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; ^{1}H 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**: ^{1}H 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; ^{1}H 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).

Acknowledgment. We are indebted to Karin M. Kirkland for several pharmacokinetic studies of key compounds and to James M. Hulsizer and his staff for the preparation of large quantities of several intermediates. We thank Drs. E. J. Warawa and B. Hesp for their support and encouragement.

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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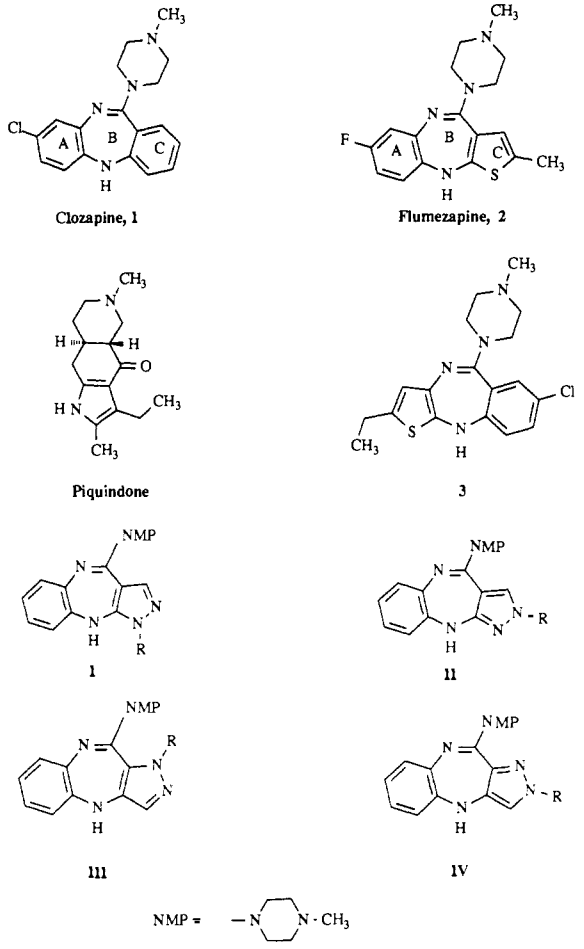
The synthesis and pharmacological evaluation of a series of pyrazolo[*b*][1,5]benzodiazepines are described. Some of the 4-piperazinyl-2,10-dihydropyrazolo[3,4-*b*][1,5]benzodiazepine derivatives demonstrated potent anxiolytic activity in the three-part operant anticonflict test in rats. Compounds **21** 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**)

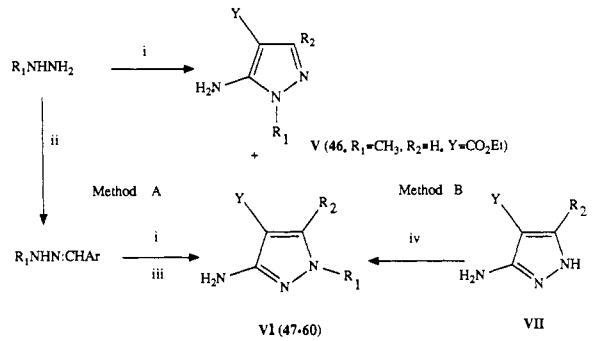
0022-2623/89/1832-2573$01.50/0

Chart I



can be enhanced by replacing the relatively electron-rich ring C with an isosteric thiophene ring. Since these properties of clozapine are believed to be responsible for its superior clinical profile of antipsychotic activity with minimal extrapyramidal side effects,[5] one of these compounds, flumezapine (2), was chosen as a candidate for clinical trial.[2b] By transposition of the fused phenyl and thiophene rings, as in the isomeric thieno[1,4]benzodiazepines, such as 3, activity was greatly reduced. The observation that the neuroleptic activity is also dependent on the position of ring fusion and minor changes to the alkyl substitution of the thiophene ring suggests that the electronic distribution within the thiophene ring in 2 and its spatial relationship to the lone pair of electrons of the

Scheme I[a]



[a] Reagents: (i) $EtOCR_2{=}CHYCN$; (ii) ArCHO; (iii) HCl, aqueous EtOH; (iv) R_1X, K_2CO_3, Adogen 464, PhMe. Ar = Ph or 4-MeOPh, Y = CO_2Et or CN.

distal nitrogen of the piperazine side chain may play a key role in recognition by the receptor(s).[4] Further changes in the electronic characteristics of ring C in 1 can also be effected by substitution with other heterocyclic rings. In our preceding publication,[6] we described the effect of this substitution by imidazole, pyridine, and 1,2,3-triazole rings. Antidopaminergic activity similar to that of flumezapine was maintained in the [1,2,3]triazolo[4,5-*b*][1,5]benzodiazepines but was absent in the imidazo and pyrido analogues.

This paper describes the synthesis and pharmacological evaluation of a series of pyrazolo[1,5]benzodiazepines. The two isomeric pyrazolo[3,4-*b*]- and pyrazolo[4,3-*b*][1,5]-benzodiazepine ring systems can each be subdivided into two isomeric systems, depending on which of the pyrazole nitrogen atoms is substituted. We describe the preparation of examples of these four isomeric series, structures I–IV[29] (Chart I).

The neuroleptic potential of these compounds was examined initially in terms of their ability to produce hypothermia and catalepsy in mice. As clozapine has been shown, in animals, to block a conditioned-avoidance response at doses lower than those required to produce catalepsy[8] and this profile of activity has been correlated with its relative lack of extrapyramidal side effects in the clinic,[5] our compounds were assessed for their activity in these tests. Many drugs which act in the central nervous system produce muscular incoordination, and therefore the compounds were tested for their ability to alter the length of time a rat could remain on a rotating rod. [^{3}H]Spiperone and [^{3}H]quinuclidinyl benzilate (QNB) in vitro receptor binding techniques have been used to study the respective affinities for the dopaminergic (D_2) and muscarinic cholinergic receptors.

It has previously been shown that clozapine[9] (1) and flumezapine[10] (2) are active in an anticonflict behavioral test of anxiolytic activity. For this reason, three of the compounds (8, 21, and 30) were assessed for their ability

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to release conflict-supressed behavior in order to determine their potential anxiolytic activities.

Chemistry

For isomers I and II, we initially prepared the precursor aminopyrazole-4-carboxylates and -carbonitriles by the method of Schmidt et al.[11] Reaction of (ethoxyalkylidene)cyanoacetates and malononitriles with alkylhydrazines gives predominately 5-amino isomer V, which was separated from the small amount of 3-amino isomer VI by recrystallization. To obtain isomer VI exclusively, the alkylhydrazine was protected by hydrazone formation with benzaldehyde,[11] or preferably 4-methoxybenzaldehyde (Scheme I). The range of alkyl substitution is thus limited by the availability of alkylhydrazines. Where the substituted hydrazines were not commercially available, they were prepared by the method of Gever and Hayes.[12] Novel 3-aminopyrazole-4-carboxylates (VI, Y = CO_2Et), prepared by this method (A), are shown in Table IV.

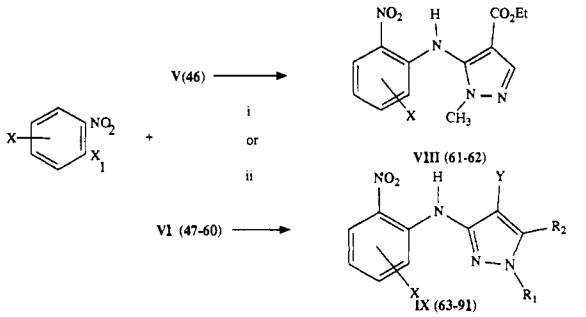
Solid–liquid phase-transfer-catalyzed alkylation of the ring N of the N-unsubstituted 3(5)-aminopyrazole-4-carbonitrile and -carboxylates (VII) was subsequently found to give predominately the required 3-amino isomer VI for alkyl groups larger than methyl.[13] Most of the aminopyrazole precursors (VI), shown in Table IV, were prepared by this method (B).

Intermediate nitroanilinopyrazolecarboxylates VIII and IX were initially prepared by reaction of the appropriate V or VI with an optionally substituted 1-fluoro-2-nitrobenzene using *n*-BuLi as a base in THF at −15 to −10 °C (method C). A persistent deep blue coloration indicated the formation of the anion of the product. With the aminopyrazolecarboxylates, yields of greater than 50% were obtained using 1.5 equiv of *n*-BuLi. It may be noted that with the aminothiophenecarboxylates a maximum yield of 50% was achieved.[14] This was explained by an equilibration of the anions of the starting amino ester and the product. The ability to obtain a greater than 50% yield is presumably due to differences in the electronegativity of the thiophene and pyrazole rings. Condensation of *o*-fluoronitrobenzenes with aminopyrazolecarboxylates was also accomplished by using solid–liquid phase-transfer catalysis, as exemplified by the preparation of compound (**61**) (method D).

