peptides in both assay systems.

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Registry No. 1, 23632-66-8; 2, 122235-68-1; 3, 122235-69-2; 4, 117014-32-1; II, 121076-34-4; II (open chain)·HCl, 122235-71-6; III, 122235-72-7; III (open chain), 121062-05-3; IV, 121062-07-5; IV (open chain)·HCl, 122269-68-5; V, 121062-08-6; V (open chain), 117499-53-3; VI, 121076-35-5; VI (open chain), 117499-55-5; VII, 122330-53-4; VII (open chain), 117499-56-6; VIII, 122330-54-5; VIII (open chain), 117499-57-7; BOC-Dpr(Fmoc)-OH, 122235-70-5; BOC-Asn-OH, 7536-55-2; Z-Asp-OH, 1152-61-0; BOC-Arg(Tos)-OH, 13836-37-8; BOC-D-Phe-OH, 18942-49-9; BOC-His(N^{π}-BOM)-OH, 79950-65-5; BOC-Trp(For)-OH, 47355-10-2; BOC-Asp(OBzl)-OH, 7536-58-5; BOC-Nle-OH, 6404-28-0; BOC-Lys(Fmoc)-OH, 84624-27-1.

Synthesis and Structure–Activity Relationships of a Series of Anxioselective Pyrazolopyridine Ester and Amide Anxiolytic Agents[1]

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A series of 1-substituted 4-amino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid esters and amides were synthesized and screened for anxiolytic activity in the shock-induced suppression of drinking (SSD) test. The compounds were also tested for their ability to displace [^{3}H]flunitrazepam (FLU) from brain benzodiazepine (BZ) binding sites. Many compounds were active in these screens and, additionally, demonstrated a selectivity for the type 1 BZ (BZ_1) receptor over the type 2 BZ (BZ_2) receptor as indicated by Hill coefficients significantly less than unity and by analysis of [^{3}H]FLU binding results from different brain regions. Based on the results of structure–activity studies of these compounds, a hypothesis was proposed to explain the structural features necessary for optimal interaction with brain BZ receptors. A detailed pharmacological evaluation of one of the most potent behaviorally active compounds (**27**) demonstrated it to be BZ_1 selective; also, in comparison to diazepam, **27** showed minimal sedative and alcohol interactive properties at therapeutically effective doses.

While the benzodiazepines (BZs) are currently the agents of choice for the treatment of anxiety, they produce a number of undesirable side effects[2] including ataxia, sedation, and a synergistic effect with ethanol and other central nervous system (CNS) depressants. Recent research efforts in the anxiolytic area have been aimed at discovering anxioselective agents,[3] i.e., compounds which at therapeutically effective doses show a reduced propensity to cause one or more of the unwanted ancillary activities associated with BZ usage. These research efforts are indeed beginning to reach fruition as evidenced by the appearance of a number of structurally novel agents purporting to exhibit anxioselective activity.[4]

Our program to discover a non-BZ anxioselective anxiolytic was aided by the discovery in 1977 of high affinity, saturable, and stereospecific binding sites in the CNS for the BZs.[5,6] The ability of the BZs to displace [^{3}H]diazepam or [^{3}H]flunitrazepam (FLU) highly correlates with their respective pharmacological[5-7] and clinical[8] properties. Consequently, the BZ binding sites have been postulated to mediate the therapeutic actions of the BZs.[5,6,9] While initial studies indicated these binding sites to be homogeneous, subsequent findings suggested the existence in the brain of two main subtypes.[10,11] The type 1 or BZ_1 receptors are located preferentially in the cerebellum while the type 2 or BZ_2 receptors are located, along with BZ_1 receptors, in the hippocampus, cortex, and other brain regions.[12,13] While the BZs appear to bind equally well to both BZ_1 and BZ_2 receptors[14] (Hill coefficient = 1[15]), certain novel potential anxiolytic compounds have been shown to demonstrate a selective affinity for the type 1 receptor (Hill coefficient in the cortex significantly < 1). For example, the triazolopyridazine CL 218,872 was shown to bind selectively to the BZ_1 receptor[10,11] and to lack the marked ataxic and depressant side effects associated with

[†] Department of Medicinal Chemistry.
[‡] Department of Pharmacology.

(1) Preliminary accounts of part of this work were presented earlier: (a) Bare, T. M.; Campbell, J. B.; Frazee, W. J.; Giles, R. E.; Goldberg, M. E.; Hesp, B.; Malick, J. B.; Meiners, B.; Patel, J.; Resch, J. F.; Salama, A.; U'Prichard, D. C.; Warawa, E. J. *Abstracts of a Symposium on Non-Benzodiazepine Anxiolytics and Hypnotics*; Rome, Italy, Feb. 16, 1987; p 11. (b) Bare, T. M.; Patel, J. B.; Salama, A. I.; Meiners, B. A. *Abstracts of Papers*, 194th National Meeting of the American Chemical Society, New Orleans, LA; August 30–September 4, 1987, American Chemical Society: Washington, DC, 1987; Division of Medicinal Chemistry, Abstract No. 88.
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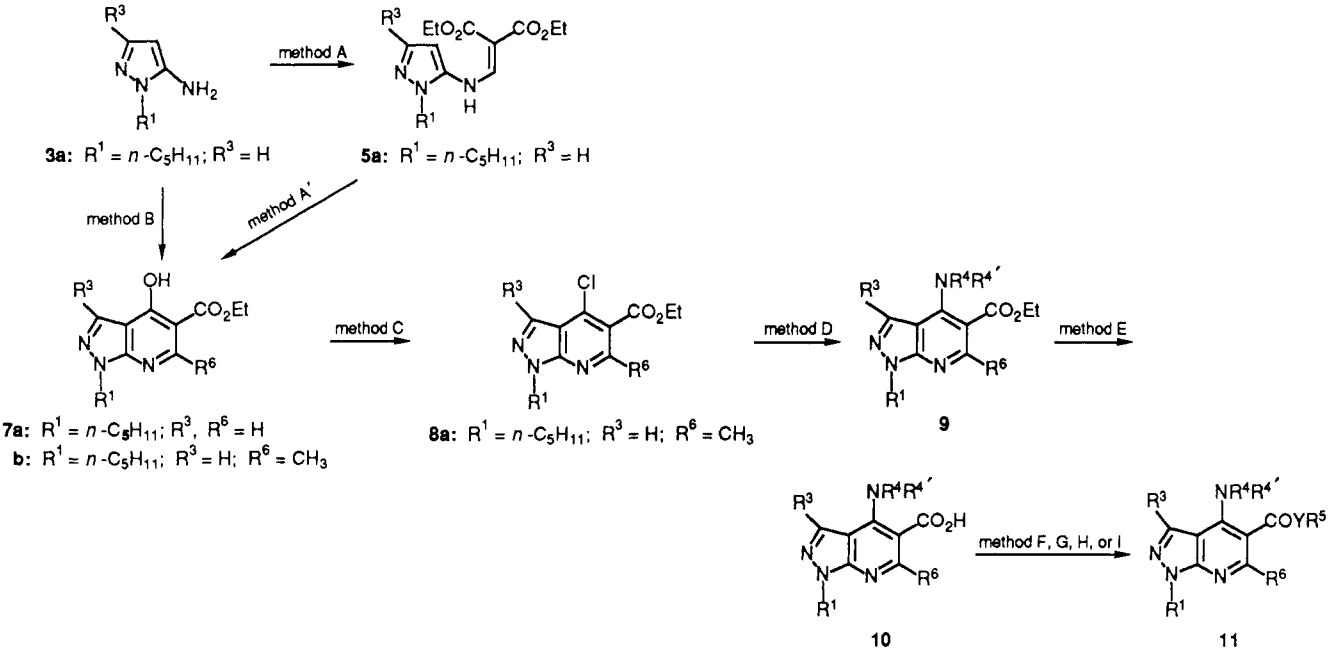
(15) For a discussion of the relationship of Hill coefficients and receptor multiplicity, see: (a) Braestrup, C.; Nielsen, M. *Trends Neurosci.* **1980**, *301*. (b) Lippa, A. S.; Meyerson, L. R.; Beer, B. *Life Sci.* **1982**, *31*, 1409.

0022-2623/89/1832-2561$01.50/0

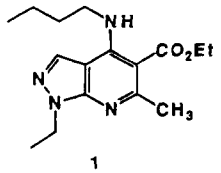
Scheme I[a,b]



[a] Method A = $EtOCH{=}C(CO_2Et)_2$ (4), 120 °C; method A′ = PhOPh, 235–255 °C; method B = $R^{6'}COCH(CO_2Et)_2$ (6), PPA, 120 °C; method C = $POCl_3$; method D = $R^4R^{4'}NH$; method E = (1) NaOH, H_2O, (2) H_3O^+; method F = K_2CO_3, R^5X, KI, DMF; method G = (1) $SOCl_2$, (2) R^5OH; method H = (1) $SOCl_2$, (2) $R^5R^{5'}NH$; method I = (1) CDI, (2) $R^5R^{5'}NH$. [b] R^1 = alkyl; R^3 = H, methyl; R^4, $R^{4'}$ = H, alkyl; R^5 = alkyl, alkenyl, alkynyl, phenyl, benzyl; $R^{5'}$ = H, alkyl, alkenyl, alkynyl; R^6 = H, alkyl; $R^{6'}$ = alkyl; Y = O, $NR^{5'}$.

the BZs.[16] These observations suggested that the BZ_1 receptors are responsible for the anxiolytic and anticonvulsant properties of antianxiety agents while the BZ_2 sites mediate the undesirable ancillary effects.[10] While recent findings[17-19] have cast doubt on this suggestion, it nonetheless formed a working hypothesis for us when we initially embarked on our quest several years ago to design a minimally sedative non-BZ anxiolytic agent which exerted its pharmacological activity via the BZ receptor.

BZ receptors were unknown when researchers at Squibb carried out their work on a series of pyrazolopyridines[20] which culminated with the discovery of several potential nonsedative anxiolytics, including tracazolate (1, ICI 136,753). This compound possesses anxiolytic activity



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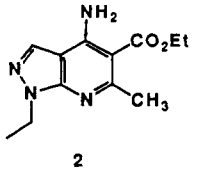

2

which is one-fourth to one-half as potent as chlordiazepoxide in several behavioral paradigms and is relatively free of the ataxia, motor incoordination, and alcohol and CNS depressant interactions characteristic of the BZs.[21] In contrast to the BZs, tracazolate enhances, rather than displaces, the binding of [^{3}H]FLU to brain binding sites.[22]

Progress toward our goal of discovering a non-BZ anxioselective agent was facilitated by a fortuitous observation concerning desbutyl tracazolate 2. This compound, a thermal degradation product and minor metabolite of tracazolate,[23] displaced [^{3}H]FLU from brain binding sites with a potency comparable to that of chlorodiazepoxide, but only possessed very weak behavioral properties in animals. The conversion of a compound that enhances [^{3}H]FLU binding to one that displaces [^{3}H]FLU by a relatively minor structural modification is quite striking and unique. This paper will describe the synthesis and structure–activity relationships (SARs) of a series of potential anxioselective pyrazolopyridine esters and amides developed on the basis of the lead obtained from desbutyl tracazolate 2.

Chemistry

Several 6-hydrido-4-hydroxy-1*H*-pyrazolo[3,4-*b*]pyridine ethyl esters (7, R^6 = H) were prepared (Scheme I) by thermal cyclization of an intermediate enamine (5) obtained from the appropriately substituted 5-aminopyrazole 3[24] and diethyl (ethoxymethylene)malonate 4 according to the procedure (method A, A′) of Hoehn and Denzel.[20] Many of the analogous 6-substituted compounds (7, R^6 = alkyl) were prepared by heating the requisite 5-aminopyrazoles 3[24] with a diethyl acylmalonate 6 in polyphosphoric acid (method B[20]). Phosphorus oxychloride (method C[20]) converted the resulting 4-hydroxy esters 7 to chloro derivatives 8, which, when treated with an amine or ammonia—usually in a pressure vessel (method D)—provided 4-aminopyrazolopyridine ethyl esters 9. Careful saponification (method E) of 9 provided carboxylic acids 10, which were then esterified (method F or G) or amidated (method H or I) to provide the desired esters (11, Y = O) or amides (11, Y = $NR^{5'}$).

