

SYNTHESIS OF HETEROCYCLE SUBSTITUTED 1-ARYL-4-PIPERIDONES

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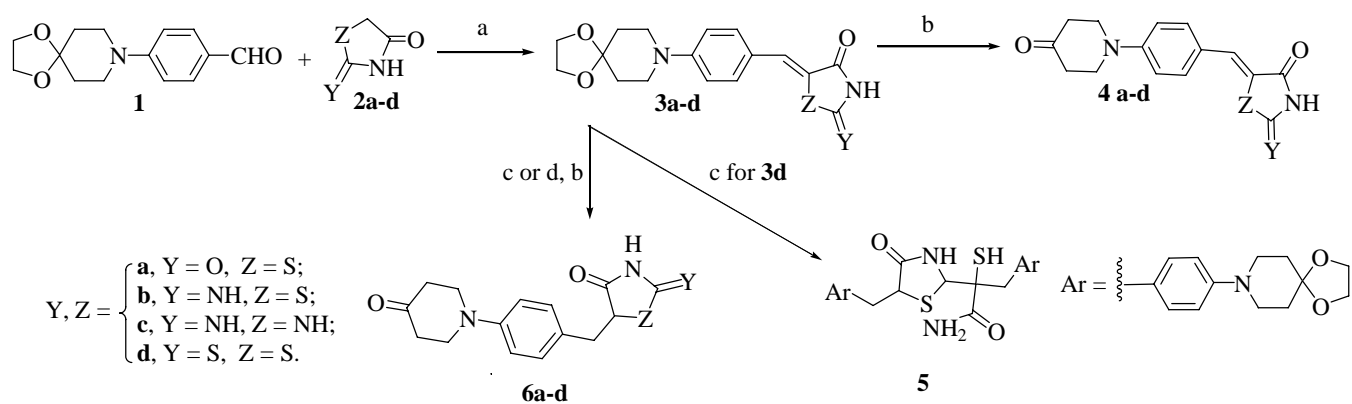
Abstract – A series of heterocycle substituted 1-aryl-4-piperidones were prepared *via* Knoevenagel condensations between nitrogen-containing 5-membered heterocycles and benzaldehyde (**1**) followed by reduction or amination. The oxadiazolidinedione ring was formed by reacting the *N*-hydroxyurea (**10**) with methyl chloroformate and sodium hydride.

As part of a research program directed at the development of human β_3 agonists, a series of 1-aryl-4-piperidones with various heterocyclic acid equivalents were required in the hope of obtaining potent and selective β_3 agonists with good pharmacokinetic properties.^{1, 2} Herein, we report the synthesis of 1-aryl-4-piperidones with nitrogen-containing 5-membered heterocycles as surrogates for the carboxylic acid functionality.³ The heterocycles reported here are thiazolidinedione, pseudothiohydantoin, hydantoin, rhodanine, oxadiazolidinedione, and thiazolidinone.

The thiazolidinone, pseudothiohydantoin, hydantoin or rhodanine substituted 1-aryl-4-piperidones (**4a-d** and **6a-d**) were prepared according to Scheme 1. Knoevenagel condensations between benzaldehyde (**1**)⁴ and 2,4-thiazolidinedione, hydantoin, pseudothiohydantoin, or rhodanine (**2a-d**) followed by acidic hydrolysis provided the olefinic piperidones (**4a-d**). The condensations were usually effected in refluxing ethanol in the presence of piperidine. It was found more satisfactory to condense benzaldehyde (**1**) with **2d** (rhodanine) in the presence of β -alanine in refluxing acetic acid. The reduced alkylpiperidone (**6a**) was obtained by a hydrogen transfer reaction⁵ (5% Na-Hg in wet THF) followed by an acidic ketal hydrolysis. A much slower reaction was observed on reduction of thiazolidinedione (**3a**) under catalytic hydrogenation due to the presence of sulfur in the molecule. Similarly, the reduced pseudothiohydantoin (**6b**) and hydantoin (**6c**) analogues were obtained by 5% Na-Hg reduction and acidic hydrolysis.

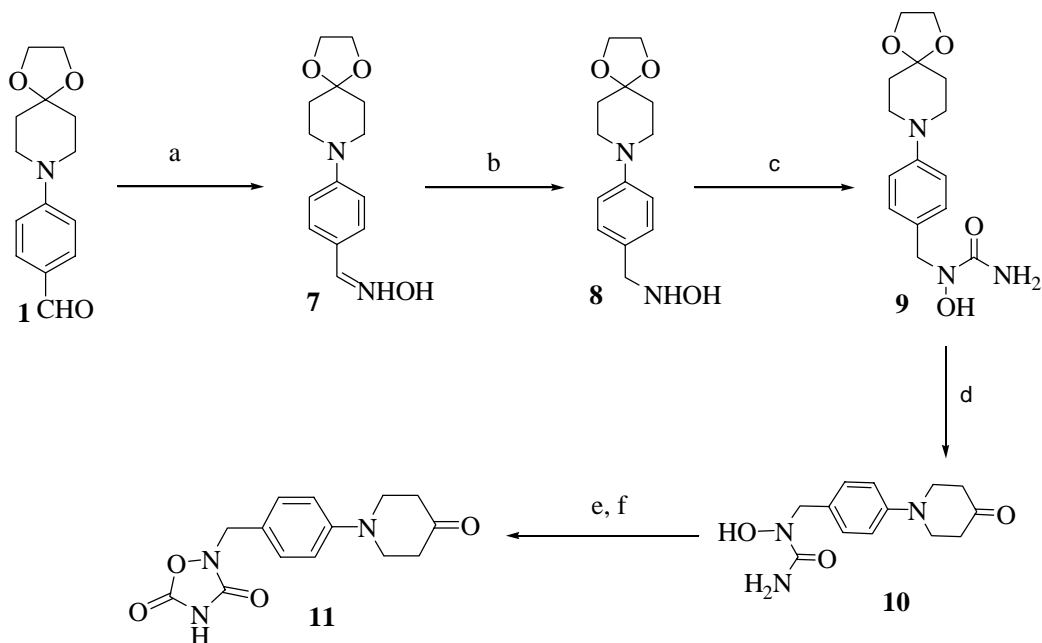
However, treatment of rhodanine (**3d**) with 5% Na-Hg resulted in the formation of a partially hydrolyzed dimeric compound (**5**).⁶ The reduced rhodanine (**6d**) was successfully prepared by reduction of **3d** with

lithium borohydride in pyridine/THF⁷ followed by acidic hydrolysis.



Scheme 1. (a) piperidine/EtOH or β -alanine/HOAc; (b) concentrated hydrochloric acid; (c) 5% Na/Hg, THF/H₂O; (d) LiBH₄/pyridine/THF.

