, yield: 41.8 mg, 99%; mp = 131.6–132.4 °C; ^{1}H NMR (400 MHz,$CDCl_3$): δ 7.39–7.36 (m, 3H), 7.33–7.28 (m, 2H), 7.22–7.16 (m, 4H), 7.11 (d, J = 8.0 Hz, 2H), 7.00–6.96 (m, 1H), 6.77 (d, J = 4.0 Hz, 2H), 5.60 (s, 1H), 5.15 (d, J = 10.0 Hz, 1H), 4.71 (d, J = 10.0 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 145.3, 135.2, 134.8, 132.1, 130.1, 130.0, 129.0, 128.8, 128.6, 128.3, 124.0, 118.1, 83.7, 77.4, 24.0, 23.4 ppm; HRMS (ESI) calculated for $C_{24}H_{24}ClN_2O_3$ $[M + H]^+$: 423.14700, found 423.14612.

4-(Benzyloxy)-3-(3-methoxyphenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3ae). White solid, yield: 37.1 mg, 89%; mp = 98.7–99.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37 (d, J = 4.0 Hz, 3H), 7.33 (d, J = 4.0 Hz, 2H), 7.28–7.16 (m, 3H), 6.98–6.95 (m, 1H), 6.85–6.78 (m, 5H), 5.61 (s, 1H), 5.17 (d, J = 10.0 Hz, 1H), 4.67 (d, J = 10.0 Hz, 1H), 3.70 (s, 3H), 1.72 (s, 3H), 1.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 159.2, 145.6,

135.1, 134.9, 130.0, 129.0, 128.9, 128.6, 128.5, 123.6, 121.3, 118.1, 114.9, 114.4, 83.6, 83.5, 77.4, 55.1, 24.0, 23.4 ppm; HRMS (ESI) calculated for $C_{25}H_{27}N_2O_4$ $[M + H]^+$: 419.19653, found 419.19495.

4-(Benzyloxy)-3-(3-chlorophenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3af). White solid, yield: 41.8 mg, 99%; mp = 99.9–100.4 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.38 (m, 3H), 7.34 (s, 2H), 7.26–7.14 (m, 5H), 7.04 (d, J = 7.6 Hz, 1H), 7.00–6.97 (m, 1H), 6.78 (d, J = 7.6 Hz, 2H), 5.54 (s, 1H), 5.16 (d, J = 10.0 Hz, 1H), 4.70 (d, J = 10.0 Hz, 1H), 1.71 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.2, 160.2, 145.7, 135.0, 130.2, 129.9, 128.9, 128.6, 128.5, 125.7, 123.6, 118.4, 113.5, 83.4, 77.3, 55.2, 24.0, 23.5 ppm; HRMS (ESI) calculated for $C_{24}H_{24}ClN_2O_3$ $[M + H]^+$: 423.14700, found 423.14612.

4-(Benzyloxy)-3-(2-methoxyphenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3ag). White solid, yield: 31.8 mg, 76%; mp = 101.2–102.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.66 (d, J = 7.2 Hz, 1H), 7.34 (d, J = 3.6 Hz, 3H), 7.31 (m, 2H), 7.25 (d, J = 8.0 Hz, 1H), 7.17–7.13 (m, 2H), 6.95 (d, J = 8.0 Hz, 2H), 6.90 (d, J = 10.0 Hz, 2H), 6.73 (d, J = 10.0 Hz, 1H), 6.47 (s, 1H), 5.15 (d, J = 8.0 Hz, 1H), 4.67 (d, J = 8.0 Hz, 1H), 3.52 (s, 3H), 1.74 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 157.9, 145.7, 134.9, 130.3, 129.7, 128.7, 128.3, 128.1, 123.4, 122.4, 120.5, 118.4, 110.6, 83.3, 77.2, 55.2, 24.0, 23.5 ppm; HRMS (ESI) calculated for $C_{25}H_{27}N_2O_4$ $[M + H]^+$: 419.19653, found 419.19522.

