ultimately, 1.03 g of diastereoisomer **5**, mp 237–239 °C. High-performance LC analysis of the product using the above mobile phase indicated that it was about 95% pure **5** contaminated with about 5% of **2**. Additional recrystallizations did not change this ratio.

Compound 5: NMR ($CDCl_3$; free base) δ 1.48–2.42 (9 H, m), 2.44–2.66 (2 H, m), 2.90–3.22 (3 H, m), 3.64 (1 H, d, J = 10 Hz), 4.68 (1 H, broadened t), 6.36–7.50 (11 H, m); MS m/e 452, 299, 285, 256, 243, 229, 210 (100%), 178, 165, 149; IR (KBr) 2.95, 3.76, 6.60, 6.76, 6.99, 7.95, 8.14, 8.46, 12.04, 12.16 μm; UV (CH_3OH) λ_{max} 243 nm (s) (log ε 6.029), 264 (8.582), 270 (8.115), 298 (s) (3.525). Anal. ($C_{27}H_{27}ON_2F_3$·HCl) C, H, N, Cl, F.

Synthesis of Diastereoisomeric L-Phenylalanine Esters. A solution of 2.40 g (5.3 mM) of racemic diastereoisomer **5** and 2.0 g (7.5 mM) of *N*-(*tert*-butoxycarbonyl)-L-phenylalanine in 80 mL of CH_2Cl_2 under an N_2 atmosphere was cooled in an ice bath. To the stirred solution was added 1.55 g (7.5 mM) of dicyclohexylcarbodiimide. The reaction mixture was then stirred for 1 h at 0–5 °C and for 1 h at room temperature. The resulting white solid was separated by filtration and washed with CH_2Cl_2. After removal of solvent from the filtrate, the residues were chromatographed on 40 g of EM Reagents 70–230 mesh silica gel, eluting with 5:1 CH_2Cl_2–ethyl acetate. The resulting product was 2.51 g of a white amorphous foam.

To this foam was added 30 mL of cold anhydrous trifluoroacetic acid (TFA). The reaction mixture was stirred in an ice bath for 30 min, at which time solution had occurred. The TFA was removed on a rotary evaporator without external warming of the flask. The residues were dissolved in cold CH_2Cl_2 and washed to neutrality with cold 1% aqueous $NaHCO_3$. The organic layer was dried with $MgSO_4$ and the solution was evaporated to a pale yellow gum (1.6 g), which was chromatographed on 40 g of EM Reagents 230–400 mesh silica gel using 35:1 ethyl acetate–CH_3OH as eluent. High-performance LC analysis of the two isolated one-spot diastereoisomeric esters utilizing a mobile phase consisting of EtOAc/CH_3OH in the ratio 97.5:2.5 (v/v) indicated that each was ≥98% pure. These samples weighed 636 and 474 mg, respectively, the disparity arising from discard of several overlapping fractions. These esters were not further characterized but were used directly in the next step.

Hydrolysis of Amino Esters to Enantiomers. A stirred solution of 625 mg of the L-phenylalanine ester of enantiomer **3** in 10 mL of CH_3OH at room temperature was treated with 10% aqueous NaOH until the solution turned cloudy and was then stirred for 30 min at room temperature. At this time, CH_3OH was removed by evaporation and 10 mL of water was added. The aqueous suspension was extracted with CH_2Cl_2, and the organic extracts were dried with $MgSO_4$. Evaporation of CH_2Cl_2 gave a pale yellow gum, which was dissolved in 5 mL of acetone and treated with an excess of ethereal HCl. The product crystallized in platelets from this solution: yield 388 mg; mp 266–267 °C; $[\alpha]^{23}_D$ +32.2° (*c* 1.67, CH_3OH). High-performance LC analysis of enantiomers derived from **2** showed diastereioisomeric purities of ≥98%. High-performance LC analysis of enantiomers derived from **5** showed diastereoisomeric purities of 97% for the levorotatory enantiomer and of 95% for the dextrorotatory enantiomer as a result of the 5% contamination of **5** with **2**. These last high-performance LC analyses were accomplished using the mobile phase developed for the mixture of **2** and **5** above.

Acknowledgment. The authors are grateful to Ms. S. Koch and C. Scott and M. Boucher for significant technical assistance, to Dr. B. M. Johnson and Ms. J. D. Gagliardo of the Pfizer Analytical Research Department for the high-performance LC analyses, and to Dr. B. W. Dominy of Pfizer Central Research for conducting the energy calculations.