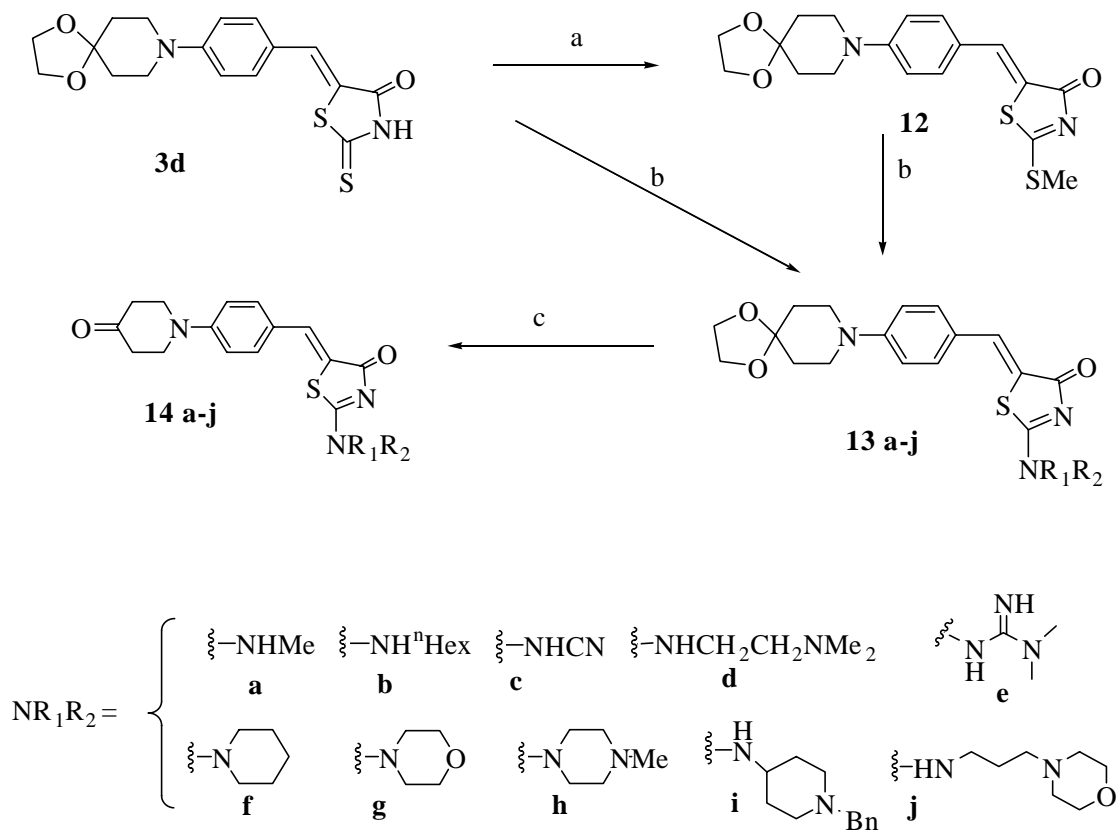
Oxadiazolidinedione substituted 1-aryl-4-piperidone (**11**) was prepared as outlined in Scheme 2. Reductive amination of benzaldehyde (**1**) with hydroxylamine produced **7**, which was treated with *N*-TMS isocyanate and ketal hydrolysis to afford hydroxyurea (**10**). The oxadiazolidinedione ring was formed by reacting the *N*-hydroxyurea (**10**) with methyl chloroformate and sodium hydride.⁸



Scheme 2. (a) NH₂OH HCl salt, NaOAc, 90%; (b) NaCNBH₃, MeOH, 78%; (c) Me₃SiNCO, THF/dioxane (1: 1), 73%; (d) concentrated hydrochloric acid, 98%; (e) ClCO₂Me, NaH, THF; (f) NaH, DMF, 85%.

Synthesis of thiazolidinone substituted 1-aryl-4-piperidone (**14a-j**) was achieved as illustrated in Scheme 3. The thiazolidinone (**14f**) was obtained by condensation of rhodanine (**3d**) with piperidine in refluxing ethanol followed by ketal hydrolysis. Alternatively, alkylation of rhodanine (**3d**) with methyl iodide provided the methylmercapto compound (**12**). Reaction of compound (**12**) with various amines such as 4-

amino-1-benzylpiperidine, *N,N*-dimethylguanidine or cyanamide followed by ketal hydrolysis gave the desired piperidones (**14a-e**) and (**14g-j**).



Scheme 3. (a) MeI, *N,N*-diisopropylethylamine, EtOH, 99%; (b) NHR_1R_2 , EtOH; (c) concentrated hydrochloric acid.

In all cases, the Knoevenagel condensations only afforded the *Z* isomers.^{7, 9-11}

In conclusion, thiazolidinedione, pseudothiohydantoin, hydantoin, rhodanine, and thiazolidinone substituted 1-aryl-4-piperidones have been prepared by Knoevenagel condensations between nitrogen-containing 5-membered heterocycles and benzaldehyde (**1**) followed by reduction or amination. The oxadiazolidinedione substituted 1-aryl-4-piperidone (**11**) was synthesized by reacting the *N*-hydroxyurea (**10**) with methyl chloroformate.

EXPERIMENTAL

Melting points were determined in open capillary tubes on a Meltemp melting point apparatus and are uncorrected. ¹H NMR spectra were determined with a Bruker DPX-300 spectrometer at 300 MHz.

Chemical shifts δ are expressed in ppm relative to the internal standard tetramethylsilane and *J* (coupling constant) in Hz. ESMS spectra were recorded in positive or negative mode on a Micromass Platform spectrometer. HRMS spectra were obtained on a Finnigan MAT-90 spectrometer. Combustion analyses were obtained using a Perkin-Elmer Series II 2400 CHNS/O analyzer. Chromatographic purifications

were performed by flash chromatography using Baker 40 μm silica gel. Thin-layer chromatography (TLC) was performed on Analtech silica gel GHLF 250 M prescored plates.

5-[4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)benzylidene]thiazolidine-2,4-dione (3a)

A mixture of benzaldehyde (**1**)⁴ (15.0 g, 60 mmol), 2,4-thiazolidinedione (7.0 g, 60 mmol) and piperidine (8.0 mL, 81.2 mmol) in 450 mL of ethanol was refluxed for 6 h. The solid which was formed on cooling the solution was collected and washed with a small amount of ethanol to give the title compound as an orange solid (20.5 g, 99%); mp 255-257 °C; ¹H NMR (DMSO-d₆) δ 1.67 (t, J = 5.6 Hz, 4 H), 3.47 (t, J = 5.6 Hz, 4 H), 3.92 (s, 4 H), 7.07 (d, J = 9.0 Hz, 2 H), 7.43 (d, J = 9.0 Hz, 2 H), 7.67 (s, 1 H), 12.40 (br s, 1 H); MS (ES) m/z : 346.8 (MH⁺); HRMS Calcd for C₁₇H₁₉N₂O₄S(MH⁺): 346.0987. Found: 346.0994. Anal. Calcd for C₁₇H₁₈N₂O₄S: C, 58.94; H, 5.24; N, 8.09. Found: C, 58.92; H, 5.11; N, 7.96.

