Synthesis of Regioisomeric 2,5-Bis-substituted-Aza-Benzothiopyranoindazoles

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The synthesis of 6-chloro-9-nitro-benzothiopyranopyridin-5-ones **2a**, **2b** and **2c** has been accomplished. Chemotype **2d** could not be prepared since attempts to cyclize 3-(2-nitro-5-chlorophenoxy)pyridine-2-carboxylic acid (**1d**) led to the decarboxylation product 3-(2-nitro-5-chlorothiophenoxy) pyridine (**40**). Analogues **2a**, **2b** or **2c** on treatment with the respectively substituted hydrazine led to the 2-(substituted)-5-nitro 7, 8- or 9-aza substituted chemotypes **3a-7a, 8b**, and **9c-13c**. The reduction of the nitro groups of these substrates was effected by treatment with hydrogen gas (palladium catalyst) or by stannous chloride to yield the 5-amino chemotypes **15a-18a**, **20b** and **21c-24c**, respectively. The conversion of these derivatives to the 2,5-bis (alkylamino)-7-, 8- and 9-aza benzothiopyranoindazoles listed in Table 3 was accomplished by direct alkylations, acylations, followed by reduction of the amido group with Red-Al or lithium aluminum hydride, or by reductive alkylations in the presence of sodium cyanoborohydride. The removal of the protective BOC-group was effected by treatment of the appropriate substrates with anhydrous hydrogen chloride to afford the respective hydrochloride salts listed in Table 4.

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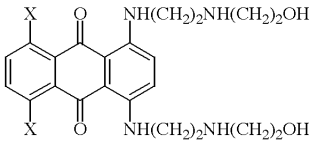
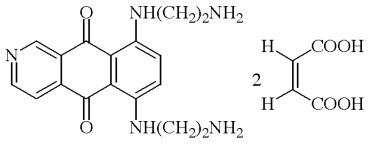
Introduction.

Despite the impressive strides that have been made in the development of antitumor agents, the need still exists for the synthesis and evaluation of potential anticancer agents with improved curative efficacies, lower host toxicities, selectivity towards tumor cells and increased effectiveness against multiple drug resistant cell lines.

Our prior studies of azabioisosteric models related to ametantrone and mitoxantrone (Figure 1) have shown that the position of the nitrogen atom has a profound effect on the expressed antitumor activity [1]. This eventually led to the development of 6,9-bis[(2-aminoethyl) amino]benz[*g*]isoquinoline-5,10-dione dimaleate salt (BBR 2778, Figure 1) which is currently entering into Phase II clinical trials.



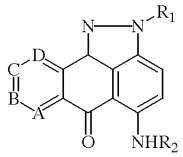
Ametantrone, X = H
Mitoxantrone, X = OH



BBR 2778 (dimaleate salt)

Figure 1. Structures of Ametantrone, Mitoxantrone and BBR 2778.

The anthrapyrazoles (Figure 2) were developed as chromophore-modified anthracene-9,10-diones with the goals of increasing the spectra of antitumor activities and reducing the cardiotoxicity exhibited by quinone analogues [2,3]. Subsequently our group developed synthetic pathways to the 7-, 8-, 9- and 10-aza-anthrapyrazoles (Figure 2) and found that the 9-aza-anthrapyrazoles exhibited the highest potency [4,5]. Two candidates of the 9-aza series are currently in Phase I clinical trials.



7-aza, A = N, B = C = D = CH
8-aza, B = N, A = C = D = CH
9-aza, C = N, A = B = D = CH
10-aza, D = N, A = B = C = CH

Azaanthrapyrazoles
R_1,R_2 = alkylamino groups

Figure 2. Structures of azaanthrapyrazoles.

The synthesis and antitumor evaluation of a number of benzothiopyranoindazoles [6-9] were subsequently reported and several of the synthetics exhibited broad-spectrum antitumor activity. In particular, CI-958 (Figure 3) is in clinical evaluation for prostate cancer

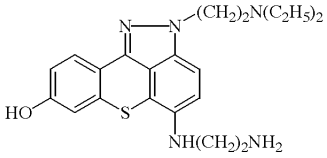
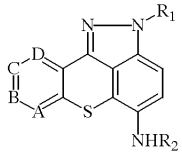


Figure 3. Structure of benzothiopyranoindazole CI 958.

treatment. These chemotypes were developed in the hope of further suppression of enzymatic reductions to radical-anion species, which might be involved in the creation of reactive oxygen radical intermediates, which could lead to cardiotoxicity problems.

It was thus of considerable interest for us to embark on a study dealing with the synthesis and antitumor evaluations of the azabioisosteres related to CI-958 but lacking the hydroxyl substitution, which might also be involved in contributing to undesirable side effects. In this manuscript we report the synthesis of three of the four possible regioisomeric 2,5-bis (substituted) aza-benzothiopyranoindazoles (hereafter referred to as aza-BTPIs) (Figure 4).



7-aza, A = N, B = C = D = CH
8-aza, B = N, A = C = D = CH
9-aza, C = N, A= B = D = CH
10-aza, D = N, A = B = C = CH

R_1, R_2 = alkylamino groups

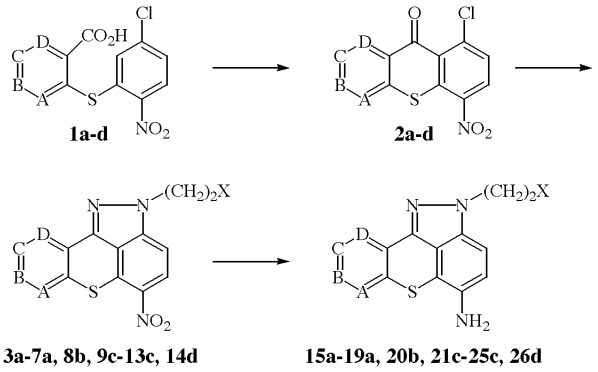
Figure 4. Azabenzothiopyranoindazoles (aza-BTPIs).

Some difficulties, which have been encountered in the preparation of the precursor leading to the 10-aza-BTPIs, will be discussed.

Synthesis.

The synthetic protocol was based on the approach previously documented for the benzothiopyranoindazoles [6,7]. The generalized pathway to the precursors leading to the 2-(substituted)-5-amino-7-, 8- and 9-aza-BTPs is outlined in Scheme 1. Although the preparation of **1d** was successful, the conversion of this substrate into intermediate **2d** was unsuccessful. Consequently, the synthesis of analogues related to **14d** and the 2-(substituted)-4-amino-10-aza-BTPIs **26d** has not been accomplished.

Scheme 1

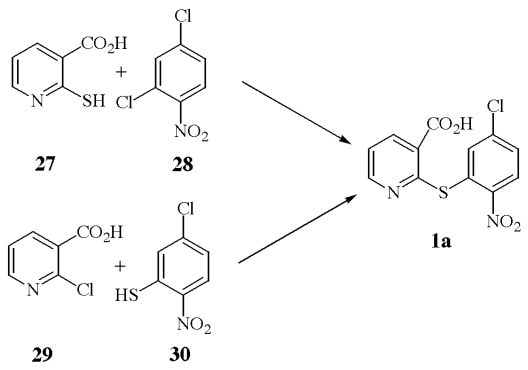


1a-d **2a-d** **3a-7a, 8b, 9c-13c, 14d** **15a-19a, 20b, 21c-25c, 26d**

a series, 7-aza, A = N, B = C = D = CH
b series, 8-aza, B = N, A = C = D = CH
c series, 9-aza, C = N, A = B = D = CH
d series, 10-aza, D = N, A = B = C = CH

The preparation of **1a** (precursor to the 7-aza-BTPIs) is illustrated in Scheme 2.

Scheme 2

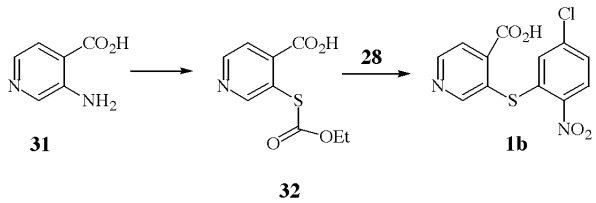


27 **28** **29** **30** **1a**

Treatment of 2-mercaptopyridine-3-carboxylic acid (**27**) with sodium ethoxide followed by addition of 2,4-dichloronitrobenzene (**28**) led to **1a**. Alternatively, this regioisomer could be prepared by heating a mixture of 2-chloronicotinic acid (**29**) with 2-nitro-5-chlorothiophenol (**30**). The preparation of **30** was based on a modification of a procedure reported in a French patent [10]. Treatment of **28** with sodium sulfide nonahydrate in a methanol solution led to a regioisomeric mixture of 2-nitro-5-chlorobenzenethiol (**30**) and 3-chloro-4-nitrobenzenethiol in a ratio of 70:30, respectively. The desired regioisomer (>98% purity) could be obtained by two recrystallizations from hexane and then from hexane containing a small amount of ethyl acetate.

The synthesis of **1b** (precursor to the 8-aza-BTPIs) is shown is Scheme 3.

Scheme 3

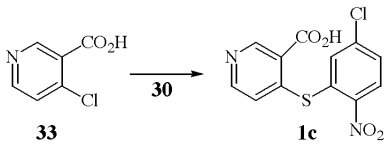


31 **32** **1b**

The diazotization of 3-aminonicotinic acid (**31**) [11,12] followed by addition of the potassium salt of *O*-ethylxanthic acid led to **32**. Treatment of **32** with sodium ethoxide in ethanol followed by the addition of **28** led to **1b**.

The preparation of **1c** (9-aza-BTPI precursor) is shown in Scheme 4.

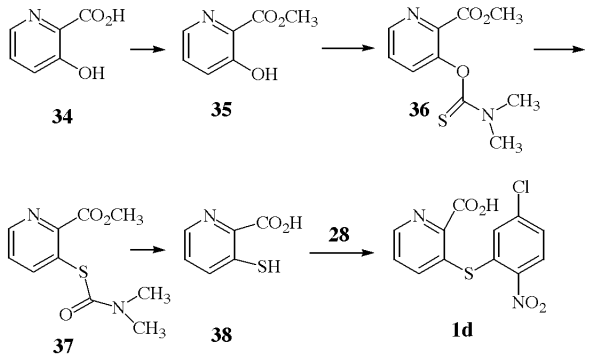
Scheme 4



Treatment of 4-chloronicotinic acid (**33**) [13] with **30** in refluxing acetone led to **1c**, which was isolated as the hydrochloride salt.

The preparation of **1d** (10-aza-BTPI precursor) is illustrated in Scheme 5.

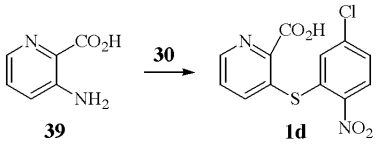
Scheme 5



Commercially available 3-hydroxy-pyridine-2-carboxylic acid (**34**) was converted to the methyl ester **35** [14] by treatment with methanol:sulfuric acid. This ester was reacted with dimethylthiocarbonyl chloride to afford the thiocarbamate **36**, upon heating in diphenyl ether at 200° underwent the Newmann-Kwart rearrangement [15-17] to yield **37**. Conversion of **37** to 3-mercaptopyridine-2-carboxylic acid (**38**) was accomplished by hydrolysis of the ester moiety with aqueous sodium carbonate. The reaction of **38** with 2,4-dichloronitrobenzene (**28**) in the presence of sodium ethoxide led to **1d**.

An alternate route to **1d** is illustrated in Scheme 6.

Scheme 6

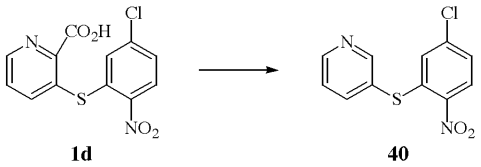


Compound **39** [12] on diazotization, followed by addition of **30** to the diazonium salt led to **1d** in good yield.