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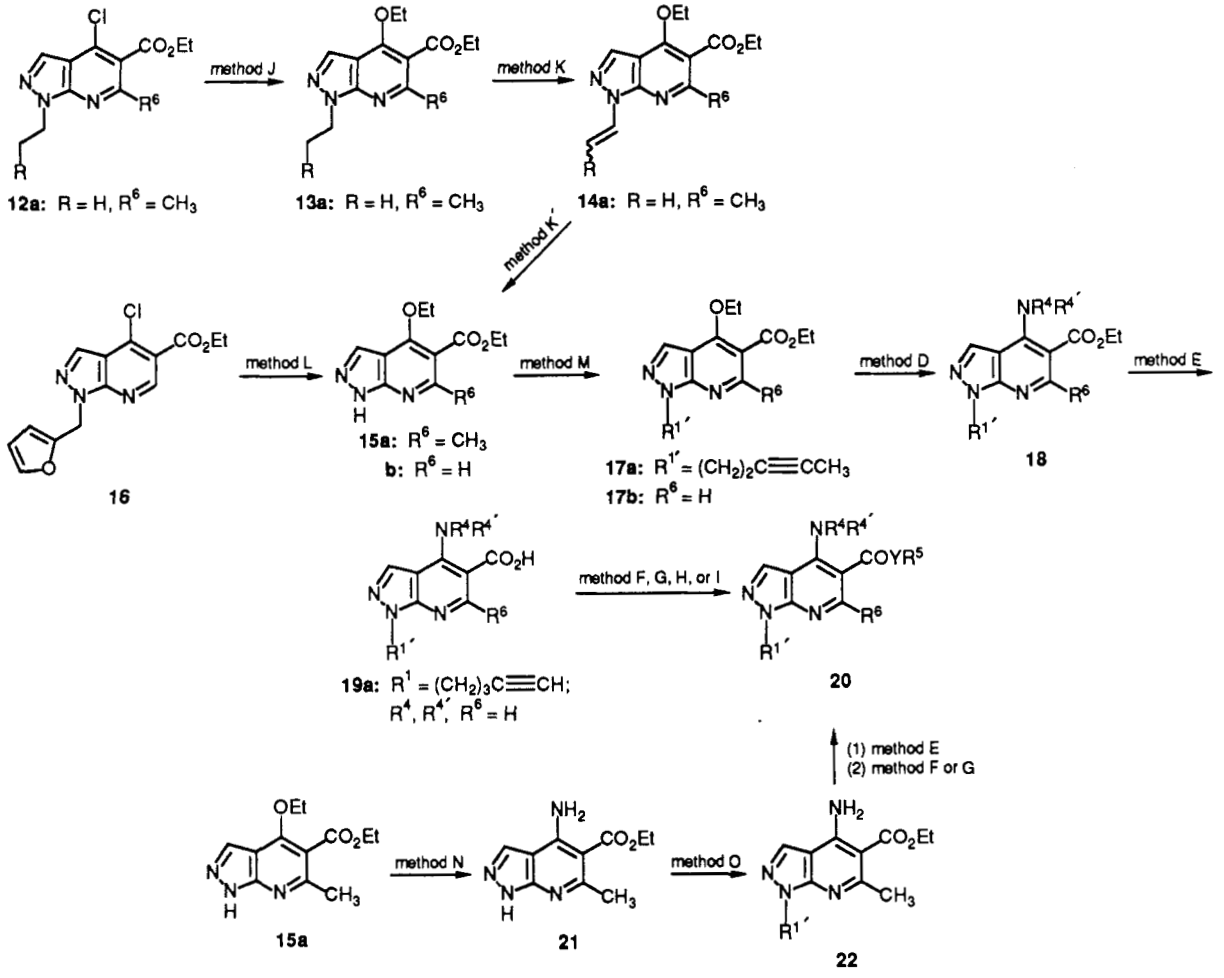
Scheme II[a,b]



[a] See footnotes for Scheme I; method J = NaOEt, EtOH; method K = NBS, CCl_4; method K′ = Na_2CO_3, THF, H_2O; method L, see ref 20; method M = K_2CO_3, $R^{1\prime}X$, DMF; method N = NH_3, pressure; method O = K_2CO_3, $R^{1\prime}X$, DMF. [b] R = H, alkyl; $R^{1\prime}$ = alkyl, alkenyl, alkynyl, benzyl.

Because the rather harsh conditions employed above for the formation of the pyrazolopyridine ring precluded the presence of certain labile 1-substituents during cyclization, alternate procedures (Scheme II) were sometimes employed to introduce this substituent after formation of the pyrazolopyridine ring. 1-Hydrido compound **15**, a key intermediate, was prepared by selenium dioxide oxidation (method L[20]) of furanylmethyl compound **16**.[20] An alternate procedure involved treating a 1-alkyl-4-ethoxypyrazolopyridine, **13** (prepared by reaction of chloro compound **12** with sodium ethoxide, method J), with *N*-bromosuccinimide (method K) to provide an intermediate vinyl pyrazole, **14**, which, under acidic or basic conditions (method K′), gave **15**. Alkylation (method M) of **15** occurred smoothly to provide the desired 1-substituted pyrazolopyridines **17** along with small quantities of the easily separated isomeric 2-substituted compounds. Amination (method D) and saponification (method E) of **17** provided the carboxylic acids **19**, which were converted to targeted esters (**20**, Y = O) or amides (**20**, Y = $NR^{5\prime}$) by using the methods (F, G, H, or I) mentioned in Scheme I. Alternatively, amination of **15a** with liquid ammonia (method N) gave **21**, which could be alkylated in the 1-position (method O) to provide amino esters **22**. Subsequently, **22** was converted by using standard methods to the targeted esters **20** (Y = O).

Several miscellaneous pyrazolopyridines were prepared as outlined in Schemes III and IV. 4-Hydrido compound **24** was obtained by catalytic hydrogenation of 4-chloro ester **23** while 5-hydrido compound **26** was obtained by thermal decarboxylation of the corresponding carboxylic acid **25**. Acylation of **27** provided 4-propionamido amide **28** while hydroxamic acid ester **30** was prepared from carboxylic acid **29** with 1-(*N*,*N*-diphenylcarbamoyl)-pyridinium chloride[25] to form an active ester, which was coupled with ethoxyamine. Primary amide **32** was isolated as a minor byproduct from the large-scale reaction of ammonia with **31**. 4-Hydroxy 5-carboxamide **34** was prepared from the corresponding carboxylic acid **33**, which, in turn, was obtained by acidic hydrolysis of chloro ester **31**. Oxidation of **31** with trifluoroperacetic acid provided *N*-oxide **35**, which was converted by a multistep sequence to 4-amino 5-carboxamide 7-*N*-oxide **39**.

Biology

The rat shock-induced suppression of drinking (SSD) test[21] was employed to determine the anxiolytic activity of the test compounds. This test is a modification of a procedure originally described by Vogel et al.;[26] the validity and reliability of this paradigm in predicting clinical anxiolytic efficacy is well-established.[26,27] Rats were ad-

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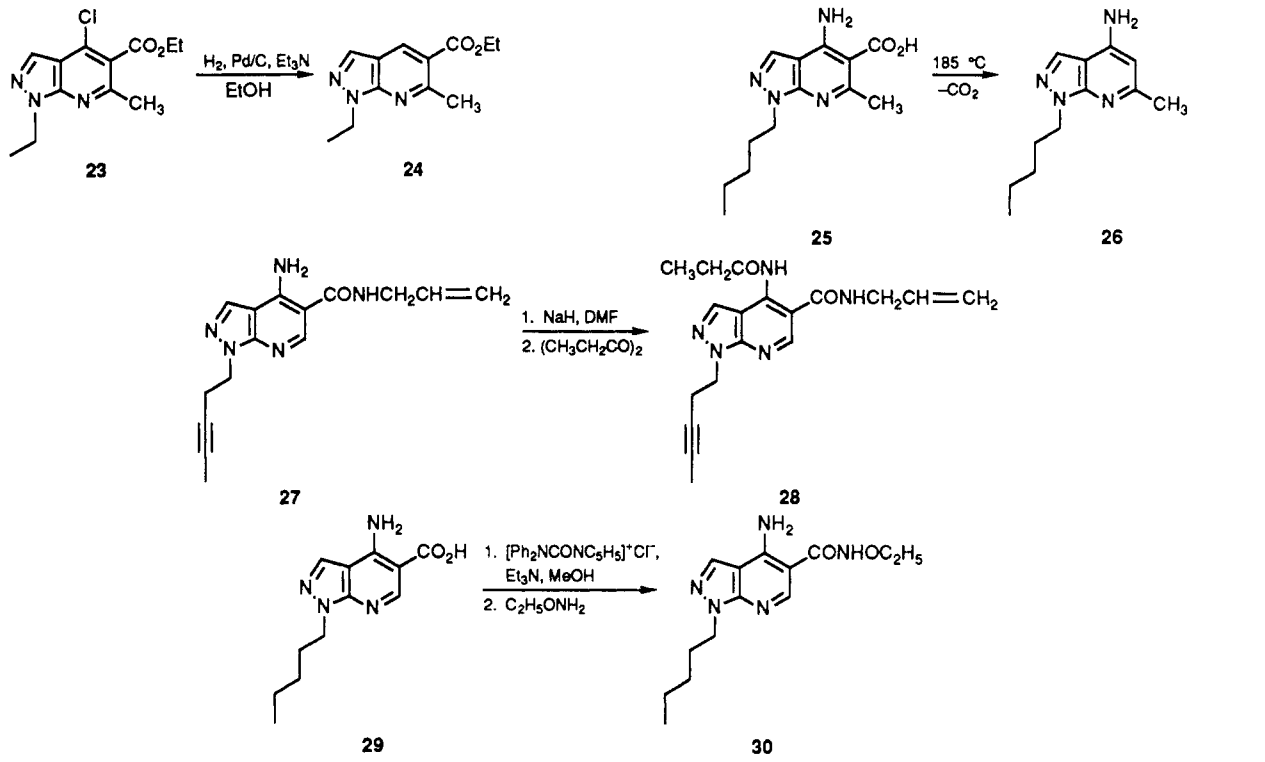
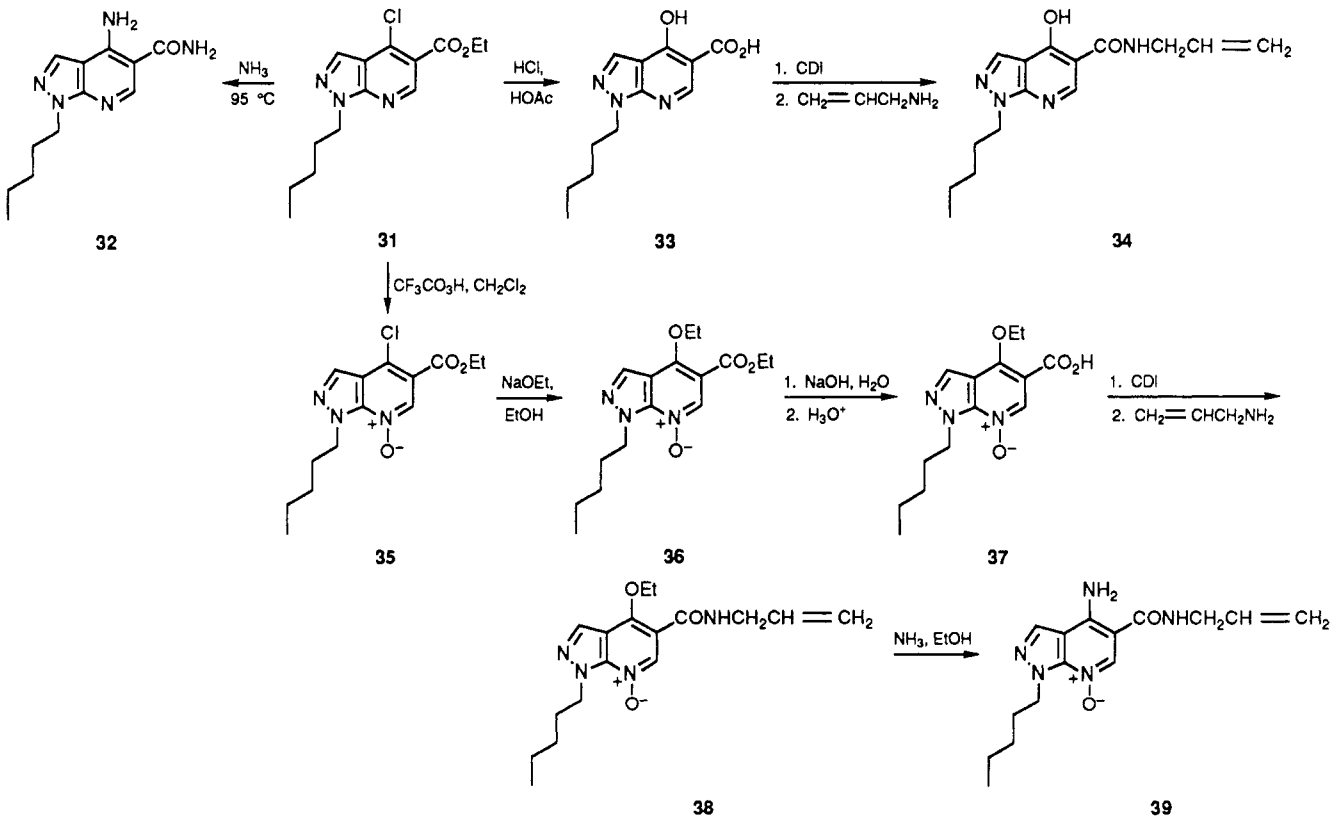
Scheme III



Scheme IV



ministered the test compounds at one or more dose levels (N = 8/dose) either orally or intraperitoneally and the minimum effective dose (MED) for each active compound determined.

The method for determining a compound's ability to displace [^{3}H]FLU from the cerebral cortex of rats has been described previously.[22] The assays were done in triplicate with less than 7% variation between values and IC_{50} values were determined with three or more concentrations.

