JOC*Note*

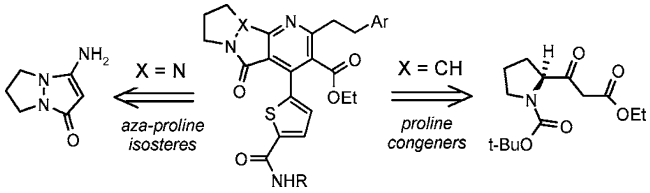
Hantzsch Synthesis of Pyrazolo[1′,2′:1,2]pyrazolo[3,4-*b*]pyridines: Partial Agonists of the Calcitonin Receptor

Eric E. Boros,* David J. Cowan, Richard F. Cox, Makda M. Mebrahtu, Michael H. Rabinowitz,† James B. Thompson, and Lawrence A. Wolfe, III

GlaxoSmithKline Research and Development, Five Moore Drive, Research Triangle Park, North Carolina 27709

eric.e.boros@gsk.com

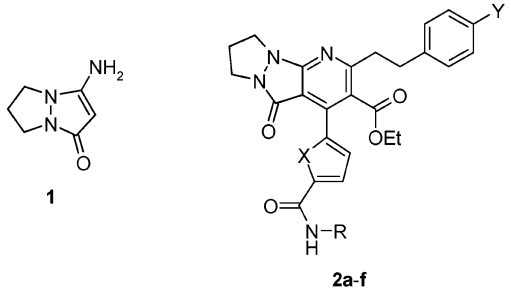
Received February 28, 2005



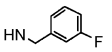
Small molecule calcitonin receptor agonists are of potential utility in the treatment and prevention of osteoporosis. Bicycloeneamine **1** was a useful intermediate in the synthesis of pyrazolopyridine calcitonin receptor partial agonists **2a**−**f**. Dihydropyridines **10a**−**c** were conveniently prepared by reaction of **1** with Knoevenagel adducts **9a**−**c**, or in the case of **10d**, by a three component reaction with **1**, β-keto-ester **7b**, and aldehyde **8c**. Oxidation of **10a**−**d** to pyridines **11a**−**d** and subsequent amide formation afforded the title compounds.

Osteoclast cells digest bone matrix and release calcium and phosphorus into the blood through a process known as resorption. When left unchecked, resorption can lead to the diseased states of osteopenia and ultimately, osteoporosis. Human calcitonin, a 32 amino acid peptide hormone, binds to high affinity G-protein coupled receptors on the osteoclast, and its release from the thyroid gland inhibits resorption and effects a reduction in blood calcium levels.[1] Moreover, administration of injectible and nasal spray formulations of salmon calcitonin[2] is known to increase bone mineral density, reduce fracture risk, and ameliorate musculoskeletal pain in humans.[3] For these reasons, small molecule calcitonin receptor agonists are of interest as biological tools and therapeutic agents in the treatment and prevention of osteoporosis.[4] Partial agonists of the calcitonin receptor may also reduce or modulate the side effects associated with a full agonist.

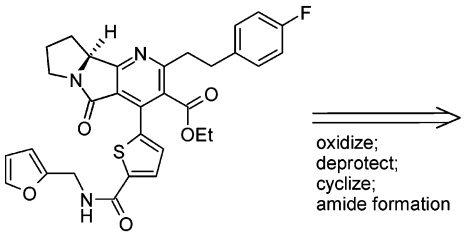
We recently developed a convenient synthesis of the unusual bicyclic eneamine 1[5] and herein describe the application of this compound to the synthesis of pyrazolo-[1′,2′:1,2]pyrazolo[3,4-*b*]pyridinecarboxamides **2a**−**f**, a potent series of calcitonin receptor partial agonists and achiral isosteres of the corresponding (*S*)-proline-derived congeners (e.g., compound **3**).