The synthesis of **2a-c** was accomplished by heating the respective acids **1a-c** in fuming sulfuric acid (Method A). In the case of **1b**, the cyclization led to poor yields of **2b** (18%). Attempts to improve on this yield by cyclization of the acid chloride derived from **1b** with aluminum trichloride did not substantially increase the yield of **2b**.

Attempts to cyclize **1d** to **2d** with fuming sulfuric acid under a variety of temperatures and conditions led to the decarboxylation product, 3-(2-nitro-5-chlorothiophenoxy) pyridine, **40** (Scheme 7).

Scheme 7



The use of concentrated sulfuric acid, trifluoromethanesulfonic acid or Eaton's reagent were also unsuccessful, as only recovered starting material was isolated. Conversion of **1d** to the acid chloride followed by cyclization with aluminum chloride was unsuccessful. Further studies are being pursued for the preparation of **2d**, the precursor to chemotypes related to **14d** and ultimately **26d**.

The conversions of the aza analogues **2a, 2b** and **2c** to the corresponding 5-nitro-aza-BTPIs **3a-7a**, **8b** and **9c-13c**, respectively, were accomplished by reaction of the appropriate hydrazines or BOC-protected hydrazines in dimethylformamide as solvent (Method B). The 5-nitro analogues along with the preparative methodology are listed in Table 1.

In several cases, such as **6a** and **12c**, the removal of the Boc-protecting group was performed by treatment with hydrogen chloride (Method C) to yield the hydrochloride salts **7a** and **13c**, respectively.

The reductions of the nitro groups of **3a-6a**, **8b** and **9c-12c** were accomplished by treatment with hydrogen gas with a palladium-charcoal catalyst (Method D) or by stannous chloride in the presence of hydrochloric acid (Method E) to afford **15a-18a**, **20b** and **21c-24c**, respectively. The reductions of the substrates with *N-tert*-butoxycarbonyl amino distal side arms were performed using Method D since the acidic conditions of Method E would remove the protective group. The conversions of **18a** and **24c** to **19a** and **25c**, respectively, were accomplished by treatment with anhydrous hydrogen chloride (Method C). The 5-amino analogues that were prepared are tabulated in Table 2.

The conversions of some of the the 5-amino chemotypes to the 2,5-bis-substituted 7, 8- and 9-aza-BTPIs were accomplished utilizing three reaction pathways, the choice of which was highly dependent on the reactant amine.

Table 1

2-Substituted-5-nitro 7-, 8- and 9-aza-BTPIs

Starting Material	Product	A	B	C	D	X	Method [a]
2a	**3a**	N	CH	CH	CH	$N(CH_3)_2$	B
2a	**4a**	N	CH	CH	CH	$N(CH_2CH)_2$	B
2a	**5a**	N	CH	CH	CH	OH	B
2a	**6a**	N	CH	CH	CH	NHBOC	B
6a	**7a**	N	CH	CH	CH	NH_2 [b]	C
2b	**8b**	CH	N	CH	CH	$N(CH_3)_2$	B
2c	**9c**	CH	CH	N	CH	$N(CH_3)_2$	B
2c	**10c**	CH	CH	N	CH	$N(CH_2CH_3)_2$	B
2c	**11c**	CH	CH	N	CH	OH	B
2c	**12c**	CH	CH	N	CH	NHBOC	B
12c	**13c**	CH	CH	N	CH	NH_2 [b]	C

[a] Method B: dimethylformamide, appropriate hydrazine. Method C: hydrogen chloride in chloroform or dichloromethane; [b] hydrochloride salts.

Table 2

2-Substituted-5-amino- 7-, 8- and 9-aza-BTPIs

Starting Material	Product	A	B	C	D	X	Method [a]
3a	**15a**	N	CH	CH	CH	$N(CH_3)_2$	D,E
4a	**16a**	N	CH	CH	CH	$N(CH_2CH_3)_2$	E
5a	**17a**	N	CH	CH	CH	OH	E
6a	**18a**	N	CH	CH	CH	NHBOC	D
18a	**19a**	N	CH	CH	CH	NH_2	C
8b	**20b**	CH	N	CH	CH	$N(CH_3)_2$	E
9c	**21c**	CH	CH	N	CH	$N(CH_3)_2$	D
10c	**22c**	CH	CH	N	CH	$N(CH_2CH_3)_2$	E
11c	**23c**	CH	CH	N	CH	OH	E
12c	**24c**	CH	CH	N	CH	NHBOC	D
24c	**25c**	CH	CH	N	CH	NH_2	C

[a] Method D: 10% Palladium on carbon, hydrogen gas, Parr bomb, 100 psi. Method E: tin(II) dichloride dihydrate, concentrated hydrochloric acid; Method C: dry hydrogen chloride in chloroform or dichloromethane.

The specific compounds, which were prepared along with the synthetic methodology leading to each, are listed in Table 3.

Direct S_N2 alkylations of **15a** to **41a**, **16a** to **43a** and **21c** to **44c,** respectively, could be effected by treatment with $Br(CH_2)_2N(CH_3)_2$ hydrobromide in the presence of potassium carbonate in refluxing toluene or in ethanol (Method F). Treatment of **15a** with $Br(CH_2)_2NH_2$ hydrobromide in refluxing ethanol (Method G) led to **42a**, bearing a primary amino group at the distal C-5 side arm. All attempts to alkylate the 8-aza analogue **20b** were unsuccessful.

The most convenient entry to those molecules with a C-5- distal primary amino side arm involved reductive amination using *N*-(tert-butoxycarbonyl)-2-aminoethanal [18] in the presence of sodium cyanoborohydride in methanol (Method H). Under these conditions **15a**, **17a**, **18a**, **20b**, **23c** and **24c** were converted into **45a**, **46a**, 47a, **48b**, **49c** and **50c**, respectively.

In the reductive amination of **17a**, the bis-reduction amination product (Figure 5) was isolated along with the desired product **46a**.

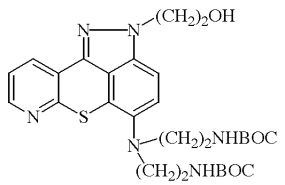
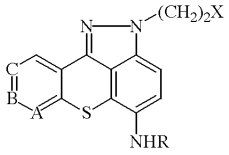


Figure 5. Structure of Bis-Amination Product from **17a.**

Table 3

Substituted Aza-benzothiopyranoindazoles

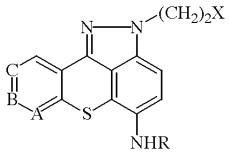


Starting Material	Product	X	R	A	B	C	Method[a]
			[DirectAlkylations]				
15a	**41a**	$N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	N	CH	CH	F
15a	**42a**	$N(CH_3)_2$	$(CH_2)_2NH_2$	N	CH	CH	G
16a	**43a**	$N(CH_2CH_2)_2$	$(CH_2)_2N(CH_3)_2$	N	CH	CH	F
21c	**44c**	$N(CH_3)_2$	$(CH_2)_2N(CH_3)_2$	N	CH	CH	F
			[ReductiveAlkylations]				
15a	**45a**	$N(CH_3)_2$	$(CH_2)_2NHBOC$	N	CH	CH	H
17a	**46a**	OH	$(CH_2)_2NHBOC$	N	CH	CH	H
18a	**47a**	HNBOC	$(CH_2)_2NHBOC$	N	CH	CH	H
20b	**48b**	$N(CH_3)_2$	$(CH_2)NHBOC$	CH	N	CH	H
23c	**49c**	OH	$(CH_2)_2NHBOC$	N	CH	CH	H
24c	**50c**	NHBOC	$(CH_2)_2NHBOC$	CH	CH	N	H
			[Acylations]				
15a	**51a**	$N(CH_3)_2$	$COCH_2NHBOC$	N	CH	CH	I
20b	**52b**	$N(CH_3)_2$	$COCH_2NHBOC$	CH	N	CH	I
21c	**53c**	$N(CH_3)_2$	$COCH_2NHBOC$	CH	CH	N	I
			[Reductions of Acylated Analogues]				
51a	**45a**	$N(CH_3)_2$	$(CH_2)_2NHBOC$	N	CH	CH	J,K
51a	**54a**	$N(CH_3)_2$	$(CH_2)_2NHCH_3$	N	CH	CH	L
52b	**48b**	$N(CH_3)_2$	$(CH_2)_2NHBOC$	CH	N	CH	J
53c	**55c**	$N(CH_3)_2$	$(CH_2)_2NHBOC$	CH	CH	N	J

[a] Method F; 2-(dimethylamino) ethyl bromide hydrobromide, potassium carbonate, toluene (or ethanol); Method G; 2-bromethylamine hydrobromide, reflux, 7 days; Method H; Sodium cyanoborohydride, N-Boc-glycine; Method I: Dicyclohexylcarbodiimide, N-Boc-glycine; Method J: Red-Al; Method K: Lithium aluminum hydride (2 eq.); Method L: Lithium aluminum hydride (5 eq.).

Table 4

Salts Prepared by Deprotections of BOC Derivatives (Method C)



Starting Material	Product	X	R	A	B	C
45a	**56a**	$N(CH_3)_2$	$(CH_2)_2NH_2$	N	CH	CH
46a	**57a**	OH	$(CH_2)_2NH_2$	N	CH	CH
47a	**58a**	NH_2	$(CH_2)_2NH_2$	N	CH	CH
48b	**59b**	$N(CH_3)_2$	$(CH_2)_2NH_2$	CH	N	CH
49c	**60c**	OH	$(CH_2)_2NH_2$	CH	CH	N
50c	**61c**	NH_2	$(CH_2)_2NH_2$	CH	CH	N
51a	**62a**	$N(CH_3)_2$	$COCH_2NH_2$	N	CH	CH
53c	**63c**	$N(CH_3)_2$	$COCH_2NH_2$	CH	CH	N
55c	**64c**	$N(CH_3)_2$	$(CH_2)_2NH_2$	CH	CH	N

Other target molecules were obtained by acylation of the C-5 amino group in **15a**, **20b** and **21c** with *N-tert*-butoxycarbonyl glycine in the presence of dicyclohexyl carbodiimide (Method I) to afford **51a, 52b** and **53c**, respectively.

These acylated analogues were carefully reduced with Red-Al (Method J) or lithium aluminum hydride (Method K) to lead to **45a**, **48b** and **55c**, respectively, with C-5 distal *tert*-butoxycarbonyl-protected primary amino groups.

During the reductions of the amide carbonyl group of the acylated chemotypes with lithium aluminum hydride, it was found that the use of less than 2 equivalents of the reducing agent (Method J) was critical in order to effect the reduction of the amido group. If the reduction of **51a** was performed using 5 equivalents of lithium aluminum hydride, **45a** (13%) **54a** (26%) and a product (26%) spectroscopically tentatively identified as resulting from reduction of the imine bond (Figure 6). One notes that **54a** arises from reduction of the *tert*-butoxycarbonyl group to a methyl group and the amide carbonyl group to a methylene group.

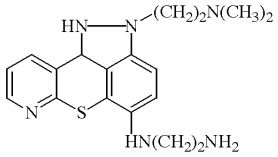


Figure 6. Product from Reduction of **51a** with 5 eqs of $LiAlH_4$.

The removal of the *tert*-butoxycarbonyl protecting group and conversions to the hydrochloride salts could be accomplished by treatment of the respective analogues with dry hydrogen chloride gas (Method C). The results of these conversions are tabulated in Table 4.

The antitumor activities of the nitro, amino and disubstituted chemotypes will be reported in a subsequent publication.

EXPERIMENTAL

Melting points were determined on a Thomas Hoover or a Fisher-Johns apparatus and are uncorrected. The nmr spectra were recorded on a Bruker ARX-500 pulsed FT spectrometer. Microanalyses were performed by Robertson Microlit Laboratories, Inc., Madison, N. J.