4-(Benzyloxy)-3-(2-chlorophenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3ah). White solid, yield: 41.7 mg, 99%; mp = 92.6–93.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 6.8.2 Hz, 1H), 7.32 (d, J = 6.4 Hz, 5H), 7.21–7.17 (m, 3H), 7.15–7.11 (m, 2H), 6.98–6.95 (m, 1H), 6.90 (d, J = 6.0 Hz, 2H), 6.42 (s, 1H), 5.09 (d, J = 9.6 Hz, 1H), 4.62 (d, J = 10.0 Hz, 1H), 1.73 (s, 3H), 1.62 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 145.0, 134.9, 134.5, 131.8, 130.5, 130.4, 129.9, 129.8, 129.4, 129.0, 128.6, 128.5, 127.0, 124.6, 118.8, 83.5, 77.5, 24.1, 23.5 ppm; HRMS (ESI) calculated for $C_{24}H_{24}ClN_2O_3$ $[M + H]^+$: 423.14700, found 423.14548.

4-(Benzyloxy)-3-(4-bromophenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3ai). White solid, yield: 45.2 mg, 97%; mp = 109.8–110.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39–7.35 (m, 5H), 7.32 (d, J = 6.8 Hz, 2H), 7.18 (t, J = 8.0 Hz, 2H), 7.04 (d, J = 8.0 Hz, 2H), 6.98 (t, J = 7.2 Hz, 1H), 6.77 (d, J = 8.0 Hz, 2H), 5.55 (s, 1H), 5.15 (d, J = 10.0 Hz, 1H), 4.71 (d, J = 10.0 Hz, 1H), 1.70 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 145.3, 134.8, 132.6, 131.3, 130.3, 129.9, 129.0, 128.8, 128.6, 123.5, 118.2, 83.7, 77.4, 23.9, 23.4 ppm; HRMS (ESI) calculated for $C_{24}H_{24}BrN_2O_3$ $[M + H]^+$: 467.09648, found 467.09604.

4-(Benzyloxy)-3-(4-fluorophenyl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3aj). White solid, yield: 45.2 mg, 87%; mp = 98.0–98.8 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (d, J = 6.0 Hz, 3H), 7.32 (d, J = 5.6 Hz, 2H), 7.20–7.16 (m, 4H), 7.00–6.91 (m, 3H), 6.79 (d, J = 7.6 Hz, 2H), 5.59 (s, 1H), 5.16 (d, J = 10.4 Hz, 1H), 4.68 (d, J = 10.0 Hz, 1H), 1.71 (s, 3H), 1.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 164.4, 161.9, 145.4, 134.8, 130.6, 130.5, 129.9, 129.4, 129.0, 128.7, 128.6, 123.9, 118.3, 115.2, 115.0, 83.6, 77.4, 24.0, 23.4 ppm; HRMS (ESI) calculated for $C_{24}H_{24}FN_2O_3$ $[M + H]^+$: 407.17655, found 407.17587.

4-(4-(Benzyloxy)-6,6-dimethyl-5-oxo-2-phenyl-1,2,4-oxadiazinan-3-yl)benzonitrile (3ak). White solid, yield: 40.8 mg, 99%; mp = 123.1–123.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.49 (d, J = 8.4 Hz, 2H), 7.44–7.36 (m, 3H), 7.33–7.28 (m, 2H), 7.21–7.16 (m, 4H), 6.99 (t, J = 8.0 Hz, 1H), 6.73 (d, J = 8.0 Hz, 2H), 5.56 (s, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.78 (d, J = 10.4 Hz, 1H), 1.69 (s, 3H), 1.67 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 145.0, 138.5, 134.7, 131.7, 129.9, 129.4, 129.3, 129.2, 129.0, 128.9, 128.7, 124.2, 118.3, 117.9, 113.1, 83.9, 83.4, 77.4, 23.9, 23.4 ppm; HRMS (ESI) calculated for $C_{25}H_{24}N_3O_3$ $[M + H]^+$: 414.18122, found 414.18063.

