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Supporting Information

Reactivity of the 4-amino-5*H*-1,2-oxathiole-2,2-dioxide heterocyclic system: A combined experimental and theoretical study

Sonia de Castro,[a] M. Teresa Peromingo,[a] Angel E. Lozano,[b] María-José Camarasa,[a] and Sonsoles Velázquez* [a]

[a] *Instituto de Química Médica (C.S.I.C.), C/ Juan de la Cierva 3, E-28006 Madrid, Spain*

[b] *Instituto de Ciencia y Tecnología de Polímeros (C.S.I.C.), Juan de la Cierva 3, E-28006 Madrid, Spain*

2-Benzyl-2-(methanesulfonyloxy)butyronitrile (4b). According to the procedure (Method C) described in the journal for compound **2a,** 1-phenyl-2-butanone **1b** (0.30 g, 2 mmol) in dichloromethane (6 mL) was reacted with trimethylsilyl cyanide (0.4 mL, 3 mmol) and boron trifluoride diethyl etherate (10.23 mL, 2 mmol). The mixture was stirred at room temperature for 2 h. Volatiles were removed and the residue was dissolved in ethyl acetate (10 mL) and washed with brine (2 × 5 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue (compound **2b**) was treated with NEt_3 (1.95 mL, 14 mmol) and methanesulfonyl chloride (0.46 mL, 6 mmol) following the procedure described for compound **4a**. The final residue was purified by flash column chromatography on silica gel (hexane: ethyl acetate, 10:1) to give **4b** (0.37 g, 74%) as a white foam. IR (film): 2536 cm^{-1}. ^1H NMR [200 MHz, $CDCl_3$] δ: 1.17 (t, 3H, *J* = 7.1 Hz) 2.10 (c, 2H, *J* = 7.1 Hz), 3.09 (s, 3H), 3.19 (s, 2H), 7.41 (m, 5H). ^{13}C NMR [50 MHz, $CDCl_3$] δ: 8.4, 32.3, 40.0, 44.1, 83.6, 117.2, 138.7, 129.3, 131.7, 133.9. MS (ES^+) m/z 254.6 $[M+1]^+$. Anal. Cald for $C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.83; H, 5.64; N, 5.34.

4-Amino-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (5b). According to the method described in the journal for the preparation of **5a**, a suspension of **4b** (250 mg , 1 mmol) and cesium carbonate (490 mg, 1.5 mmol) in dry acetonitrile (3 mL) was stirred at room temperature for 2 h. The final residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 6:1) to give **5b** (205 mg, 81%) as a white solid. M.p. (toluene): 165-166 ºC. IR (film): 3503, 3408 cm^{-1}. ^1H NMR [200 MHz, $(CD_3)_2CO$] δ: 0.90 (t, *J* = 7.0 Hz, 3H), 1.75 (m, 1H), 1.98 (m, 1H), 3.22 (s, 2H), 5.40 (s, 1H), 6.19 (bs, 2H, NH_2), 7.26 (m, 5H). ^{13}C NMR [50 MHz, $(CD_3)_2CO$] δ: 5.8, 27.8, 42.8, 87.9, 91.8, 126.1, 127.1, 130.1, 134.4, 156.2. MS (ES^+) m/z 254.1 $[M+1]^+$, 276.0 $[M+Na]^+$, 507.2 $[2M+1]^+$, 529.3 $[2M+Na]^+$. Anal. Cald for$C_{12}H_{15}NO_3S$: C, 56.90; H, 5.97; N, 5.53. Found: C, 56.65; H, 5.72; N, 5.29.

2-Cyano-1,3-diphenyl-1-propene (6).[18] A solution of **4a** (100 mg, 0.32 mmol) and DBU (104 μL, 0.7 mmol) in dry acetonitrile (5 mL) was stirred at room temperature for 5 h. Then, it was neutralized with acetic acid to pH ~7 and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 8:1) to give **6** (28 mg, 40%) as a white foam. ^1H NMR [200 MHz, $(CD_3)_2CO$] δ: 3.75 (s, 2H), 6.89 (s, 1H), 7.23-7.77 (m, 10H) ^{13}C NMR [75 MHz, $CDCl_3$] δ: 42.0, 110.7, 118.5, 127.2, 128.6, 128.6, 128.7, 129.9, 133.5, 136.4, 143.9. MS (ES^+) m/z 220.1 $[M+1]^+$, 242.1 $[M+Na]^+$, 463.3 $[2(M+Na)]^+$.

5-Benzyl-4-[(dimethylamino)methylen]amino-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (10b). According to the method described in the journal for the preparation of **10a**, a solution of **5b** (1g, 3.96 mmol) in dry DMF (15 mL) was reacted with *N*,*N*-dimethylformamide dimethyl acetal (2.1 mL). The final residue was purified by flash chromatography (hexane/ethyl acetate 1:1) to

give **10b** (1.18 g, 97%) as a white solid. M.p. (dichloromethane/hexane): 161-162 ºC. ^{1}H NMR [200 MHz, $(CD_3)_2CO$] δ: 0.85 (t, *J* = 7.3 Hz, 3H), 1.70 (m, 1H), 1.95 (m, 1H), 3.13, 3.16 (2s, 6H), 3.22 (s, 2H), 5.97 (s, 1H), 7.28 (m, 5H), 8.06 (m, 1H). ^{13}C NMR [50 MHz, $(CD_3)_2CO$] δ: 6.0, 33.2, 39.2, 42.8, 94.4, 96.4, 125.8, 126.9, 130.2, 134.6, 156.9, 163.4. Anal. Calcd. for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08; S, 10.40. Found: C, 58.33; H, 6.50; N, 8.89; S, 10.22.

