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Bromo-lactamization of isoxazole *via* neighboring group participation: toward spiro-isoxazoline γ- and δ-lactams†

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Spiro-heterocycles containing natural products and synthetic analogues have a broader biomedicinal application due to their rigid 3D conformation and structural implications. In this context, constructing spiro-isoxazoline systems have continued our interest in natural products and synthetic units to investigate their novel biological activities. Herein, a bromo-lactamization mediated neighboring group participation approach has been utilized on various isoxazole-amides to construct an array of spiro-isoxazoline-lactams. The easy synthesis with diverse functionalization in the periphery of a novel 3D framework could be interesting for biomedical investigation.

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Introduction

The spirocyclic compounds are the essential building blocks in natural products and synthetic compounds, delivering a wide range of biological activities and diverse applications in organic synthesis.[1] The structural rigidity and three-dimensional feature of spiro-frameworks significantly impact ligand binding entropy, facilitating the spiro-unit to be an effective pharmacophore in drug discovery compared to two-dimensional aromatic compounds.[1a,2] Among a wide range of spirocyclic compounds, spiro-lactams have received much interest due to their structural novelty and diversity in drug discovery, emerging as a prominent class.[3] Herein, a few representative examples[3a,b,4] of heterocyclic, carbocyclic, and dimeric spiro-lactams have been presented that show significant biological properties (Fig. 1).

While the presence of β-, γ-, and δ-lactams are widely found with various spiro-carbocycles and -heterocycles,[3] the spiro-isoxazoline-lactams are very uncommon in natural or synthetic sources; consequently, its synthesis is highly desirable for biological intervention. In the past, several impressive protocols were explored using bromonium-ion-mediated cyclization to synthesize related spiro units. For example, d'Alcontres *et al.* reported[5] the synthesis of the spiro-5-isoxazoline system from an internal amide functionality where *O*-cyclization *via* a possible five-member bromo cyclization provided the desired compound; however, no trace of *N*-cyclization was reported (Scheme 1).

In 2015, Shi *et al.* reported an enantioselective bromo amino cyclization strategy for the synthesis of spiro system but oxazolidinones (Scheme 1).[6] For *N*-heterocyclic compounds, such as pyrrolidines and piperidines, haloaminocyclization of olefinic amines has been the topic of significant research.[7] However, halo-lactamization of an unactivated olefinic amide remained a formidable challenge because hard-*O* and soft-*N* nucleophiles compete with each other.[8] Despite continued success with halo-*N*-cyclization of olefinic urea, olefinic carbamate, and olefinic amide,[9] halo-*N*-lactamization of spiocyclic compounds is limited;[10] to our knowledge, no report on spiro-isoxazoline-lactams exists. As a result, the desire to understand and address the issues associated with spiro-lactamization of isoxazole drove these findings in reaction discovery.

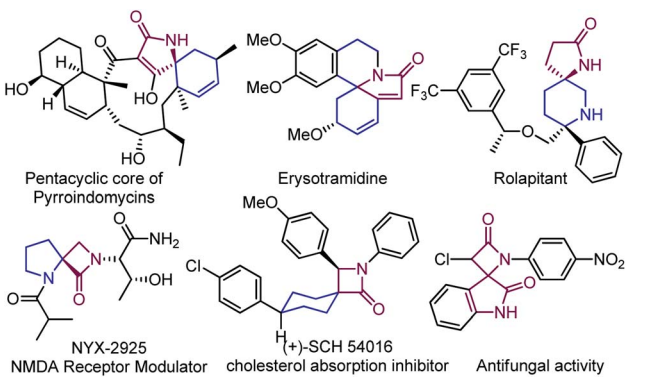

Fig. 1 Spiro-lactam containing natural products and synthetic compounds.

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† Electronic supplementary information (ESI) available: Copies of ^{1}H, and ^{13}C NMR for synthesized compounds have been included. See DOI: 10.1039/d2ra01070d

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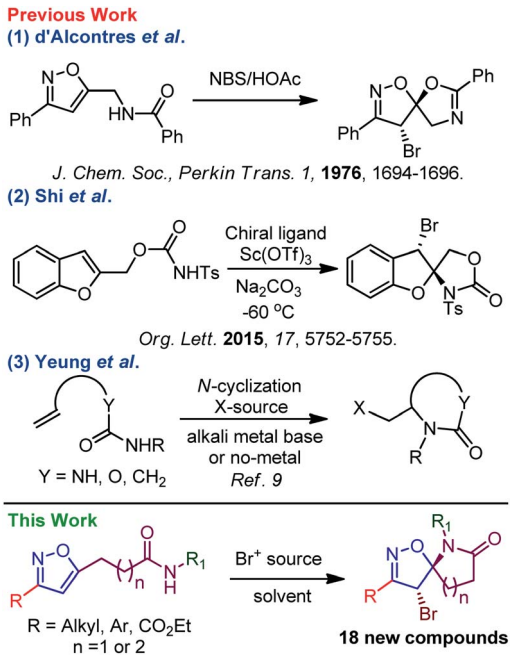
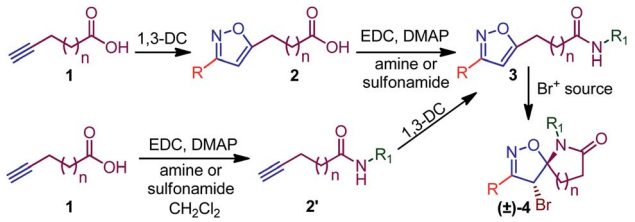


Scheme 1 Previous and current approach towards spiro-isoxazoline-lactams.



Scheme 2 General scheme for the synthesis of spiro-isoxazoline-lactam.

Based on our previous outcomes on spiroisoxaolines[10] and proceeding interest in developing novel pharmacophore, spiro-isoxazoline-lactam was our immediate target. We detailed an effective bromo-lactamization on an isoxazoles framework to get diverse spiro-isoxazoline-lactams in this context. It is essential to highlight that sulfonamide is a crucial functional group in many pharmaceutical drugs, widely known as "sulfa drugs", to exhibit antimicrobial activity.[11] Therefore, we postulated that a sulfonamide, *O*- and *N*-heteroatoms, and substituents in the periphery of the 3D scaffold could potentially induce the drug nature of the molecule. Moreover, the selectivity of bromonium-ion formation and subsequent nucleophilic attack *via* neighboring group participation will generate two adjacent stereocenters; however, a non-stereoselective mode of reactivity has been demonstrated to primarily obtain the desire spiro-lactams.

Results and discussion

The precursor isoxazole amide was synthesized following two methods. Our first effort was to transform a previously synthesized isoxazole acid **2** (ref. 10*a*,*c*) to its corresponding amid **3**, using a conventional method.[12] Conversely, an alkynoic acid **1** was first converted to its corresponding amide **2′**, which was later used as a precursor for 1,3-dipolar cycloaddition to obtain **3**. Subsequently, a suitable bromo-lactamization of isoxazole amide **3** provided spiro-isoxazoline-amide **4** as a single diastereomer. The isoxazole ring was constructed using *in situ* nitrile oxide-mediated 1,3-dipolar cycloaddition.[10a,c] As depicted in the scheme, an array of substituted isoxazoles was obtained using a range of nitrile oxide precursors.[10a,c] Moreover, we have chosen the first method as most of the isoxazole acids[10a,c] were available to us (Scheme 2).

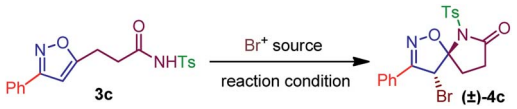
To validate the synthetic feasibility of isoxazoline-lactam (**4c**), our initial optimization for the bromo-lactamization was carried out with *N*-tosylamide (**3c**) as the test substrate and 1,3-Dibromo-5,5-Dimethylhydantoin (DBDMH) as the bromine source (Table 1). Other electrophilic brominating agents like *N*-bromosuccinimide (NBS), pyridinium perbromide (PTB), benzyltrimethylammonium bromide (BTMATB), and molecular bromine (Br_2) were subsequently screened during optimization (Table 1). To our delight, spiro-isoxazoline-lactam **4c** was isolated as a racemic mixture, albeit in 30% yield, when **3c** was treated with DBDMH in CH_2Cl_2 at 0 °C (entry 1, Table 1). The reaction rate significantly improved at room and reflux temperatures compared to entry 1, producing **4c** 85% and 80% yield. We speculate that a destabilization of bromonium ion formation at reflux temperature could possibly retard the reaction rate. The presence of K_2CO_3 as an additive was not surprising as compound **4c** was isolated in 75% yield in entry 4, Table 1. Other chlorinated solvents like $CHCl_3$ and $ClCH_2CH_2Cl$ were suitable for bromo-lactamization to generate **4c** in 84% and 82% yield. So far, we preferred to use the CH_2Cl_2 under the reaction condition.

