Synthesis and Antitumor Activity of a New Class of Pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepinone Analogues of Pyrrolo[1,4][2,1-*c*]benzodiazepines

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A new class of pyrrolo[1,4]benzodiazepine (PBD) analogues featuring a pyrazolo[4,3-*e*]pyrrolo-[1,2-*a*][1,4]diazepinone ring system has been designed and synthesized. These compounds, **2a–o**, are characterized by the substitution of the aromatic A ring, characteristic of the PBDs, with a disubstituted pyrazole ring bearing alkyl and benzyl substituents at N_6 or N_7 and alkyl or carbomethoxy substituents at C_8. Biological evaluation revealed an appreciable *in vitro* cytotoxic activity for compounds **2a,b,f–i**.

Introduction

The pyrrolo[2,1-*c*][1,4]benzodiazepine (PBD) family of antitumor antibiotics includes members such as anthramycin, tomaymycin, sibiromycin, neothramycin A and B, chicamycin, and DC-81.[1–3] These antibiotics exert their biological activity by reacting covalently in the minor groove of DNA to form an aminal linkage between the electrophilic carbinolamine present at the C_{11} position and the N_2 of guanine.[1a,4] The PBDs are not only specific for N_2 of guanine, but are only reactive toward guanines in certain sequences, and therefore show sequence selectivity. The greatest binding preference is found for 3′-Pu-G-Pu sequences (Pu = purine; G = guanine) while the lowest selectivity is observed for a guanine flanked by two pyrimidines (Py-G-Py, Py = pyrimidine). Intermediate behavior is observed for guanines placed between a purine and a pyrimidine.[5,6]

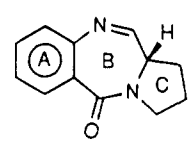
In the case of anthramycin and tomaymycin, the precise structure of the drug–DNA adducts have been elucidated.[1a] Recent studies performed with C_7-linked[7] and C_8-linked[8a,b] dimeric PBD analogues have demonstrated that the C_8-linked analogues are highly efficient irreversible DNA interstrand cross-linking agents with enhanced sequence specificity.

Although anthramycin has the best antitumor activity within the PBD family, it produces cardiotoxicity and tissue necrosis which have precluded its clinical application.[9] The PBD cardiotoxicity mechanism is very similar to that of the anthracyclines, and it appears to be related to the formation of *o*-quinone imine species by oxidation.[2]

A rational approach to the development of clinically useful drugs in this series has been proposed,[2] and a number of workers have investigated synthetic methodologies for the preparation of rationally designed analogues in order to establish more complete structure–activity relationships.[10,11] The scope for improvement of the antitumor profile of many naturally-occurring and synthetic analogues of the PBDs encouraged us to undertake a program devoted to the design of new analogues.

We have recently reported[12] some preliminary studies on heterocyclic PBD analogues in which the A ring of the PBD skeleton 1 is replaced with a 1,3- or 1,5-disubstituted pyrazole nucleus of type **2a,b**. These compounds, according to the CPK model proposed by Thurston and Hurley,[2] contain all the structural requirements necessary for antitumor activity, including the carbinolamine group required for covalent binding to DNA. Moreover, preliminary modeling studies suggested that this structural modification to the A ring should still allow steric superimposition of the molecules on the equivalent PBD analogues and lead to possible DNA binding.[13] Biological evaluation of these new pyrazolic PBD analogues revealed an appreciable *in vitro* antitumor activity in L1210 cells for some compounds (e.g., $IC_{50} = 0.5\ \mu M$ for **2g**) that has encouraged further investigations.

In this paper, we provide details of the synthesis of the previously reported novel pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepininone tricyclic system (**2**), by two different routes. This has allowed the preparation of several pyrazolic PBD analogues (**2a–o**) bearing different substituents at the N_6, N_7, and C_8 positions. All the new analogues have been evaluated for antitumor activity.



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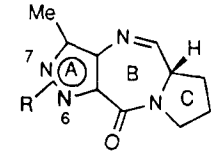

2a,b

a : R = N6-Me
b : R = N7-Me

Chemistry

In a preliminary communication,[12a] we investigated a synthetic route to **2a,b** based on Kaneko's Al/Hg reduction of an imino thioether functionality.[14] This involved a two-step sequence starting from the appropriate dilactam which included: (i) thiation with Lawesson's reagent and (ii) methylation of the thioamides with methyl iodide in the presence of potassium

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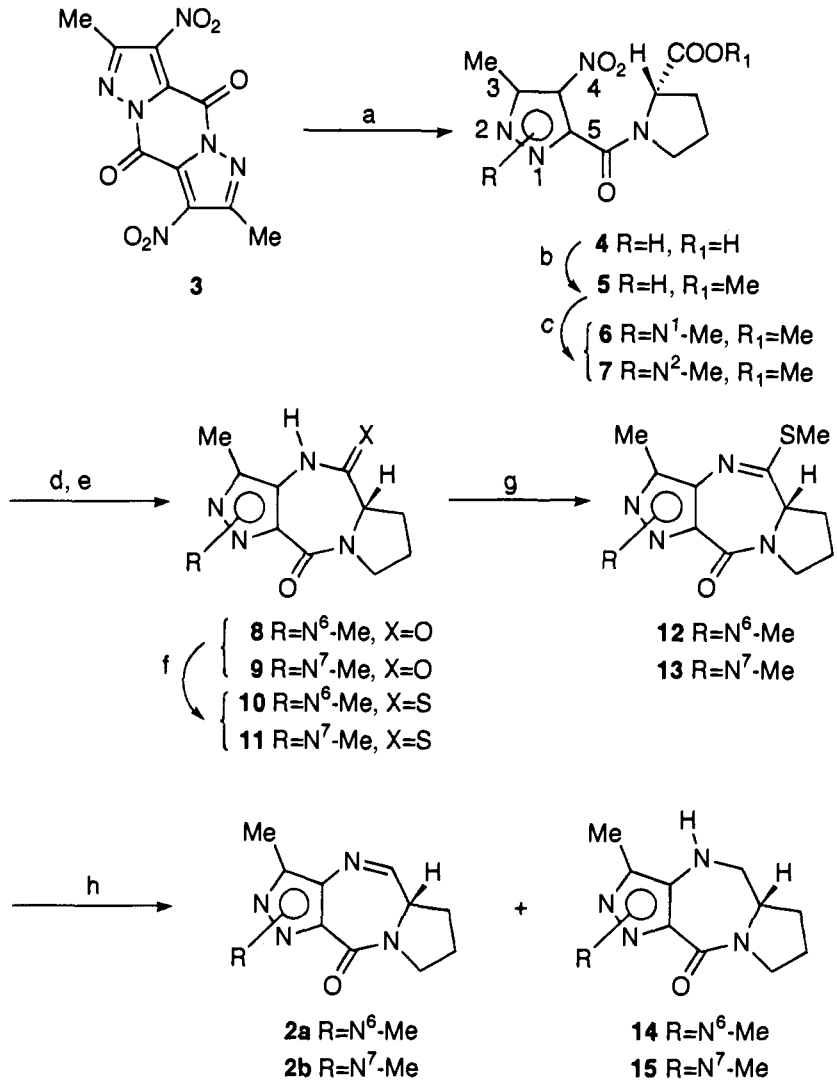
Scheme 1[a]



[a] (a) L-Proline, TMG; (b) MeOH, H^+; (c) MeI, MeONa; (d) $TiCl_3$; (e) MeONa; (f) Lawesson's reagent; (g) MeI, K_2CO_3, THF; (h) Al/Hg, THF/H_2O, 0 °C.

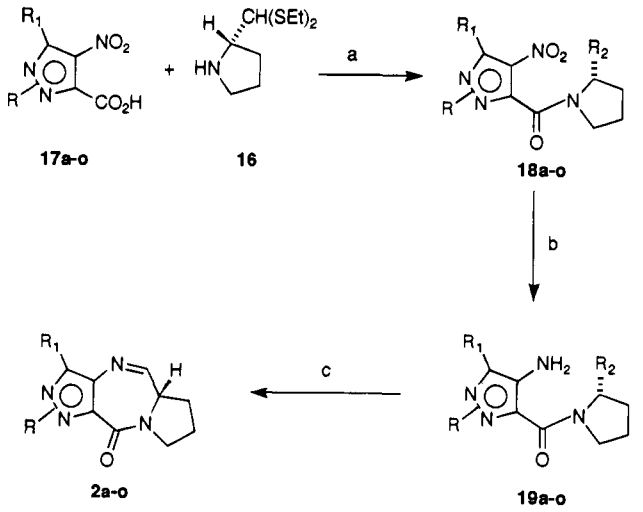
carbonate. This synthetic route suffers from some drawbacks[10,14b] such as the Al/Hg reduction of imino thioethers which requires long reaction times (0 °C, 20 h) and the contamination of the final product with variable amounts (15–20%) of the saturated N_{10}–C_{11} amine product derived from overreduction of the imino thioether which requires tedious silica gel chromatographic purification (Scheme 1).

