possess physicochemical properties favorable for peroral absorption. Thus, preliminary experiments in rabbits with various glycolamide esters of naproxen have shown that these are completely absorbed upon peroral administration and that only the parent naproxen is detectable in the blood, indicating very rapid ester hydrolysis in vitro in accordance with in vitro plasma hydrolysis studies.

(32) Preliminary studies indicate that the N,N-disubstituted glycolamide esters are stable to gastrointestinal enzymes (e.g., α-chymotrypsin).

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A New Thienylpyrazoloquinoline: A Potent and Orally Active Inverse Agonist to Benzodiazepine Receptors

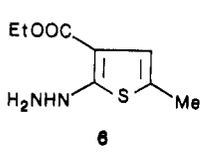
Sir:

Benzodiazepine (BZ) receptor inverse agonists[1] that possess pharmacological effects opposite to those of the benzodiazepines such as diazepam have recently been attracting attention. One such agent, methyl β-carboline-3-carboxylate (β-CCM), has been shown to enhance performance in learning and memory tasks in animal models.[2] The disadvantage of β-CCM is that it evokes clonicotonic convulsions in mice.[1a] However, β-CCE (an ethyl ester analogue of β-CCM) has been found to be an inverse agonist that does not generate convulsions,[1b,d] although its activity decreases after oral administration. The orally effective BZ antagonist 2-phenyl-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (CGS 8216)[3] has an inverse agonistic character but weak intrinsic activity.[1e,4]

Here we report on a new thienylpyrazoloquinoline compound, **5** (S-135), which is a potent and orally active inverse agonist with high affinity to BZ receptors but produces no convulsions by itself. Furthermore, its regioisomer **7**, also having a high affinity to BZ receptors, is classified as an agonist.

Chemistry. Our synthetic strategy involved joining an alkoxycarbonyl as a protecting group to the starting hydrazinothiophenes, which are extremely unstable when they have no electron-withdrawing groups adjacent to their hydrazino moiety.[5] Treatment of methyl 3-hydrazino-5-methylthiophene-2-carboxylate (**1**)[6] with ethyl 4-chloroquinoline-3-carboxylate (**2**)[7] in ethanol at room temperature gave adduct **3**, which was cyclized by sodium hydroxide in aqueous ethanol at room temperature to afford **4a**. Compound **4a** was hydrolyzed by heating with excess sodium hydroxide in aqueous ethanol to obtain an acid **4b**. Decarboxylation of **4b** with copper in quinoline at ca. 190 °C provided 2-(5-methylthien-3-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]quinolin-3-one (**5**) [mp 293–295 °C dec. Anal. ($C_{15}H_{11}N_3OS$) C, H, N, S] (Scheme I).

A similar sequence using ethyl 2-hydrazino-5-methylthiophene-3-carboxylate (**6**)[8] as starting material led to 2-(5-methylthien-2-yl)-2,5-dihydro-3*H*-pyrazolo[4,3-*c*]-quinolin-3-one (**7**) [mp 309–311 °C dec. Anal. ($C_{15}H_{11}N_3OS$) C, H, N, S].



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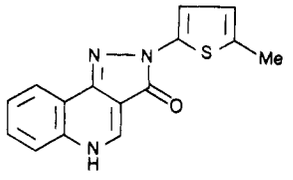

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Pharmacology. The pharmacological data are summarized in Table I, showing the activities of the agonists and the inverse agonists assessed on the basis of inhibition or facilitation of the pentylenetetrazole (PTZ) induced convulsions, respectively. Both **5** and **7** had a greater affinity for BZ receptors than diazepam. In the mouse PTZ test,[9] **7** prevented tonic convulsions and death induced by the PTZ challenge (125 mg/kg sc) 1 h after oral administration, while **5** facilitated the convulsions. These effects were completely antagonized by the BZ antagonist Ro 15-1788.[10] Therefore, **7** and **5** are classified as an agonist and an inverse agonist, respectively, in spite of their structural similarity. In the anticonflict test[9] in rats, **7** showed an ED_{50} value of 5.94 mg/kg 30 min after oral administration, whereas the corresponding value of diazepam was 1.05 mg/kg.

The proconvulsant effect of **5** was compared with those of known inverse agonists by the following procedure. The test compounds were administered to 8–16 male mice in

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(2) Venault, P.; Chapouthier, G.; Prado de Carvalho, L.; Simiand, J.; Morre, M.; Dodd, R. H.; Rossier, J. *Nature (London)* **1986**, *321*, 864.

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(5) To our knowledge, hydrazinothiophenes without an electron-withdrawing group have not been synthesized.

