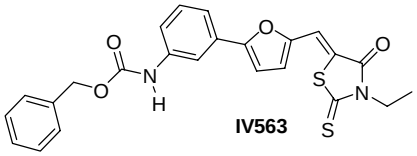
Supporting information for Carter *et al*. (2001) *Proc. Natl. Acad. Sci. USA* **98** (21), 11879–11884. (10.1073/pnas.211178398)

Synthesis of Key Compounds

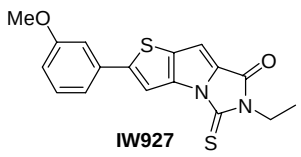
Unless otherwise noted, all reactions were conducted in oven-dried glassware with magnetic stirring under an atmosphere of dry nitrogen, and were monitored by thin layer chromatography (TLC). All commercially available reagents and solvents were purchased at the highest grade possible and then used as received. Flash chromatography (1) was performed by using silica gel 60 (230-400 mesh, EM Reagents, Gibbstown, NJ). Melting points were determined with a Thomas Hoover capillary melting point apparatus equipped with a Fluke 51 K/J thermocouple and are uncorrected. Infrared spectra were taken on a Perkin–Elmer 1600 FTIR spectrometer. ^{1}H NMR spectra were recorded on a Varian Unity Inova 300-MHz spectrometer. Chemical shifts are reported in ppm from tetramethylsilane with the solvent resonance as the internal standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, m = multiplet, app = apparent), coupling constant(s), and integration. Low resolution mass spectra were obtained on a Finnigan (San Jose, CA) Navigator-aQa API spectrometer. High resolution mass spectra were obtained on a Finnigan MAT95S spectrometer. Analytical TLC was performed on EM Reagents 0.25 mm silica gel 60-F_{254} plates, with visualization using UV light.



IV563

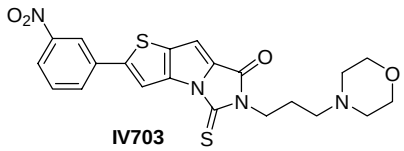
To a solution of *N*-ethyl rhodanine (1.11 g, 6.9 mmol) in 20 ml of acetic acid was added 1.50 g (6.9 mmol) of 5-(3-nitrophenyl)furfural and 1.70 g (20.7 mmol) of sodium acetate. The resultant mixture was heated at 100ºC for 30 h, cooled to room temperature (RT), and diluted with 50 ml of water. The solids were collected and dried overnight to afford 2.96 g (100% yield) of 3-ethyl-5-[5-(3-nitrophenyl)furan-2-ylmethylene]-2-thioxo-1,3-thiazolidin-4-one as an orange powder. To a suspension of this product (1.12 g , 3.11 mmol) in 3 ml of THF was added 10 ml of acetic acid, 0.5 ml of water, and 750 mg (13.8 mmol) of iron powder. The resultant mixture was heated at 55ºC for 15 h, cooled to RT, diluted with EtOAc, and filtered through Celite. The filtrate was washed three times with sat. $NaHCO_3$ and once with brine, and then dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (4 × 10 cm of SiO_2; 30–40% EtOAc/hexanes) to afford 350 mg (34% yield) of the desired 3-ethyl-5-[5-(3-aminophenyl)furan-2-ylmethylene]-2-thioxo-1,3-thiazolidin-4-one as a red powder. To a solution of this product (41 mg, 0.12 mmol) in 5 ml of pyridine was added 35 μl (0.25 mmol) of benzylchloroformate. The reaction mixture was quenched with water and partitioned between dichloromethane and sat. $NaHCO_3$. The organic layer was washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (2 × 10 cm SiO_2; 35% EtOAc/hexanes) to afford 30 mg (54% yield) of IV563 as an orange powder: mp = 213 to 216ºC; ^{1}H-NMR (300 MHz, d_6-DMSO): δ 10.1 (s, 1H), 8.04 (s, 1H), 7.68 (s, 1H), 7.55-7.33 (m, 8H), 7.24 (d, J = 3.7 Hz, 1H), 5.20 (s, 2H), 4.07 (q, J = 7.1 Hz, 2H), 1.20 (t, J = 7.0 Hz, 3H); IR (KBr) 1727, 1697,

1600, 1591, 1537, 1474, 1330, 1237 cm^{-1}; HRMS calculated for $C_{24}H_{21}N_2O_4S_2$ $(M+H)^+$: 465.0943; found: 465.0953.