Synthesis and Anxiolytic Activity of a Series of Pyrazino[1,2-*a*][1,4]benzodiazepine Derivatives

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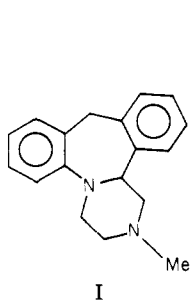
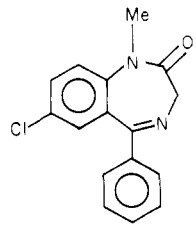
The synthesis and biological evaluation of some derivatives of pyrazino[1,2-*a*][1,4]benzodiazepines for anxiolytic and antidepressant activity are presented. Significant levels of anxiolytic activity were noted for 7-(*o*-chlorophenyl)-9-chloro-1,2,3,4,4a,5-hexahydro-3-methylpyrazino[1,2-*a*][1,4]benzodiazepine (**4b**).

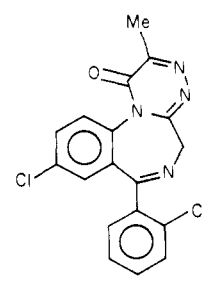
As part of a continuing search for a compound which has both anxiolytic and antidepressant properties, it was of interest to synthesize certain 7-substituted 1,2,3,4,4a,5-hexahydropyrazino[1,2-*a*][1,4]benzodiazepines. These structures combine features of the antidepressant mianserin (I)[1] and the benzodiazepine anxiolytic diazepam (II). It was anticipated that some anxiolytic activity would be retained, since benzodiazepines with additional fused rings, e.g., III, have been claimed to have potent anxiolytic properties.[2]



I



II



III

Accordingly, some 7-substituted 1,2,3,4,4a,5-hexahydropyrazino[1,2-*a*][1,4]benzodiazepines and further hydrogenated derivatives were synthesized.

Chemistry. The compounds were prepared as depicted in Scheme I. 1-(*p*-Chlorophenyl)-4-methyl-5-cyano-2,3-

(1) (a) A. Coppen, R. Gupta, S. Montgomery, K. Ghose, J. Bailey, B. Burns, and J. J. DeRidder, *Br. J. Psychiatry*, 129, 342–345 (1976); (b) P. J. Fell, D. C. Quantock, and W. J. van der Burg, *Eur. J. Clin. Pharmacol.*, 5, 166 (1973); (c) W. J. van der Burg, I. L. Bonta, J. Delobelle, C. Ramon, and B. Vargaftig, *J. Med. Chem.*, 13, 35 (1970).

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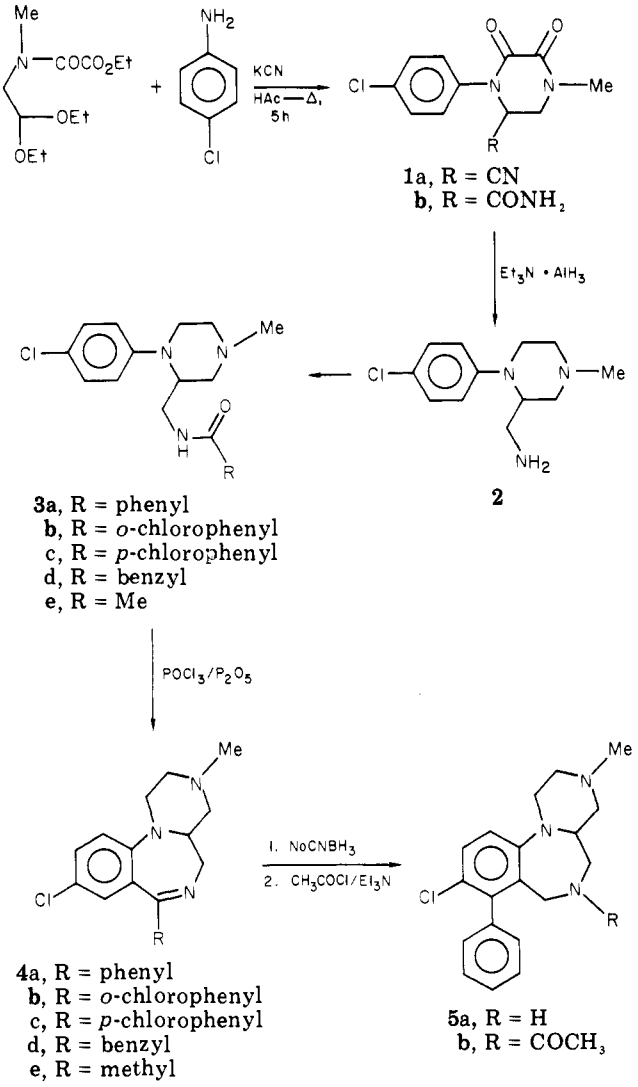
Scheme I