4-(Benzyloxy)-6,6-dimethyl-3-(4-nitrophenyl)-2-phenyl-1,2,4-oxadiazinan-5-one (3al). White solid, yield: 45.2 mg, 97%; mp = 137.2–138.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04 (d, J = 8.4 Hz, 2H), 7.41–7.35 (m, 3H), 7.32 (d, J = 6.8 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.20–7.16 (m, 2H), 7.01–6.97 (m, 1H), 6.74 (d, J = 8.0 Hz, 2H), 5.62 (s, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.80 (d, J = 10.4 Hz, 1H), 1.70 (s, 3H), 1.68 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 148.3, 144.9, 140.4, 134.7, 130.0, 129.5, 129.2, 128.9, 128.7, 124.3, 123.1, 118.0, 84.0, 83.1, 77.4, 24.0, 23.4 ppm; HRMS (ESI) calculated for $C_{24}H_{24}N_3O_5$ $[M + H]^+$: 434.17105, found 434.17041.

2-Benzyl-4-(benzyloxy)-6,6-dimethyl-3-phenyl-1,2,4-oxadiazinan-5-one (3am). White solid, yield: 32.4 mg, 81%; mp = 98.1–98.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47 (s, 5H), 7.33–7.29 (m, 4H), 7.27 (d, J = 5.2 Hz, 2H), 7.21–7.19 (m, 2H), 7.14 (d, J = 6.0 Hz, 2H), 5.11 (s, 1H), 5.02 (d, J = 9.2 Hz, 1H), 4.41 (d, J = 9.2 Hz, 1H), 3.63 (d, J = 13.6 Hz, 1H), 3.47 (d, J = 13.6 Hz, 1H), 1.47 (s, 3H), 1.41 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 136.1, 134.9, 134.2, 129.8, 129.7, 129.4, 129.2, 128.8, 128.6, 128.3, 128.0, 127.4, 81.9, 77.2, 57.2, 24.0, 23.7 ppm; HRMS (ESI) calculated for $C_{25}H_{27}N_2O_3$ $[M + H]^+$: 403.20162, found 403.20114.

2-Benzyl-4-(benzyloxy)-3-ethyl-6,6-dimethyl-1,2,4-oxadiazinan-5-one (3an). White solid, yield: 27.3 mg, 77%; mp = 92.3–93.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47–7.45 (m, 2H), 7.40–7.38 (m, 3H), 7.33–7.30 (m, 5H), 5.00 (s, 2H), 4.23–4.21 (m, 1H), 3.99 (d, J = 13.2 Hz, 1H), 3.60 (d, J = 13.2 Hz, 1H), 2.06–2.09 (m, 1H), 1.80–1.75 (m, 1H), 1.29 (s, 3H), 1.27 (s, 3H), 1.06–1.02 (m, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 136.2, 135.1, 129.8, 129.4, 128.9, 128.5, 128.1, 127.5, 81.9, 81.4, 76.4, 57.4, 23.9, 23.5, 21.5 ppm; HRMS (ESI) calculated for $C_{21}H_{27}N_2O_3$ $[M + H]^+$: 355.20162, found 355.20074.

4-(Benzyloxy)-2,6,6-trimethyl-3-phenyl-1,2,4-oxadiazinan-5-one (3ao). White solid, yield: 30.3 mg, 93%; mp = 67.7–68.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.44–7.40 (m, 5H), 7.31–7.28 (m, 3H), 7.10 (d, J = 6.0 Hz, 2H), 5.00 (d, J = 9.6 Hz, 1H), 4.90 (s, 1H), 4.39 (d, J = 10.0 Hz, 1H), 2.35 (s, 3H), 1.71 (s, 3H), 1.51 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 134.8, 134.1, 129.8, 129.7, 129.1, 128.7, 128.6, 128.3, 87.6, 81.9, 77.1, 41.3, 24.1, 23.9 ppm; HRMS (ESI) calculated for $C_{19}H_{23}N_2O_3$ $[M + H]^+$: 327.17032, found 327.16949.