2-(2-Nitro-5-chloro)thiophenoxynicotinic acid (**1a**).

Route 1.

The 2-mercaptopyridine-3-carboxylic acid (**27**) (10.0 g, 0.064 mole) was added to a sodium ethoxide solution, which was prepared by addition of sodium metal (3.1 g, 0.13 mole) to ethanol (5 ml). To the magnetically stirred suspension was added 2,4-dichloronitrobenzene (**28**) (12.4 g, 0.064 mole). The mixture was heated at reflux for 24 hours and concentrated to dryness. Water was added to dissolve the resultant solid and the aqueous phase was extracted with ether (2 x 25 ml). Acidification of the aqueous layer with concentrated hydrochloric acid to *pH* 1 led to a yellow solid which was collected by filtration, dried (9.2 g) and recrystallized from ethylene glycol monoethyl ether (175 ml) to yield **1a** (12.1 g, 65%), mp 248-249°; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 8.39 (dd, J = 1.7, 4.7 Hz, 1H), 8.27 (dd, J = 1.7, 7.9 Hz, 1H), 8.10 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 2.3 Hz, 1H), 7.76 (dd, J = 2.3, 8.7 Hz, 1H), 7.30 (dd, J = 4.7, 7.7 Hz, 1H).

Anal. Calcd. for $C_{12}H_7ClN_2O_4S$: C, 46.39; H, 2.27; N, 9.01. Found: C, 46.39; H, 2.27; N, 8.80.

Route 2.

A solution of **30** (0.26 g, 1.4 mmoles) in acetone (10 ml) was added to 2-chloronicotinic acid (**29**) (0.11 g, 0.7 mmole). The suspension was refluxed for 5 hours and the resultant mixture was cooled to room temperature. The bright yellow precipitate was collected by filtration, washed with acetone to afford a yellow solid (0.12 g, 55%) whose properties were identical to the product obtained in Route 1. Additional product was obtained by concentration of the filtrate.

3-(2-Nitro-5-chlorothiophenoxy)isonicotinic Acid (**1b**).

The crude xanthate ester **32** (2.0 g, 8.23 mmoles) was added to a sodium ethoxide solution which was prepared by dissolving sodium metal (0.38 g, 16.5 mmoles) in anhydrous ethanol (18 ml). The resulting suspension was heated at reflux for 1 hour and a solution of 2,4-dichloronitrobenzene (**28**) (1.6 g, 8.3 mmoles) in ethanol (10 ml) was added. The mixture was refluxed for 15 hours, cooled and concentrated to dryness. Water was added and the aqueous layer was extracted twice with ether. The aqueous phase was acidified (*pH* 1) by addition of concentrated hydrochloric acid. The resultant solid was collected by filtration, dried and recrystallized from ethylene glycol monomethyl ether to yield **1b** (1.79 g, 70%), mp 210-213°; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 8.77 (d, J = 4.8 Hz, 1H), 8.67 (s, 1H), 8.23 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 4.8 Hz, 1H), 7.56 (dd, J = 2.2, 8.8 Hz, 1H), 6.99 (d, J = 2.1 Hz, 1H).

Anal. Calcd. For $C_{12}H_7ClN_2O_4S$: C, 46.39; H, 2.27; N, 9.01. Found: C, 46.77; H, 2.43; N, 8.76.

4-(2-Nitro-5-chlorothiophenoxy)pyridine-3-carboxylic acid Hydrochloride (**1c**).

A solution of **33** (1.09 g, 5.77 mmoles) in acetone (12 ml) was added to **30** (0.85 g, 5.41 mmoles). The yellow coloration of the thiol quickly disappeared and the mixture was refluxed for 1 hour. Upon cooling to room temperature, the product was collected by filtration and washed with acetone to yield **1c** (1.72 g, 92% as the hydrochloride salt) as a pale yellow solid, mp 228-229°; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 9.05 (s, 1H), 8.50 (d, J = 5.9 Hz, 1H), 8.23 (d, J = 8.7 Hz, 1H), 7.98 (d, J = 2.0 Hz, 1H), 7.92 (dd, J = 2.2, 8.7 Hz, 1H), 6.98 (d, J = 5.9 Hz, 1H).

Anal. Calcd. For $C_{12}H_8Cl_2N_2O_4S$: C, 41.52; H, 2.32; N, 8.07. Found: C, 41.33; H, 2.34; N, 7.78.

3-(2-Nitro-5-chlorothiophenoxy)pyridine-2-carboxylic Acid (**1d**).

Route 1.

Acid **38** (0.20 g, 1.29 mmoles) was added to a sodium ethoxide solution which was prepared by treatment of anhydrous ethanol (3.0 ml) with sodium metal (0.062 g, 2.7 mmoles). To the magnetically stirred suspension, a solution of **28** (0.25 g, 1.29 mmoles) in anhydrous ethanol (1 ml) was slowly added *via* a dropping funnel. The mixture was stirred at room temperature for 3 hours and concentrated to dryness. The residue was washed with ether and added to water (2 ml). Acidification of the aqueous phase with concentrated hydrochloric acid to *pH* 2 led to a precipitate which was collected by filtration and dried to afford **1d** (0.30 g, 75%), mp 147-148°; ^{1}H nmr δ 8.70 (dd, J = 1.3, 4.6 Hz, 1H); 8.23 (d, J = 8.8 Hz, 1H), 7.79 (dd, J = 1.2, 8.0 Hz, 1H); 7.63 (dd, J = 4.6, 8.0 Hz, 1H), 7.60 (dd, J = 2.1, 8.8 Hz, 1H), 7.04 (d, J = 2.1 Hz, 1H).

Anal. Calcd. for $C_{12}H_7ClN_2O_4S$: C, 46.39; H, 2.27; N, 9.01. Found: C, 46.28; H, 2.04; N, 8.98.

Route 2.

A solution of **39** (0.20 g, 1.45 mmoles) in concentrated hydrochloric acid (0.40 ml) and water (1.0 ml) was stirred at 5° while a solution of sodium nitrite (0.10 g, 1.45 mmoles) was added dropwise. The solution was stirred for 15 minutes, buffered with sodium acetate and added slowly through a cannula to a mixture of **30** (0.28 g, 1.45 mmoles), sodium hydroxide (0.29 g, 7.25 mmoles) in water (1.5 ml). The mixture was warmed at 50° for 20 minutes, cooled to room temperature and acidified with concentrated hydrochloric acid to *pH* 2. The solid was collected by filtration to afford **1d** (0.33 g, 77%) which was identical to the product obtained utilizing route 1.

6-Chloro-9-nitro-5*H*-[1]benzothiopyrano[2,3-*b*]pyridin-5-one (**2a**) (Method A).

Acid **1a** (0.65 g, 2.08 mmoles) was added to fuming sulfuric acid (2 ml, 18-24% sulfur trioxide content) and the mixture was placed in an oil bath preheated to 75°. The solution was heated at 125-130° for 1.25 hours. The mixture was removed form the oil bath, cooled to room temperature and poured over ice water (150 ml). The yellow precipitate was collected by filtration, washed well with water and dried (0.60 g). This material was dissolved in hot dimethylformamide (11 ml) which on cooling immediately afforded a solid which was collected by filtration, washed with ether and dried to yield **2a** (0.54 g, 89%) as a beautiful yellow product, mp 267-270°; ^{1}H nmr δ 8.84 (dd, J = 1.77, 4.60 Hz, 1H), 8.60 (J = 1.77, 8.05 Hz, 1H), 8.51 (d, J = 8.80 Hz, 1H), 7.68 (d, J = 8.80 Hz, 1H), 7.51 (dd, J = 4.60, 8.00 Hz, 1H).

Anal. Calcd. For $C_{12}H_5ClN_2O_3S$: C, 49.24; H, 1.72; N, 9.58. Found: C, 49.23; H, 1.63; N, 9.51.

6-Chloro-9-nitro-5*H*[1]benzothiopyrano[2,3-*c*]pyridin-5-one (**2b**).

(Method A). Acid **1b** (0.67 g, 2.16 mmoles) was added to fuming sulfuric acid (2 ml, 18-24% free sulfur trioxide) and the mixture was stirred under a nitrogen atmosphere at room tempera ure for 10 minutes. The mixture was poured over ice water (70 ml) and the greenish-yellow precipitate was collected by filtration and dried. The crude product was boiled in chloroform (100 ml) and some insoluble material was removed by filtration. The filtrate was concentrated to afford **2b** (0.10 g, 17%) as a bright yellow solid, mp 272-275°; ^{1}H nmr (deuteriochloroform): δ 9.02 (s, 1H), 8.79 (d, J = 5.2 Hz, 1H), 8.54 (d, J = 8.8 Hz, 1H), 8.09 (d, J = 5.2 Hz, 1H), 7.70 (d, J = 8.8Hz, 1H).

Anal. Calcd. For $C_{12}H_5ClN_2O_3S$: C, 49.24; H, 1.72; N, 9.58. Found: C, 49.12; H, 1.74; N, 9.47.

6-Chloro-9-nitro-5*H*-[1]benzothiopyrano[3,2-*c*]pyridin-5-one (**2c**).

(Method A). Hydrochloride salt **1c** (0.60 g, 1.93 mmoles) was added to fuming sulfuric acid (3.3 ml, 18-24% free sulfur trioxide) and the mixture was placed in an oil bath preheated to 40°. The dark reddish-amber solution was heated to 60° during 50 minutes and held at this temperature for 1 hour. The cooled mixture was poured over ice water (25 ml) and then neutralized by the addition of solid sodium bicarbonate. The resultant bright yellow solid was collected by filtration and dried (0.44 g). The crude solid was boiled in chloroform (40 ml), treated with activated charcoal and filtered through a celite bed to remove the charcoal. Concentration of the filtrate led to **2c** (0.41 g, 72%), mp 220-222°; ^{1}H nmr (deuteriochloroform): δ 9.43 (s,1H), 8.74 (d, J = 5.5 Hz, 1H), 8.50 (d, J = 8.8 Hz, 1H), 7.70 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 5.5 Hz, 1H).

Anal. Calcd. for $C_{12}H_5ClN_2O_3S$: C, 49.24; H, 1.72; N, 9.58. Found: C, 49.41; H, 1.75; N, 9.53.

N,*N*-Dimethyl-5-nitro-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]-indazole-2-ethanamine (**3a**).

(Method B). A suspension of **2a** (2.5 g, 8.6 mmoles) in dimethylformamide (25 ml) under a nitrogen atmosphere was cooled in an ice bath and *N*-2-[2-(dimethylamino)-ethyl]hydrazine (1.0 g, 9.7 mmoles) was added dropwise. The coloration immediately changed from yellow to bright orange. The suspension was stirred for 15 hours at room temperature and the mixture was quenched over ice water. The *pH* was adjusted to 10.5-11 by the addition of a saturated solution of potassium carbonate. The mixture was extracted with chloroform (2 x 100 ml) and the chloroform layer was washed with cold water (50 ml) and brine (2 x 50 ml). The chloroform was dried over magnesium sulfate, the drying agent removed by filtration and the filtrate concentrated to yield **3a** (2.5 g, 86%) as a golden brown solid which readily crystallized from acetonitrile, mp 173-174°; ^{1}H nmr (deuteriochloroform): δ 8.55 (dd, J = 1.4, 4.6 Hz, 1H), 8.41 (dd, J = 1.4, 7.9 Hz, 1H), 8.23 (d, J = 9.2 Hz, 1H), 7.33 (dd, J = 4.6, 7.8 Hz, 1H), 7.05 (d, J = 9.2 Hz, 1H), 4.48 (t, J = 6.6 Hz, 2H), 2.88 (t, J = 6.6 Hz, 2H), 2.30 (s, 6H).