Discussion and Results

The targeted compounds were tested in both the SSD test and the [^{3}H]FLU binding assay. Structural modifications of the pyrazolopyridine ring substituents revealed several interesting structure–activity relationships. By lengthening the 1-ethyl substituent of desbutyl tracazolate

2, optimal in vitro and in vivo activity was obtained with a linear four (41) or five (42) carbon unit (Table I). As the length of the 1-alkyl substituent progressed past six carbon units (compound 44, for example), biological activity rapidly diminished. The Hill coefficients (n_H) of these compounds became significantly less than 1 (<0.8) as the length of the 1-alkyl substituent increased past three carbon units (n_Hs for 2, 40, 41, 42, and 43 are 0.88, 0.85, 0.71, 0.62, and 0.73,[28] respectively). Hill coefficients significantly less than 1 may suggest preferential binding of the test agent to one of the BZ receptor subtypes present in the cortex.[15] This suggestion was subsequently verified[28] by determining the affinity of 42 to be 5 times greater in the BZ_1-containing cerebellum ([^{3}H]FLU IC_{50} = 12 nM) than in the cortex ([^{3}H]FLU IC_{50} = 58 nM), which contains both BZ_1 and BZ_2 receptor subtypes. Also, of the 1-linear alkyl substituted analogues of 2, only the *n*-butyl and *n*-pentyl compounds (41 and 42) showed oral activity in the SSD test.

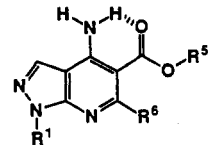
Additional structural modifications (Table I) of the 1-position of the pyrazolopyridine ethyl esters showed that alteration of the 1-*n*-butyl or 1-*n*-pentyl substituents by branching with a single methyl group in the 3-position (45 and 46) was not detrimental toward in vitro activity; however, branching at the 2-position (47) and disubstitution at the 3- and 4-positions (48 and 49, respectively) lead to marked decreases in activity. Introduction of a triple bond at the 4-position of the 1-pentyl tail provided a compound (50) with good in vitro and in vivo activities while the 1-pent-3-ynyl compound (51) retained in vivo activity with greatly diminished in vitro activity. The 1-benzyl substituent (52) lacked in vivo activity but retained modest in vitro activity. Generally speaking, optimal in vivo and/or in vitro activities were obtained when the 4-aminopyrazolopyridine esters were substituted in the 1-position with a linear four-, five-, or six-unit hydrocarbon chain possibly containing a double (see discussion below) or triple bond at the 2-, 3-, or 4-position and/or a methyl branch at the 3-position. Most of the structure–activity studies modifying the remaining positions of the pyrazolopyridine system were carried out with these optimal groupings in the 1-position.

Placement of a methyl substituent at the 3-position of desbutyl tracazolate (to provide compound 53) completely eliminated in vitro and in vivo activities. The 4-substituent must be a primary amino group to obtain potent displacing activity in the [^{3}H]FLU binding assay. The 4-methylamino, 4-ethylamino, and 4-propylamino analogues of 1 (54, 55, and 56, respectively) were inactive in vitro while the 4-*n*-butylamino compound (tracazolate, 1) enhanced the binding of [^{3}H]FLU to brain binding sites. Dimethylamino (57), hydroxy (58), and hydrogen (24) substituents in the 4-position caused a marked or complete loss of both in vitro and in vivo activities.

The 5-carboxylic acid ester grouping is necessary for good biological activity. Both the 5-hydrido (26) and 5-carboxylic acid (25) compounds are devoid of desired activity. Optimal biological activity is obtained when the alkoxy portion of the ester group is cyclopropylmethyl or a linear three- or four-carbon unit, which may contain a double or triple bond. Within the homologous 1-pentyl series, the allyl, propargyl, and cyclopropylmethyl esters (63, 64, and 68, respectively) demonstrated maximum in vitro and/or in vivo activity. Several allyl esters containing branched (71, 72) or unsaturated (73, 74, 78, 79) 1-substituents showed particularly potent affinities ([^{3}H]FLU IC_{50} = 5.5–16 nM) for the BZ binding sites. However, even the most potent compounds suffered from a relatively short (1–2 h) duration of SSD action, which appeared to be due to a fairly rapid rate of metabolic inactivation.[29,30]

The 6-methyl group is necessary for good behavioral activity in the pyrazolopyridine ester series. Larger alkyl groups in the 6-position (for example, 84 and 85) cause a marked decrease or loss of both in vivo and in vitro activity. The 6-desmethyl compounds are generally more potent in the in vitro screen but, contrary to expectations based on binding data, do not show a corresponding increase in in vivo activity (compare, for example, 86 with 63 or 87 with 71).

In addition to the biological findings described above for the pyrazolopyridine esters, spectral evidence indicated that the carbonyl group of the ester participated in an intramolecular hydrogen bond with the 4-amino group. This interaction would be expected to cause the ester carbonyl to be coplanar (or nearly so) with the pyrazolopyridine ring system (structure 121). As a working hypothesis, the intramolecular hydrogen bond and coplanar arrangement of the ester carbonyl was presumed to be necessary for BZ receptor interaction; consequently, any modification which perturbed this active conformation would be detrimental to the biological properties of the molecule. The 6-methyl substituent may be optimal for in vivo activity for the pyrazolopyridine esters because it is small enough not to significantly interact sterically with the coplanar ester group and/or a sterically sensitive area of the receptor. Interaction of a 6-methyl compound with the receptor is generally less efficient than that of the corresponding 6-hydrido compound. The size of the methyl group may, however, be sufficient to somewhat hinder the approach of plasma and microsomal esterases, thus slowing in vivo ester hydrolysis to an inactive carboxylic acid and providing higher plasma levels of the parent species imparting the desired biological activity.



121

Additional evidence to support this hypothesis has been obtained by examining the SSD activity of two representative esters (42 and 88) in the presence of a metabolizing enzyme inhibitor. The main metabolite of ethyl ester 42 in the rat is carboxylic acid 25 resulting from ester hydrolysis;[29] minor metabolites arising from the oxidation of the 1-*n*-pentyl substituent account for the remaining detectable metabolites.[29] In the presence of SKF 525A—a liver microsomal enzyme inhibitor which is also a competitive antagonist of plasma and microsomal esterases[31]—the SSD potencies of 42 and 88 are increased 4- and 8-fold, respectively.[30] Plasma and brain levels of parent compound are also significantly increased in the presence of SKF 525A.[29,30] These findings suggested that if the ester grouping could be made more resistant to metabolism, a long-acting, more potent compound would be obtained. Since amides may be bioisoteric with esters[32]

(28) Meiners, B. A.; Salama, A. I. Unpublished results.

(29) Kirkland, K. M. Unpublished results.

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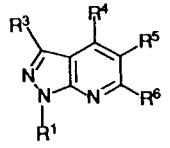
Table I. Synthetic Routes and Physical and Pharmacological Properties of 1*H*-Pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Esters and Amides



compd	R^1	R^3	R^4	R^5	R^6	synthetic route[a]	% yield[b]	mp, °C	formula[c]	SSD MED, mg/kg[d]	[^{3}H]FLU IC_{50}, nM or (% inhibn, nM)[e]
					Esters and Miscellaneous Compounds						
1	CH_2CH_3	H	$NH(CH_2)_3CH_3$	$CO_2CH_2CH_3$	CH_3	1	73	73.5–75[f]	$C_{16}H_{24}N_4O_2$	40 po	*g*
2	CH_2CH_3	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	81	124.5–126	$C_{12}H_{16}N_4O_2$	75 ip	460
24	CH_2CH_3	H	H	$CO_2CH_2CH_3$	CH_3	*h*	85	55.5–57.5	$C_{12}H_{15}N_3O_2$	NS[i] at 160 ip	(14, 5000)
25	$(CH_2)_4CH_3$	H	NH_2	CO_2H	CH_3	4	72	176–176.5	$C_{13}H_{18}N_4O_2$	NS at 50 ip	NS at 5000 nM
26	$(CH_2)_4CH_3$	H	NH_2	H	CH_3	*h*	80	183–185.5	$C_{12}H_{18}N_4$	NS at 50 ip	(13, 5000)
40	$(CH_2)_2CH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	70	98–99.5	$C_{13}H_{18}N_4O_2$	80 ip	410
41	$(CH_2)_3CH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	55	77–79	$C_{14}H_{20}N_4O_2$	40 po	50
42	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	85	200–203	$C_{15}H_{22}N_4O_2$·HCl	50 po	58
43	$(CH_2)_5CH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	64	204–207	$C_{16}H_{24}N_4O_2$·HCl	50 ip	320
44	$(CH_2)_6CH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	76	192–195	$C_{17}H_{26}N_4O_2$·HCl	NS at 25 ip	(61, 2000)
45	$(CH_2)_2CH(CH_3)_2$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	35	215–219	$C_{15}H_{22}N_4O_2$·HCl·0.05H_2O	100 po	39
46	$(CH_2)_2CH(CH_3)CH_2CH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	80	217–222	$C_{16}H_{24}N_4O_2$·HCl	25 ip	79
47	$CH_2CH(CH_3)CH_2CH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	53	218–222	$C_{15}H_{22}N_4O_2$·HCl	25 ip	391
48	$(CH_2)_2C(CH_3)_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	70	141–143	$C_{16}H_{24}N_4O_2$·HCl	NS at 50 ip	(38, 500)
49	$(CH_2)_3C(CH_3)_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	1	79	226–227	$C_{17}H_{26}N_4O_2$·HCl	NS at 25 ip	404
50	$(CH_2)_3C{\equiv}CH$	H	NH_2	$CO_2CH_2CH_3$	CH_3	2	60	113.5–114.5	$C_{15}H_{18}N_4O_2$	25 po	31
51	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_3	3	96	121.5–122.5	$C_{15}H_{18}N_4O_2$	25 po	590
52	$CH_2C_6H_5$	H	NH_2	$CO_2CH_2CH_3$	CH_3	3	82	130–131	$C_{17}H_{18}N_4O_2$	NS at 25 ip	156
53	CH_2CH_3	CH_3	NH_2	$CO_2CH_2CH_3$	CH_3	1	71	83–86	$C_{13}H_{18}N_4O_2$	NS at 25 ip	NS at 5000 nM
54	CH_2CH_3	H	$NHCH_3$	$CO_2CH_2CH_3$	CH_3	1	72	110–112.5	$C_{13}H_{18}N_4O_2$	NS at 25 ip	NS at 5000 nM
55	CH_2CH_3	H	$NHCH_2CH_3$	$CO_2CH_2CH_3$	CH_3	1	62	71.5–73.5	$C_{14}H_{20}N_4O_2$	25 ip	NS at 5000 nM
56	CH_2CH_3	H	$NH(CH_2)_2CH_3$	$CO_2CH_2CH_3$	CH_3	1	60	47.5–51.5	$C_{15}H_{22}N_4O_2$	NS at 25 ip	NS at 5000 nM
57	CH_2CH_3	H	$N(CH_3)_2$	$CO_2CH_2CH_3$	CH_3	1	88	81–82.5	$C_{14}H_{20}N_4O_2$	NS at 25 ip	(13, 800)
58	$(CH_2)_4CH_3$	H	OH	$CO_2CH_2CH_3$	CH_3	B	39	49–51	$C_{15}H_{21}N_3O_3$	NS at 50 ip	NS at 500 nM
59	$(CH_2)_4CH_3$	H	NH_2	CO_2CH_3	CH_3	6	65	193.5–195	$C_{14}H_{20}N_4O_2$·HCl	25 ip	(54, 5000)
60	$(CH_2)_4CH_3$	H	NH_2	$CO_2(CH_2)_2CH_3$	CH_3	5	67	194–199	$C_{16}H_{24}N_4O_2$·HCl	25 ip	50
61	$(CH_2)_4CH_3$	H	NH_2	$CO_2(CH_2)_3CH_3$	CH_3	6	57	191–194	$C_{17}H_{26}N_4O_2$·HCl[j]	50 ip	113
62	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH(CH_3)_2$	CH_3	6	60	201–208	$C_{16}H_{24}N_4O_2$·HCl·0.28H_2O[k]	50 po	(48, 5000)
63	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	6	59	64–66.5	$C_{16}H_{22}N_4O_2$	25 po	21
64	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2C{\equiv}CH$	CH_3	5	67	95–96	$C_{16}H_{20}N_4O_2$	25 po	89
65	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2C_6H_5$	CH_3	5	79	66.5–67	$C_{20}H_{24}N_4O_2$	NS at 25 ip	100
66	$(CH_2)_4CH_3$	H	NH_2	$CO_2(CH_2)_2CH{=}CH_2$	CH_3	5	80	50–51	$C_{17}H_{24}N_4O_2$	NS at 50 ip	174
67	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2C(CH_3){=}CH_2$	CH_3	5	70	80–81	$C_{17}H_{24}N_4O_2$	NS at 25 ip	69
68	$(CH_2)_4CH_3$	H	NH_2	CO_2CH_2– 	CH_3	6	58	62.5–65.5	$C_{17}H_{24}N_4O_2$	12.5 po	131
69	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2CH(CH_3)_2$	CH_3	6	61	46–48	$C_{17}H_{26}N_4O_2$	NS at 25 ip	(55, 500)
70	$(CH_2)_4CH_3$	H	NH_2	$CO_2(CH_2)_2$– 	CH_3	6	71	55–57	$C_{18}H_{26}N_4O_2$	50 ip	51
71	$(CH_2)_2CH(CH_3)_2$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	5	81	89.5–90	$C_{16}H_{22}N_4O_2$	50 po	13
72	$(CH_2)_2$– 	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	7	31	81–83	$C_{16}H_{20}N_4O_2$	25 po	16
73	$CH_2CH{=}C(CH_3)_2$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	7	68	76–78	$C_{16}H_{20}N_4O_2$	NS at 25 ip	6.4
74	$(CH_2)_3C{\equiv}CH$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	7	89	99.5–100	$C_{16}H_{18}N_4O_2$	12.5 po	5.5
75	$(CH_2)_2CH{=}CH_2$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	7	58	64–64.5	$C_{15}H_{18}N_4O_2$	25 po	54
76	$CH_2CH{=}CH_2$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	7	69	115.5–116	$C_{14}H_{16}N_4O_2$	25 po	112
77	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	7	48	113.5–115	$C_{16}H_{18}N_4O_2$[l]	25 po	79
78	$(CH_2)_3CH{=}CH_2$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	7	62	62–62.5	$C_{16}H_{20}N_4O_2$	25 po	9.7
79	$(CH_2)_4C{\equiv}CH$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	8	58	69–70	$C_{17}H_{20}N_4O_2$	25 po	8.6

