(d, 1 H, J = 7 Hz), 6.92 (d, 1 H, J = 7 Hz), 5.71 (m, 2 H, J = 6 Hz), 4.99 (d, 2 H, J = 6 Hz), 4.60 (m, 1 H), 4.55 (d, 2 H, J = 6 Hz); MS (D-EI, MeOH), m/e 234 (26), 203 (10), 173 (10), 148 (13), 134 (100). Anal. ($C_{11}H_{14}N_4O_2 \cdot {}^1/_4H_2O$) C, H, N.

4-Amino-1-[4-hydroxy-3-(hydroxymethyl)but-2-enyl]-imidazo[4,5-*c*]pyridine (9b). Hydrolysis of compound **27g** required refluxing conditions and the product **9b** was isolated as the hydrochloride salt: yield 80 mg (98%), mp 226–227 °C; ^{1}H NMR (DMSO-d_6 + D_2O) δ 8.40 (s, 1 H), 7.67 (d, 1 H, J = 8 Hz), 7.22 (d, 1 H, J = 8 Hz), 5.50 (t, 1 H, J = 7 Hz), 5.02 (d, 2 H, J = 7 Hz), 4.13 (s, 2 H, (*Z*) H-4′), 3.95 (s, 2 H, (*E*) H-4′); MS (D-EI, MeOH) m/e 234.111 58 (calcd), 234.112 72 (found) (30), 185 (10), 148 (13), 134 (100).

Acknowledgment. This work was supported by U.S. Public Health Service Research Grant GM-29332.

Registry No. **1a**, 114978-79-9; **1b**, 114979-16-7; **2a**, 114978-80-2; **2b**, 114978-82-4; **3a**, 104715-57-3; **3b**, 114978-83-5; **4a**, 114979-05-4; **4b**, 114979-13-4; **5**, 115016-40-5; **6**, 5122-38-3; **7**, 114979-06-5; **7**·HCl, 114979-08-7; **8**, 114979-07-6; **8**·HCl, 114979-09-8; **9a**, 114979-10-1; **9a**·HCl, 107053-43-0; **9b**, 114979-14-5; **9b**·HCl, 114979-15-6; **10**, 114979-11-2; **11**, 114979-12-3; **12a**, 114978-78-8; **12b**, 114978-81-3; **13**, 114978-77-7; **14**, 22323-80-4; **15a**, 106757-56-6; **15b**, 85881-88-5; (*E*)-**15c**, 74094-41-0; (*Z*)-**15c**, 74094-42-1; **15d**, 114978-87-9; **15e**, 114978-88-0; **16**, 22323-83-7; **17**, 66183-63-9; **18**, 116-09-6; **19**, 53343-13-8; **20**, 96-26-4; **21**, 114978-84-6; **22**, 6207-26-7; **23**, 114978-85-7; **24**, 114978-86-8; **25a**, 106757-58-8; **25b**, 115016-37-0; (*E*)-**25c**, 114978-89-1; (*Z*)-**25c**, 114978-90-4; **25d**, 114978-91-5; **25e**, 114978-92-6; **26a**, 114978-93-7; **26b**, 115016-38-1; (*E*)-**26c**, 114978-95-9; (*Z*)-**26c**, 114978-96-0; **26d**, 114978-99-3; **26e**, 114979-01-0; **27a**, 114978-94-8; **27b**, 115016-39-2; (*E*)-**27c**, 114978-97-1; (*Z*)-**27c**, 114978-98-2; **27d**, 114979-00-9; **27e**, 114979-02-1; **27f**, 114979-03-2; **27g**, 114979-04-3; $Ph_3P{=}CHCO_2Me$, 2605-67-6; $(MeO)_2POCH_2CO_2Me$, 5927-18-4; EC 3.3.1.1, 9025-54-1; adenine, 73-24-5; 3-deazaadenine, 6811-77-4; sodium adenine, 52994-56-6.

Thienylpyrazoloquinolines: Potent Agonists and Inverse Agonists to Benzodiazepine Receptors

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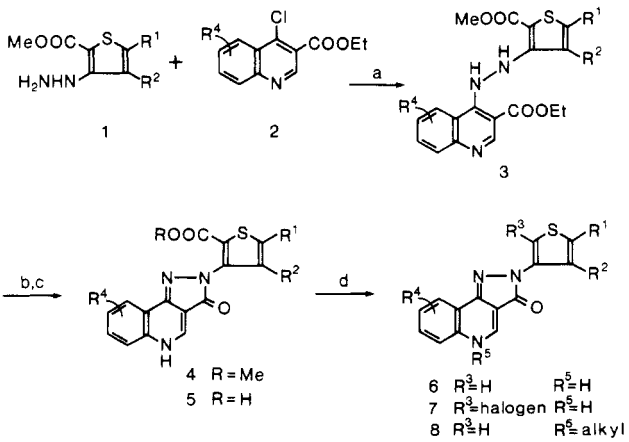
Synthesis and structure–activity relationships of a series of 2-(thien-3-yl)- and 2-(thien-2-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-ones are reported. A number of the compounds possessed 1 order of magnitude higher affinity for the receptors than diazepam. Planarity was one of the structural requirements for binding to benzodiazepine receptors. The activities of agonists and inverse agonists were assessed on the basis of inhibition or facilitation of the pentylenetetrazole-induced convulsions, respectively. Thien-3-yl compounds exhibited inverse agonist activity whereas thien-2-yl analogues with a 5′-alkyl group showed agonist activity. Substitution on the quinoline moiety did not enhance in vivo activity. The most potent compounds were the 5-methylthien-3-yl derivative **6a** as an inverse agonist and the 5-methylthien-2-yl compound **13a** as an agonist.

Since the discovery of benzodiazepine (BZ) receptors in the central nervous system,[1] rapid advances have been made toward understanding the mechanism of benzodiazepine action.[2] The BZ receptor as an allosteric regulatory site of the γ-aminobutyric acid (GABA) receptor is considered to mediate two opposing effects, one to amplify or facilitate the action of GABA ("positive" efficacy[3]), the other to reduce the action of GABA ("negative" efficacy); by convention, agents facilitating GABA-receptor/Cl^- channel function via the BZ receptor are called agonists, and agents reducing the receptor/channel function have been termed inverse agonists.[3,4] Antagonists at BZ receptors block the effect of both agonists and inverse agonists by competitively inhibiting their binding to the BZ receptor. Diazepam, β-CCM,[5] and Ro 15-1788[6] are representative of an agonist, an inverse agonist, and an antagonist, respectively. Generally, the agonists have anxiolytic and anticonvulsant properties, while the inverse agonists exhibit anxiogenic and convulsant effects. From detailed pharmacological investigations, Braestrup et al.[7a] have suggested that BZ receptor ligands in fact comprise a continuous spectrum of agents with a graduated variety of efficacy at the receptor: (1) full agonists, (2) partial agonists, (3) pure agonists, (4) partial inverse agonists, and (5) full inverse agonists. They also demonstrated that some β-carboline derivatives exhibit a wide spectrum by changing the substituents on the parent skeleton. Yokoyama et al.[8] have reported that the phenylpyrazolo-

Scheme I[a]



[a] (a) EtOH/room temperature. (b) 1 N aqueous NaOH/EtOH/room temperature. (c) 1 N aqueous NaOH/EtOH/reflux. (d) Cu/quinoline/190 °C.

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[‡] Division of Pharmacology.

(1) (a) Squires, R. F.; Braestrip, C. *Nature (London)* **1977**, *266*, 732. (b) Möhler, H.; Okada, T. *Science (Washington, D.C.)* **1977**, *198*, 849.
(2) A recent review: Haefely, W.; Kyburz, E.; Gerecke, M.; Möhler, H. *Advances in Drug Research*; Testa, B., Ed.; Academic: Orlando, 1985; Vol. 14, pp 165–322.