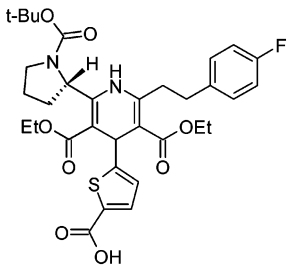
1 **2a-f**

compd	HN-R	X	Y
2a		S	F
2b		S	F
2c		S	F
2d		O	F
2e		CH=CH	CF_3
2f		CH=CH	F

The functionally diverse pyrrolopyridinecarboxamide **3** represents a rare class of potent small molecule calcitonin receptor partial agonists.[6] Compound **3** and its analogues are prepared on solid support or in solution by Hantzsch dihydropyridine methodology as previously described.[6,7] Oxidation of the intermediate dihydropyridine **4** and subsequent deprotection, cyclization, and amide formation generates the target **3** (eq 1).[6]



3



4 (1)

* Corresponding author. Phone: (919) 483-8116; fax: (919) 315-0430.

† Current Address: Johnson and Johnson Pharmaceutical Research and Development, 3210 Merryfield Row, San Diego, CA 92121.

(1) Mehta, N. M.; Malootian, A.; Gilligan, J. P. *Curr. Pharm. Design* **2003**, *9*, 2659−2676.

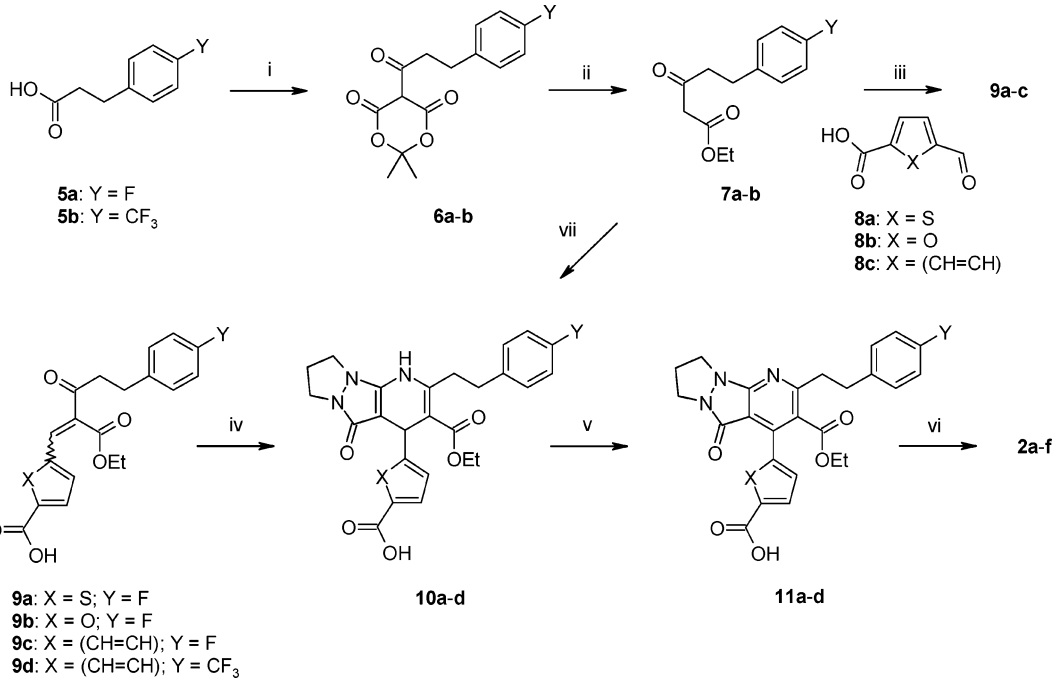
(2) Yamauchi, H.; Suzuki, H.; Orima, H. *J. Bone Miner. Metab.* **2003**, *21*, 198−204.

(3) Avioli, L. V. *Trends Endocrinol. Metab.* **1997**, *8*, 89−92.