However, sodium hydride proved to be the most efficient base (method E), not only giving consistently higher yields than those obtained with *n*-BuLi but also giving similar yields of IX with *o*-chloro- and *o*-bromonitrobenzenes as compared to that of the usually more reactive *o*-fluoro analogues. This simplified the variation of the phenyl substitution in this series compared to the analogous thienobenzodiazepines,[2a] which had been synthesized before the advantageous use of sodium hydride for this condensation was found.

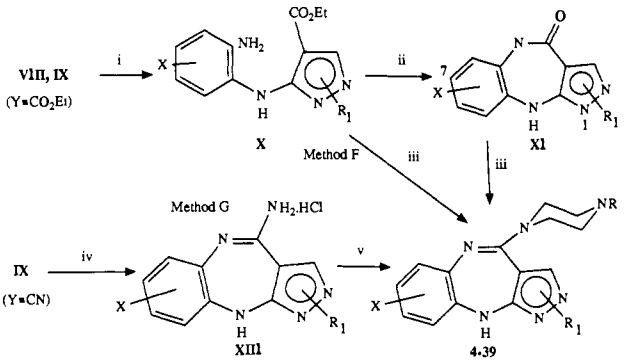
Using *n*-BuLi as the base with 1,2,4-trifluoro-5-nitrobenzene gave *p*- as well as *o*-fluorine displacement. Sodium hydride was once again found to be a superior base giving **74** exclusively, free of any *para* displacement product. Similarly, in contrast to the use of *n*-BuLi,[14] sodium hydride also resulted in selective *o*- displacement with 2-amino-5-methylthiophene-3-carbonitrile.[15] The structure

Scheme II[a]



[a] (i) X_1 = F; *n*-BuLi, THF (Method C) or K_2CO_3, Adogen 464, $PhCH_3$ (Method D). (ii) X_1 = F, Cl, Br; NaH, THF (Method E). Y = CO_2Et or CN.

Scheme III[a]



[a] Reagents: (i) Pd/C, H_2; (ii) $NaCH_2SOCH_3$; (iii) *N*-methylpiperazine, $TiCl_4$, PhOMe; (iv) $SnCl_2$, aqueous EtOH, HCl; (v) *N*-methylpiperazine, DMSO, $PhCH_3$.

of **74** was confirmed by ^{13}C NMR. For either isomer, two carbon signals would exhibit a one bond carbon–fluorine coupling, but the presence of an additional two bond coupling on both of these signals ($^2J_{CF}$ = 14.5 and 13.7 Hz) proves that the fluorines are ortho to one another. The various halonitrobenzenes were obtained commercially except for 1-fluoro-4-iodo-2-nitrobenzene, which was prepared by the method of Arotsky et al.[16] Methods C–E are summarized in Scheme II, and the various nitronitriles and carboxylates are tabulated in Table V.

The structures of isomeric VIII and IX (Y = CO_2Et) were confirmed spectroscopically. The NMR spectrum of IX shows a characteristic downfield shift of the phenyl H-6 resonance, relative to that of VIII, due to deshielding by the lone pair of the pyrazole N-2. For example, the H-6 resonance appears at δ 8.91 and 6.53 for **64** and **62**, respectively.[30]

The nitro groups of VIII and IX (Y = CO_2Et) were hydrogenated using 10% Pd/C as catalyst. In most cases the diamino esters X were used without further purification. Initially we cyclized X with sodium (methylsulfinyl)methanide to give lactam XI. No thermal rearrangement similar to that observed with thieno[2,3-*b*][1,5]benzodiazepin-4(5*H*)-ones, was seen.[14] The preparation of **95** (XI, X = 7-F, R_1 = 1-CH_3) is given as an example. Pyrazolobenzodiazepin-4(5*H*)-ones (XI) readily reacted with *N*-methylpiperazine and titanium tetrachloride in anisole to give the desired amidines, as exemplified by the preparation of **5**.

As with analogous thienobenzodiazepines,[2a] reacting diamino esters X with an excess of *N*-methylpiperazine

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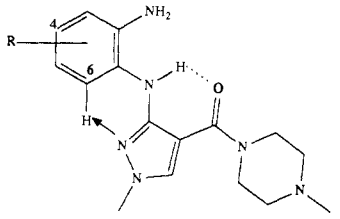
and titanium tetrachloride in refluxing anisole (method F, Scheme III) gave reasonable yields of the title compounds. The cyclization probably occurs via the intermediacy of diaminopiperazinecarboxamides (XII), which cyclize at the higher temperature. The preparation of one carboxamide (**96**) (XII, X = 4-CF_3) at 60 °C from diamino



XII (R = 4-CF_3, **96**)

ester **94** is included in the Experimental Section. The NMR spectrum of **96** shows a similar effect to that reported for nitro esters IX.[17] The phenyl H-6 resonance is also shifted relatively downfield as a doublet (δ 8.00), presumably due to interaction with the lone pair of the pyrazole 2-nitrogen brought into close proximity by the 6-membered hydrogen-bonded ring as shown.

The preparation of the title compounds via transamination of the cyclic aminoamidines (XIII) proved to be most efficient. Reduction of IX (Y = CN) with anhydrous stannous chloride in aqueous ethanolic HCl led directly to XIII as the hydrochloride salts. In most cases these salts were used without further purification, however compound XIII (X = 7-Cl, R_1 = 2-CH_3) was converted to the free base (**42**) for pharmacological testing. Transamination of XIII with *N*-methylpiperazine and other secondary amines was facilitated by DMSO and by use of the salt in preference to the free base. The reaction was best carried out with toluene as cosolvent at the reflux temperature of the latter (method G), while removing traces of water with a Dean–Stark apparatus. It was found necessary to purge the solvent mixture with N_2 before addition of the aminoamidine salt, especially for halo-substituted compounds, otherwise some loss of halogen, other than fluorine, was found in the final product. Compounds **6** and **9** were prepared as potential metabolites of **8**. The piperazine *N*-desmethyl derivative (**6**) was prepared from XIII (X = 7-F, R_1 = 2-CH_3) by method G using anhydrous piperazine. Compound **8** was oxidized to the piperazine distal *N*-oxide (**9**) with *m*-chloroperbenzoic acid by the procedure of Craig.[18] Piperazine distal-N-substituted derivatives other than methyl were prepared either by the use of a suitably substituted piperazine (method G) or by alkylation of **6** (method H).

One example of structure III, compound **40**, was prepared from 4-amino-1,3-dimethylpyrazole-5-carbonitrile[19] using method E and G; and it was found to slowly decompose in air and light. An example of structure IV, compound **41**, was also synthesized from ethyl 4-amino-1,5-dimethylpyrazole-3-carboxylate (**97**) by using methods E and F. Intermediate **97** was prepared by esterification and catalytic reduction of 1,5-dimethyl-4-nitropyrazole-3-carboxylic acid[20] (Scheme I). Compounds (**4–45**) are shown in Table I.

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Results and Discussion

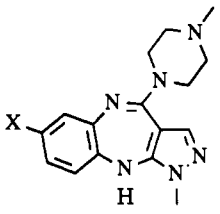
The biological results obtained in tests designed to identify compounds with a profile similar to clozapine (**1**) are presented in Table II. In general, the potency of the compounds in these tests was much lower than that obtained for equivalently substituted thieno[2,3-*b*][1,5]-benzodiazepines.[2,4] In this latter series we found that a short alkyl group at position 2 greatly enhanced activity.[2a] Analogously, compounds of type II (**7**, **8**) were found to be more active than their isomers of type I (**4**, **5**) and also type III (**40**), where a 2-alkyl group was necessarily absent.

Standard neuroleptics are thought to produce their antipsychotic activity by antagonistic binding to dopamine (D_2) receptors. The ability of a compound to compete in vitro with [^{3}H]spiperone for binding sites in calf caudate tissue is indicative of this interaction. In this test, compounds with a 2-CH_3 and a 2-C_2H_5 (**8**, **10** and **21**, **22**, respectively) had a similar level of binding activity. Extension of this 2-alkyl chain beyond ethyl, however, had a variable effect on the IC_{50} values with compounds **11** (7-F, 2-*n*-C_3H_7) and **24** (7-Cl, 2-cyclopentyl) being the most potent of the series in this test. Phenyl substitution in positions 2 and 3 (**14**, **17**, respectively) has little effect on binding, whereas an alkyl group at position 3 (**16**) lowers affinity, a result also seen with its isomer of type IV (**41**). It may be mentioned that in the thieno[2,3-*b*]benzodiazepine series[4] a greatly reduced antidopaminergic effect with an increase in anticholinergic activity was seen with a methyl group at the 3-position. This was attributed to the steric effect of this group restricting the rotation of the piperazine ring, as shown by broadening of the piperazine methylene proton signals in the NMR spectra. Compounds **16** and **40** in the present series with similar substitution, however, showed only slight broadening of the piperazine-ring proton signals, indicating minimal steric hindrance. However, compound **16** does show a small increase in affinity for cholinergic receptors.