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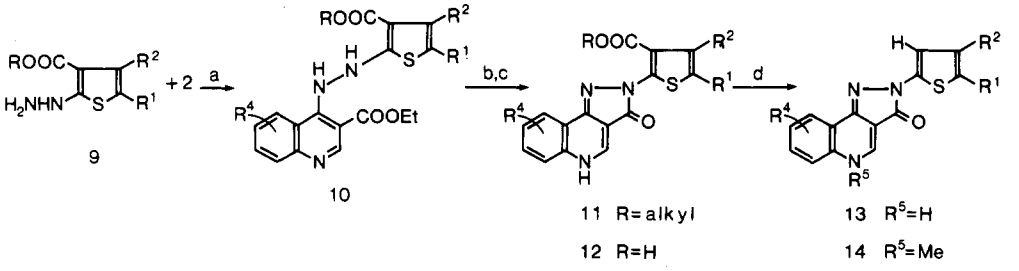
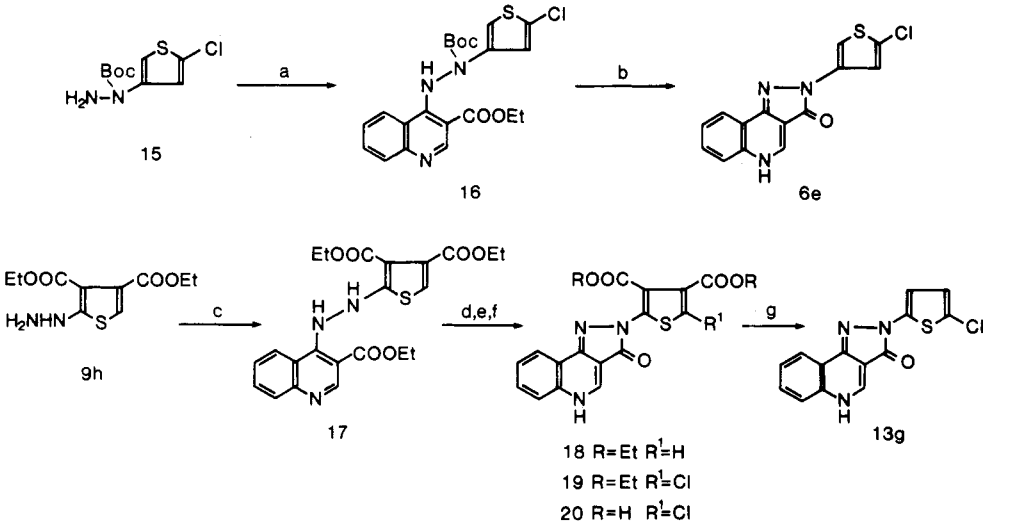
Scheme II[a]



[a] See footnote in Scheme I.

Scheme III[a]



[a] (a) EtOH/40 °C. (b) CF_3COOH–CH_2Cl_2/50 °C, evaporated, 1 N aqueous NaOH/EtOH/room temperature. (c) EtOH/room temperature. (d) 1 N NaOH/EtOH/room temperature. (e) Cl_2/CCl_4–$CHCl_3$/10–15 °C, (f) 1 N aqueous NaOH/MeOH/60 °C. (g) Cu/quinoline/200 °C.

quinoline CGS 9896 and its analogue CGS 8216 are respectively an agonist and an antagonist at the BZ receptor. Later CGS 8216 was found to have inverse agonist activity although its potency was low.[3,9] Interestingly, recent studies[5c,7b] have suggested that the partial inverse agonists are potential nootropic agents.

In a previous paper,[10] we reported that thienylpyrazoloquinoline **6a** (S-135) is a potent orally active inverse agonist to BZ receptors and its regioisomer **13a** has agonist activity. Interestingly, **6a** was characterized as a partial inverse agonst in spite of its potent proconvulsive activity because it did not generate convulsions at a high dose by itself. Here we describe the detailed synthesis and structure–activity relationships of the thienylpyrazoloquinolines including **6a** and **13a**.

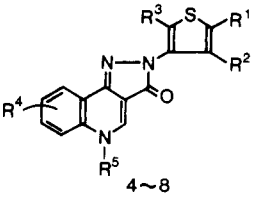
Chemistry

Schemes I and II illustrate our synthetic routes to 2-thien-3-yl- and 2-thien-2-yl derivatives of 2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolines, respectively. The synthetic strategy involved stabilization of extremely unstable hydrazinothiophenes[11] by joining an alkoxycarbonyl group, which was removed after construction of the skeleton. Treatment of 3-hydrazinothiophene-2-carboxylates **1**[12] with 4-chloroquinoline-3-carboxylates (**2**) in ethanol at room temperature gave adducts (**3**), which were cyclized by sodium hydroxide in aqueous ethanol at room temperature to afford esters (**4**). Compounds **4** were hydrolyzed by heating with excess sodium hydroxide in aqueous ethanol to produce acids (**5**). Decarboxylation of **5** with copper in quinoline at elevated temperature provided 2-thien-3-yl-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-ones (**6**). Regioselective halogenation and N-alkylation of **6** gave the derivatives **7** and **8**, respectively.

A similar sequence using 2-hydrazinothiophene-3-carboxylates (**9**)[12] as starting material led to 2-thien-2-yl-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-ones (**13**) as

(3) Braestrup, C.; Nielson, M.; Honoré, T.; Jensen, L. H.; Petersen, E. N. *Neuropharmacology* **1983**, *22*, 1451.
(4) Polc, P.; Bonetti, E. P.; Schaffner, R.; Haefely, W. *Arch. Pharmacol.* **1982**, *321*, 260.
(5) (a) Braestrup, C.; Nielsen, M. *Nature (London)* **1981**, *294*, 472. (b) Jones, B. J.; Oakley, N. R. *Br. J. Pharmacol.* **1981**, *74*, 884. (c) Venault, P.; Chapouthier, G.; deCarvalho, L. P.; Simiand, J.; Morre, M.; Dodd, R. H.; Rossier, J. *Nature (London)* **1986**, *312*, 864.
(6) Hunkeler, W.; Möhler, H.; Pieri, L.; Polc, P.; Bonetti, E. P.; Cumin, R.; Schaffner, R.; Haefely, W. *Nature (London)* **1981**, *290*, 514.
(7) (a) Braestrup, C.; Honoré, T.; Nielsen, M.; Petersen, E. N.; Jensen, H. *Biochem. Pharmacol.* **1984**, *33*, 859. (b) Duka, T.; Stephens, D. N.; Krause, W.; Dorow, R. *Psychopharmacology* **1987**, *93*, 421.
(8) Yokoyama, N.; Ritter, B.; Neubert, A. D. *J. Med. Chem.* **1982**, *25*, 337.
(9) Boast, C. A.; Bernard, P. S.; Barbaz, B. S.; Bergen, K. M. *Neuropharmacology* **1983**, *22*, 1511.
(10) Takada, S.; Shindo, H.; Sasatani, T.; Matsushita, A.; Eigyo, M.; Kawasaki, K.; Murata, S. *J. Med. Chem.* **1987**, *30*, 454.
(11) To our knowledge, hydrazinothiophenes without an electron-withdrawing group have not been synthesized.
(12) (a) Hentschel, M.; Gewald, K. *J. Prakt. Chem.* **1974**, *316*, 878. (b) Huddleston, P. R.; Baker, J. M.; Admzewska, Y. Z. *J. Chem. Res. Synop.* **1980**, 238.

Table I. Pharmacological Activities of Thien-3-ylpyrazoloquinolines



4~8

compd	R^1	R^2	R^3	R^4	R^5	K_i,[a] nM (mean ± SD)	agonist act.[b] ED_{50},[d] mg/kg po	inverse agonist act.[c] PTZ = 75 mg/kg sc; ED_{50},[d] mg/kg po	inverse agonist act.[c] PTZ = 90 mg/kg sc; ED_{50},[d] mg/kg po
6a	Me	H	H	H	H	0.32 ± 0.02		1.67 (1.23–2.23)	0.92 (0.64–1.25)
6b	H	H	H	H	H	0.73 ± 0.44		7.62 (4.60–10.52)	2.49 (1.51–3.99)
6c	H	Me	H	H	H	6.86 ± 0.28		84.42[f]	22.32 (10.87–77.48)
4b	H	H	COOMe	H	H	142 ± 27	inactive to 50	inactive to 50	inactive to 50
5b	H	H	COOH	H	H	17.8 ± 5.3	inactive to 50	inactive to 50	inactive to 50
6d	Et	H	H	H	H	0.41 ± 0.14		inactive to 50	10.26 (4.80–18.92)
6e	Cl	H	H	H	H	0.73 ± 0.24		23.18 (16.16–36.28)	11.54 (4.87–20.58)
7a	Me	H	Cl	H	H	4.69 ± 2.15	inactive to 50	inactive to 50	inactive to 50
7b	Me	H	Br	H	H	27.2 ± 8.21	inactive to 50	inactive to 50	inactive to 50
6f	Me	H	H	7-Cl	H	0.78 ± 0.34	inactive to 50	inactive to 50	inactive to 50
6g	Me	H	H	8-Cl	H	0.63 ± 0.12		13.49 (10.38–16.84)	7.70 (5.61–10.54)
6h	Me	H	H	7-F	H	0.64 ± 0.28		37.7% at 50[e]	6.15 (1.90–13.27)
6i	Me	H	H	8-F	H	0.37 ± 0.18		2.58 (8.84–17.94)	1.32 (0.78–3.66)
6j	Me	H	H	7-Me	H	0.96 ± 0.34	inactive to 50		inactive to 50
6k	Me	H	H	8-Me	H	0.38 ± 0.07		12.89 (8.84–17.94)	5.24 (3.84–7.07)
8a	Me	H	H	H	Me	215 ± 78		2.94 (2.33–3.46)	1.48 (0.99–2.61)
8b	Me	H	H	H	Et	436 ± 95		13.34 (8.36–20.46)	5.24 (3.66–7.08)