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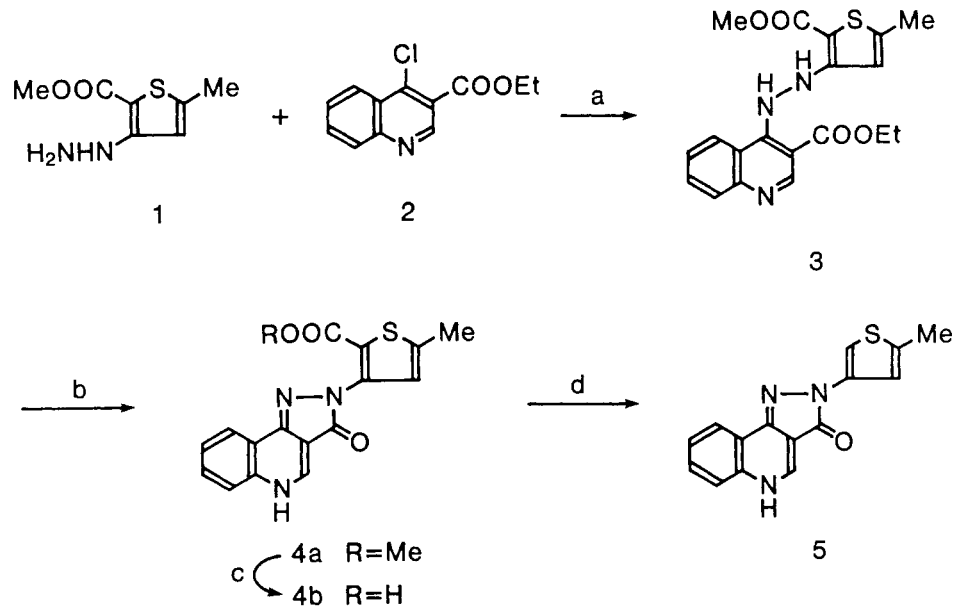
Scheme I[a]



[a] (a) EtOH/room temperature. (b) 1 N aqueous NaOH (1.1 equiv)/EtOH/room temperature. (c) 1 N aqueous NaOH (3 equiv)/EtOH/reflux. (d) Cu/quinoline/190 °C.

Table I. Pharmacological Activities of Thienylpyrazoloquinolines

compd	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	inverse agonist act.[c] PTZ = 90 mg/kg sc: ED_{50},[d] mg/kg
5	0.316 ± 0.024		1.67 (1.23–2.23) po	0.92 (0.64–1.25) po
7	0.320 ± 0.018	4.59 (2.70–7.09)		
diazepam	5.02 ± 0.371	0.67 (0.47–0.94)		
β-CCM	1.47 ± 0.058		inactive to 50 po	inactive to 50 po
			0.49 (0.34–0.73) iv	0.29 (0.24–0.40) iv
β-CCE	1.14 ± 0.08		inactive to 50 po	37.5% at 50[e] po
			1.00 (0.62–1.62) iv	0.46 (0.27–0.71) iv
CGS 8216	0.221 ± 0.01		inactive to 50 po	12.77 (5.43–33.74) po
			inactive to 25 iv	0.20 (0.09–0.50) iv

[a] Displacing potential to [^{3}H]diazepam binding in rat cerebral cortex. Presumed K_i values were calculated with IC_{50} values obtained by graphical interpolation. Values are means ± SD for five different experiments. See ref 9 for details. [b] Mouse pentylenetetrazole anticonvulsant test. See ref 9 for experimental 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] Percent potentiation at that dose.

a group orally 1 h or intravenously immediately before subcutaneous administration of a subconvulsive dose (75 or 90 mg/kg) of PTZ. The dose (ED_{50}) at which 50% of the mice died was calculated by the probit method. In this test, **5** exhibited the greatest potency by both iv and po routes. Although high intravenous activities of β-CCM and β-CCE were observed, they produced no or very weak effects by the oral route. CGS 8216 was orally effective only when given in combination with a dose of 90 mg/kg sc of PTZ but was about 10 times less potent than **5**. Moreover, **5** itself did not cause convulsions in rats or mice even at a dose of 1000 mg/kg po.[11]

Further studies on the characterization of **5** and the structural requirements for agonists and inverse agonists are underway.

(11) Braestrup et al. (ref 1e) have described that the BZ receptor allosterically down-regulates the gain in the GABAergic system when occupied by the inverse agonist, a ligand with negative efficacy. According to their classification, compound **5** as well as CGS 8216 and β-CCE is "a partial inverse agonist" of which efficacy is not enough to generate convulsion by itself.

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