Anal. Calcd. for $C_{16}H_{15}N_5O_2S$: C, 56.29; H, 4.43; N, 20.51. Found: C, 56.04; H, 4.21; N, 20.28.

N,*N*-Diethyl-5-nitro-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine (**4a**).

Treatment of **2a** with *N*-2-[2-(diethylamino)ethyl]hydrazine following Method B led to **4a** (75%), recrystallized from acetonitrile, mp 132-133°; ^{1}H nmr (deuteriochloroform): δ 8.56 (dd, J = 1.7, 4.6 Hz, 1H), 8.43 (dd, J = 1.7, 7.8 Hz, 1H), 8.25 (d, J = 9.3 Hz, 1H), 7.33 (dd, J = 4.6, 7.8 Hz, 1H), 7.08 (d, J = 9.3 Hz, 1H), 4.44 (t, J = 6.4 Hz, 2H), 2.98 (t, J = 6.4 Hz, 2H), 2.54 (q, J = 7.1 Hz, 4H), 0.94 (t, J = 7.1 Hz, 6H).

Anal. Calcd. for $C_{18}H_{19}N_5O_2S$: C, 58.52; H, 5.18; N, 18.91. Found: C, 58.59; H, 5.08; N, 19.11.

2-[2-(Hydroxyethyl)]-5-nitro-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazole (**5a**).

Treatment of **2a** with *N*-[2-(hydroxyethyl)]hydrazine according to Method B led to crude material which was purified by flash chromatography by elution with methanol:dichloromethane 0.5:99.5 and gradually changing to 5:95 which eluted the product **5a** (0.51 g, 50%), mp 266-268°. A portion was recrystallized from acetonitrile for elemental analysis; ^{1} H nmr (deuteriochloroform): δ 8.67 (dd, J = 1.7, 4.8 Hz, 1H), 8.41 (dd, J = 1.7, 8.0 Hz, 1H), 8.29 (d, J = 9.3 Hz, 1H), 7.34 (dd, J = 4.6, 7.9 Hz, 1H), 7.11 (d, J = 9.3 Hz, 1H), 4.53 (t, J = 4.8 Hz, 2H), 4.20 (q, J = 4.8 Hz, 2H).

Anal. Calcd. for $C_{14}H_{10}N_4O_3S$: C, 53.50; H, 3.21; N, 17.82. Found: C, 53.33; H, 2.89; N, 17.62.

1,1-Dimethylethyl [2-(5-nitro-2*H*-pyrido[3',2':5,6]thiopyrano-[4,3,2-*cd*]indazol-2-yl)ethyl]carbamate (**6a**).

Treatment of **2a** with *N*-[2-(*tert*-butoxycarbonyl-amino)ethyl]hydrazine using Method B led to crude **6a** (85%), mp 237-238°, which was purified by flash chromatography eluting with methanol:dichloromethane 0.5:99.5 followed by recrystallization from acetonitrile; ^{1}H nmr (deuteriochloroform): δ 8.43 (dd, J = 1.6, 4.6 Hz, 1H), 8.34 (dd, J = 1.6, 7.8 Hz, 1H), 8.20 (d, J = 9.2 Hz, 1H), 7.30 (dd, J = 4.6, 7.8 Hz, 1H), 7.10 (d, J = 9.2Hz, 1H), 5.04 (brs, 1H), 4.55 (t, J = 5.6 Hz, 2H), 3.70 (q, J = 5.8 Hz, 2H), 1.59 (s, 9H).

Anal. Calcd. for $C_{19}H_{19}N_5O_4S$: C, 55.20; H, 4.63; N, 16.94. Found: C, 55.40; H, 4.69; N, 16.97.

5-Nitro-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine dihydrochloride (**7a**).

(Method C). Hydrogen chloride gas was briefly passed through a solution of **6a** in chloroform (1 ml). The precipitated salt **7a** (95%) was collected by filtration; ^{1}H nmr (deuterium oxide) δ 7.87 (dd, J = 1.6, 4.5 Hz, 1H), 7.58 (dd, J = 1.6, 7.6 Hz, 1H), 7.28 (d, J = 9.1 Hz, 1H), 6.98 (dd, J = 4.5, 7.6 Hz, 1H), 6.55 (d, J = 9.1 Hz, 2H), 4.25 (t, J = 6.4 Hz, 2H), 3.35 (t, J = 6.4 Hz, 2H).

Anal. Calcd. for $C_{14}H_{11}N_5O_2S$•2HCl•H2O; C, 43.31; H, 3.89; N, 18.04. Found: C, 43.06; H, 4.03; N, 18.42.

2-[2-(Dimethylamino)ethyl)]-5-nitro-2*H*-pyrido[4',3':5,6]thiopyrano[4,3,2-*cd*]indazole (**8b**).

Treatment of **2b** with *N*-2-[2-(dimethylamino)ethyl]hydrazine according to method B led to **8b** (86%), mp 205-206°, which was crystallized from acetonitrile; ^{1}H nmr (deuteriochloroform): δ 8.81 (s, 1H), 8.58 (d, J = 5.2 Hz, 1H), 8.28 (d, J = 9.4 Hz, 1H), 8.00 (d, J = 5.2 Hz, 1H), 7.10 (d, J = 9.3 Hz, 1H), 4.51 (t, J = 6.5 Hz, 2H), 2.92 (t, 6.5 Hz, 2H), 2.31 (s, 6H).

Anal. Calcd. for $C_{16}H_{15}N_5O_2S$: C, 56.29; H, 4.43; N, 20.51. Found: C, 55.92; H, 4.80; N, 20.44.

N,*N*-Dimethyl-5-nitro-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine (**9c**).

Treatment of **2c** with *N*-[2-(dimethylamino)ethyl]hydrazine using Method B led to **9c** (80%), which readily crystallized from acetonitrile, mp 214-216°; ^{1}H nmr (deuteriochloroform): δ 9.40 (s, 1H), 8.52 (d, J = 5.5 Hz, 1H), 8.27 (d, J = 9.3 Hz, 1H), 7.46 (d, J = 5.6 Hz, 1H), 7.12 (d, J = 9.3 Hz, 1H), 4.51 (t, J = 6.5 Hz, 2H), 2.91 (t, J = 6.5 Hz, 2H), 2.27 (s, 6H).

Anal. Calcd. for $C_{16}H_{15}N_5O_2S$: C, 56.29; H, 4.43; N, 20.51. Found: C, 56.19; H, 4.80; N, 20.44.

N,*N*-Diethyl-5-nitro-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine (**10c**).

Treatment of **2c** with *N*-2-[2-(diethylamino)ethyl]hydrazine according to procedure B led to **10c** (96%) which readily crystallized from acetonitrile, mp 143-144°; ^{1}H nmr (deuteriochloroform): δ 9.38 (s, 1H), 8.50 (d, J = 5.4 Hz, 1H), 8.23 (d, J = 9.3 Hz, 1H), 7.45 (d, J = 5.4 Hz, 1H), 7.11 (d, J = 9.3 Hz, 1H), 4.45 (t, J = 6.4 Hz, 2H), 2.98 (t, J = 6.4 Hz, 2H), 2.54 (q, J = 7.1 Hz, 4H), 0.92 (t, J = 7.1 Hz, 6H).

Anal. Calcd. for $C_{18}H_{19}N_5O_2S$: C, 58.52; H, 5.19; N, 18.96. Found: C, 58.32; H, 5.16; N, 18.90.

5-Nitro-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanol (**11c**).

Treatment of **2c** with *N*-2-[2-(hydroxyethyl)]hydrazine according to Method B afforded **11c** (90%), mp 269-270° (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 8.94 (s, 1H), 8.10 (d, J = 5.3 Hz, 1H), 7.84 (d, J = 9.3 Hz, 1H), 6.94 (d, J = 9.3 Hz, 1H), 4.35 (t, J = 5.2 Hz, 1H), 4.16 (t, J = 4.7 Hz, 2H), 3.65 (q, J = 4.7, 5.2 Hz, 2H).

Anal. Calcd. for $C_{14}H_{10}N_4O_3S$: C, 53.50; H, 3.21; N, 17.82. Found: C, 53.22: H, 3.01: N, 17.61.

1,1-Dimethylethyl [2-(5-Nitro-2*H*-pyrido[3',4';5,6]thiopyrano-[4,3,2-*cd*]indazol-2-yl)ethyl]carbamate (**12c**).

Treatment of **2c** with *N*-[2-*tert*-butoxycarbonyl-amino)ethyl]hydrazine according to method B afforded **12c** (0.74 g, 79%), which was recrystallized from acetonitrile; mp 267-268°C; ^{1}H nmr (deuteriochloroform): δ 9.38 (s, 1H), 8.50 (d, J = 4.8 Hz, 1H), 8.27 (d, J = 9.1 Hz, 1H), 7.46 (d, J = 4.8 Hz, 1H), 7.13 (d, J = 8.9 Hz, 1H), 4.78 (br s, 1H), 4.59 (t, J = 5.5 Hz, 2H), 3.70 (q, J = 5.5 Hz, 2H), 1.42 (s, 9H).

Anal. Calcd. for $C_{19}H_{19}N_5O_4S$: C, 55.20; H, 4.63; N, 16.94. Found: C, 55.53; H, 4.59; N, 17.06.

5-Nitro-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine Dihydrochloride (**13c**).

Treatment of **12c** with hydrogen chloride according to method C led to **13c**; ^{1}H nmr (deuterium oxide) δ 9.30 (s, 1H), 8.61 (d, J = 6.2 Hz, 1H), 8.16 (d, J = 9.3 Hz, 1H), 8.06 (d, J = 6.2 Hz, 1H), 7.41 (d, J = 9.3 Hz, 1H), 4.86 (t, J = 5.6 Hz, 2H), 3.75 (t, J = 5.6 Hz, 2H).

Anal. Calcd. for $C_{14}H_{11}N_5O_2S$•2HCl: C, 43.53; H, 3.39; N, 18.13. Found: C, 43.26; H, 3.53; N, 18.50.

N,*N*-Dimethyl-5-amino-2*H*-pyrido[3',2':5,6]thiopyrano-[4,3,2-*cd*]indazole-2-ethanamine (**15a**).

(Method D). A mixture of **3a** (2.12 g, 6.2 mmoles) and 10% palladium on carbon (0.35 g) in glacial acetic acid was placed in a Parr bomb and hydrogenated for 18 hours at about 100 psi. The mixture was filtered through a celite bed and the filtrate was concentrated to yield a dark amber oil, which was dissolved in chloroform (200 ml). The solution was washed with 5% aqueous ammonium hydroxide (200 ml), water (200 ml) and brine (2 x 200 ml). The chloroform was dried over sodium sulfate, the drying agent removed by filtration and the filtrate concentrated to yield **15a** (1.7 g, 88%) as a reddish-yellow solid, mp 184-186°, which readily crystallized from acetonitrile; ^{1}H nmr (deuteriochloroform): δ 8.28 (dd,

J = 1.6, 4.7 Hz, 1H), 8.16 (dd, J = 1.6, 7.8 Hz, 1H), 7.10 (dd, J = 4.7, 7.8 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 4.35 (t, J = 7.1 Hz, 2H), 3.39 (s, 2H), 2.81 (t, J = 7.1 Hz, 2H), 2.24 (s, 6H).

Anal. Calcd. for $C_{16}H_{17}N_5S$: C, 61.71; H, 5.50; N, 22.49. Found: C, 61.61; H, 5.27; N, 22.10.

(Method E). A solution of tin(II) chloride dihydrate (0.5 g, 2.66 mmoles) in concentrated hydrochloric acid (1 ml) was added to a solution of **3a** (200 mg, 0.59 mmole) in a mixture of ethanol:concentrated hydrochloric acid 1 ml: 1 ml. The mixture was heated at reflux for 14 hours and then cooled to room temperature. The precipitate was collected by filtration, placed in water (1 ml) and neutralized by the addition of a sodium hydroxide solution (10 *M*). The lemon-yellow solid was collected by filtration, washed with water and dried to afford **5a** (0.15 g, 85%), identical in all respects to the product obtained using Method D.