To scan with other solvents, using toluene under reflux condition, provided 75% of lactam **4c**. While using ether as a solvent, 50% of conversion was realized. The presence of polar solvents like MeOH and DMF with K_2CO_3 were not surprised as we observed 40–45% transformation in entries 9 and 10. Keeping CH_2Cl_2 as the best solvent, we next examined other brominating agents. NBS efficiently delivered the lactamized product **4c** in 80% yield. However, PTB and BTMATB were not good brominating agents for our system as we isolated **4c** in 10–30% yield in entries 12 and 13. Moreover, molecular bromine was not successful either as we have isolated **4c** with 50% yield. Finally, BDMS (Bromodimethylsulfonium bromide) in CH_2Cl_2 at rt provided 65% of the desired product **4c** (Table 3, entry 15). Therefore, we decided to use DBDMH/CH_2Cl_2/rt as an optimized condition for our system to obtain the spiro-lactam satisfactorily.

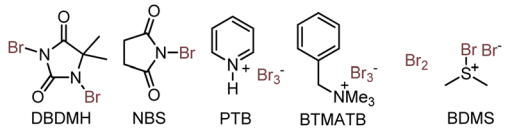
We next synthesized a list of isoxazole-amides using our previously synthesized acids (Table 2).

Having isoxazole-amides and optimized condition in hand, the scopes of the spiro-lactamization were investigated (Table 3). Initially, Ts-amide containing various substituted isoxazoles were examined. It was found that alkyl group on isoxazole ring **3**, like methyl (**3a**) and propyl (**3b**), were well tolerated, giving products **4a** and **4b** in 88% and 85% yield (Table 3); however,

Table 1 Optimization of bromo-lactamization[a]



Entryy	Br^+ Source	Additive	Solvent	Temp (°C)	Time (h)	Yield (%)[b]
1	DBDMH	—	CH_2Cl_2	0	24	30
2	DBDMH	—	CH_2Cl_2	rt	24	85
3[d]	DBDMH	—	CH_2Cl_2	50	6	80
4[c]	DBDMH	K_2CO_3	CH_2Cl_2	rt	24	75
5	DBDMH	—	$CHCl_3$	rt	24	84
6	DBDMH	—	$Cl(CH_2)_2Cl$	rt	24	82
7	DBDMH	—	Toluene	120	6	75
8	DBDMH	—	Ether	rt	24	50
9[c]	DBDMH	K_2CO_3	DME	rt	24	40
10[c]	DBDMH	K_2CO_3	MeOH	rt	24	45
11	NBS	—	CH_2Cl_2	rt	24	80
12	PTB	—	CH_2Cl_2	rt	24	30
13	BTMATB	—	CH_2Cl_2	rt	24	10
14	Br_2	—	CH_2Cl_2	rt	24	50
15	BDMS	—	CH_2Cl_2	rt	24	65



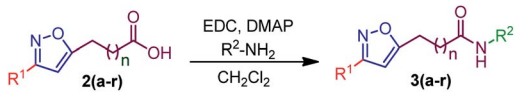
[a] The reactions were carried out with substrate **3c** (0.25 mmol) and Br^+-source (0.3 mmol) in solvent (2.0 mL) at rt for 24h. [b] Isolated yield based on **3c**. [c] K_2CO_3 (0.24 mmol) for entries **4**, **9**, and **10**. [d] Reaction carried out at reflux temperature for entries **3** and **7**.

a mono- and di-bromination on Ts-functionality were identified, probably due to the reactive methyl group.[13] Next various aromatic substituted isoxazoles were tested against optimized conditions, where phenyl substituted isoxazole-amide was found to produce the spirolactam **4c** in 85% yield. Furthermore, the electron-donating groups such as 4-Me and 4-OMe on phenyl ring were also competent, delivering the corresponding product **4d** and **4e** in 89% and 75% yield. However, over bromination was identified in **4e** due to an unavoidable α-bromination.[14] Halogen substituents (–F, –Cl, –Br, and –I) on phenyl ring were also compatible, leading to the formation of **4f–j** in 85–95% yield. Electron withdrawing groups such as $–CF_3$ and $–CO_2Et$ on the isoxazole ring were also competent, producing the corresponding **4k** and **4l** in 90% and 80% yield. We next investigated the effect of other amides over Ts-amide to evaluate the efficiency of bromo-lactamization. In this regard, while treated **3m**, **3n**, and **3o** DBDMH/CH_2Cl_2/rt, we isolated **4m**, **4n**, and **4o** in a 75–79% yield. Regardless of focusing on limited examples, it is worth mentioning that **4o** comprises a six-membered lactam ring, which also expands the scope toward a higher membered spiro-lactam. While investigating the reactivity of Cs-amide, we found –Me, –Pr, and –Ph containing isoxazoles were equally efficient in delivering the desired products **4p-4r** in 89–95% yield (Table 3). Among three types of amides, the PMB-amides were relatively less reactive. We reasoned that the less reactivity of PMB-amide could be due to the less acidic nature of PMB amide compared to Ts- and Cs-amides. Seemingly, we synthesized alkyl, aromatic, and ester substituted spiro-lactams. Regardless of investigating the synthetic scopes, we also envisaged that various functionality in the periphery of a 3D molecule could infuse biophysical properties in the molecules to deliver the drug-like nature.

While the alkyl functionality is responsible for introducing the hydrophobicity in the molecule, the aromatic substitution containing various functionalizations is responsible for the molecular electronic properties. Moreover, an ester functionality could be transformed into acid and amide derivatives to investigate different biological properties. Overall, this study displayed a possible route toward a novel 3D-molecular architect with a diverse peripheral functionality of biological interest.

A possible mechanistic pathway has been depicted in Scheme 3. The selective bromonium ion formation on isoxazoline double bond generates the intermediate **A**. Subsequently, a facile proton abstraction from the pendent amide by hydantoin anion produces *N*-nucleophile. As a result, the neighbouring nucleophile can attack the bromonium ion intermediate **A** in two possible pathways. Following the red-line pathway, the *N*-nucleophile can directly attack on the bromonium ion **A** to produce the desired lactam **C**. Alternatively, a blue-line-pathway could follow an oxonium-ion mediated opening of bromonium ion to generate an intermediated **B**, followed by favourable 5-*exo*-trig cyclization, leading to the development of spiro-lactam **C** (Scheme 3). Furthermore, based on our previous bromo-lactonization, we hypothesized that the

Table 2 Synthesis of isoxazole-lactams 3(a–r)[a]a



Entry	Acids (R^1)	Amines (R^2)	Time (h)	Yield (%)[b]
1	Me (**2a**)	4-Ts	24	78 (**3a**)
2	nPr (**2b**)	4-Ts	24	80 (**3b**)
3	Ph (**2c**)	4-Ts	18	82 (**3c**)
4	4-MeC_6H_4 (**2d**)	4-Ts	12	82 (**3d**)
5	4-$OMeC_6H_4$ (**2e**)	4-Ts	12	79 (**3e**)
6	4-FC_6H_4 (**2f**)	4-Ts	12	85 (**3f**)
7	4-ClC_6H_4 (**2g**)	4-Ts	12	88 (**3g**)
8	2,6-di-Cl-C_6H_3 (**2h**)	4-Ts	12	80 (**3h**)
9	4-BrC_6H_4 (**2i**)	4-Ts	12	86 (**3i**)
10	4-lC_6H_4 (**2j**)	4-Ts	12	79 (**3j**)
11	4-$CF_3C_6H_4$ (**2k**)	4-Ts	12	88 (**3k**)
12	CO_2Et (**2l**)	4-Ts	24	78 (**3l**)
13	Me (**2a**)	PMB	18	80 (**3m**)
14	Ph (**2c**)	PMB	18	85 (**3n**)
15[c]	Ph (**2o**)	PMB	18	87 (**3o**)
16	Me (**2a**)	4-Cs[d]	24	89 (**3p**)
17	nPr (**2b**)	4-Cs[d]	24	89 (**3q**)
18	Ph (**2c**)	4-Cs[d]	12	88 (**3r**)

[a] DMAP (1.4 equiv.) was added to a suspension of EDC (1.3 equiv.) in DCM (1 M). The corresponding carboxylic acid (1 equiv.) and amine (1.2 equiv.) were then added at 0 °C. The mixture was stirred at room temperature for (12–24) hours. [b] Isolated yield based on **2**. [c] $n = 2$. [d] (4-Cs = 4-$ClC_6H_4SO_2$).