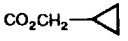
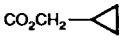
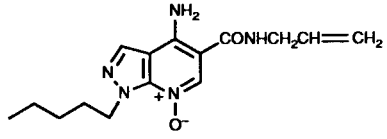
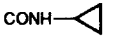
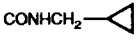
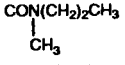
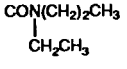
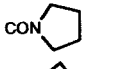
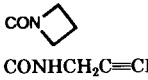
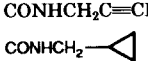
80	$(CH_2)_2C{\equiv}CH$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	8	72	115–116	$C_{15}H_{16}N_4O_2$	50 po	160
81	$(CH_2)_3CH_3$	H	NH_2	$CO_2CH_2CH{=}CH_2$	CH_3	7	67	62–63	$C_{15}H_{20}N_4O_2$	25 po	21
82	$(CH_2)_3C{\equiv}CH$	H	NH_2		CH_3	8	83	94–96	$C_{17}H_{20}N_4O_2$	12.5 po	22
83	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2		CH_3	7	60	132.5–133	$C_{17}H_{20}N_4O_2$	12.5 po	315
84	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2CH_3$	CH_2CH_3	1	54	148.5–150	$C_{16}H_{24}N_4O_2{\cdot}HCl$	NS at 100 ip	302
85	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2CH_3$	$CH_2(CH_3)_2$	1	40	191.5–193	$C_{17}H_{26}N_4O_2{\cdot}HCl$	NS at 25 ip	(54, 5000)
86	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2CH{=}CH_2$	H	10	81	147–148	$C_{15}H_{20}N_4O_2$	NS at 100 po	16
87	$(CH_2)_2CH(CH_3)_2$	H	NH_2	$CO_2CH_2CH{=}CH_2$	H	10	88	124–126	$C_{15}H_{20}N_4O_2{\cdot}0.05H_2O$	25 ip	5.7
88	$(CH_2)_4CH_3$	H	NH_2	$CO_2CH_2CH_3$	H	9	81	149.5–150.5	$C_{14}H_{20}N_4O_2$	NS at 25 ip	57
					Amides						
27	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2	$CONHCH_2CH{=}CH_2$	H	14	63	180.5–181.5	$C_{15}H_{17}N_5O$	0.8 po	81
28	$(CH_2)_2C{\equiv}CCH_3$	H	$NHCOCH_2CH_3$	$CONHCH_2CH{=}CH_2$	H	*h*	6.5	157.5–158.5	$C_{18}H_{21}N_5O_2$	1.6 po	(28, 500)
30	$(CH_2)_4CH_3$	H	NH_2	$CONHOCH_2CH_3$	H	*h*	54	142.5–144	$C_{14}H_{21}N_5O_2$	12.5 po	531
32	$(CH_2)_4CH_3$	H	NH_2	$CONH_2$	H	*h*	6	201–202	$C_{12}H_{17}N_5O$	12.5 po	2447
34	$(CH_2)_4CH_3$	H	OH	$CONHCH_2CH{=}CH_2$	H	*h*	72	197–198	$C_{15}H_{20}N_4O_2$	50 po	NS at 500 nM
39						*h*	58	232–237	$C_{15}H_{21}N_5O_2{\cdot}HCl$	12.5 po	53
89	$(CH_2)_4CH_3$	H	NH_2	$CONH(CH_2)_3CH_3$	CH_3	11	18	202–202.5	$C_{17}H_{27}H_5O$	NS at 50 ip	(31, 5000)
90	$(CH_2)_4CH_3$	H	NH_2	$CONHCH_2CH{=}CH_2$	CH_3	11	12	184–185	$C_{16}H_{23}N_5O{\cdot}0.1H_2O$	50 po	(0, 50)
91	$(CH_2)_4CH_3$	H	NH_2	$CONHCH_3$	H	12	88	273–274	$C_{13}H_{19}N_5O{\cdot}HCl$	12.5 po	354
92	$(CH_2)_4CH_3$	H	NH_2	$CONHCH_2CH_3$	H	12	77	238–242.5	$C_{14}H_{21}N_5O{\cdot}HCl$	12.5 po	109
93	$(CH_2)_4CH_3$	H	NH_2	$CONH(CH_2)_2CH_3$	H	12	72	143–145	$C_{15}H_{23}N_5O$	25 po	89
94	$(CH_2)_4CH_3$	H	NH_2	$CONH(CH_2)_3CH_3$	H	12	90	125–127	$C_{16}H_{25}N_5O$	50 po	80
95	$(CH_2)_4CH_3$	H	NH_2	$CONHCH(CH_3)_2$	H	12	85	168–169	$C_{15}H_{23}N_5O$	25 ip	414
96	$(CH_2)_4CH_3$	H	NH_2		H	12	84	151.5–153	$C_{15}H_{21}N_5O$	12.5	312
97	$(CH_2)_4CH_3$	H	NH_2		H	12	83	143–144	$C_{16}H_{23}N_5O$	6.3 po	35
98	$(CH_2)_4CH_3$	H	NH_2	$CONHCH_2CH{=}CH_2$	H	12	82	139–140	$C_{15}H_{21}N_5O$	12.5	28
99	$(CH_2)_4CH_3$	H	NH_2	$CONHCH_2C{\equiv}CH$	H	12	87	169–170.5	$C_{15}H_{19}N_5O$	6.3 po	60
100	$(CH_2)_4CH_3$	H	NH_2	$CONHCH_2C{\equiv}CCH_3$	H	12	63	133–134	$C_{16}H_{21}N_5O$	6.3 po	84
101	$(CH_2)_4CH_3$	H	NH_2	$CONHC_6H_5$	H	12	65	215–216	$C_{18}H_{21}N_5O$	50 ip	790
102	$(CH_2)_4CH_3$	H	NH_2	$CONHCH_2C_6H_5$	H	12	65	160–161	$C_{19}H_{23}N_5O$	25 po	36
103	$(CH_2)_4CH_3$	H	NH_2	$CONCH_3CH_2CH{=}CH_2$	H	12	55	111–138	$C_{16}H_{23}N_5O{\cdot}HCl$	12.5 po	NS at 500 nM
104	$(CH_2)_4CH_3$	H	NH_2	$CONCH_3CH_2C{\equiv}CH$	H	12	91	203.5–204.5	$C_{16}H_{21}N_5O{\cdot}HCl$	6.3 po	NS at 500 nM
105	$(CH_2)_4CH_3$	H	NH_2		H	12	78	148–150	$C_{16}H_{25}N_5O{\cdot}HCl$	6.3 po	NS at 500 nM
106	$(CH_2)_4CH_3$	H	NH_2	$CON(CH_3)_2$	H	12	79	207–208	$C_{14}H_{21}N_5O{\cdot}HCl$	12.5 po	NS at 500 nM
107	$(CH_2)_4CH_3$	H	NH_2	$CON(CH_2CH_3)_2$	H	12	67	177–178	$C_{16}H_{25}N_5O{\cdot}HCl$	25 po	NS at 500 nM
108	$(CH_2)_4CH_3$	H	NH_2		H	12	72	195–196	$C_{17}H_{27}N_5O{\cdot}HCl$	25 po	NS at 500 nM
109	$(CH_2)_4CH_3$	H	NH_2	$CON(CH_2CH{=}CH_2)_2$	H	12	43	198–200	$C_{18}H_{25}N_5O{\cdot}HCl$	25 po	NS at 500 nM
110	$(CH_2)_4CH_3$	H	NH_2	$CON(CH_2C{\equiv}CH)_2$	H	12	80	164–166	$C_{18}H_{21}N_5O{\cdot}HCl$	12.5 po	NS at 500 nM
111	$(CH_2)_4CH_3$	H	NH_2		H	12	86	204–207	$C_{16}H_{23}N_5O{\cdot}HCl$	50 ip	NS at 500 nM
112	$(CH_2)_4CH_3$	H	NH_2		H	12	67	148–149.5	$C_{15}H_{21}N_5O{\cdot}HCl{\cdot}0.33H_2O$	50 po	137
113	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2	$CONHCH_2C{\equiv}CH$	H	12	45	191–192	$C_{15}H_{15}N_5O$	3.1 po	114
114	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2		H	13	50	184–185	$C_{16}H_{19}N_5O$	3.1 po	271

Table I (Continued)

compd	R^1	R^3	R^4	R^5	R^6	synthetic route[a]	% yield[b]	mp, °C	formula[c]	SSD MED, mg/kg[d]	[^{3}H]FLU IC_{50}, nM or (% inhibn, nM)[e]
115	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2	$CONH(CH_2)_2CH_3$	H	14	71	184–186	$C_{15}H_{19}N_5O$	6.3 po	500
116	$(CH_2)_3C{\equiv}CH$	H	NH_2	$CONHCH_2CH{=}CH_2$	H	15	51	117.5–119	$C_{15}H_{17}N_5O$	6.3 po	9.3
117	$(CH_2)_2CH{=}CH_2$	H	NH_2	$CONHCH_2CH{=}CH_2$	H	15	68	123–124	$C_{15}H_{19}N_5O$	3.1 po	10
118	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2	$CON(CH_2)_2CH_3$ (CH$_3$)	H	14	69	199–204	$C_{16}H_{21}N_5O{\cdot}HCl$	12.5 po	NS at 500 nM
119	$(CH_2)_2C{\equiv}CCH_3$	H	NH_2	$CONCH_2CH{=}CH_2$ (CH$_3$)	H	14	77	174–176.5	$C_{16}H_{19}N_5O{\cdot}HCl$	12.5 po	NS at 500 nM
120	$(CH_2)_4CH_3$	H	$NH(CH_2)_3CH_3$	$CONHCH_2CH{=}CH_2$	H	12	87	105–108	$C_{19}H_{29}N_5O$	NS at 25 ip	NS at 500 nM
diazepam										5 po	6
chlordiazepoxide										10 po	330

[a] Letters refer to the methods described in the Experimental Section; numbers refer to the following sequences of methods for synthesis of compounds: 1, BCD; 2, BCJKNO; 3, BCJKMD; 4, BCDE; 5, BCDEF; 6, BCDEG; 7, BCJKMDEF; 8, BCJKNOEF; 9, ACD; 10, ACDEF; 11, BCDEH; 12, ACDEH; 13, ACJKMDEH; 14, LMDEH; 15, LMDEI. [b] Yield of last step. [c] All compounds had elemental analyses (C, H, N) within ±0.4% of theoretical values unless indicated otherwise. [d] The minimum effective dose (MED) is the dose (in rats) that produced a significant ($p < 0.05$, Student's t test) increase in the mean number of shocks taken over the vehicle control;[21] po—oral administration; ip—intraperitoneal administration. [e] Receptor binding is expressed in one of two ways: (1) As an IC_{50} or the concentration (nM) of compound required for half-maximal inhibition of [^{3}H]FLU binding to BZ receptors in the rat cerebral cortex[22] or (2) for less potent compounds, as % inhibition of [^{3}H]FLU binding (in rat cerebral cortex) at a single dose (nM).[22] [f] Literature[20] mp 75–77 °C. [g] Enhances binding to brain BZ binding sites.[22] [h] Procedure described in the Experimental Section. [i] NS = no significant activity. [j] C: calcd, 57.54; found, 58.08. [k] N: calcd, 15.20; found, 15.75. [l] C: calcd, 64.41; found, 64.98.

and are generally considered to be metabolically more stable than the corresponding esters,[33] several pyrazolopyridine-5-carboxamides were synthesized and screened by using the SARs found for the esters as a rough guide.

Because the most favorable biological activity of the pyrazolopyridine esters was obtained with a linear pentyl, pentenyl, or pentynyl substituent in the 1-position, most of the amides synthesized possessed these substituents. In contrast to the esters, the amides which contained a methyl substituent in the 6-position (**89** and **90**) were inactive or weakly active in both the in vitro and in vivo tests. However, several of the 6-desmethyl amides possessed behavioral activity comparable or, in many cases, superior to the best compounds in the ester series.