The synthesis of **2a,b** as depicted in Scheme 1 began by coupling the readily available diketopiperazine **3** with L-proline in a 1:1 mixture of DMF–water in the presence of tetramethylguanidine to afford the acid **4** in good yield,[15] which was in turn converted into the ester **5**. Alkylation of **5** with methyl iodide in the presence of a methanolic solution of sodium methoxide gave a 1:1 mixture of the corresponding 1,3-dimethyl and 1,5-dimethyl derivatives **6** and **7**. After chromatographic separation, the pure nitro derivatives **6** and **7** were both reduced with aqueous $TiCl_3$ in methanol solution and cyclized *in situ* by sodium methoxide to give the corresponding dilactams **8** and **9** in good overall yield. In order to introduce the imine functionality in the 1,4-diazepine ring of **8** and **9**, the method developed by Kaneko *et al.* was employed that involves the aluminum amalgam reduction of imino thioethers. Thiation of the secondary amide function of **8** and **9** was achieved selectively with Lawesson's reagent to give the thioamides **10** and 11 which were in turn methylated to give the corresponding imino thioethers **12** and **13** in reasonable yield. Treatment of **12** and **13** with Al–Hg amalgam in aqueous THF at 0–5 °C for 24 h gave a mixture of products which, after purification, led to the target compounds **2a** (35%) and **2b** (42%) along with minor amounts of the overreduction products **14** (15%) and **15** (12%). Compounds **2a** and **2b** were unambiguously established to be in the imine forms by ^1H and ^{13}C NMR spectroscopy.

During these studies we also attempted to apply the recent procedure reported by Mori *et al.*[16] to prepare carbinolamine compounds *via* $NaBH_4$ reduction of the N_{10}-methoxymethyl-protected dilactams prepared by alkylation of **8** and **9** with methoxymethyl chloride in the presence of sodium hydride. In our hands, this reduction procedure did not work either under the reported conditions or under other variations.

In order to gain more direct access to pyrazolic PBD analogues, another convergent synthetic route recently reported by Thurston *et al.*[10,11a] was investigated. This utilizes (2*S*)-pyrrolidine-2-carboxaldehyde diethyl thioacetal (**16**) as a building block accessible in bulk starting from L-proline[17] (Scheme 2). This approach has demonstrated great synthetic potential for the preparation

Scheme 2[a]



[a] Reagents: (a) $(COCl)_2$, benzene; TEA, THF; (b) $SnCl_2 \cdot 2H_2O$, MeOH, reflux; (c) $HgCl_2$, $CaCO_3$, $MeCN/H_2O$.

of pyrazole PBD analogues.[12a,b] After coupling of the appropriate *o*-nitropyrazolecarboxylic acids **17a–o** and **16**, this method allowed an efficient conversion to carbinolamine-containing compounds in two high-yielding steps. The sequence involved reduction of the nitro group to an amino functionality under nonhydrogenolytic conditions to give **19a–o** (stannous chloride dihydrate in refluxing methanol), followed by deprotection of the aldehyde under mild and nonracemizing conditions (mercuric chloride and calcium carbonate in acetonitrile/water at room temperature) to afford the imino derivatives **2a–o**.

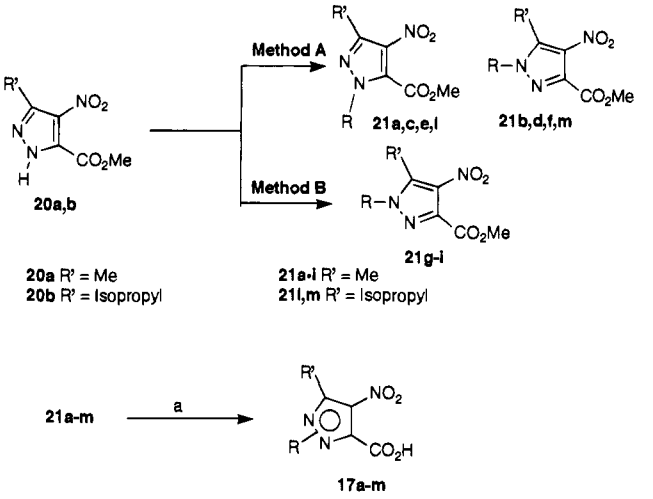
The pyrazolecarboxylic acids **17a–m** were readily prepared starting from the corresponding methyl 3-alkyl-4-nitropyrazole-5-carboxylic acids **20a,b**, through alkylation with the appropriate alkyl halide in the presence of sodium methoxide (method A) or sodium hydride (method B). Under the latter conditions, the methyl 1-substituted-5-methyl-4-nitropyrazole-3-carboxylates were generally isolated as single isomers (N_2 isomer, **21g–i**), whereas with sodium methoxide approximately equimolar mixtures of both N_1 and N_2 alkylated isomers were obtained (**21a–f,l,m**) which could be separated chromatographically. The alkylation site for compounds **21a–m** was unambiguously assigned through ^1H and ^{13}C NMR spectrometry analysis based on previous experience.[18] The N_1 and N_2 isomers **21a–m** were readily hydrolyzed with potassium hydroxide at room temperature to afford the required *o*-nitropyrazolic acids **17a–m** (Scheme 3) (Table 1).

The pyrazolic acids **17n** and **17o** were prepared according to a recent literature procedure,[19] involving alkaline and acid partial hydrolysis, respectively, of the dimethyl 1-methyl-4-nitro-3,5-pyrazoledicarboxylic acid ester, obtained through oxidation of 3-methyl-4-nitropyrazole-5-carboxylic acid with $KMnO_4$ followed by esterification and N-methylation.

After having unambiguously assigned the structures of the nitropyrazolic acids **17a–o**, analogues **2a–o** were prepared. Coupling of the acyl chlorides, readily prepared by treatment of the corresponding acids **17a–o** with oxalyl chloride at room temperature, with (2*S*)-pyrrolidine-2-carboxaldehyde diethyl thioacetal **16** in THF solution in the presence of triethylamine gave the corresponding (2*S*)-*N*-(nitropyrazolyl)prolines **18a–o** in good yield. These intermediates were reduced by refluxing for 1–2 h with stannous chloride dihydrate in methanol to give the corresponding amino diethyl thioacetals **19a–o** in nearly quantitative yield. Deprotection of the thioacetals **19a–o** resulting in cyclization to the final compounds **2a–o** was effected by treatment at room temperature with mercuric chloride and calcium carbonate in acetonitrile/water. In accordance with the work of Thurston *et al.*,[10,11a] compounds **2a–n** were always isolated in the imine form because the workup procedure involved chloroform extraction (Table 2). Only compound **2o** was isolated as the carbinolamine ethyl ether due to the addition of ethanol during chromatographic purification.

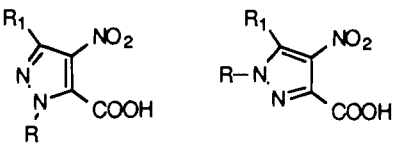
In view of their complex ^1H and ^{13}C NMR spectra, the structures of **18a–o** were confirmed by countersynthesis. DIBAL reduction of the nitro ester **6** produced the nitro aldehyde **22**, which was then converted into the nitro diethyl thioacetal (**18a**) using ethanethiol and trimethylsilyl chloride in chloroform. These compounds were identical to those prepared by the previous route (Scheme 4).

Scheme 3[a]



[a] (a) KOH, H_2O, MeOH.

Table 1. Physical and Chemical Data for Pyrazolecarboxylic Acids **17a–n**

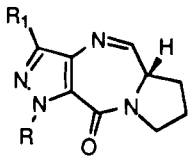


17a,c,e,l,n **17b,d,f-i,m,o**

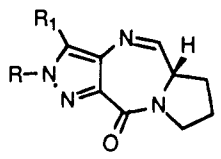
compd	R_1	R	yield (%)	mp (°C)[a]	mol wt	formula[b]
17a	Me	Me	66	170	185.1	$C_6H_7N_3O_4$
17b	Me	Me	78	145	185.1	$C_6H_7N_3O_4$
17c	Me	Et	81	71	199.1	$C_7H_9N_3O_4$
17d	Me	Et	86	149	199.1	$C_7H_9N_3O_4$
17e	Me	CH_2Ph	69	183	261.2	$C_{12}H_{11}N_3O_4$
17f	Me	CH_2Ph	85	133	261.2	$C_{12}H_{11}N_3O_4$
17g	Me	$4ClPhCH_2$	57	185	295.6	$C_{12}H_{10}N_3O_4Cl$
17h	Me	$4\text{-}MeOPhCH_2$	45	126	291.2	$C_{13}H_{13}N_3O_5$
17i	Me	$3,4\text{-}(Me)_2PhCH_2$	47	110	289.2	$C_{14}H_{15}N_3O_5$
17l	$CH(Me)_2$	CH_2Ph	79	148	289.2	$C_{14}H_{15}N_3O_4$
17m	$CH(Me)_2$	CH_2Ph	65	167	282.2	$C_{14}H_{15}N_3O_4$
17n	COOMe	Me	75	150	229.1	$C_7H_7N_3O_6$
17o	COOMe	Me	67	190	229.1	$C_7H_7N_3O_6$

[a] Crystallization solvent: ethyl acetate/petroleum ether. [b] Analytical data for C, H, N were within ±0.4% of the theoretical value for all compounds.