N,*N*-Diethyl-5-amino-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*}indazole-*2*-ethanamine (**16a**).

Following method E, **4a** was converted into **16a** (80%), mp 180-181° (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 8.28 (dd, J = 4.7, 1.8 Hz, 1H), 8.16 (dd, J = 7.8, 1.8 Hz, 1H), 7.10 (dd, J = 7.8, 4.7 Hz, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.76 (d, J = 8.7 Hz, 1H), 4.30 (t, J = 7.1 Hz, 2H), 3.37 (br s, 2H), 2.92 (t, J = 7.1 Hz, 2H), 2.57 (q, J = 7.1 Hz, 4H), 1.00 (t, J = 7.1 Hz, 6H).

Anal. Calcd. for $C_{18}H_{21}N_5S$: C, 63.69; H, 6.24; N, 20.63. Found: C, 63.58; H, 6.21; N, 20.45.

N'-(2-Hydroxyethyl)-5-amino-2*H*-pyrido[3',2':5,6]thiopyrano-[4,3,2-*cd*]indazole-(**17a**).

Treatment of **5a** according to method E led to **17a** (79%), mp 255-257° (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 9.27 (dd, J = 4.6, 1.7 Hz, 1H), 9.15 (dd, J = 7.8, 1.5 Hz, 1H), 8.14 (dd, J = 7.8, 4.6 Hz, 1H), 7.97 (d, J = 8.7 Hz, 1H), 7.86 (d, J = 8.7 Hz, 1H), 5.49 (t, J = 5.6 Hz, 1H), 5.36 (t, J = 5.5 Hz, 2H)), 4.97 (q, J = 5.4 Hz, 2H), 4.87 (br s, 2H).

Anal. Calcd. for $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70. Found: C, 59.31; H, 3.87; N, 19.30.

1,1-Dimethylethyl [2-(5-Amino-2*H*-pyrido[3',2':5,6]thiopyrano-[4,3,2-*cd*]indazol-2-yl]ethyl]carbamate (**18a**).

Following method D, **6a** was converted into **18a** (86%) which was purified by flash chromatography over silica gel by elution with dichloromethane containing a small amount of methanol and gradually increasing to methanol:dichloromethane (98:2), mp 190-191° (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 8.35 (dd, J = 7.6, 1.5 Hz, 1H); 8.21 (dd, J = 7.6, 1.5 Hz, 1H); 8.18 (dd, J = 7.7, 4.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 4.92 (br s, 1H), 4.42 (t, J = 5.4 Hz, 2H), 3.69 (br s, 2H), 3.67 (q, J = 5.4 Hz, 2H), 1.49 (s, 9H).

Anal. Calcd. for $C_{19}H_{21}N_5O_2S$: C, 59.51; H, 5.52; N, 18.26. Found: C, 59.31; H, 5.51; N, 18.20.

5-Amino-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine Trihydrochloride (**19a**).

Treatment of **18a** with dry hydrogen chloride according to method C led to **19a** (quantitatively); ^{1}H nmr (deuterium oxide) δ 8.11 (m, 2H), 7.37 (m, 1H); 7.22 (d, J = 8.9 Hz, 1H), 7.15 (d, J = 8.9 Hz, 1H), 4.65 (t, J = 5.8 Hz, 2H), 3.64 (t, J = 5.8 Hz, 2H).

Anal. Calcd for $C_{14}H_{13}N_5S{\cdot}3HCl$: C, 42.82; H, 4.11; N, 17.83. Found: C, 42.86; H, 4.33; N, 17.57.

N,*N*-Dimethyl-5-amino-2*H*-pyrido[4',3':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine (**20b**).

Treatment of **8b** according to method E led to **20b** (77%) which was recrystallized from acetonitrile, mp 240-242°; ^{1}H nmr (deuteriochloroform): δ 8.45 (s, 1H), 8.34 (d, J = 5.0 Hz, 1H), 7.76 (d, J = 5.0 Hz, 1H), 6.87 (d, J = 8.7 Hz, 1H), 6.80 (d, J = 8.7 Hz, 1H), 4.37 (t, J = 7.0 Hz, 2H), 3.38 (br s, 2H), 2.83 (t, J = 7.0 Hz, 2H), 2.31 (s, 6H).

Anal. Calcd. for $C_{16}H_{17}N_5S$: C, 61.71; H, 5.50; N, 22.49. Found: C, 61.71; H, 5.38; N, 22.53.

N,*N*-Dimethyl-5-amino-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine (**21c**).

Treatment of **9c** following method D led to **21c** (65%) which was recrystallized from acetonitrile, mp 162-165°; ^{1}H nmr (deuteriochloroform): δ 9.10 (s, 1H), 8.25 (d, J = 5.4 Hz, 1H); 7.12 (d, J = 5.4 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 6.78 (d, J = 8.7 Hz, 1H), 4.35 (t, J = 7.0 Hz, 2H), 3.34 (br s, 2H), 2.82 (t, J = 7.0 Hz, 2H), 2.30 (s, 6H).

Anal. Calcd. for $C_{16}H_{17}N_5S$: C, 61.71; H, 5.50; N, 22.49. Found: C, 61.35; H, 5.46; N, 22.31.

N,*N*-Diethyl-5-amino-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]-indazole-2-ethanamine (**22c**).

The reduction of **10c** was performed using method E to yield **22c** (quantitatively) which was recrystallized from acetonitrile, mp 117-118°; ^{1}H nmr (deuteriochloroform): δ 9.09 (s, 1H), 8.24 (d, J = 5.5 Hz, 1H), 7.13 (d, J = 5.5 Hz, 1H), 6.88 (d, J = 8.6 Hz, 1H), 6.77 (d, J = 8.6 Hz, 1H), 4.31 (t, J = 7.9 Hz, 2H), 3.33 (br s, 2H), 2.92 (t, J = 7.0 Hz, 2H), 2.58 (q, J = 7.1 Hz, 4H), 1.01 (t, J = 7.1 Hz, 6H).

Anal. Calcd. for $C_{18}H_{21}N_5S$: C, 63.69; H, 6.24; N, 20.63. Found: C, 63.50; H, 6.15; N, 20.71.

5-Amino-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanol (**23c**).

Analogue **11c** was converted into **23c** (79%) using method E, mp 225-227° (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform, dimethylsulfoxide-d_6): δ 8.83 (s, 1H), 8.21 (d, J=5.4 Hz, 1H); 7.31 (d, J = 5.4 Hz, 1H); 7.05 (d, J = 8.8 Hz, 1H); 6.82 (d, J = 8.8Hz, 1H); 4.82 (d, J = 5.0 Hz, 1H); 4.72 (s, 2H); 4.27 (t, J = 5.4 Hz, 2H); 3.68 (q, J = 5.4, 5.0 Hz, 2H).

Anal. Calcd, $C_{14}H_{12}N_4OS$: C, 59.14; H, 4.25; N, 19.70. Found: C, 59.39; H, 3.95; N, 19.63.

1,1-Dimethylethyl [2-(5-Amino-2*H*-pyrido[3',4':5,6]thiopyrano-[4,3,2-*cd*]indazole-2-yl)ethyl]carbamate (**24c**).

Analogue **12c** was converted into **24c** (90%, recrystallized from acetonitrile) using method D, mp 263-264°; ^{1}H nmr (deuteriochloroform): δ 9.08 (s, 1H), 8.24 (d, J = 5.4 Hz, 1H), 7.13(d, J = 5.4 Hz, 1H); 6.88 (d, J = 8.97 Hz, 1H); 6.78 (d, J = 8.8 Hz, 1H); 4.91 (broad s, 1H); 4.36 (t, J = 5.2 Hz, 2H); 3.64 (q, J = 5.2 Hz, 2H); 3.38 (broad s, 2H); 1.42 (s, 9H).

Anal. Calcd. For $C_{19}H_{21}N_5O_2S$: C, 59.51; H, 5.52; N, 18.26. Found: C, 59.72; H, 5.39; N, 18.45.

5-Amino-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]indazole-2-ethanamine Trihydrochloride (**25c**).

Treatment of **24c** with dry hydrogen chloride according to method C yielded **25c** (quantitatively); ^{1}H nmr (deuterium oxide) δ: 8.87 (s, 1H), 8.87 (s, 1H), 8.29 (d, J = 6.4 Hz, 1H), 7.86 (d, J = 6.4 Hz, 1H), 7.21 (d, J = 8.9 Hz, 1H), 7.14 (d, J = 8.9 Hz, 1H), 4.62 (t, J = 5.8 Hz, 2H), 3.55 (t, J = 5.8 Hz, 2H).

Anal. Calcd. for $C_{14}H_{13}N_5S.3HCl$: C, 42.62; H, 4.11; N, 17.83. Found: C, 42.67; H, 3.97; N, 17.80.

2-Nitro-5-chlorothiophenol (**30**).

Sodium sulfide nonahydrate (19.0 g, 0.078 mole) was placed in methanol (75 ml) and the mixture was stirred until the entire sulfide dissolved. The mixture was placed in an ice bath and a solution of 2.4-dichloronitrobenzene (**28**) (15.0 g, 0.078 mole) in methanol (50 ml) was added from a dropping funnel over a period of 1.25 hours (an additional amount of methanol (20 ml) was added to the funnel). The resultant suspension was allowed to warm to room temperature and stirred for 23 hours. At this point, a deep red coloration along with some yellow insoluble material resulted. The mixture was quenched over ice water (300 ml) and the insoluble material was removed by filtration. The filtrate was then refiltered through a celite bed and the filtrate acidified with concentrated hydrochloric acid to *pH* 1.5. The yellow precipitate was allowed to stand for a few hours, collected by filtration and air dried to yield a yellow crude solid (5.4 g) (^{1}H nmr analysis indicated about 30% of the undesired regioisomer). The crude product was heated in hexane (175 ml) and then decanted from a small amount of an orange oil. On cooling and standing for 24 hours, a yellow solid was collected by filtration (3.4 g) which was still contaminated with about 10% of the other regioisomer (^{1}H nmr analysis) TLC on silica gel using 4:1 hexane: ethyl acetate]. This crude product (3.4 g) was redissolved in hot hexane (70 ml) to which ethyl acetate (1-2 ml) was added. On cooling **30** was obtained as yellow crystals, 1.8 g (98% purity), mp 87-88°, lit. mp 96° [10]; ^{1}H nmr (deuteriochloroform): δ 8.18 (d, J = 8.9 Hz, 1H), 7.44 (d, J = 2.1 Hz, 1H), 7.23 (dd, J = 8.9, 2.2 Hz, 1H), 4.08 (s, 1H).

3-(Thiocarbonic Acid *O*-Ethyl Ester)-*S*-4-pyridylcarboxylic Acid (**32**).

A solution of sodium nitrite (3.0 g, 43.5 mmoles) in water (14 ml) was added to a mixture of **31** (6.0 g, 43.5 mmoles) in water (34 ml) containing hydrochloric acid (11 ml) kept at 0-5°. The resultant diazonium salt solution was buffered to *pH* 7 by the addition of potassium acetate and then added dropwise to potassium ethyl xanthate (11.34 g, 70.7 mmoles) in water (43 ml) held at 60-70 °C. On cooling to 10 °C, the mixture was neutralized with hydrochloric acid and the precipitate collected by filtration and dried to yield **32** (6.2 g, 60%), mp 225-228° (lit. crude, none listed [19]; ^{1}H nmr (dimethyl sulfoxide-d_6) δ 8.79 (m, 2H), 7.79 (d, J = 4.9 Hz, 1H), 4.54 (q, J = 7.0 Hz, 2H), 1.22 (t, J = 7.0 Hz, 3H).

