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ONE-POT REGIOSELECTIVE SYNTHESIS OF DIAZASPIRO[5.5]UNDECANE-1,5-DIONE-9-THIONE DERIVATIVES CATALYZED BY REUSABLE 1-METHYLIMIDAZOLIUM TRIFLUOROMETHYLSULFONATE UNDER SOLVENT-FREE CONDITIONS

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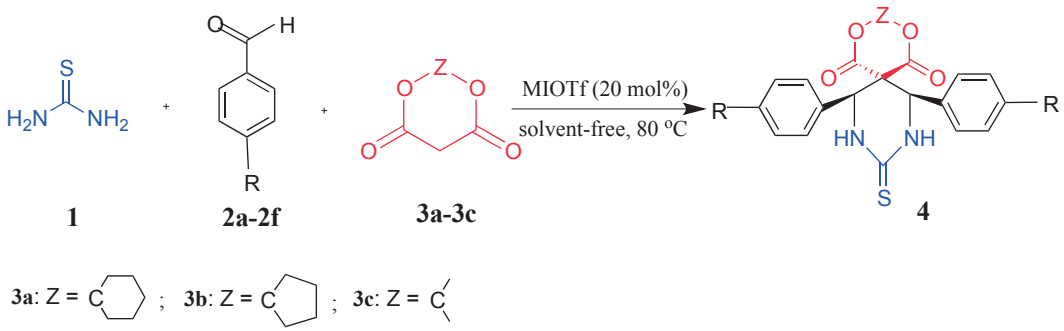
Abstract — A green and environmentally benign Biginelli-like synthesis of 2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione derivatives by one-pot three-component reaction of aromatic aldehydes with thiourea and 1,3-dioxane-4,6-dione catalyzed by reusable 1-methylimidazolium trifluoromethylsulfonate under solvent-free conditions is described.

Diazaspiro[5.5]undecane-1,5-dione-9-thione and its derivatives play an important role in synthetic organic chemistry and chemistry of natural products due to a wide range of their biological and pharmacological properties,[1,2] including antiviral, antitumor, antihypertensive, hypertensive, anti-HIV, narcotic and analgesic.[3-6] In addition, they are also spiro heterocyclic units in several bioactive natural products.[7-9] Therefore, the preparation of diazaspiro[5.5]undecane-1,5-dione-9-thione derivatives is of much current importance.

Numerous procedures for the Biginelli-like synthesis of 2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5,9-trione have been reported in the literature. These involve the use of various Brønsted acids or Lewis acids such as cellulosesulfuric acid,[10] $H_7P_2W_{18}VO_{62}$,[11] *p*-toluenesulfonic acid,[12] $H_3PW_{12}O_{40}$,[13] iodine,[14,15] TMSCl,[16,17] $SnCl_2$,[18] $NiCl_2$,[19] NBS/AIBN,[20] and boric acid.[21] Many other methods for preparing these compounds have been used, including microwave[22] and ultrasound irradiation.[11] However, many of these methodologies have not been entirely satisfactory, suffering drawbacks from low yields, long reaction

times, high catalyst loading, environmentally unfavorable solvents, or tedious work-up. Thus, an efficient, and environmentally friendly method using economical catalyst is actively desirable.

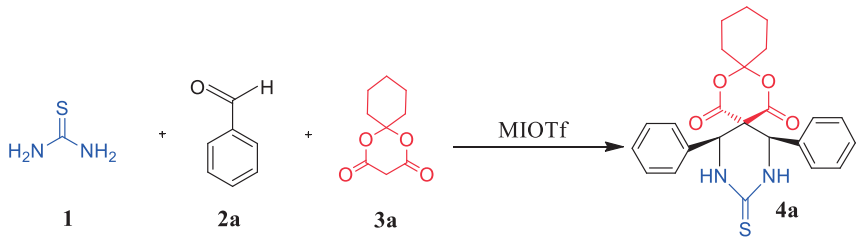
In order to overcome the above mentioned drawbacks and to support the concept of sustainable chemistry. Herein, we would report 1-methylimidazolium trifluoromethylsulfonate (MIOTf) as an e ffective and reusable catalyst for the synthesis of diazaspiro[5.5]undecane-1,5-dione-9-thione deriva tives via one-pot three-component reaction of aromatic aldehydes with thiourea and 1,3-dioxane-4,6-dione under solvent-free conditions (Scheme 1).