Br-atom and N-atom are opposite, resulting in racemization for **4**.

Conclusion

In conclusion, we have developed a straightforward method for synthesizing a wide range of spiro-isoxazoline-lactams as a novel source of 3D molecules with diverse functionalization in the periphery. Along with alkyl and aryl functionalities, an ester group could be expanded to access a wide range of amides for biological investigation. Moreover, the successful incorporation of a couple of sulfonamides and amide functionalities provided a novel class of spiro-sulfa compounds to investigate. Knowing the diverse application of our previously synthesized spiro-compounds, we speculate that the desired spiro-isoxazoline-lactams could exhibit a seminal scope to exhibit novel biological activities.

Experimental section

(a)Materials and methods

Unless otherwise stated, all solvents and reagents were commercially obtained and used without prior purification. The reaction progress was monitored by analytical thin-layer chromatography using 60 Å silica gel medium and 250 μm layer thickness. Compounds were visualized by 254 nm light, basic $KMnO_4$ (40 g of K_2CO_3 + 6 g of $KMnO_4$ in 600 mL of water, then 5 mL of 10% NaOH added), and subsequent development either no or gentle heating. The crude products were purified using hexanes and ethyl acetate ratio as eluent by flash column chromatography over silica gel (60 Å, 0.060–0.200 mm).

(b) Instrumental information

All NMR spectra were measured at 25 °C in the indicated deuterated solvents. ^{1}H-NMR and ^{13}C-NMR spectra were recorded in 500 MHz and 125 MHz, respectively. The NMR data are reported as follows: proton and carbon chemical shifts (δ) in ppm using tetramethylsilane as an internal standard, coupling constants (J) in hertz (Hz), and resonance multiplicities (br = broad, s = singlet, d = doublet, t = triplet, and m = multiplet). The residual protic solvent of $CDCl_3$ (^{1}H, δ 7.26 ppm); (^{13}C, δ 77.0 ppm central resonance of the triplet), and C_3D_6O (^{1}H, δ 2.05 ppm; ^{13}C, δ 29.84 ppm) were used as the internal references in the ^{1}H and ^{13}C-NMR spectra. Melting points are uncorrected. Fourier transform infrared (FTIR) spectra were measured on neat NaCl. The absorptions are given in wavenumbers (cm^{-1}). High-resolution mass spectrometry (HRMS) analyses were performed based on positive electrospray ionization on a Bruker 12 Tesla APEX – Qe FTICR-MS with an Apollo II ion source. Either protonated molecular ions $[M + nH]^{n+}$ or sodium adducts $[M + Na]^+$ were used for empirical formula confirmation.

General procedure for nitrone preparation

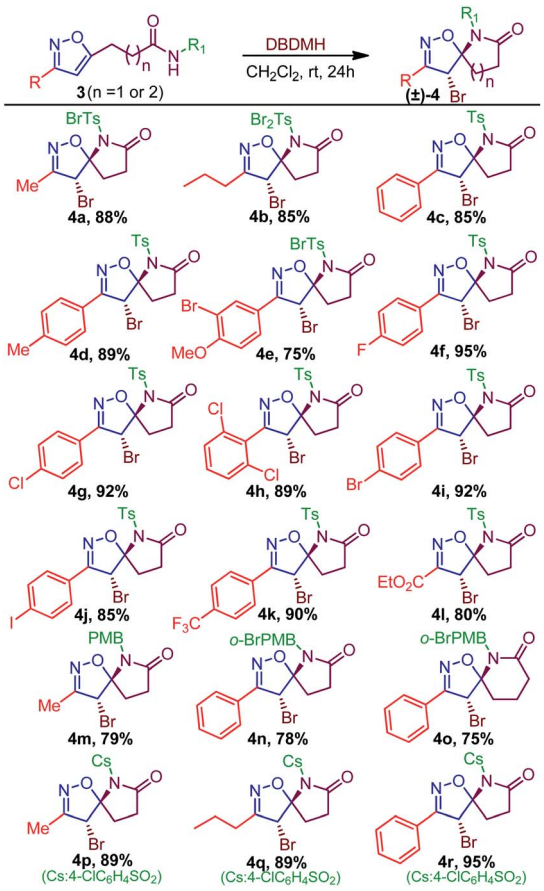
A mixture of hydroxylamine hydrochloride (1 mmol) and sodium bicarbonate (1.5 mmol), aldehyde (1 mmol), and anhydrous $MgSO_4$ (1.5 mmol) in either dichloromethane or ether was stirred till the consumption of the starting materials (confirmed by TLC analysis). Upon completion, the mixture was filtered. The filtrate was concentrated *in vacuo* to yield the crude product, chromatographer on silica gel using ethyl acetate/hexane mixture as an eluant to afford the pure nitrones.

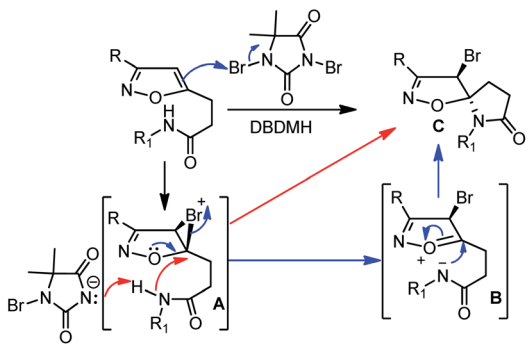
General procedure for the synthesis of isoxazole amide 3(a–r)

The isoxazole acid **2** (1.0 mmol, 1.0 equiv.) was added into a solution of 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide hydrochloride, EDCI (201.7 mg, 1.3 mmol, 1.3 equiv.), and DMAP (171.0 mg, 1.4 mmol, 1.4 equiv.) in CH_2Cl_2 (5 mL) at 0 °C. 4-Methoxybenzylamine ($PMBNH_2$) (164.6 mg) or p-toluene sulfonamide ($pTsNH_2$) (205.5 mg) or 4-chlorobenzenesulfonamide (4-$CsNH_2$) (230.0 mg) (1.2 mmol, 1.2 equiv.) was then added in one portion to the mixture. The mixture was allowed to warm slowly to room temperature and stirred for 24 h. Upon completion, the mixture was diluted with CH_2Cl_2 (10 mL) and washed with 1 N HCl solution (10 mL). The organic layer was removed, and the aqueous layer was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic layers were dried with $MgSO_4$ and concentrated under a vacuum. The crude residue was subjected to flash chromatography on silica gel (hexanes/ethyl acetate = 4/1–2/1) to deliver the product **3**.

3-(3-methylisoxazol-5-yl)-*N*-tosylpropanamide (3a). White solid, yield: 240.5 mg, 78% (hexane/ethyl acetate = 4/1); Mp: 178–180 °C; IR: ν_{max} 3129, 3056, 2954, 2925, 2857, 2798, 1715,

Table 3 Synthesis of spiro-isoxazoline-lactams (±)-4(a–r)





Scheme 3 Plausible mechanism for bromo-lactamization.