Methyl-3-hydroxypyridine-2-carboxylate (**35**).

The 3-hydroxy-pyridine-2-carboxylic acid (**34**, 2.0 g, 3.60 mmoles) was refluxed in methanol (100 ml) containing sulfuric acid (4 ml) for 15 hours. The mixture was concentrated to about 40 ml, diluted with water (150 ml), adjusted to *pH* 6 with sodium carbonate and then extracted with chloroform (3 x 100 ml). The extracts were washed with water (2 x 100 ml), dried over magnesium sulfate and concentrated to dryness. The white crystalline solid was collected by filtration to yield **35** (1.7 g, 77%), mp 73-74°; lit mp 70-73° [14]; ^{1}H nmr (deuteriochloroform): δ 8.23 (dd, J = 1.1, 2.9 Hz, 1H), 7.39-7.32(m, 2H), 4.01 (s, 3H).

Methyl 3-[2-(Dimethylamino)thiocarbonyl])-*O*-2-pyridylcarboxylate (**36**).

A solution of **35** (3.50 g, 0.023 mole), dimethylthiocarbamoyl chloride (2.84 g, 0.024 mole), 1,4-diazabicyclo[2.2.2]octane (8.7 g, 0.070 mole) in dry dimethylformamide (7.0 ml) was stirred at room temperature for 4 hours. The mixture was poured over crushed ice (100 ml), the solid was recovered by filtration and dried to afford 4.25 g (77%), mp. 76-77, lit. mp 76-77° [20]. An analytical sample was recrystallized for benzene: petroleum ether (35-60°); ^{1}H nmr (deuteriochloroform): δ 8.60 (m, 1H), 7.53 (m, 2H), 3.94 (s, 3H), 3.47 (s, 3H), 3.42 (s, 3H).

Anal. Calcd. For $C_{10}H_{12}N_2O_3S$: C, 49.99; H, 5.03; N, 11.66. Found: C, 49.92; H, 4.86; N, 11.55.

Methyl 3-[[(Dimethylamino)carbonyl]thio]-2-pyridinecarboxylate (**37**).

A mixture of **36** (2.5 g, 1.010 moles) and diphenyl ether (21 ml) was heated in an oil bath held at 200-210°. After 1.75 hours, the mixture was removed from the bath, cooled and purified by flash chromatography over silica gel using chloroform:methanol 99:1 as the eluent. The product fractions were pooled and concentrated to a thick oil under a slow stream of nitrogen gas. The resultant solid (2.4 g, 96%) was recrystallized from a mixture of petroleum ether (35-60°) and benzene to yield **37** (2.1 g, 84%); mp 80-81°; ^{1}H nmr (deuterichloroform): δ 8.60 (dd, J = 1.5, 4.6 Hz, 1H), 7.96 (dd, J = 1.5, 8.0 Hz, 1H), 7.39 (dd, J = 4.6, 8.0 Hz, 1H), 3.93 (s, 3H), 3.0 (broad d, 6H).

Anal. Calcd. for $C_{10}H_{12}O_3N_2S$: C, 49.99; H, 5.03; N, 11.66. Found: C, 50.23; H, 5.03; N, 11.56.

3-Mercaptopyridine-2-carboxylic Acid (**38**).

A mixture of **37** (1.30 g, 5.42 mmole), sodium carbonate (1.6 g, 15.09 mmoles), water (6.2 ml) and methanol (40 ml) was refluxed under a nitrogen atmosphere for 20 hours. The excess sodium carbonate was removed by filtration. The mixture was concentrated to an aqueous residue that was acidified to *pH* 2. This easily oxidizable solid (a mixture of the mercapto pyridine and the corresponding disulfide) was collected by rapid filtration, washed with water and dried. Upon crystallization from water, **38** separated as orange prisms that were collected by filtration, 0.25 g (30%), mp 183-184°; lit. mp 181-182° [20]. The aqueous filtrate on standing deposited crystals of the disulfide.

3-(2-Nitro-5-chlorothiophenoxy)pyridine (**40**).

A mixture of the acid **40** (0.010 g, 0.39 mmole) in fuming sulfuric acid (18-24% SO_3) (0.5 ml) was heated at 135° for 30 minutes and then quenched over crushed ice (2 ml). The aqueous layer was treated with sodium bicarbonate and extracted with chloroform (3 ml, 3 times). The organic layer was dried over magnesium sulfate and concentrated to dryness to an oil; ^{1}H nmr (deuteriochloroform): δ 8.80 (s, 1H), 8.78 (m, 1H), 8.20 (d, J_{HH}= 8.8 Hz, 1H), 7.92 (dd, J=1.8, 7.8 Hz, 1H), 7.47 (dd, J = 4.8, Hz, 7.8 Hz, 1H), 7.23 (dd, J = 2.0, 8.8 Hz, 1H), 6.73 (d, J = 2.0 Hz, 1H).

Anal. Calcd. for $C_{11}H_7ClN_2O_2S$: C, 49.54; H, 2.65; N, 10.50. Found: 49.53; 2.75; N: 10.30.

N'-[2-[2-(Dimethylamino)ethyl]-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazol-5-yl]-*N*,*N*-dimethyl-1,2-ethanediamine (**41a**).

(Method F). A mixture of **15a** (0.50 g, 1.61 mmoles), 2-(dimethylamino)ethyl bromide hydrobromide (0.98 g, 4.2 mmoles) and potassium carbonate (1.37 g, 9.96 mmoles) in toluene (15 ml) was refluxed for 15 hours. The mixture was cooled and the residue, which was collected by filtration, was triturated with hot acetonitrile. The filtrate was concentrated to 15 ml and allowed to stand overnight. The product was collected by filtration as a golden brown material (0.36 g, 59%). This crude material was dissolved in hot acetonitrile (10 ml), cooled to room temperature and placed in the refrigerator overnight. The beautiful golden-brown needles of **41a** (0.26 g, 45%) were collected by filtration; mp 110-111°; ^{1}H nmr (deuteriochloroform): δ 8.27 (dd, J = 1.6, 4.7 Hz, 1H), 8.16 (dd, J = 1.6, 7.7 Hz, 1H), 7.09 (dd, J = 4.7, 7.7 Hz, 1H), 6.92 (d, J = 8.7 Hz, 1H), 6.87 (d, J = 7.1 Hz, 1H), 4.37 (t, J = 7.0 Hz, 2H), 3.25 (t, J = 5.9 Hz, 2H), 2.83 (t, J = 7.0 Hz, 2H), 2.60 (t, J = 5.9 Hz, 2H), 2.32 (s, 6H), 2.34 (s, 6H).

Anal. Calcd. For $C_{20}H_{26}N_6S$: C, 62.80; H, 6.85; N, 21.97. Found: C, 62.64; H, 6.52; N, 21.75.

N'-[2-[2-(Dimethylamino)ethyl]-2*H*-pyrido[3'2':5,6]thiopyrano-[4,3,2-*cd*]indazol-5-yl]-1,2-ethanediamine) (**42a**).

(Method G). A mixture of **15a** (0.25 g, 0.80 mmole), 2-bromoethylamine hydrobromide (0.50 g, 2.40 mmoles) and anhydrous ethanol (5.0 ml) was heated at reflux under nitrogen for 7 days. The reaction mixture was filtered hot, and the collected solids were washed with ethanol. The ^{1}H nmr spectrum in dimethyl sulfoxide -d_6 showed the presence of the desired product and the starting material in 1:2 ratio. The product was dissolved in water (2 ml) and basified to *pH* 9 with potassium carbonate. The aqueous layer was extracted with chloroform (3 x 5 ml), dried over magnesium sulfate and concentrated to dryness. The residue was purified by column chromatography over silica gel using gradient elution by chloroform: methanol as eluent commencing with 95:5 and gradually changing to 25:75. The desired product was eluted with chloroform:methanol:-ammonium hydroxide 25:75:1. Removal of the eluents led to **42a** (0.015 g, 15%) as a yellow solid which darkened on standing, mp = 125-127°; ^{1}H nmr (deuteriochloroform): δ 8.27 (dd, J = 1.5, 4.8 Hz, 1H), 8.14 (dd, J = 7.2, 1.5 Hz, 1H), 7.08 (dd, J = 4.8, 7.2 Hz, 1H), 6.84 (d, J = 8.6 Hz, 1H), 6.75 (d, J = 8.6 Hz, 1H), 4.36 (t, J = 6.8 Hz, 2H), 3.57 (t, J = 5.9 Hz, 2H), 2.97 (t, J = 5.9 Hz, 2H), 2.84 (t, J = 6.8 Hz, 2H), 2.32 (s, 6H).

Anal. Calcd. for $C_{18}H_{22}N_6S\bullet H_2O$: C, 58.04; H, 6.49; N, 22.56. Found: C, 57.85; H, 6.30; N, 22,40.

N'-[2-[2-(Diethylamino)ethyl-2*H*-pyrido[3',2';5,6]thiopyrano-[4,3,2-*cd*]indazole-5-yl]-*N*,*N*-dimethyl-1,2-ethanediamine (**43a**).

Analogue **16a** was converted into **43a** (25%) using method F; mp 85-87° (recrystallized from acetonitrile); ^{1}H nmr (deuteriochloroform): δ 8.29 (dd, J = 1.8, 3.8 Hz, 1H), 8.16 (dd, J=1.8, 7.8 Hz, 1H), 7.10 (dd, J = 4.7, 7.3 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.41 (t, J = 7.1 Hz, 2H), 3.33 (t, J = 6.1 Hz, 2H), 3.04 (t, J = 7.1 Hz, 2H), 2.71 (m, 6H), 2.33 (s, 6H) 1.05 (t, 6H).

Anal. Calcd. for $C_{22}H_{30}N_6S$: C, 64.36; H, 7.36; N, 20.47. Found: C, 64.04; H, 7.25; N, 20.37.

N'-[2-[2-(Dimethylamino)ethyl]2*H*-pyrido[3',2':5,6]thiopyrano-[4,3,2-*cd*]indazol-5-yl]-*N*,*N*-dimethyl-1,2-ethanediamine (**44c**).

(Method F). A mixture of **21c** (0.050 g, 0.16 mmole) and 2-(dimethylamino)ethyl bromide hydrobromide (0.112 g, 0.90 mmole) in anhydrous ethanol (1 ml) was refluxed for 24 hours. The mixture was cooled and the residue, which was collected by filtration, was dissolved in water (2 ml). The aqueous solution was made basic by addition of a sodium bicarbonate solution and extracted with chloroform (3 x 3 ml). The extracts were concentrated and the residual solid was dissolved in methanol:ethyl acetate (1:1) and chromatographed over silica gel to afford **44c** (5 mg, 10%), mp 163-165°; ^{1}H nmr (deuteriochloroform): δ 9.09 (s, 1H), 8.25 (d, J = 5.3 Hz, 1H), 7.15 (d, J = 5.4 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.90 (d, J = 8.8 Hz, 1H), 4.45 (t, J = 6.9 Hz, 2H), 3.34 (t, J = 5.9 Hz, 2H), 3.00 (t, J = 6.9 Hz, 2H), 2.87 (t, J = 5.9 Hz, 2H), 2.45 (s, 6H), 3.29 (s, 6H).

Anal. Calcd. for $C_{20}H_{26}N_6S$: C, 62.80; H, 6.85; N. 21.97. Found: C, 62.75; H, 6.62; N, 21.67.

1,1-Dimethylethyl [2-[[2-(Dimethylamino)ethyl]-2*H*-pyrido-[3',2';5,6]thiopyrano[4,3,2-*cd*]indazol-5-yl]amino]ethyl]carbamate (**45a**).

Route 1.