Scheme 1. Synthesis of **4**

For optimization of conditions, the reaction of benzaldehyde (**2a**), thiourea (**1**) and 2,2-pentylidene-1,3-dioxane-4,6-dione (**3a**) was chosen as a model reaction. In our initial screening experiments, the effects of solvents were examined. Different solvents including glycerol, polyethylene glycol 400, DMF, water, ethanol, ethyl acetate and MIOTf were used (Table 1, entries 1-7). Results show that the yield reached to 63% effectively under neat conditions (Table 1, entry 11). After screening the catalyst dosage, it was found that the best yield was obtained in the presence of 20 mol% MIOTf (Table 1, entry 8). The optimum reaction time and reaction temperature were also found respectively. The best results was obtained when the reaction was conducted at 80 °C, for 4 h, in the presence of 20 mol% MIOTf in neat conditions (Table 1, Entry 8).

Table 1. Optimization of reaction conditions for the synthesis of **4a**[a]



Entry	Solvent	Catalyst amounts(mol%)	Temp.(℃)	Time(h)	Yield (%)[b]
1	glycerol	0	80	6	<5
2	polyethylene glycol 400	0	80	6	<5
3	H_2O	0	80	6	<5

4	DMF	0	80	6	22
5	EtOH	0	reflux	6	35
6	EtOAC	0	reflux	6	41
7	none	MIOTf(100)	80	6	56
8	none	MIOTf(20)	80	4	84
9	none	CF_3SO_3H(20)	80	4	60
10	none	MIOTf(15)	80	5	72
11	none	MIOTf(0)	80	4	63
12	none	MIOTf(25)	80	4	84
13	none	MIOTf(20)	70	4	80
14	none	MIOTf(20)	90	4	83

[a]Reaction conditions:benzaldehyde (10 mmol); thiourea (5 mmol); 2,2-pentylidene-1,3-dioxane-4,6-dione (5 mmol) in 20 mL solvent or solvent-free. [b]Isolated yield.

The ^{1}H NMR spectrum of compound **4a** exhibited one single sharp line readily recognized as arising from two CH protons (δ_H 5.31 ppm). The phenyl moieties gave rise to multiplets in the aromatic region of the spectrum (δ_H 7.17-7.38 ppm). A broad singlet (δ_H 8.89 ppm) was observed for the two NH groups. The ^{13}C NMR spectrum of **4a** showed 13 distinct resonances in agreement with the σ symmetric structure. The σ symmetric stereoisomer is confirmed by the observation of three different signals for three carbonyl groups at δ 160.32, 165.89 and 178.03 ppm. Furthermore, compound **4a** was also characterized by X-ray crystallography as showed in Figure 1.

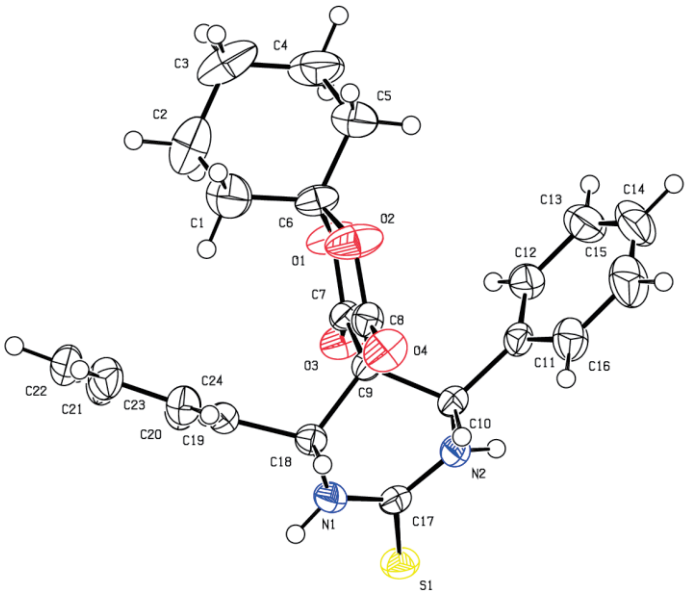
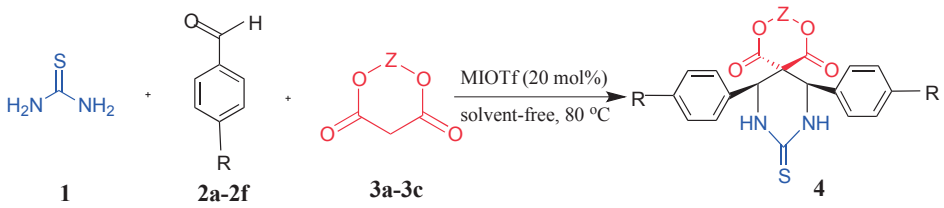