1613, 1469, 1814, 1339, 1172, 1128, 1089, 867, 812, 658, 551, 536 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.89 (d, J = 7.6 Hz, 2H), 7.42 (d, J = 7.7 Hz, 2H), 5.83 (s, 1H), 2.92 (t, J = 7.0 Hz, 2H), 2.74 (t, J = 6.9 Hz, 2H), 2.43 (s, 3H), 2.14 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 171.1, 169.3, 159.3, 144.5, 136.9, 129.3 (2C), 128.1 (2C), 101.6, 33.1, 20.9, 20.6, 10.3; HRMS (ESI) m/z: calcd for $(C_{14}H_{16}N_2O_4S)Na^+$: 331.0723; found 331.0721.

3-(3-Propylisoxazol-5-yl)-*N*-tosylpropanamide (3b). White solid, yield: 269.1 mg, 80% (hexane/ethyl acetate = 5/1); Mp: 150–152 °C; IR: ν_{max} 3354, 3255, 3117, 3072, 2958, 2925, 2871, 2856, 2798, 1712, 1601, 1465, 1417, 1378, 1342, 1288, 1168, 1132, 1090, 865, 808, 661, 553, 535 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.89 (d, J = 8.0 Hz, 2H), 7.41 (d, J = 7.8 Hz, 2H), 5.87 (s, 1H), 2.94 (t, J = 7.0 Hz, 2H), 2.75 (t, J = 7.1 Hz, 2H), 2.50 (t, J = 7.4 Hz, 2H), 2.43 (s, 3H), 1.59 (dd, J = 14.8, 7.3 Hz, 2H), 0.91 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 171.1, 169.3, 163.4, 144.5, 136.9, 129.3 (2C), 128.1 (2C), 100.6, 33.1, 27.5, 21.3, 20.9, 20.6, 13.1; HRMS (ESI) m/z: calcd for $(C_{16}H_{20}N_2O_4S)Na^+$: 337.1216; found 337.1215.

3-(3-Phenylisoxazol-5-yl)-*N*-tosylpropanamide (3c). White solid, yield: 303.7 mg, 82% (hexane/ethyl acetate = 4/1); IR: ν_{max} 3356, 3241, 3066, 3040, 2923, 1732, 1604, 1444, 1343, 1296, 1166, 1119, 1083, 859, 768, 666, 533, 557 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.89 (d, J = 8.4 Hz, 2H), 7.80–7.78 (m, 2H), 7.51–7.47 (m, 3H), 7.35 (d, J = 8.0 Hz, 2H), 6.48 (s, 1H), 3.05 (t, J = 7.2 Hz, 1H), 2.85 (t, J = 7.2 Hz, 1H), 2.35 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.3, 169.3, 162.0, 144.5, 136.8, 129.4 (2C), 129.3 (2C), 128.8, 127.9 (2C), 126.6 (2C), 126.1, 99.0, 33.0, 22.1, 20.5; HRMS (ESI) m/z: calcd for $(C_{19}H_{18}N_2O_4S)H^+$: 371.1060; found 371.1059.

3-(3-(*p*-tolyl)isoxazol-5-yl)-*N*-tosylpropanamide (3d). White solid, yield: 315.2 mg, 82% (hexane/ethyl acetate = 4/1); Mp: 162–164 °C; IR: ν_{max} 3356, 3257, 3235, 1725, 1713, 1605, 1435, 1300, 1159, 1087, 908, 864, 811, 544 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.89 (d, J = 7.5 Hz, 2H), 7.67 (d, J = 7.3 Hz, 2H), 7.34 (d, J = 7.5 Hz, 2H), 7.29 (d, J = 7.5 Hz, 2H), 6.44 (s, 1H), 3.03 (t, J = 6.9 Hz, 2H), 2.83 (t, J = 6.9 Hz, 2H), 2.37 (s, 3H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 172.2, 169.6, 161.9, 144.4, 139.9, 137.1, 129.6, 129.5, 129.4, 129.3, 128.0, 127.9, 126.6, 126.5, 126.4, 98.9, 33.2, 21.2 (2C), 20.5; HRMS (ESI) m/z: calcd for $(C_{20}H_{20}N_2O_4S)H^+$: 385.1216; found 385.1219.

3-(3-(4-methoxyphenyl)isoxazol-5-yl)-*N*-tosylpropanamide (3e). White solid, yield: 316.3 mg, 79% (hexane/ethyl acetate = 4/1); Mp: 96–98 °C; IR: ν_{max} 3102, 2954, 2922, 2854, 1716, 1613, 1528, 1457, 1435, 1349, 1297, 1169, 1124, 1086, 1026, 905, 852, 812, 681, 659, 599, 533 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.88 (d, J = 8.3 Hz, 2H), 7.73 (d, J = 9.0 Hz, 2H), 7.34 (d, J = 7.9 Hz, 2H), 7.04 (d, J = 8.9 Hz, 2H), 6.42 (s, 1H), 3.85 (s, 4H), 3.02 (t, J = 7.2 Hz, 2H), 2.81 (t, J = 7.2 Hz, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.1, 170.1, 161.6, 161.1, 144.1, 137.4, 129.2 (2C), 127.9 (4C), 121.8, 114.2 (2C), 98.8, 54.8, 33.3, 21.2, 20.6; HRMS (ESI) m/z: calcd for $(C_{20}H_{20}N_2O_5S)Na^+$: 423.0985; found 423.0985.

3-(3-(4-fluorophenyl)isoxazol-5-yl)-*N*-tosylpropanamide (3f). White solid, yield: 330.1 mg, 85% (hexane/ethyl acetate = 4/1); Mp: 164–166 °C; IR: ν_{max} 3354, 3260, 3091, 2926, 2858, 1717, 1594, 1526, 1437, 1347, 1222, 1174, 1127, 1086, 913, 849, 802, 657, 557 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.88 (d, J = 8.4 Hz, 2H), 7.85 (dd, J = 9.0, 5.4 Hz, 2H), 7.35 (d, J = 7.9 Hz, 2H), 7.27 (t, J = 8.9 Hz, 2H), 6.50 (s, 1H), 3.05 (t, J = 7.2 Hz, 2H), 2.83 (t, J = 7.2 Hz, 2H), 2.36 (s, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.7, 169.7, 163.6 (d, J = 247.6), 161.1, 144.2, 137.2, 129.3 (2C) 128,7 (t, J = 9.1 Hz), 128.0 (2C), 125.86 (d, J = 3.3 Hz), 115.8 (d, J = 21.8 Hz), 99.0 33.2, 21.2, 20.6; HRMS (ESI) m/z: calcd for $(C_{19}H_{17}FN_2O_4S)Na^+$: 411.0785; found 411.0783.

3-(3-(4-Chlorophenyl)isoxazol-5-yl)-*N*-tosylpropanamide (3g). White solid, yield: 356.3 mg, 88% (hexane/ethyl acetate = 4/1);

Mp 166–168 °C; IR: ν_{max} 3357, 3299, 3260, 2918, 1715, 1603, 1446, 1427, 1336, 1170, 1133, 1085, 861, 847, 815, 668, 544 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.88 (d, J = 8.4 Hz, 2H), 7.82 (d, J = 8.7 Hz, 2H), 7.54 (d, J = 8.7 Hz, 2H), 7.36 (d, J = 7.9 Hz, 2H), 6.52 (s, 1H), 3.06 (t, J = 7.2 Hz, 2H), 2.85 (t, J = 7.2 Hz, 2H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 172.7, 169.3, 161.1, 144.5, 136.9, 135.2, 129.3 (2C), 129.1 (2C), 128.2 (2C), 128.0 (2C), 126.03, 99.2, 33.0, 21.1, 20.6; HRMS (ESI) m/z: calcd for $(C_{19}H_{17}ClN_2O_4S)Na^+$: 427.0489; found 427.0487.

3-(3-(2,6-dichlorophenyl)isoxazol-5-yl)-*N*-tosylpropanamide (3h). White solid, yield: 351.4 mg, 80% (hexane/ethyl acetate = 4/1); Mp: 138–140 °C; IR: ν_{max} 3354, 3235, 2967, 2923, 1732, 1597, 1558, 1430, 1388, 1331, 1172, 1129, 1085, 863, 812, 786, 662, 538 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.91 (d, J = 8.4 Hz, 2H), 7.60–7.51 (m, 3H), 7.35 (d, J = 8.5 Hz, 2H), 6.11 (s, 1H), 3.11 (t, J = 7.1 Hz, 2H), 2.86 (t, J = 7.2 Hz, 2H), 2.37 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 172.3, 169.6, 158.6, 144.4, 137.1, 134.9 (2C), 131.7, 129.4 (2C), 128.2 (2C), 128.1 (2C), 126.1, 102.7, 33.2, 21.1, 20.7; HRMS (ESI) m/z: calcd for $(C_{19}H_{16}Cl_2N_2O_4S)H^+$: 439.0281; found 439.0286.