5-[4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)benzylidene]-2-iminothiazolidin-4-one (3b)

The same procedure described above for **3a** was employed with 5.0 g (20.2 mmol) of benzaldehyde (**1**)⁴, 2 mL of piperidine and 2.78 g (24 mmol) of pseudothiohydantoin to afford 6.50 g (94%) of the title compound as an orange solid; mp >300 °C (decomp); ¹H NMR (DMSO-d₆) δ 1.68 (t, J = 5.6 Hz, 4 H), 3.43 (t, J = 5.6 Hz, 4 H), 3.91 (s, 4 H), 7.06 (d, J = 8.9 Hz, 2 H), 7.41 (d, J = 8.9 Hz, 2 H), 7.48 (s, 1 H), 8.99 (br s, 1 H), 9.33 (br s, 1 H); MS (ES) m/z : 345.9 (MH⁺); HRMS Calcd for C₁₇H₂₀N₃O₃S (MH⁺): 346.1226. Found: 346.1205. Anal. Calcd for C₁₇H₁₉N₃O₃S: C, 59.11; H, 5.54; N, 12.16. Found: C, 58.80; H, 5.71; N, 12.38.

5-[4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)benzylidene]imidazolizolidine-2,4-dione (3c)

The same procedure described above for **3a** was employed with 5.0 g (20.2 mmol) of benzaldehyde (**1**)⁴, 4 mL of piperidine and 3.0 g (30.0 mmol) of hydantoin to afford 5.90 g (90%) of the title compound as an orange solid; mp 265-267 °C; ¹H NMR (DMSO-d₆) δ 1.68 (t, J = 5.8 Hz, 4 H), 3.38 (t, J = 5.8 Hz, 4 H), 3.91 (s, 4 H), 6.34 (s, 1 H), 6.95 (d, J = 8.7 Hz, 2 H), 7.49 (d, J = 8.7 Hz, 2 H), 10.33 (br s, 1 H), 11.05 (br s, 1 H); MS (ES) m/z : 330.0 (MH⁺); HRMS Calcd for C₁₇H₂₀N₃O₄(MH⁺): 330.1454. Found: 330.1477.

5-[4(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)benzylidene]-2-thioxothiazolidin-4-one (3d)

A mixture of benzaldehyde (**1**)⁴ (4.96 g, 20.0 mmol), rhodanine (2.66 g, 20.0 mmol), and β -alanine (2.0 g, 22.5 mmol) in 50 mL of acetic acid was refluxed for 2 h. The solid which was formed on cooling the solution was collected and washed with a small amount of acetic acid to give the title compound as a red

solid (4.8 g, 66%); mp >240 °C (decomp); ¹H NMR (CDCl₃) δ 1.81 (t, *J* = 5.5 Hz, 4 H), 3.55 (t, *J* = 5.5 Hz, 4 H), 4.00 (s, 4 H), 6.92 (d, *J* = 8.9 Hz, 2 H), 7.58 (d, *J* = 8.9 Hz, 2 H), 7.38 (s, 1 H); MS (ES) *m/z*: 362.8 (MH⁺); HRMS Calcd for C₁₇H₁₉N₂O₃S₂(MH⁺): 363.0837. Found: 363.0852. Anal. Calcd for C₁₇H₁₈N₂O₃S₂: C, 56.33; H, 5.01; N, 7.73. Found: C, 56.28; H, 4.89; N, 7.73.

5-[4-(Oxopiperidin-1-yl)benzylidene]thiazolidine-2,4-dione (4a)

Compound (**3a**) (1.60 g, 4.6 mmol) was treated with concentrated hydrochloric acid (150 mL) at rt. After 4 h ~28% ammonium hydroxide was added dropwise and the precipitate was collected by filtration, washed with water, and dried over phosphorus pentoxide to give 1.30 g (93%) of the title compound as an orange solid; mp >255 °C (decomp); ¹H NMR (DMSO-*d*₆) δ 2.45 (t, *J* = 6.0 Hz, 4 H), 3.76 (d, *J* = 6.0 Hz, 4 H), 7.10 (d, *J* = 9.0 Hz, 2 H), 7.48 (d, *J* = 9.0 Hz, 2 H), 7.70 (s, 1 H), 12.41 (br s, 1 H); MS (ES) *m/z*: 301.0 (M-H)⁻; HRMS Calcd for C₁₅H₁₄N₂O₃S(M⁺): 302.0726. Found: 302.0731.

1-[4-(2-Imino-4-oxothiazolidin-5-ylidenemethyl)phenyl]piperidin-4-one (4b)

The same procedure described above for **4a** was employed with 1.50 g (4.3 mmol) of **3b** and 150 mL of concentrated hydrochloric acid to afforded 1.25 g (96%) of the title compound as a yellowish solid; mp >260 °C (decomp); ¹H NMR (DMSO-*d*₆) δ 2.44 (t, *J* = 6.0 Hz, 4 H), 3.74 (t, *J* = 6.0 Hz, 4 H), 7.14 (d, *J* = 6.7 Hz, 2 H), 7.46 (d, *J* = 6.7 Hz, 2 H), 7.50 (s, 1 H), 9.00 (br s, 1 H), 9.24 (br s, 1 H); MS (ES) *m/z*: 301.9 (MH⁺); HRMS Calcd for C₁₅H₁₆N₃O₂S (MH⁺): 302.0961. Found: 302.0957.

5-[4-(4-Oxopiperidin-1-yl)benzylidene]imidazolidine-2,4-dione (4c)

The same procedure described above for **4a** was employed with 0.99 g (3.0 mmol) of **3c** and 50 mL of concentrated hydrochloric acid to afforded 0.65 g (76%) of the title compound as a yellowish solid; mp >240 °C (decomp); ¹H NMR (DMSO-*d*₆) δ 2.43 (t, *J* = 6.0 Hz, 4 H), 3.70 (t, *J* = 6.0 Hz, 4 H), 6.36 (s, 1 H), 7.01 (d, *J* = 9.0 Hz, 2 H), 7.53 (d, *J* = 9.0 Hz, 2 H), 10.35 (br s, 1 H), 11.10 (br s, 1 H); MS (ES) *m/z*: 285.9 (MH⁺); HRMS Calcd for C₁₅H₁₆N₃O₃ (MH⁺): 286.1192. Found: 286.1169.