Figure 1. X-Ray crystal structure of **4a**

To explore the scope and limitations of this reaction further, we have extended it to various *para*-substituted benzaldehydes in the presence of 2,2-pentylidene-1,3-dioxane-4,6-dione (**3a**), 2,2-butylidene-1,3-dioxane-4,6-dione (**3b**) or 2,2-dimethyl-1,3-dioxane-4,6-dione (**3c**) (Table 2). It was found that a wide array of electronically diverse aromatic aldehydes **2a-2f** was tolerant to produce **4a-4p** in good to high yields.

Table 2. MIOTf-catalyzed synthesis of **4**[a]



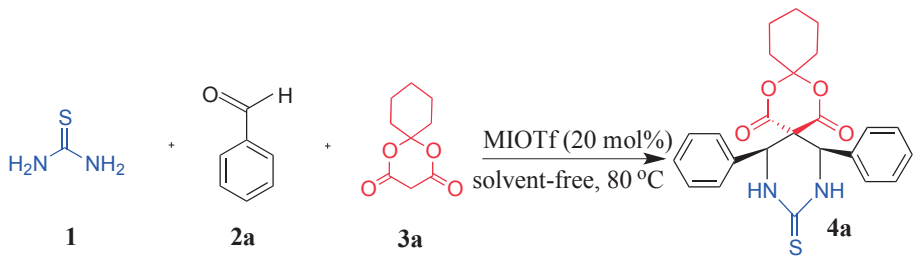
1 **2a-2f** **3a-3c** **4**

Entry	O-Z-O	R	Time(h)	Product	yields (%)[b]
1	3a	**2a**(R=H)	4	**4a**	84
2	3a	**2b**(R=4-F)	3	**4b**	78
3	3a	**2c**(R=4-Cl)	3	**4c**	81
4	3a	**2d**(R=4-Me)	5	**4d**	78
5	3a	**2e**(R=4-NO_2)	3	**4e**	80
6	3a	**2f**(R=4-MeO)	6	**4f**	72
7	3b	**2a**(R=H)	4	**4g**	82
8	3b	**2b**(R=4-F)	4	**4h**	75
9	3b	**2c**(R=4-Cl)	4	**4i**	76
10	3b	**2d**(R=4-Me)	6	**4j**	76
11	3c	**2a**(R=H)	5	**4k**	86
12	3c	**2b**(R=4-F)	3	**4l**	81
13	3c	**2c**(R=4-Cl)	4	**4m**	83
14	3c	**2d**(R=4-Me)	6	**4n**	79
15	3c	**2e**(R=4-NO_2)	3	**4o**	76
16	3c	**2f**(R=4-MeO)	6	**4p**	70

[a] Reaction conditions: aromatic aldehydes (**2a-2f**, 10 mmol); thiourea (5 mmol); 1,3-dioxane-4,6-diones (5 mmol); MIOTf (20 mol%); temperature 80 °C. [b] Isolated yield.

To test the reusability of the MIOTf (Table 3), the reaction mixture was treated with ethyl acetate. The filtrate consisting the acidic ionic liquid, was recovered after removal of ethyl acetate under reduced pressure and was reused for the next run under the same conditions. The catalyst was reused five times with the yields of 84%, 84%, 82%, 78% and 75%, respectively.