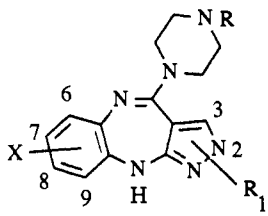
Consistent with our previous observation,[2a] compounds with other than a 4-piperazinyl group are inactive (**42–45**), whereas in this series alternative groups to methyl at the piperazine distal nitrogen (**6**, **36–38**), other than *N*-carbethoxy (**39**), retain activity. The unsubstituted phenyl derivative (**7**) and 7-F-substituted compound (**8**) have similar activity. The 7-Cl and 7-Br compounds (**21**, **30**) have increased potency, which is reduced with the 7-I compound (**31**). By changing the position of the chlorine atom around the phenyl ring, it is apparent that substitution at positions 6 and 7 (**20**, **21**) confers the greatest activity, with similar substitution at positions 8 and 9 (**26**, **27**) being less effective. The low level of activity of **26** (8-Cl) is surprising as **18** (8-F) is equipotent with **8** (7-F). It is also interesting to note that, in contrast, to the trend seen with the 7-monohalogenated derivatives (**8**, **21**), compound **19** (7,8-di-F) is more active than the 7,8-di-Cl derivative (**28**). This suggests that position 8 has a steric requirement.

Very few of the compounds tested blocked a conditioned avoidance response (CAR) in rats, an activity thought to be correlated with clinical antipsychotic efficacy. This is not altogether surprising as the majority are less active on [^{3}H]spiperone binding than clozapine, which has a low affinity for D_2 receptors and blocks a CAR only at doses greater than 30 mg/kg po. The only exception to this low level of activity is **21**, which has an ED_{min} of 10 mg/kg po in this test (Table II). This is twice the ED_{min} obtained with the thieno[2,3-*b*][1,5]benzodiazepine flumezapine. Compound **21** is, however, much less active than flumezapine on [^{3}H]spiperone binding.

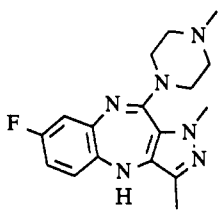
Table I. 4-Piperazinyl- and 4-Aminopyrazolo[*b*][1,5]benzodiazepines



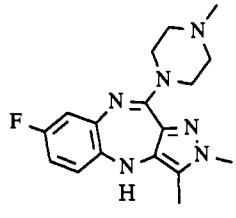
4-5



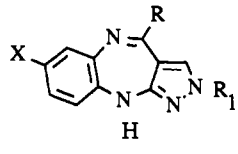
6-39



40



41



42-45

no.	R	X	R_1	% yield (method)	mp, °C	recrystn solvent[b]	formula	anal.
4	CH_3	H	1-CH_3	34 (F)	191	A	$C_{16}H_{20}N_6$	C, H, N
5	CH_3	7-F	1-CH_3	25 (*a*)	154–155	EA/nH	$C_{16}H_{19}FN_6$	C, H, N
6	H	7-F	2-CH_3	65 (G)	183–185	A	$C_{15}H_{17}FN_6$	C, H, N, F
7	CH_3	H	2-CH_3	39 (F)	212	A	$C_{16}H_{20}N_6$	C, H, N
8	CH_3	7-F	2-CH_3	35 (F)	191–191.5	A	$C_{16}H_{19}FN_6$	C, H, N, F
9	CH_3, 4-oxide	7-F	2-CH_3	29 (*a*)	228	A/E	$C_{16}H_{19}FN_6O$[c]	C, H, N
10	CH_3	7-F	2-C_2H_5	52 (F)	181	A	$C_{17}H_{21}FN_6$	C, H, N
11	CH_3	7-F	2-*n*-C_3H_7	53 (F)	146	A	$C_{18}H_{23}FN_6$	C, H, N, F
12	CH_3	7-F	2-*i*-C_3H_7	82 (F)	74–76	CH/nH	$C_{18}H_{23}FN_6$	C, H, N, F
13	CH_3	7-F	2-*n*-C_6H_{13}	52 (F)	99	CH/nH	$C_{21}H_{29}FN_6$	C, H, N, F
14	CH_3	7-F	2-C_6H_5	58 (F)	107.5–110	EA/nH	$C_{21}H_{21}FN_6$	C, H, N, F
15	CH_3	7-F	2-$CH_2C_6H_5$	37 (G)	117–119	EA	$C_{22}H_{23}FN_6$	C, H, N
16	CH_3	7-F	2,3-di-CH_3	48 (F)	234	EA/CH	$C_{17}H_{21}FN_6$	C, H, N, F
17	CH_3	7-F	2-CH_3, 3-C_6H_5	53 (F)	223	A	$C_{22}H_{23}FN_6$	C, H, N
18	CH_3	8-F	2-CH_3	39 (F)	192	A	$C_{16}H_{19}FN_6$	C, H, N, F
19	CH_3	7,8-di-F	2-CH_3	36 (G)	214	EA	$C_{16}H_{18}F_2N_6$	C, H, N, F
20	CH_3	6-Cl	2-CH_3	61 (G)	214	A	$C_{16}H_{19}ClN_6$	C, H, N, Cl
21	CH_3	7-Cl	2-CH_3	46 (G)	174–176.5	T	$C_{16}H_{19}ClN_6$	C, H, N
22	CH_3	7-Cl	2-C_2H_5	25 (G)	165	A	$C_{17}H_{21}ClN_6$	C, H, N, Cl
23	CH_3	7-Cl	2-*i*-C_4H_9	23 (G)	161	A	$C_{19}H_{25}ClN_6$	C, H, N, Cl
24	CH_3	7-Cl	2-*c*-C_5H_9	38 (G)	151	A	$C_{20}H_{25}ClN_6$	C, H, N, Cl
25	CH_3	7-Cl	2-*n*-$C_{10}H_{21}$	12 (G)	88	A	$C_{25}H_{37}ClN_6$	C, H, N, Cl
26	CH_3	8-Cl	2-CH_3	48 (G)	221	C/nH	$C_{16}H_{19}ClN_6$	C, H, N, Cl
27	CH_3	9-Cl	2-CH_3	26 (G)	140	C/nH	$C_{16}H_{19}ClN_6$	C, H, N, Cl
28	CH_3	7,8-di-Cl	2-CH_3	23 (G)	158	A	$C_{16}H_{18}Cl_2N_6$	C, H, N, Cl
29	CH_3	7,8-di-Cl	2-C_2H_5	69 (G)	214	A	$C_{17}H_{20}Cl_2N_6$	C, H, N, Cl
30	CH_3	7-Br	2-CH_3	24 (G)	162	A	$C_{16}H_{19}BrN_6$	C, H, N, Br
31	CH_3	7-I	2-CH_3	62 (G)	113	C/nH	$C_{16}H_{19}IN_6$	C, H, N, I
32	CH_3	8-CH_3	2-CH_3	34 (F)	211	A	$C_{17}H_{22}N_6$	C, H, N
33	CH_3	7-CF_3	2-CH_3	55 (G)	129–130	EA/nH	$C_{17}H_{19}F_3N_6$	C, H, N, F
34	CH_3	7-COC_6H_5	2-CH_3	43 (G)	141	A	$C_{23}H_{24}N_6O$	C, H, N, O
35	CH_3	7-SO_2CH_3	2-CH_3	10 (G)	140–141	A	$C_{17}H_{22}N_6O_2S$	C, H, N, O
36	CH_2-*c*-C_3H_5	7-F	2-CH_3	62 (H)	188–189	EA	$C_{19}H_{23}FN_6$	C, H, N, F
37	$CH_2C_6H_5$	7-F	2-CH_3	48 (H)	241–245	EA/E	$C_{22}H_{23}FN_6$	C, H, N, F
38	CH_2CH_2OH	7-F	2-CH_3	54 (G)	193–194	B	$C_{17}H_{21}FN_6O$	C, H, N, F
39	$CO_2C_2H_5$	7-F	2-CH_3	47 (G)	215–217	EA/nH	$C_{18}H_{21}FN_6O_2$	C, H, N, F
40	CH_3	7-F	1,3-di-CH_3	10 (G)	90	EA/nH	$C_{17}H_{21}FN_6$	C, H, N, F
41	CH_3	7-F	2,3-di-CH_3	49 (F)	190	C/nH	$C_{17}H_{21}FN_6$	*d*
42	NH_2	7-Cl	2-CH_3	87 (*a*)	240	C/nH	$C_{11}H_{10}ClN_5$	C, H, N, Cl
43	$NH(CH_2)_2N(CH_3)_2$	7-F	2-CH_3	48 (G)	185–187	EA/nH	$C_{15}H_{19}FN_6$	C, H, N, F
44	*c*-NC_5H_{10}	7-F	2-CH_3	52 (G)	228–230	CH	$C_{16}H_{18}FN_5$	C, H, N, F
45	*c*-NC_4H_8O	7-F	2-CH_3	56 (G)	230–233	EA/nH	$C_{15}H_{16}FN_5O$	C, H, N, F

[a] See the Experimental Section. [b] Solvent of crystallization: A = CH_3CN; B = benzene; C = $CHCl_3$; CH = cyclohexane; E = diethyl ether, EA = ethyl acetate; nH = *n*-hexane; T = toluene. [c] Crystallized as a monohydrate. [d] High-resolution mass spectrum calculated 329.188998, found 329.188975.