1-[4-(4-Oxo-2-thioxothiazolidin-5-ylidenemethyl)phenyl]piperidin-4-one (4d)

The same procedure described above for **4a** was employed with 0.90 g (2.5 mmol) of **3d** and 25 mL of concentrated hydrochloric acid to afforded 0.71 g (89%) of the title compound as a red solid; mp >250 °C (decomp); ¹H NMR (DMSO-*d*₆) δ 2.46 (t, *J* = 6.1 Hz, 4 H), 3.79 (t, *J* = 6.1 Hz, 4 H), 7.11 (d, *J* = 9.0 Hz, 2 H), 7.48 (d, *J* = 9.0 Hz, 2 H), 7.56 (s, 1 H); MS (ES) *m/z*: 316.9 (M-H)⁻; HRMS Calcd for C₁₅H₁₄N₂O₂S₂(M⁺): 318.0497. Found: 318.0502.

2-{5-[4-(1,4-Dioxa-8-aza-spiro[4.5]dec-8-yl)benzyl]-4-oxothiazolidin-2-yl}-3-[4-(1,4-dioxa-8-aza-spiro[4.5]dec-8-yl)phenyl]-2-mercaptopropionamide (5)

A mixture of **3d** (3.62 g, 10.0 mmol) and 5% Na-Hg (23.0 g, 50.0 mmol) in water (30 mL) and THF (100 mL) was stirred at rt overnight. The organic layer was decanted from mercury and water. The solvent was evaporated and the residue was purified by flash chromatography (hexanes/ethyl acetate 2/5) followed by recrystallization from methylene chloride/hexanes to afford 0.75 g (23%) of the title compound as a white solid; mp 138°C (decomp); ¹H NMR (DMSO-d₆) δ 1.65-1.75 (m, 8 H), 2.50-3.00 (m, 4 H), 3.10-3.30 (m, 8 H), 3.89 (s, 4 H), 3.91 (s, 4 H), 4.07 (br d, *J* = 9.0 Hz, 1 H), 4.80 (s, 1 H), 6.81 (d, *J* = 8.4 Hz, 2 H), 6.89 (d, *J* = 8.4 Hz, 2 H), 6.98 (d, *J* = 8.4 Hz, 2 H), 7.09 (d, *J* = 8.4 Hz, 2 H), 7.50 (s, 1 H), 7.54 (s, 1 H), 8.23 (s, 1 H); MS (ES) *m/z*: 328.0 ((M + 2H)²⁺, 100%), 655.1 (MH⁺, 25%); HRMS Calcd for C₃₃H₄₃N₄O₆S₂ (MH⁺): 655.2624. Found: 655.2588. Anal. Calcd for C₃₃H₄₂N₄O₆S₂: C, 60.53; H, 6.46; N, 8.56. Found: C, 60.65; H, 6.60; N, 8.47.

5-[4-(4-Oxopiperidin-1-yl)benzyl]thiazolidine-2,4-dione (6a)

A mixture of **3a** (2.20 g, 6.3 mmol) and 5% Na-Hg (16.0 g, 34.8 mmol) in water (20 mL) and THF (60 mL) was stirred at rt overnight. The organic layer was decanted from mercury and water. The solvent was evaporated and the residue was treated with 100 mL of concentrated hydrochloric acid. After 3 h ~28% ammonium hydroxide was added dropwise and the precipitate was collected by filtration, washed with water, and dried over phosphorus pentoxide to give 1.20 g (63%) of the title compound as an off-white solid; mp 152-154 °C; ¹H NMR (DMSO-d₆) δ 2.40 (t, *J* = 5.9 Hz, 4 H), 3.01 (dd, *J* = 14.1, 9.2 Hz, 1 H), 3.29 (dd, *J* = 14.1, 4.2 Hz, 1 H), 3.57 (t, *J* = 5.9 Hz, 4 H), 4.86 (dd, *J* = 9.2, 4.2 Hz, 1 H), 6.96 (d, *J* = 8.6 Hz, 2 H), 7.10 (d, *J* = 8.6 Hz, 2 H); MS (ES) *m/z*: 304.8 (MH⁺, 100%), 609.0 (2MH⁺, 100%), 914.1 (3MH⁺, 10%); HRMS Calcd for C₁₅H₁₆N₂O₃S(M⁺): 304.0881. Found: 304.0905. Anal. Calcd for C₁₅H₁₆N₂O₃S: C, 59.19; H, 5.36; N, 9.20. Found: C, 58.96; H, 5.16; N, 8.91.

1-[4-(2-Imino-4-oxothiazolidin-5-yl-methyl)phenyl]piperidin-4-one (6b)

The same procedure described above for **6a** was employed with 4.0 g (11.6 mmol) of **4b**, 21.3 g (46.4 mmol) of 5% Na-Hg and 250 mL of concentrated hydrochloric acid to afford 2.51 g (71%) of the title compound as a yellowish solid; mp >260 °C (decomp); ¹H NMR (DMSO-d₆) δ 2.40 (t, *J* = 5.9 Hz, 4 H), 2.79 (dd, *J* = 14.2, 9.7 Hz, 1 H), 3.28 (dd, *J* = 14.2, 4.0 Hz, 1 H), 3.56 (t, *J* = 5.9 Hz, 4 H), 4.54 (dd, *J* = 9.7, 4.0 Hz, 1 H), 6.92 (d, *J* = 8.6 Hz, 2 H), 7.10 (d, *J* = 8.6 Hz, 2 H), 8.68 (br s, 1 H), 8.90 (br s, 1 H); MS (ES) *m/z*: 303.9 (MH⁺); HRMS Calcd for C₁₅H₁₈N₃O₂S (MH⁺): 304.1119. Found: 304.1113.

5-[4-(4-Oxo-piperidin-1-yl)benzyl]imidazolidine-2,4-dione (6c)

The same procedure described above for **6a** was employed with 1.80 g (5.4 mmol) of **4c**, 10.0 g (21.7 mmol) of 5% Na-Hg and 150 mL of concentrated hydrochloric acid to afford 1.20 g (77%) of the title compound as an off-white solid; mp >165 °C (decomp); ¹H NMR (DMSO-d₆) δ 2.39 (t, *J* = 6.0 Hz, 4 H), 2.83 (d, *J* = 4.8 Hz, 2 H), 3.55 (t, *J* = 6.0 Hz, 4 H), 4.25 (t, *J* = 4.8 Hz, 1 H), 6.92 (d, *J* = 8.7 Hz, 2 H), 7.05 (d, *J* = 8.7 Hz, 2 H), 7.91 (s, 1 H); MS (ES) *m/z*: 287.9 (MH⁺); HRMS Calcd for C₁₅H₁₈N₃O₃(MH⁺): 288.1348. Found: 288.1396.