(4) For recent syntheses of calcitonin peptide analogues and natural product calcitonin agonists, see: (a) Hongbin, Y. Y.; Men, H.; Lee, C. *J. Am. Chem. Soc.* **2004**, *126*, 14720−14721. (b) Kapurniotu, A. *Curr. Med. Chem.* **2004**, *11*, 2845−2865. (c) Taylor, J. W.; Jin, Q. K.; Sbacchi, M.; Wang, L.; Belfiore, P.; Garnier, M.; Kazantzis, A.; Kapurniotu, A.; Zaratin, P. F.; Scheideler, M. A. *J. Med. Chem.* **2002**, *45*, 1108−1121.

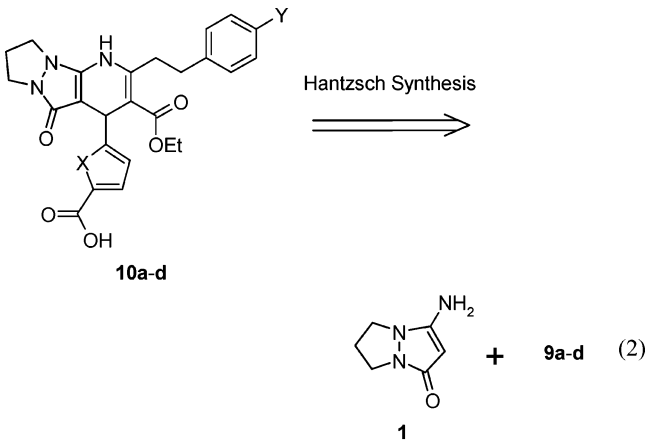
10.1021/jo050370b CCC: $30.25
Published on Web 05/21/2005

SCHEME 1 [a]



[a] Key: (i) Meldrum's acid, DCC, DMAP, CH_2Cl_2; (ii) EtOH, reflux; (iii) C_6H_6, piperidine, Dean–Stark; (iv) **1**·HCl (generated in situ), EtOH, NaOEt, reflux; (v) ceric ammonium nitrate, CH_3CN; (vi) RNH_2, EDC·HCl, HOBT, DMF; (vii) **1**·HCl, **7b**, **8c**, EtOH, NaOEt, reflux.

During a medicinal chemistry effort to evaluate core-template isosteres of **3**, we wished to prepare the novel aza-analogues **2**, in which the stereogenic carbon of **3** is replaced by nitrogen.[8] A Hantzsch synthesis[9] of dihydropyridines **10** was proposed, starting from Knoevenagel adducts **9** and enamine **1** (eq 2). In contrast to the



(2)

synthesis of **3** (eq 1), which requires late stage deprotection and cyclization steps, the synthesis of **2** generates the fused tricyclic core in one step. Interestingly, applications of **1** in organic synthesis are limited;[5,10] however, its compact, electron-rich structure appeared well-suited for the Hantzsch protocol.

Bicyclic eneamine **1** was generated from 1-cyanoacetylpyrazolidine as previously described.[5] Syntheses of **9a**–**c** were accomplished in three steps from the appropriate hydrocinnamic acids **5a**–**b** as shown in Scheme 1. Coupling of **5a**–**b** with Meldrum's acid afforded the tricarbonyl intermediates **6a**–**b**, which were heated in refluxing ethanol to generate β-ketoesters **7a**–**b**.[11] Condensation of **7a** with aldehydes **8a**–**c** provided Knoevenagel[12] adducts **9a**–**c** and set the stage for their Hantzsch cyclization to dihydropyridines **10a**–**c**.

Syntheses of **10a**–**c** were accomplished by treating **9a**–**c** with **1**·HCl (generated in situ from 1-cyanoacetylpyrazolidine hydrochloride[5]) followed by the addition of NaOEt (Scheme 1). Under these conditions, dihydropyridines **10a**–**c** were obtained in 41–64% yields. To streamline the process, a three-component Hantzsch reaction was investigated with aldehyde **8c**, β-keto ester **7b**, and **1**·HCl (eq 3). Heating these reactants with NaOEt in EtOH at reflux afforded **10d** in 51% yield.