The results for the three 7-halo substituted compounds (**8**, **21**, and **30**) in the three part operant test are compared with those of the clinically effective anxiolytic chlordiazepoxide (CDP) in Table III. In component 1 ("reward") the VI_{30} schedule leads to high rates of responding, which are susceptible to reduction by both sedatives and stimulant drugs. Compound **21** at 20 and 40 mg/kg po and CDP at 20 mg/kg po cause a significant decrease in the rates of responding in this schedule, which is thought to be due to a sedative effect of these compounds. The rate of responding in component 2 ("timeout") is very much lower than in "reward" and can be increased by compounds with stimulant activity. As can be seen from Table III all compounds tested increased the rate of responding. Compound **21** was the most active in this respect, causing a significant effect at the lowest dose tested (2.5 mg/kg po). The lack of a significant increase at 40 mg/kg po with **21** is due to the rate-reducing effect of this dose noted in the "reward" component.

Component 3 ("conflict"), like component 2, leads to a low rate of responding, which is increased by compounds which have clinical anxiolytic activity. All the compounds tested released this conflict-suppressed behavior. As in the "timeout" component, **21** and **30** were more active and **8** equiactive in component 3 with the clinically effective anxiolytic CDP. The rate-reducing effects of **21** at 40 mg/kg po are again evident in this component of the test.

Because these compounds demonstrated potential anxiolytic activity, compound **8** was selected as a clinical candidate for the treatment of anxiety. In a subacute dog

Table II. Pharmacological Results[a]

no.[b]	[^{3}H]spiperone binding: IC_{50}, μM	[^{3}H]QNB binding: IC_{50}, μM	ED, mg/kg, po			mouse behavior: ED_{min}, mg/kg po	
			rat rotarod	CAR	catalepsy	hypo.	cat.
4	1500	>100	>50	>50	>50	>400	>400
5	NT	NT	>50	>50	NT	100	>200
6	5.2	>10	>50	>50	NT	200	>400
7	6.3	38	>50	>50	50	50	200
8	2.6	150	>20	100	>100	1.6	50
9	>10	>1	>50	>50	NT	50	100
10	3.3	14	>40	50	50	6	>400
11	0.18	16	50	40	>50	25	200
12	1.1	7.2	40	25	>50	50	200
13	0.7	18	>50	>50	>50	100	>400
14	2.6	>10	>50	50	NT	>200	>200
15	0.4	>100	>50	50	NT	100	>400
16	97	3.2	>50	>50	50	25	200
17	2.1	>100	>50	>50	NT	200	>400
18	2.6	43	>40	>20	>50	1.6	100
19	0.76	21	>50	50	NT	25	>200
20	0.86	>100	>50	>50	NT	25	>400
21	0.68	8.9	>10	10	>25	0.8	12.5
22	0.34	>1.0	20	>15	NT	6.25	>400
23	3.3	>10	>50	>50	NT	50	200
24	0.14	>10	>50	50	NT	50	>400
25	2.5	>10	>50	>50	NT	>400	>400
26	>10	>100	>50	>50	NT	100	>400
27	4.7	>100	>50	>50	NT	184	184
28	>10	>1.0	>50	>20	NT	25	50
29	3.8	>1.0	20	>20	NT	50	200
30	0.68	>10	>10	>5	NT	12.5	25
31	>1.0	NT	25	>20	NT	50	50
32	5.6	>100	>50	>50	>50	200	>400
33	1.6	>10	>30	25	NT	50	200
34	>10	>1.0	>50	>50	NT	>400	>400
35	>10	>100	>50	NT	NT	>200	>200
36	0.9	>10	30	>15	NT	50	100
37	2.7	>100	50	>50	NT	50	>200
38	5.1	>100	>50	>50	NT	>200	>200
39	>10	>100	>50	>50	NT	>200	>200
40	>10	>100	>50	>50	NT	>200	>200
41	>10	NT	NT	NT	NT	NT	NT
42	>10	>100	>50	>25	NT	25	>25
43	>10	6.1	>50	>50	NT	>400	>400
44	>10	>10	>50	50	NT	400	>400
45	>100	>100	>50	>50	NT	200	>400
1	0.25	0.18	40	30	80	50	100
2	0.02	0.08	10	5	20	1.6	6.25

[a] NT = not tested. [b] 1 = clozapine, 2 = flumezapine.

Table III. Anticonflict Behavior

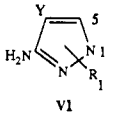
no.	dose, mg/kg po					
	0	2.5	5.0	10	20	40
			Reward			
8	47.3 ± 5.2*[b]		45.1 ± 7.4	42.1 ± 5.0	45.9 ± 4.8	48.3 ± 6.1
21	24.9 ± 3.3	24.9 ± 0.9	27.5 ± 3.2	26.3 ± 3.2	5.4 ± 0.6*	14.1 ± 2.6*
30	18.7 ± 2.6	21.9 ± 2.9	22.1 ± 2.5	23.0 ± 4.5	14.1 ± 2.7	
CDP[a]	70.2 ± 9.0		70.8 ± 2.4	68.8 ± 8.7	54.3 ± 7.3*	
			Timeout			
8	5.4 ± 0.8		5.7 ± 0.8	7.4 ± 2.6	15.4 ± 5.2*	15.4 ± 5.2*
21	2.1 ± 0.6	9.3 ± 1.7*	7.9 ± 2.0*	6.5 ± 2.1	9.6 ± 3.5*	4.6 ± 1.7
30	2.0 ± 1.1	2.1 ± 0.7	6.0 ± 2.3*	8.0 ± 3.9	4.4 ± 1.1*	
CDP[a]	1.4 ± 0.3		2.2 ± 0.5	3.4 ± 0.8	3.7 ± 1.5*	
			Conflict			
8	3.0 ± 1.1		3.9 ± 2.5	9.6 ± 4.2*	6.9 ± 3.4*	10.1 ± 4.8*
21	1.1 ± 0.4	5.6 ± 2.3*	6.0 ± 2.9*	8.1 ± 2.5*	7.8 ± 2.8*	4.8 ± 1.6*
30	0.5 ± 0.2	2.2 ± 0.9*	2.6 ± 0.9*	5.0 ± 3.4*	4.1 ± 1.6*	
CDP[a]	0.6 ± 0.5		1.9 ± 0.5	4.2 ± 2.2*	3.3 ± 0.7	

[a] CDP = chlordiazepoxide. [b] An asterisk denotes that $p < 0.05$.

toxicity study, however, it produced a high incidence of granulocytopoenia and its progression to the clinic was terminated.

Electronic characteristics are considered to be important in the initial stages of molecular recognition and spatial orientation of a ligand for binding to receptor(s). The differences in the activity profile observed may be explained by the characteristic electron distribution and basicity of the different fused heteroarene rings. It appears that suitably orientated thienobenzodiazepines can retain

Table IV. 3-Aminopyrazole-4-carbonitriles and -carboxylates

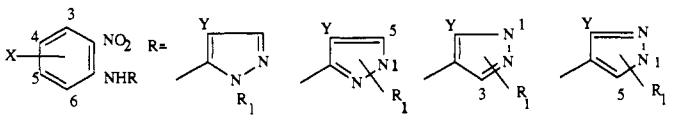


VI

no.	R_1	Y	% yield (method)	mp, °C	recrystn solvent	formula	anal.
47	1-CH_3	$CO_2C_2H_5$	*a*				
48	1-CH_3	CN	*b*				
49	1-C_2H_5	$CO_2C_2H_5$	*b*				
50	1-C_2H_5	CN	35 (B)	68	CCl_4	$C_6H_8N_4$	C, H, N
51	1-*n*-C_3H_7	$CO_2C_2H_5$	*c*	34–37	*e*	$C_9H_{15}N_3O_2$	C, H, N
52	1-*i*-C_3H_7	$CO_2C_2H_5$	*b*				
53	1-*i*-C_4H_9	CN	29 (B)	69	MeOH	$C_8H_{12}N_4$	C, H, N
54	1-*c*-C_5H_9	CN	50 (B)	128	CCl_4	$C_9H_{12}N_4$	C, H, N
55	1-*n*-C_6H_{13}	$CO_2C_2H_5$	47 (B)	49	hexane	$C_{12}H_{21}N_3O_2$	C, H, N
56	1-*n*-$C_{10}H_{21}$	CN	29 (B)	69	MeOH	$C_{14}H_{24}N_4$	C, H, N
57	1-C_6H_5	$CO_2C_2H_5$	*b*				
58	1-$CH_2C_6H_5$	CN	41 (B)	132–134	EtOAc–hexane	$C_{11}H_{10}N_4$	C, H, N
59	1,5-di-CH_3	$CO_2C_2H_5$	*d*				
60	1-CH_3, 5-C_6H_5	$CO_2C_2H_5$	28 (B)	126	CH_2Cl_2–hexane	$C_{13}H_{15}N_3O_2$	C, H, N

[a] See ref 11. [b] See ref 27. [c] See the Experimental Section. [d] See ref 28. [e] Distilled $bp_{0.2torr}$ 108–109 °C.