3-(3-(4-bromophenyl)isoxazol-5-yl)-*N*-tosylpropanamide (3i). White solid, yield: 386.4 mg, 86% (hexane/ethyl acetate = 4/1); Mp: 192–194 °C; IR: ν_{max} 3357, 3308, 3260, 2972, 2918, 1716, 1602, 1443, 1426, 1336, 1132, 1085, 1009, 815, 667, 544 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.88 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.3 Hz, 2H), 7.75 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.7 Hz, 2H), 6.52 (s, 1H), 3.05 (t, J = 7.2 Hz, 2H), 2.84 (t, J = 7.2 Hz, 2H), 2.40 (s, 3H), 2.36 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 172.8, 169.4, 161.1, 144.4, 136.9, 132.1 (2C), 129.3 (2C), 128.4 (2C), 128.1 (2C), 126.1, 123.5, 99.1, 33.1, 21.1, 20.5; HRMS (ESI) m/z: calcd for $(C_{19}H_{17}BrN_2O_4S)Na^+$: 470.9985; found 470.9985.

3-(3-(4-iodophenyl)isoxazol-5-yl)-*N*-tosylpropanamide (3j). White solid, yield: 392.1 mg, 79% (hexane/ethyl acetate = 4/1); Mp: 214–216 °C; IR: ν_{max} 3082, 2055, 2951, 2922, 2851, 1717, 1601, 1436, 1427, 1376, 1335, 1169, 1131, 1083, 1003, 861, 814, 669, 541 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.89 (t, J = 7.8 Hz, 4H), 7.60 (d, J = 8.5 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 6.52 (s, 1H), 3.05 (t, J = 7.2 Hz, 2H), 2.84 (t, J = 7.2 Hz, 2H), 2.36 (s, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ 172.8, 169.3, 161.3, 144.4, 138.2 (2C), 136.9, 129.3 (2C), 129.0, 128.4 (2C), 128.1 (2C), 99.1, 95.4, 33.0, 21.11 20.6; HRMS (ESI) m/z: calcd for $(C_{19}H_{17}IN_2O_4S)Na^+$: 518.9846; found 518.9848.

***N*-tosyl-3-(3-(4-(trifluoromethyl)phenyl)isoxazol-5-yl)propanamide (3k).** White solid, yield: 385.8 mg, 88% (hexane/ethyl acetate = 4/1); Mp: 148–150 °C; IR: ν_{max} 3357, 3257, 3229, 3109, 2967, 2923, 1714, 1599, 1460, 1331, 1160, 1118, 1085, 1019, 845, 811, 673, 536 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 8.03 (d, J = 8.1 Hz, 2H), 7.89 (d, J = 8.4 Hz, 2H), 7.85 (d, J = 8.1 Hz, 2H), 7.35 (d, J = 8.6 Hz, 2H), 6.62 (s, 1H), 3.08 (t, J = 7.4 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.34 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 173.2, 169.4, 160.9, 144.4, 137.0, 133.2, 130.9 (q, J = 32.5 Hz), 129.3 (2C), 128.0 (2C), 127.2 (d, J = 6.1 Hz, 2C), 126.0 (d, J = 13.9 Hz, 2C), 124.2 (q, J = 271.4 Hz), 99.4, 33.0, 21.1, 20.5; HRMS (ESI) m/z: calcd for $(C_{20}H_{17}F_3N_2O_4S)Na^+$: 461.0753; found 461.0749.

Ethyl-5-(3-(4-methylphenylsulfonamido)-3-oxopropyl)-isoxazole-3-carboxylate (3l). White solid, yield: 285.8 mg, 78% (hexane/ethyl acetate = 4/1); Mp: 106–108 °C; IR: ν_{max} 3171, 3138, 3073, 3028, 2984, 2928, 1729, 1690, 1592, 1456, 1253, 1139, 1086, 1018, 932, 843, 811, 787, 660, 550 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 7.88 (d, J = 8.4 Hz, 2H), 7.39 (d, J = 8.0 Hz, 2H), 6.45 (s, 1H), 4.37 (q, J = 7.1 Hz, 2H), 3.07 (t, J = 7.2 Hz, 2H), 2.87 (t, J = 7.2 Hz, 2H), 2.42 (s, 3H), 1.35 (t, J = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, CD_3COCD_3): δ 173.9, 169.3, 159.6, 156.3, 144.5, 136.8, 129.3 (2C), 128.1 (2C), 101.7, 61.5, 32.8, 21.0, 20.7, 13.5; HRMS (ESI) m/z: calcd for $(C_{16}H_{18}N_2O_6S)H^+$: 367.0958; found 367.0959.

***N*-(4-methoxybenzyl)-3-(3-methylisoxazol-5-yl)propenamide (3m).** Colorless oil, yield: 219.5 mg, 80% (hexane/ethyl acetate = 4/1); IR: ν_{max} 3299, 3119, 2920, 2838, 1637, 1606, 1547, 1511, 1437, 1416, 1231, 1173, 1031, 1001, 813, 524 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.14 (d, J = 8.2 Hz, 2H), 6.83 (d, J = 8.2 Hz, 2H), 5.94 (s, 1H), 4.26 (br s, 2H), 3.75 (s, 3H), 3.02 (t, J = 7.1 Hz, 2H), 2.57 (t, J = 7.1 Hz, 2H), 2.18 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD): δ 171.9, 159.9, 158.9 (2C), 130.4 (2C), 128.5, 113.4 (2C), 101.7, 54.2, 42.2, 32.9, 22.1, 9.8; HRMS (ESI) m/z: calcd for $(C_{15}H_{18}N_2O_3)H^+$: 275.1390; found 275.1389.

***N*-(4-methoxybenzyl)-3-(3-phenylisoxazol-5-yl)propanamide (3n).** Colorless oil, yield: 285.9 mg, 85% (hexane/ethyl acetate = 4/1); IR: ν_{max} 3297, 3109, 3064, 2949, 2913, 2839, 1640, 1552, 1513, 1470, 1435, 1255, 1174, 1032, 919, 812, 765, 689 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.76–7.75 (m, 2H), 7.44 (br m, 3H), 7.13 (d, J = 7.6 Hz, 2H), 6.78 (d, J = 7.6 Hz, 2H), 6.34 (s, 1H), 5.78 (s, 1H, NH), 4.36 (d, J = 4.9 Hz, 2H), 3.73 (s, 3H), 3.20 (t, J = 7.0 Hz, 2H), 2.64 (t, J = 7.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.1, 170.4, 162.5, 159.1, 130.0, 129.9, 129.1 (2C), 129.09, 128.9 (2C), 126.7 (2C), 114.1 (2C), 99.8, 55.2, 43.2, 34.0, 22.8; HRMS (ESI) m/z: calcd for $(C_{20}H_{20}N_2O_3)Na^+$: 359.1366; found 359.1365.

***N*-(4-methoxybenzyl)-4-(3-phenylisoxazol-5-yl)butanamide (3o).** Colorless oil, yield: 304.8 mg, 87% (hexane/ethyl acetate = 4/1); Mp: 141–143 °C; IR: ν_{max} 3294, 3125, 3064, 3007, 2950, 2930, 2834, 1638, 1550, 1513, 1469, 1410, 1032, 952, 911, 811, 765, 729, 692 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, J = 3.89 Hz, 2H), 7.43 (br m, 3H), 7.20 (d, J = 8.1 Hz, 2H), 6.85 (d, J = 8.1 Hz, 2H), 6.30 (s, 1H), 5.82 (s, 1H), 4.37 (d, J = 5.2 Hz, 2H), 3.79 (s, 3H), 2.86 (t, J = 7.1 Hz, 2H), 2.28 (t, J = 7.1 Hz, 2H), 2.14–2.09 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.1, 171.6, 162.4, 159.0, 130.3, 129.9, 129.2 (2C), 129.2, 128.8 (2C), 126.7 (2C), 114.1 (2C), 99.3, 55.3, 43.1, 35.2, 26.0, 23.4; HRMS (ESI) m/z: calcd for $(C_{21}H_{22}N_2O_3)Na^+$: 373.15226; found 373.15221.