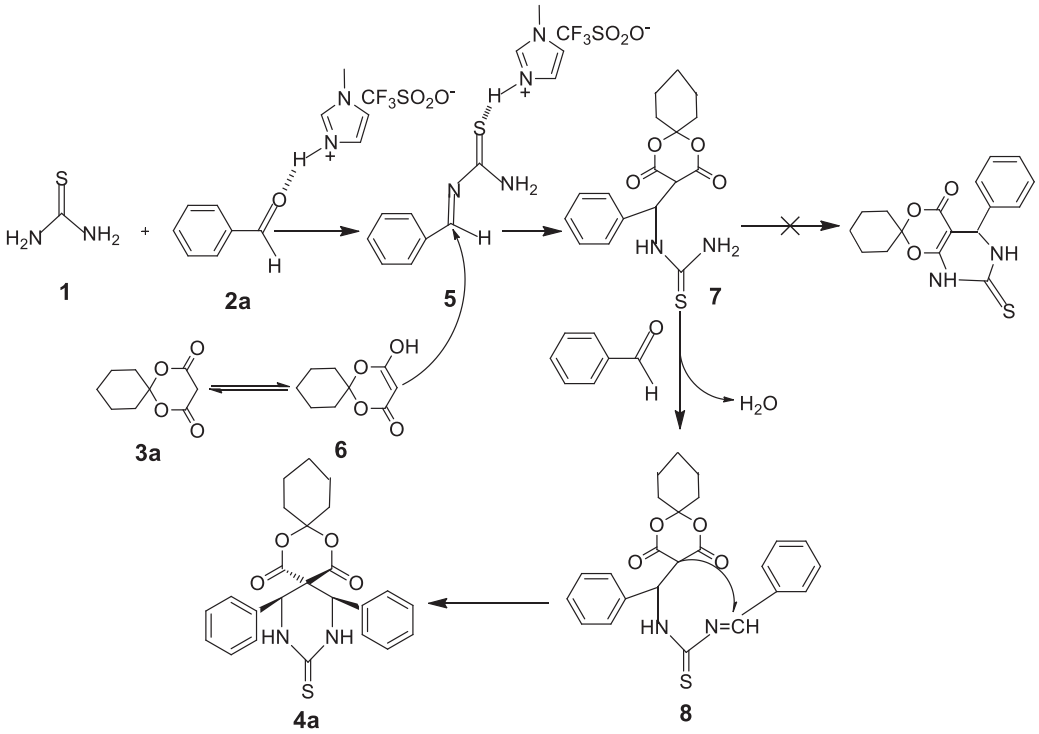
Table 3. Recycling experiments



1 **2a** **3a** **4a**

Times	1st run	2st run	3st run	4st run	5st run
Yield(%)	84	84	82	78	75

From the above results and literatures,[6,23] a reasonable mechanism for one-pot, three-component synthesis of 3,3-pentylidene-(7*S*, 11*R*)-diphenyl-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione **4a** is depicted in Scheme 2. Firstly, the reaction of benzaldehyde and thiourea would easily form the intermediate *N*-acylimine **5**, followed by a Michael-type addition reacting with **6** to give the open chain ureide **7**. Subsequently, intermediate **7** involved condensation of benzaldehyde to form intermediate **8** and ultimately cyclized to the spiro-heterocyclic compound **4a**.



Scheme 2. Proposed mechanism for the synthesis of **4a**

EXPERIMENTAL

All chemicals were purchased from Aladdin, Aldrich and Fluka Chemical Companies and without further purification. Melting points were measured on XT-4 digital micro melting point apparatus and are uncorrected. IR spectra were taken on a Nicolet-360 FT-IR spectrometer by incorporating samples in KBr disks. ^{1}H NMR spectra were recorded on a BRUKER AVANCE 400 MHz spectrometer using DMSO-d_6 as the solvent and TMS as the internal standard.^{13}C NMR data were collected on a BRUKER AVANCE 100 MHz instrument with DMSO-d_6 as the solvent and TMS as the internal standard. The analytical MS of the compounds was performed on Agilent LC-MSD Trap VL Apparatus.

Preparation of 1-methylimidazolium trifluoromethylsulfonate (MIOTF),[24]

A solution of trifluoromethanesulfonic acid (27.2 mL, 200.0 mmol) in CH_2Cl_2 (20 mL) was added to *N*-methylimidazole (16.0 mL, 200.0 mmol) in CH_2Cl_2 (20 mL) solution at 0-5 ℃. Then the mixture was stired at room temperature for 30 min. The precipitate was filtered under suction, washed with 2-methoxy-2-methylpropane (3×10 mL) to remove non-ionic residues and dried under vacuum.

Physical and spectroscopic data of 1-methylimidazolium trifluoromethylsulfonate (MIOTf): colorless crystal; ^{1}H NMR(DMSO-d_6, 400 MHz): δ 3.86 (s, 3 H, CH_3), 7.66-7.70 (m, 2 H), 9.04 (s, 1 H), 14.15 (s, 1 H); ^{13}C NMR (DMSO-d_6, 100 MHz) : δ 35.88, 119.53, 120.19, 122.74, 123.61, 136.26.