Table 2. Physical and Chemical Data for **2a–o**



2a,c,e,l,n

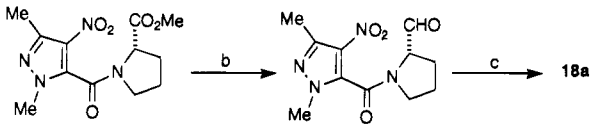


2b,d,f-i,m,o

compd	R_1	R	yield (%)	mp (°C)[a]	mol wt	formula[b]
2a	Me	Me	95	oil	218.2	$C_{11}H_{14}N_4O$
2b	Me	Me	30	139	218.2	$C_{11}H_{14}N_4O$
2c	Me	Et	53	oil	232.2	$C_{12}H_{16}N_4O$
2d	Me	Et	27	oil	232.2	$C_{12}H_{16}N_4O$
2e	Me	CH_2Ph	62	oil	294.3	$C_{17}H_{18}N_4O$
2f	Me	CH_2Ph	52	oil	294.3	$C_{17}H_{18}N_4O$
2g	Me	$4ClPhCH_2$	47	128	328.8	$C_{17}H_{17}N_4OCl$
2h	Me	$4\text{-}MeOPhCH_2$	24	121	324.3	$C_{18}H_{20}N_4O_2$
2i	Me	$3,4\text{-}(Me)_2PhCH_2$	39	115	322.4	$C_{19}H_{22}N_4O$
2l	$CH(Me)_2$	CH_2Ph	42	oil	322.4	$C_{19}H_{22}N_4O$
2m	$CH(Me)_2$	CH_2Ph	75	130	322.4	$C_{19}H_{22}N_4O$
2n	COOMe	Me	88	oil	262.2	$C_{12}H_{14}N_4O_3$
2o	COOMe	Me	67	150	308.3	$C_{14}H_{20}N_4O_4$[c]

[a] Crystallization solvent: ethyl acetate/petroleum ether. [b] Analytical resutls for C, H, N were within ±0.4% of the theoretical value for all compounds. [c] Compound **2o** was isolated as carbinolamine ethyl ether.

Scheme 4[a]



6 **22** **18a**

[a] (b) Dibal; (c) EtSH, Me_3SiCl.

Evaluations

All the synthesized compounds **2a–o** were evaluated for *in vitro* cytotoxicity in L1210, L1210/L-PAM, LoVo, and LoVo/DX cell lines. The cytotoxicity data and the relative ratio indices, expressed as IC_{50} values for resistant versus sensitive lines, are reported in Table 3 along with the activity of reference compounds doxorubicin, tomaymycin (methyl ether), melphalan (L-PAM), and DC-81.

Results and Discussion

The rationale behind the synthesis of the heterocyclic analogues reported here has been to design molecules with the following features: (i) a possibly higher binding affinity and modified sequence selectivity for the DNA minor groove, due to the potential new hydrogen bonds that might occur between the A-ring atoms and DNA bases; (ii) a reduced cardiotoxicity due to the impossibility of C_9-quinone formation as occurs with anthramycin.

As is shown in Table 3, the most interesting molecules among those synthesized are **2b**, **2d**, and **2f–i**. These compounds feature an imine (—N=CH—) at N_{10}–C_{11}, and the presence of different substituents on the pyrazole ring, such as substitution at C_8 with a methyl group and substitution at N_7 with alkyl moieties (**2b** has a methyl group and **2f–i** benzyl or benzyl-substituted groups). Among the most cytotoxic compounds containing the pyrazole ring, it is interesting to note that (1) substitution at N_7 (**2b**, **2d**, **2f–i**) increases cytotoxicity with respect to the N_6-substituted compounds (**2a**,**2c**,**2e**) in L1210 and L1210/L-PAM cell lines; (2) the N_7-benzyl or N_7-substituted benzyl compounds (e.g., **2f**, **2g**, **2i**) are similar or superior to N_7-methyl- or -ethyl-substituted compounds (e.g., **2b**, **2d**) in term of cytotoxicity; (3) with the same substituent at N_6 (**2a** and **2n**), replacement of the C_8-methyl group (**2a**) with a carboxy methyl ester (**2n**) does not increase cytotoxicity; (4) in the L1210 cell line, the introduction of a sterically demanding substituent at C_8 (e.g., isopropyl, **2m**) leads to a decrease in cytotoxicity compared to the C_8-methyl compound (**2f**). In general, the compounds **2b**, **2d**, **2f–i** show a cytotoxicity in the L1210 cell line comparable and in same cases better than the reference standard L-PAM.

However, all of these analogues are significantly less potent than the reference PBD compounds, tomaymycin methyl ether, and the anthracycline doxorubicin, although, it is interesting that compounds **2d**, **2g**, **2i**, **2m** appear to be able to overcome the resistance induced by doxorubicin in the LoVo cell line (LoVo/DX).

In conclusion, these structure–activity relationship studies suggest that for PBD pyrazole analogues of this type, the presence of an unsubstituted imine at N_{10}–C_{11} is required for cytotoxicity (e.g., compounds **12–15** are inactive). For maximum cytotoxicity, the pyrazole ring should be preferably substituted with a benzyl group at N_7 and with a methyl group at C_8.

However, more importantly, with the exception of analogue **2g**, the relative loss of cytotoxicity of these pyrazole analogues compared to DC-81 (IC_{50} = 0.38 μM, Table 3) suggests that this type of modification to the A ring may not be a suitable means to enhance the cytotoxicity of the pyrrolobenzodiazepines. This observation, coupled with the significant difference in cytotoxicity between DC-81 (IC_{50} = 0.38 μM) and tomaymycin methyl ether (IC_{50} = 0.012 μM), suggests that the C ring of the PBDs may be more important in influencing the degree of cytotoxicity than the A ring. Although the DNA binding of these analogues has not yet been investigated, the fact that cytotoxicity can be maintained (e.g., **2g**) on moving from a benzo to a pyrazole A ring should encourage the search for other types of PBD analogues that include a heterocyclic A ring.

Experimental Section

Chemistry. Melting points were determined with a Büchi capillary melting point apparatus and are uncorrected. Bakerflex plates (silica gel IB2-F) were used for TLC. Column chromatography (flash) was performed using the indicated solvent mixture (v/v) on Kieselgel 60 (60–200 mesh) supplied by E. Merck. Nuclear magnetic resonance spectra were determined with a Brucker AC 200 spectrometer. Chemical shifts are given in ppm (δ scale); signals are reported as follows: s, singlet; d, doublet; t, triplet; b, broad; q, quartet for solutions in $CDCl_3$ or Me_2SO-d_6. The IR spectra were recorded in nujol on a Perkin-Elmer 298; wavenumbers are given in cm^{-1}.

Combustion analyses for carbon, hydrogen, and nitrogen were performed on a Perkin-Elmer 241 instrument by ICI Americas Analytical Department and are within ±0.4% of theoretical values. Compounds **3**, **20a**, **20b** were prepared according to literature procedures.[20,21]

(2*S*)-*N*-[(3-Methyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxylic Acid (4). To a solution of **3** (1.2 g, 42 mmol) and L-proline (4.83 g, 42 mmol) in 60 mL of water and 40 mL of DMF, stirred and cooled to 0 °C, was added 1,1,3,3-tetramethylguanidine (5.28 mL, 42 mmol). After stirring for 24 h at room temperature, the solution was concentrated, diluted with 50 mL of water, and cooled to 0 °C. The white precipitate was collected by filtration and recrystallized from

Table 3. *In Vitro* Cytotoxicity of Anthramycin Analogues in Comparison to Tomaymycin, DC-81, Doxorubicin, and Melphalan in LoVo and LoVo/DX Human Colon Carcinoma and L1210 and L1210/L-PAM Murine Leukemia Cell Lines

	IC_{50} (μM)[a]			IC_{50} (μM)[a]		
compd	LoVo	LoVo/DX	RI[b]	L1210	L1210/L-PAM	RI[b]
2a	42	39	0.9	22 ± 68[c]	ND	ND
2b	27	32	1.2	8 ± 22[c]	ND	ND
2c	>215	>215	ND	40	101	2.5
				69	125	1.8
2d	15[c]	6 ± 0.8[c]	0.4	7	6	0.9
				6	13	2
2e	46	38	0.8	20 ± 3[c]	ND	ND
2f	54	25	0.5	3 ± 1[c]	ND	ND
2g	37 ± 6[c]	11 ± 4[c]	0.3	0.5	0.16	2.8
				0.8	0.27	3.1
2h	48.4 ± 4[c]	32 ± 10[c]	0.7	19	3	1.8
				11	6	5.8
2i	40 ± 4[c]	6 ± 0.6[c]	0.2	4	8	2.2
				5	4	0.7
2m	30 ± 13	8 ± 0.1	0.2	12 ± 5[c]	11 ± 3[c]	0.97
2n	54	60	1.12	27 ± 6[c]	ND	ND
2o	>162[c]	>162[c]	ND	31	69	2.2
				41	62	1.5
doxorubicin	0.057 ± 0.022[d]	7.6 ± 3[d]	133	0.05 ± 0.018[e]	0.06 ± 0.018[f]	1.06
tomaymycin methyl ether	0.009 ± 0.002[e]	0.004 ± 0.002[e]	0.5	0.012 ± 0.003	0.015 ± 0.003[e]	1.4
melphalan	4.09 ± 0.6[e]	4.9 ± 0.7[f]	1.18	15.33 ± 2.7[f]	47.01 ± 6.6[f]	3.1
DC-81				0.38[h]		

[a] IC_{50}: concentration inhibiting 50% growth after 144 h (LoVo and LoVo/Dx) or 48 h (L1210 and L1210/L-PAM) exposure. [b] RI: IC_{50} resistant line/IC_{50} sensitive cell line. [c] Mean of 3 experiments ± standard deviation. [d] Mean of 83 experiments ± standard deviation. [e] Mean of 12 experiments ± standard deviation. [f] Mean of 14 experiments ± standard deviation. [g] Mean of five nine experiments ± standard deviation. [h] Data taken from ref 25. ND, not determined.

ethyl acetate/petroleum ether to give 7.5 g of pure **4** as a white solid, mp 220 °C, yield 70%.