***N*-((4-chlorophenyl)sulfonyl)-3-(3-methylisoxazol-5-yl)propanamide (3p).** Colorless oil, yield: 292.6 mg, 89% (hexane/ethyl acetate = 4/1); IR: ν_{max} 3330, 3237, 3135, 29,50, 2803, 1722, 1611, 1476, 1421, 1346, 1326, 1278, 1169, 1126, 1089, 871, 820, 753, 622 cm^{-1}; ^1H NMR (500 MHz, CD_3OD): δ 7.94 (d, J = 8.7 Hz, 2H), 7.57 (d, J = 8.8 Hz, 2H), 5.83 (s, 1H), 2.92 (t, J = 7.2 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 2.17 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3OD): δ 171.5, 161.2, 159.9, 142.4, 137.8, 129.4 (2C), 128.8 (2C), 101.6, 33.1, 20.9, 9.7; HRMS (ESI) m/z: calcd for $(C_{13}H_{13}ClN_2O_4S)H^+$: 329.0357; found 329.0356; HRMS (ESI) m/z: calcd for $(C_{13}H_{13}ClN_2O_4S)H^+$: 329.0357; found 329.0356.

***N*-((4-chlorophenyl)sulfonyl)-3-(3-propylisoxazol-5-yl)propanamide (3q).** Colorless oil, yield: 282.6 mg, 89% (hexane/ethyl

acetate = 4/1); IR: ν_{max} 3119, 3066, 2964, 2932, 2875, 2810, 1716, 1606, 1587, 1476, 1349, 1132, 1083, 863, 824, 753, 626, cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 8.01 (d, J = 8.3 Hz, 2H), 7.65 (d, J = 8.3 Hz, 2H), 5.88 (s, 1H), 2.95 (t, J = 6.8 Hz, 2H), 2.77 (t, J = 7.0 Hz, 2H), 2.51 (t, J = 7.4 Hz, 2H), 1.60 (dd, J = 14.6, 7.3 Hz, 2H), 0.92 (t, J = 7.3 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 171.1, 169.8, 163.4, 139.2, 138.7, 129.8 (2C), 128.9 (2C), 100.5, 33.2, 27.5, 21.3, 21.0, 13.1; HRMS (ESI) m/z: calcd for $(C_{15}H_{17}ClN_2O_4S)Na^+$: 379.0489; found 379.04916.

***N*-((4-chlorophenyl)sulfonyl)-3-(3-phenylisoxazol-5-yl)propanamide (3r).** Colorless oil, yield: 343.9 mg, 88% (hexane/ethyl acetate = 4/1); IR: ν_{max} 3329, 3231, 2961, 2924, 2855, 1717, 1598, 1579, 1462, 1351, 1168, 1120, 1081, 906, 852, 820, 752, 621 cm^{-1}; ^1H NMR (500 MHz, CD_3COCD_3): δ 8.02 (d, J = 8.2 Hz, 2H), 7.80 (d, J = 6.7 Hz, 2H), 7.61 (d, J = 8.2 Hz, 2H), 7.50–7.48 (m, 3H), 6.72 (br s, 1H, NH), 6.51 (s, 1H), 3.06 (t, J = 7.0 Hz, 2H), 2.87 (t, J = 7.0 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, CD_3COCD_3): δ 172.3, 169.6, 162.0, 139.3, 138.5, 129.9 (2C), 129.3, 129.0 (2C), 128.9 (2C), 127.9, 126.5 (2C), 99.1, 33.1, 21.1; HRMS (ESI) m/z: calcd for $(C_{18}H_{15}ClN_2O_4S)Na^+$: 413.0333; found 413.0331.

General procedure for the synthesis of isoxazole amide (±)-4(a–r). To a stirred solution of isoxazole amides **3** (0.5 mmol) in anhydrous CH_2Cl_2 (5 mL) was added DBDMH (171.6 mg, 0.6 mmol) at rt. The solution was stirred for 24 h before quenching with a saturated Na_2SO_3 aqueous solution (3 mL) and diluted with CH_2Cl_2 (10 mL). The organic layer was extracted with CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated. The residue was purified by silica gel column chromatography (hexane/ethyl acetate = 4/1, v/v) to afford the product **4**.

4-Bromo-3-methyl-6-tosyl-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4a). Colorless oil, yield: 102.1 mg, 88% (hexanes/ethyl acetate = 4/1). IR: ν_{max} 3031, 2957, 2924, 2853, 1751, 1718, 1406, 1364, 1240, 1174, 1115, 1085, 1059, 941, 874, 818, 765, 670, 613, 566, 539 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.00 (d, J = 8.5 Hz, 2H), 7.54 (d, J = 8.4 Hz, 2H), 5.87 (s, 1H), 4.48 (s, 2H), 2.86–2.80 (m, 1H), 2.61–2.44 (m, 3H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.1, 158.4, 144.4, 137.1, 129.5 (2C), 129.4 (2C), 103.5, 58.2, 33.4, 31.2, 29.5, 11.9; HRMS (ESI) m/z: calcd for $(C_{14}H_{14}Br_2N_2O_4S)Na^+$: 486.8933; found 486.8939.

4-Bromo-3-propyl-6-tosyl-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4b). Colorless oil, yield: 243.6 mg, 85% (hexanes/ethyl acetate = 4/1). IR: ν_{max} 3117, 3037, 2998, 2919, 2850, 1769, 1454, 1404, 1375, 1275, 1175, 1120, 1082, 904, 872, 750, 685, 638, 585 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 8.5 Hz, 2H), 7.73 (d, J = 8.5 Hz, 2H), 6.63 (s, 1H), 6.30 (s, 1H), 3.03–2.90 (m, 2H), 2.87–2.80 (m, 1H), 2.64–2.51 (m, 3H), 1.66–1.54 (m, 2H), 1.39 (t, J = 7.0 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.5, 162.3, 147.6, 138.2, 129.6 (2C), 127.2 (2C), 105.7, 57.6, 55.3, 42.8, 38.5, 33.9, 29.3, 12.1; HRMS (ESI) m/z: calcd for $(C_{16}H_{17}Br_3N_2O_4S)Na^+$: 592.8351; found 592.8358.

4-Bromo-3-phenyl-6-tosyl-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4c). White solid, yield: 202.2 mg, 90% (hexanes/ethyl acetate = 4/1). Mp: 84–86 °C; IR: ν_{max} 3021, 2967, 2918, 2850, 1739, 1365, 1229, 1216, 1085, 891, 673, 575 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.4 Hz, 2H), 7.86–7.83 (m, 2H), 7.51–7.50 (m, 3H), 7.31 (d, J = 8.0 Hz, 2H), 6.43 (s, 1H), 2.96–2.88 (m, 1H), 2.67–2.51 (m, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.1, 159.8, 145.8, 131.0, 129.5, 129.4 (2C), 129.0 (2C), 128.9 (2C), 127.6 (2C), 126.9, 104.5, 54.6, 33.6, 29.6, 21.7; HRMS (ESI) m/z: calcd for $(C_{19}H_{17}BrN_2O_4S)Na^+$: 470.9985; found 470.9985.

4-Bromo-3-(*p*-tolyl)-6-tosyl-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4d). Colorless oil, yield: 206.2 mg, 89% (hexanes/ethyl acetate = 4/1); IR: ν_{max} 3035, 2970, 2921, 2850, 1741, 1365, 1229, 1216, 1087, 890, 813, 672, 571, 528 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.88 (d, J = 8.4 Hz, 2H), 7.74 (d, J = 8.2 Hz, 2H), 7.30 (d, J = 7.3 Hz, 4H), 6.42 (s, 1H), 2.94–2.87 (m, 1H), 2.67–2.50 (m, 3H), 2.42 (s, 3H), 2.41 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.2, 159.8, 145.8, 141.5, 134.4, 129.7 (2C), 129.4 (2C), 129.0 (2C), 127.6 (2C), 124.0, 104.5, 54.8, 33.6, 29.6, 21.7, 21.6; HRMS (ESI) m/z: calcd for $(C_{20}H_{19}Br_2N_2O_4)Na^+$: 485.0141; found 485.0138.