(5) Boros, E. E.; Bouvier, F.; Randhawa, S.; Rabinowitz, M. H. *J. Heterocycl. Chem.* **2001**, *38*, 613–616.

(6) Bhandari, A.; Boros, E. E.; Cowan, D. J.; Handlon, A. L.; Hyman, C. E.; Oplinger, J. A.; Rabinowitz, M. H.; Turnbull, P. S. International Patent Application WO 03,076,440 (2003); *Chem. Abstr.* **2003**, *139*, 261291.

(7) Bhandari, A.; Li, B.; Gallop, M. A. *Synthesis* **1999**, 1951–1960.

(8) For examples of isosteric stereogenic carbon replacement in antibacterial agents and HIV–protease inhibitors, see: (a) Snyder, L. B.; Meng, Z.; Mate, R.; D'Andrea, S. V.; Marinier, A.; Quesnelle, C. A.; Gill, P.; DenBleyker, K. L.; Fung-Tomc, J. C.; Frosco, M.; Martel, A.; Barrett, J. F.; Bronson, J. J. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 4735–4739. (b) Getman, D. P.; DeCrescenzo, G. A.; Heintz, R. M.; Reed, K. L.; Talley, J. J.; Bryant, M. L.; Clare, M.; Houseman, K. A.; Marr, J. J.; Mueller, R. A.; Vazquez, M. L.; Shieh, H.-S.; Stallings, W. C.; Stegeman, R. A. *J. Med. Chem.* **1993**, *36*, 288–291.

(9) For reviews of the Hantzsch dihydropyridine synthesis and related multicomponent cyclocondensation reactions, see: (a) Sausins, A.; Duburs, G. *Heterocycles* **1988**, *27*, 269–289. (b) Simon, C.; Constantieux, T.; Rodriguez, J. *Eur. J. Org. Chem.* **2004**, 4957–4980.

(10) Greenwald, R. B. U.S. Patent 4,128,425 (1978); *Chem. Abstr.* **1979**, *90*, 95418n.

(11) Oikawa, Y.; Sugano, K.; Yonemitsu, O. *J. Org. Chem.* **1978**, *43*, 2087–2088.

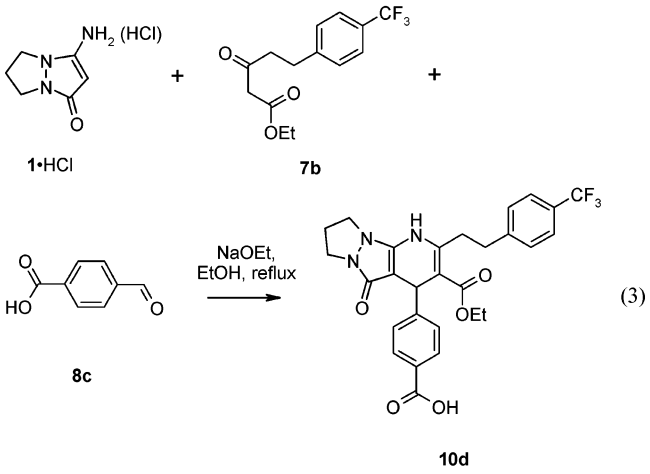
(12) For a review of the Knoevenagel condensation, see Jones, G. *Org. React.* **1967**, *15*, 204–599.

TABLE 1. Human Calcitonin Activation Properties of Pyrazolopyridines 2a−f and Pyrrolopyridine 3[a]

compd	EC_{50} (nM)	% hCal max[b]	*n*[c]
2a	3.1 ± 0.7	27 ± 2	3
2b	4.9 ± 0.2	29 ± 2	3
2c	2.5 ± 0.4	28 ± 2	3
2d	11 ± 2	34 ± 1	3
2e	23 ± 8	48 ± 17	5
2f	7 ± 4	22 ± 1	3
3	8 ± 5	38 ± 3	5

[a] Data are expressed as means ± SE. [b] Percentage of the maximal human calcitonin response. [c] Number of measurements.