5-Benzyl-5-ethyl-4-[(*E*)-2,4-(dimethoxycarbonyl)buta-1,3-dienyl]amino-5*H*-1,2-oxathiole 2,2-dioxide (13). A solution of **5b** (100 mg, 0.39 mmol), methyl propiolate (42 μL, 0.47 mmol) and DMAP (44 mg, 0.36 mmol) in dry acetonitrile (10 mL) was stirred at room temperature for 12 h. Then, ethyl acetate was added (5 mL) and the mixture was washed with 0.1 N HCl (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried, filtered, and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:1) to give **13** (17 mg, 10%) as a white solid. M.p. (hexane/ethyl acetate): 81-82 ºC. IR (film): 3503, 1714 cm^{-1}.^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 0.92 (m, 3H), 2.20 (m, 2H), 3.25 (AB system, *J* = -14.6 Hz, 1H), 3.33 (AB system, 1H, *J* = -14.6 Hz), 3.68 (s, 3H), 3.90 (s, 3H), 6.36 (d, 1H, *J* =16.0 Hz), 6.79 (s, 1H), 7.32 (m, 5H), 7.39 (d, 1H, *J* =16.0 Hz), 7.97 (d, 1H, *J* = 11.4 Hz), 10.28 (d, 1H, *J* = 11.4 Hz). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 7.9, 29.5, 44.1, 51.9, 53.9, 93.7, 100.2, 106.7, 116.9, 129.5, 129.5, 132.1, 134.8, 140.7, 146.9, 151.6, 168.3, 169.7. MS (ES^+) m/z 422.1 $[M+1]^+$, 444.1 $[M+Na]^+$, 865.2 $[2M+Na]^+$. Anal. Calcd. for $C_{20}H_{23}NO_7S$: C, 57.00; H, 5.50; N, 3.32. Found: C, 56.90; H, 5.39; N, 3.41. The next moving band gave 22 mg (17 %) of **12** as a white foam. The slowest moving band afforded 40 mg (40%) of unreacted starting material **5b**.

5-Benzyl-4-ethoxycarbonylureido-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (21). According to the method described in the journal for the preparation of **20**, a solution of **5b** (100 mg, 0.39 mmol) and ethoxycarbonyl isocyanate (123 μL, 1.17 mmol) in dry acetonitrile (4 mL) was stirred in an Ace pressure tube for 2 h at 100ºC. The final residue was purified by HPFC on an Horizon system (hexane/ethyl acetate, 2:1) to give **21** (88 mg, 60%) as a white amorphous solid. M.p. (hexane/ethyl acetate): 198-199 ºC. IR (film): 3400, 3380, 1733 cm^{-1}. ^{1}H NMR [200 MHz, $(CD_3)_2CO$] δ: 0.92 (t, 3H, *J* = 7.4 Hz), 1.31 (t, 3H, *J* = 7.1 Hz), 1.95 (m, 2H), 3.18 and 3.22 (AB system, 2H, *J* = 14.4 Hz), 4.30 (c, 2H, *J* = 7.1 Hz), 6.98 (s, 1H), 7.28 (m, 5H), 9.91 (bs, 1H, NH), 10.34 (bs, 1H, NH). ^{13}C NMR [50 MHz, $(CD_3)_2CO$] δ: 7.0, 14.1, 28.9, 40.3, 62.3, 92.7, 102.6, 127.2, 128.1, 130.6, 133.3, 145.8, 149.7, 154.0. MS (ES^+) m/z 369.0 $[M+1]^+$, 391.0 $[M+Na]^+$, 759.2 $[2M+Na]^+$. Anal. Calcd for $C_{16}H_{20}N_2O_6S$: C, 52.16; H, 5.47;N, 7.60. Found: C, 51.90; H, 5.11; N, 7.43.

4-Benzoylureido-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (22). According to the method described in the journal for the preparation of **20**, a solution of **5b** (100 mg, 0.39 mmol) and benzoyl isocyanate (147 μL, 1.17 mmol) in dry acetonitrile (4 mL) was stirred in an Ace pressure tube for 2h at 100ºC. The final residue was purified by CCTLC on the Chromatotron

(hexane/ethyl acetate, 2:1) to give **22** (126 mg, 81%) as a white amorphous solid. M.p. (hexane/ethyl acetate): 181-182 ºC. IR (film): 3315, 1742, 1735 cm^{-1}. ^1H NMR [400 MHz, $(CD_3)_2CO$] δ: 0.97 (t, 3H, *J* = 7.3 Hz), 1.99 (m, 2H), 3.27 and 3.35 (AB system, 2H, *J* = 14.4 Hz), 7.07 (s, 1H), 7.33 (m, 5H), 7.62 (t, 2H, *J* = 8.1 Hz), 7.78 (m, 1H), 8.13 (m, 2H), 10.55 (bs, 1H, NH), 11.33 (bs, 1H, NH). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ: 7.1, 29.0, 43.1, 92.8, 103.5, 127.3, 128.1, 128.6, 128.7, 130.6, 131.7, 133.3, 133.6, 145.7, 150.7, 169.1. MS (ES^+) m/z 401.0 $[M+1]^+$, 423.0 $[M+Na]^+$, 823.0 $[2M+Na]^+$. Anal. Cald for $C_{20}H_{20}N_2O_5S$: C, 59.99; H, 5.03; N, 7.00. Found C, 59.73; H, 4.94; N, 6.85.