Methyl (2*S*)-*N*-[(3-Methyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxylate (5). A solution of **4** (7.1 g, 21.7 mmol) in MeOH (50 mL) was heated at reflux for 8 h in the presence of a catalytic amount of concentrated H_2SO_4 (1 mL). The solvent was removed under vacuum. The residue was treated with saturated $NaHCO_3$ (50 mL). The resulting suspension was extracted with ethyl acetate (3 × 50 mL). The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The crude product was recrystallized from ethyl acetate/petroleum ether to give 6.1 g of **5** as white solid: mp 163 °C; yield 80%; IR (Nujol) 3180, 1730, 1610, 1580, 1490, 1390 cm^{-1}; ^{1}H-NMR ($CDCl_3$) ppm 2.4 (m, 3H), 3.65 (m, 2H), 3.6 (s, 3H), 4.0 (m, 2H), 4.4 (m, 2H), 4.8 (m, 1H), 12.8 (sb, 1H); ^{13}C-NMR ($CDCl_3$) 11.2 (CH_3), 22.7 (CH_2), 29.4 (CH_2), 30.8 (CH_2), 52.5 (CH), 59.1 ($COOCH_3$), 129.4 (C-4), 141.6 (C-5), 142.4 (C-3), 162.3 (CON), 171.9 ($COOCH_3$).

Methyl (2*S*)-*N*-[(1,3-Dimethyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxylates (6) and Methyl (2*S*)-*N*-[(1,5-Dimethyl-4-nitropyrazol-3-yl)carbonyl]pyrrolidine-2-carboxylates (7). To a stirred solution of **5** (3 g, 10 mmol) in absolute methanol (30 mL) containing sodium (0.23 g, 10 mmol) was added methyl iodide (2.8 mL, 44 mmol). The solution was stirred for 24 h at room temperature (TLC, ethyl acetate/petroleum ether, 9:1). The solvent was removed under vacuum. The residue was treated with water (30 mL), and the suspension was extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with brine (1 × 30 mL), dried (Na_2SO_4), and evaporated *in vacuo*. The residual oil was chromatographed on silica gel eluting with ethyl acetate/petroleum ether, 9:1. Evaporation of the first fraction gave **6** (1.5 g) as a white solid which was recrystallized from ethyl acetate/petroleum ether: mp 121 °C; yield 48%; IR (Nujol) 1760, 1650, 1505, 1370 cm^{-1}; ^{1}H-NMR ($CDCl_3$) ppm (mixture of rotational isomers 3:1) 1.9–2.2 and 2.3–2.45 (m, 4H minor and major methylene rotamers), 2.53 (s, 3H), 3.3–3.5 (m, 2H), 3.6 and 3.8 (s, 3H, minor and major methyl rotamers), 3.83 and 2.88 (s, 3H, minor and major carboxymethyl rotamers), 4.2–4.3 and 4.7–4.8 (m, 1H, minor and major CHN rotamers); ^{13}C-NMR ($CDCl_3$) ppm (mixture of rotational isomers 3:1) 13.4 and 13.5 (Me-C), 22.9 and 24.3 (CH_2), 29.3 and 30.8 (CH_2), 37.9 and 38.3 (Me-N), 46.9 and 47.5 (CH_2), 52.6 and 52.7 (OMe) 58.5 and 59.8 (CH), 129 (2 × C4), 136.6 and 137 (C5), 145.3 and 145.5 (C3), 157.8 and 158.3 (CON), 171.7 and 171.9 (COO). The evaporation of the second fraction gave **7** (1.2 g) as a yellow oil which crystallized from petroleum ether: mp 85 °C; yield 38%; IR (Nujol) 1720, 1640, 1500, 1350 cm^{-1}; ^{1}H-NMR ($CDCl_3$) ppm (mixture of rotational isomers 2.5:1) 1.8–2.1 (m, 4H), 2.62 and 2.65 (s, 3H, minor and major methyl rotamers), 3.3–3.6 (m, 2H), 3.65 and 3.79 (s, 3H, minor and major methyl rotamers), 3.80 and 3.82 (s, 3H, minor and major carboxymethyl rotamers), 4.3–4.4 and 4.6–4.7 (m, 1H, minor and major CHN rotamers); ^{13}C-NMR ($CDCl_3$) ppm (mixture of rotational isomers 2.5:1) 11.1 and 14.1 (Me-C), 22.7 and 24.5 (CH_2), 29.4 and 30.9 (CH_2), 37.3 and 37.4 (Me-N), 46.4 and 48.0 (CH_2), 52.3 (OMe), 58.7 and 60.6 (CH), 139 and 139.9 (C5), 142.6 and 142.7 (C3), 160.7 and 160.9 (CON), 171.9 and 172.3 (COO).

(10a*S*)-6,8-Dimethyl-1,2,3,9,10,10a-hexahydro-5*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,10-dione (8). To a solution of **6** (1 g, 3.3 mmol) in methanol (15 mL) under N_2 was added titanium trichloride (20 mL, 20% in H_2O) at a rate of 2 mL/min. After the addition, stirring was continued for 2 h. The solution was extracted with CH_2Cl_2 (3 × 30 mL) followed by 10% methanol/CH_2Cl_2 (3 × 40 mL). The organic layers were dried with Na_2SO_4 and evaporated to give a white solid. This product was dissolved in methanol (40 mL), and sodium methoxide (25 mL, 25% in methanol) was added. After the mixture was stirred for 24 h, the solvent was evaporated. The product was suspended in 30 mL of brine and evaporated. The residue was crystallized from CH_2Cl_2/petroleum ether to give **8** (0.75 g) as a white solid: mp 180 °C; yield 93%; IR (Nujol) 3210, 3020, 1670, 1630 cm^{-1}; ^{1}H-NMR ($CDCl_3$) ppm 1.9 (m, 3H), 2.28 (s, 3H), 2.8 (m, 1H), 3.5–3.7 (m, 2H), 4.09 (s, 3H), 4.1 (m, 1H), 9.44 (sb, 1H); ^{13}C-NMR ($CDCl_3$) ppm 10.4 (Me-C), 23.1 (CH_2), 25.8 (CH_2), 38.0 (Me-N), 46.1 (CH_2), 57.2 (CH), 121.1 (C8a), 126.6 (C5a), 136.2 (C8), 157.9 (CON), 168.4 (CONH).

(10a*S*)-7,8-Dimethyl-1,2,3,9,10,10a-hexahydro-5*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepine-5,10-dione (9). The preparation was performed in the same manner as with **8** using **7** as starting material. Compound **9** was obtained as a white solid: mp 269 °C; yield 35%; IR (Nujol) 3400, 3200, 1680, 1620 cm^{-1}; ^{1}H-NMR ($CDCl_3$) ppm 1.7–2.0 (m, 3H), 2.2 (s, 3H), 2.45 (m, 1H), 3.5 (m, 2H), 4.3 (s, 3H), 4.2 (m, 1H), 10.1 (sb, 1H); ^{13}C-NMR ($CDCl_3$) ppm 8.2 (Me-C), 23.1 (CH_2), 25.8 (CH_2), 36.9 (Me-N), 45.9 (CH_2N), 56.8 (CH), 119.1 (C8a), 128.4 (C5a), 136.2 (C8), 160.3 (CON), 168.8 (CONH).

(10a*S*)-6,8-Dimethyl-1,2,3,9,10,10a-hexahydro-5*H*-10-thioxopyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (10). A mixture of **8** (0.5 g, 2 mmol) and Lawesson's reagent

(0.43 g, 1 mmol) in dry toluene (100 mL) was refluxed under N_2 to 6 h. The solvent was evaporated, and saturated K_2CO_3 (150 mL) was added. After stirring for 0.5 h, the slurry was extracted with CH_2Cl_2 (3 × 30 mL). Drying and evaporation gave crude **10** (0.35 g). An analytical sample was prepared by recrystallization from ethyl ether/petroleum ether to give pure **10** as a yellow solid: mp 155 °C; yield 60%; IR (Nujol) 3240, 3170, 1640, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) ppm 1.8–2.2 (m, 3H), 2.3 (s, 3H), 3.1–3.3 (m, 1H), 3.5–3.7 (m, 2H), 4.1 (s, 3H), 4.2–4.3 (m, 1H), 10 (sb, 1H); ^{13}C NMR ($CDCl_3$) ppm 11 (Me-C), 23.2 (CH_2), 29.7 (CH_2), 38.8 (Me-N), 46.8 (CH_2), 61.3 (CH), 122 (C8a), 128.6 (C5a), 136.8 (C8), 158.4 (CO), 197.9 (CS).

(10a*S*)-7,8-Dimethyl-1,2,3,9,10,10a-hexahydro-5*H*-10-thioxopyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (11). The preparation was performed in the same manner as with **10** using **9** as starting material to afford **11** as a white solid: mp 310 °C; yield 37%; IR (Nujol) 3400, 3200, 1600, 1140 cm^{-1}; ^1H-NMR (DMSO-d_6) ppm 2.3 (m, 3H), 2.25 (s, 3H), 3.0 (m, 1H), 3.3 (m, 2H), 3.8 (m, 3H), 4.6 (m, 1H), 12.4 (sb, 1H); ^{13}C-NMR (DMSO-d_6) ppm 8.7 (Me-C), 22.6 (CH_2), 29.4 (CH_2), 37.2 (Me-N), 53.2 (CH_2), 65.2 (CH), 118.2 (C8a), 129.8 (C5a), 143.5 (C8), 183.7 (CO), 196 (CS).