4-(Benzyloxy)-6,6-dimethyl-3-(naphthalen-1-yl)-2-phenyl-1,2,4-oxadiazinan-5-one (3ap). White solid, yield: 40.3 mg, 92%; mp = 143.8–144.6 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.83–7.80 (m, 1H), 7.78–7.74 (m, 2H), 7.65 (s, 1H), 7.52–7.49 (m, 2H), 7.45 (d, J = 8.4 Hz, 1H), 7.37–7.31 (m, 3H), 7.27 (d, J = 6.4 Hz, 2H), 7.18–7.14

(m, 2H), 6.96–6.93 (m, 1H), 6.87 (d, J = 8.0 Hz, 2H), 5.83 (s, 1H), 5.17 (d, J = 10.0 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 1.80 (s, 3H), 1.72 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.5, 145.6, 134.9, 133.7, 132.6, 131.2, 130.0, 129.1, 128.9, 128.7, 128.5, 128.2, 128.0, 127.7, 126.7, 126.3, 125.7, 123.8, 118.5, 83.6, 77.4, 24.1, 23.5 ppm; HRMS (ESI) calculated for $C_{28}H_{27}N_2O_3$ $[M + H]^+$: 439.20162, found 439.20071.

4-(Benzyloxy)-3-(furan-2-yl)-6,6-dimethyl-2-phenyl-1,2,4-oxadiazinan-5-one (3aq). White solid, yield: 37.3 mg, 99%; mp = 120.8–121.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.40–7.28 (m, 6H), 7.24 (t, J = 8.0 Hz, 2H), 7.00 (t, J = 7.2 Hz, 1H), 6.87 (d, J = 8.0 Hz, 2H), 6.30 (s, 2H), 5.75 (s, 1H), 5.18 (d, J = 10.0 Hz, 1H), 4.74 (d, J = 10.0 Hz, 1H), 1.67 (s, 3H), 1.66 (s, 3H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 147.8, 145.5, 143.0, 134.8, 129.8, 129.0, 128.7, 128.6, 123.5, 117.0, 111.0, 110.5, 83.5, 77.6, 23.8, 23.4 ppm; HRMS (ESI) calculated for $C_{22}H_{23}N_2O_4$ $[M + H]^+$: 379.16523, found 379.16406.

4-(Benzyloxy)-2,3-diphenyl-1-oxa-2,4-diazaspiro[5.5]undecan-5-one (3ca). White solid, yield: 39.4 mg, 92%; mp = 106.7–107.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.37–7.35 (m, 3H), 7.31–7.29 (m, 2H), 7.25 (s, 1H), 7.23–7.20 (m, 2H), 7.17 (s, 2H), 7.15–7.13 (m, 2H), 6.94–6.90 (m, 1H), 6.79 (d, J = 8.0 Hz, 2H), 5.56 (s, 1H), 5.14 (d, J = 10.0 Hz, 1H), 4.63 (d, J = 10.0 Hz, 1H), 2.36–2.33 (m, 1H), 2.18–2.16 (m, 2H), 1.87–1.86 (m, 1H), 1.70–1.68 (m, 2H), 1.60–1.56 (m, 2H), 1.47–1.42 (m, 1H), 1.40–1.32 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 146.0, 135.0, 133.6, 129.9, 129.2, 128.9, 128.8, 128.6, 128.5, 127.9, 123.3, 84.7, 83.9, 77.3, 32.7, 32.0, 30.0, 29.7, 25.0, 24.5, 22.0, 21.4, 21.2 ppm; HRMS (ESI) calculated for $C_{27}H_{29}N_2O_3$ $[M + H]^+$: 429.21727, found 429.21619.