Reaction of 5a,b with aldehydes. General procedure.

To a solution of **5a,b** (1 equiv) in dry THF (5 mL), NaH 60% dispersion in mineral oil (2 equiv) was added, and the mixture was stirred at room temperature for 10 min. Then, corresponding aldehyde (2 equiv) was added and the mixture was stirred for 10 min at 70 ºC. Methanol (2 mL) was added and solution was stirred to room temperature for 5 min. The solvent was evaporated and ethyl acetate (5 mL) was added. The organic layer was successively washed with 0.1 N HCl (2 × 5 mL) and brine (2 × 5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron. The chromatography eluent, yield, and analytical and spectroscopic data of the isolated products are indicated below for each reaction.

4-Amino-3-benzoyl-5-benzyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (24).

According to the general procedure, **5b** (100 mg, 0.39 mmol) was reacted with NaH (31 mg, 0.78 mmol) and benzaldehyde (80 μL, 0.78 mmol) for 10 min at 70 ºC. Chromatography of the final residue on the Chromatotron (dichloromethane/methanol, 25:1) yielded 108 mg (77%) of **24** as a white amorphous solid.

4-Amino-5-benzyl-5-ethyl-3-(furan-2-yl)carbonyl-5*H*-1,2-oxathiole-2,2-dioxide (27).

Compound **5b** (100 mg, 0.39 mmol) was reacted with NaH (32 mg, 0.78 mmol) and 2-furaldehyde (64 μL, 0.78 mmol) according to the general procedure. Chromatography of the final residue on the Chromatotron (hexane/ethyl acetate, 3:1) yielded 100 mg (74%) of **27** as a white amorphous solid. M.p. (hexane/ethyl acetate): 178-179 ºC. IR (film): 1623 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2CO$] δ: 0.94 (t, 3H, *J* = 7.5 Hz), 1.89 (m, 1H), 2.20 (m, 1H), 3.33 and 3.40 (AB system, 2H, *J* = 14.3 Hz), 6.66 (dd, 1H, *J* = 1.7 and 3.6 Hz), 7.26 (m, 5H), 7.62 (d, 1H, *J* = 3.6 Hz), 7.84 (d, 1H, *J* = 1.7 Hz), 8.18 (bs, 1H, NH), 9.56 (bs, 1H, NH). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 7.9, 30.7, 44.8, 91.8, 104.4, 113.5, 119.1, 128.5, 129.4, 132.2, 135.1, 148.3, 151.9, 169.7, 173.5. MS (ES^+) m/z 348.0 $[M+1]^+$, 717.0 $[2M+Na]^+$. Anal. Calcd for $C_{17}H_{17}NO_5S$: C, 58.78; H, 4.93;N, 4.03. Found: C, 58.55; H, 4.68;N, 3.99.

4-Amino-5-benzyl-3-cyclohexylcarbonyl-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (28).

According to the general procedure, **5b** (100 mg, 0.39 mmol) was reacted with NaH (32 mg, 0.78 mmol) and cyclohexanaldehyde (94 μL, 0.78 mmol) for 10 min at room temperature.

Chromatography of the final residue on the Chromatotron (hexane/ethyl acetate, 3:1) yielded 80 mg (73%) of **28** as a white amorphous solid. M.p. (hexane/ethyl acetate): 205-206 ºC. IR (film): 3466, 1649 cm^{-1}. ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ: 0.91 (t, 3H, *J* = 7.3 Hz), 1.17-1.44 (m, 5H), 1.65-1.90 (m, 6H), 2.16 (m, 1H), 2.76 (m, 1H), 3.27 and 3.33 (AB system, 2H, *J* = 14.3 Hz), 7.28 (m, 5H), 7.99 (bs, 1H, NH), 9.04 (bs, 1H, NH). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 7.5, 26.2, 26.3, 26.5 29.4, 29.6, 29.9, 44.4, 48.9, 91.5, 105.3, 128.1, 128.9, 131.8, 134.8, 167.2, 196.8. MS (ES^+) m/z 364.0 $[M+1]^+$. Anal. Calcd for $C_{19}H_{25}NO_4S$: C, 62.78; H, 6.93;N, 3.85; S, 8.82. Found: C, 62.55; H, 6.69; N, 3.71; S, 8.78.

4-Amino-5,5-dibenzyl-3-bromo-5*H*-1,2-oxathiole-2,2-dioxide (30a). According to the method described in the journal for the preparation of **29**, a solution of **5a** (100 mg, 0.32 mmol), $NaHCO_3$ (267 mg, 3.2 mmol) in dry ethanol (10 mL), to a 5% solution of bromine in ethanol was added slowly until the solution get colour. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 2:1) to give **30a** (123 mg, 98%) as a white amorphous solid. M.p. (hexane/ethyl acetate): 197-198 ºC. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 3.19 and 3.39 (AB system, 2H, *J* = 14.6 Hz), 6.58 (bs, 2H), 7.27 (m, 10H). MS (ES^+) m/z .394.1 $[M+1]^+$, showing the Br isotopic pattern. Anal. Cald for $C_{17}H_{16}BrNO_3S$: C, 51.79; H, 4.09; N, 3.55; S, 8.13. Found: C, 51.53; H, 3.99; N, 3.42; S, 7.99.