4-Bromo-3-(4-methoxyphenyl)-6-tosyl-1-oxa-2,6-diazaspiro-[4.4]non-2-en-7-one (±)-(4e). Colorless oil, yield: 238.9 mg, 75% (hexanes/ethyl acetate = 4/1). IR: ν_{max} 3104, 2955, 2924, 2854, 1717, 1613, 1529, 1458, 1437, 1350, 1297, 1169, 1124, 1085, 1025, 905, 854, 812, 680, 660, 600, 530 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.97 (d, J = 8.0 Hz, 2H), 7.73 (d, J = 7.5 Hz, 1H), 7.75 (d, J = 8.1 Hz, 2H), 7.00 (d, J = 8.6 Hz, 1H), 6.33 (s, 1H), 4.47 (s, 2H), 3.97 (s, 3H), 2.94–2.98 (m, 1H), 2.69–2.53 (m, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 173.1, 158.5, 157.9, 144.5, 136.9, 132.4, 129.5 (2C), 129.4 (2C), 128.3, 127.6, 120.4, 111.8, 104.6, 56.4, 54.4, 33.5, 31.2, 29.5; HRMS (ESI): m/z calcd for $(C_{20}H_{17}Br_3N_2O_5S)Na^+$: 656.8300; found 656.8308.

4-Bromo-3-(4-fluorophenyl)-6-tosyl-1-oxa-2,6-diazaspiro-[4.4]non-2-en-7-one (±)-(4f). Colorless oil, yield: 222.0 mg, 95% (hexanes/ethyl acetate = 4/1). IR: ν_{max} 3026, 2967, 2922, 2851, 1744, 1602, 1512, 1364, 1229, 1158, 1050, 840, 671, 570 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 8.4 Hz, 2H), 7.84 (dd, J = 8.8, 5.2 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 7.19 (t, J = 8.6 Hz, 2H), 6.38 (s, 1H), 2.96–2.87 (m, 1H), 2.65–2.51 (m, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.2, 164.3 (d, J = 252.1 Hz), 158.9, 145.9, 134.3, 129.8 (d, J = 8.6 Hz, 2C), 129.5 (2C), 128.9 (2C), 123.2 (d, J = 3.4 Hz), 116.2 (d, J = 22.1 Hz, 2C), 104.6, 54.7, 33.5, 29.6, 21.8; HRMS (ESI) m/z: calcd for $(C_{19}H_{16}BrFN_2O_4S)Na^+$: 488.9890; found 488.9888.

4-Bromo-3-(4-chlorophenyl)-6-tosyl-1-oxa-2,6-diazaspiro-[4.4]non-2-en-7-one (±)-(4g). White solid, yield: 222.5 mg, 92% (hexanes/ethyl acetate = 4/1). Mp: 178–180 °C; IR: ν_{max} 3029, 3002, 2970, 2923, 2845, 1738, 1366, 1216, 1229, 901, 667, 544 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.87 (d, J = 8.2 Hz, 2H), 7.79 (d, J = 8.5 Hz, 2H), 7.47 (d, J = 8.4 Hz, 2H), 7.31 (d, J = 8.4 Hz, 2H), 6.39 (s, 1H), 2.91 (dt, J = 12.7, 9.4 Hz, 1H), 2.66–2.50 (m, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.1, 159.0, 145.9, 137.1, 134.3, 129.5 (2C), 129.3 (2C), 128.9 (2C), 128.9 (2C), 126.4, 104.7, 54.4, 33.5, 29.5, 21.8; HRMS (ESI) m/z: calcd for $(C_{19}H_{16}BrClN_2O_4S)Na^+$: 504.9595; found 504.9592.

4-Bromo-3-(2,6-dichlorophenyl)-6-tosyl-1-oxa-2,6-diazaspiro-[4.4]non-2-en-7-one (±)-(4h). White solid, yield: 230.6 mg, 89% (hexanes/ethyl acetate = 4/1). Mp: 206–208 °C; IR: ν_{max} 3030, 2997, 2921, 2853, 1746, 1430, 1376, 1290, 1235, 1180, 1167, 1898, 811, 784, 660, 550 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, J = 8.4 Hz, 2H), 7.46 (d, J = 1.0 Hz, 1H), 7.44 (s, 1H), 7.39–

7.36 (m, 1H), 7.34 (d, J = 8.1 Hz, 2H), 6.96 (s, 1H), 3.14–3.09 (m, 1H), 2.58–2.48 (m, 3H), 2.44 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.4, 155.6, 145.8, 144.6, 134.8, 131.8 (2C), 129.5 (2C), 129.4 (2C), 128.6 (2C), 126.2, 105.4, 55.8, 34.2, 29.3, 21.8; HRMS (ESI) m/z: calcd for $(C_{19}H_{15}BrCl_2N_2O_4S)Na^+$: 538.9205; found 538.9855.

4-Bromo-3-(4-bromophenyl)-6-tosyl-1-oxa-2,6-diazaspiro-[4.4]non-2-en-7-one (±)-(4i). White solid, yield: 243.0 mg, 92% (hexanes/ethyl acetate = 4/1). Mp: 198–200 °C; IR: ν_{max} 3091, 3059, 3004, 2921, 2853, 1736, 1592, 1489, 1367, 1245, 1179, 1164, 1087, 902, 812, 666, 609, 540 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 8.4 Hz, 2H), 7.71 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 7.31 (d, J = 8.1 Hz, 2H), 6.37 (s, 1H), 2.95–2.87 (m, 1H), 2.63–2.51 (m, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.0, 159.1, 145.9, 134.3, 132.3 (2C), 129.5 (2C), 129.1 (2C), 128.9 (2C), 125.8, 125.6, 104.6, 54.2, 33.5, 29.5, 21.8; HRMS (ESI) m/z: calcd for $(C_{19}H_{16}Br_2N_2O_4S)Na^+$: 548.9089; found 548.9087.

4-Bromo-3-(4-iodophenyl)-6-tosyl-1-oxa-2,6-diazaspiro-[4.4] non-2-en-7-one (±)-(4j). White solid, yield: 244.5 mg, 85% (hexanes/ethyl acetate = 4/1). Mp: 160–162 °C; IR: ν_{max} 3034, 2954, 2921, 2854, 1797, 1753, 1591, 1489, 1398, 1361, 1248, 1174, 1121, 1086, 1008, 894, 861, 812, 671, 607, 571 536 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.85 (t, J = 7.5 Hz, 3H), 7.71 (d, J = 8.6 Hz, 1H), 7.64 (d, J = 8.6 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.31 (d, J = 8.1 Hz, 2H), 6.37 (s, 1H), 2.93–2.87 (m, 1H), 2.66–2.51 (m, 3H), 2.42 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.0, 159.1, 145.9, 138.2 (2C), 134.3, 132.3, 129.5 (2C), 129.1 (2C), 128.9 (2C), 104.6, 97.7, 54.2, 33.5, 29.5, 21.8; HRMS (ESI) m/z: calcd for $(C_{19}H_{16}BrIN_2O_4S)Na^+$: 596.8951; found 596.8960.

4-Bromo-6-tosyl-3-(4-(trifluoromethyl)phenyl)-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4k). White solid, yield: 232.8 mg, 90% (hexanes/ethyl acetate = 4/1). Mp: 208–210 °C; IR: ν_{max} 3029, 2921, 2856, 1744, 1592, 1411, 1323, 1249, 1165, 1126, 1069, 943, 850, 813, 668, 552 cm^{-1}; ^1H NMR (50 0 MHz, $CDCl_3$): δ 7.97 (d, J = 8.1 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.76 (d, J = 8.3 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 6.42 (s, 1H), 2.98–2.90 (m, 1H), 2.64–2.55 (m, 3H), 2.43 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 172.9, 158.8, 146.0, 132.6 (d, J = 32.9 Hz), 130.4 (d, J = 1.3 Hz), 129.5 (2C), 128.9 (2C), 127.9 (2C), 125.8 (q, J = 3.7 Hz), 104.8, 54.0, 33.5, 29.5, 21.7; HRMS (ESI) m/z: calcd for $(C_{20}H_{16}BrF_3N_2O_4S)Na^+$: 538.9858; found 538.9857.