Knoevenagel adduct **9d** is a likely intermediate in the reaction, although additional mechanisms involving reaction of **1** with **7b** or **8c** are plausible.



(3)

Dihydropyridines **10a**−**d** were judged to be 86−98% pure based on HPLC and were used in the next step without further purification. Oxidation of **10a**−**d** with ceric ammonium nitrate in CH_3CN gave the corresponding pyridines **11a**−**d** in 66−76% yields. Conversion of **11a**−**d** to carboxamides **2a**−**f** was achieved with EDC·HCl, HOBT, and the requisite primary amine in DMF. The desired products **2a**−**f** were purified by flash chromatography on silica gel in 50−91% yields and were fully characterized.

As shown in Table 1, the title compounds are effective calcitonin receptor partial agonists with potencies comparable to the chiral proline-derived analogue **3**. All compounds in Table 1 displayed 1−2 digit nanomolar potency values (EC_{50}), and 22−48% maximum efficacy, relative to human calcitonin (i.e., the percentage of maximal human calcitonin response).[13,14] Aromatic and heteroaromatic rings at the 4-pyridyl position were well-tolerated as were a variety of 4′-carboxamide groups. The corresponding 4′-carboxylic acids **11a**−**d** were significantly less active under similar assay conditions.

In summary, bicyclic eneamine **1** was of general utility in both two- and three-component Hantzsch syntheses of pyrazolopyridine calcitonin receptor partial agonists **2a**−**f**. The title compounds represent achiral isosteres of the corresponding proline-derived analogues (e.g., compound **3**), and their exemplification further diversifies the portfolio of existing small molecule calcitonin mimetics. Additional details concerning the synthesis and biological activity of **2a**−**f**, **3**, and their congeners will be reported in due course.

Experimental Procedures

General Procedure for Synthesis of Dihydropyridines 10a−c from Knoevenagel Adducts 9a−c. A stirred solution of 1-cyanoacetylpyrazolidine hydrochloride[5] (2.4 mmol) in EtOH (5 mL) was heated at reflux for 30 min to generate **1**·HCl. Compound **9** (2 mmol) and solid NaOEt (2 mmol) were added, and the reflux was maintained an additional 2 h. The stirred mixture was cooled to room temperature and diluted with water (75 mL), and the precipitated product (**10**) was collected by filtration. This material was used in the next step without further purification.

5-{3-[(Ethoxy)carbonyl]-2-[2-(4-fluorophenyl)ethyl]-5-oxo-1,5,8,9-tetrahydro-4*H*,7*H*-pyrazolo[1′,2′:1,2]pyrazolo-[3,4-*b*]pyridin-4-yl}thiophene-2-carboxylic acid (10a). This compound was prepared from **9a** (61% yield): ^{1}H NMR (d_6-DMSO) δ 12.74 (br s, 1H), 9.92 (s, 1H), 7.46 (br s, 1H), 7.24 (m, 2H), 7.08 (t, 2H, J = 8.5), 6.77 (br s, 1H), 5.01 (s, 1H), 4.01 (q, 2H, J = 7), 3.45 (m, 2H), 3.38 (m, 1H), 3.29 (m, 1H), 2.90 (m, 2H), 2.80 (m, 2H), 2.29 (m, 2H), 1.09 (t, 3H, J = 7); ES$^+$ MS: 370 (20), 498 (M + H$^+$, 70).

Hantzsch Synthesis of Dihydropyridine 10d from 1, 7b, and 8c. A stirred mixture of **1**·HCl[5] (1.2 g, 6.83 mmol), **7b** (1.91 g, 6.63 mmol), **8c** (995 mg, 6.63 mmol), and NaOEt (451 mg, 6.63 mmol) in EtOH (45 mL) was heated at reflux for 8 h. Water (50 mL) and EtOAc (50 mL) were added, and the mixture was stirred for 30 min. The suspended solids were collected by filtration, triturated with EtOAc, and dried under high vacuum to afford **10d** as an off-white solid (1.83 g, 51% yield). This material was used without further purification.