4-Amino-5-benzyl-3-bromo-5-ethyl-5*H*-1,2-oxathiole-2,2-dioxide (30b). According to the method described in the journal for the preparation of **30a**, a solution of **5b** (100 mg, 0.39 mmol), $NaHCO_3$ (330 mg, 3.9 mmol) in dry ethanol (10 mL), was added slowly to a 5% solution of bromine in ethanol until the solution get colour. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 2:1) to give **30b** (101 mg, 95%) as a white amorphous solid. M.p. (hexane/ethyl acetate): 109-110 ºC ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 0.88 (t, 3H, *J* = 7.3 Hz), 1.80 (m, 1H), 2.09 (m, 1H), 3.28 (s, 2H), 6.46 (bs, 2H), 7.28 (m, 5H). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 7.0, 29.0, 43.8, 75.7, 94.0, 127.5, 128.8, 131.1, 134.6, 152.8. MS (ES^+) m/z 332.0 $[M+1]^+$, showing the Br isotopic pattern. Anal. Cald for $C_{17}H_{16}BrNO_3S$: C, 43.38; H, 4.25; N, 4.22; S, 9.65. Found: C, 43.50; H, 4.14; N, 4.08; S, 9.39.

4-Amino-5-benzyl-5-ethyl-3-nitroso-5*H*-1,2-oxathiole-2,2-dioxide (31b). According to the method described in the journal for the preparation of **31a**, to a solution of **5b** (100 mg, 0.39 mmol) in acetic acid (9 mL): water (0.9 mL): methanol (1 mL), sodium nitrite (54 mg, 0.78 mmol) was added. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 6:1) to give **31b** (67 mg, 61%) as a purple solid. M.p. (dichloromethane/hexane): 166-167ºC. IR (film): 3469, 1681 cm^{-1}. ^{1}H NMR [300 MHz, $(CD_3)_2SO$] δ: 0.90 (t, 3H, *J* = 7.5 Hz), 1.91 (m, 1H), 2.21 (m, 1H), 3.37 (s, 2H), 7.27 (m, 5H), 10.09 (bs, 1H, NH_2), 11.58 (bs, 1H, NH_2). MS (ES^+) m/z 283.1 $[M+1]^+$, 305.0 $[M+Na]^+$. Anal. Calcd. for $C_{12}H_{14}N_2O_4S$: C, 51.05; H, 5.00; N, 9.92; S, 11.36. Found: C, 50.79; H, 4.78; N, 9.78; S, 11.28.

5-Benzyl-5-ethyl-4-oxo-1,2-oxathiolane-2,2-dioxide (32b). According to the method described in the journal for the preparation of **32a**, a solution of **5b** (100 mg, 0.39 mmol) in 1N HCl in methanol (2 mL, 9 mmol) was stirred at room temperature for 14 h. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 3:1) to give **32b** (76 mg, 76%) as a white solid. M.p. (ethanol/water): 103-104 ºC. IR (film): 1769 cm^{-1}. **Tautomer (A):** ^{1}H NMR [300 MHz, $CDCl_3$] δ:1.07 (t, 3H, *J* = 7.1 Hz), 1.96 (m, 1H), 2.08 (m, 1H), 2.99 and 3.63 (AB system, 2H, *J* = 14.5 Hz), 3.19 and 3.63 (AB system, 2H, *J* = 17.0 Hz), 7.21 (m, 2H), 7.31 (m, 3H).^{13}C NMR [100 MHz, $CDCl_3$] δ: 7.3, 29.0, 41.2, 53.6, 101.6, 127.8, 128.7, 130.7, 132.6, 200.8. **Tautomer (B):** ^{1}H NMR [400 MHz, $(CD_3)_2SO$] δ: 0.84 (t, 3H, *J* = 7.2 Hz), 1.70 (m, 1H), 1.85 (m, 1H), 3.09 (s, 2H), 6.03 (s, 1H), 7.27 (m, 5H), 12.75 (bs, 1H, OH). ^{13}C NMR [100 MHz, $(CD_3)_2SO$] δ: 7.3, 28.1, 42.2, 93.1, 94.7, 127.0, 127.9, 130.7, 134.2, 166.2. MS (ES^+) m/z 255.1 $[M+1]^+$. Anal. Calcd for $C_{12}H_{14}O_4S$: C, 56.68; H, 5.55; S, 12.61. Found: C, 56.39; H, 5.32; S, 12.55.

1-Cyano-1-(methanesulfonyloxy)cyclopentane (37). According to the method described for the preparation of **4a,b**, a solution of cyclopentanone (177 µL, 2 mmol) in dichloromethane (6 mL) was first reacted with trimethylsilyl cyanide (375 µL, 3 mmol) and boron trifluoride diethyl etherate (253 µL, 2 mmol). After the work-up, the residue was dissolved in dry dichloromethane and NEt_3 (1.95 mL, 14 mmol) was added. The mixture was cooled at -30 ºC and methanesulfonyl chloride (464 µL, 6 mmol) was slowly added. The final residue, after the work-up, was purified by flash column chromatography on silica gel (hexane: ethyl acetate, 9:1) to give **37** (272 mg, 72%) as a white foam. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.90 (m, 4H), 2.31 (m, 2H), 2.49 (m, 2H), 3.19 (s, 3H). MS (ES^+) m/z 190.3 $[M+1]^+$. Anal. Calcd for $C_7H_{11}NO_3S$: C, 44.43; H, 5.86; N, 7.40; S, 16.64. Found: C, 44.21; H, 5.93; N, 7.35; S, 16.47.