General procedure of the preparation of products 4

3,3-Pentylidene-(7*S*,11*R*)-diphenyl-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4a): To a 50 mL tube equiped with a stirring bar were added thiourea (**1**, 5 mmol), 2,2-pentylidene-1,3-dioxane-4,6-dione (**3a**, 5 mmol), aromatic aldehyde (**2a-2f**, 10 mmol) and 1-methylimidazolium trifluoromethylsulfonate (MIOTf) 20 mol%. The vessel was then sealed with a screw cap and at 80 ºC for 4.0 h. Upon completion of the reaction, as confirmed by thin-layer chromatography (petroleum ether/EtOAC 2:1), the reaction mixture was treated with EtOAc. The filtrate consisting the acidic ionic liquid, was recovered after removal of EtOAc under reduced pressure and was reused for subsequent reactions. The crude solid product was filtered, then washed with water and purified by recrytallization from EtOAc to afford the pure product **4a**: White solid; mp 210-212 ℃. IR (KBr, cm^{-1}): ν 3162, 3063, 1772, 1741, 1653,1204 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.45 (s, 4 H), 1.07 (s, 6 H), 5.31 (s, 2 H), 7.17-7.38 (m, 10 H), 8.89 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.88, 23.26, 37.01, 57.54 (C_{spiro}), 62.11, 106.37, 128.33, 129.89, 134.762, 160.32, 165.89, 178.03; ESI-MS *m*/*z*: 437.2 [M+H]$^{+}$.

3,3-Pentylidene-(7*S*,11*R*)-bis(4-flurophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4b): White solid; mp 216-218 ℃. IR (KBr, cm^{-1}): ν 3208, 3072, 1768, 1733, 1683,1229 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.56 (s, 4 H), 1.13 (s, 6 H), 5.34 (s, 2 H), 7.19-7.28 (m, 8 H), 8.98 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.87, 23.20, 37.18, 57.51 (C_{spiro}), 61.39, 106.48, 115.95, 116.17, 130.58, 130.86, 130.91, 130.94, 160.45, 161.88, 164.33, 165.83, 177.98; ESI-MS *m*/*z*: 473.1 [M+H]$^{+}$.

3,3-Pentylidene-(7*S*,11*R*)-bis(4-chlorophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4c) : White solid; mp 216-217 ℃. IR (KBr, cm^{-1}): ν 3218, 3080, 1769, 1730, 1654, 1596,1299 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.56 (s, 4 H), 1.13 (s, 6 H), 5.34 (s, 2 H), 7.18 (d, *J* = 8.0 Hz, 4 H), 7.49 (d, *J* = 8.0 Hz, 4 H), 9.02 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.89, 23.16, 57.29 (C_{spiro}), 61.42, 106.53, 129.19, 130.27, 133.62, 134.64, 160.34, 165.71, 178.01; ESI-MS *m*/*z*: 505.1 [M+H]$^{+}$.

3,3-Pentylidene-(7*S*,11*R*)-bis(4-methylphenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4d): White solid; mp 222-224 ℃. IR (KBr, cm^{-1}): ν 3148, 3049, 1769, 1735, 1554,1204 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.47 (s, 4 H), 1.09 (s, 6 H), 2.27 (s, 6 H), 5.23 (s, 2 H), 7.05 (d, *J* = 8.0 Hz, 4 H), 7.19 (d, *J* = 8.0 Hz, 4 H), 8.79 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.93, 23.28, 37.03, 57.54 (C_{spiro}), 61.95, 106.29, 128.18, 129.56, 131.78, 139.42, 160.48, 166.06, 177.94; ESI-MS *m*/*z*: 465.2 [M+H]$^{+}$.

3,3-Pentylidene-(7*S*,11*R*)-bis(4-nitrophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4e): light yellow solid; mp 214-215 ℃. IR (KBr, cm^{-1}): ν 3229, 3078, 1769, 1727, 1691, 1527, 1347 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.49 (s, 4 H), 1.07 (s, 6 H), 5.58 (s, 2 H), 7.46 (d, J = 8.0 Hz, 4 H), 8.29 (d, J = 8.0 Hz, 4 H), 9.28 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.79, 23.04, 37.25, 56.87 (C_{spiro}), 61.39, 106.88, 124.27, 130.14, 141.73, 148.72, 160.15, 165.32, 178.07; ESI-MS m/z: 527.1 $[M+H]^+$.