4-(3-[(Ethoxy)carbonyl]-5-oxo-2-{2-[4-(trifluoromethyl)-phenyl]ethyl}-1,5,8,9-tetrahydro-4*H*,7*H*-pyrazolo[1′,2′:1,2]-pyrazolo[3,4-*b*]pyridin-4-yl)benzoic Acid (10d). ^{1}H NMR (d_6-DMSO) δ 12.63 (br s, 1H), 9.77 (s, 1H), 7.77 (d, 2H, J = 8), 7.65 (d, 2H, J = 8), 7.46 (d, 2H, J = 8), 7.21 (d, 2H, J = 8), 4.76 (s, 1H), 3.87 (q, 2H, J = 7), 3.41 (m, 2H), 3.22 (m, 2H), 2.96 (m, 4H), 2.24 (m, 2H), 0.95 (t, 3H, J = 7); ES$^+$ MS: 542 (M + H$^+$, 100).

General Procedure for Oxidation of Dihydropyridines 10a−d to Pyridines 11a−d. A solution of ceric ammonium nitrate (2 mmol) in 3:1 actonitrile/water (4 mL) was added dropwise to a stirred solution of **10** (1 mmol) in acetonitrile (5 mL) at room temperature. The reaction mixture was stirred for 4 h and concentrated at reduced pressure. Trituration of the crude product with water/ethanol provided **11** as a filterable solid. This material was used without further purification.

5-{3-[(Ethoxy)carbonyl]-2-[2-(4-fluorophenyl)ethyl]-5-oxo-8,9-dihydro-5*H*,7*H*-pyrazolo[1′,2′:1,2]pyrazolo[3,4-*b*]-pyridin-4-yl}thiophene-2-carboxylic Acid (11a). This compound was prepared from **10a** (67% yield): ^{1}H NMR (d_6-DMSO) δ 13.30 (br s, 1H), 7.69 (d, 1H, J = 3.8), 7.22 (m, 3H), 7.06 (t, 2H, J = 9), 4.04 (q, 2H, J = 7), 3.87 (t, 2H, J = 67), 3.79 (t, 2H, J = 7), 3.00 (m, 4H), 2.55 (m, 2H, J = 7), 0.94 (t, 3H, J = 7).

General Procedure for Synthesis of Calcitonin Agonists 2a−f from 11a−d. Solid EDC·HCl (0.16 mmol) was added to a stirred solution of **11** (0.15 mmol), the requisite primary amine (0.15 mmol), and HOBT (0.25 mmol) in DMF (2.5 mL). The reaction mixture was stirred at room temperature overnight, concentrated at reduced pressure, and reconstituted in CH_2Cl_2. The organic phase was washed with water and purified by silica gel chromatography (eluting with 0−5% MeOH/CH_2Cl_2) to afford **2** as a light yellow solid.

Ethyl 2-[2-(4-Fluorophenyl)ethyl]-4-(5-{[(2-furanylmethyl)amino]carbonyl}-2-thienyl)-5-oxo-8,9-dihydro-5*H*,7*H*-pyrazolo[1′,2′:1,2]pyrazolo[3,4-*b*]pyridine-3-carboxylate (2a). This compound was prepared from **11a** and furfu-

(13) Human calcitonin was cloned according to procedures described in ref 14.

(14) Chen, W. J.; Armour, S.; Way, J.; Chen, G.; Watson, C.; Irving, P.; Cobb, J.; Kadwell, S.; Beaumont, K.; Rimele, T.; Kenakin, T. *Mol. Pharmacol.* **1997**, *52*, 1164−1175.