(10a*S*)-6,8-Dimethyl-10-(methylthio)-1,2,3,10a-tetrahydro-5*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (12). A mixture of **10** (0.2 g, 0.79 mmol), methyl iodide (0.13 mL, 2 mmol), and powdered K_2CO_3 (0.33 g, 2.3 mmol) in THF (20 mL) was refluxed for 4 h. The reaction was monitored by TLC (CH_2Cl_2/toluene/MeOH, 8.5:1:0.5, multiple developments). The solvent was evaporated, and the slurry was partitioned between water and CH_2Cl_2 (2 × 70 mL). The organic layers were dried with Na_2SO_4 and evaporated. The residue was recrystallized from CH_2Cl_2/petroleum ether to give 0.14 g of a yellow solid: mp 73 °C; yield 67%: IR (Nujol) 1640, 1580 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.2 (m, 3H), 2.3 (s, 3H), 2.5 (m, 3H), 2.8 (m, 1H), 3.7 (m, 2H), 4.1 (s, 3H), 4.2 (m, 1H); ^{13}C-NMR ($CDCl_3$) ppm 10.5 (Me-C), 13.3 (Me-S), 24.0 (CH_2), 27.8 (CH_2), 38.8 (Me-N), 46.2 (CH_2), 58.2 (CH), 126.0 (C8a), 131.5 (C5a), 143.0 (C8), 158.6 (CO), 164.1 (C-S).

(10a*S*)-7,8-Dimethyl-10-(methylthio)-1,2,3,10a-tetrahydro-5*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (13). The preparation was performed in the same manner as **13** using **11** as starting material. Compound **13** was obtained as a yellow solid: mp 229 °C; yield 65%; IR (CH_2Cl_2) 1710, 1640 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.2 (m, 3H), 2.3 (s, 3H), 2.4 (s, 3H), 2.6 (m, 1H), 3.7 (m, 2H), 3.8 (s, 3H), 4.1 (m, 1H); ^{13}C-NMR ($CDCl_3$) ppm 8.6 (Me-C), 13.2 (Me-S), 24.0 (CH_2), 27.8 (CH_2), 37.1 (Me-N), 46.1 (CH_2), 58.3 (CH), 129.7 (C8a), 134.2 (C5a), 136.4 (C8), 161.5 (CO), 164.5 (CS).

(10a*S*)-6,8-Dimethyl-1,2,3,10a-tetrahydro-5*H*-pyrazolo-[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (2a). A solution **12** (1.5 g, 5.6 mmol) in H_2O/THF (40 mL, 25%) was cooled to 0 °C under N_2. Freshly prepared aluminum amalgam[22] from aluminium foil (1.5 g, 56 mmol) was immediately added to the above solution. After stirring at 0 °C for 24 h, the gray slurry was filtered through Celite and the THF was evaporated. After partitioning of the residue between brine and 10% MeOH–CH_2Cl_2, the organic layer was dried (Na_2SO_4) and evaporated. The residue was chromatographed on silica gel (acetone/hexane, 6:4). Two products were isolated, **2a** and **14**.

2a: yellow oil, 0.45 g; yield 35%, ^1H-NMR ($CDCl_3$) ppm 1.94–2.02 (m, 2H), 2.26 (s, 3H), 2.28–2.3 (m, 2H), 3.39–3.51 (m, 2H), 3.5 (m, 1H), 4.07 (s, 3H), 7.33–7.35 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 10.6 (Me-C), 23.9 (CH_2), 29.9 (Me-N), 39.6 (CH_2), 45.9 (CH_2), 54.9 (CH), 127.79 (C8a), 131.10 (C5a), 144.01 (C8), 157.8 (CO), 158.9 (C10).

14: white solid; mp 158 °C; ^1H-NMR ($CDCl_3$) ppm 1.84–2.22 (m, 2H), 2.66 (s, 3H), 2.78–2.9 (m, 2H), 3.19–3.25 (m, 2H), 3.5–3.64 (m, 2H), 3.7 (m, 1H), 4.2 (s, 3H), 10.9 (sb, 1H).

(10a*S*)-7,8-Dimethyl-1,2,3,10a-tetrahydro-5*H*-pyrazolo-[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (2b). The preparation was performed in the same manner as **2a** using **13** as starting material. The reaction afforded two products: **2b** as a yellow oil, yield 42%, and **15** as a white solid, yield 15%.

2b: ^1H-NMR ($CDCl_3$) ppm 1.94–1.97 (m, 2H), 2.25 (s, 3H), 2.30 (m, 2H), 3.60–3.80 (m, 2H), 3.81 (m, 1H), 3.85 (s, 3H), 7.36–7.38 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 8.88 (Me-C), 24.06 (CH_2), 30.31 (Me-N), 37.29 (CH_2), 46.19 (CH_2), 55.29 (CH), 129.6 (C8a), 136.10 (C5a), 137.88 (C8), 159.98 (CO), 160.99 (C10).

15: mp 176 °C; ^1H NMR ($CDCl_3$) ppm 1.9–2.25 (m, 2H), 2.58 (s, 3H), 2.69–2.74 (m, 2H), 3.47–3.55 (m, 2H), 3.78–3.89 (m, 2H), 3.9 (m, 1H), 4.1 (s, 3H), 11.1 (sb, 1H).

General Procedure for Alkylation of Pyrazole Derivatives 20a and 20b. Method A. To a stirred solution of **20a** or **20b** (15 mmol) in absolute methanol (20 mL) containing sodium methoxide (prepared from 15 mmol of sodium) was added the appropriate alkyl halide (15 mmol). The mixture was refluxed for 8 h, and the solvent was then removed under vacuum. The residue was treated with water (20 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried over Na_2SO_4 and evaporated under reduced pressure. The isomeric mixture obtained was separated by chromatography on silica gel, eluting with ethyl acetate/petroleum ether, 1:1 (entries **21a–d**); ethyl acetate/petroleum ether, 3:7 (entries **21e,f**); ethyl acetate/petroleum ether, 9:1 (entries **21l,m**).

Methyl 1,3-dimethyl-4-nitropyrazole-5-carboxylate (21a): yield 35% as white crystals; mp 52 °C (diethyl ether); IR (Nujol) 1730, 1560, 1480, 1350 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.17 (s, 3H), 2.65 (s, 3H), 3.99 (s, 3H).

Methyl 1,5-dimethyl-4-nitropyrazole-3-carboxylate (21b): yield 30% as white crystals; mp 40 °C (petroleum ether 40–60 °C); IR (Nujol) 1720, 1560, 1470, 1360, 1250 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.15 (s, 3H), 2.75 (s, 3H), 3.89 (s, 3H).

Methyl 1-ethyl-3-methyl-4-nitropyrazole-5-carboxylate (21c): yield 34% as yellow oil; IR (Nujol) 1740, 1560, 1250, 1150, 1110, 1090, 950, 850, 820 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 1.5 (t, 3H), 2.50 (s, 3H), 4.0 (s, 3H), 4.25 (q, 2H).

Methyl 1-ethyl-5-methyl-4-nitropyrazole-3-carboxylate (21d): yield 24% as white solid; mp 50 °C (diethyl ether); IR (Nujol) 1750, 1570, 1500, 1270, 1140, 1110, 1080, 880, 830 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 1.5 (t, 3H), 2.62 (s, 3H), 3.97 (s, 3H), 4.19 (q, 2H).

Methyl 1-benzyl-3-methyl-4-nitropyrazole-5-carboxylate (21e): yield 50% as yellow oil; IR (Nujol) 1720, 1530, 1190 cm^{-1}; ^1H NMR ($CDCl_3$) ppm 2.5 (s, 3H), 3.86 (s, 3H), 5.37 (s, 2H), 7.26–7.32 (m, 5H).

Methyl 1-benzyl-5-methyl-4-nitropyrazole-3-carboxylate (21f): yield 40% as a yellow oil; IR (Nujol) 1740, 1560, 1240, 1090, 860, 820 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.5 (s, 3H), 3.96 (s, 3H), 5.31 (s, 2H), 7.32–7.37 (m, 5H).

Methyl 1-benzyl-3-isopropyl-4-nitropyrazole-5-carboxylate (21l): yield 36% as pale yellow oil; IR (Nujol) 1740, 1390, 1230, 1150, 1030, 870, 820, 740 cm^{-1}; ^1H-NMR (DMSO-d_6) ppm 1.18 (d, 3H), 1.20 (d, 3H), 3.27 (m, 1H), 3.92 (s, 3H), 5.45 (s, 2H), 7.11–7.18 (m, 2H), 7.29–7.42 (m, 3H).

Methyl 1-benzyl-5-isopropyl-4-nitropyrazole-3-carboxylate (21m): yield 56% as pale yellow oil; IR (Nujol) 1730, 1230, 1130, 1030, 870, 810, 730 cm^{-1}; ^1H-NMR (DMSO-d_6) ppm 1.16 (d, 3H), 1.18 (d, 3H), 3.25 (m, 1H), 3.96 (s, 3H), 5.41 (s, 2H), 7.11–7.15 (m, 2H), 7.27–7.36 (m, 3H).

Method B. To a stirred solution of **20a** (12 mmol) in dry toluene was added NaH (12 mmol, 60% dispersion in mineral oil). The mixture was refluxed for 30 min. After cooling to room temperature the appropriate alkyl halide (12 mmol) and NaI (0.12 mmol) were added at room temperature. After stirring for 12 h (TLC monitoring), the mixture was diluted with water (40 mL), the organic phase was separated, and the aqueous phase was extracted with ethyl acetate (3 × 30 mL). The combined organic phase was washed with brine (1 × 30 mL), dried over Na_2SO_4, and evaporated *in vacuo*.

Methyl 1-(*p*-chlorobenzyl)-5-methyl-4-nitropyrazole-3-carboxylate (21g): yield 69% as colorless oil; IR (Nujol) 1710, 1510, 1090 cm^{-1}; ^1H-NMR (DMSO-d_6) ppm 2.6 (s, 3H), 3.88 (s, 3H), 5.51 (s, 2H), 7.30 (d, 2H), 7.45 (d, 2H).