Table V. 3- and 5-[(2-Nitrophenyl)amino]pyrazole-4-carbonitriles and -carboxylates



61-62 63-91 92 93

no.	X	R_1	Y	% yield (method)	mp, °C	recrystn solvent[a]	formula	anal.
61	H	1-CH_3	$CO_2C_2H_5$	35 (D)	66	P	$C_{13}H_{14}N_4O_4$	C, H, N, O
62	4-F	1-CH_3	$CO_2C_2H_5$	36 (C)	101–102	P	$C_{13}H_{13}FN_4O_4$	C, H, N, F
63	H	1-CH_3	$CO_2C_2H_5$	14 (C)	146	P	$C_{13}H_{14}N_4O_4$	C, H, N, O
64	4-F	1-CH_3	$CO_2C_2H_5$	55 (C)	162	E	$C_{13}H_{13}FN_4O_4$	C, H, N, F, O
65	4-F	1-C_2H_5	$CO_2C_2H_5$	20 (C)	136	E	$C_{14}H_{15}FN_4O_4$	C, H, N, F, O
66	4-F	1-*n*-C_3H_7	$CO_2C_2H_5$	30 (C)	109	E	$C_{15}H_{17}FN_4O_4$	C, H, N, F
67	4-F	1-*i*-C_3H_7	$CO_2C_2H_5$	15 (C)	106.5	C	$C_{15}H_{17}FN_4O_4$	C, H, N, F
68	4-F	1-*n*-C_6H_{13}	$CO_2C_2H_5$	14 (C)	73	E	$C_{18}H_{23}FN_4O_4$	C, H, N, F
69	4-F	1-C_6H_5	$CO_2C_2H_5$	58 (E)	174	EA-E	$C_{18}H_{15}FN_4O_4$	C, H, N
70	4-F	1-$CH_2C_6H_5$	CN	42 (E)	152–154	EA-E	$C_{17}H_{12}FN_5O_2$	C, H, N
71	4-F	1,5-di-CH_3	$CO_2C_2H_5$	36 (C)	174	E	$C_{14}H_{15}FN_4O_4$	C, H, N
72	4-F	1-CH_3, 5-C_6H_5	$CO_2C_2H_5$	64 (E)	*b*	E	$C_{19}H_{17}FN_4O_4$	*b*
73	5-F	1-CH_3	$CO_2C_2H_5$	18 (C)	165	E	$C_{13}H_{13}FN_4O_4$	C, H, N, F
74	4,5-di-F	1-CH_3	CN	29 (*c*)	214	E	$C_{11}H_7F_2N_5O_2$	C, H, N, F
75	3-Cl	1-CH_3	CN	36 (E)	190	E	$C_{11}H_8ClN_5O_2$	C, H, N, Cl
76	4-Cl	1-CH_3	CN	72 (E)	205	EA-E	$C_{11}H_8ClN_5O_2$	C, H, N, Cl
77	4-Cl	1-C_2H_5	CN	62 (E)	172	EA-E	$C_{12}H_{10}ClN_5O_2$	C, H, N, Cl
78	4-Cl	1-*i*-C_4H_9	CN	69 (E)	151	E	$C_{14}H_{14}ClN_5O_2$	C, H, N, Cl
79	4-Cl	1-*c*-C_5H_9	CN	68 (E)	145	E	$C_{15}H_{14}ClN_5O_2$	C, H, N, Cl
80	4-Cl	1-*n*-$C_{10}H_{21}$	CN	75 (E)	72	E	$C_{20}H_{26}ClN_5O_2$	C, H, N, Cl
81	5-Cl	1-CH_3	CN	58 (E)	187	EA-E	$C_{11}H_8ClN_5O_2$	C, H, N, Cl
82	6-Cl	1-CH_3	CN	50 (E)	197	E	$C_{11}H_8ClN_5O_2$	C, H, N, Cl
83	4,5-di-Cl	1-CH_3	CN	78 (E)	225	EA-E	$C_{11}H_7Cl_2N_5O_2$	C, H, N, Cl
84	4,5-di-Cl	1-C_2H_5	CN	26 (E)	170	EA-E	$C_{12}H_9Cl_2N_5O_2$	C, H, N, Cl
85	4-Br	1-CH_3	CN	48 (E)	208	EA-E	$C_{11}H_8BrN_5O_2$	C, H, N, Br
86	4-I	1-CH_3	CN	71 (E)	212	EA-E	$C_{11}H_8IN_5O_2$	C, H, N, I
87	5-CH_3	1-CH_3	$CO_2C_2H_5$	19 (C)	122	E	$C_{14}H_{16}N_4O_4$	C, H, N
88	4-CF_3	1-CH_3	$CO_2C_2H_5$	45 (C)	158	P	$C_{14}H_{13}F_3N_4O_4$	C, H, N
89	4-CF_3	1-CH_3	CN	68 (E)	183–184	E	$C_{12}H_8F_3N_5O_2$	C, H, N, F
90	4-COC_6H_5	1-CH_3	CN	85 (E)	211	E	$C_{18}H_{13}N_5O_3$	C, H, N, O
91	4-SO_2CH_3	1-CH_3	CN	37 (E)	*b*	E	$C_{12}H_{11}N_5O_4S$	C, H, N, S
92	4-F	1,3-di-CH_3	CN	84 (E)	160	E	$C_{12}H_{10}FN_5O_2$	C, H, N, F
93	4-F	1,5-di-CH_3	$CO_2C_2H_5$	19 (E)	150	E	$C_{14}H_{15}FN_5O_2$	C, H, N

[a] Solvent of crystallization: C = cyclohexane, E = EtOH, EA = EtOAc, P = *i*-PrOH. [b] Used without purification in the next stage. [c] See the Experimental Section.

a profile of activity (both antidopaminergic and anticholinergic) similar to that of the dibenzodiazepine, clozapine. Thiophene is relatively electron rich and isosteric with benzene.

On the other hand, [1,2,3]triazolobenzodiazepines incorporating an amphoteric 1,2,3-triazole moiety maintain a similar level of antidopaminergic activity with greatly reduced anticholinergic properties.[6] The basicity of the heteroarene group also seems to play an important role in determining the activity. Compounds containing a fused 2-methyl[1,2,3]triazole show good potency, whereas the 3-methyl isomer is devoid of activity. 2-Methyl[1,2,3]-

triazole is a much weaker base than its 3-methyl isomer, probably due to its ability to form a pyrazolium-type cation, while the latter can assume an imidazolium-type cation. Imidazole is a stronger base than pyrazole, presumably due to the stability of its symmetrical mesomeric cation. Similarly there is a lack of activity shown by the other heteroarenobenzodiazepines incorporating strong basic components, e.g. imidazole and pyridine.[31]

It has been suggested[4] that the disposition of the lone pair of the distal nitrogen of the piperazine ring, particularly with respect to the C ring of the tricyclic systems, is important for antidopaminergic activity. This has also been supported by piquindone,[21] where the nitrogen has been conformationally fixed relative to the pyrrole ring (equivalent to ring C of the tricyclics), which retains the D_2-antagonist activity although rings A and B of the tricyclics are absent. Modulation of the C ring also has a profound effect on the activity profile.[6] The neuroleptic activity (antidopaminergic and anticholinergic), which is common to both the dibenzodiazepine clozapine and thienobenzodiazepine flumezapine, is absent in pyrazolobenzodiazepines (**8**, **21**, and **30**), whereas all these compounds share the anxiolytic activity. Each of the pharmacological responses shown by these compounds may be due to the affinity of some of their structural features for a particular receptor. We can speculate that the part of the molecules containing the A and B rings and piperazine side chain, common to all these compounds, which also have structural similarities to the benzodiazepine anxiolytics, may be responsible for the observed anxiolytic response. The loss of neuroleptic activity in the pyrazolobenzodiazepine series of compounds may be due to the relative electron-deficient nature of the pyrazole ring in comparison to thiophene and benzene.