[a] Displacing potential to [^{3}H]diazepam binding in rat cerebral cortex. See the Experimental Section for details. [b] Mouse pentylenetetrazole anticonvulsant test. See text for schedule details. [c] Mouse proconvulsant activity. See text for schedule details. [d] ED_{50} values and their 95% confidence limits were calculated by the probit method. [e] Percentage of the animals affected at that dose. [f] Estimated ED_{50}. 95% confidence limits are not given because of poor dose dependency.

shown in Scheme II. Since 5-unsubstituted 2-hydrazinothiophene-3-carboxylates (**9**: R^1 = H) were difficult to prepare from the corresponding 2-aminothiophenes,[13] 5′-unsubstituted compounds **13e** and **13f** were synthesized from 5-(alkoxycarbonyl)-2-hydrazinothiophene derivatives (**9**: R^1 = COOR). It was also hard to utilize a 5-chloro-3-hydrazinothiophene-2-carboxylate or a 5-chloro-2-hydrazinothiophene-3-carboxylate as starting material due to their lability. Therefore, alternate methods were applied to obtain 5′-chloro compounds **6e** and **13g** (Scheme III).

Pharmacological Methods

Binding test to the BZ receptor[1b] was carried out with [^{3}H]diazepam and the receptor preparation obtained from the cerebral cortex of Wistar rats. The procedure is given in the Experimental Section.

Agonist activity was evaluated by inhibition of the pentylenetetrazole (PTZ) induced convulsions. Groups of 8–16 male mice were challenged with a convulsive dose (125 mg/kg, sc) of PTZ 1 h after oral administration of the test compounds. The dose required to prevent tonic convulsions and death in 50% of the animals during a 2-h observation period was calculated by the probit method.

Inverse agonist activity was evaluated by potentiation of PTZ-induced convulsions. Groups of 8–16 male mice were challenged with a subconvulsive dose (75 or 90 mg/kg, sc) of PTZ 1 h after oral administration of the test compounds. The dose required to produce tonic convulsions and death in 50% of the animals during a 2-h observation period was calculated by the probit method.

Both the agonist and inverse agonist activities are apparently mediated via BZ receptors because these effects were completely antagonized by the BZ antagonist Ro 15-1788.[6]

Results and Discussion

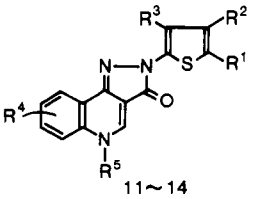
The structures and pharmacological data for thien-3-ylpyrazoloquinolines and their thien-2-yl analogues are shown in Tables I and II, respectively. With the binding affinities, a number of the compounds tested were 1 order of magnitude more potent than diazepam. The substituents (R^2 or R^3) at the 4′- or 2′-position on the thiophene ring reduced the affinity in the thien-3-yl series (**6c**, **4b**, and **5b** vs **6b**; **7a** and **7b** vs **6a**). Similar reduction was seen on the substituent (R^3) at the 3′-position in thien-2-yl analogues (**11a** and **12a** vs **13a**). These substituents can cause torsion between the pyrazoloquinoline skeleton and the thiophene ring.[14] Therefore, in this series of derivatives, the planarity of the whole molecule must be one of the essential factors for binding to the receptors. The substituents at the 7- or 8-position retained or slightly lowered the affinity. The low affinities of the 5-alkyl analogues (**8a**, **8b**, and **14**) suggest that the proton at the 5-position contributes to binding to the receptors.

In the in vivo assays, thien-3-yl compounds mostly exhibited inverse agonist activity, while thien-2-yl analogues showed agonist activity although some compounds (**13e**,

(13) Hydrazinothiophenecarboxylates are generally prepared from the corresponding aminothiophenecarboxyaltes by diazotization and subsequent reduction. Geward et al. (ref 12a) have reported that esters of 5-unsubstituted 2-aminothiophene-3-carboxylic acids suffer from self-coupling during their diazotization, affording triazines. However, when diethyl 2-aminothiophene-3,4-dicarboxylate was subjected to diazotization and reduction, diethyl 2,5-diaminothiophene-3,4-dicarboxylate (**9i**) was obtained as a major byproduct in the preparation of **9h** (see the Experimental Section). This observation suggests that treatment of a 5-unsubstituted 2-aminothiophene-3-carboxylate with nitric acid gives a 5-nitroso compound.

(14) The X-ray analysis of **6a** and **4j**, a closely related analogue of **4b**, suggested that **4b** possesses a twisted structure with a torsional angle of about 50°, while **6a** has an almost planar structure (unpublished results from M. Shiro et al.).

Table II. Pharmacological Activities of Thien-2-ylpyrazoloquinolines



11~14

compd	R^1	R^2	R^3	R^4	R^5	K_i,[a] nM (mean ± SD)	agonist act.[b] ED_{50},[d] mg/kg po	inverse agonist act.[c] PTZ = 75 mg/kg sc; ED_{50},[d] mg/kg po	inverse agonist act.[c] PTZ = 90 mg/kg sc; ED_{50},[d] mg/kg po
13a	Me	H	H	H	H	0.32 ± 0.02	4.59 (2.70–7.09)		
13b	Et	H	H	H	H	1.02 ± 0.43	14.29 (9.04–21.74)		
13c	*n*-Bu	H	H	H	H	1.48 ± 0.48	12.5 (8.40–18.59)		
13d	Me	Me	H	H	H	0.73 ± 0.11	30.64 (20.22–43.71)		
13e	H	H	H	H	H	0.41 ± 0.18	inactive to 50	50% at 50[e]	9.54 (5.14–15.76)
13f	H	Me	H	H	H	0.48 ± 0.16	inactive to 50	inactive to 50	62.5% at 50[e]
13g	Cl	H	H	H	H	2.48 ± 0.46	inactive to 50		25% at 50[e]
11a	Me	H	COOEt	H	H	9.84 ± 3.40	inactive to 50		inactive to 50
12a	Me	H	COOH	H	H	21.6 ± 0.78	inactive to 50		inactive to 50
13h	Me	H	H	7-Cl	H	1.05 ± 0.06	inactive to 50		inactive to 50
13i	Me	H	H	8-Cl	H	0.75 ± 0.41	25% at 50[e]		inactive to 50
13j	Me	H	H	7-F	H	0.65 ± 0.26	16.28 (8.11–32.42)		
13k	Me	H	H	8-F	H	0.92 ± 0.39	30.4 (17.20–149.9)		
13l	Me	H	H	7-Me	H	2.34 ± 1.36	inactive to 50		inactive to 50
13m	Me	H	H	8-Me	H	0.83 ± 0.16	25% at 50[e]		inactive to 50
14	Me	H	H	H	Me	1023 ± 636	13.4 (7.96–21.17)		
diazepam						5.02 ± 0.37	0.67 (0.47–0.94)		
CGS 9896						0.83 ± 0.15	1.17 (1.06–2.93)		
CGS 8216						0.22 ± 0.01		inactive to 50	12.77 (5.43–33.74)

[a–e] Footnotes as in Table I.

13f, and **13g**) in the latter series had weak inverse agonist activity. It is interesting to note that the compounds showing agonist activity had an alkyl substituent at the 5′-position in the thien-2-yl analogues; the order of potency was Me > Et, *n*-Bu (**13a**, **13b**, and **13c**). On the other hand, the order of inverse agonist activity in the thien-3-yl compounds was Me > H > Cl > Et for the substituent at the 5′-position (**6a**, **6b**, **6e**, and **6d**). Among the derivatives tested, **6a** was the most potent for the inverse agonist activity, and **13a** was the most active agonist.