IW927

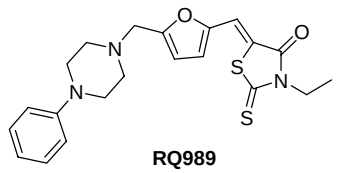
5-Bromo-2-thiophenecarboxaldehyde (5.72 g, 29.9 mmol) and tetrakis(triphenylphosphine)palladium(0) (3.46 g, 2.99 mmol) were combined in dimethoxyethane (75 ml) and the solution was degassed by bubbling nitrogen through for 10 min. 3-Methoxyphenylboronic acid (5.0 g, 32.9 mmol) and aqueous sodium bicarbonate (7.55 g, 89.8 mmol in 50 ml H_2O) were added successively and then the reaction was refluxed for 4 h. The mixture was cooled to RT, and 1 N HCl (120 ml) was added. The solution was extracted three times with EtOAc, and the combined organic layers were twice washed with brine and then dried ($MgSO_4$). After evaporation of the solvent *in vacuo*, the residue was purified by flash chromatography (SiO_2, 25% EtOAc/hexane) to provide 5-(3-methoxyphenyl)-2-thiophenecarboxaldehyde as a viscous oil (4.92 g, 75% yield). This material was converted into methyl 2-(3-methoxyphenyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate following the procedure of Kontosikova (2). Thus, 5-(3-methoxyphenyl)-2-thiophenecarboxaldehyde (4.90 g, 22.4 mmol) in methyazidoacetate (ref. 3; 15 ml) was added dropwise over 2 h to a mixture of potassium t-butoxide in THF (1M, 148 ml) and methanol (148 ml) at –10ºC. The reaction was allowed to warm to RT, stirred for 30 min, poured into 5% citric acid (800 ml), and stirred rapidly for 0.5 h. The solids were filtered, washed with water, and dried under vacuum to give methyl 2-azido-3-[5-(3-methoxyphenyl)-2-thienyl]-2-propenate as a yellow solid (4.33 g, 61% yield). Methyl 2-azido-3-[5-(3-methoxyphenyl)-2-thienyl]-2-propenate (4.33 g, 13.7 mmol) was heated to reflux in *p*-xylene (200 ml) for 1 h. The mixture was cooled to RT and concentrated *in vacuo* to 50 ml. The resulting solids were filtered and dried under vacuum to provide methyl 2-(3-methoxyphenyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (3.78 g, 96% yield) as a yellow powder. Methyl 2-(3-methoxyphenyl)-4H-thieno[3,2-b]pyrrole-5-carboxylate (0.10 g, 0.35 mmol), diisopropylethylamine (41 mg, 0.31 mmol), and ethyl isothiocyanate (91 mg, 1.04 mmol) were combined in a heavy-walled glass tube with a threaded Teflon plug and heated behind a blast shield at 135ºC for 3 h. The reaction mixture was cooled to RT and diluted with chloroform (0.5 ml). The product was isolated by flash chromatography (SiO_2, 30% EtOAc/hexane) and then recrystallized (EtOAc/hexane) to provide IW927 (57 mg, 48% yield) as a yellow crystalline solid: mp 185 ºC; TLC R_f 0.22 (10% EtOAc/hexane); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.76 (s, 1H), 7.28–7.35 (m, 2H), 7.19 (d, J = 2.2 Hz, 1H), 7.00 (s, 1H), 6.91 (m, 1H), 3.95 (q, J = 6.9 Hz, 2H), 3.89 (s, 3H), 1.32 (t, J = 6.9 Hz, 3H); IR (KBr) 1725, 1410 cm^{-1}; MS m/z 384 $[M+(AcCN+H)]^+$; HRMS calculated for $C_{17}H_{14}N_2O_2S_2$: 343.0575; found 343.0569.