3-Cyano-3-(methanesulfonyloxy)tetrahydrofurane (38). According to the method described for the preparation of **4a,b**, a solution of dihydrofuran-3(2*H*)-one[22] (172 mg, 2 mmol) in dichloromethane (6 mL) was reacted with trimethylsilyl cyanide (400 µL, 3 mmol) and boron trifluoride diethyl etherate (253 µL, 2 mmol). The residue, after the work-up, was dissolved in dry dichloromethane and reacted with NEt_3 (1.95 mL, 14 mmol). Methanesulfonyl chloride (464 µL, 6 mmol) was slowly added at -20 ºC. The mixture was stirred at -20 ºC for 1 h and at 0 ºC for an additional hour. The final residue was purified by flash column chromatography on silica gel (hexane: ethyl acetate, 9:1) to give **38** (241 mg, 63%) as an orange oil. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 2.75 (t, 2H, J = 7.0 Hz), 3.24 (s, 3H), 4.05 (t, 2H, J = 7.0 Hz), 4.17 and 4.30 (AB system, 2H, *J* = 10.7 Hz). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 32.4, 40.6, 67.7, 77.5, 80.4, 117.4. MS (ES^+) m/z 192.6 $[M+1]^+$. Anal. Calcd for $C_6H_9NO_4S$: C, 37.69; H, 4.74; N, 7.33; S, 16.77. Found: C, 37.55; H, 4.39; N, 7.43; S, 16.53.

1-Benzyl-3-cyano-3-(methanesulfonyloxy)pyrrolidine (39). To a solution of 1-benzyl-3-pyrrolidinone (328 µL, 2 mmol) and potassium cyanide (390 mg, 6 mmol) in water (10 mL) at 0 ºC, a solution of $NaHSO_3$ (520 mg, 5 mmol) in water (3 mL) was added. The mixture was stirred at 0 ºC for 1.5 h and extracted with dichloromethane (2 × 10 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated to dryness. The residue was dissolved in dry dichloromethane (10 mL) and NEt_3 (836 µL, 14 mmol) was added at -30 ºC. Methanesulfonyl chloride (856 µL, 11 mmol) was slowly added and the mixture was stirred at -30 ºC for 20 min. The suspension was filtered through celite and washed with dichloromethane. The filtrate was evaporated and redissolved in ethyl acetate (10 mL) and washed with water (2 × 10 mL). The organic layer was dried (Na_2SO_4), After filtration and evaporation of the solvent, the residue was purified by flash column chromatography on silica gel (hexane: ethyl acetate, 2:1) to give **39** (420 mg, 75%) as a viscous brown oil. ^{1}H NMR [300 MHz, $(CD_3)_2CO$], δ: 2.55 (m, 1H), 2.70 (m, 1H), 2.81 (m, 2H), 3.15 and 3.30 (AB system, 2H, *J* = 10.9 Hz), 3.32 (s, 3H), 3.76 (s, 2H), 7.34 (m, 5H). ^{13}C NMR [75 MHz, $(CD_3)_2CO$], δ: 39.7, 40.5, 51.6, 58.9, 64.9, 79.6, 119.0, 128.1, 129.1, 129.4, 138.8. MS (ES^+) m/z 281.3 $[M+1]^+$. Anal. Calcd for $C_{13}H_{16}N_2O_3S$: C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 55.46; H, 5.58; N, 9.74; S, 11.29.

4-Amino-1-oxa-2-thiaspiro[4.4]non-3-ene-2,2-dioxide (40). According to the method described for the preparation of **5a**, a suspension of **37** (190 mg, 1 mmol) and cesium carbonate (490 mg, 1.5 mmol) in dry acetonitrile (3 mL) was stirred at room temperature for 2 h. The final residue was purified by flash column chromatography on silica gel (hexane/ethyl acetate, 1:1) to give **40** (172 mg, 91%) as a white solid. M.p. (hexane/ethyl acetate): 141-142ºC. IR (film): 3504, 3410, 1650 cm^{-1}. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.85 (s, 4H), 1.99 (m, 2H), 2.20 (m, 2H), 5.45 (s, 1H), 6.07 (bs, 2H, NH_2). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 25.5, 38.6, 89.3, 98.0, 159.2. MS (ES^+) m/z 190.0 $[M+1]^+$, 212.0 $[M+Na]^+$, 379.0 $[2M+1]^+$, 401.0 $[2M+Na]^+$. Anal. Calcd. for $C_7H_{11}NO_3S$: C, 44.43; H, 5.86; N, 7.40; S, 16.94. Found: C, 44.09; H, 5.76; N, 7.35; S, 16.69.

4-Amino-1,7-dioxa-2-thiaspiro[4.4]-non-3-ene-2,2-dioxide (41). According to the method described for the preparation of **5a**, a suspension of **38** (190 g, 1 mmol) and cesium carbonate (490 mg, 1.5 mmol) in dry acetonitrile (3 mL) was stirred at room temperature for 2 h. The final residue was purified by flash column chromatography on silica gel (dichloromethane/methanol, 20:1), to give **41** (134 mg, 70%) as a white solid. M.p. (hexane/ethyl acetate): 122-123 ºC. IR (film): 3498, 3401, 1652 cm^{-1}. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 2.30 (m, 1H), 2.57 (td, 1H, *J* = 8.7 and 13.8 Hz), 3.99 (m, 4H), 5.58 (s, 1H), 6.25 (bs, 2H, NH_2). ^{13}C NMR [75 MHz, $(CD_3)_2CO$] δ: 38.8, 69.3, 76.7, 90.2, 94.9, 156.5. MS (ES^+) m/z 192.0 $[M+1]^+$, 214.0 $[M+Na]^+$. Anal. Calcd. for $C_6H_9NO_4S$: C, 37.69; H, 4.74; N, 7.33; S, 16.77. Found: C, 37.39; H, 4.55; N, 7.29; S, 16.68.