Substitution at the 7- or 8-position of **6a** and **13a** generally decreased in vivo activity. The 7-fluoro derivative (**6h**) of **6a** and the 7- and 8-fluoro compounds (**13j** and **13k**) of **13a** were several times less potent than the parent compounds. Only the 8-fluoro-substituted derivative **6i** retained its activity. The chloro and methyl substituents at the 7-position of **6a** and those at the 7- or 8-position of **13a** provided almost inactive compounds (**6f**, **6j**, **13h**, **13i**, **13l**, and **13m**). Interestingly, the 5-alkylated analogues (**8a**, **8b**, and **14**) of **6a** and **13a**, having a large K_i value, maintained substantial potency, although the other compounds (**4b**, **5b**, **7b**, **11a**, and **12a**) with a K_i value of ≥10 nM were inactive in the in vivo assay. The former compounds appear to be transformed to biologically active **6a** or **13a** by metabolic dealkylation.

As compared to CGS compounds[8] (2-phenylpyrazoloquinolines), **13a** was less potent than the 2-*p*-chlorophenyl analogue CGS 9896 in the agonist activity, whereas **6a** and **6b** exhibited much greater potency than the 2-phenyl derivative CGS 8216 in the inverse agonist activity. Therefore, it is likely that replacement of the phenyl with the thienyl moieties at the 2-position on the pyrazoloquinoline skeleton shifted the entire spectrum of this class of compounds toward inverse agonist properties.

Experimental Section

Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen. Melting points were determined on a Yanagimoto micro melting points apparatus and are uncorrected. NMR spectra were recorded on a Varian T-60 or EM-390 spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane as the internal standard. Elemental analyses were performed by the analytical department of Shionogi Research Laboratories and are within ±0.4% of the theoretical values unless otherwise noted. Water determinations of the final products were made by the Karl Fischer method.

Synthetic Methods. Specific examples presented below illustrate general synthetic methods A–D for the preparations for **6** and **13** in Schemes I and II.

Methyl 3-Hydrazinothiophene-2-carboxylates (1). These compounds (**1a–d**) were prepared from the corresponding methyl 3-aminothiophene-2-carboxylates by the general method described in ref 12a: **1a** (5-Me), mp 105–107 °C; **1b** (4,5-unsubstituted), mp 71–72 °C; **1c** (4-Me), mp 73–74.5 °C; **1d** (5-Et), mp 48–49 °C.

Ethyl 4-Chloroquinoline-3-carboxylates (2). These compounds (**2a–g**) were prepared by the method described by Kaslow et al.:[15] **2a** (unsubstituted), mp 40–42 °C; **2b** (6-Cl), mp 90–91 °C; **2c** (7-Cl), mp 81–84 °C; **2d** (6-Me), mp 64–65.5 °C; **2e** (7-Me), mp 42–45 °C; **2f** (6-F), mp 62–63 °C; **2g** (7-F), mp 55–58 °C.

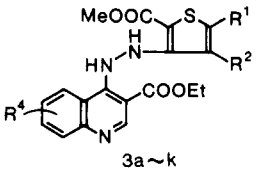
Ethyl 4-[2-[2-(Methoxycarbonyl)-5-methylthien-3-yl]-hydrazino]quinoline-3-carboxylate (3a) (Method A). To a solution of ethyl 4-chloroquinoline-3-carboxylate (**2a**; 2.36 g, 10.0 mmol) in ethanol (50 mL) was added methyl 3-hydrazino-5-methylthiophene-2-carboxylate (**1a**; 1.96 g, 10.5 mmol). After being stirred at room temperature for 1.5 h, the mixture was concentrated in vacuo. The residue was dissolved in chloroform and washed with cold aqueous sodium carbonate and with water. The solution was dried ($MgSO_4$) and concentrated in vacuo. The resulting yellow solid was recrystallized from ethanol to give **3a** (3.64 g, 94% yield) as pale yellow crystals: mp 200–204 °C; NMR (DMSO-d_6) δ 1.33 (3 H, t, J = 8 Hz), 2.43 (3 H, s), 3.77 (3 H, s), 4.33 (2 H, q, J = 8 Hz), 7.12 (1 H, s), 7.0–7.55 (4 H, m), 8.08 (1 H, s), 8.17 (1 H, br s), 10.28 (1 H, br s). Anal. ($C_{19}H_{19}N_3O_4S$) C, H, N.

The other compounds **3** and **10** in Table III were prepared in a similar manner.

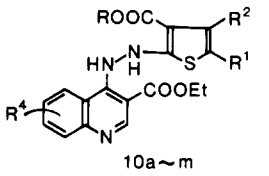
2-[2-(Methoxycarbonyl)-5-methylthien-3-yl]-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (4a) (Method B). To a suspension of **3a** (13.4 g, 34.8 mmol) in ethanol (200 mL) was

(15) Kaslow, C. E.; Clark, Wm. R. *J. Org. Chem.* **1953**, *18*, 55.

Table III. Physical Properties of 3 and 10 Prepared by Method A



3a~k

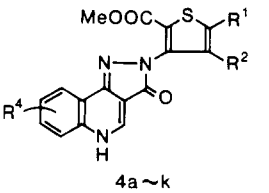


10a~m

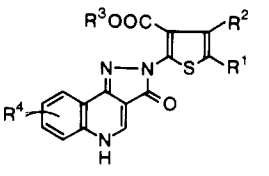
compd	R^1	R^2	R	R^4	yield, %	mp, °C	formula[a]
3a	Me	H		H	94	200–204	$C_{19}H_{19}N_3O_4S$
3b	H	H		H	98	161–162	$C_{18}H_{17}N_3O_4S \cdot {}^1/_5H_2O$
3c	H	Me		H	96	188–191	$C_{19}H_{19}N_3O_4S$
3d	Et	H		H	84	166–168	$C_{20}H_{21}N_3O_4S$
3f	Me	H		7-Cl	95	198–199	$C_{19}H_{18}N_3O_4SCl$
3g	Me	H		6-Cl	90	222–223	$C_{19}H_{18}N_3O_4SCl$
3i	Me	H		6-F	93	198–201	$C_{19}N_{18}N_3O_4SF$
3j	Me	H		7-Me	88	176–178	$C_{20}H_{21}N_3O_4S$
3k	Me	H		6-Me	90	197–201	$C_{20}H_{21}N_3O_4S$
10a	Me	H	Et	H	92	173–174	$C_{20}H_{21}N_3O_4S$
10b	Et	H	Et	H	84	156–158	$C_{21}H_{23}N_3O_4S$
10c	*n*-Bu	H	Me	H	91	173–175	$C_{22}H_{25}N_3O_4S$
10d	Me	Me	Et	H	69	161–164	$C_{21}H_{23}N_3O_4S$
10f	COOEt	Me	Et	H	91	221–224 dec	$C_{23}H_{25}N_3O_6S$
10h	Me	H	Me	7-Cl	88	186–187	$C_{19}H_{18}N_3O_4SCl$
10i	Me	H	Me	6-Cl	87	196–197	$C_{19}H_{18}N_3O_4SCl$
10j	Me	H	Me	7-F	76	186–188 dec	$C_{19}H_{18}N_3O_4SF$
10k	Me	H	Me	6-F	88	184–186	$C_{19}H_{18}N_3O_4SF$
10l	Me	H	Me	7-Me	83	169–170	$C_{20}H_{21}N_3O_4S$
10m	Me	H	Me	6-Me	93	180–182	$C_{20}H_{21}N_3O_4S$

[a] Analyses for C, H, N were within ±0.4% of the theoretical values unless otherwise noted.