piperazinedione (**1a**) was obtained by heating ethyl *N*-(2,2-diethoxyethyl)-*N*-methyloxamate with *p*-chloroaniline and potassium cyanide in acetic acid. A small amount of the corresponding carboxamide derivative (**1b**) resulting from hydrolysis of the nitrile was observed. Reaction of **1a** with alane–triethylamine complex yielded [1-(*p*-chlorophenyl)-4-methyl-2-piperazinyl]methylamine (**2**). Attempted reduction of **1a** using (a) alane or (b) lithium aluminum hydride under a variety of conditions resulted in some dehalogenation as well as reduction. Acylation of **2** was accomplished by using the appropriate carboxylic acid chlorides to yield **3**, which cyclized smoothly when heated with a mixture of phosphorus oxychloride and phosphorus pentoxide to yield the desired 7-substituted 1,2,3,4,4a,5-hexahydropyrazino[1,2-*a*][1,4]benzodiazepines (**4**). Reduction of the 7-phenyl analogue (**4a**) with sodium cyanoborohydride afforded the 1,2,3,4,4a,5,6,7-octahydropyrazino[1,2-*a*][1,4]benzodiazepine (**5a**), which could be acetylated under standard conditions to the corresponding acetyl derivative (**5b**).

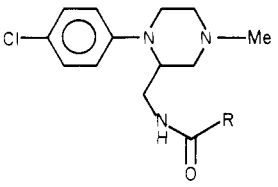
Pharmacology. The compounds were evaluated for anxiolytic activity by measuring their ability to bind to the diazepam receptor[3] and also their ability to reduce the incidence of metrazole-induced seizures in rats.[4] Measurement of antidepressant potential was assessed by the ability of the compounds to inhibit the uptake of norepinephrine and serotonin by crude synaptosomes from rat whole brain.[5] Potential neuroleptic activity was measured by the ability of the compounds to block the inhibition of tyrosine hydroxylase by apomorphine.[6]

Only compounds **4a** and **4b** had significant activity in the diazepam receptor assay, but the activity of **4b** was still significantly less than diazepam itself. In the rat metrazole assay only compound **4b** showed good activity. Similarly, in the amine-uptake screens, **4b** showed activity but considerably weaker than the standard agent, e.g., desipramine (DMI). **4c**, while devoid of activity in the above assays, showed some activity in the ApoTH screen but again only at relatively high concentration.

Compounds **4a** and **4e** showed significant activity as antihistamines in the "in vitro" inhibition of histamine activation of adenylate cyclase in guinea pig cerebral cortex.[7] Vesicles from a cell-free preparation of guinea pig cerebral cortex are preincubated with [^{3}H]adenine to form endogenous [^{3}H]ATP. The vesicles are then incubated with 50 μM histamine in the absence and in the presence of test compound.

Biological activity and physical data for the compounds are summarized in Table II.

Table I. 2-[(Acylamino)methyl]-1-(*p*-chlorophenyl)-4-methylpiperazines



no.	R	mp, °C	formula	anal.	% yield
3a	Ph	136–137	$C_{19}H_{22}ClN_3O$	C, H, N	48
3b	*o*-Cl-Ph	152–153	$C_{19}H_{21}Cl_2N_3O$	C, H, N	56
3c	*p*-Cl-Ph	134–136	$C_{19}H_{21}Cl_2N_3O$	C, H, N	61
3d	Bzl	167–168	$C_{20}H_{24}ClN_3O$	C, H, N	50
3e	Me	145–146			60

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The IR and NMR data were consistent for the assigned structures. Analyses for C, H, and N were within ±0.4% of the theoretical values.