4-(Benzyloxy)-2,3,6-triphenyl-1,2,4-oxadiazinan-5-one (3ea). Colorless oil, yield: 24.4 mg, 56%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.54–7.52 (m, 2H), 7.43–7.41 (m, 2H), 7.36–7.34 (m, 5H), 7.32–7.31 (m, 4H), 7.26–7.24 (m, 1H), 7.20–7.16 (m, 2H), 7.12–7.09 (m, 1H), 7.01–6.98 (m, 1H), 6.83–6.79 (m, 2H), 5.84 (d, J = 54.8 Hz, 1H), 5.60 (d, J = 41.6 Hz, 1H), 5.19–5.14 (m, 1H), 4.72 (d, J = 9.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.1, 165.5, 145.3, 144.9, 135.3, 134.9, 134.8, 134.0, 132.9, 130.0, 129.8, 129.6, 129.4, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.1, 125.3, 124.3, 120.5, 118.3, 85.2, 83.2, 83.1, 77.7 ppm; HRMS (ESI) calculated for $C_{28}H_{25}N_2O_3$ $[M + H]^+$: 437.18597, found 437.18463.

2-Benzyl-4-(benzyloxy)-3-phenyl-1-oxa-2,4-diazaspiro[5.5]-undecan-5-one (3cm). White solid, yield: 34.5 mg, 78%; mp = 76.4–77.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (s, 5H), 7.29–7.25 (m, 6H), 7.20–7.18 (m, 2H), 7.11 (d, J = 5.2 Hz, 2H), 5.06 (s, 1H), 4.98 (d, J = 10.0 Hz, 1H), 4.36 (d, J = 4.4 Hz, 1H), 3.58 (d, J = 11.6 Hz, 1H), 3.45 (d, J = 13.2 Hz, 1H), 2.20–2.16 (m, 1H), 1.89 (s, 2H), 1.73–1.71 (m, 1H), 1.42–1.35 (m, 3H), 1.26 (s, 1H), 1.12–1.09 (m, 2H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 136.5, 135.0, 134.4, 129.9, 129.8, 129.7, 129.4, 129.2, 128.8, 128.7, 128.6, 128.5, 128.3, 128.0, 127.5, 83.1, 82.8, 77.4, 77.0, 76.7, 57.5, 32.7, 29.7, 24.9, 24.5, 22.1, 21.5, 19.9 ppm; HRMS (ESI) calculated for $C_{28}H_{31}N_2O_3$ $[M + H]^+$: 443.23292, found 443.23169.

4-(Benzyloxy)-3-(2-methoxyphenyl)-2-phenyl-1-oxa-2,4-diazaspiro[5.5]undecan-5-one (3cg). White solid, yield: 30.7 mg, 67%; mp = 87.1–87.7 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.61–7.59 (m, 1H), 7.33–7.30 (m, 5H), 7.23–7.19 (m, 1H), 7.14–7.10 (m, 2H), 6.92–6.88 (m, 4H), 6.76 (d, J = 10.0 Hz, 1H), 6.40 (s, 1H), 5.13 (d, J = 10.0 Hz, 1H), 4.65 (d, J = 10.0 Hz, 1H), 3.47 (s, 3H), 2.20–2.16 (m, 2H), 1.83–1.74 (m, 1H), 1.70–1.67 (m, 3H), 1.63–1.54 (m, 2H), 1.49–1.46 (m, 1H), 1.42 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 157.8, 146.0, 135.0, 130.2, 129.8, 129.7, 128.7, 128.3, 128.0, 123.0, 122.4, 120.3, 117.6, 110.5, 84.5, 77.2, 55.1, 32.1, 29.9, 29.7, 27.0, 25.1, 21.4, 21.3 ppm; HRMS (ESI) calculated for $C_{28}H_{31}N_2O_4$ $[M + H]^+$: 459.22783, found 459.22702.