Table IV. Physical Properties of 4 and 11 Prepared by Method B



4a~k



11a~m

compd	R^1	R^2	R^3	R^4	yield, %	mp, °C	formula[a]
4a	Me	H		H	97	260–261	$C_{17}H_{13}N_3O_3S$
4b	H	H		H	96	240–241	$C_{16}H_{11}N_3O_3S \cdot H_2O$[b]
4c	H	Me		H	88	265–276 dec	$C_{17}H_{13}N_3O_3S$
4d	Et	H		H	94	150–155	$C_{18}H_{15}N_3O_3S$
4f	Me	H		7-Cl	81	167–169	$C_{17}H_{12}N_3O_3SCl$
4g	Me	H		8-Cl	87	195–199	$C_{17}H_{12}N_3O_3ClS \cdot {}^1/_2H_2O$
4i	Me	H		8-F	96	189–191 dec	$C_{17}H_{12}N_3O_3SF \cdot H_2O$
4j	Me	H		7-Me	69	153–156	$C_{18}H_{15}N_3O_3S \cdot {}^3/_4H_2O$
4k	Me	H		8-Me	79	179–181 dec	$C_{18}H_{15}N_3O_3S \cdot H_2O$
11a	Me	H	Et	H	94	248–250 dec	$C_{18}H_{15}N_3O_3S$
11b	Et	H	Et	H	90	175–178	$C_{19}H_{17}N_3O_3S \cdot {}^1/_4H_2O$
11c	*n*-Bu	H	Me	H	93	210–212	$C_{20}H_{19}N_3O_3S$
11d	Me	Me	Et	H	66	252–253	$C_{19}H_{17}N_3O_3S$
11f	COOEt	Me	Et	H	90	282–285	$C_{21}H_{19}N_3O_5S$
11h	Me	H	Me	7-Cl	93	261–263	$C_{17}H_{12}N_3O_3SCl$[c]
11i	Me	H	Me	8-Cl	92	166–169	$C_{17}H_{12}N_3O_3SCl \cdot H_2O$
11j	Me	H	Me	7-F	99	252–260 dec	$C_{17}H_{12}N_3O_3SF \cdot {}^1/_3H_2O$
11k	Me	H	Me	8-F	93	168–171	$C_{17}H_{12}N_3O_3SF \cdot {}^1/_5H_2O$
11l	Me	H	Me	7-Me	88	246–248	$C_{18}H_{15}N_3O_3S \cdot {}^1/_4H_2O$
11m	Me	H	Me	8-Me	96	162–164 dec	$C_{18}H_{15}N_3O_3S \cdot H_2O$

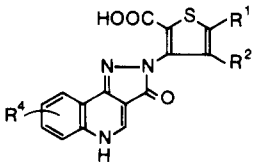
[a] Analyses for C, H, N were within ±0.4% of the theoretical values unless otherwise noted. [b] H_2O: calcd, 5.52; found, 5.19. [c] N: calcd, 11.24; found, 10.74.

added 1 N aqueous sodium hydroxide (38 mL, 38 mmol) at room temperature. After the crystals were completely dissolved, the mixture was acidified with acetic acid and concentrated to remove the ethanol. The resulting solid was filtered, washed with water, and recrystallized from ethanol to give **4a** (11.50 g, 97% yield) as yellow crystals: mp 260–261 °C; NMR (DMSO-d_6) δ 2.52 (3 H, s), 3.67 (3 H, s), 7.08 (1 H, s), 7.4–7.9 (3 H, m), 8.0–8.3 (1 H, m), 8.69 (1 H, s). Anal. ($C_{17}H_{13}N_3O_3S$) C, H, N.

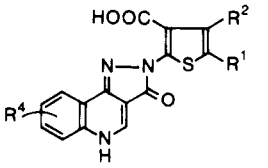
The other compounds 4 and 11 in Table IV were prepared in a similar manner.

2-(2-Carboxy-5-methylthien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (5a) (Method C). A solution of **4a** (10.18 g, 28.5 mmol) in ethanol (200 mL) and 1 N aqueous sodium hydroxide (90 mL) was refluxed for 1 h. After cooling, the mixture was acidified with acetic acid, and the resulting crystals were collected by filtration. The crystals were washed with water and dried to give **5a** (9.02 g, 96% yield) as pale yellow crystals: mp 280–284 °C; NMR (DMSO-d_6) δ 2.50 (3 H, s), 7.5–7.9 (4 H, m), 8.08 (1 H, m), 8.88 (1 H, s). Anal. ($C_{16}H_{11}N_3O_3S$) C, H, N.

Table V. Physical Properties of 5 and 12 Prepared by Method C



5a~k

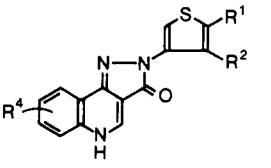


12a~m

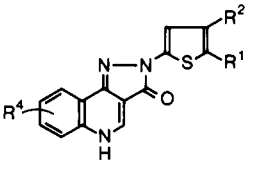
compd	R^1	R^2	R^4	yield, %	mp, °C	formula[a]
5a	Me	H	H	93	260–261 dec	$C_{16}H_{11}N_3O_3S$
5b	H	H	H	94	263–265 dec	$C_{15}H_9N_3O_3S$
5c	H	Me	H	91	297–299 dec	$C_{16}H_{11}N_3O_3S \cdot {}^1/_4H_2O$
5d	Et	H	H	98	239–242 dec	$C_{17}H_{13}N_3O_3S$
5f	Me	H	7-Cl	94	337–340 dec	$C_{16}H_{10}N_3O_3SCl$
5g	Me	H	8-Cl	92	344–347 dec	$C_{16}H_{10}N_3O_3SCl \cdot {}^5/_4H_2O$
5i	Me	H	8-F	87	324–328 dec	$C_{16}H_{10}N_3O_3SF \cdot H_2O$
5j	Me	H	7-Me	85	301–304 dec	$C_{17}H_{13}N_3O_3S \cdot {}^1/_2H_2O$
5k	Me	H	8-Me	83	321–324 dec	$C_{17}H_{13}N_3O_3S \cdot {}^2/_5H_2O$
12a	Me	H	H	97	300–303 dec	$C_{16}H_{11}N_3O_3S$[b]
12b	Et	H	H	92	280–283 dec	$C_{17}H_{13}N_3O_3S \cdot {}^1/_2H_2O$
12c	*n*-Bu	H	H	95	280–281 dec	$C_{19}H_{17}N_3O_3S \cdot {}^1/_2H_2O$
12d	Me	Me	H	76	289–291 dec	$C_{17}H_{13}N_3O_3S \cdot {}^1/_2H_2O$
12f	COOH	Me	H	98	248–251 dec	$C_{17}H_{11}N_3O_5S \cdot {}^3/_5H_2O$
12h	Me	H	7-Cl	95	316–317 dec	$C_{16}H_{10}N_3O_3SCl \cdot {}^1/_2H_2O$
12i	Me	H	8-Cl	96	312–314 dec	$C_{16}H_{10}N_3O_3SCl \cdot H_2O$
12j	Me	H	7-F	98	297–302 dec	$C_{16}H_{10}N_3O_3SF \cdot H_2O$
12k	Me	H	8-F	86	299–301 dec	$C_{16}H_{10}N_3O_3SF \cdot {}^3/_5H_2O$
12l	Me	H	7-Me	86	308–311 dec	$C_{17}H_{13}N_3O_3S \cdot {}^1/_2H_2O$
12m	Me	H	8-Me	91	293–295 dec	$C_{17}H_{13}N_3O_3S \cdot {}^1/_5H_2O$

[a] Analyses for C, H, N were within ±0.4% of the theoretical values unless otherwise noted. [b] C: calcd, 59.06; found, 58.50.

Table VI. Physical Properties of 6 and 13 Prepared by Method D



6a~k



13a ~ m

compd	R^1	R^2	R^4	yield, %	mp, °C	formula[a]
6a	Me	H	H	85	293–295 dec	$C_{15}H_{11}N_3OS$
6b	H	H	H	90	323–325 dec	$C_{14}H_9N_3OS$
6c	H	Me	H	93	313–315 dec	$C_{15}H_{11}N_3OS$
6d	Et	H	H	80	266–268 dec	$C_{16}H_{13}N_3OS \cdot {}^1/_3H_2O$[b]
6f	Me	H	7-Cl	65	323–327 dec	$C_{15}H_{10}N_3OSCl$
6g	Me	H	8-Cl	81	349–352 dec	$C_{15}H_{10}N_3OSCl$
6i	Me	H	8-F	86	326–329 dec	$C_{15}H_{10}N_3OSF$
6j	Me	H	7-Me	68	311–314 dec	$C_{16}H_{13}N_3OS$
6k	Me	H	8-Me	82	330–332 dec	$C_{16}H_{13}N_3OS$
13a	Me	H	H	82	309–311 dec	$C_{15}H_{11}N_3OS$
13b	Et	H	H	91	277–280 dec	$C_{16}H_{13}N_3OS \cdot {}^1/_4H_2O$[c]
13c	*n*-Bu	H	H	70	266–270 dec	$C_{18}H_{17}N_3OS$
13d	Me	Me	H	63	323–328 dec	$C_{16}H_{13}N_3OS \cdot H_2O$[d]
13f	H	Me	H	81	310–312 dec	$C_{15}H_{11}N_3OS$
13h	Me	H	7-Cl	63	320–325 dec	$C_{15}H_{10}N_3OSCl$
13i	Me	H	8-Cl	86	328–333 dec	$C_{15}H_{10}N_3OSCl$
13j	Me	H	7-F	63	322–325 dec	$C_{15}H_{10}N_3OSF$
13k	Me	H	8-F	86	320–325 dec	$C_{15}H_{10}N_3OSF$
13l	Me	H	7-Me	63	322–325 dec	$C_{16}H_{13}N_3OS$
13m	Me	H	8-Me	96	330–333 dec	$C_{16}H_{13}N_3OS$

[a] Analyses for C, H, N were within ±0.4% of the theoretical values unless otherwise noted. [b] H_2O: calcd, 1.99; found, 2.09. [c] H_2O: calcd, 1.50; found, 1.69. [d] H_2O: calcd, 5.75; found, 5.45.