Experimental Section

Chemistry. Melting points were determined with a Kofler hot-stage apparatus and are uncorrected. All compounds were characterized by physical methods using IR, UV, NMR, and MS. NMR spectra were run on a Bruker AM300 spectrometer in $CDCl_3$ using TMS as reference for ^1H and $CDCl_3$ (δ 77.2) for ^{13}C spectra. Mass spectra were recorded on a VG 7070E double-focusing spectrometer using CI ionization with NH_3 at 200 eV. Column chromatography was carried out with Florisil, Woelm alumina, or Sorbsil U30 grade silica gel. $MgSO_4$ was used as a drying agent. Microanalyses are within ±0.4% of calculated values.

Method A. Ethyl 3-amino-1-propylpyrazole-4-carboxylate (51) was prepared by the method of Schmidt et al.[11] from 1-propylhydrazine which had been synthesized from 1-propylamine by the method of Gever and Hayes:[12] overall yield 33% from hydroxylamine-*O*-sulphonic acid; distilled $bp_{0.2torr}$ 108–109 °C; mp 34–37 °C. Anal. ($C_9H_{15}N_3O_2$) C, H, N.

Method B. Ethyl 3-Amino-1-hexylpyrazole-4-carboxylate (55). Ethyl 3-aminopyrazole-4-carboxylate (15.5 g, 0.1 mol), 1-bromohexane (21.9 g, 0.13 mol), Adogen 464 (2.5 g), and potassium carbonate (27.6 g, 0.2 mol) were heated under reflux in toluene (250 mL) with the addition of NaOH (12.5 M, 0.1 mL) for 6 h. The cooled mixture was washed with water and dried and the solvent was removed to leave an oil, which was chromatographed (SiO_2, Et_2O) and crystallized from *n*-hexane (11.3 g, 47%), mp 49 °C. Anal. ($C_{12}H_{21}N_3O_2$) C, H, N.

Ethyl 4-Amino-1,5-dimethylpyrazole-3-carboxylate (97). To 1,5-dimethyl-4-nitropyrazole-3-carboxylic acid[20] (3.95 g, 0.021 mol) in DMF (100 mL) and triethylamine (12.5 mL) was added diethyl sulfate (5.8 mL, 0.044 mol) and the mixture was stirred at 60 °C for 20 h. The solution was poured onto a mixture of ice and dilute aqueous ammonia solution, and the product was extracted into $CHCl_3$. After drying and evaporation of the solvent, the residual oil was distilled in a short path distillation apparatus, $bp_{0.8torr}$ 220 °C, dissolved in EtOH (100 mL), and hydrogenated at 60 psi with Pd/C (10%, 0.7 g) as catalyst. The product obtained after removal of catalyst and solvent was used in the next stage (2.83 g, 77%). High-resolution mass spectrum, calcd for $C_8H_{13}N_3O_2$, 183.100 777, found 183.100 781.

Method C. Ethyl 3-[(4-Fluoro-2-nitrophenyl)amino]-1-methylpyrazole-4-carboxylate (64). To a solution of ethyl 3-amino-1-methylpyrazole-4-carboxylate[11] (**47**, 1.7 g, 0.01 mol) in dry THF (25 mL) under a N_2 atmosphere at −15 °C was added, dropwise, *n*-BuLi (9.5 mL of 1.6 M solution in hexane, 0.015 mol) at −10 to −15 °C. The mixture was stirred at −15 °C for 10 min and then a solution of 1,4-difluoro-2-nitrobenzene (1.6 g, 0.01 mol) in THF (15 mL) was added at −15 to −10 °C. The ink-blue solution was stirred at ambient temperature for 1 h, poured onto ice-cold HCl (1 M, 50 mL), and extracted into $CHCl_3$. After drying and evaporation of the solvent, the residue was crystallized from EtOH (1.7 g, 55%), mp 162 °C. Anal. ($C_{13}H_{13}FN_4O_4$) C, H, N, F.

Method D. Ethyl 1-Methyl-5-[(2-nitrophenyl)amino]-pyrazole-4-carboxylate (61). Ethyl 5-amino-1-methylpyrazole-4-carboxylate[11] (8.85 g, 0.05 mol), 2-fluoronitrobenzene (7.01 g, 0.05 mol), Adogen 464 (2.5 g), and potassium carbonate (13.8 g, 0.1 mol) were stirred under reflux in toluene (100 mL) with NaOH (12.5 M, 0.5 mL) for 6 h. The mixture was poured onto HCl (1 M), extracted into EtOAc, chromatographed (SiO_2, CH_2Cl_2), and crystallized from 2-propanol (5.1 g, 35%), mp 66 °C. Anal. ($C_{13}H_{14}N_4O_4$) C, H, N, O.

Method E. 3-[(4-Chloro-2-nitrophenyl)amino]-1-methylpyrazole-4-carbonitrile (76). To 3-amino-1-methylpyrazole-4-carbonitrile[27] (**48**, 3.66 g, 0.03 mol) in dry THF (40 mL) was added sodium hydride (50% oil dispersion, 2.28 g, 0.045 mol) and the mixture was stirred for 10 min. 1,4-dichloro-2-nitrobenzene (5.76 g, 0.03 mol) was added and the solution was stirred under a N_2 atmosphere for 20 h. The mixture was poured onto ice-cold HCl (1 M), the precipitate was filtered and crystallized from EtOH–EtOAc (5.0 g, 72%), mp 205 °C. Anal. ($C_{11}H_8ClN_5O_2$) C, H, N, Cl.

3-[(4,5-Difluoro-2-nitrophenyl)amino]-1-methylpyrazole-4-carbonitrile (74). A solution of 3-amino-1-methylpyrazole-4-carbonitrile[27] (**48**, 1.22 g, 0.01 mol) and 1,2,4-trifluoro-5-nitrobenzene (1.77 g, 0.01 mol) in dry THF (20 mL) was added to a stirred suspension of sodium hydride (50% oil dispersion, 0.84 g, 0.0175 mol) in THF (10 mL) under a N_2 atmosphere. The mixture was stirred for 20 h, poured onto ice, acidified with HCl (2 M), extracted into CH_2Cl_2, washed with H_2O, dried, and evaporated. The residue was chromatographed (SiO_2, CH_2Cl_2) to give a single isomer, which was crystallized from EtOH (0.80 g, 29%): mp 214 °C; ^{13}C NMR ($CDCl_3$) δ 143.2 ($^1J_{CF}$ = 247 Hz, $^2J_{CF}$ = 14.5 Hz, C-7), 155.5 ($^1J_{CF}$ = 259 Hz, $^2J_{CF}$ = 13.7 Hz, C-8). Anal. ($C_{11}H_7F_2N_5O_2$) C, H, N, F.

Ethyl 3-[[2-Amino-4-(trifluoromethyl)phenyl]amino]-1-methylpyrazole-4-carboxylate (94). Nitro ester **88** (9.2 g, 0.026 mol) was hydrogenated in a mixture of EtOAc and EtOH (1:1, 300 mL) at 60 psi with Pd/C (10%, 900 mg). After removal of the catalyst and evaporation of the solvent, the residue was crystallized from CCl_4 (7.6 g, 90%), mp 162 °C. Anal. ($C_{14}H_{15}F_3N_4O_2$) C, H, N, F.

7-Fluoro-1,10-dihydro-1-methylpyrazolo[5,4-*b*][1,5]-benzodiazepin-4(5*H*)-one (95). Nitro ester **62** (6.2 g, 0.02 mol)

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(29) Concurrent with the work described here and in our patent,[1] alternative syntheses to these previously novel ring systems have been published.[7]
(30) The full NMR data for related compounds and an explanation of this observation is given in our earlier publication.[17]
(31) See the discussion in ref 6.

was hydrogenated at 60 psi in a mixture of EtOAc–EtOH (1:1, 200 mL) with Pd/C (10%, 600 mg). After removal of the catalyst and solvent, the crude diamine, dissolved in DMSO (10 mL), was added to a solution of sodium (methylsulfinyl)methanide prepared from sodium hydride (50% oil dispersion, 1.5 g) in DMSO (30 mL), at 65 °C. After stirring at 65 °C for 20 min, the mixture was poured onto ice and the precipitate was filtered, dried, and crystallized from MeOH–EtOAc (4.15 g, 90%), mp >290 °C. Anal. ($C_{11}H_9FN_4O$) C, H, N, F.