1-[4-(4-Oxo-2-thioxothiazolidin-5-ylmethyl)phenyl]piperidin-4-one (6d)

Lithium borohydride (0.17 g, 6.3 mmol) was added in portions to a stirred solution of **3d** (0.90 g, 2.5 mmol) in pyridine (2.5 mL) and THF (12 mL) at rt under nitrogen. The mixture was heated to reflux and stirred for 3 h. The cooled mixture was carefully added to a stirred solution of hydrochloric acid (3 mL) and iced water (~50 mL). Extracted into ethyl acetate, the combined organic extracts were washed with water, dried (MgSO₄) and the solvent was removed in vacuo. The resulting residue was treated with 100 mL of concentrated hydrochloric acid. After 16 h ~28% ammonium hydroxide was added dropwise until pH about 7, and extracted with methylene chloride. The organic extracts were dried over MgSO₄. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 1/1) gave 0.40 g (50%) of the title compound as a yellow solid; mp 152-154 °C; ¹H NMR (CDCl₃) δ 2.55 (t, *J* = 6.0 Hz, 4 H), 3.15 (dd, *J* = 14.2, 9.7 Hz, 1 H), 3.34 (dd, *J* = 14.2, 4.1 Hz, 1 H), 3.60 (t, *J* = 6.0 Hz, 4 H), 4.58 (dd, *J* = 9.7, 4.1 Hz, 1 H), 6.89 (d, *J* = 8.6 Hz, 2 H), 7.15 (d, *J* = 8.6 Hz, 2 H), 9.05 (br s, 1 H); MS (ES) *m/z*: 321 (MH⁺, 100%); HRMS Calcd for C₁₅H₁₇N₂O₂S₂(MH⁺): 321.0730. Found: 321.0732. Anal. Calcd for C₁₅H₁₆N₂O₂S₂: C, 56.22; H, 5.03; N, 8.74. Found: C, 56.20; H, 4.91; N, 8.34.

4-(1,4-Dioxa-8-azaspiro[4.5]dec-8-yl)benzaldehyde oxime (7)

A solution of sodium acetate (6.64 g, 60.7 mmol) in water (10 mL) was added into a mixture of benzaldehyde (**1**) (5.0 g, 20.2 mmol), hydroxylamine hydrochloride (4.22 g, 60.7 mmol), ethyl alcohol (300 mL), and water (50 mL). The mixture was stirred at 70 °C for 10 h, then poured into water and extracted with ethyl acetate. The organic extracts were dried over MgSO₄. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 2/1) gave a white solid (6.3 g, 90% yield); mp 151-152 °C; ¹H NMR (DMSO-d₆) δ 1.63 (m, 4 H), 3.35 (m, 4 H), 3.90 (s, 4 H), 6.96 (m, 2 H), 7.40 (m, 2 H), 7.96 (s, 1 H), 10.75 (s, 1 H); MS (ES) *m/z*: 263 (MH⁺); Anal. Calcd for C₁₄H₁₈N₂O₃: C, 64.11; H, 6.92; N, 10.68. Found: C, 64.24; H, 6.81; N, 10.64.

8-{4-[(Hydroxyamino)methyl]phenyl}-1,4-dioxo-8-azaspiro[4.5]decane (8)

Hydrochloric acid (4N, in dioxane) was added dropwise into a mixture of **7** (5.3 g, 20.2 mmol), sodium cyanoborohydride (6.3 g, 101.2 mmol), methyl alcohol (200 mL) and methyl orange (10 mg) until an acidic solution (pH about 4) was achieved. The mixture was then stirred for 1 h, poured into water, neutralized with NaOH (2N) and extracted with ethyl acetate. The organic extracts were dried over MgSO₄. Evaporation and purification by flash chromatography (hexanes/ethyl acetate/methyl alcohol 10/5/1) gave a white solid (4.2 g, 78% yield); mp 107-109 °C; ¹H NMR (DMSO-d₆) δ 1.64 (m, 4 H), 3.20 (m, 4 H), 3.74 (s, 2 H), 3.90 (s, 4 H), 5.84 (br s, 1 H), 6.86 (m, 2 H), 7.14 (m, 2 H), 7.19 (br s, 1 H); MS (ES) m/z: 265 (MH⁺).

N-[4-(1,4-Dioxo-8-azaspiro[4.5]dec-8-yl)benzyl]-N-hydroxyurea (9)

Trimethylsilyl isocyanate (2.1 mL, 14.9 mmol) was added dropwise into a mixture of **8** (2.61 g, 9.9 mmol), THF (20 mL) and dioxane (20 mL). The mixture was stirred at rt for 24 h, poured into water and extracted with ethyl acetate. The organic extracts were dried over MgSO₄. Evaporation and purification by flash chromatography (hexanes/ethyl acetate/methyl alcohol 10/5/1) gave a white solid (2.20 g, 73%); mp 153-154 °C; ¹H NMR (DMSO-d₆) δ 1.70 (m, 4 H), 3.21 (m, 4 H), 3.89 (s, 4 H), 4.37 (s, 2H), 6.23 (br s, 2 H), 6.86 (m, 2 H), 7.10 (m, 2 H), 9.19 (s, 1 H); MS (ES) m/z: 308 (MH⁺); Anal. Calcd for C₁₅H₂₁N₃O₄: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.37; H, 6.78; N, 13.47.

N-Hydroxy-N-[4-(4-oxo-1-piperidiny)benzyl]urea (10)

A mixture of **9** (2.20 g, 7.2 mmol) and 10 mL of concentrated hydrochloric acid was stirred at rt for three days. The mixture was then neutralized with ammonium hydroxide, and extracted with ethyl acetate. The organic extracts were dried over MgSO₄. Evaporation and purification by flash chromatography (ethyl acetate) gave a white solid (1.86 g, 98%); mp 138-140 °C; ¹H NMR (DMSO-d₆) δ 2.41 (m, 4 H), 3.60 (m, 4 H), 4.43 (s, 2 H), 6.37 (br s, 2 H), 7.03 (m, 2 H), 7.21 (m, 2 H), 9.31 (s, 1 H); MS (ES) m/z: 264 (MH⁺).

2-[4-(4-Oxo-1-piperidiny)benzyl]-1,2,4-oxadiazolidine-3,5-dione (11)

Sodium hydride (60% in mineral oil, 0.46 g, 11.4 mmol) was added into a mixture of **10** (1.50 g, 5.7 mmol) and THF (10 mL). The mixture was stirred at rt for 2 h and then methyl chloroformate (2.0 mL, 22.8 mmol) was added. The new mixture was stirred for 2 h, poured into water, acidified with hydrochloric acid (2 N) to pH about 6, and extracted with ethyl acetate. The organic extracts were dried over MgSO₄. Evaporation gave a yellow solid (1.58 g). Part of that material (0.46 g, 1.43 mmol) was dissolved in DMF (4 mL) and treated with sodium hydride (60% in mineral oil, 0.057 g, 1.43 mmol). The mixture was stirred for 1 h, poured into water, acidified with hydrochloric acid (2N) and extracted with

ethyl acetate. The organic extracts were dried over MgSO₄. Evaporation and purification by flash chromatography (hexanes/ethyl acetate 1/1) gave the title compound as a yellow solid (0.35 g, 85%); ¹H NMR (DMSO-d₆) δ 2.42 (m, 4 H), 3.62 (m, 4 H), 4.76 (s, 2 H), 7.10 (m, 2 H), 7.23 (m, 2 H), 12.43 (br s, 1 H); MS (ES) m/z: 290 (MH⁺).