rylamine (84% yield): ^{1}H NMR (d_6-DMSO) δ 9.08 (t, 1H, $J = 6$), 7.76 (d, 1H, $J = 4$), 7.56 (s, 1H), 7.21 (m, 3H), 7.06 (t, 2H, $J = 9$), 6.37 (t, 1H, $J \sim 3$), 6.27 (d, 1H, $J \sim 3$), 4.43 (d, 2H, $J = 6$), 4.05 (q, 2H, $J = 7$), 3.86 (t, 2H, $J = 7$), 3.79 (t, 2H, $J = 7$), 3.00 (m, 4H), 2.54 (m, 2H, $J = 7$), 0.96 (t, 3H, $J = 7$); ES$^+$ MS: 575 (M + H$^+$, 100); Anal. Calcd for $C_{30}H_{27}FN_4O_5S$: C, 62.71; H, 4.74; N, 9.75. Found: C, 62.49; H, 4.75; N, 9.81.

Ethyl 2-[2-(4-Fluorophenyl)ethyl]-5-oxo-4-(5-{[(3-pyridinylmethyl)amino]-carbonyl}-2-thienyl)-8,9-dihydro-5*H*,7*H*-pyrazolo[1′,2′:1,2]pyrazolo[3,4-b]pyridine-3-carboxylate (2b). This compound was prepared from **11a** and 3-(aminomethyl)pyridine (71% yield): ^{1}H NMR (d_6-DMSO) δ 9.21 (t, 1H, $J = 6$), 8.52 (s, 1H), 8.44 (d, 1H, $J = 5$), 7.76 (d, 1H, $J = 4$), 7.69 (d, 1H, $J = 8$), 7.34 (dd, 1H, $J = 8, 5$), 7.23 (d, 1H, $J = 4$), 7.21 (m, 2H), 7.06 (t, 2H, $J = 9$), 4.46 (d, 2H, $J = 6$), 4.05 (q, 2H, $J = 7$), 3.86 (t, 2H, $J = 7$), 3.79 (t, 2H, $J = 7$), 3.00 (m, 4H), 2.54 (m, 2H, $J = 7$), 0.96 (t, 3H, $J = 7$); ES$^+$ MS: 586 (M + H$^+$, 100); Anal. Calcd for $C_{31}H_{28}FN_5O_4S$: C, 63.58; H, 4.82; N, 11.96. Found: C, 63.69; H, 4.89; N, 11.88.

Ethyl 2-[2-(4-Fluorophenyl)ethyl]-4-[5-({[(3-fluorophenyl)methyl]amino}-carbonyl)-2-thienyl]-5-oxo-8,9-dihydro-5*H*,7*H*-pyrazolo[1′,2′:1,2]pyrazolo[3,4-*b*]pyridine-3-carboxylate (2c). This compound was prepared from **11a** and 3-fluorobenzylamine (80% yield): ^{1}H NMR (d_6-DMSO) δ 9.19 (t, 1H, $J = 6$), 7.78 (d, 1H, $J = 4$), 7.36 (m, 1H), 7.23−7.20 (m, 3H), 7.14−7.04 (m, 5H), 4.45 (d, 2H, $J = 6$), 4.05 (q, 2H, $J = 7$), 3.86 (t, 2H, $J = 7$), 3.79 (t, 2H, $J = 7$), 3.00 (m, 4H), 2.54 (m, 2H, $J = 7$), 0.96 (t, 3H, $J = 7$); ES$^+$ MS: 603 (M + H$^+$, 100); Anal. Calcd for $C_{32}H_{28}F_2N_4O_4S$: C, 63.78; H, 4.68; N, 9.30. Found: C, 63.63; H, 4.62; N, 9.27.