(Method H). A mixture of **15a** (0.14 g, 0.45 mmole) and *N*-*tert*-butoxycarbony-2-aminoethanal (0.087 g, 0.55 mmole) in methanol (5 ml) containing 3A molecular sieves (0.2 g) was stirred in an ice bath for 0.5 hours. Glacial acetic acid was added followed by the addition of sodium cyanoborohydride (0.043 g, 5.32 mmoles). The mixture was stirred at room temperature for 4 days. On cooling to 0 °C, a saturated solution of sodium bicarbonate (2 ml) was added slowly. The product was extracted into dichloromethane (3 x 5 ml), the organic layer dried over sodium sulfate, concentrated and flask chromatographed (silica gel, 0.5 x 20 cm) eluting sequentially with 2, 4, 6 and 8% methanol in chloroform. The middle eluents on concentration afforded **45a** (0.19 g, 91%), mp 78-80°, TLC, silica gel with fluorescent indicator, R_f=0.69 (dichloromethane: methanol, 92:8); ^{1}H nmr (deuteriochloroform): δ 8.29 (dd, J = 1.7, 4.7 Hz, 1H), 8.17 (dd, J = 1.7, 7.8 Hz, 1H), 7.11 (dd, J = 4.7, 7.8 Hz, 1H), 6.91 (dd, J = 8.8, 7.8 Hz, 2H), 4.86 (brs, 1H), 4.36(t, J = 7.0 Hz, 2H), 3.36 (brs, 4H), 2.82 (t, J = 6.9 Hz, 2H), 2.32 (s, 6H), 1.48 (s, 9H).

Anal. Calcd. for $C_{23}H_{30}N_6O_2S.4H_2O$: C, 53.06, H, 6.20; N, 16.14. Found: C, 53.29; H, 6.03; N, 15.79.

Route 2.

(Method J). A Red-Al solution (0.6 ml, 1.02 mmoles, Aldrich 3.4 *M* in toluene) was added dropwise over a period of 3 minutes to a stirred suspension of **51a** (100 mg, 0.22 mmole) in toluene (1 ml) held at 70°. The resultant bright red solution was heated for an additional 5 hours at 70-75°, cooled to room temperature and treated cautiously with a saturated aqueous ammonium chloride solution. The yellow suspension was diluted with dichloromethane (3 ml) and the mixture was filtered through a celite bed. The organic layer was dried over magnesium sulfate and concentrated to yield crude **45a** (100 mg). This material was purified by column chromatography over silica gel eluting sequentially with 2, 4, 8, 10 and 20% methanol in dichloromethane. The center eluents were concentrated to afford a yellow solid (50 mg, 52%), mp 77-80°.

Route 3.

(Method K). To a suspension of lithium aluminum hydride (0.015 g, 0.37 mmole) in anhydrous tetrahydrofuran (2.0 ml), **51a** (0.10 g, 0.21 mmole) was added as a solution in tetrahydrofuran (2.0 ml). The resulting suspension was heated at reflux for 2.5 hours. The mixture was cooled in an ice bath and quenched very cautiously with water followed by the addition of sodium potassium tartrate. The mixture was diluted with dichloromethane (5 ml), the organic layer was separated, dried over magnesium sulfate and concentrated to dryness. The crude orange solid was purified by column chromatography over silica gel, eluting sequentially with 2, 4, 6, 8, 10 and 20% methanol in dichloromethane. The center eluents were concentrated to afford a yellow film which upon tritruation with diethyl ether led to **45a** (0.035 g, 36%) as a lemon-yellow solid which was identical in all respects to the previously prepared samples.

1,1-Dimethylethyl [2-[[2-(2-2-Hydroxyethyl)-2*H*-pyrido[3',2':5,6]-thiopyrano-[4,3,2-*cd*]indazol-5-yl]amino]ethyl]carbamate (**46a**).

Reaction of **17a** according to Method H followed by chromatography (eluent methanol:dichloromethane 7:93) led initially to a lemon yellow solid (75%) (structure in figure 5) ; mp 80-83°; ^{1}H nmr (deuteriochloroform): δ 8.29 (dd, J = 4.7, 1.7 Hz, 1H), 8.15 (dd, J = 7.8, 1.7 Hz, 1H), 7.17 (d, J = 8.8 Hz, 1H), 7.09 (dd, J = 7.8, 4.7 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 5.09 (br s, 1H), 4.35 (t, J = 4.9 Hz, 2H), 4.09 (t, J = 4.8 Hz, 2H), 3.13 (q, J = 5.5 Hz, 4H), 3.06 (t, J = 5.5 Hz, 4H), 1.46 (s, 18 H). Further elution with methanol:dichloromethane:ammonium hydroxide 50:50:1 led to **46a** (0.010 g, 25%) as a yellow solid; mp 187-190 °C; ^{1}H nmr (deuteriochloroform): δ 8.27 (dd, J = 4.7, 1.7 Hz, 1H); 8.13 (dd, J = 7.8, 1.7 Hz, 1H), 7.09 (dd, J = 7.8, 4.7 Hz, 1H), 6.96 (d, J = 8.8 Hz, 1H), 6.85 (d, J = 8.8 Hz, 1H), 4.85 (br s, 1H), 4.35 (t, J = 4.9 Hz, 2H), 4.09 (t, J = 4.8 Hz, 2H), 3.13 (br s, 4H), 1.48 (s, 9H).

Anal. Calcd. for $C_{21}H_{25}N_5O_3S$: C, 59.00; H, 5.89; N, 16.38. Found: C, 58.82; H, 5.67; N, 16.01.

1,1-Dimethylethyl [2-[5-[[(1,1-Dimethylethoxy)carbonyl]-amino]ethyl]amino-2*H*-pyrido[3',2';5,6]thiopyrano[4,3,2-*cd*]-indazol-2-yl]ethyl]carbamate (**47a**).

Following procedure H, **18a** led to **47a** (61%) as a lemon yellow solid which was recrystallized from chloroform:ethyl acetate; mp 159-160°; ^{1}H nmr (deuteriochloroform): δ 8.30 (dd, J = 4.7, 1.5 Hz, 1H), 8.15 (dd, J = 7.8, 1.5 Hz, 1H), 7.11 (dd, J = 7.7, 4.7 Hz, 1H), 6.96 (d, J = 8.6 Hz, 1H), 6.87 (d, J = 8.6 Hz, 1H), 4.87 (br s, 1H), 4.82 (br s, 1H), 4.36 (br s, 2H), 3.62 (br s, 2H), 3.36 (br s, 4H), 1.46 (s, 9H), 1.43 (s, 9H).

Anal. Calcd. for $C_{26}H_{34}N_6O_4S\bullet 2H_2O$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.50; H, 6.65; N, 14.83.

1,1-Dimethylethyl 2-[[2-(2-Dimethylamino)ethyl-2-*H*-pyrido-[4',3':5,6]thiopyrano-[4,3,2-*cd*]indazol-5-yl]amino]ethyl]carbamate (**48b**).

Treatment of **20b** according to Method H led to **48b** as a yellow solid (75%); mp 173-174° which was purified by chromatography over silica gel eluting sequentially with 2, 4, 8, 10 and 20 % methanol in chloroform;.[1] H nmr (deuteriochloroform): δ 8.49 (s, 1H), 8.36 (d, J = 5.0 Hz, 1H), 7.79 (d, J = 5.0 Hz, 1H), 7.01 (d, J = 8.8 Hz, 1H), 6.89 (d, J = 8.8 Hz, 1H), 4.95 (br s, 1H), 4.38 (t, J = 7.0 Hz, 2H), 3.35 (br d, 4H), 2.85 (t, J = 7.0 Hz, 2H), 2.32 (s, 6H), 1.47 (s, 9H).

Anal. Calcd. for $C_{23}H_{30}N_6O_2S$: C, 60.77; H, 6.65; N, 18.49. Found: C, 60.54; H, 6.62; N, 18.37.

1,1-Dimethylethyl [2-[[2-(2-Hydroxyethyl)-2*H*-pyrido[3',4':5,6]-thiopyrano[4,3,2-*cd*]indazol-5-yl]-amino]]ethyl]carbamate (**49c**).

(Method D). Treatment of **23c** according to method H led to crude **49c** which was purified by flash chromatographed over silica gel eluting sequentially with 2, 4, 6 and 8% methanol in dichloromethane to afford **49c** (15%), mp 159-161 °C; ^{1}H nmr (deuteriochloroform): δ 8.89 (s, 1H), 7.88 (d, J = 5.3 Hz, 1H), 6.95 (m, 2H), 6.85 (d, J = 8.8 Hz, 1H), 4.82 (br s, 1H), 4.34 (t, J = 4.4 Hz, 2H), 4.14 (t, J = 4.4 Hz, 2H), 3.38 (m, 4H), 1.48 (s, 9H).

Anal. Calcd. for $C_{21}H_{25}N_5O_3S$: C, 59.00; H, 5.89; N, 16.38. Found: C, 59.05; H, 5.76; N, 16.31.

1,1-Dimethylethyl [2-[5-[[(1,1,-Dimethylethoxy)carbonyl]-amino]ethyl]amino]-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]-indazol-2-yl]ethyl]carbamate (**50c**).

Following method H, **24c** was converted into **50c** (62%), mp 145-146° (recrystallized from chloroform:ethyl acetate); ^{1}H nmr (deuteriochloroform):δ 9.14 (s, 1H), 8.30 (d, J = 5.5 Hz, 1H), 7.18 (d, J = 5.3 Hz, 1H), 6.99 (d, J = 8.8 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 4.92 (br s, 1H), 4.42 (t, J = 5.5 Hz, 2H), 3.68 (q, J = 5.2 Hz, 2H), 3.40 (m, 4H), 1.53 (s, 9H), 1.48 (s, 9H).

Anal. Calcd for $C_{26}H_{34}N_6O_4S\bullet 2H_2O$: C, 55.50; H, 6.81; N, 14.94. Found: C, 55.75; H, 6.52; N, 14.72.

1,1-Dimethylethyl [2-[[2-(Dimethylamino)ethyl]-2*H*-pyrido-[3'2':5,6]thiopyrano[4,3,2-*cd*]indazol-5-yl]amino]-2-oxoethyl]carbamate (**51a**).

(Method I). Dicyclohexylcarbodiimide (210 mg, 1.02 mmoles) was slowly added to a magnetically stirred solution of **15a** (300 mg, 0.96 mmoles) and *N*-*tert*-butoxycarbonyl glycine (168 mg, 0.96 mmole) in dry tetrahydrofuran (8 ml) at 0°. The mixture was stirred at 0-5° in a cold room for 20 hours and the dicyclohexylurea that precipitated was removed by filtration. The filtrate was refrigerated overnight and additional urea was removed by filtration. The filtrate was concentrated to dryness by rotary evaporation and the brownish red solid was collected by filtration (434 mg). The material was recrystallized from acetonitrile: chloroform 4:1 to give **51a** (240 mg, 54%) as a yellow solid. The ^{1}H nmr spectrum showed a trace of urea. Purification (100 mg) was best accomplished by column chromatography over silica gel using gradient elution by ethyl acetate:methanol as eluent, commencing with 5:1 and gradually changing to 1:1 (which eluted the desired product). Removal of the eluents led to **51a** (50 mg, 50%), mp 173-175°, ^{1}H nmr (deuteriochloroform): δ 8.34 (dd, J = 1.7, 4.7 Hz, 1H), 8.23 (dd, J = 1.7, 7.8 Hz, 1H), 7.60 (br s, 1H), 7.49 (d, J = 8.7 Hz, 1H), 7.15 (dd, J = 4.7, 7.8 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H), 5.21 (s, 1H), 4.39 (t, J = 6.9 Hz, 2H), 4.00 (d, J = 6.0 Hz, 2H), 2.82 (t, J = 8.9 Hz, 2H), 2.33 (s, 6H), 1.49 (s, 9H).

Anal. Calcd. For $C_{23}H_{28}N_6O_3S$: C, 58.96; H, 6.02; N, 17.94. Found: C, 58.64; H, 6.04; N, 17.75.