5-[4-(1,4-Dioxa-8-aza-spiro[4,5]dec-8-yl)benzylidene]-2-methylsulfanylthiazo-4-one (12)

A mixture of **3d** (1.50 g, 4.14 mmol), *N,N*-diisopropylethylamine (0.65 g, 5 mmol), methyl iodide (1.13 g, 8 mmol) in ethanol (50 mL) was stirred at rt overnight. Water (300 mL) was then added and the mixture was stirred for 1 h. The solid which was formed was collected, washed with water, and dried over MgSO₄ to give the title compound as a red solid; mp 163-165 °C; ¹H NMR (CDCl₃) δ 1.80 (t, *J* = 5.8 Hz, 4 H), 2.88 (s, 3 H), 3.50 (t, *J* = 5.8 Hz, 4 H), 4.00 (s, 4 H), 6.90 (d, *J* = 9.0 Hz, 2 H), 7.45 (d, *J* = 9.0 Hz, 2 H), 7.80 (s, 1 H); MS (ES) m/z: 376.9 (MH⁺, 100%), 752.9 ((2M + H)⁺, 5%); HRMS Calcd for C₁₈H₂₀N₂O₃S₂ (M⁺): 376.0915. Found: 376.0888. Anal. Calcd for C₁₈H₂₀N₂O₃S₂: C, 57.42; H, 5.35; N, 7.44. Found: C, 57.34; H, 5.18; N, 7.34.

5-[4-(1,4-Dioxa-8-aza-spiro[4,5]dec-8-yl)benzylidene]-2-methylaminothiazo-4-one (13a)

A mixture of **12** (0.56 g, 1.5 mmol) and methylamine (7.5 mL, 2.0 M solution in tetrahydrofuran) in ethanol (100 mL) was refluxed overnight. After cooling to rt hexanes (70 mL) was added and the solid which was formed was collected and washed with hexanes to give 0.31 g (58%) of the title compound as a yellowish solid; mp 250-252 °C; ¹H NMR (CDCl₃) δ 1.75-1.85 (m, 4 H), 3.19 (s, 3 H), 3.40-3.50 (m, 4 H), 4.00 (s, 4 H), 6.98 (d, *J* = 9.0 Hz, 2 H), 7.46 (d, *J* = 9.0 Hz, 2 H), 7.71 (s, 1 H); MS (ES) m/z: 359.9 (MH⁺, 100%), 719.0 ((2M+H)⁺, 10%); HRMS Calcd for C₁₈H₂₁N₃O₃S (M⁺): 359.1304. Found: 359.1307.

5-[4-(1,4-Dioxa-8-aza-spiro[4,5]dec-8-yl)benzylidene]-2-hexylaminothiazol-4-one (13b)

The same procedure described above for **13a** was employed with 3.76 g (10.0 mmol) of **12** and 5.06 g (50.0 mmol) of hexylamine to afforded 3.20 g (75%) of the title compound as a yellowish solid; mp 185-187 °C; ¹H NMR (DMSO-d₆) δ 0.87 (t, *J* = 6.6 Hz, 3 H), 1.20-1.40 (m, 6 H), 1.50-1.60 (m, 2 H), 1.66 (br t, *J* = 5.6 Hz, 4 H), 3.40-3.60 (m, 6 H), 3.92 (s, 4 H), 7.06 (d, *J* = 8.9 Hz, 2 H), 7.39 (d, *J* = 8.9 Hz, 2 H), 7.48 (s, 1 H), 9.50 (br s, 1 H); MS (ES) m/z: 430.0 (MH⁺, 100%); HRMS Calcd for C₂₃H₃₁N₃O₃S (M⁺): 429.2086. Found: 429.2081.

5-[4-(1,4-Dioxa-8-aza-spiro[4,5]dec-8-yl)benzylidene]-4-oxo-4,5-dihydrothiazol-2-ylcyanamide (13c)

A solution of cyanamide (0.25 g, 6.0 mmol) in ethanol (50 mL) was treated in portions with potassium *tert*-butoxide (0.62 g, 5.5 mmol) at 0~5 °C. The mixture was stirred for 15 min and then **12** (1.70 g, 4.52 mmol) in ethanol (50 mL) was added. The reaction mixture was refluxed for 3 h. Upon cooling with addition of 40 mL of hexanes the precipitated solid was collected as a red solid; mp >300 °C (decomp); ¹H NMR (DMSO-*d*₆) δ 1.68 (br t, *J* = 5.6 Hz, 4 H), 3.45 (br t, *J* = 5.6 Hz, 4 H), 3.92 (s, 4 H), 7.05 (d, *J* = 9.0 Hz, 2 H), 7.33 (s, 1 H), 7.39 (d, *J* = 9.0 Hz, 2 H); MS (ES) *m/z*: 370.9 (MH⁺, 100%); HRMS Calcd for C₁₈H₁₉N₄O₃S (MH⁺): 371.1172. Found: 371.1172.

2-(3-Dimethylaminopropylamino)-5-[4-(1,4-dioxo-8-aza-spiro[4.5]dec-8-yl)benzylidene]thiazol-4-one (13d)

The same procedure described above for **13a** was employed with 3.76 g (10.0 mmol) of **12** and 5.11 g (50 mmol) of 3-dimethylaminopropylamine to afford 3.60 g (84%) of the title compound as a yellowish solid; mp 230-232 °C; ¹H NMR (DMSO-*d*₆) δ 1.60-1.70 (m, 6 H), 2.10 (s, 6 H), 2.25 (t, *J* = 7.0 Hz, 2 H), 3.30-3.50 (m, 6 H), 3.85 (s, 4 H), 7.07 (d, *J* = 9.0 Hz, 2 H), 7.40 (d, *J* = 9.0 Hz, 2 H), 7.48 (s, 1 H), 9.50 (br s, 1 H); MS (ES) *m/z*: 431.1 (MH⁺, 100%); HRMS Calcd for C₂₂H₃₀N₄O₃S (M⁺): 430.2038. Found: 430.2040.

5-[4-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-yl)benzylidene]-2-morpholin-4-ylthiazol-4-one (13g)

The same procedure described above for **13a** was employed with 3.76 g (10.0 mmol) of **12** and 8.70 g (100 mmol) of morpholine to afford 4.01 g (78%) of the title compound as a yellowish solid; mp 228-230 °C; ¹H NMR (DMSO-*d*₆) δ 1.68 (br t, *J* = 5.6 Hz, 4 H), 3.45 (br t, *J* = 5.6 Hz, 4 H), 3.60-3.70 (m, 2H), 3.70-3.80 (m, 4 H), 3.90-3.92 (m, 2 H), 3.92 (s, 4 H), 7.05 (d, *J* = 7.6 Hz, 2 H), 7.49 (d, *J* = 7.6 Hz, 2 H), 7.52 (s, 1 H); MS (ES) *m/z*: 416.0 (MH⁺, 100%); HRMS Calcd for C₂₁H₂₅N₃O₄S (M⁺): 415.1565. Found: 415.1570.