4-(Benzyloxy)-3-(2-chlorophenyl)-2-phenyl-1-oxa-2,4-diazaspiro-[5.5]undecan-5-one (3ch). White solid, yield: 39.7 mg, 86%; mp = 96.9–97.5 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.81 (d, J = 7.2 Hz, 1H), 7.32 (s, 5H), 7.23–7.17 (m, 3H), 7.13 (d, J = 8.0 Hz, 2H), 6.93 (d, J = 7.6 Hz, 3H), 6.39 (s, 1H), 5.10 (d, J = 10.0 Hz, 1H), 4.62 (d, J = 10.0 Hz, 1H), 2.18–2.16 (m, 2H), 1.87 (s, 1H), 1.72–1.68 (m, 3H), 1.63–1.57 (m, 2H), 1.50–1.42 (m, 1H), 1.40–1.33 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.3, 145.4, 134.9, 134.6, 131.9, 130.5, 130.3, 129.9, 129.3, 129.2, 128.8, 128.6, 128.5, 128.4, 126.8, 84.7, 77.4, 77.2, 77.0, 76.7, 32.7, 32.0, 30.1, 29.7, 25.0, 24.5, 22.1, 21.3, 21.2 ppm; HRMS (ESI) calculated for $C_{27}H_{28}ClN_2O_3$ $[M + H]^+$: 463.17830, found 463.17780.

4-(Benzyloxy)-3-(naphthalen-1-yl)-2-phenyl-1-oxa-2,4-diazaspiro[5.5]undecan-5-one (3cp). White solid, yield: 43.0 mg, 90%; mp = 123.5–124.0 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.77–7.75 (m, 1H), 7.73–7.71 (m, 1H), 7.69–7.67 (m, 1H), 7.56 (s, 1H), 7.45–7.43 (m, 2H), 7.36–7.30 (m, 4H), 7.26–7.24 (m, 2H), 7.12 (t, J = 8.4 Hz, 2H), 6.89 (t, J = 7.2 Hz, 1H), 6.83 (d, J = 8.0 Hz, 2H), 5.73 (s, 1H), 5.15 (d, J = 10.4 Hz, 1H), 4.61 (d, J = 10.4 Hz, 1H), 2.39–2.36 (m, 1H), 2.22 (s, 2H), 1.90–1.89 (m, 1H), 1.71–1.68 (m, 3H), 1.61–1.57 (m, 2H), 1.49–1.45 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.4, 145.9, 134.9, 134.8, 133.6, 132.6, 131.2, 130.0, 129.3, 129.0, 128.9, 128.7, 128.6, 128.5, 128.4, 128.2, 127.8, 127.6, 126.6, 126.2, 125.7, 123.8, 117.5, 84.8, 77.4, 32.7, 32.1, 30.0, 27.0, 25.0, 24.5, 22.1, 21.4, 21.3 ppm; HRMS (ESI) calculated for $C_{31}H_{31}N_2O_3$ $[M + H]^+$: 479.23292, found 479.23166.

4-(Benzyloxy)-3-(furan-2-yl)-2-phenyl-1-oxa-2,4-diazaspiro[5.5]-undecan-5-one (3cq). White solid, yield: 25.5 mg, 61%; mp = 77.5–78.2 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 6H), 7.26–7.20 (m, 2H), 6.97 (t, J = 7.2 Hz, 1H), 6.87–6.85 (m, 2H), 6.24 (d, J = 1.2 Hz, 2H), 5.65 (s, 1H), 5.16 (d, J = 10.4 Hz, 1H), 4.42 (d, J = 10.4 Hz, 1H), 2.35–2.32 (m, 1H), 2.17–2.12 (m, 1H), 2.07–2.04 (m, 1H), 1.83–1.81 (m, 1H), 1.72–1.65 (m, 3H), 1.64–1.57 (m, 2H), 1.51–1.47 (m, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ 169.9, 147.9, 145.9, 142.9, 134.8, 129.9, 129.3, 128.9, 128.7, 128.6, 128.5, 123.3, 116.7, 110.8, 110.4, 84.6, 77.6, 32.6, 31.9, 29.7, 25.0, 24.5, 22.0, 21.4, 21.2 ppm; HRMS (ESI) calculated for $C_{25}H_{27}N_2O_4$ $[M + H]^+$: 419.19653, found 419.19577.

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