The other compounds **5** and **12** in Table V were prepared in a similar manner.

2-(5-Methylthien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (6a) (Method D). The mixture of **5a** (5.00 g, 15.1 mmol), copper powder (1.0 g), and quinoline (50 mL) was stirred at 190 °C for 1 h. The copper was removed by filtration and the filtrate was mixed with 1 N aqueous sodium hydroxide, followed by extraction with ether to remove the quinoline. The separated aqueous layer was treated with activated charcoal and filtered. The filtrate was acidified with acetic acid and the resulting precipitate was filtered, washed with water, and dried. The solid was recrystallized from ethanol to afford yellow crystals as an ethanol adduct, which upon heating at 140 °C gave **6a** (3.65 g, 86% yield) as yellow crystals; mp 293–295 °C dec; NMR (DMSO-d_6) δ 2.50 (3 H, s), 7.56 (2 H, s), 7.5–7.8 (3 H, m), 8.1–8.3 (1 H, m), 8.72 (1 H, s). Anal. ($C_{15}H_{11}N_3OS$) C, H, N.

The other compounds 6 and 13 in Table VI were prepared in a similar manner.

2-(2-Carboxy-5-methylthien-3-yl)-7-fluoro-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (5h). To prepare this compound, methods A, B, and C were successively applied except that the products were not purified at each step. To a solution of ethyl 4-chloro-7-fluoroquinoline-3-carboxylate (**2g**; 507 mg, 2 mmol) in ethanol (25 mL) was added methyl 3-hydrazino-5-methylthiophene-2-carboxylate (**1a**; 410 mg, 2.2 mmol). After being stirred at room temperature for 2 h, the mixture was concentrated in vacuo. The residue was dissolved in chloroform and washed with cold aqueous sodium bicarbonate and water. The solution was dried ($MgSO_4$) and concentrated in vacuo to give a solid, which was suspended in ethanol (15 mL), followed by addition of 1 N aqueous sodium hydroxide (2.5 mL). After being stirred for 1 h, the mixture was acidified with acetic acid (0.5 mL) and diluted with water (10 mL). The resulting precipitate was filtered and washed with water. The above solid was dissolved in a mixture of ethanol (20 mL) and 1 N aqueous sodium hydroxide (7 mL). The solution was refluxed for 1 h and then concentrated to remove the ethanol, followed by dilution with water (10 mL). The aqueous solution was treated with active charcoal and filtered through Celite. The filtrate was acidified with acetic acid (1 mL) and the resulting solid was filtered and washed with ethanol. This gave the acid **5h** (508 mg, 74% from **2g**), which was used in the next reaction without further purification.

7-Fluoro-2-(5-methylthien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (6h). A mixture of **5h** (500 mg, 1.46 mmol), copper powder (50 mg), and quinoline (5 mL) was heated at 195 °C for 2 h. After being allowed to cool, the mixture was diluted with ether (100 mL) and extracted with aqueous sodium hydroxide (ca. 0.5 N, 30 mL). The aqueous extract was washed with ether, treated with active charcoal, and filtered. The filtrate was treated successively with 1 N hydrochloric acid (8 mL) and acetic acid (1 mL) to give a precipitate, which was filtered and washed with water. The solid was crystallized from ethanol to afford **6h** (320 mg, 68%): mp 345–348 °C; NMR (DMSO-d_6) δ 2.50 (3 H, s), 7.31–7.55 (4 H, m), 8.06–8.37 (1 H, m), 8.26 (1 H, s). Anal. ($C_{15}H_{10}N_3OSF$) C, H, N.

2-(2-Chloro-5-methylthien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (7a). To a suspension of **6a** (110 mg, 0.39 mmol) in chloroform (1 mL) was added a solution of chlorine (1.3 M, 0.42 mL) in carbon tetrachloride. The mixture was stirred at room temperature for 2 h, precipitating a yellow solid. The solid was collected by filtration, dissolved in 1 N aqueous sodium hydroxide, and acidified with acetic acid. Silica gel chromatography of the resulting solid gave **7a** (77 mg, 60% yield): mp 238–241 °C dec; NMR (DMSO-d_6) δ 2.44 (3 H, s), 6.99–7.03 (1 H, m), 7.40–8.18 (4 H, m), 8.70 (1 H, s). Anal. ($C_{15}H_{10}N_3OSCl$) H, N; C: calcd, 57.05; found, 56.60.

2-(2-Bromo-5-methylthien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (7b). To a suspension of **6a** (300 mg, 1.07 mmol) in chloroform (10 mL) was added dropwise a solution of bromine (270 mg, 1.7 mmol) in chloroform (2 mL) at room temperature. After this mixture were stirred at room temperature for 2 h, the same workup and purification as in **7a** gave **7b** (180 mg, 47% yield): mp 200–203 °C dec; NMR (DMSO-d_6) δ 2.45 (3 H, s), 6.97 (1 H, d), 7.42–7.78 (3 H, m), 8.07–8.21 (1 H, m), 8.21 (1 H, d). Anal. ($C_{15}H_{10}N_3OSBr$) H, N; C: calcd, 50.01; found, 49.42.

5-Alkyl-2-(5-methylthien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-ones (8a,b). To a suspension of **6a** (562 mg, 2.0 mmol) in anhydrous tetrahydrofuran (5 mL) was added 88 mg of 60% sodium hydride (in mineral oil). The mixture was refluxed for 2 h and cooled to room temperature. To the mixture was added a solution of alkyl iodide (1.1 equiv) in tetrahydrofuran. The mixture was stirred at room temperature overnight and poured into water. The precipitating crystals were filtered, washed with water and ethanol, and dried to give **8** as yellow crystals.

8a (R^5 = Me): mp 256–258 °C dec, 76% yield; NMR ($CDCl_3$–CD_3OD) δ 2.53 (3 H, s), 3.97 (3 H, s), 7.50–7.70 (5 H, m), 8.43 (1 H, s), 8.35–8.50 (1 H, m). Anal. ($C_{16}H_{13}N_3OS$) C, H, N.

8b (R^5 = Et): mp 216–218 °C dec, 65% yield; NMR ($CDCl_3$) δ 1.52 (3 H, t), 2.52 (3 H, s), 4.30 (2 H, q), 7.40–7.65 (5 H, m), 8.32 (1 H, s), 8.36–8.49 (1 H, m). Anal. ($C_{17}H_{15}N_3OS$) C, H, N.

Alkyl 2-Hydrazinothiophene-3-carboxylates (9). These compounds (**9a–d,f,g**) were prepared from the corresponding alkyl 2-aminothiophene-3-carboxylates by the general method described in ref 12a: **9a** (R^1 = Me, R^2 = H, R = Et), mp 59.5–61 °C; **9b** (R^1 = Et, R^2 = H, R = Et), mp 34–36 °C; **9c** (R^1 = *n*-Bu, R^2 = H, R = Et), mp 57–61 °C; **9d** (R^1 = R^2 = Me, R = Et), mp 79–82 °C dec; **9f** (R^1 = COOEt, R^2 = Me, R = Et), mp 150–152 °C; **9g** (R^1 = Me, R^2 = H, R = Me), mp 120–121.5 °C.

Ethyl 5-Hydrazinothiophene-2-carboxylate Hydrochloride (9e). This compound was prepared from ethyl 5-aminothiphene-2-carboxylate by the method[16] described for preparation of the corresponding methyl ester. **9e**: mp 160–170 °C dec. Anal. ($C_7H_{11}N_2O_2SCl$) C, H, N.