For example, in the homologous 6-desmethyl series containing the 1-pentyl tail, primary amide **32** had modest SSD activity but weak affinity for the BZ receptor. For secondary amides, incrementally increasing the length of the *N*-alkyl substituent from methyl to *n*-butyl (**91**–**94**) decreased SSD potency and increased affinity for the BZ receptor. Branching of the *N*-alkyl substituent (**95**) was detrimental to both in vivo and in vitro activities; however, the cyclopropyl (**96**) and cyclopropylmethyl (**97**) amides possess good SSD activity and modest-to-good activity in vitro. Incorporation of unsaturation into the secondary amide alkyl group gave compounds (**98**–**100**) with good SSD activity and modest affinity for the BZ receptor. While the secondary phenyl amide (**101**) was weak in vitro and in vivo, the benzyl amide (**102**) was relatively potent.

Several *N*-methyl tertiary amides (for example, **103**–**106**) in the 1-pentyl-6-desmethyl series possessed good SSD activity with the most potent compounds having an MED of 6.25 mg/kg, po. SSD activity appeared to be retained with the two *N*-ethyl tertiary amides (**107** and **108**) as well as with the *N*,*N*-diallyl (**109**) and *N*,*N*-dipropargyl (**110**) compounds. In contrast to the secondary amides, the tertiary compounds, with the notable exception of the azetidinyl compound (**122**), lack affinity for the BZ receptor. Pharmacokinetic studies with a representative tertiary methyl amide have shown that the in vivo activity of these neurochemically silent compounds is probably due, at least partially, to metabolism to the neurochemically active secondary amides.[29]

Replacement of the 1-pentyl substituent of secondary amides with linear five-carbon groups containing double or triple bonds generally increased the behavioral potency of the resulting compounds 2–4-fold (compare, for example, **113** vs **99**, **114** vs **97**, **115** vs **93**, **116** and **117** vs **98**). A remarkable exception was observed with 1-pent-3-ynyl allyl amide **27**, which increased 16-fold in its SSD potency over the corresponding 1-pentyl analogue **98**, giving an MED of 0.8 mg/kg, po. While the behavioral potencies of the 1-pent-3-ynyl compounds invariably increased over their pentyl analogues, the in vitro activities all decreased. Introducing the 1-pent-3-ynyl substituent into some of the more potent tertiary *N*-methyl amides did not cause any consistent or marked changes in biological activity (compare **118** with **105** or **119** with **103**).

Other compounds of note in the amide series are hydroxamic acid ester **30** and *N*-oxide **39**, both of which have moderate potencies in vivo and in vitro. The 4-(*n*-butylamino)pyrazolopyridine amides (for example, **120**), in contrast to the corresponding esters, which are enhancers

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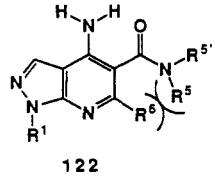
(33) Low, L. K.; Castagnoli, N. In *Burger's Medicinal Chemistry*, 4th ed.; Wolff, M. E., Ed.; John Wiley & Sons: New York, 1980; pp 178–182.

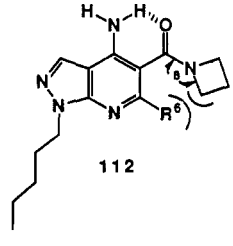
of [^{3}H]FLU binding, are inactive both in vivo and in vitro. Replacing the 4-amino group with hydroxy gave very weak or inactive compounds (**34**). 4-Propionamido compound **28** is potent in the SSD test but inactive in displacing [^{3}H]FLU from brain binding sites in vitro. This compound probably acts as a prodrug for the very potent 4-amino compound **27**.

From structure–activity considerations observed with the pyrazolopyridine esters, several deductions can be made concerning the interaction of these compounds with the BZ receptor. The receptor cavity which receives the 1-substituent of the pyrazolopyridine optimally accommodates a linear chain four to five carbon units in length. Additionally, a single methyl group branch at the 3-position of this linear chain appears to be beneficial for interacting with the receptor. Likewise, unsaturation at the 2,3, 3,4, and 4,5 positions of the 1-alkyl substituent appears to be accommodated without significant loss of behavioral and/or receptor binding activity. There appears to be an area on the receptor which is intolerant to anything larger than a hydrogen on the 3-position of the pyrazolopyridine. The primary 4-amino group is necessary for potent interaction with the BZ receptor. While one of the amino hydrogens bonds intramolecularly with the ester (or amide) carbonyl to impart coplanarity, the other hydrogen may be situated favorably to interact with a hydrogen-bonding area on the receptor. Alkyl substitution on the 4-amino substituent destroys or considerably weakens the affinity of the pyrazolopyridine for the BZ receptor; however, if the substituent is *n*-butyl, the resulting compound (at least in the ester series) enhances the binding of [^{3}H]FLU to the BZ receptor. Optimal interaction of the pyrazolopyridine ester with the BZ receptor is achieved when the ester alkoxy group is allyl, propyl, cyclopropylmethyl, or ethyl. And, as mentioned previously, a hydrogen substituent at the 6-position generally imparts optimal interaction of the pyrazolopyridine with the receptor. While a 6-methyl group is also tolerated, anything larger considerably weakens or eliminates receptor interaction, presumably because of perturbation of the "active" coplanar ester conformation and/or steric interaction with a sensitive area on the receptor.

In a general sense the SARs of the pyrazolopyridine amides are quite similar to those of the pyrazolopyridine esters. The major difference between the two series is the poor affinity for the BZ receptor demonstrated by the 6-methyl-substituted amides. This lack of affinity may be attributed to steric interaction between the 6-methyl group and the amide substituents (R^5, $R^{5'}$), which forces the carbonyl group out of the plane of the pyrazolopyridine ring (structure **122**). Loss of coplanarity, according to our



122



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receptor interaction hypothesis, disrupts the active conformation necessary for receptor binding. The same consideration appears to be important for the tertiary amides. These compounds do not bind to the receptor presumably because of a steric interaction between the amide substituents and the 6-hydrogen of the pyrazolopyridine ring. However, for secondary and primary amides, where at least one of the amide substituents is hydrogen, this interaction is apparently absent or minimal so that carbonyl coplanarity/intramolecular hydrogen bonding/receptor interaction are all possible. This coplanarity principle was nicely illustrated by examining azetidinyl amide **112**, which is the only tertiary amide synthesized that interacts with the BZ receptor. We predicted that the constraints inherent in the four-membered azetidine ring, by increasing the angle β, would tend to decrease the steric interaction between the 6-hydrogen of the pyrazolopyridine and the α-methylene of the azetidine ring to allow carbonyl coplanarity. The dramatic appearance of [^{3}H]FLU displacing ability in going from the pyrrolidinyl (**111**) to azetidinyl (**112**) amide appears to confirm this hypothesis.

Table II. Comparative Pharmacological Properties of 4-Amino-1-pent-3-ynyl-*N*-2-propenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (**27**) and Diazepam[a]

	27	diazepam
SSD (rat, MED)	0.8 mg/kg, po	5.0 mg/kg, po
rotorod (rat, ED_{50})	25.1 mg/kg, po	10.2 mg/kg, po
sedative liability index (SLI)[b]	31.4	2.0
[^{3}H]FLU (IC_{50}, nM)		
cortex	81	7.3
cerebellum	19	9.3
antimetrazole (rat, ED_{50})	1.0 mg/kg, po	8.4 mg/kg, po
monkey conflict (MED)	3.1 mg/kg, po	1.6 mg/kg, po
EtOH-induced impairment of rotorod performance (rat, ED_{50})	3.1 mg/kg, po	2.5 mg/kg, po
ethanol interaction ratio (EIR)[c]	3.9	0.5

[a] Biological methods used to produce the results in this table are described in ref 34. [b] See ref 34, 35. [c] See ref 34, 36.

Because of its potent SSD activity, compound **27** (ICI 190,622) was chosen for more detailed examination in screens (Table II) predictive of anxiolytic activity and side-effect liability.[34] This compound is 6 times more potent than diazepam (DZ) in the SSD test (Table II) and has a 3 h (vs 1 h for DZ) duration of action at its MED.[30] In the rotorod test, which is used to assess sedation or ataxia, **27** required higher doses than DZ to induce ataxia. The sedative liability index (SLI[35]), which provides an indication of the separation between the anxiolytic and ataxic doses, is 15 times greater for **27** than for DZ. These data suggest that, in comparison to DZ, **27** should possess minimal sedative properties at therapeutically effective doses. Compound **27** binds more potently to BZ binding sites in the cerebellum ([^{3}H]FLU IC_{50} = 19 nM) than in the cortex ([^{3}H]FLU IC_{50} = 81 nM), thus indicating a BZ_1 selective agent. Additional neurochemical studies[34] have demonstrated that **27** appears to act competitively (not allosterically) at the BZ receptor and that it is a full BZ receptor agonist. The compound is a potent antagonist of metazole-induced convulsions (ED_{50} = 1.0 mg/kg, po) and is also active in the primate conflict test (MED = 3.1 mg/kg, po). By using the rotorod test to determine ethanol interaction liabilities, the ethanol interaction ratio (EIR[36]) for **27** was found to be 8 times that for DZ. This suggests that **27** should be considerably less likely to cause an adverse interaction with ethanol at therapeutic doses when compared to DZ. Therefore, on the basis of pharmacological studies in animals, **27** represents a novel non-BZ anxioselective anxiolytic that preferentially binds to the

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(35) SLI = (rotorod (rat) ED_{50}, mg/kg)/(SSD MED, mg/kg).
(36) EIR = (rotorod (rat) ED_{50} (drug + ethanol), mg/kg)/(SSD MED, mg/kg). A subthreshold dose (0.8 g/kg, ip) of ethanol was used for EIR determinations.

BZ_1 receptor. The compound appears to offer significant advantages over the BZs and, consequently, was chosen as a potential candidate for development.

In conclusion, it has been demonstrated that several compounds in a series of 1-substituted 4-amino-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic acid esters and amides possess pharmacological properties predictive of anxiolytic activity. The compounds are active in the SSD test and in displacing [^{3}H]FLU from brain binding sites. Several compounds appear to be selective for the BZ_1 receptor subtype as indicated by Hill coefficients significantly less than unity and by regional analysis of [^{3}H]FLU binding in the brain. Structure–activity relationships for these compounds were determined, and a hypothesis was proposed to explain the structural features necessary for interaction with brain BZ binding sites. These compounds generally appear to be less sedative than the BZs and a detailed pharmacological profile of **27** showed this material to be a potential anxioselective anxiolytic agent.

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Proton nuclear magnetic resonance spectra (^{1}H NMR) were determined on a Varian EM-360, IBM NR-80, Bruker WM-250, or Bruker AM-300 spectrometer with tetramethylsilane as an internal standard. Mass spectra (MS) were determined on a Varian MAT 44, Kratos MS-80, or Finnigan 4500 spectrometer operating in either the electron impact (EI) or the chemical ionization (CI) mode; the EI mode was employed unless indicated otherwise. Infrared spectra were run on a Perkin-Elmer 727B spectrophotometer. Elemental analyses were determined on a Control Equipment Corp. Model 240 XA elemental analyzer and are within ±0.4% unless indicated otherwise. Analytical thin-layer chromatography (TLC) was carried out on prelayered silica gel GHLF plates (Analtech, Newark, DE) using ultraviolet light for visualization while flash chromatography was performed with silica gel (J.T. Baker, 40-μM average particle diameter) with the solvents indicated.

5-Amino-1-pentylpyrazole[24] (3a). To a stirred solution of 40.27 g (0.473 mol) of (2-cyanoethyl)hydrazine in 348 mL of toluene was added dropwise 42.8 g (0.497 mol) of valeraldehyde in 87 mL of toluene. After stirring for 3 h at room temperature, the reaction mixture was concentrated to give 80.50 g of a crude intermediate hydrazone as an amber oil. This oil was then added to a solution of sodium *n*-butoxide [prepared by reacting 2.0 g (87 mg-atom) of sodium with 435 mL of 1-butanol] in 1-butanol and refluxed for 5 h. The resulting cooled solution was concentrated to leave 89.7 g of a dark, viscous oil, which was distilled to give 31.68 g (43.7%) of **3a** as a light yellow oil: bp 106–112 °C (0.4 mm) [lit.[24] bp 103–104 °C (0.3 mm)]; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, 7.5 Hz), 1.30 (m, 4 H), 1.77 (m, 2 H), 3.74 (br s, 2 H, NH_2), 3.90 (t, 2 H, 7.5 Hz), 5.49 (d, 1 H, 2.5 Hz), 7.24 (d, 1 H, 2.5 Hz); MS *m/e* 153 (M^+).