5-[4-(1,4-Dioxo-8-aza-spiro[4.5]dec-8-yl)benzylidene]-2-(4-methylpiperazin-1-yl)thiazol-4-one (13h)

The same procedure described above for **13a** was employed with 1.88 g (5.0 mmol) of **12** and 5.0 g (50.0 mmol) of 4-methylpiperazine to afford 2.1 g (98%) of the title compound as a yellowish solid; mp 240-242 °C; ¹H NMR (DMSO-*d*₆) δ 1.68 (br t, *J* = 5.6 Hz, 4 H), 2.22 (s, 3 H), 2.40-2.50 (m, 4 H), 3.41 (br t, *J* = 5.6 Hz, 4 H), 3.60-3.65 (m, 2 H), 3.90-4.05 (m, 2 H), 4.05 (s, 4 H), 7.05 (d, *J* = 8.7 Hz, 2 H), 7.46 (d, *J* = 8.7 Hz, 2 H), 7.53 (s, 1 H); MS (ES) *m/z*: 429.0 (MH⁺, 100%); HRMS Calcd for C₂₂H₂₈N₄O₃S (M⁺): 428.1882. Found: 428.1869.

5-[4-(1,4-Dioxo-8-aza-spiro[4,5]dec-8-yl)benzylidene]-2-(2-morpholin-4-yl-ethylamino)thiazol-4-one (13j)

The same procedure described above for **13a** was employed with 0.39 g (1.0 mmol) of **12** and 1.30 g (10.0 mmol) of 2-morpholin-4-yl-ethylamine to afford 0.37 g (78%) of the title compound as a yellowish solid; mp 265-267 °C; ¹H NMR (DMSO-d₆) δ 1.68 (t, *J* = 5.5 Hz, 4 H), 2.35-2.55 (m, 6 H), 3.44 (t, *J* = 5.5 Hz, 4 H), 3.55-3.65 (m, 6 H), 3.92 (s, 4 H), 7.07 (d, *J* = 8.9 Hz, 2 H), 7.40 (d, *J* = 8.9 Hz, 2 H), 7.47 (s, 1 H), 9.43 (br s, 1 H); MS (ES) *m/z*: 229.9 ((M+2H)²⁺, 40%), 458.9 (MH⁺, 100%), 917.2 ((2M+H)⁺, 3%); HRMS Calcd for C₂₃H₃₀N₄O₄S (M⁺): 458.1988. Found: 458.1979.

1-[4-(2-Methylamino-4-oxo-4H-thiazol-5-ylidenemethyl)phenyl]piperidin-4-one (14a) The same procedure described above for **4a** was employed with 0.25 g (0.7 mmol) of **13a** and 18 mL of concentrated hydrochloric acid to afford 0.20 g (91%) of the title compound as a yellowish solid; mp 254-256 °C; ¹H NMR (DMSO-d₆) δ 2.43 (t, *J* = 5.9 Hz, 4 H), 3.05 (s, 3 H), 3.73 (t, *J* = 5.9 Hz, 4 H), 7.13 (d, *J* = 7.3 Hz, 2 H), 7.46 (d, *J* = 7.3 Hz, 2 H), 7.50 (s, 1 H), 9.41 (br s, 1 H); MS (ES) *m/z*: 315.8 (MH⁺, 100%), 631.0 ((2M+H)⁺, 10%); HRMS Calcd for C₁₆H₁₇N₃O₂S (M⁺): 315.1041. Found: 315.1057.

1-[4-(2-Hexylamino-4-oxo-4H-thiazol-5-ylidenemethyl)phenyl]piperidin-4-one (14b)

The same procedure described above for **4a** was employed with 2.30 g (5.4 mmol) of **13b** and 150 mL of concentrated hydrochloric acid to afford 1.50 g (73%) of the title compound as a yellowish solid; mp >180 °C (decomp); ¹H NMR (DMSO-d₆) δ 0.87 (t, *J* = 6.5 Hz, 3 H), 1.20-1.40 (m, 6 H), 1.50-1.75 (m, 2 H), 2.43 (t, *J* = 5.9 Hz, 4 H), 3.40-3.55 (m, 2 H), 3.74 (t, *J* = 5.9 Hz, 4 H), 7.12 (d, *J* = 8.9 Hz, 2 H), 7.44 (d, *J* = 8.9 Hz, 2 H), 7.50 (s, 1 H), 9.47 (t, *J* = 5.3 Hz, 1 H); MS (ES) *m/z*: 386.0 (MH⁺, 100%); HRMS Calcd for C₂₁H₂₇N₃O₂S (M⁺): 385.1824. Found: 385.1809.

4-Oxo-5-[4-(4-oxopiperidin-1-yl)benzylidene]-4,5-dihydrothiazol-2-yl-cyanamide (14c)

The same procedure described above for **4a** was employed with 1.60 g (3.9 mmol) of **13c** and 50 mL of concentrated hydrochloric acid to afford 0.51 g (40%) of the title compound as a red solid; mp >250 °C (decomp); ¹H NMR (DMSO-d₆) δ 2.43 (t, *J* = 6.0 Hz, 4 H), 3.76 (t, *J* = 6.0 Hz, 4 H), 7.12 (d, *J* = 9.0 Hz, 2 H), 7.36 (s, 1 H), 7.47 (d, *J* = 9.0 Hz, 2 H); MS (ES) *m/z*: 326.7 (MH⁺, 100%); HRMS Calcd for C₁₆H₁₅N₄O₂S (MH⁺): 327.0910. Found: 327.0909.

1-[4-[2-(3-Dimethylaminopropylamino)-4-oxo-4H-thiazol-5-ylidenemethyl]phenyl]piperidin-4-one (14d)

The same procedure described above for **4a** was employed with 2.50 g (5.8 mmol) of **13d** and 150 mL of concentrated hydrochloric acid to afford 1.02 g (45%) of the title compound as a yellowish solid; mp >190 °C (decomp); ¹H NMR (DMSO-d₆) δ 1.60-1.80 (m, 2 H), 2.24 (s, 6 H), 2.30-2.45 (m, 6 H), 3.51 (t, *J* = 6.9 Hz, 2 H), 3.74 (t, *J* = 5.9 Hz, 4 H), 7.12 (d, *J* = 9.0 Hz, 2 H), 7.44 (d, *J* = 9.0 Hz, 2 H), 7.53 (s, 1 H); MS (ES) *m/z*: 387.0 (MH⁺, 100%); HRMS Calcd for C₂₀H₂₆N₄O₂S (M⁺): 386.1776. Found: 386.1768.