Methyl 1-(*p*-methoxybenzyl)-5-methyl-4-nitropyrazole-3-carboxylate (21h): yield 76% as pale yellow oil; IR (Nujol) 1750, 1610, 1560, 1090 cm^{-1}; ^1H-NMR (DMSO-d_6) ppm 2.56 (s, 3H), 3.68 (s, 3H), 3.85 (s, 3H), 5.45 (s, 2H), 6.80–6.86 (d, 2H), 7.14–7.20 (d, 2H).

Methyl 1-(3′,4′-dimethylbenzyl)-5-methyl-4-nitropyrazole-3-carboxylate (21i): yield 57% as yellow oil; IR (Nujol)

1730, 1560, 1110 cm^{-1}; ^1H-NMR (DMSO-d_6) ppm 2.16 (s, 3H), 2.24 (s, 3H), 2.5 (s, 3H), 3.95 (s, 3H), 5.29 (s, 2H), 6.5–7.2 (m, 3H).

General Procedure for Hydrolysis of Methyl Esters (21a–m). A solution of the methyl ester (**21a–m**) (5 mmol) in methanol (20 mL) and 1 N KOH (5 mmol) was refluxed. After the reaction was complete (TLC), the solution was concentrated, carefully adjusted to pH 4 with 10% HCl, and extracted with ethyl acetate (4 × 40 mL). The combined organic extracts were dried on Na_2SO_4 and evaporated *in vacuo*. The crude product was crystallized from ethyl acetate/petroleum ether.

1,3-Dimethyl-4-nitropyrazole-5-carboxylic acid (17a): IR (Nujol) 3440, 1730, 1560, 1510, 1250, 1150 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.15 (s, 3H), 3.99 (s, 3H), 13.28 (sb, 1H).

1,5-Dimethyl-4-nitropyrazole-3-carboxylic acid (17b): IR (Nujol) 3540, 1740, 1480, 1350, 1230, 1190 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.13 (s, 3H), 3.89 (s, 3H), 9.2 (sb, 1H).

1-Ethyl-3-methyl-4-nitropyrazole-5-carboxylic acid (17c): IR (Nujol) 3500, 1740, 1570, 1500, 1360 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 1.34 (t, 3H), 2.38 (s, 3H), 4.16 (q, 2H), 13.30–13.38 (sb, 1H).

1-Ethyl-5-methyl-4-nitropyrazole-3-carboxylic acid (17d): IR (Nujol) 3550, 1740, 1550, 1500, 1360, 1240 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 1.32 (t, 3H), 2.55 (s, 3H), 4.15 (q, 2H), 13.30–13.45 (sb, 1H).

1-Benzyl-3-methyl-4-nitropyrazole-5-carboxylic acid (17e): IR (Nujol) 3450, 1740, 1560, 1500, 1490, 1460, 1360, 1220 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.40 (s, 3H), 5.40 (s, 2H), 7.24–7.38 (m, 5H), 13.05 (sb, 1H).

1-Benzyl-5-methyl-4-nitropyrazole-3-carboxylic acid (17f): IR (Nujol) 3550, 1720, 1540, 1500, 1430, 1380, 1200 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.56 (s, 3H), 5.45 (s, 2H), 7.22–7.38 (m, 5H), 13.65 (sb, 1H).

1-(*p*-Chlorobenzyl)-5-methyl-4-nitropyrazole-3-carboxylic acid (17g): IR (Nujol) 3450, 1750, 1560, 1230 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.56 (s, 3H), 5.48 (s, 2H), 7.29 (d, 2H), 7.46 (d, 2H), 13.98 (sb, 1H).

1-(*p*-Methoxybenzyl)-5-methyl-4-nitropyrazole-3-carboxylic acid (17h): IR (Nujol) 3550, 1750, 1560, 1500, 1220 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 2.56 (s, 3H), 3.79 (s, 3H), 5.48 (s, 2H), 6.88 (d, 2H), 7.18 (d, 2H), 13.98 (sb, 1H).

1-(3′,4′-Dimethylbenzyl)-5-methyl-4-nitropyrazole-3-carboxylic acid (17i): IR (Nujol) 3550, 1710, 1500, 1470, 1250, 1200 cm^{-1}; ^1H-NMR ($CDCl_3$) 2.19 (s, 6H), 2.50 (s, 3H), 5.35 (s, 2H), 6.9–7.11 (m, 2H), 7.22–7.24 (m, 1H), 13.38 (sb, 1H).

1-Benzyl-3-isopropyl-4-nitropyrazole-5-carboxylic acid (17l): IR (Nujol) 3500, 1730, 1550, 1380, 1220 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 1.10 (s, 3H), 1.17 (s, 3H), 3.48 (m, 1H), 5.57 (s, 2H), 7.22 (d, 2H), 7.31–7.38 (m, 3H), 12.38 (sb, 1H).

1-Benzyl-5-isopropyl-4-nitropyrazole-3-carboxylic acid (17m): IR (Nujol) 3500, 1740, 1550, 1460, 1200 cm^{-1}; ^1H-NMR ($CDCl_3$) ppm 1.12 (s, 3H), 1.15 (s, 3H), 3.45 (m, 1H), 5.54 (s, 2H), 7.18 (d, 2H), 7.31–7.38 (m, 3H), 12.98 (sb, 1H).

1-Methyl-3-(methoxycarbonyl)-4-nitropyrazole-5-carboxylic Acid (17n). The diester (0.49 g, 2.18 mmol) was dissolved in methanol (20 mL) and treated with a solution of KOH in methanol (10 mL of a 2.19 M standardized solution; 1.01 equiv). The mixture was stirred at 20 °C for 20 h. After removal of the solvent under vacuum, the residue was dissolved in water (20 mL) and the solution was adjusted to pH 4 with aqueous 10% HCl. The solvent was evaporated under vacuum, and the residue was recrystallized from chloroform/petroleum ether to give 0.750 g: yield 75%; mp 150 °C; IR (Nujol) 3550, 1770, 1660, 1550, 1510, 1330, 1310 cm^{-1}; ^1H-NMR (DMSO-d_6) ppm 3.85 (s, 3H, COOMe), 4.15 (s, 3H, N-Me), 5.4 (sb, 1H, COOH); ^{13}C-NMR (DMSO-d_6) ppm 40.9 (NMe), 52.6 (COOMe), 117.0 (C4), 129.4 (C5), 132.03 (C3), 157.4 (COOH), 158.9 (COOMe).

1-Methyl-5-(methoxycarbonyl)-4-nitropyrazole-3-carboxylic Acid (17o). The diester (4 g, 16 mmol) was dissolved in a mixture of dioxane (12 mL) and water (29 mL), and a solution of concentrated H_2SO_4 (0.35 mL, 6.35 mmol) was added carefully. The mixture was heated under reflux for 18 h, cooled, and concentrated under reduced pressure until precipitation began. The mixture was then kept at 0 °C for 4 h and the precipitate collected. The crude product was recrystallized from ethyl acetate (1 g, yield 28%): mp 190 °C; IR (Nujol) 3580, 1740, 1540, 1450, 1380, 1280, 1220 cm^{-1}; ^1H-NMR (DMSO-d_6) ppm 3.94 (s, 3H, COOMe), 4.26 (s, 3H, NMe), 5.01 (sb, 1H, COOH); ^{13}C-NMR (DMSO-d_6) ppm 41.24 (NMe), 53.25 (COOMe), 127.5 (C4), 133.6 (C5), 135.83 (C3), 156.5 (COOH), 158.73 (COOMe).

General Procedure for Preparation of Nitro amides (18a–o). A catalytic amount of DMF (2 drops) was added to a stirred suspension of the acid **17a–o** (4 mmol) and oxalyl chloride (4.8 mmol) in dry benzene (30 mL). The solution was stirred for 3 h at 20 °C. The solvent was removed under vacuum. The resulting colorless oil was dissolved in dry THF (20 mL) and added dropwise to an ice-cold solution of **16** (4 mmol) and triethylamine (1.12 mL, 8 mmol) in dry THF (40 mL). After the addition was complete, the reaction mixture was stirred for 24 h at room temperature. The mixture was filtered and evaporated *in vacuo* to give an oily residue which was extracted with ethyl acetate and HCl (0.5 M, 3 × 20 mL), saturated $NaHCO_3$ solution (3 × 20 mL), and brine (20 mL). Drying (Na_2SO_4) and evaporation *in vacuo* afforded the coupling product.

(2*S*)-*N*-[(1,3-Dimethyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18a): yellow oil; yield 49%; ^1H-NMR ($CDCl_3$) ppm 1.23–1.52 (m, 6H), 1.7–2.5 (m, 4H), 2.27 (s, 3H), 2.6–3.0 (m, 4H), 3.1–3.6 (m, 2H), 3.9 (s, 3H), 4.71–4.73 (m, 1H), 4.75 (d, 1H).

(2*S*)-*N*-[(1,5-Dimethyl-4-nitropyrazol-3-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18b): yellow oil; yield 65%; ^1H-NMR ($CDCl_3$) ppm 1.25–1.52 (m, 6H), 1.7–2.3 (m, 4H), 2.63 (s, 3H), 2.7–2.8 (m, 4H), 3.4 (m, 2H), 3.85 (s, 3H), 4.72–4.74 (m, 1H), 4.86 (d, 1H).

(2*S*)-*N*-[(1-Ethyl-3-methyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18c): yellow oil; yield 81%; ^1H-NMR ($CDCl_3$) ppm 1.25–1.4 (m, 6H), 1.45 (t, 3H), 1.7–2.4 (m, 4H), 2.5 (s, 3H), 2.6–2.9 (m, 4H), 3.1–3.5 (m, 2H), 4.15 (q, 2H), 4.61–4.63 (m, 1H), 4.84 (d, 1H).