Method A. [[(1-Pentyl-5-pyrazolyl)amino]methylene]malonic Acid Diethyl Ester (5a). A stirred mixture of 15.56 g (101.5 mmol) of **3a** and 21.96 g (101.5 mmol) of diethyl (ethoxymethylene)malonate was heated at 120 °C for 2 h and then distilled with a Kugelrohr apparatus to give 26.53 g (81%) of intermediate enamine **5a** as a light yellow oil: bp 140–150 °C (0.045 mm); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, 3 H, 6 Hz), 1.31 (t, 3 H, 7 Hz), 1.38 (t, 3 H, 7 Hz), 1.15–1.55 (m, 4 H), 1.85 (m, 2 H), 4.05 (t, 2 H, 7 Hz), 4.24 (q, 2 H, 7 Hz), 4.33 (q, 2 H, 7 Hz), 6.05 (d, 1 H, 2 Hz), 7.42 (d, 1 H, 2 Hz), 8.16 (d, 1 H, 13 Hz), 11.05 (d, 1 H, 13 Hz); MS *m/e* 323 (M^+).

Method A'. 4-Hydroxy-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (7a). A solution of 11.63 g (35.96 mmol) of **5a** in 29 mL of diphenyl ether was heated at 235–255 °C under a nitrogen atmosphere for 2 h; provisions were made to remove the ethanol formed in the reaction by using a Dean–Stark apparatus. The reaction mixture was then concentrated to leave a dark, solid residue, which was recrystallized from toluene to provide 2.53 g (25%) of **7a** as light tan crystals: mp 70–71.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, 6 Hz), 1.32 (m, 4 H), 1.44 (t, 3 H, 8 Hz), 1.93 (m, 2 H), 4.50 (m, 4 H), 8.15 (s, 1 H), 8.87 (s, 1 H), 12.26 (s, 1 H); MS *m/e* 277 (M^+). Anal. ($C_{14}H_{19}N_3O_3$) C, H, N.

Method B. 4-Hydroxy-6-methyl-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (7b). To 52 g of stirred polyphosphoric acid (PPA) was added 12.02 g (78.4 mmol) of **3a** and 15.86 g (78.4 mmol) of diethyl acetylmalonate. The resulting mixture was then stirred at 120 °C for 3 h, allowed to cool, and then diluted with water with vigorous stirring. The resulting mixture was extracted with four portions of ether, which were combined, dried ($MgSO_4$), filtered, and concentrated to leave 18.25 g (80%) of **7b** as an amber oil, which crystallized to an off-white solid and was used without further purification for the next step. An analytical sample was obtained by recrystallization of a small portion from hexane to give white crystals: mp 49–51 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, 8 Hz), 1.33 (m, 4 H), 1.45 (t, 3 H, 8 Hz), 1.93 (m, 2 H), 2.83 (s, 3 H), 4.43 (t, 2 H, 8 Hz), 4.49 (q, 2 H, 8 Hz), 8.08 (s, 1 H), 10.83 (s, 1 H, OH); MS *m/e* 291 (M^+). Anal. Calcd for $C_{15}H_{21}N_3O_3$: C, H, N.

Method C. 4-Chloro-6-methyl-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (8a). A solution of 1.05 g (3.60 mmol) of **7b** and 4.5 mL (49 mmol) of phosphorus oxychloride ($POCl_3$) was refluxed for 3.2 h and then concentrated to remove the $POCl_3$. The residue was diluted with water and the resulting mixture was extracted with ether. The combined extracts were dried ($MgSO_4$), filtered, and concentrated to leave 0.83 g (74%) of chloro compound **8a** as an amber oil, which was used without further purification: ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, 7 Hz), 1.32 (m, 4 H), 1.44 (t, 3 H, 7 Hz), 1.94 (m, 2 H), 2.68 (s, 3 H), 4.48 (m, 4 H), 8.06 (s, 1 H); MS (CI) *m/e* 310, 312 (M + 1).

Method D. 4-Amino-6-methyl-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (42). A solution of 14.02 g (45.3 mmol) of **8a** in 80 mL of ethanol saturated with ammonia gas was heated in a stainless steel pressure vessel at 125–130 °C for 10 h. The cooled reaction mixture was concentrated and the residue was triturated with ether and filtered. The filtrate was dried ($MgSO_4$), filtered, and concentrated to leave 12.85 g of crude amine **42** as a crystalline solid. This material was passed through a short silica gel column (ether) to provide 12.20 g of a white solid after evaporation of the ether eluant. Recrystallization of this solid from hexane gave 11.23 g (85%) of amino ester **42** as white crystals, mp 56–57 °C: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, 3 H, 7 Hz), 1.32 (m, 4 H), 1.42 (t, 3 H, 8 Hz), 1.92 (m, 2 H), 2.77 (s, 3 H), 4.39 (m, 4 H), 6.82 (br s, 2 H), 7.90 (s, 1 H); MS *m/e* 290 (M^+). Anal. ($C_{15}H_{22}N_4O_2$) C, H, N.

The hydrochloride salt of **42** was prepared by treating an ether solution of 2.34 g (8.06 mmol) of **42** with excess ethereal HCl. The resulting precipitate was collected and recrystallized from ethanol to give 1.40 g (53%) of the hydrochloride salt of **42** as white crystals: mp 200–203 °C; ^{1}H NMR (Me_2SO-d_6) δ 0.85 (t, 3 H, 8 Hz), 1.28 (m, 4 H), 1.35 (t, 3 H, 8 Hz), 1.81 (m, 2 H), 2.83 (s, 3 H), 4.40 (q, 2 H, 8 Hz), 4.62 (m, 2 H), 8.62 (s, 1 H); MS *m/e* 290 (M^+).

Method E. 4-Amino-6-methyl-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid (25). A solution of 13.50 g (46.5 mmol) of amino ester **42** and 7.36 g (184 mmol) of sodium hydroxide in 329 mL of 95% ethanol was warmed at 45–50 °C for 38 h and then concentrated. The residue was dissolved in 300 mL of water, filtered, and acidified with acetic acid whereupon a white precipitate formed. The solid was collected, washed with water, and air-dried to give 9.53 g of a white solid. Recrystallization of this material from ethyl acetate provided 8.80 g (72%) of **25** was white crystals: mp 176–176.5 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 0.82 (t, 3 H, 8 Hz), 1.26 (m, 4 H), 1.80 (m, 2 H), 2.62 (s, 3 H), 4.25 (t, 2 H, 8 Hz), 7.89 (br s, 2 H), 8.20 (s, 1 H), 12.80 (br s, 1 H); MS *m/e* 262 (M^+).

Method F. 4-Amino-6-methyl-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Allyl Ester (63). A mixture of 1.75 g (12.7 mmol) of anhydrous potassium carbonate, 2.21 g (8.42 mmol) of amino acid **25**, 0.02 g (0.1 mmol) of potassium iodide, and 1.02 g (8.43 mmol) of allyl bromide in 21.6 mL of dimethylformamide (DMF) was stirred at room temperature for 1.5 h and then poured into water. The resulting mixture was extracted with ether, and the combined extracts were washed several times with water, dried ($MgSO_4$), filtered, and concentrated

to leave 2.56 g of an amber oil, which crystallized. Recrystallization from hexane gave 2.27 g (89%) of **63** as a white crystalline solid: mp 64–66.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, 8 Hz), 1.33 (m, 4 H), 1.92 (m, 2 H), 2.80 (s, 3 H), 4.39 (t, 2 H, 8 Hz), 4.85 (m, 2 H), 5.31 (d, 1 H, 10.5 Hz), 5.42 (d, 1 H, 17.5 Hz), 6.00–6.18 (m, 1 H), 6.75 (br s, 2 H), 7.90 (s, 1 H); MS *m/e* 302 (M^+).

Method G. 4-Amino-6-methyl-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Cyclopropylmethyl Ester (68). A stirred solution of 3.22 g (12.3 mmol) of amino acid **25** in 23 mL (0.32 mol) of thionyl chloride was warmed at 45–50 °C for 1 h and then concentrated to leave the crude acid chloride as a yellow solid. This solid was suspended in 35 mL of dry toluene and 8.9 g (123 mmol) of cyclopropylcarbinol was added to the cooled (ice bath), stirred mixture, which was stirred overnight at room temperature. The reaction mixture was made basic with triethylamine and filtered, and the filtrate was washed successively with 5% aqueous acetic acid, water, and aqueous sodium bicarbonate. After drying ($MgSO_4$), the organic material was filtered and concentrated to leave 3.82 g of a light yellow oil, which crystallized. Recrystallization of this material from hexane gave 3.19 g (82%) of **68** as a white solid: mp 62.5–65.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.26–0.79 (m, 4 H), 0.87 (t, 3 H, 6 Hz), 1.30 (m, 4 H), 1.91 (m, 2 H), 2.81 (s, 3 H), 4.16 (d, 2 H, 7 Hz), 4.39 (t, 2 H, 7 Hz), 6.73 (br s, 2 H), 7.88 (s, 1 H); MS *m/e* 316 (M^+).

Method H. 4-Amino-1-pentyl-*N*-*n*-propyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (93). To a stirred suspension of 0.96 g (3.9 mmol) of **29** in 15 mL of chloroform was added 1.8 g (15 mmol) of thionyl chloride. The reaction mixture was stirred for 1 h at room temperature, cooled in an ice bath, and treated with 3.3 g (56 mmol) of *n*-propylamine with vigorous stirring. The mixture was allowed to warm to room temperature, washed with water until the washes were neutral, dried ($MgSO_4$), filtered, and concentrated. The residual solid was recrystallized from toluene to give 0.77 g (72%) of **93** as white crystals: mp 143–145 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, 8 Hz), 1.02 (t, 3 H, 8 Hz), 1.24 (m, 4 H), 1.67 (m, 2 H), 1.93 (m, 2 H), 3.43 (q, 2 H, 8 Hz), 4.42 (t, 2 H, 8 Hz), 6.06 (br s, 1 H), 6.86 (br s, 2 H), 7.96 (s, 1 H), 8.41 (s, 1 H); MS *m/e* 289 (M^+).

Method I. 4-Amino-1-pent-4-ynyl-*N*-2-propenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (116). To a stirred solution of 1.08 g (4.42 mmol) of **19a** in 20 mL of DMF was added 0.79 g (4.9 mmol) of 1,1′-carbonyldiimidazole. After stirring of the reaction mixture for 3 h, 0.76 g (13 mmol) of allylamine was added and the stirring continued for 1 h. The reaction mixture was poured into water and extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to give 0.90 g of a light yellow oil, which crystallized. Recrystallization from toluene provided 0.64 g (51%) of **116** as white crystals: mp 117.5–119 °C; ^{1}H NMR ($CDCl_3$) δ 1.98 (t, 1 H, 2.5 Hz), 2.2 (m, 4 H), 4.07 (m, 2 H), 4.54 (t, 2 H, 8 Hz), 5.22 (d, 1 H, 11 Hz), 5.29 (d, 1 H, 18 Hz), 5.87–6.04 (m, 1 H), 6.14 (br s, 1 H), 7.00 (br s, 2 H), 7.97 (s, 1 H), 8.44 (s, 1 H); MS *m/e* 283 (M^+).

Method J. 4-Ethoxy-1-ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (13a). To a stirred solution of 2.80 g (10.5 mmol) of **12a** was added a solution of sodium ethoxide [prepared by reacting 0.27 g (11.5 mg-atom) of sodium with 15 mL of absolute ethanol] in ethanol. After refluxing for 2 h, the reaction was cooled and concentrated to leave an orange oil. The oil was dissolved in ether and the ether solution was washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to leave 2.01 g of an orange solid. Recrystallization from hexane gave 1.40 g (48%) of **13a** as off-white crystals: mp 56–58 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, 7 Hz), 1.50 (t, 3 H, 7 Hz), 1.51 (t, 3 H, 7 Hz), 2.58 (s, 3 H), 4.41 (q, 2 H, 7 Hz), 4.51 (q, 2 H, 7 Hz), 4.64 (q, 2 H, 7 Hz), 8.04 (s, 1 H); MS (CI) *m/e* 278 (M + 1). Anal. ($C_{14}H_{19}N_3O_3$) C, H, N.

Method K. 4-Ethoxy-6-methyl-1-vinyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (14a). A stirred mixture of 1.93 g (6.96 mmol) of **13a** and 2.73 g (15.3 mmol) of *N*-bromosuccinimide (NBS) in 70 mL of carbon tetrachloride was refluxed for 3 h and then cooled in an ice bath. The mixture was filtered and the filtrate was concentrated to leave crude vinyl compound **14a** as a pale yellow gum: ^{1}H NMR (CCl_4) δ 1.30 (t, 3 H, 8 Hz), 1.47 (t, 3 H, 8 Hz), 2.52 (s, 3 H), 4.09 (dd, 1 H, J_{BC} = 11 Hz, J_{AC} = 4.5 Hz), 4.28 (q, 2 H, 8 Hz), 4.60 (q, 2 H, 8 Hz), 4.78 (t, 1 H, $J_{AB} = J_{BC}$ = 11 Hz), 7.05 (dd, 1 H, J_{AB} = 11 Hz, J_{AC} = 4.5 Hz), 8.12 (s, 1 H).