***N,N*-Dimethyl-*N'*-{4-oxo-5-[4-(4-oxopiperidin-1-yl)benzylidene]-4,5-dihydrothiazol-2-yl}guanidine (14e)**

A solution of 1,1-dimethylguanidine sulfate (2.05 g, 7.5 mmol) in ethanol (50 mL) was treated in portions with potassium *tert*-butoxide (1.44 g, 12.9 mmol). The mixture was stirred for 40 min and then rapidly filtered into a suspension of **12** (1.88 g, 5 mmol) in ethanol (20 mL). The reaction mixture was refluxed for 2 h. Upon cooling with addition of a small amount of hexanes the precipitated solid was collected and dissolved in 25 mL of concentrated hydrochloric acid. After 30 min ~28% ammonium hydroxide was added dropwise and the precipitate was collected by filtration, washed with water, and dried over phosphorus pentoxide to give 1.80 g (97%) of the title compound as a yellowish solid; mp 218-220 °C; ¹H NMR (DMSO-d₆) δ 2.49 (t, *J* = 6.0 Hz, 4 H), 2.90-3.20 (m, 6 H), 3.73 (t, *J* = 6.0 Hz, 4 H), 7.10 (d, *J* = 9.0 Hz, 2 H), 7.47 (d, *J* = 9.0 Hz, 2 H), 7.50 (s, 1 H); MS (ES) *m/z*: 372.0 (MH⁺); HRMS Calcd for C₁₈H₂₂N₅O₂S (MH⁺): 372.1416. Found: 372.1404.

1-[4-(4-Oxo-2-piperidin-1-yl -4*H*-thiazol-5-ylidene)methyl]phenyl]piperidin-4-one (14f)

A solution of **12** (1.69 g, 4.5 mmol) and piperidine (4.25 g, 50 mmol) in 100 mL of ethanol was refluxed for 2 h. The excess piperidine and the solvent were removed and the residue was dissolved in 200 mL of concentrated hydrochloric acid. After 30 min ~28% ammonium hydroxide was added dropwise and the precipitate was collected by filtration, washed with water, and dried over phosphorus pentoxide to give 1.60 g (97%) of the title compound as a yellowish solid; mp >70 °C (decomp); ¹H NMR (DMSO-d₆) δ 1.50-1.75 (m, 6 H), 2.43 (t, *J* = 5.9 Hz, 4 H), 3.55-3.70 (m, 2 H), 3.74 (t, *J* = 5.9 Hz, 4 H), 3.80-3.95 (m, 2 H), 7.10 (d, *J* = 8.9 Hz, 2 H), 7.51 (d, *J* = 8.9 Hz, 2 H), 7.54 (s, 1 H); MS (ES) *m/z*: 370.0 (MH⁺, 100%), 739.1 ((2M+H)⁺, 5%); HRMS Calcd for C₂₀H₂₃N₃O₂S (M⁺): 369.1511. Found: 369.1518.

1-[4-(2-Morpholin-4-yl-4-oxo-4*H*-thiazol-5-ylidene)methyl]phenyl]piperidin-4-one (14g)

The same procedure described above for **4a** was employed with 3.80 g (9.2 mmol) of **13g** and 150 mL of concentrated hydrochloric acid to afford 2.9 g (85%) of the title compound as a yellowish solid; mp

250-252 °C; ¹H NMR (DMSO-d₆) δ 2.44 (t, *J* = 6.0 Hz, 4 H), 3.60-3.80 (m, 10 H), 3.85-3.95 (m, 2 H), 7.10 (d, *J* = 8.9 Hz, 2 H), 7.51 (d, *J* = 8.9 Hz, 2 H), 7.57 (s, 1 H); MS (ES) *m/z*: 372.0 (MH⁺, 100%); HRMS Calcd for C₁₉H₂₁N₃O₃S (M⁺): 371.1303. Found: 371.1310.

1-{4-[2-(4-Methylpiperazin-1-yl)-4-oxo-4*H*-thiazol-5-ylidenemethyl]phenyl}piperidin-4-one (14h)

The same procedure described above for **4a** was employed with 1.90 g (4.4 mmol) of **13h** and 100 mL of concentrated hydrochloric acid to afford 1.60 g (94%) of the title compound as a yellowish solid; mp >200 °C (decomp); ¹H NMR (DMSO-d₆) δ 2.24 (s, 3 H), 2.40-2.60 (m, 8 H), 3.60-3.70 (m, 2 H), 3.74 (t, *J* = 6.0 Hz, 4 H), 3.85-3.95 (m, 2 H), 7.10 (d, *J* = 8.9 Hz, 2 H), 7.51 (d, *J* = 8.9 Hz, 2 H), 7.55 (s, 1 H); MS (ES) *m/z*: 385.0 (MH⁺, 100%); HRMS Calcd for C₂₀H₂₄N₄O₂S (M⁺): 384.1620. Found: 384.1616.

1-{4-[2-(1-Benzylpiperidin-4-ylamino)-4-oxo-4*H*-thiazol-5-ylidenemethyl]phenyl}piperidin-4-one (14i)

The same procedures described above for **13a** and **4a** were employed to afford 66% of the title compound as a yellowish solid; mp 95-97 °C; ¹H NMR (DMSO-d₆) δ 1.50-4.00 (m, 9 H), 2.43 (t, *J* = 5.9 Hz, 4 H), 3.33 (s, 2 H), 3.74 (t, *J* = 5.9 Hz, 4 H), 7.12 (d, *J* = 8.7 Hz, 2 H), 7.20-7.50 (m, 5 H), 7.44 (d, *J* = 8.7 Hz, 2 H), 7.52 (s, 1 H); MS (ES) *m/z*: 475.0 (MH⁺, 100%), 949.3 ((2M+H)⁺, 2%); HRMS Calcd for C₂₇H₃₀N₄O₂S (M⁺): 474.2089. Found: 474.2085.

1-{4-[2-(2-Morpholin-4-yl-ethylamino)-4-oxo-4*H*-thiazol-5-ylidenemethyl]phenyl}piperidin-4-one (14j)

The same procedure described above for **4a** was employed with 0.18 g (0.39 mmol) of **13j** and 12 mL of concentrated hydrochloric acid to afford 0.14 g (86%) of the title compound as a yellowish solid; mp 243-245 °C; ¹H NMR (DMSO-d₆) δ 2.30-2.55 (m, 10 H), 3.50-3.70 (m, 6 H), 3.74 (t, *J* = 5.9 Hz, 4 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 7.45 (d, *J* = 8.7 Hz, 2 H), 7.50 (s, 1 H), 9.46 (br s, 1 H); MS (ES) *m/z*: 414.9 (MH⁺, 100%), 829.1 ((2M+H)⁺, 2%); HRMS Calcd for C₂₁H₂₆N₄O₃S (M⁺): 414.1726. Found: 414.1734.

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