1-[[3-[[2-Amino-4-(trifluoromethyl)phenyl]amino]-1-methylpyrazol-4-yl]carbonyl]-4-methylpiperazine (96). Diamino ester **94** (4.75 g, 0.014 mol) was stirred under a N_2 atmosphere in a mixture of *N*-methylpiperazine (25 mL) and anisole (65 mL). A solution of $TiCl_4$ (4.2 mL) in anisole (20 mL) was added and the mixture was stirred at 65 °C for 0.5 h. The titanium salts were precipitated with aqueous ammonia (20 M, 10 mL) and 2-propanol (10 mL) and removed by filtration, washing with EtOAc. The filtrate was washed with water and dried, and the solvent was evaporated to leave a residue, which was crystallized from CH_3CN (3.6 g, 65%): mp 170 °C; ^1H NMR ($CDCl_3$) δ 2.32 (s, 3 H, NCH_3), 2.44, 3.76 (m, 8 H, piperazine-CH_2), 3.80 (br, 2 H, NH_2), 3.83 (s, 3 H, pyrazole NCH_3), 6.99 (d, 1 H, H-3), 7.10 (dd, 1 H, H-5), 7.42 (s, 1 H, pyrazole H-5), 8.00 (d, 1 H, H-6), 8.58 (br, 1 H, NH). Anal. ($C_{17}H_{21}F_3N_6O$) C, H, N, F.

7-Fluoro-1,10-dihydro-1-methyl-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-*b*][1,5]benzodiazepine (5). Lactam **95** (2 g, 0.0086 mol) was stirred in a mixture of *N*-methylpiperazine (20 mL) and anisole (15 mL). A solution of $TiCl_4$ (1.1 mL, 0.01 mol) in anisole (10 mL) was added under a N_2 atmosphere and the mixture was stirred at 130 °C for 0.5 h. The reaction was cooled to 70 °C and the titanium salts were precipitated as above and removed by filtration, washing with EtOAc. The filtrate, after washing with water, was chromatographed (Florisil, EtOAc) and the product crystallized from EtOAc–*n*-hexane (0.68 g, 29%), mp 154–155 °C. Anal. ($C_{16}H_{19}FN_6$) C, H, N.

Method F. 2-Ethyl-7-fluoro-2,10-dihydro-4-(4-methyl-1-piperazinyl)pyrazolo[3,4-*b*][1,5]benzodiazepine (10). Nitro ester **65** (3 g, 0.009 mol) was hydrogenated at 60 psi in a mixture of EtOAc (75 mL) and EtOH (25 mL) with Pd/C (10%, 0.3 g). After removal of the catalyst and solvent, the crude diamine was dissolved in a mixture of *N*-methylpiperazine (12.5 mL) and anisole (50 mL). A solution of $TiCl_4$ (3 mL) in anisole (12 mL) was added and the mixture was heated under N_2 at 100 °C for 1 h and then under reflux for 24 h. After cooling to 70 °C, the titanium salts were precipitated as above and removed by filtration, washing with EtOAc. The crude product was chromatographed (Florisil, EtOAc) and crystallized from CH_3CN (1.6 g, 52%), mp 181 °C. Anal. ($C_{17}H_{21}FN_6$) C, H, N.

7-Chloro-2,10-dihydro-2-methylpyrazolo[3,4-*b*][1,5]benzodiazepin-4-amine (42). To nitronitrile **76** (16 g, 0.06 mol) in EtOH (500 mL) was added a solution of anhydrous stannous chloride (33.1 g, 0.175 mol) in HCl (12 M, 175 mL). The mixture was heated under reflux for 2 h, cooled, and filtered to give the hydrochloride salt (14.3 g, 87%), mp >260 °C. This salt (2.0 g) was partitioned between aqueous NH_3 (1 M) and $CHCl_3$. The organic phase was evaporated and the residue was crystallized from $CHCl_3$–*n*-hexane (1.3 g), mp 240 °C. Anal. ($C_{11}H_{10}ClN_5$) C, H, N, Cl.

Method G. 2,10-Dihydro-7-iodo-2-methyl-4-(4-methylpiperazinyl)pyrazolo[3,4-*b*][1,5]benzodiazepine (31). Nitronitrile **86** (4 g, 0.011 mol) was reduced as above and the crude amidine hydrochloride was added to a mixture of *N*-methylpiperazine (10 mL), DMSO (25 mL), and toluene (25 mL), which had previously been purged with N_2 for 0.5 h. The stirred mixture was heated under N_2 at reflux for 20 h and then cooled to 60 °C and water (25 mL) was added. The precipitate was filtered, dried, and crystallized from CH_3CN (2.7 g, 62%), mp 113 °C. Anal. ($C_{16}H_{19}IN_6$) C, H, N, I.

Method H. 4-[4-(Cyclopropylmethyl)-1-piperazinyl]-7-fluoro-2,10-dihydro-2-methylpyrazolo[3,4-*b*][1,5]benzodiazepine (36). A solution of **6** (1.0 g, 0.0034 mol), (bromomethyl)cyclopropane (0.5 g, 0.0037 mol) and triethylamine (0.0375 g, 0.0037 mol) in acetonitrile (30 mL) was stirred at ambient temperature for 20 h. The solution was diluted with water and extracted into $CHCl_3$. The organic extract was washed and dried, the solvent was removed under reduced pressure, and the residue was crystallized from EtOAc (0.74 g, 62%), mp 188–189 °C. Anal. ($C_{19}H_{23}FN_6$) C, H, N, F.

4-(7-Fluoro-2,10-dihydro-2-methylpyrazolo[3,4-*b*][1,5]-benzodiazepin-4-yl)-1-methylpiperazine 1-Oxide, Monohydrate (9). To a solution of **8** (2 g, 0.0064 mol), in CH_2Cl_2 (50 mL) at 0 to −5 °C, was added *m*-chloroperbenzoic acid (85%, 1.5 g, 0.007 mol) portionwise. After stirring for 30 min, the solution was filtered through a column of basic alumina eluting with $CHCl_3$–MeOH (9:1) to give **9** as the monohydrate (0.6 g, 29%), mp 228 °C (MeCN–Et_2O). Anal. ($C_{16}H_{19}FN_6O\cdot H_2O$) C, H, N.

Pharmacological Methods. All compounds were dissolved in distilled water or suspended in 0.5% (carboxymethyl)cellulose. Solutions or suspensions were administered orally except where mentioned otherwise.

Mouse Behavior. Groups of three CFW mice (21–23 g) were assessed for changes in body temperature and for the presence of catalepsy at 0.25, 2.5, and 5.0 h after oral administration of the compound.

(a) Catalepsy. Animals were tested for their ability to remain with one hind limb on a rubber bung (2 cm high) and also to remain on a vertical grid. The animal was considered to be cataleptic, if, in the opinion of a trained observer, it remained in the set position for a period significantly longer than a control animal. The ED_{min} value is the dose below which no catalepsy was observed at any time period.

(b) Hypothermia. The rectal temperature of the three mice in each group were measured at the three time periods after compound administration. The mean temperature change from the initial mean temperature of each group for all three time periods were summed. Hypothermia was considered to be present if the sum of the mean temperature reduction was >4 °C.

Muscular Incoordination in Rats (Rat Rotarod). Groups of five male Olac–Wistar rats (140–150 g), fed and watered ad libitum, were assessed for the presence of muscular incoordination at 1 and 2 h after oral administration of the compound. The animals were placed individually on a horizontal rotating rod (2 rpm) formed from a kymograph spindle covered with corrugated paper to a mean diameter of 32 mm. The time the animals remained on the rod, up to a maximum of 30 s, was recorded and the mean time for each group compared with that of a vehicle-treated control group. The compound was considered to have produced muscular incoordination if the mean time on the rod was significantly ($p < 0.05$ Mann–Whitney "*U*" Test) lower than that of the controls.

Conditioned-Avoidance Response (CAR) in Rats. The method used was essentially that described by Jacobsen and Sonne.[22] Olac–Wistar rats (120–130 g) were trained to pass from one side of a shuttle box to the other on hearing a 5-s buzzer. Failure to respond within 1 s from the end of the buzzer resulted in the animals receiving a mild electric shock. The compound under test was administered to only those animals which showed a high level of conditioned response. Groups of five animals were dosed orally 1 h 50 min prior to placing them individually in the shuttle boxes. After a 10-min habituation period, they were tested for 20 min. During this period the number of times the buzzer sounded, as well as the number of shocks received by the animal, was recorded. The degree of conditioned-avoidance blockade was calculated by expressing the number of shocks received as a percentage of the number of stimuli presented.

Rat Catalepsy. The method used was essentially that described by Costall and Olley.[23] Groups of eight Olac–Wistar rats (180–190 g) were assessed for the presence of catalepsy at 0.5, 1, 1.5, 2, 3, 4, and 5 h after the oral administration of the compound. The front paws of each animal were placed on a wooden rod 1.5 cm in diameter suspended 7 cm above a table. The length of time the animal maintained this position was recorded up to a maximum of 20 min. Animals were considered to be noncataleptic if they removed their front paws from the bar within 10 s. Each cataleptic animal was assigned a score of from 0 to 5 depending on how long they maintained the imposed posture (0 = <10 s; 1 = 10 s–2.5 min; 2 = 2.5–5 min; 3 = 5–10 min; 4 = 10–20 min; 5 = >20 min). The maximum scores obtained for each animal, regardless of time after dosing, were summed, thus giving a maximum score of 40 for each group.