3,3-Pentylidene-(7*S*,11*R*)-bis(4-methoxyphenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4f): White solid; mp 202-204 ℃. IR (KBr, cm^{-1}): ν 3216, 3060,1768, 1734, 1656, 1251 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.47 (s, 4 H), 1.09 (s, 6 H), 3.74 (s, 6 H), 5.26 (s, 2 H), 7.05 (d, J = 8.0 Hz, 4 H), 7.21 (d, J = 8.0 Hz, 4 H), 8.91 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.79, 23.04, 37.25, 54.75, 56.12 (C_{spiro}), 61.63, 106.00, 113.28, 113.51, 125.44, 128.60, 159.67, 159.89, 165.08, 178.16; ESI-MS m/z: 497.2 $[M+H]^+$.

3,3-Butylidene-(7*S*,11*R*)-diphenyl-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4g): White solid; mp 196-198 ℃. IR (KBr, cm^{-1}): ν 3154, 3061, 2955, 1775, 1743, 1653, 1565 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.69-0.81 (m, 4 H), 1.32-1.36 (m, 4 H), 5.31 (s, 2 H), 7.18 (m, 10 H), 8.90 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.27, 38.35, 37.01, 57.39 (C_{spiro}), 62.06, 114.64, 128.28, 129.22, 129.92, 134.71, 160.41, 166.02, 178.06; ESI-MS m/z: 423.1 $[M+H]^+$.

3,3-Butylidene-(7*S*,11*R*)-bis(4-flurophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-bthione (4h): White solid; mp 204-206 ℃. IR (KBr, cm^{-1}): ν 3202, 3046, 2948, 1772, 1743, 1606, 1549 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80-0.94 (m, 4 H), 1.35-1.40 (m, 4 H), 5.34 (s, 2 H), 7.19-7.28 (m, 8 H), 8.99 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.41, 38.54, 57.41 (C_{spiro}), 61.33, 114.77, 116.04, 116.25, 130.51, 130.60, 130.83, 130.86, 160.51, 161.85, 164.29, 165.92, 178.00; ESI-MS m/z: 459.1 $[M+H]^+$.

3,3-Butylidene-(7*S*,11*R*)-bis(4-chlorophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4i): White solid; mp 213-215 ℃. IR (KBr, cm^{-1}): ν 3233, 3029, 2969, 1773, 1740, 1596, 1540 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79-0.95 (m, 4 H), 1.37-1.40 (m, 4 H), 5.34 (s, 2 H), 7.18 (d, J = 8.0 Hz, 4 H), 7.49 (d, J = 8.0 Hz, 4 H), 9.03 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 22.42, 38.54, 57.12 (C_{spiro}), 61.33, 114.84, 129.26, 130.20, 133.53, 134.61, 160.34, 165.76, 178.03; ESI-MS m/z: 491.1 $[M+H]^+$.

3,3-Butylidene-(7*S*,11*R*)-bis(4-methylphenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4j): White solid; mp 202-204 ℃. IR (KBr, cm^{-1}): ν 3156, 3023, 1771, 1739, 1558, 1214 cm^{-1}; ^{1}H NMR(400 MHz, DMSO-d_6) δ 0.71-0.87 (m, 4 H), 1.30-1.37 (m, 4 H), 2.27 (s, 6 H), 5.24 (s, 2 H), 7.05 (d, J = 8.0 Hz, 4 H), 7.19 (d, J = 8.0 Hz, 4 H), 8.79 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ

21.15, 22.30, 38.36, 57.42 (C_{spiro}), 61.86, 114.61, 128.12, 129.64, 131.72, 139.37, 160.48, 166.12, 177.97; ESI-MS *m*/*z*: 451.2 $[M+H]^+$.

3,3-Dimethyl-(7*S*,11*R*)-diphenyl-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4k): white solid; mp 204-206 ºC.[15] IR (KBr, cm^{-1}): ν 3200, 3060, 1770, 1734, 1653, 1209; ^1H NMR (400 MHz, DMSO-d_6) δ 0.50 (s, 6 H), 5.32 (s, 2 H), 7.18-7.39 (m, 10 H), 8.97 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.15, 56.84 (C_{spiro}), 61.98, 106.35, 128.35, 129.22, 129.93, 134.72, 160.14, 165.74, 177.98; ESI-MS *m*/*z*: 397.1 $[M+H]^+$.