Diethyl 2-Hydrazinothiophene-3,4-dicarboxylate Hydrochloride (9h). To a solution of diethyl 2-aminothiophene-3,4-dicarboxylate (4.86 g, 20 mmol) in concentrated hdyrochloric acid (30 mL) was added dropwise a solution of sodium nitrite (1.52 g, 22 mmol) in water (15 mL) at −10 to 5 °C. The resulting suspension was stirred for 30 min at the same temperature and was added to a solution of stannous chloride (26 g) in concentrated hydrochloric acid (40 mL) at 0–5 °C. The mixture was stirred at 5 °C for 30 min. The resulting mixture was filtered and the solid was mixed with water and ethyl acetate. After alkalization with 1 N aqueous sodium hydroxide, the mixture was extracted with ethyl acetate. The extract was washed with water, dried ($MgSO_4$), and evaporated in vacuo. The residue was chromatographed on silica gel. Elution with dichloromethane–hexane (4:1) gave **9h** (1.955 g, 38%): mp 53.5–55 °C; NMR ($CDCl_3$) δ 1.29 (3 H, t), 1.34 (3 H, t), 4.22 (2 H, q), 4.2 (2 H, br, NH), 6.68 (1 H, s), 8.13 (1 H, br, NH). Anal. ($C_{10}H_{14}N_2O_4S$) C, H, N.

Further elution with dichloromethane–ether (20:1) afforded diethyl 2,5-diaminothiophene-3,4-dicarboxylate (**9i**; 1.35 g, 26%): mp 156.5–159 °C; NMR ($CDCl_3$) δ 1.27 (6 H, t), 4.21 (4 H, t), 5.25 (4 H, br, NH). Anal. ($C_{10}H_{14}N_2O_4S$) C, H, N.

2-[5-(Ethoxycarbonyl)thien-2-yl]-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (11e). To a solution of ethyl 4-chloroquinoline-3-carboxylate (**2a**; 942 mg, 4 mmol) in ethanol (10 mL) was added ethyl 5-hydrazinothiophene-2-carboxylate hydrochloride (**9e**; 981 mg, 1.1 equiv). The mixture was stirred at 50–55 °C for 30 min and concentrated. The resulting residue was mixed with aqueous sodium bicarbonate and extracted with chloroform. The extract was washed with water, dried, and evaporated. Purification of the residue by silica gel column chromatography gave **11e** (645 mg, 48% yield) as yellow crystals: mp 327–329 °C dec; NMR (DMSO-d_6) δ 1.31 (3 H, t), 4.29 (2 H, q), 7.38 (1 H, d), 7.50–7.89 (4 H, m), 8.19–8.30 (1 H, m), 8.88 (1 H, s). Anal. ($C_{17}H_{13}N_3O_3S\cdot{}^1/_2H_2O$) C, H, N.

2-Thien-2-yl-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (13e). To a suspension of **11e** (340 mg, 0.98 mmol) in methanol (5 mL) was added 1 N aqueous sodium hydroxide (5 mL). The mixture was stirred at 50–55 °C for 30 min. After cooling, 1 N hydrochloric acid (4 mL) and acetic acid (0.5 mL) were added to the mixture. The precipitating crystals were collected by filtration, washed with water, and dried. The suspension of the resulting acid (ca. 280 mg) and copper powder (140 mg) in quinoline (3 mL) was heated at 190 °C under nitrogen for 20 min and cooled. After removal of the copper, the mixture was shaken with ether and 1 N aqueous sodium hydroxide. The aqueous layer was separated and acidified with acetic acid to afford **13e** (210 mg, 80% yield) as crystals: mp 323–325 °C; NMR (DMSO-d_6) δ 6.92–7.14 (2 H, m), 7.37 (1 H, dd), 7.50–7.75 (3 H, m), 8.16–8.27 (1 H, m), 8.77 (1 H, m). Anal. ($C_{14}H_9N_3OS$) C, H, N.

5-Methyl-2-(5-methylthien-2-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (14). The same procedure was employed for the preparation of **8**. **14**: mp 271–274 °C dec; NMR (DMSO-d_6) δ 2.40 (3 H, d), 4.02 (3 H, s), 6.63 (1 H, dd), 7.11 (1 H, d), 8.87 (1 H, s). Anal. ($C_{16}H_{13}N_3OS$) C, H, N.

1-(*tert*-Butoxycarbonyl)-1-(5-chlorothien-3-yl)hydrazine Hydrochloride (15). According to the method of Binder et al.,[17] 5-chlorothiophene-3-carboxylic acid was converted to *N*-(*tert*-butoxycarbonyl)thiophen-3-amine, which was treated with *O*-(*p*-nitrobenzoyl)hydroxylamine, affording **15** as a hydrochloride salt: mp 125–131 °C dec; NMR ($CDCl_3$) δ 1.54 (9 H, s), 6.87 (1 H, d), 7.23 (1 H, d). Anal. ($C_9H_{13}N_2O_2SCl\cdot HCl$) C, H, N.

(16) Mackay, D. *Can. J. Chem.* **1966**, *44*, 2881.
(17) (a) Binder, D.; Habinson, G.; Noe, C. R. *Synthesis* **1977**, 255. (b) Binder, D.; Habinson, G.; Noe, C. R. *Ibid.* **1977**, 487.

Ethyl 4-[2-(5-Chlorothien-3-yl)-2-(*tert*-butoxycarbonyl)hydrazino]quinoline-3-carboxylate (16). To a solution of ethyl 4-chloroquinoline-3-carboxylate (**2a**: 380 mg, 1.61 mmol) in ethanol (10 mL) was added 1-(*tert*-butoxycarbonyl)-1-(5-chlorothien-3-yl)hydrazine hydrochloride (**15**; 400 mg, 1.61 mmol). The mixture was stirred at 40 °C for 1 h and concentrated in vacuo. The residue was mixed with chloroform, washed with aqueous sodium bicarbonate and water, dried ($MgSO_4$), and concentrated. Purification of the residue by silica gel column chromatography (benzene–ethyl acetate = 30:1) gave **16** (670 mg, 93% yield): mp 134–135 °C; NMR ($CDCl_3$) δ 1.08 (9 H, s), 1.46 (3 H, t), 4.47 (2 H, q), 7.19–8.18 (6 H, m), 9.28 (1 H, s). Anal. ($C_{21}H_{22}N_3O_4SCl$) C, H, N.

2-(5-Chlorothien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (6e). To a solution of **16** (600 mg, 1.34 mmol) in dichloromethane (15 mL) was added trifluoroacetic acid (10 mL) at room temperature. The mixture was stirred at 50 °C for 20 min and concentrated in vacuo. The residue was dissolved in ethanol (30 mL) and mixed with cold 1 N sodium hydroxide (8 mL) and stirred at room temperature for 1.5 h. After evaporation of the organic solvent, the mixture was diluted with water (10 mL) and extracted with ether to remove the neutral portion. The aqueous layer was filtered, and the filtrate was acidified by addition of acetic acid to give a crude solid, which was recrystallized from ethanol to afford **6e** (210 mg, 52% yield): mp 287–289 °C; NMR (DMSO-d_6) δ 7.45–7.83 (5 H, m), 8.17–8.27 (1 H, m), 8.75 (1 H, s). Anal. ($C_{14}H_8N_3OSCl$) C, H, N.

Ethyl 4-[2-[3,4-Bis(ethoxycarbonyl)thien-2-yl]hydrazino]quinoline-3-carboxylate (17). To a solution of ethyl 4-chloroquinoline-3-carboxylate (**2a**; 1.33 g, 5.64 mmol) in ethanol (30 mL) was added diethyl 2-hydrazinothiophene-3,4-dicarboxylate (**9h**; 1.53 g, 6.31 mmol). The mixture was stirred at room temperature for 1 h and concentrated. The residue was dissolved in chloroform and washed with cooled aqueous sodium bicarbonate and with water. The solution was dried ($MgSO_4$) and evaporated to give a crude product, which was recrystallized from ethanol, affording **17** (2.34 g, 91% yield) as red crystals: mp 178–181 °C dec; NMR DMSO-d_6) δ 1.26 (6 H, t), 1.33 (3 H, t), 4.21 (2 H, q), 4.24 (2 H, q), 4.34 (2 H, q), 6.93 (1 H, s), 8.25 (1 H, s). Anal. ($C_{22}H_{23}N_3O_6S$) C, H, N.

2-[3,4-Bis(ethoxycarbonyl)thien-2-yl]-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (18). To a suspension of **17** (2.36 g, 5.16 mmol) in ethanol (50 mL) was added 1 N sodium hydroxide (6.6 mL) at room temperature. After being stirred for 30 min, the mixture was acidified with acetic acid and concentrated in vacuo. The residue was mixed with water and filtered and washed with water and ethanol. Recrystallization of the product from methanol gave **18** (1.99 g, 92% yield): mp 255–258 °C; NMR (DMSO-d_6) δ 1.29 (6 H, t), 4.25 (2 H, q), 4.33 (2 H, q), 7.93 (1 H, s), 8.82 (1 H, s). Anal. ($C_{20}H_{17}N_3O_5S \cdot {}^1/_3H_2O$) C, H, N.