Method K′. 4-Ethoxy-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (15a). The above crude vinyl compound **14a** was dissolved in 25 mL of tetrahydrofuran containing 5 mL of saturated aqueous sodium carbonate and 7 mL of water and was stirred vigorously at room temperature for 18 h. This reaction mixture was diluted with water and the resulting mixture was extracted with ethyl acetate. The combined extracts were dried ($MgSO_4$), filtered, and concentrated to leave a white solid, which was recrystallized from ethyl acetate/hexane to give 1.08 g (62%) of **15a** as white crystals: mp 183–183.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.40 (t, 3 H, 7 Hz), 1.53 (t, 3 H, 7 Hz), 2.70 (s, 3 H), 4.42 (q, 2 H, 7 Hz), 4.68 (q, 2 H, 7 Hz), 8.07 (s, 1 H), 13.56 (br s, 1 H); MS *m/e* 249 (M^+). Anal. ($C_{12}H_{15}N_3O_3$) C, H, N.

Method M. 4-Ethoxy-1-pent-3-ynyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (17a). A mixture of 8.13 g (34.6 mmol) of **15b**, 14.3 g (103 mmol) of pulverized anhydrous potassium carbonate, and 10.7 g (72.8 mmol) of 1-bromo-3-pentyne in 58 mL of DMF was stirred at 55–60 °C for 4.5 h. Additional quantities of 1-bromo-3-pentyne (5.3 g, 34 mmol) and potassium carbonate (14.3 g, 103 mmol) were added to the reaction mixture after the first hour. The reaction mixture was cooled and filtered and the filtrate was concentrated at 45–50 °C. The residue was diluted with water and extracted with ether and ethyl acetate. The combined extracts were washed with water, dried ($MgSO_4$), filtered, and concentrated to leave a tan solid. Flash chromatography of this material (silica gel, ethyl acetate/hexane, 1/1) provided 7.67 g (74%) of **17a** as an off-white solid. An analytical sample was prepared by recrystallization from toluene to give white crystals: mp 93–95 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, 3 H, 8 Hz), 1.63 (t, 3 H, 8 Hz), 1.71 (t, 3 H, 3 Hz), 2.77 (m, 2 H), 4.39 (q, 2 H, 8 Hz), 4.62 (t, 2 H, 8 Hz), 4.75 (q, 2 H, 8 Hz), 8.18 (s, 1 H), 8.91 (s, 1 H); MS *m/e* 301 (M^+). Anal. ($C_{16}H_{19}N_3O_3$) C, H, N.

Method N. 4-Amino-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (21). A mixture of 4.0 g (16 mmol) of **15a** and 20 mL of liquid ammonia was heated at 120 °C in a stainless steel pressure vessel for 18 h. The vessel was cooled and the ammonia was allowed to evaporate. The solid residue was removed and was washed thoroughly with methanol and then hexane to provide 3.12 g (88%) of crude amino ester **21** as white crystals, mp 295 °C dec. An analytical sample of **21** was obtained by recrystallization of a portion of the crude material from DMF to give white crystals: mp 296 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 1.33 (t, 3 H, 7 Hz), 2.59 (s, 3 H), 4.30 (q, 2 H, 7 Hz), 7.69 (br s, 2 H), 8.21 (s, 1 H), 13.15 (s, 1 H); MS *m/e* 220 (M^+). Anal. ($C_{10}H_{12}N_4O_2$) C, H. N.

Method O. 4-Amino-6-methyl-1-pent-4-ynyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (50). To a stirred mixture of 6.21 g (28.2 mmol) of **21** and 11.7 g (85.1 mmol) of potassium carbonate in 50 mL of DMF was added 6.04 g (31.1 mmol) of 1-iodopent-1-yne. The resulting mixture was stirred at 50 °C for 24 h and, after cooling, was poured into ethyl acetate/water. The organic phase was separated and the aqueous layer was extracted with ethyl acetate. The organic material was combined, washed with water and then brine, dried ($MgSO_4$), filtered, and concentrated to leave a brown semisolid. This material was flash chromatographed (silica gel, hexanes/ethyl acetate, 2/1 → 1/1) to provide 4.86 g (60.2%) of **50** as a white, crystalline solid. A 0.99-g portion was recrystallized from toluene/hexanes to give 0.95 g of analytically pure **50**: mp 113.5–114.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (t, 3 H, 8 Hz), 1.99 (t, 1 H, 3 Hz), 2.19 (m, 4 H), 2.78 (s, 3 H), 4.39 (q, 2 H, 8 Hz), 4.50 (t, 2 H, 8 Hz), 6.68 (br s, 2 H), 7.89 (s, 1 H); MS *m/e* 286 (M^+).

1-Ethyl-6-methyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (24). A mixture of 1.50 g (5.61 mmol) of **23**, 1.2 mL (0.85 g, 8.4 mmol) of triethylamine, and 0.45 g of 10% Pd/C in 20 mL of ethanol was hydrogenated at atmospheric pressure at room temperature. Hydrogen uptake ceased after the theoretical quantity of hydrogen was absorbed, and the mixture was filtered and concentrated. The solid residue was taken up in ether, washed with water, dried ($MgSO_4$), filtered, and concentrated to leave a white solid. Recrystallization from hexane provided 1.11 g (85%) of **24** as a white solid: mp 55.5–57.5 °C;

^{1}H NMR ($CDCl_3$) δ 1.42 (t, 3 H, 7 Hz), 1.63 (t, 3 H, 7 Hz), 2.94 (s, 3 H), 4.40 (q, 2 H, 7 Hz), 4.57 (q, 2 H, 7 Hz), 8.02 (s, 1 H), 8.65 (s, 1 H); MS *m/e* 233 (M^+).

4-Amino-6-methyl-1-*n*-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine (26). A 1.21 g (4.61 mmol) portion of **25** was heated at 180–185 °C under nitrogen until gas evolution stopped. The residue was recrystallized from toluene to provide 0.81 g (80%) of **26** as an off-white, crystalline solid: mp 183–185.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, 7 Hz), 1.35 (m, 4 H), 1.95 (m, 2 H), 2.52 (s, 3 H), 4.41 (t, 2 H, 7 Hz), 4.76 (br s, 2 H), 6.15 (s, 1 H), 7.87 (s, 1 H); MS *m/e* 218 (M^+).

1-Pent-3-ynyl-*N*-2-propenyl-4-propionamido-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (28). To a stirred suspension of 0.55 g (23 mmol) of sodium hydride in 90 mL of DMF was added 2.94 g (10.4 mmol) of **27**. After 45 min at room temperature, this solution was added to a stirred solution of 13.5 g (104 mmol) of propionic anhydride in 60 mL of DMF. After stirring of the resulting mixture for 5 min, it was quenched by adding carefully 5 mL of water. The resulting solution was partially concentrated (about $^1/_3$ of the DMF removed) and then poured into water and extracted with ether. The combined ether extracts were filtered to remove a small quantity of a precipitate which formed, dried ($MgSO_4$), filtered, and concentrated to leave 3.27 g of a tacky yellow solid. This material was flash chromatographed (silica gel, EtOAc/hexane, 4/5) to provide 0.58 g of the crude product. Recrystallization from toluene provided 0.23 g (6.5%) of **28** as a white solid: mp 157.5–158.5 °C; ^{1}H NMR ($CDCl_3$) δ 1.31 (t, 3 H, 7 Hz), 1.71 (t, 3 H, 2.5 Hz), 2.58 (q, 2 H, 7 Hz), 2.75 (m, 2 H), 4.10 (m, 2 H), 4.59 (t, 2 H, 7 Hz), 5.28 (m, 2 H), 5.95 (m, 1 H), 6.45 (t, 1 H, 4 Hz), 8.55 (s, 1 H), 8.59 (s, 1 H); MS (CI) *m/e* 340 (M + 1).

Ethyl 4-Amino-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-hydroxamate (30). To a stirred solution of 1.1 g (4.4 mmol) of **29** and 0.56 g (5.5 mmol) of triethylamine in 35 mL of methanol was added a solution of 1.43 g (4.6 mmol) of 1-(*N*,*N*-diphenylcarbamoyl)pyridinium chloride[25] in 5.6 mL of methanol. After stirring for 20 min, the reaction mixture was cooled in an ice bath and added to a cold, stirred solution of 14.6 mmol of ethoxyamine [prepared by adding 3.32 mL (14.6 mmol) of a 25% methanolic sodium methoxide solution to a solution of 1.42 g (14.6 mmol) of ethoxyamine hydrochloride in 10 mL of methanol]. The resulting mixture was stirred at room temperature for 1.5 h and then concentrated. The residue was diluted with water and the resulting mixture was extracted with ether. The combined extracts were dried ($MgSO_4$), filtered, and concentrated to leave 1.98 g of an amber oil. This material was flash chromatographed (silica gel, ether) to separate the desired product. The fractions containing the desired product were concentrated to leave a white foam, which was induced to crystallize by dissolving in hot toluene containing a small amount of chloroform and then cooling. The resulting crystalline precipitate was collected and air-dried to give 0.69 g (54%) of **30** as white crystals: mp 142.5–144 °C; ^{1}H NMR ($CDCl_3$) δ 0.86 (t, 3 H, 8 Hz), 1.28 (m, 4 H), 1.35 (t, 3 H, 8 Hz), 1.89 (m, 2 H), 4.08 (q, 2 H, 8 Hz), 4.40 (t, 2 H, 8 Hz), 6.89 (br s, 2 H), 7.95 (s, 1 H), 8.40 (s, 1 H), 8.86 (s, 1 H); MS (CI) *m/e* 292 (M + 1).

4-Amino-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (32). This material was isolated as described below as a byproduct in the preparation of the corresponding carboxylic acid **29**. A mixture of 24.88 g (84.1 mmol) of **31** and 60 mL of liquid ammonia was heated in a stainless steel pressure vessel at 90–100 °C for 12 h. After cooling to room temperature, the ammonia was allowed to evaporate and the solid, white residue was triturated with water and filtered. The collected solid (24 g), a mixture of the ethyl ester and primary amide, was dissolved in a mixture of ethanol (210 mL), sodium hydroxide (13.5 g, 337 mmol), and water (24 mL) and the resulting mixture was heated at 45–50 °C for 10 h. The reaction mixture was concentrated and the residue was dissolved in water and extracted with ethyl acetate and then ether. The combined extracts were dried ($MgSO_4$), filtered, and concentrated to leave a residue, which was flash chromatographed (silica gel, methanol/chloroform, 7/93) to obtain carboxamide **32**. Recrystallization from ethanol provided 1.23 g (5.9%) of **32** as white crystals: mp 201–202 °C: ^{1}H NMR (Me_2SO-d_6) δ 0.81 (t, 3 H, 8 Hz), 1.22 (m, 4 H), 1.81 (m, 2 H), 4.29 (t, 2 H, 8 Hz), 7.12 (br s, 1 H), 7.84 (br s, 1 H), 8.22 (s, 1 H), 8.26 (br s, 2 H), 8.56 (s, 1 H); MS *m/e* 247 (M^+).

4-Hydroxy-1-pentyl-*N*-2-propenyl-1*H*-pyrazolo[3,4-*b*]-pyridine-5-carboxamide (34). a. 4-Hydroxy-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid (33). A solution of 7.10 g (24.0 mmol) of **31** in 50 mL of acetic acid containing 25 mL of concentrated hydrochloric acid was refluxed for 6 h, cooled, and diluted with water whereupon a precipitate formed. This solid was collected, washed with water, and dried over phosphorus pentoxide under vacuum to give 5.08 g (84.9%) of **33** as a white solid. An analytical sample was obtained by recrystallization of a small portion from ethanol to give **33** as white crystals: mp 205 °C dec; ^{1}H NMR (Me_2SO-d_6) δ 0.83 (t, 3 H, 7 Hz), 1.24 (m, 4 H), 1.82 (m, 2 H), 4.35 (t, 2 H, 7 Hz), 8.21 (s, 1 H), 8.65 (s, 1 H); MS *m/e* 249 (M^+). Anal. ($C_{12}H_{15}N_3O_3$) C, H, N.

b. 4-Hydroxy-1-pentyl-*N*-2-propenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide (34). To a stirred solution of 1.00 g (4.01 mmol) of **33** in 20 mL of DMF was added 0.78 g (4.81 mmol) of 1,1′-carbonyldiimidazole. After this solution was stirred at room temperature for 5 h, 0.76 g (13.3 mmol) of allylamine was added and the resulting solution was stirred overnight at room temperature. The reaction mixture was poured into water and the resulting solution was acidified to pH 3 with 10% hydrochloric acid. A precipitate formed and the mixture was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to leave a white solid. Flash chromatography (silica gel, 4% methanol in chloroform) of this material provided the product as a white solid, which was recrystallized from ethyl acetate/hexane to give 0.83 g (72%) of **34** as white crystals (tautomeric mixture of 4-hydroxy and 4-keto compounds): mp 197–198 °C; ^{1}H NMR ($CDCl_3$) δ 0.81 (m, 3 H), 1.27 (m, 4 H), 1.88 (m, 2 H), 4.08 (m, 2 H), 4.27, 4.45 [2 t, 2 H (ratio ca. 1.7:1, respectively), 8 Hz, NCH_2CH_2], 5.22 (m, 2 H), 5.92 (m, 1 H), 6.53, 11.79 (2 br s, 1 H, OH, pyridinone NH), 8.06, 8.16 (2 s, 6-H), 8.53 (s, 1 H), 10.59 (br s with shoulder, 1 H, amide NH); MS *m/e* 288 (M^+).