3,3-Dimethyl-(7*S*,11*R*)-bis(4-flurophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4l): white solid; mp 208-210 ºC.[15] IR (KBr, cm^{-1}): ν 3228, 3074, 1767, 1735, 1653, 1228; ^1H NMR (400 MHz, DMSO-d_6) δ 0.61 (s, 6 H), 5.34 (s, 2 H), 7.19-7.30 (m, 8 H), 9.04 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.30, 56.88 (C_{spiro}), 61.25, 106.45, 116.05, 116.27, 130.59, 130.68, 130.86, 130.89, 160.27, 161.83, 164.28, 165.67, 177.93; ESI-MS *m*/*z*: 433.1 $[M+H]^+$.

3,3-Dimethyl-(7*S*,11*R*)-bis(4-chlorophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4m): white solid; mp 208-209 ℃.[15] IR (KBr, cm^{-1}): ν 3220, 3067, 1767, 1735, 1595, 1296; ^1H NMR (400 MHz, DMSO-d_6) δ 0.62 (s, 6 H), 5.35 (s, 2 H), 7.18 (d, *J* = 8.0 Hz, 4 H), 7.51 (d, *J* = 8.0 Hz, 4 H), 9.08 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 28.29, 56.62 (C_{spiro}), 61.26, 106.52, 129.27, 130.29, 133.57, 134.60, 160.11, 165.52, 177.96; ESI-MS *m*/*z*: 465.0 $[M+H]^+$.

3,3-Dimethyl-(7*S*,11*R*)-bis(4-methylphenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4n): white solid; mp 222-224 ℃.[15] IR (KBr, cm^{-1}): ν 3148, 3049, 1769, 1735, 1554,1204; ^1H NMR (400 MHz, DMSO-d_6) δ 0.54 (s, 6 H), 2.27 (s, 6 H), 5.24 (s, 2 H), 7.06 (d, *J* = 8.0 Hz, 4 H), 7.20 (d, *J* = 8.0 Hz, 4 H), 8.87 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 21.16, 28.21, 56.88 (C_{spiro}), 61.77, 106.30, 128.20, 129.37, 129.65, 131.72, 139.38, 160.21, 165.86, 177.89; ESI-MS *m*/*z*: 425.1 $[M+H]^+$.

3,3-Dimethyl-(7*S*,11*R*)-bis(4-nitrophenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4o): light yellow solid; mp 232-234 ℃.[15] IR (KBr, cm^{-1}): ν 3220, 3084, 1767, 1740, 1607,1285; ^1H NMR (400 MHz, DMSO-d_6) δ 0.57 (s, 6 H), 5.59 (s, 2 H), 7.47 (d, *J* = 8.0 Hz, 4 H), 8.32 (d, *J* = 8.0 Hz, 4 H), 9.34 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.38, 55.15 (C_{spiro}), 60.17, 105.78, 122.97, 123.29, 129.07, 129.29, 140.61, 147.59, 158.84, 164.07, 176.94; ESI-MS *m*/*z*: 487.1 $[M+H]^+$.

3,3-Dimethyl-(7S,11R)-bis(4-methoxyphenyl)-2,4-dioxa-8,10-diazaspiro[5.5]undecane-1,5-dione-9-thione (4p): white powder; mp188-190 ℃.[15] IR (KBr, cm^{-1}): ν 3205, 3060,1766, 1734, 1653,1247; ^1H NMR (400 MHz, DMSO-d_6) δ 0.60 (s, 6 H), 3.73 (s, 6 H), 5.22 (s, 2 H), 6.96 (d, *J* = 8.0 Hz, 4 H), 7.09 (d, *J* = 8.0 Hz, 4 H), 8.84 (s, 2 H, NH); ^{13}C NMR (100 MHz, DMSO-d_6) δ 27.23, 54.68, 56.00 (C_{spiro}), 60.46, 105.20, 113.13, 113.48, 125.41, 128.50, 159.34, 159.42, 164.89, 176.76; ESI-MS *m*/*z*: 457.1 $[M+H]^+$.

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