1-(***p*-Chlorophenyl**)-4-met**hyl-5-cyano-2,3-piperazinedione** (1a). A solution of *p*-chloroaniline (2.8 g, 0.022 mol), KCN (1.56 g, 0.024 mol), and ethyl *N*-(2,2-diethoxyethyl)-*N*-methyloxamate (4.96 g, 0.02 mol) in acetic acid (40 mL) and water (20 mL) was heated at reflux temperature for 5 h. The reaction mixture was then diluted with water. The crude solids thus obtained were filtered and washed with ether. The product was recrystallized from MeOH (40 mL) to yield the desired piperazine (43%): mp 233–235 °C; NMR (CF_3COOD) δ 3.6 (s, 3 H, N-Me), 4.3 (AB quartet, 2 H), 5.16 (t, 1 H), 7.67–7.24 (m, 4 H, aromatic H). Anal. ($C_{12}H_{10}N_3O_2Cl$) C, H, N.

When the crude solids containing 1a above were dissolved in acetonitrile using a Soxhlet extractor, **1b** was obtained as an insoluble residue in small yield, mp 289–291 °C. Anal. ($C_{12}H_{12}ClN_3O_3$) C, H, N.

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Table II. 7-Substituted Pyrazino[1,2-*a*][1,4]benzodiazepines

compd	R	mp, °C	recrystn solvent	% yield	formula[a]	diazepam receptor binding[c]	rat metrazole[d]	histamine-activated adenylate cyclase[e]	reuptake inhibn[f] NE	reuptake inhibn[f] 5HT	ApoTH[g] (drug concn, μM)
4a	Ph	221–222	Me_2CO–Et_2O	89	$C_{19}H_{12}ClN_3 \cdot 1.5C_4H_4O_4$	9	inact	9			
4b	*o*-Cl-Ph	201–202	Me_2CO–Et_2O	97	$C_{19}H_{11}Cl_2N_3 \cdot C_4H_4O_4$	0.8	5.65	30	30	45	
4c	*p*-Cl-Ph	225–226	Me_2CO–Et_2O	97	$C_{19}H_{11}Cl_2N_3 \cdot 1.5C_4H_4O_4$	>100	inact	>50			10 (10)
4d	Bzl	113–115		38	$C_{20}H_{22}ClN_3 \cdot 1.5C_4H_4O_4$[b]	>100	inact	>50			
4e	Me	167–168	Me_2CO–Et_2O	75	$C_{14}H_{18}ClN_3 \cdot C_4H_4O_4$	>100	inact	5			
5a	H	*h*	Me_2CO–Et_2O	95		>100	inact	>50			
5b	Ac	210–211	Me_2CO	88	$C_{22}H_{24}ClN_3O \cdot C_4H_4O_4$	>100	inact				
haloperidol						0.005					28 (0.1)
diazepam											23 (1)
mianserin							inact	0.19	36	35	
desimipramine								10.5	0.08	6.5	
clomipramine								4.4	9.5	0.75	

[a] Unless otherwise indicated, C, H, N analyses were within ±0.4% of the theoretical values where molecular formulas are given. [b] N: calcd, 8.18; found, 8.81. [c] IC_{50}, μM. [d] Results expressed as ED_{50} po or at a standard dose of 30 mg/kg po. [e] Results expressed as IC_{50}, μM. [f] IC_{50}, μM. [g] Results expressed as percent of apomorphine (Apo) inhibition of tyrosine hydroxylase (TH) at various drug concentrations. [h] Amorphous.

[1-(*p*-Chlorophenyl)-4-methyl-2-piperazinyl]methylamine (2). To a cold solution of alane–triethylamine complex in benzene (350 mL of a 1.07 M solution) in dry THF (1 L) was added a mixture of **1a** and **1b** (20.98 g, 0.08 mol). The reaction mixture was stirred at room temperature for 16 h and then heated to reflux temperature for an additional 1.5 h. The reaction was quenched with 1:1 THF/H_2O (46 mL) and then with NaOH (18.5 g) in H_2O (140 mL), followed by extraction with toluene (2 × 125 mL). The combined toluene extracts were evaporated under reduced pressure to yield the product **2** (17.0 g, 89%), which was an oil, and used in the next step without further purification: NMR ($CDCl_3$) δ 1.1 (s, 2 H, NH_2), 2.26 (s, 3 H, NCH_3), 2.32–3.34 (m, 8 H, methylenes), 3.54 (m, 1 H, CH), 6.68–7.32 (m, 4 H, aromatic H); MS *m/e* 239 (M^+). Anal. ($C_{12}H_{18}ClN_3$) C, H, N.