IV703

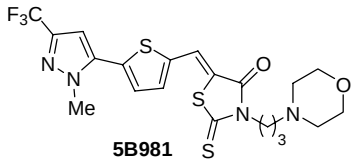
IV703 was synthesized in an analogous manner to IW927, substituting 3-nitrophenylboronic acid and 3-morpholinopropyl isothiocyanate where appropriate: mp 171 to 172ºC; TLC R_f 0.16 (50% ethyl acetate/hexane); ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.51 (t, J = 1.8 Hz, 1H), 8.21 (m, 1H), 8.12 (m, 1H), 7.98 (s, 1H), 7.79 (t, J = 8.0 Hz, 1H), 7.22 (s, 1H), 3.99 (t, J =

7.0 Hz, 2H), 3.51 (m, 4H), 2.45 (t, J = 6.6 Hz, 2H), 2.38 (m, 4H), 1.95 (quin, J = 6.6 Hz, 2H); IR (KBr) 1738, 1409, 1365 cm^{-1}; MS m/z 456 (M^+); HRMS calculated for $C_{21}H_{20}N_4O_4S_2$: 456.0926; found: 456.0928.



RQ989

5-(Chloromethyl)-2-furaldehyde (0.25 g, 1.73 mmol; ref. 4) and phenylpiperizine (0.56 g, 3.45 mmol) were combined in THF (10 ml) and stirred for 15 h at RT. The THF was removed *in vacuo* and the residue was triturated with EtOAc. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 35% EtOAc/hexanes) to afford 30 mg of 5-[(*N*-phenylpiperizinyl)methyl]-2-furaldehyde. This aldehyde (30 mg, 0.11 mmol) was combined with *N*-ethyl rhodanine (18 mg, 0.11 mmol) in DMF (50 µl). The solution was charged with acetic acid (55 µl) and sodium acetate (4.5 mg) and heated at 85ºC for 4 h. The reaction was cooled and partitioned between EtOAc and H_2O. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; 25 to 50% EtOAc/hexanes) to afford 40 mg of RQ989 as a yellow oil, which solidified on standing: mp 116ºC (decomposes); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.42 (s, 1H), 7.26–7.22 (m, 2H), 6.92–6.79 (m, 4H), 6.48 (bs, 1H), 4.16 (q, J = 7.0 Hz, 2H), 3.76 (bs, 2H), 3.24 (bs, 4H), 2.75 (bs, 4H), 1.26 (t, J = 6.9 Hz, 3H); IR (KBr) 1705, 1609, 1565, 1502 cm^{-1}; HRMS calculated for $C_{21}H_{24}N_3O_2S_2$ $(M+H)^+$: 414.1310; found: 414.1314.



5B981

A mixture of glycine methyl ester hydrochloride (13.25 g, 105 mmol) and *N*-methyl morpholine (200 mmol) in toluene was heated at reflux and charged with 3-morpholinopropylisothiocyanate (15 g, 95 mmol). After several hours, the reaction was cooled and extracted with brine (three times). The aqueous phase was extracted once with EtOAc, and the combined organic extracts were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to give *N*-(3-morpholino)propyl rhodanine. To a mixture of the unpurified *N*-(3-morpholino)propyl rhodanine (50 mg, 0.19 mmol) and 2-[1-methyl-3-trifluoromethyl)pyrazol-5-yl]thiophene-5-carboxaldehyde (Maybridge, 50 mg, 0.19 mmol) in DMF (1 ml) was added sodium acetate (8 mg) and acetic acid (100 µl). The mixture was heated at reflux for 3 h, cooled, and partitioned between H_2O and CH_2Cl_2. The organic phase was dried (Na_2SO_4), filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography (SiO_2; CH_2Cl_2 to 5% MeOH/CH_2Cl_2) to give 20 mg of pure 5B981 as a yellow solid: mp 135 ºC (decomp.); ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.72 (s, 1H), 7.30 (s, 2H), 6.81 (s, 1H), 4.16 (t, J = 7.0 Hz, 2 H), 3.97 (s, 3H), 3.60 (t, J = 4.5 Hz, 4H), 2.45-2.30 (m, 6H), 1.87 (quin, J = 6.9 Hz, 2 H); IR (KBr) 1693, 1590, 1564 cm^{-1}; HRMS calculated for $C_{20}H_{22}F_3N_4O_2S_3$ $(M+H)^+$: 503.0857; found: 503.0862.

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