2-[5-Chloro-3,4-bis(ethoxycarbonyl)thien-2-yl]-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (19). To a suspension of **18** (617 mg, 1.48 mmol) in chloroform (20 mL) was added a solution of chlorine in carbon tetrachloride (1.35 M, 1.4 mL) at 0–5 °C. The mixture was stirred at 10–15 °C for 40 min and filtered. The filtrate was concentrated and the residue was dissolved in ether and extracted with aqueous sodium hydroxide. The aqueous extract was acidified with acetic acid and the resulting solid was chromatographed on silica gel to give **19** (289 mg, 43% yield) as yellow crystals: mp 158–161 °C dec; NMR (DMSO-d_6) δ 1.25 (3 H, t), 1.27 (3 H, t), 4.27 (2 H, q), 4.30 (2 H, q), 8.87 (1 H, s). Anal. ($C_{20}H_{16}N_3O_5SCl$) C, H, N.

2-(5-Chloro-3,4-dicarboxythien-2-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (20). To a suspension of **19** (350 mg, 0.78 mmol) in methanol (5 mL) was added aqueous 1 N sodium hydroxide (5 mL). The mixture was stirred at 60 °C for 1.5 h. After cooling, the mixture was acidified with acetic acid. The resulting crystals were collected by filtration, washed with water, and dried to give **20** (229 mg, 74% yield): mp 332–337 °C dec; NMR (DMSO-d_6) δ 7.3–7.8 (3 H, m), 8.0–8.2 (1 H, m), 8.67 (1 H, s). Anal. ($C_{16}H_8N_3O_5SCl \cdot {}^1/_2H_2O$) C, H, N.

2-(5-Chlorothien-2-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (13g). The mixture of **20** (200 mg), copper powder (200 mg), and quinoline (4 mL) was heated at 200 °C for 20 min. After cooling, the copper was removed by filtration and the filtrate was mixed with aqueous sodium hydroxide and extracted with ether to remove the organic solvent. The aqueous layer was filtered and the filtrate was acidified with acetic acid. The resulting crystals were collected by filtration and recrystallization from ethanol to afford **13g** (128 mg, 80% yield): mp 309–312 °C dec; NMR (DMSO-d_6) δ 7.85 (1 H, d), 8.82 (1 H, s). Anal. ($C_{14}H_8N_3OSCl \cdot H_2O$) C, H, N; H_2O: calcd, 5.63; found, 5.25.

Benzodiazepine Receptor Binding Assays.[1b] Wistar rats were decapitated, and the cerebral cortex was dissected. The cortex was homogenized in 20 volumes of ice-cold Tris·HCl buffer (50 mM, pH 7.4) with a Physcotron (15 s, setting 60, NITI-ON Medical Instruments) and centrifuged (4 °C) for 10 min at 30000*g*. The tissue was resuspended in an equal volume of buffer and recentrifuged. This procedure was repeated two more times. The final pellet was resuspended, frozen in a liquid nitrogen bath, and stored at −80 °C. For the binding assay, the frozen membrane preparations were thawed and centrifuged. The pellet was resuspended in 100 volumes (protein concentrations, 0.5–0.6 mg/mL) of ice-cold 50 mM Tris·HCl buffer containing 100 mM NaCl and 5 mM KCl, and 480-μL aliquots of this homogenate were added to 20 μL of a solution of [^{3}H]diazepam (final concentration, 2 nM) and varying amounts of the test compound. The mixture was incubated at 0 °C for 60 min, and the incubations were terminated by addition of 2.5 mL of ice-cold incubation buffer, followed by rapid filtration through Whatman GF/C filters. The filters were washed three times with 2.5 mL of the buffer and placed in minivials containing 5 mL of Clear-sol I. After 12 h, the radioactivity was counted with an Aloka LSC-673 liquid scintillation counter. Nonspecific binding was determined by parallel experiments with nonradioactive diazepam (final concentration, 1 μM) and accounted for less than 10% of total binding. Each value was determined in duplicate, and IC_{50} values were estimated from semilogarithmic plots. K_i values were calculated from the following equation: $K_i = IC_{50}/(1 + (L/K_D))$, where L is the ligand concentration (2 nM) and K_D is the dissociation constant for [^{3}H]diazepam determined by parallel experiments.

The data are means of at least three individual determinations.

Registry No. **1a**, 75681-14-0; **1b**, 75681-13-9; **1c**, 104680-36-6; **1d**, 104680-37-7; **2a**, 13720-94-0; **2b**, 211684-41-2; **2c**, 19499-19-5; **2d**, 56824-87-4; **2e**, 50593-19-6; **2f**, 77779-49-8; **2g**, 26893-13-0; **3a**, 106358-24-1; **3b**, 114652-10-7; **3c**, 114652-11-8; **3d**, 114652-12-9; **3f**, 114652-13-0; **3g**, 114652-14-1; **3i**, 114652-15-2; **3j**, 114652-16-3; **3k**, 114652-17-4; **4a**, 104635-77-0; **4b**, 104635-67-8; **4c**, 104635-78-1; **4d**, 104635-84-9; **4f**, 104635-83-8; **4g**, 104635-81-6; **4i**, 104650-09-1; **4j**, 104635-82-7; **4k**, 104635-79-2; **5a**, 104635-86-1; **5b**, 104635-76-9; **5c**, 104679-57-4; **5d**, 104679-64-3; **5f**, 104679-63-2; **5g**, 104679-60-9; **5h**, 114652-18-5; **5i**, 104679-61-0; **5j**, 104679-62-1; **5k**, 104679-58-5; **6a**, 104679-67-6; **6b**, 104679-66-5; **6c**, 104679-68-7; **6d**, 104679-75-6; **6e**, 104679-77-8; **6f**, 104679-74-5; **6s**, 104679-71-2; **6h**, 114652-19-6; **6i**, 104679-72-3; **6j**, 104679-73-4; **6k**, 104679-69-8; **7a**, 104679-84-7; **7b**, 104679-85-8; **8a**, 104679-97-2; **8b**, 104679-98-3; **9a**, 104680-42-4; **9b**, 104680-33-3; **9c**, 104680-35-5; **9d**, 104680-34-4; **9e**, 104680-28-6; **9f**, 54857-70-4; **9g**, 54857-72-6; **9h**, 104680-24-2; **9i**, 80691-81-2; **10a**, 114652-20-9; **10b**, 114674-38-3; 10c, 114652-21-0; **10d**, 114652-22-1; **10f**, 114652-23-2; **10h**, 114652-24-3; **10i**, 114652-25-4; **10j**, 114652-26-5; **10k**, 114652-27-6; **10l**, 114652-28-7; **10m**, 114652-29-8; **11a**, 104635-40-7; **11b**, 104635-42-9; **11c**, 114652-30-1; **11d**, 104635-43-0; **11e**, 104679-78-9; **11f**, 104635-52-1; **11h**, 104635-51-0; **11i**, 104635-48-5; **11j**, 114652-31-2; **11k**, 104635-49-6; **11l**, 104635-50-9; **11m**, 104635-46-3; **12a**, 104635-41-8; **12b**, 104635-53-2; **12c**, 104635-56-5; **12d**, 104635-54-3; **12f**, 104635-63-4; **12h**, 104635-62-3; **12i**, 104635-59-8; **12j**, 114652-32-3; **12k**, 104635-60-1; **12l**, 104635-61-2; **12m**, 104635-57-6; **13a**, 104635-65-6; **13b**, 104635-66-7; **13c**, 104635-69-0; **13d**, 104680-43-5; **13e**, 104679-79-0; **13f**, 104635-74-7; **13g**, 104635-75-8; **13h**, 104635-73-6; **13i**, 104635-71-4; **13j**, 114652-33-4; **13k**, 104650-08-0; **13l**, 104635-72-5; **13m**, 104650-07-9; **14**, 104679-86-9; **15**, 114652-34-5; **16**, 114652-35-6; **17**, 114652-36-7; 18, 104650-06-8; **19**, 104679-90-5; **20**, 104635-64-5; diethyl 2-aminothiophene-3,4-dicarboxylate, 104680-25-3; *N*-(*tert*-butoxycarbonyl)thiophen-3-amine, 19228-91-2; *O*-(*p*-nitrobenzoyl)hydroxylamine, 35657-36-4.