2-[(Acylamino)methyl]-1-(*p*-chlorophenyl)-4-methylpiperazines (3). The amides shown in Table I were prepared by acylation of the amine **2** with the appropriate acid chloride in methylene chloride with excess triethylamine. The products were recrystallized from methylene chloride–ether.

7-Substituted 9-Chloro-1,2,3,4,4a,5-hexahydro-3-methylpyrazino[1,2-*a*][1,4]benzodiazepines (4). A typical cyclization example was as follows: **3a** (5.68 g, 0.0165 mol) was added to a mixture of $POCl_3$ (65 mL, 0.71 mol) and P_2O_5 (23.4 g, 0.17 mol). The reaction was heated at reflux temperature for 16 h and then poured into a mixture of 4 N HCl (412 mL) and ice (412 g). After 30 min, the mixture was basified with 50% NaOH solution and then extracted with CH_2Cl_2 (2 × 100 mL). The combined extracts were washed with H_2O, dried ($MgSO_4$), and evaporated to dryness under reduced pressure to yield an amorphous foam. The residue (4.79 g, 89%) was dissolved in methanol (100 mL) and converted to its fumarate salt, which was recrystallized from a mixture of Me_2CO–Et_2O: mp 221–222 °C; NMR ($CDCl_3$) δ 2.30 (s, 3 H, NCH_3), 2.42–3.92 (m, 9 H, methylenes), 6.83–7.68 (m, 8 H, aromatic H); MS *m/e* 325 (M^+).

7-Substituted 9-Chloro-1,2,3,4,4a,5,6,7-octahydro-3-methylpyrazino[1,2-*a*][1,4]benzodiazepines (5). A. To a cooled solution of **4a** (6.46 g, 0.02 mol) in glacial HOAc (75 mL) was added $NaBH_3CN$ (0.04 mol) in small portions. The reaction was stirred at room temperature for 18 h, then concentrated to a small volume, basified with 3 N NaOH solution, and extracted with ether. The ethereal extracts were dried over anhydrous $MgSO_4$ and filtered, and the solvent was evaporated under reduced pressure to yield **5a** as an amorphous solid.

B. A solution of **5a** (3.08 g) in dry CH_2Cl_2 (50 mL) was treated with Et_3N (2.61 mL) and Ac_2O (1.33 mL), and the mixture was heated at reflux temperature for 16 h. On cooling to room temperature, the reaction mixture was washed with dilute NaOH and extracted with CH_2Cl_2. The CH_2Cl_2 extracts were dried over anhydrous $MgSO_4$, filtered, and evaporated to dryness under reduced pressure to yield **5b**, which was converted to its fumarate salt: mp 210–211 °C; NMR ($CDCl_3$) 1.94 (s, 1 H, exchangeable), 2.1–3.34 (m, 9 H, methylenes), 2.37 (s, 3 H, NCH_3), 5.19 (s, $^1/_3$ H, benzyl), 5.75 (s, $^2/_3$ H, benzyl), 6.45–7.58 (m, 8 H, aromatic). Anal. ($C_{21}H_{24}ClN_3O \cdot C_4H_4O_4$) C, H, N.

Biological Methods. Diazepam Binding. Crude synaptosomal membranes were prepared as described by Braestrup and Squires.[3] Binding was assayed by a slight modification of the procedure of Möhler and Okada.[7] Aliquots of the crude synaptosomal membrane suspension (0.5 mL, equivalent to 10 mg of original tissue) were added to tubes (on ice) containing [^{3}H]-diazepam (*methyl*-^{3}H, New England Nuclear, 39 Ci/mmol) plus or minus test compound in 50 mM Tris-HCl, pH 7.5. The final volume was 1 mL; the final concentration of [^{3}H]diazepam was 2.0 nM. Test compounds were present over a wide concentration range; triplicate tubes were included at each concentration.

Specific binding was defined as the difference between total binding and binding in the presence of 1 μM unlabeled diazepam. The IC_{50} values (concentrations of test compounds required to inhibit the specific binding of 2.0 nM [^{3}H]diazepam by 50%) were determined graphically.

Metrazol Seizures.[4] Male CRW (Wistar) rats weighing 130–200 g were fasted for 18 h but allowed water ad libitium prior to testing. The test agents as a suspension in the standard 3% corn starch vehicle were administered in a dose volume of 10 mg/kg per gram of body weight. A protective effect against metrazol (24 mg/kg iv) given 90 min later was evidenced by failure

of the animals to exhibit clonic seizures.