4-Amino-7-aza-7-benzyl-1-oxa-2-thiaspiro[4.4]-non-3-ene-2,2-dioxide (42). A solution of compound **39** (370 mg, 1.3 mmol) and cesium carbonate (630 mg, 1.9 mmol) in dry acetonitrile (3 mL) was stirred at room temperature for 5 h. Solvent was removed, and the remaining residue was dissolved in ethyl acetate (30 mL) and washed successively with water (2 × 20 mL), brine (2 × 10 mL) and dried (Na_2SO_4). After filtration and evaporation of the solvent, the residue was purified by HPFC on an Horizon system (dichloromethane/methanol, 10:1) to give **42** (260 mg, 69%) as a viscous brown oil. IR (film): 3483, 1649 cm^{-1}. ^1H NMR [400 MHz, $(CD_3)_2CO$] δ: ^1H NMR [300 MHz, $(CD_3)_2CO$] δ: 2.23 (ddd, 1H, *J* = 3.7, 8.4 and 14.4 Hz), 2.43 (td, 2H, *J* = 8.4 and 14.4 Hz), 2.66 (c, 1H, *J* = 8.4 Hz), 2.73 and 3.12 (AB system, 2H, *J* = 10.4 Hz), 2.93 (dt, 1H, *J* = 3.6 and 8.4 Hz), 3.70 (s, 2H), 5.41 (s, 1H), 6.13 (bs, 2H, NH_2), 7. 35 (m, 5H). ^{13}C NMR [100 MHz, $(CD_3)_2CO$] δ: 36.3, 52.3, 59.1, 62.5, 86.5, 90.9, 127.4, 128.5, 128.9, 138.4, 158.7. MS (ES^+) m/z 281.2 $[M+1]^+$, 303.2 $[M+Na]^+$, 583.3 $[2M+Na]^+$. Anal. Calcd for $C_{13}H_{16}NO_3S$: C, 55.70; H, 5.75; N, 9.99; S, 11.44. Found: C, 55.53; H, 5.43; N, 9.68; S, 11.23.

1,7-Dioxa-4-methoxycarbonylethylamino-2-thiaspiro[4.4]-non-3-ene-2,2-dioxide (44). According to the method described in the journal for the preparation of **43**, a solution of **41** (80 mg, 0.42 mmol) and H-β-Ala-OMe·HCl (176 mg, 1.26 mmol) in methanol (4 mL) was stirred in an Ace pressure tube for 31 h at 100 ºC. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (dichloromethane/methanol, 50:1) to give **44** (88 mg, 76%) as a white solid. M.p. (hexane/ethyl acetate): 110-111 ºC. IR (film): 3409, 1736 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2CO$] δ: 2.24 (m, 1H), 2.49 (td, 1H, *J* = 8.9 and 13.9 Hz), 2.67 (t, 2H, *J* = 6.6 Hz), 3.43 (c, 2H, *J* = 6.6 Hz), 3.63 (s, 3H), 3.90-4.01 (m, 4H), 5.67 (s, 1H), 6.25 (bs, 1H, NH). ^{13}C NMR, [75 MHz, $CDCl_3$] δ: 33.0, 38.6, 41.7, 51.9, 68.7, 76.4, 87.7, 93.9, 155.7, 172.4. MS (ES^+) m/z 278.0 $[M+1]^+$, 300.0 $[M+Na]^+$, 577.0 $[2M+Na]^+$. Anal. Calcd. for $C_{10}H_{15}NO_6S$: C, 43.31; H, 5.45; N, 5.05; S, 11.56. Found: C, 43.22; H, 5.12; N, 4.87; S, 11.36.

7-Aza-7-benzyl-4-methoxycarbonylmethylamino-1-oxa-2-thiaspiro[4.4]-non-3-ene-2,2-dioxide (45). According to the method described in the journal for the preparation of **43**, a solution of **42** (180 mg, 0.64 mmol) and H-Gly-OMe·HCl (241 mg, 1.92 mmol) in methanol (5 mL) was stirred in an Ace pressure tube for 24 h at 100 ºC. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (dichloromethane/methanol, 50:1) to give **45** (150 mg, 67%) as a white foam. IR (film): 3283, 1751 cm^{-1}. ^1H NMR [300 MHz, $(CD_3)_2CO$] δ: 2.24 (ddd, 1H, *J* = 3.3, 8.4 and 14.1 Hz), 2.46 (td, 1H, *J* = 8.3 and 14.1 Hz), 2.62 (m, 1H), 2.70 and 3.21 (AB system, 2H, *J* = 9.9 Hz), 3.00 (dt, 1H, *J* = 2.7 and 8.7 Hz), 3.74 (s, 3H), 4.00 (s, 2H), 5.51 (s, 1H), 6.60 (bs, 1H), 7.44 (m, 5H).^{13}C NMR, [75 MHz, $(CD_3)_2CO$] 33.8, 46.3, 52.5, 52.6, 59.7, 62.7, 86.2, 90.2, 128.1, 129.2, 129.6, 138.5, 159.9, 170.2. MS (ES^+) m/z 353.3 $[M+1]^+$. Anal. Calcd. for $C_{16}H_{20}N_2O_5S$: C, 54.53; H, 5.72; N, 7.95; S, 9.10. Found: C, 54.36; H, 5.67, N, 7.80; S, 8.98.