(2*S*)-*N*-[(1-Ethyl-5-methyl-4-nitropyrazol-3-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18d): yellow oil; yield 60%; ^1H-NMR ($CDCl_3$) ppm 1.2–1.4 (m, 6H), 1.45 (t, 3H), 1.7–2.5 (m, 4H), 2.65 (s, 3H), 2.7–2.9 (m, 4H), 3.45 (m, 2H), 4.2 (q, 2H), 4.71–4.73 (m, 1H), 4.86 (d, 1H).

(2*S*)-*N*-[(1-Benzyl-3-methyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18e): colorless oil; yield 65%; ^1H-NMR ($CDCl_3$) ppm 1.1–1.4 (m, 6H), 1.7–2.4 (m, 4H), 2.6 (s, 3H), 2.6–3.0 (m, 4H), 3.2–3.5 (m, 2H), 4.7 (m, 1H), 4.9 (d, 1H), 5.1–5.5 (m, 2H), 7.3–7.6 (m, 5H).

(2*S*)-*N*-[(1-Benzyl-5-methyl-4-nitropyrazol-3-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18f): pale yellow oil; yield 68%; ^1H-NMR ($CDCl_3$) ppm 1.1–2.4 (m, 6H), 2.27 (m, 4H), 3.4–3.7 (m, 3H), 3.8–4.1 (m, 4H), 4.3–4.5 (m, 2H), 4.8 (m, 1H), 4.9 (m, 1H), 5.4 (m, 2H), 7.5–7.6 (m, 5H).

(2*S*)-*N*-[[1-(*p*-Chlorobenzyl)-5-methyl-4-nitropyrazol-3-yl]carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18g): yellow oil; yield 85%; ^1H-NMR ($CDCl_3$) ppm 1.2–1.4 (m, 6H), 1.9–2.4 (m, 4H), 2.6 (s, 3H), 2.6–2.9 (m, 4H), 3.4–3.5 (m, 2H), 4.7 (m, 1H), 4.85 (d, 1H), 5.28 (s, 2H), 7.1–7.4 (m, 4H).

(2*S*)-*N*-[[1-(*p*-Methoxybenzyl)-5-methyl-4-nitropyrazol-3-yl]carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18h): yellow oil; yield 91%; ^1H-NMR ($CDCl_3$) ppm 1.2–1.4 (m, 6H), 2.3–2.45 (m, 4H), 2.6 (s, 3H), 2.6–2.9 (m, 4H), 3.3 (m, 2H), 3.8 (s, 3H), 4.7 (m, 1H), 4.85 (d, 1H), 5.25 (s, 2H), 6.87 (d, 2H, J = 8.8 Hz), 7.12 (d, 2H, J = 8.8 Hz).

(2*S*)-*N*-[[1-(3′,4′-Dimethylbenzyl)-5-methyl-4-nitropyrazol-3-yl]carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18i): yellow oil; yield 34%; ^1H-NMR ($CDCl_3$) ppm 1.2–1.5 (m, 6H), 1.7–2.3 (m, 4H), 2.6 (s, 3H), 2.6–2.9 (m, 4H), 3.5 (m, 2H), 4.74 (m, 1H), 4.87 (d, 1H), 5.24 (s, 2H), 7.3–7.4 (m, 3H).

(2*S*)-*N*-[(1-Benzyl-3-isopropyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18l): yellow oil; yield 55%; ^1H-NMR ($CDCl_3$) ppm 1.55–1.75 (m, 6H), 1.8–2.4 (m, 5H), 2.7–2.9 (m, 6H), 3.43 (m, 6H), 4.7–4.76 (m, 1H), 4.86 (d, 1H), 5.39 (s, 2H), 7.29–7.50 (m, 5H).

(2S)-N-[(1-Benzyl-5-isopropyl-4-nitropyrazol-3-yl]carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18m): white solid crystallized from ethyl acetate/petroleum ether; yield 55%; mp 148 °C; ^{1}H-NMR ($CDCl_3$) ppm 1.55–1.7 (m, 6H), 1.8–2.4 (m, 5H), 2.6–2.9 (m, 6H), 3.3–3.6 (m, 6H), 4.71–4.73 (m, 1H), 4.86 (d, 1H), 5.39 (s, 2H), 7.19–7.40 (m, 5H).

(2S)-N-[(1-Methyl-3-carbomethoxy-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18n): yellow oil; yield 30%; ^{1}H-NMR ($CDCl_3$) ppm 1.24–1.28 (m, 6H), 1.72–2.44 (m, 4H), 2.6–2.9 (m, 4H), 3.3–3.5 (m, 2H), 4.0 (s, 3H), 4.3 (s, 3H), 4.7 (m, 1H), 4.85 (d, 1H).

(2S)-N-[(1-Methyl-5-carbomethoxy-4-nitropyrazol-3-yl)carbonyl]pyrrolidine-2-carboxaldehyde diethyl thioacetal (18o): yellow oil; yield 83%; ^{1}H-NMR ($CDCl_3$) ppm 1.4–1.5 (m, 6H), 1.7–2.5 (m, 4H), 2.6–2.9 (m, 4H), 3.6–3.9 (m, 2H), 3.98 (s, 3H), 4.12 (s, 3H), 4.7 (m, 1H), 4.9 (d, 1H).

4-Nitropyrazole-3,5-dicarboxylic Acid. To a stirred solution of 3-methyl-4-nitropyrazole-5-carboxylic acid (5.6 g, 3.26 mmol) and KOH (0.19 g, 3.16 mmol) in water (200 mL) at 0 °C was added $KMnO_4$ (12 g, 1.59 mmol) in 1 g portions every 10 min. After the addition was complete, the mixture was heated under reflux for 5 h, cooled in an ice bath, and acidified with concentrated H_2SO_4 (7 mL), and the solvent was removed under vacuum. The residue was dissolved in hot water (50 mL), and $AgNO_3$ (1.4 g, 8.24 mmol) was added. The suspension was heated under reflux for 15 min, cooled, and filtered. The filtrate was acidified with concentrated HCl (0.75 mL). After 4 h at 0 °C, the precipitate of diacid **20d** was collected by filtration to afford 3.3 g of a white solid: yield 45%; mp 206 °C.

1-Methyl-3,5-Bis(methoxycarbonyl)-4-nitropyrazole. A solution of the above prepared diacid (2 g, 9.9 mmol) in concentrated H_2SO_4 (1 mL) and MeOH (50 mL) was heated under reflux for 24 h. The solvent was removed under vacuum, and the residue was treated with saturated $NaHCO_3$ solution (30 mL). After 10 h at 20 °C, the suspension was filtered. The white precipitate was dried under vacuum to constant weight to give 1 g of the diester (yield 44%, mp 118 °C) sufficiently pure to be used in the next reaction.

To a stirred solution of the diester (0.9 g, 3.9 mmol) in absolute methanol (25 mL) containing sodium (90 mg, 3.9 mmol) was added methyl iodide (0.3 mL, 3.9 mmol). The solution was refluxed for 10 h (TLC monitoring), the solvent was removed under vacuum, and the residue was treated with water (30 mL) and extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were washed with brine (1 × 20 mL), dried (Na_2SO_4), and evaporated *in vacuo*. The crude product was recrystallized from ethyl acetate/petroleum ether: 0.55 g of a white solid; yield 59%; mp 135 °C; IR (Nujol) 1750, 1730, 1650, 1610, 1470, 1380, 1270 cm^{-1}; ^{1}H-NMR ($CDCl_3$) ppm 3.93 (s, 3H, COOMe), 3.95 (s, 3H, COOMe), 4.25 (s, 3H, N-Me).

(10aS)-8-Alkyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]-pyrrolo[1,2-a][1,4]diazepin-5-one (N_6 or N_7 Substituted) (2a–o). A solution of the appropriate nitro amide **18a–o** (1.65 mmol, 1 equiv) and stannous chloride dihydrate (8.25 mmol, 5 equiv) in methanol (40 mL) was refluxed until TLC analysis (ethyl acetate/petroleum ether, 1:1) indicated that all the starting material had reacted. The reaction mixture was carefully adjusted to pH 8 with saturated $NaHCO_3$ solution and then extracted with ethyl acetate (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated *in vacuo* to afford the corresponding crude amino diethyl thioacetal **19a–o** as a practically pure yellow oil. Due to their instability, the amino amides **19a–o** were directly used in the next step without further purification.

A solution of the crude amino diethyl thioacetal **19a–o** (1.1 mmol, 1 equiv), mercuric chloride (2.22 mmol, 2.2 equiv), and calcium carbonate (3.02 mmol, 2.5 equiv) in CH_3CN/H_2O (4:1, 5 mL) was stirred at room temperature for 24 h or until TLC (ethyl acetate/petroleum ether, 7:3) indicated that reaction was complete. The reaction mixture was diluted with chloroform (30 mL) and filtered through Celite. The solution was extracted with saturated $NaHCO_3$ solution (2 × 20 mL) and brine (20 mL). The combined aqueous phase was back-extracted with chloroform (2 × 20 mL), and the combined organic phases were dried (Na_2SO_4) and evaporated *in vacuo* to afford the crude imine, which was purified by flash chromatography on silica gel (Table 2).

(10aS)-6,8-Dimethyl-1,2,3,10a-tetrahydro-5H-pyrazolo-[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2a): ^{1}H-NMR ($CDCl_3$) ppm 1.94–2.02 (m, 2H), 2.26 (s, 3H), 2.28–2.3 (m, 2H), 3.39–3.51 (m, 2H), 3.54–3.7 (m, 1H), 4.07 (s, 3H), 7.34 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 10.6, 23.9, 29.9, 38.91, 45.9, 54.9, 127.79, 131.10, 144.01, 157.8, 158.9.