Ethyl 4-(5-{[(1*R*)-2,3-Dihydro-1*H*-inden-1-ylamino]carbonyl}-2-furanyl)-2-[2-(4-fluorophenyl)ethyl]-5-oxo-8,9-dihydro-5*H*,7*H*-pyrazolo[1′,2′:1,2]pyrazolo[3,4-*b*]pyridine-3-carboxylate (2d). This compound was prepared from **11b** and (*R*)-1-aminoindane (81% yield): ^{1}H NMR (d_6-DMSO) δ 8.56 (d, 1H, $J = 8$), 8.03 (d, 1H, $J = 4$), 7.37 (d, 1H, $J = 4$), 7.26−7.15 (m, 6H), 7.06 (t, 2H, $J = 9$), 5.47 (q, 1H, $J = 8$), 4.31 (m, 2H), 3.86 (m, 4H), 2.99 (m, 5H), 2.85 (m, 1H), 2.56 (m, 2H, $J = 7$), 2.43 (m, 1H), 1.92 (m, 1H), 1.08 (t, 3H, $J = 7$); ES$^+$ MS: 595 (M + H$^+$, 100); Anal. Calcd for $C_{34}H_{31}FN_4O_5$: C, 68.68; H, 5.25; N, 9.42. Found: C, 68.40; H, 5.33; N, 9.35.

Ethyl 4-(4-{[(2-Furanylmethyl)amino]carbonyl}phenyl)-5-oxo-2-{2-[4-(trifluoromethyl)phenyl]ethyl}-8,9-dihydro-5*H*,7*H*-pyrazolo[1′,2′:1,2]pyrazolo[3,4-*b*]pyridine-3-carboxylate (2e). This compound was prepared from **11d** and furfurylamine (50% yield): ^{1}H NMR (d_6-DMSO) δ 9.05 (br t, 1H, $J \sim 6$), 7.88 (d, 2H, $J = 8$), 7.61 (d, 2H, $J = 8$), 7.55 (s, 1H), 7.42 (d, 2H, $J = 8$), 7.38 (d, 2H, $J = 8$), 6.37 (m, 1H, $J \sim 3$), 6.26 (d, 1H, $J \sim 3$), 4.46 (d, 2H, $J \sim 6$), 3.88 (q, 2H, $J = 7$), 3.85 (t, 2H, $J = 7$), 3.76 (t, 2H, $J = 7$), 3.11 (s, 4H), 2.53 (m, 2H, $J = 7$), 0.76 (t, 3H, $J = 7$); ES$^+$ MS: 619 (M + H$^+$, 100); Anal. Calcd for $C_{33}H_{29}F_3N_4O_5 \cdot (0.5\ H_2O)$: C, 63.15; H, 4.82; N, 8.93. Found: C, 63.13; H, 4.72; N, 8.99.

Ethyl 2-[2-(4-Fluorophenyl)ethyl]-4-(4-{[(2-furanylmethyl)amino]carbonyl}-phenyl)-5-oxo-8,9-dihydro-5*H*,7*H*-pyrazolo[1′,2′:1,2]pyrazolo[3,4-*b*]pyridine-3-carboxylate (2f). This compound was prepared from **11c** and furfurylamine (91% yield): ^{1}H NMR (d_6-DMSO) δ 9.06 (t, 1H, $J = 6$), 7.88 (d, 2H, $J = 8$), 7.56 (s, 1H), 7.38 (d, 2H, $J = 8$), 7.22 (t, 2H, $J \sim 9$), 7.07 (t, 2H, $J \sim 9$), 6.37 (s, 1H), 6.26 (d, 1H, $J = 3$), 4.46 (d, 2H, $J = 6$), 3.89 (m, 4H), 3.77 (t, 2H, $J = 7$), 3.06 (m, 2H), 2.98 (m, 2H), 2.54 (m, 2H, $J = 7$), 0.78 (t, 3H, $J = 7$); ES$^+$ MS: 569 (M + H$^+$, 100); Anal. Calcd for $C_{32}H_{29}FN_4O_5 \cdot (0.5\ H_2O)$: C, 66.54; H, 5.24; N, 9.70. Found: C, 66.52; H, 5.13; N, 9.70.

Supporting Information Available: General experimental methods; procedures for the calcitonin reporter assay; procedures for synthesis of **7a**−**b** and **9a**−**c**; ^{1}H NMR data for **7a**−**b**, **9a**−**c**, **10b**−**c**, and **11b**−**d**; MS data for **10b**−**c**; ^{1}H NMR spectra of **10a**−**d** and **11a**−**d**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO050370B