7-Aza-7-benzyl-4-methoxycarbonylethylamino-1-oxa-2-thiaspiro[4.4]-non-3-ene-2,2-dioxide (46). According to the method described in the journal for the preparation of **43**, a solution of **42** (100 mg, 0.36 mmol) and H-β-Ala-OMe·HCl (151 mg, 1.08 mmol) in methanol (4 mL) was stirred for 48 h in an Ace pressure tube at 100 ºC. The solvent was evaporated and the residue was purified by flash column chromatography on silica gel (dichloromethane/methanol, 100:1) to give **46** (81 mg, 62%) as a white foam. ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 2.25 (ddd, 1H, *J* = 3.0, 8.4 and 14.1 Hz), 2.39 (m, 1H), 2.66 (m, 1H), 2.73 and 3.13 (AB system, 2H, *J* = 10.2 Hz), 2.95 (dt, 1H, *J* = 3.0 and 8.4 Hz), 3.42 (t, 2H, *J* = 6.6 Hz), 3.67 (s, 3H), 3.72 (m, 2H), 5.53 (s, 1H), 6.40 (bs, 1H, NH), 7.37 (m, 5H). MS (ES^+) m/z 367.3 $[M+1]^+$, 755.5 $[2M+Na]^+$. Anal. Calcd. for $C_{17}H_{22}N_2O_5S$: C, 55.72; H, 6.05; N, 7.64; S, 8.75. Found: C, 55.54; H, 5.88, N, 7.43; S, 8.46.

4-Benzoylamino-1,7-dioxa-2-thiaspiro[4.4]-non-3-ene-2,2-dioxide (48). According to the method described in the journal for the preparation of **47**, a solution of **41** (100 mg, 0.52 mmol) and DMAP (285 mg, 2.34 mmol) in dry acetonitrile (5 mL), benzoyl chloride (179 μL, 1.56 mmol) was added. The mixture was stirred at room temperature for 1 h. Salts were filtered and solvent was evaporated and ethyl acetate was added. The organic layer was successively washed with 1N HCl (2 x 5 mL) and brine (2 x 5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 3:1) to yield 110 mg (71%) of **48** as a white amorphous solid**.** ^{1}H NMR [400 MHz, $(CD_3)_2CO$] δ: 2.36 (m, 1H), 2.87 (td, 2H, *J* = 9.2 and 14.0 Hz), 3.99 and 4.34 (AB system, 2H, *J* = 10.4 Hz), 4.03-4.10 (m, 2H), 4.15 (dt, 1H, *J* = 3.2 and 9.2 Hz), 7.53 (m, 2H), 7.58 (s, 1H), 7.62 (m, 1H), 7.90 (m, 1H), 8.05 (m, 1H), 9.64 (bs, 1H). ^{13}C NMR, [100 MHz, $(CD_3)_2CO$] δ: 38.9, 69.7, 75.6, 96.3, 106.6, 130.0, 130.3, 130.4, 131.4, 134.6, 134.7, 146.4, 169.3. MS (ES^+) m/z 296.0 $[M+1]^+$. Anal. Calcd. for $C_{13}H_{13}NO_5S$: C, 52.87; H, 4.44; N, 4.74; S, 10.86 Found: C, 52.82; H, 4.29, N, 4.89; S, 10.75.

7-Aza-4-benzoylamino-7-benzyl-1-oxa-2-thiaspiro[4.4]-non-3-ene-2,2-dioxide (49).

According to the method described in the journal for the preparation of **47**, a solution of **42** (100 mg, 0.36 mmol) and DMAP (176 mg, 1.44 mmol) in dry acetonitrile (5 mL), benzoyl chloride (124 μL, 1.08 mmol) was added. The mixture was stirred at room temperature for 3 h. Salts were filtered and solvent was evaporated and ethyl acetate was added. The organic layer was successively washed with 1N HCl (2 x 5 mL) and brine (2 x 5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 3:1) to yield 108 mg (78%) of **49** as a white foam**.** IR (film): 3390, 1703 cm^{-1}. ^{1}H NMR [400 MHz, CD_3Cl] δ: 2.40-2.56 (m, 2H), 2.68 (m, 1H), 2.82 and 3.31 (AB system, 2H, *J* = 10.0 Hz), 3.25 (m, 1H), 3.71 and 3.76 (AB system, 2H, *J* = 12.4 Hz), 7.20 (m, 2H), 7.22 (s, 1H), 7.28 (m, 3H), 7.53 (t, 2H, *J* = 8.0 Hz), 7.67 (t, 1H, *J* = 7.6 Hz), 7.75 (d, 2H, *J*

= 7.2 Hz), 10.00 (bs, 1H). ^{13}C NMR, [100 MHz, CD_3Cl] δ: 35.1, 51.8, 59.8, 61.3, 88.2, 100.8, 127.4, 128.1, 128.7, 129.0, 129.2, 132.2, 133.3, 136.1, 148.4, 165.9. MS (ES^+) m/z 385.0 $[M+1]^+$, 407.0 $[M+Na]^+$, 791.0 $[2M+Na]^+$. Anal. Calcd. for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29; S, 8.34. Found: C, 62.39; H, 5.32, N, 7.40; S, 8.11.