Ethyl-4-bromo-7-oxo-6-tosyl-1-oxa-2,6-diazaspiro-[4.4]non-2-ene-3-carboxylate (±)-(4l). Colorless semi solid, yield: 178.1 mg, 80% (hexanes/ethyl acetate = 4/1). IR: ν_{max} 3170, 3136, 3071, 3028, 2984, 2928, 1730, 1690, 1592, 1455, 1250, 1139, 1086, 1018, 932, 840, 812, 787, 660, 551 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.89 (d, J = 8.0 HZ, 2H), 7.33 (d, J = 8.0 Hz, 2H), 6.21 (s, 1H), 4.41 (br m, 2H), 2.44 (s, 3H), 2.34 (d, J = 14.1 Hz, 2H), 2.21 (t, J = 14.1 Hz, 1H), 1.81 (t, J = 13.6 Hz, 1H), 1.4 (t, J = 6.6 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 169.2, 158.6, 151.0, 145.4, 135.2, 129.4 (2C), 129.2 (2C), 109.8, 67.5, 63.1, 30.9, 30.3, 21.7, 13.9; HRMS (ESI) m/z: calcd for $(C_{16}H_{17}BrF_3N_2O_6S)Na^+$: 466.9883; found 466.9889.

4-Bromo-6-(4-methoxybenzyl)-3-methyl-1-oxa-2,6-diazaspiro-[4.4]non-2-en-7-one (±)-(4m). White solid, yield: 139.5 mg, 79% (hexanes/ethyl acetate = 4/1). Mp: 198–200 °C; IR: ν_{max} 3295, 3062, 2929, 2836, 1630, 1546, 1513, 1440, 1303, 1247, 1214, 1072, 1036, 818, 751 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.16 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.5 Hz, 2H), 5.85 (s, 1H), 4.34 (d, J = 5.6 Hz, 2H), 3.78 (s, 3H), 3.11 (t, J = 7.6 Hz, 2H), 2.60 (dd, J = 16.3, 8.3 Hz 2H), 2.23 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.1, 168.0, 159.5, 129.2 (2C), 128.2, 114.1 (2C), 92.7, 55.3, 43.2, 42.6, 32.7, 21.8, 10.6; HRMS (ESI) m/z: calcd for $(C_{15}H_{17}BrN_2O_3)H^+$: 353.0495; found 353.0495.

4-Bromo-6-(3-bromo-4-methoxybenzyl)-3-phenyl-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4n). White solid, yield: 192.7 mg, 78% (hexanes/ethyl acetate = 4/1). Mp: 100–102 °C; IR: ν_{max} 3307, 3066, 3009, 2929, 2838, 1669, 1541, 1497, 1440, 1398, 1279, 1258, 1136, 1054, 1021, 923, 811, 769, 695, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.82 (d, J = 4.9 Hz, 2H), 7.49–7.44 (m, 4H), 7.15 (d, J = 8.3 Hz, 1H), 6.79 (d, J = 8.3 Hz, 1H), 5.93 (s, 1H), 4.36 (d, J = 5.2 Hz, 2H), 3.83 (s, 3H), 3.23 (t, J = 7.3 Hz, 2H), 2.69 (d, J = 7.3 Hz, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 170.2, 160.5, 155.3, 132.7, 131.6, 130.2, 128.7 (2C), 128.1 (2C), 128.0, 127.7, 112.0, 111.7, 91.0, 56.2, 42.6 (2C), 32.7, 22.0; HRMS (ESI) m/z: calcd for $(C_{20}H_{18}Br_2N_2O_3)Na^+$: 514.95764; found 514.9583.

4-Bromo-6-(3-bromo-4-methoxybenzyl)-3-phenyl-1-oxa-2,6-diazaspiro[4.5]dec-2-en-7-one (±)-(4o). White solid, yield: 161.0 mg, 75% (hexanes/ethyl acetate = 4/1). Mp: 96–98 °C; IR: ν_{max} 3310, 3066, 3008, 2929, 2851, 1731, 1667, 1497, 1405, 1258, 1153, 1055, 1021, 912, 810, 769, 695, 667 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.83–7.78 (m, 2H), 7.49–7.44 (m, 4H), 7.20 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 8.2 Hz, 1H), 5.81 (s, 1H), 4.36 (d, J = 5.3 Hz, 2H), 3.88 (s, 3H), 2.93 (t, J = 6.9 Hz, 2H), 2.30 (t, J = 6.9 Hz, 2H), 2.18–2.13 (m 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 171.5, 160.4, 155.3, 132.8 (2C), 131.8, 130.2 (2C), 128.7 (2C), 128.1 (2C), 111.9, 101.7, 90.9, 56.3, 42.6 (2C), 35.1, 25.2, 22.7; HRMS (ESI) m/z: calcd for $(C_{21}H_{20}Br_2N_2O_3)Na^+$: 528.9733; found 528.9741.

4-Bromo-6-((4-chlorophenyl)sulfonyl)-3-methyl-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4p). White solid, yield: 181.4 mg, 89% (hexanes/ethyl acetate = 4/1). Mp: 150–152 °C; IR: ν_{max} 3018, 2918, 2849, 1739, 1574, 1475, 1367, 1241, 1187, 1084, 872, 755, 622 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 8.9 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H), 5.85 (s, 1H), 2.86–2.80 (m, 1H), 2.60–2.44 (m, 3H), 2.27 (s, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.1, 158.4, 141.4, 135.8, 130.5 (2C), 129.2 (2C), 103.6, 58.1, 33.4, 29.5, 11.9; HRMS (ESI) m/z: calcd for $(C_{13}H_{12}BrClN_2O_4S)Na^+$: 428.9282; found 428.9281.

4-Bromo-6-((4-chlorophenyl)sulfonyl)-3-propyl-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4q). Colorless oil, yield: 193.9 mg, 89% (hexanes/ethyl acetate = 4/1). IR: ν_{max} 3092, 2961, 2927, 2873, 2854, 1756, 1585, 1477, 1370, 1248, 1175, 1084, 875, 756, 626 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.97 (d, J = 8.8 Hz, 2H), 7.50 (d, J = 8.9 Hz, 2H), 5.91 (s, 1H), 2.88–2.80 (m, 1H), 2.63–2.58 (m, 1H), 2.57–2.55 (m, 1H), 2.53–2.49 (m, 2H), 2.44–2.41 (m, 1H), 1.84–1.77 (m, 2H), 1.08 (t, J = 7.4 Hz, 3H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.1, 161.2, 141.3, 135.8, 130.5 (2C), 129.2 (2C), 103.4, 57.8, 33.7, 29.5, 28.7, 19.0, 14.0; HRMS (ESI) m/z: calcd for $(C_{15}H_{16}BrClN_2O_4S)H^+$: 434.9775; found 434.9773.

4-Bromo-6-((4-chlorophenyl)sulfonyl)-3-phenyl-1-oxa-2,6-diazaspiro[4.4]non-2-en-7-one (±)-(4r). White solid, yield:

223.1 mg, 95% (hexanes/ethyl acetate = 4/1). Mp: 92–94 °C; IR: ν_{max} 329, 3235, 2969, 2923, 2847, 1737, 1570, 1356, 1326, 1216, 1149, 1087, 821, 754, 625, 528 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.86 (d, J = 8.5 Hz, 2H), 7.78 (d, J = 6.1 Hz, 2H), 7.50–7.26 (m, 5H), 5.33 (s, 1H), 2.98–2.86 (m, 2H), 2.74–2.89 (m, 2H); $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$): δ 173.7, 158.9, 140.3, 139.3, 131.5, 129.4 (2C), 129.1 (2C), 127.9 (2C), 127.4 (2C), 126.0, 114.5, 50.0, 28.9, 28.46; HRMS (ESI) m/z: calcd for $(C_{18}H_{14}BrClN_2O_4S)Na^+$: 490.9438; found 490.9437.

Conflicts of interest

There are no conflicts to declare.

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