Effects on the Uptake of Norepinephine and Serotonin by Crude Synaptosomes. Experiments were performed with crude preparations of synaptosomes from rat whole brain. The procedure of Thornberg and Moore[5] was followed with minor modifications. Incubations were carried out for 5 or 15 min with L-[^{3}H]norepinephrine (20 or 21.2 nM unless otherwise specified) or [^{3}H]serotonin (9.2–14 nM unless otherwise specified). The test compounds were dissolved in ethanol; the final concentration of ethanol in the assay mixture was 1% (v/v).

Effect on Apomorphine Inhibition of Tyrosine Hydroxylase in Synaptosomes. These experiments were conducted essentially according to the protocol described by Bronaugh and co-workers.[6] Percent prevention of apomorphine (Apo) inhibition was calculated according to Christiansen and Squires[8] as follows:

(% of control act. with test compd and Apo − % of control act. with Apo)/ (% of control act. with test compd in the absence of Apo − % of control act. with Apo) × 100

Effects on Histamine-Activated Adenylate Cyclase Preparations. Guinea pig cerebrum or hippocampus particles were prepared, prelabeled with [2-^{3}H]adenine, and activated with histamine (50 μM), 2-methylhistamine (200 μM), or 4-methylhistamine (100 or 200 μM) essentially as described by Chasin et al.[9] The test drugs were added at concentrations ranging from 0.01 to 100 μM. Quantitation of cyclic AMP was based on the procedure of Krishna et al.[10] The percent inhibition by test compounds was calculated after subtraction of the basal value for formation of cyclic AMP.

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Nitrobenzyl Halides and Carbamates as Prototype Bioreductive Alkylating Agents

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o-Nitrobenzyl and *p*-nitrobenzyl alcohols, halides, and N-substituted carbamates were prepared as potential bioreductive alkylating agents, and first half-wave reduction potentials of these compounds were measured by differential pulse polarography. The cytotoxicities of these agents were examined by determining the colony-forming ability of EMT6 tumor cells following exposure to each agent at concentrations of 0.01 to 500 μM for 1 h at 37 °C under conditions of normal aeration and chronic hypoxia. The *o*-nitrobenzyl compounds were significantly more cytotoxic to hypoxic cells than to oxygenated cells. This selective cytotoxicity is hypothesized to result from alkylation following more efficacious bioreductive activation of these compounds by hypoxic cells. Nitrobenzyl compounds with such selective toxicity to hypoxic neoplastic cells may prove to be particularly valuable in combination therapy designed for the treatment of solid tumors.

The cellular subpopulations in solid tumors are physiologically more heterogeneous with respect to the degree of oxygenation and rate of proliferation than are the cellular components of hematological or particularly well-vascularized tumors. With respect to these considerations, a solid neoplastic mass may be envisioned to consist of at least four classes of malignant cells: cells which are well-oxygenated, relatively rapidly traversing the cell cycle and which may correspond in drug sensitivities to exponentially growing cells in culture; nonproliferating oxygenated cells which may correspond in susceptibility to chemotherapeutic agents to plateau phase cells in culture; and cells in various degrees of hypoxia. The hypoxic cell population may be composed of cells with either relatively normal or prolonged cell cycle times or may be blocked in their progression through the cell cycle. The hypoxic cell compartment contains viable neoplastic stem cells which are capable of reentering the rapidly proliferating cellular pool of the tumor. It is well-established that hypoxic cells are relatively resistant to the cytotoxic effects of ionizing radiation, and, since hypoxic cells may be either noncycling or slowly progressing through the cell cycle, they are also presumed to be relatively resistant to cell cycle specific chemotherapy. Thus, the hypoxic cell population has the capacity to limit the curability of solid tumors, and, for this reason, agents directed specifically against hypoxic cells would appear to have considerable potential in cancer therapy in combination with other agents or treatment modalities designed to erradicate the other cellular classes that may be present.[1]

The nitroheterocyclic radiosensitizers were first examined because of their ability to sensitize hypoxic cells to the lethal effects of ionizing radiation.[2] These compounds also have been shown to be selectively cytotoxic to hypoxic cells;[3-13] this differential toxicity appears to depend upon the preferential reductive activation of the nitro-

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