(10aS)-7,8-Dimethyl-1,2,3,10a-tetrahydro-5H-pyrazolo-[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2b): ^{1}H-NMR ($CDCl_3$) ppm 1.94–1.97 (m, 2H), 2.25 (s, 3H), 2.30 (m, 2H), 3.60–3.80 (m, 2H), 3.81 (m, 1H), 3.85 (s, 3H), 7.37 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 8.88, 24.06, 30.3, 37.29, 46.19, 55.29, 129.61, 136.10, 137.88, 159.98, 160.99.

(10aS)-6-Ethyl-8-methyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2c): ^{1}H-NMR ($CDCl_3$) ppm 1.47 (t, 3H), 2.04–2.15 (m, 2H), 2.32–2.34 (m, 2H), 2.35 (s, 3H), 3.65 (q, 2H), 3.8–3.9 (m, 1H), 4.54–4.60 (m, 2H), 7.41 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 10.82, 16.09, 24.08, 46.06, 46.77, 55.03, 60.42, 127.18, 131.11, 144.25, 157.74, 158.90.

(10aS)-7-Ethyl-8-methyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2d): ^{1}H-NMR ($CDCl_3$) ppm 1.46 (t, 3H), 1.97–2.04 (m, 2H), 2.29–2.35 (m, 2H), 2.39 (s, 3H), 3.69 (q, 2H), 3.88–3.91 (m, 1H), 4.21–4.25 (m, 2H), 7.44 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 8.79, 15.13, 24.13, 30.40, 45.38, 46.29, 55.34, 129.75, 135.20, 138.05, 159.92, 161.17.

(10aS)-6-Benzyl-8-methyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2e): ^{1}H-NMR ($CDCl_3$) ppm 1.9–2.3 (m, 4H), 2.35 (s, 3H), 3.5–3.8 (m, 3H), 5.61 (d, J = 14.6 Hz, 1H), 5.87 (d, J = 14.6 Hz, 1H), 7.3–7.4 (m, 5H), 7.47 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 10.9, 24.05, 30.04, 46.10, 54.57, 55.02, 127.55 (2 × C), 127.76 (2 × C), 128.49 (2 × C), 131.58, 137.60, 144.93, 157.70, 159.21.

(10aS)-7-Benzyl-8-methyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2f): ^{1}H-NMR ($CDCl_3$) ppm 1.7–2.4 (m, 4H), 2.27 (s, 3H), 3.4–3.7 (m, 3H), 5.4 (s, 2H), 7.1–7.4 (m, 5H), 7.51 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 8.95, 24.49, 46.66, 54.48, 55.53, 55.89, 128.12, 128.54, 129.49 (2 × C), 130.9, 136.46, 137.37, 139.17, 161.06, 161.99.

(10aS)-7-(p-Chlorobenzyl)-8-methyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2g): ^{1}H-NMR ($CDCl_3$) ppm 2.00–2.09 (m, 2H), 2.28 (s, 3H), 2.30–2.36 (m, 2H), 3.6–3.73 (m, 2H), 3.8–3.93 (m, 1H), 5.38 (dd, 2H), 7.11–7.31 (m, 4H), 7.46 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 9.04, 24.07, 30.33, 46.32, 53.80, 55.32, 128.66 (2 × C), 129.03 (2 × C), 130.17, 133.91, 134.01, 136.06, 138.49, 160.40, 160.97.

(10aS)-7-(p-Methoxybenzyl)-8-methyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2h): ^{1}H-NMR ($CDCl_3$) ppm 2.05–2.09 (m, 2H), 2.28 (s, 3H), 2.39–2.41 (m, 2H), 3.65–3.75 (m, 2H), 3.78 (s, 3H), 3.84–3.89 (m, 1H), 5.35 (dd, 2H), 6.83 (d, 2H), 7.16 (d, 2H), 7.44 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 9.10, 24.08, 30.35, 46.29, 54.16, 55.29, 114.16 (2 × C), 127.47, 128.81 (2 × C), 130.01, 135.89, 138.14, 159.37, 160.08, 161.00.

(10aS)-7-(3′,4′-Dimethylbenzyl)-8-methyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2i): ^{1}H-NMR ($CDCl_3$) ppm 2.04 (d, 1H), 2.21 (s, 3H), 2.24 (s, 3H), 2.27 (s, 3H), 3.48–3.74 (m, 6H), 5.31–5.39 (m, 2H), 6.5 (d, 1H), 6.99–7.04 (m, 2H), 7.43 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 9.13, 14.91, 19.45, 24.08, 30.36, 46.29, 53.23, 55.31, 124.83, 125.79, 129.56, 132.78, 134.58, 136.51, 140.90, 145.88, 150.06, 153.88, 160.12.

(10aS)-6-Benzyl-8-isopropyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2l): ^{1}H-NMR ($CDCl_3$) ppm 1.28–1.37 (m, 6H), 2.1 (m, 2H), 2.29 (m, 2H), 3.16 (m, 1H), 3.24 (m, 3H), 5.57 (d, 2H), 7.24–7.28 (m, 5H), 7.39 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 21.69, 22.29, 24.07, 26.16, 30.02, 46.01, 54.56, 54.88 (2 × C), 127.36, 127.57 (2 × C), 128.38 (2 × C), 130.56, 137.87, 153.61, 157.8, 158.54.

(10aS)-7-Benzyl-8-isopropyl-1,2,3,10a-tetrahydro-5H-pyrazolo[4,3-e]pyrrolo[1,2-a][1,4]diazepin-5-one (2m): ^{1}H-

NMR ($CDCl_3$) ppm 1.13 (d, 3H), 1.3 (d, 3H), 2.02–2.03 (m, 2H), 2.29–2.32 (m, 2H), 3.07–3.11 (m, 1H), 3.66–3.72 (m, 2H), 3.92–3.96 (m, 1H), 5.46 (q, 2H), 7.15 (m, 2H), 7.28–7.34 (m, 3H), 7.42 (d, 1H, J = 4 Hz, N=CH). ^{13}C-NMR ($CDCl_3$) ppm 19.93, 22.30, 24.19, 26.47, 30.36, 46.28, 54.85, 55.02, 126.92 (2 × C), 127.97, 128.81 (2 × C), 129.67, 136.30, 144.18, 139.00, 158.87, 161.19.

(10a*S*)-8-(Methoxycarbonyl)-6-methyl-1,2,3,10a-tetrahydro-5*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (2n): ^{1}H-NMR ($CDCl_3$) ppm 1.64–2.4 (m, 4H), 2.5–2.7 (m, 1H), 4.07 (s, 3H), 4.09–4.2 (m, 1H), 4.1 (s, 3H), 5.1 (m, 1H), 7.02 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 23.00, 29.30, 47.33, 47.98, 58.59, 80.03, 119.59, 123, 134.56, 59.77, 160.60, 211.00.

(10*R*,10a*S*)-8-(Methoxycarbonyl)-7-methyl-1,2,3,10a-tetrahydro-5*H*-pyrazolo[4,3-*e*]pyrrolo[1,2-*a*][1,4]diazepin-5-one (2o): ^{1}H-NMR ($CDCl_3$) ppm 1.04 (t, 3H), 2.3–2.6 (m, 6H), 3.4–3.7 (m, 3H), 3.84 (s, 3H), 4.00 (s, 3H), 4.71 (d, 1H exchange with water), 7.01 (d, 1H, J = 4 Hz, N=CH); ^{13}C-NMR ($CDCl_3$) ppm 14.55, 21.99, 30.66, 47.33, 51.16, 58.79, 60.91, 82.67, 108.00, 115.36, 130.23, 133.93, 159.07, 159.50.

Convergent Synthesis: (2*S*)-*N*-[(1,3-Dimethyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxaldehyde (22). A solution of $(i\text{-Bu})_2AlH$ (6.74 mL of a 1 M solution in hexane, 6.74 mmol, 2.5 equiv) was added dropwise over a period of 15 min to a stirred solution of **6** (0.78 g, 2.69 mmol) in anhydrous toluene (30 mL) under dry N_2 at −55 °C. The mixture was stirred for an additional 40 min, and the excess reagent was decomposed by careful addition of methanol (30 mL) followed by 5% HCl (50 mL). The resulting mixture was allowed to warm to 0 °C and the organic layer removed. The aqueous layer was extracted with ethyl acetate (3 × 30 mL), and the organic layers were combined, washed with brine (2 × 20 mL), and dried (Na_2SO_4). The solvent was evaporated *in vacuo* below 40 °C to afford the crude aldehyde as a yellow oil. Purification by column chromatography (ethyl acetate/dichloromethane/methanol, 8.5:1.5:0.5) gave pure **22** as a pale yellow oil (0.4 g; yield 55%): ^{1}H-NMR ($CDCl_3$) ppm 2.01–2.55 (m, 2H), 2.53 (s, 3H), 3.36–3.40 (m, 2H), 3.78–3.88 (m, 3H), 3.90 (s, 3H), 9.68 (s, 1H).

(2*S*)-*N*-[(1,3-Dimethyl-4-nitropyrazol-5-yl)carbonyl]pyrrolidine-2-carboxaldehyde Diethyl Thioacetal (18a). The compound **18a** was prepared starting from **22** by the method described in the general procedure. Yellow oil, yield 59%. Spectral data were identical to those obtained with the convergent approach starting from **17a**.

Cytotoxicity. Materials and Method. The synthesized compounds **2a–o**, **12–15** were evaluated for cytotoxicity by growth inhibition studies in L1210 murine leukemia and its L1210/L-PAM subline cells resistant to melphalan (L-PAM), and LoVo human coloncarcinoma and its subline (LoVo/DX) resistant to Doxorubicin (DX).[23]

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