4-Amino-7-aza-3-benzoyl-7-benzyl-1-oxa-2-thiaspiro[4.4]-non-3-ene-2,2-dioxide (50). A solution of **42** (100 mg, 0.36 mmol) and DMAP (176 mg, 1.44 mmol) in dry acetonitrile (5 mL), benzoyl chloride (124 μL, 1.08 mmol) was added. The mixture was stirred at 80 ºC in an Ace pressure tube for 3 h. Salts were filtered and solvent was evaporated and ethyl acetate was added. The organic layer was successively washed with 1N HCl (2 x 5 mL) and brine (2 x 5 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (dichloromethane/methanol, 20:1) to yield 92 mg (67%) of **50** as a white foam. ^{1}H NMR [300 MHz, CD_3Cl] δ: 2.43 (m, 1H), 3.42 (m, 3H), 4.33 (d, 2H, *J* = 12.9 Hz) 4.68 (d, 1H, *J* = 12.9 Hz) 4.82 (d, 1H, *J* = 12.9 Hz), 6.81 (s, 1H), 7.39 (m, 3H), 7.44 (t, 2H, *J* = 7.8 Hz), 7.56 (m, 3H), 7.97 (d, 2H, *J* = 7.2 Hz). ^{13}C NMR [100 MHz, CD_3Cl_3] δ: 37.1, 54.1, 58.8, 61.7, 91.8, 121.4, 125.6, 128.6, 128.9, 129.3, 129.8, 130.4, 133.0, 155.1, 168.2. MS (ES^+) m/z 385.1 $[M+1]^+$, 769.2 $[2M+H]^+$. Anal. Calcd. for $C_{20}H_{20}N_2O_4S$: C, 62.48; H, 5.24; N, 7.29; S, 8.34. Found: C, 62.55; H, 5.18, N, 7.32; S, 8.09.

4-[(*E*)-2-(Methoxycarbonyl)vinyl]amino-1-oxa-2-thiaspiro[4.4]non-3-ene-2,2-dioxide (51) and (*Z*)-51. According to the method described in the journal for the preparation of **12**, a solution of **40** (100 mg, 0.53 mg), methyl propiolate (57 μL, 0.64 mmol) and DMAP (78 mg, 0.64 mmol) in dry acetonitrile (10 mL) was stirred at -20 ºC for 6.5 h. The solvent was removed and ethyl acetate was added (5 mL) and the mixture was washed with 1N HCl (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried, filtered, and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:2). The data were obtained from a 88:12 mixture (65 mg, 45%) of **(*E*)-51** and **(*Z*)-51**. **(*E*)-51** ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 1.84-1.90 (m, 4H), 1.99-2.08 (m, 2H), 2.15-2.23 (m, 2H), 3.64 (s, 3H), 5.51 (d, 1H, *J* = 15.0 Hz), 6.61 (s, 1H), 7.57 (d, 1H, *J* = 15.0 Hz), 8.73 (bs, 1H). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 25.8, 39.9, 52.3, 96.8, 102.5, 119.9, 143.4, 154.0, 168.6. **(*Z*)-51** ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 3.74 (s, 3H), 5.60 (d, 1H, *J* = 8.3 Hz), 6.39 (s, 1H), 6.25 (d, 1H, *J* = 8.3 Hz), 9.47 (bs, 1H). (ES^+) m/z 274.1 $[M+1]^+$. Anal. Calcd. for $C_{11}H_{15}NO_5S$: C, 48.34; H, 5.53; N, 5.12; S, 11.73. Found: C, 48.45; H, 5.49; N, 5.18; S, 11.57

7-Aza-7-benzyl-4-[(*E*)-2-(methoxycarbonyl)vinyl]amino-1-oxa-2-thiaspiro[4.4]non-3-ene-2,2-dioxide (53) and (*Z*)-53. According to the method described in the journal for the preparation of **12**, a solution of **42** (100 mg, 0.36 mg), methyl propiolate (38 μL, 0.43 mmol) and DMAP (52 mg, 0.64 mmol) in dry acetonitrile (10 mL) was stirred at -20 ºC for 4 h. The solvent was removed and ethyl acetate was added (5 mL) and the mixture was washed with 1N

HCl (2 × 5 mL) and brine (2 × 5 mL). The organic layer was dried, filtered, and evaporated to dryness. The final residue was purified by CCTLC on the Chromatotron (hexane/ethyl acetate, 1:2). The data were obtained from a 95:5 mixture (67 mg, 51%) of **(*E*)-53** and **(Z)-53**. **(*E*)-53:** ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 2.31-2.49 (m, 2H), 2.58-2.73 (m, 2H), 3.15 (m, 2H), 3.75-3.78 (m, 2H), 3.75 (s, 3H), 5.42 (d, 1H, *J* = 13.8 Hz), 5.79 (s, 1H,), 7.22-7.38 (m, 6H), 8.55 (bs, 1H). ^{13}C NMR [75 MHz, $CDCl_3$] δ: 34.3, 50.4, 59.7, 61.5, 62.4, 89.4, 104.2, 120.5, 131.1, 133.2, 133.5, 134.5, 135.1, 135.7, 143.1, 144.6, 166.9. **(*Z*)-53:** ^{1}H NMR [300 MHz, $(CD_3)_2CO$] δ: 3.80 (s, 3H), 5.21 (d, 1H, *J* = 8.6 Hz), 5.74 (s, 1H), 10.30 (bs, 1H). (ES^+) m/z 365.2 $[M+1]^+$. Anal. Calcd. for $C_{17}H_{20}N_2O_5S$: C, 56.03; H, 5.53; N, 7.69; S, 8.80. Found: C, 55.96; H, 5.43; N, 7.72; S, 8.65.

Figure 1-SI. General structure of TSAO nucleosides.