4-Amino-7-oxo-1-pentyl-*N*-2-propenyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxamide Hydrochloride (39). a. 4-Chloro-7-oxo-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (35). To a cold (ice bath), stirred solution of 16.8 mL (25.0 g, 119 mmol) of trifluoroacetic anhydride in 66 mL of methylene chloride was added 2.7 mL (3.4 g, 100 mmol) of 90% hydrogen peroxide over a 2-min period. The mixture was stirred for 15 min and then allowed to warm to room temperature. To this solution was added 19.5 g (66.1 mmol) of **31** in 66 mL of methylene chloride over 10 min while the reaction mixture temperature was maintained at 30–35 °C by using an ice bath. After 2 h at room temperature, the mixture was poured into 800 mL of water with stirring. The resulting mixture was treated portionwise with a solution of 12.8 g (102 mmol) of sodium sulfite in 120 mL of water. Solid sodium bicarbonate was then added in portions until the mixture was slightly basic. The mixture was extracted 3 times with methylene chloride, and the combined extracts were dried ($MgSO_4$), filtered, and concentrated to give 19.96 g of a mixture of starting material **31** and desired product **35**. Flash chromatography (silica gel, ether/hexane, 1/1) of this material provided 4.25 g of starting material **31** and 13.57 g of *N*-oxide **35** as a solid. Recrystallization of the latter from hexane provided 12.04 g (74.9%, based on recovered starting material) of **35** as white crystals: mp 50–52.5 °C; ^{1}H NMR ($CDCl_3$) δ 0.91 (t, 3 H, 8 Hz), 1.36 (m, 4 H), 1.41 (t, 3 H, 8 Hz), 1.97 (m, 3 H), 4.46 (q, 2 H, 8 Hz), 5.02 (t, 2 H, 8 Hz), 8.24 (s, 1 H), 8.77 (s, 1 H); MS *m/e* 311 (M^+). Anal. ($C_{14}H_{18}ClN_3O_3$) C, H, N.

b. 4-Ethoxy-7-oxo-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid Ethyl Ester (36). A solution of 8.05 g (25.8 mmol) of **35** in 40 mL of anhydrous ethanol was stirred for 20 min with 27.6 mmol of freshly prepared sodium ethoxide in 13.8 mL of ethanol at 8–12 °C. The mixture was allowed to warm to room temperature over 3 h and then concentrated to leave a yellow solid. This material was partitioned with ethyl acetate/water and the organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to give a light yellow solid. Flash chromatography (silica gel, ethyl acetate) gave 5.17 g (62.4%) of **36** as a white solid. A portion was recrystallized from toluene/hexane to give analytically pure **36** as white crystals, mp 103.5–106 °C; ^{1}H NMR ($CDCl_3$) δ 0.88 (t, 3 H, 8 Hz), 1.32 (m, 4 H), 1.38 (t, 3 H, 8 Hz), 1.58 (t, 3 H, 8 Hz), 1.96 (m, 2 H), 4.37 (q, 2 H, 8 Hz), 4.66 (q, 2

H, 8 Hz), 5.08 (t, 2 H, 8 Hz), 8.22 (s, 1 H), 8.68 (s, 1 H); MS *m/e* 321 (M^+). Anal. ($C_{16}H_{23}N_3O_4$) C, H, N.

c. 4-Ethoxy-7-oxo-1-pentyl-1*H*-pyrazolo[3,4-*b*]pyridine-5-carboxylic Acid (37). A solution of 5.00 g (15.6 mmol) of **36** in 40 mL of ethanol containing 0.75 g (18.8 mmol) of sodium hydroxide and 4 mL of water was stirred at room temperature for 45 min. The reaction mixture was concentrated and the residue was dissolved in 250 mL of water. The resulting solution was acidified with acetic acid and the resulting precipitate was collected, washed with water, and partially air-dried. Recrystallization from ethanol gave 3.25 g (71.0%) of **37** as white crystals: mp 173 °C dec; ^1H NMR (Me_2SO-d_6) δ 0.84 (t, 3 H, 6 Hz), 1.24 (m, 4 H), 1.42 (t, 3 H, 7 Hz), 1.85 (m, 2 H), 3.32 (br s, 1 H), 4.65 (q, 2 H, 7 Hz), 4.97 (t, 2 H, 7 Hz), 8.39 (s, 1 H), 8.62 (s, 1 H); MS (CI) *m/e* 294 (M + 1). Anal. ($C_{14}H_{19}N_3O_4$) C, H. N.

d. 4-Ethoxy-7-oxo-1-pentyl-*N*-2-propenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxamide (38). To a stirred suspension of **37** (1.10 g, 3.75 mmol) in 22 mL of DMF was added 0.67 g (4.13 mmol) of 1,1′-carbonyldiimidazole. After stirring of the reaction mixture at room temperature for 1 h, 0.64 g (11.3 mmol) of allylamine was added, and the resulting mixture was stirred for 15 min. The reaction mixture was poured into water and the resulting mixture was extracted with ethyl acetate. The combined extracts were washed with water and brine, dried ($MgSO_4$), filtered, and concentrated to leave 1.01 g (81%) of slightly impure **38** as a pale yellow crystalline solid, mp 112–143 °C. This crude material was used for the next step and consisted of less than 10% of an impurity along with greater than 90% of the desired **38**: ^1H NMR ($CDCl_3$) δ 0.88 (t, 3 H, 7 Hz), 1.35 (m, 4 H), 1.63 (t, 3 H, 7 Hz), 1.97 (m, 2 H), 4.10 (m, 2 H), 4.77 (q, 2 H, 7 Hz), 5.08 (t, 2 H, 7 Hz), 5.23 (m, 2 H), 5.97 (m, 1 H), 7.73 (t, 1 H, 4 Hz), 8.21 (s, 1 H), 8.96 (s, 1 H); MS *m/e* 332 (M^+).

e. 4-Amino-7-oxo-1-pentyl-*N*-2-propenyl-1*H*-pyrazolo-[3,4-*b*]pyridine-5-carboxamide Hydrochloride (39). A mixture of 0.98 g (2.9 mmol) of the above crude **38** in 60 mL of ethanol saturated with ammonia was heated at 60–70 °C in a stainless steel pressure vessel for 12 h. The vessel was cooled to room temperature, and the contents were concentrated to leave a tan solid. This material was flash chromatographed (silica gel, 2.5% methanol in chloroform) to provide 0.61 g of **39**. This material was dissolved in 15 mL of ethanol and acidified with ethereal hydrogen chloride. The resulting precipitate was collected, washed with ethanol/ether, and air-dried to give 0.58 g (58%) of the hydrochloride salt of **39** as white plates: mp 232–237 °C dec; ^1H NMR (Me_2SO-d_6) δ 0.85 (t, 3 H, 7 Hz), 1.27 (m, 4 H), 1.87 (m, 2 H), 3.50 (br s, 2 H), 3.91 (m, 2 H), 4.62 (t, 2 H, 7 Hz), 5.20 (m, 2 H), 5.89 (m, 1 H), 8.67 (s, 1 H), 9.00 (s, m, 2 H), 9.56 (s, 1 H); MS (CI) *m/e* 304 (M + 1).

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Registry No. **1**, 41094-88-6; **2**, 96740-58-8; **3a**, 3524-20-7; **4**, 87-13-8; **5a**, 89158-72-5; **6**, 570-08-1; **7a**, 89158-73-6; **7b**, 89158-21-4; **8a**, 89159-08-0; **12a**, 41095-07-2; **13a**, 89865-78-1; **14a**, 122358-78-5; **15a**, 89865-79-2; **15b**, 41094-93-3; **17a**, 103586-33-0; **19a**, 103586-39-6; **21**, 89865-92-9; **23**, 41095-07-2; **24**, 122358-79-6; **25**, 89865-44-1; **25** (acid chloride), 122359-16-4; **26**, 122358-80-9; **27**, 103586-12-5; **28**, 103586-31-8; **29**, 89865-57-6; **30**, 103586-30-7; **31**, 89158-74-7; **32**, 103585-83-7; **33**, 122358-81-0; **34**, 122358-82-1; **35**, 89158-75-8; **36**, 89158-76-9; **37**, 103586-44-3; **38**, 103586-45-4; **39**, 103586-29-4; **39**·HCl, 103586-28-3; **40**, 122358-83-2; **41**, 122358-84-3; **42**, 89865-43-0; **42**·HCl, 122359-15-3; **43**, 122359-17-5; **43**·HCl, 122358-85-4; **44**, 122359-18-6; **44**·HCl, 122358-86-5; **45**, 122359-19-7; **45**·HCl, 122358-87-6; **46**, 89865-73-6; **46**·HCl, 89865-74-7; **47**, 122359-20-0; **47**·HCl, 122358-88-7; **48**, 122359-21-1; **48**·HCl, 122358-89-8; **49**, 122359-22-2; **49**·HCl, 122358-90-1; **50**, 89866-32-0; **51**, 89866-12-6; **52**, 89866-21-7; **53**, 122358-91-2; **54**, 122358-92-3; **55**, 122358-93-4; **56**, 122358-94-5; **57**, 122358-95-6; **58**, 89158-21-4; **59**, 122359-23-3; **59**·HCl, 122358-96-7; **60**, 122359-24-4; **60**·HCl, 122358-97-8; **61**, 122359-25-5; **61**·HCl, 122358-98-9; **62**, 122359-26-6; **62**·HCl, 122358-99-0; **63**, 89865-45-2; **64**, 89865-48-5; **65**, 89865-49-6; **66**, 89865-50-9; **67**, 89865-66-7; **68**, 89865-53-2; **69**, 122359-00-6; **70**, 122359-01-7; **71**, 89865-68-9; **72**, 89866-56-8; **73**, 89866-48-8; **74**, 89866-33-1; **75**, 89866-38-6; **76**, 89866-35-3; **77**, 89866-13-7; **78**, 89866-41-1; **79**, 89865-96-3; **80**, 89865-98-5; **81**, 122359-02-8; **82**, 122359-03-9; **83**, 122359-04-0; **84**, 122359-27-7; **84**·HCl, 122359-05-1; **85**, 122359-28-8; **85**·HCl, 122359-06-2; **86**, 89865-58-7; **87**, 89865-65-6; **88**, 89865-56-5; **89**, 122359-07-3; **90**, 122359-08-4; **91**, 103586-01-2; **91**·HCl, 103586-00-1; **92**, 103586-05-6; **92**·HCl, 103586-04-5; **93**, 103604-65-5; **94**, 122359-09-5; **95**, 122359-10-8; **96**, 103585-84-8; **97**, 103585-87-1; **98**, 103585-85-9; **99**, 103585-86-0; **100**, 103586-20-5; **101**, 122359-11-9; **102**, 103585-88-2; **103**, 103585-95-1; **103**·HCl, 103585-96-2; **104**, 103585-97-3; **104**·HCl, 103585-98-4; **105**, 103585-90-6; **105**·HCl, 103585-89-3; **106**, 103586-03-4; **106**·HCl, 103586-02-3; **107**, 103585-93-9; **107**·HCl, 103585-94-0; **108**, 103586-07-8; **108**·HCl, 103586-06-7; **109**, 103586-09-0; **109**·HCl, 103586-08-9; **110**, 103586-11-4; **110**·HCl, 103586-10-3; **111**, 122359-29-9; **111**·HCl, 122359-12-0; **112**, 122359-30-2; **112**·HCl, 122359-13-1; **113**, 103604-66-6; **114**, 103586-14-7; **115**, 103586-22-7; **116**, 103586-24-9; **117**, 122359-14-2; **118**, 103586-16-9; **118**·HCl, 103586-17-0; **119**, 103586-18-1; **119**·HCl, 103586-19-2; **120**, 103586-23-8; $NC(CH_2)_2NHN{=}CH(CH_2)_3CH_3$, 89158-20-3; 1-bromo-3-pentyne, 18719-27-2; 1-iodopent-4-yne, 2468-55-5; diazepam, 439-14-5; chlordiazepoxide, 58-25-3; (2-cyanoethyl)hydrazine, 353-07-1; valeraldehyde, 110-62-3; cyclopropylcarbinol, 2516-33-8.

Synthesis and Pharmacological Evaluation of a Series of 4-Piperazinylpyrazolo[3,4-*b*]- and -[4,3-*b*][1,5]benzodiazepines as Potential Anxiolytics[1]

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The synthesis and pharmacological evaluation of a series of pyrazolo[*b*][1,5]benzodiazepines are described. Some of the 4-piperazinyl-2,10-dihydropyrazolo[3,4-*b*][1,5]benzodiazepine derivatives demonstrated potent anxiolytic activity in the three-part operant anticonflict test in rats. Compounds **21** and **30** were more active than the clinically effective anxiolytic chlordiazepoxide in releasing conflict-suppressed behavior. This study shows a dissociation of the anxiolytic and antidopaminergic activities found in the thieno- and dibenzodiazepine derivatives flumezapine and clozapine, respectively. Examples of the three other dihydropyrazolo[*b*][1,5]benzodiazepine ring systems are described and evaluated for comparison and were found to be less active.

In previous publications[2-4] the neuroleptic activity of a series of thienobenzodiazepines was reported. We demonstrated that the antidopaminergic and anticholinergic activity observed in the atypical neuroleptic clozapine (**1**)

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