Dopaminergic Receptor Binding ([^{3}H]Spiperone). The assay was carried out in the striatum of the rat brain by using

the method described previously.[24]

Muscarinic Cholinergic Receptor Binding ([^{3}H]QNB). This assay was also carried out on male Olac rat brain by the method previously described.[4]

Anticonflict Behavior. The method used was as described by Tye et al.[25] and was based on that of Geller and Seifter.[26]

Male wistar rats, maintained on a 23-h food-deprivation schedule, but with water available ad libitum in the home cage, were trained in a standard rodent operant test chamber to press the left of two levers for food reward on a continuous reinforcement schedule. Once this had been mastered, the schedule of reinforcement was altered to a variable interval 30 s (VI_{30}) with limits of 5 and 55 s.

The animals were then trained on the multiple schedule comprising three components.

Component 1 (Reward). Nine minutes where lever pressing was reinforced according to the VI_{30} schedule. This period was signalled by illumination of the house light and each reinforced response by illumination of the food magazine light for 0.5 s.

Component 2 (Timeout). Three minutes during which lever pressing was not reinforced. This period was signalled by darkness.

Component 3 (Conflict). Three minutes during which every tenth response was reinforced (Fixed ratio 10) as well as punished (0.8 mA electric foot shock delivered through the grid floor for 0.5 s). This period was signalled by illumination of the house light and another three lights (one above each lever and one located centrally above the food magazine). As in the first component, reinforced responses were signalled by illumination of the magazine light for 0.5 s.

This sequence of three components was presented twice in the same order during the daily, 30-min test session. Animals were trained until stable rates of responding were achieved over several days. On test days the animals received the drug or vehicle, according to a predetermined randomized sequence, 60 min prior to behavioral testing. Differences in mean responses per min from control were analyzed by the Wilcoxan test and the statistical significance indicated where appropriate.

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Registry No. **4**, 122799-79-5; **5**, 122799-80-8; **6**, 79291-90-0; **7**, 79291-78-4; **8**, 79291-79-5; **9**, 79291-94-4; **10**, 79291-69-3; **11**, 79291-75-1; **12**, 79291-76-2; **13**, 79291-77-3; **14**, 122799-81-9; **15**, 122821-42-5; **16**, 79291-71-7; **17**, 122821-43-6; **18**, 79291-73-9; **19**, 79291-74-0; **20**, 79291-91-1; **21**, 79291-72-8; **22**, 79291-87-5; **23**, 79291-88-6; **24**, 79291-89-7; **25**, 122799-82-0; **26**, 79291-83-1; **27**, 122799-83-1; **28**, 79291-84-2; **29**, 122799-84-2; **30**, 79291-85-3; **31**, 79291-81-9; **32**, 122799-85-3; **33**, 79291-86-4; **34**, 122799-86-4; **35**, 122799-87-5; **36**, 79291-92-2; **37**, 79291-93-3; **38**, 122799-88-6; **39**, 122799-89-7; **40**, 122799-90-0; **41**, 122799-91-1; **42**, 79291-63-7; **42**·HCl, 79291-64-8; **43**, 122799-92-2; **44**, 122799-93-3; **45**, 122799-94-4; **46**, 31037-02-2; **47**, 21230-43-3; **48**, 21230-50-2; **49**, 90641-64-8; **50**, 122799-95-5; **51**, 122799-96-6; **52**, 2121-23-5; **53**, 122799-97-7; **54**, 122799-98-8; **55**, 122799-99-9; **56**, 122800-00-4; **57**, 16078-63-0; **58**, 122800-01-5; **59**, 34605-61-3; **60**, 122821-44-7; **61**, 74772-07-9; **62**, 122800-02-6; **63**, 74772-08-0; **64**, 79291-38-6; **65**, 79291-40-0; **66**, 79291-43-3; **67**, 79291-44-4; **68**, 79291-45-5; **69**, 122800-03-7; **70**, 122800-04-8; **71**, 79291-58-0; **72**, 122800-05-9; **73**, 79291-42-2; **74**, 122800-06-0; **75**, 79291-56-8; **76**, 79291-46-6; **77**, 79291-52-4; **78**, 122800-07-1; **79**, 79291-54-6; **80**, 122800-08-2; **81**, 79291-48-8; **82**, 122800-09-3; **83**, 79291-49-9; **84**, 122800-10-6; **85**, 79291-50-2; **86**, 79291-47-7; **87**, 122800-11-7; **88**, 79291-41-1; **89**, 79291-51-3; **90**, 122800-12-8; **91**, 122800-13-9; **92**, 122800-14-0; **93**, 122800-15-1; **94**, 79291-60-4; **95**, 122800-16-2; **96**, 122800-17-3; **97**, 122800-18-4; XIII (X = 7-F, R_1 = 2-Me), 122821-45-8; ethyl 3-aminopyrazole-4-carboxylate, 6994-25-8; 1-bromohexane, 111-25-1; 1,5-dimethyl-4-nitropyrazole-3-carboxylic acid, 3920-41-0; ethyl 4-nitro-1,5-dimethylpyrazole-3-carboxylate, 122800-19-5; 1,4-difluoro-2-nitrobenzene, 364-74-9; *N*-methylpiperazine, 109-01-3; 3-aminopyrazole-4-carbonitrile, 16617-46-2; 2-fluoronitrobenzene, 1493-27-2; 1,4-dichloro-2-nitrobenzene, 89-61-2; 1,2,4-trifluoro-5-nitrobenzene, 2105-61-5; 2,4-difluoro-1-nitrobenzene, 446-35-5; 1,3-dichloro-2-nitrobenzene, 601-88-7; 2,4-dichloro-1-nitrobenzene, 611-06-3; 1,2-dichloro-3-nitrobenzene, 3209-22-1; 1,2,4-trichloro-5-nitrobenzene, 89-69-0; 1,4-dibromo-2-nitrobenzene, 3460-18-2; 1-fluoro-4-iodo-2-nitrobenzene, 364-75-0; 2-fluoro-4-methyl-1-nitrobenzene, 446-34-4; 1-fluoro-2-nitro-4-(trifluoromethyl)-benzene, 367-86-2; (4-fluoro-3-nitrophenyl)phenylmethane, 82571-93-5; 1-fluoro-4-(methylsulfonyl)-2-nitrobenzene, 453-72-5; (bromomethyl)cyclopropane, 7051-34-5; 4-amino-1,3-dimethylpyrazole-5-carbonitrile, 32183-14-5; piperazine, 110-85-0.

Additions and Corrections

1987, Volume 30

Christopher B. Chapleo,* Peter L. Myers, Alan C. B. Smith, Ian F. Tulloch, and Donald S. Walter: Substituted 1,3,4-Thiadiazoles with Anticonvulsant Activity. 3. Guanidines.

Page 951. The list of authors should be as follows: Christopher B. Chapleo,* Peter L. Myers, Alan C. B. Smith, Ian F. Tulloch, Stephen Turner, and Donald S. Walter.

1988, Volume 31

Andre Rosowsky,* Henry Bader, Ronald A. Forsch, Richard G. Moran, and James H. Freisheim: Methotrexate Analogues. 31. Meta and Ortho Isomers of Aminopterin, Compounds with a Double Bond in the Side Chain, and a Novel Analogue Modified at the α-Carbon: Chemical and in Vitro Biological Studies.

Page 765. Right-hand column, line 7 and line 10, the concentrations should read 15–25 nM and 30–40 nM, respectively, and not 15–25 and 30–40 μM.

L. G. Humber,* E. Ferdinandi, C. A. Demerson, S. Ahmed, U. Shah, D. Mobilio, J. Sabatucci, B. De Lange, F. Labbadia, P. Hughes, J. DeVirgilio, G. Neuman, T. T. Chau, and B. M. Weichman: Etodolac, a Novel Antiinflammatory Agent. The Syntheses and Biological Evaluation of Its Metabolites.

Page 1715. The last sentence in paragraph 2 should read: The derivatized metabolite isolated from human urine was identical with **34**, isomer A, by HPLC and NMR comparisons.

Rajeshwar D. Bindal and John A. Katzenellenbogen*: Bis(4-hydroxyphenyl)[2-(phenoxysulfonyl)phenyl]-methane: Isolation and Structure Elucidation of a Novel Estrogen from Commercial Preparations of Phenol Red (Phenolsulfonphthalein).

Page 1978. The correct spelling for the first author's name is Rajeshwar D. Bindal.