1,1-Dimethylethyl [2-[[2-(Dimethylamino)ethyl]-2*H*-pyrido-[4',3':5,6]-thiopyrano-[4,3,2-*cd*]indazol-5-yl]amino]-2-oxoethyl]carbamate (**52b**).

Analogue **20b** was converted into **52b** using Method I. The crude mixture was purified by silica gel chromatography using gradient elution with mixtures of ethyl acetate:methanol as the

eluent. The initial eluent was 5:1 with gradual changes to 1:1, which eluted the product. Concentration of the product fractions led to **52b** (50%), mp 168-170°; ^{1}H nmr (deuteriochloroform): δ 8.39 (d, J = 5.0 Hz, 1H), 7.85 (br s, 1H), 7.77 (d, J = 5.0 Hz, 1H), 7.39 (d, J = 8.7 Hz, 1H), 6.92 (d, J = 8.8 Hz, 1H), 5.43 (br s, 1H), 4.37 (t, J = 6.8 Hz, 2H), 4.00 (d, J = 5.9 Hz, 2H), 2.82 (t, J = 6.8 Hz, 2H), 2.30 (s, 6H), 1.52 (s, 9H).

Anal. Calcd. for $C_{23}H_{28}N_6O_3S$: C, 58.96; H, 6.02; N, 17.94. Found: 58.72; H, 5.93; N, 17.94.

1,1-Dimethylethyl [2-[[2-(Dimethylamino)ethyl]-2*H*-pyrido-[3',4':5,6]-thiopyrano-[4,3,2-*cd*]indazol-5-yl]amino]-2-oxoethyl]carbamate (**53c**).

Analogue **21c** was converted into **53c** using Method I. After purification over silica gel using methanol:ethyl acetate (1:1) **53c** (43%) was obtained, mp 155-156°; ^{1}H nmr (deuteriochloroform): δ 9.17 (s, 1H), 8.31 (d, J = 5.4 Hz, 1H), 7.70 (br s, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.73 (d, J = 5.4 Hz, 1H), 7.00 (d, J = 8.8 Hz, 1H), 5.21 (br s, 1H), 4.40 (t, J = 6.9 Hz, 2H), 3.99 (d, J = 6.0 Hz, 2H), 2.84 (t, J = 6.9 Hz, 2H), 2.33 (s, 6H), 1.48 (s, 9H).

Anal. Calcd. for $C_{23}H_{28}N_6O_3S$: C, 58.96; H, 6.02; N, 17.94. Found: C, 58.72; H, 6.35; N, 17.86.

N'-[2-(Dimethylamino)ethyl-2*H*-pyrido[3',2':5,6]thiopyrano-[4,3,2-*cd*]indazole-5-yl]-*N*-methyl-1,2-ethanediamine (**54a**).

(Method K). To a suspension of lithium aluminum hydride (0.040 g, 1.05 mmoles) in tetrahydrofuran (5.0 ml), **51a** (0.10 g, 0.21 mmole) was added as a solution in tetrahydrofuran (2 ml). The resultant suspension was heated at reflux for 5 hours. The mixture was cooled in an ice bath, quenched with water and sodium potassium tartrate was added. The products were extracted with dichloromethane (5 ml), the extracts dried over magnesium sulfate and concentrated to dryness. The resultant crude orange solid was purified by flash chromatography over silica gel initially eluting with methanol:dichloromethane 7:93 to afford **45a** (0.010 g, 13%). The second part of the eluent led to a product (Figure 6) (0.020 g, 26%), mp 150-152°; ^{1}H nmr (deuteriochloroform): δ 8.33 (dd, J = 4.6, 1.7 Hz, 1H), 8.22 (dd, J = 7.8, 1.7 Hz, 1H), 7.21 (d, J = 8,8 Hz, 1H), 7.13 (dd, J = 7.8, 4.6 Hz, 1H), 6.99 (d, J = 8.7 Hz, 1H), 5.38 (s, 1H), 4.39 (t, J = 6.9 Hz, 2H), 3.83 (t, J = 7.7 Hz, 2H), 3.60 (t, J = 7.7 Hz, 2H), 2.81 (J, J = 6.9 Hz, 2H), 2.30 (s, 6H). The third fractions which eluted with methanol:dichloromethane:ammonium hydroxide 50:50:1 led to **54a** (0.030 g, 38%), mp 114-115°; ^{1}H nmr (deuteriochloroform): δ 8.27 (dd, J = 4.7, 1.8 Hz, 1H), 8.14 (dd, J = 7.8, 1.8 Hz, 1H), 7.08 (dd, J = 7.8, 4.7 Hz, 1H), 6.89 (d, J = 8.7 Hz, 1H), 6.88 (d, J = 8.7 Hz, 1H), 4.34 (t, J = 7.1 Hz, 2H), 3.30 (t, J = 5.7 Hz, 2H), 2.86 (t, J = 5.7 Hz, 2H), 2.80 (t, J = 7.1 Hz, 2H), 2.47 (s, 3H), 2.30 (s, 6H).

Anal. Calcd. for $C_{19}H_{26}N_6S$: C, 61.59; H, 7.07; N, 22.68. Found: C, 61.48; H, 6.75; N, 22.48.

1,1-Dimethylethyl [2-[[2-(2-Dimethylaminoethyl)-2*H*-pyrido[3',4':5,6]-thiopyrano[4,3,2]indazol-5-yl]amino]ethyl]-carbamate (**55c**).

Following method J, **53c** led to crude **55c** which was purified by column chromatography over silica gel using methanol:-chloroform as the eluent to yield **55c** (30%) as a yellow solid; mp 123-125°; ^{1}H nmr (deuteriochloroform): δ 9.10 (s, 1H), 8.25 (d, J = 5.4 Hz, 1H), 7.35 (br s, 1H), 7.11 (d, J = 5.4 Hz, 1H), 6.95 (d, J = 8.8 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 5.88 (br s, 1H), 4.38 (t, J = 6.9 Hz, 2H), 3.32 (d, J = 5.4 Hz, 4H), 2.86 (t, J = 6.9 Hz, 2H), 2.33 (s, 6H), 1.49 (s, 9H).

Anal. Calcd. for $C_{23}H_{30}N_6O_2S$ C, 60.77; H, 6.65; N, 18.49. Found: 60.54; H, 6.42; N, 18.90.

N'-[2-(Dimethylamino)ethyl]-2*H*-pyrido[3',2':5,6]thiopyrano-[4,3,2-*cd*]indazol-5-yl-1,2-ethanediamine Trihydrochloride (**56a**).

Using method C, **45a** was converted into **56a** (95%), mp >260°; ^{1} H nmr (deuterium oxide): δ 8.23 (dd, J = 4.8, 1.4 Hz, 1H), 8.09 (dd, 7.8, 1.4 Hz, 1H), 7.26 (dd, J = 7.8, 4.9 Hz, 1H), 7.13 (d, J = 8.8 Hz, 1H), 7.08 (d, J = 8.8 Hz, 1H), 4.71 (t, J = 5.9 Hz, 2H), 3.79 (t, J = 5.9 Hz, 2H), 3.59 (t, J = 6.2 Hz, 2H), 3.34 (t, J = 6.2 Hz, 2H), 3.05 (s, 6H).

Anal. Calcd. for $C_{18}H_{22}N_6S$•3HCl•2H_2O: C, 43.25; H, 5.85; N, 16.81. Found: C, 43.02; H, 5.63; N, 16.72.

N'-[(2-Hydroxyethyl]amino]-2*H*-pyrido[3':2':5,6]thiopyrano-[4,3,2-*cd*]indazol-5-yl]-1,2-ethanediamine Dihydrochloride (**57a**).

Using Method C, **46a** was converted into **57a** (quantitatively); ^{1}H nmr (deuterium oxide): δ 8.22 (dd, J = 4.7, 1.5 Hz, 1H), 8.14 (dd, J = 7.8, 1.5 Hz, 1H), 6.86 (d, J = 8.6 Hz, 1H), 7.54 (d, J = 8.9 Hz, 1H), 6.80 (d, J = 8.9 Hz, 1H), 7.11 (dd, J = 7.8 Hz, 4.7 Hz, 1H), 4.40 (t, J = 4.8 Hz, 2H), 4.03 (t, J = 4.8 Hz, 2H), 3.48 (t, J = 5.9 Hz, 2H), 3.20 (t, J = 5.9 Hz, 2H).

Anal. Calcd. for $C_{16}H_{17}N_5OS$•2HCl: C, 48.00; H, 4.78; N, 17.71. Found: C, 48.18; H, 5.11; N, 17.56.

N'-[2-[(Aminoethyl)-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]indazol-5-yl]-1,2-ethanediamine Trihydrochloride (**58a**).

Following Method C **47a** was quantitatively converted into **58a**; ^{1}H nmr δ 7.87 (dd, J = 4.5, 1.6 Hz, 1H), 7.58 (dd, J = 7.6, 1.6 Hz, 1H), 7.28 (d, J = 9.1 Hz, 1H), 6.98 (dd, J = 7.6, 4.5 Hz, 1H), 6.55 (d, J = 9.1 Hz, 1H), 4.25 (m, 4H), 3.35 (m , 4H).

Anal. Calcd. for $C_{16}H_{18}N_6S$•3HCl•H_20: C, 42.25; H, 5.11; N, 18.52. Found: C, 42.31: H, 5.011; N, 18.04.

N'-[2-[2-(Dimethylamino)ethyl-2*H*-pyrido[4',3':5,6]thiopyrano-[4,3,2-*cd*]indazol-5-yl]-1,2-ethanediamine Trihydrochloride (**59b**).

Protected analogue **48b** was converted to **59b** (98%) using method C; 'H nmr (deuterium oxide): δ 8.57 (s, 1H), 8.42 (d, J = 5.7 Hz, 1 H), 7.97 (d, J = 5.7 Hz, I H), 7.31 (d, J = 8.9 Hz, 1 H), 7.23 (d, J = 8.5 Hz, I H), 4.85 (t, J = 5.8 Hz, 1 H), 3.87 (t, J = 5.8 Hz, I H), 3.63 (t, J = 5.8 Hz, 2H), 3.35 (t, J = 5.8 Hz, 2), 3.0 (s, 6H).

Anal. Calcd for $C_{18}H_{22}N_6S$·3HCl·2H_2O: C, 43.25; H, 5.85; N, 16.81. Found: C, 43.13; H, 5.92; N, 16.51.

N'-[2-Hydroxyethyl]-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]-indazol-5-yl]-1,2-ethanediamine Dihydrochloride (**60c**).

Treatment of **49c** as in method C led to **60c** (98%); ^{1}H nmr (deuteriium oxide): δ 8.75 (s, 1H), 7.68 (d, J = 5.3 Hz, 1H), 7.54 (d, J = 8.9 Hz, 1H), 7.31 (d, J = 8.9 Hz, 1H), 6.86 (d, J = 5.3 Hz, 1H), 4.39 (t, J = 4.8 Hz, 2H), 4.07 (t, J = 4.8 Hz, 2H), 3.45 (t, J = 5.9 Hz, 2H), 3.15 (t, J = 5.9 Hz, 2H).

Anal. Calcd. for $C_{16}H_{17}N_5OS$•2HCl•H_2O: C, 45.95; H, 5.06; N. 16.75. Found: C, 46.21; H, 5.31; N, 17.01.

N'-[2-(Aminoethyl)amino]-2*H*-pyrido[3',4':5,6]thiopyrano[4,3,2-*cd*]indazol-5-yl]-1,2-ethanediamine Dihydrochloride (**61c**).

Following method C, **50c** was converted into **61c** (quantitatively); ^{1}H nmr (deuterium oxide): δ 8.79 (d, J = 6.5 Hz, 1H), 8.23 (d, J = 6.5 z, 1H), 7.76 (d, J = 6.5 Hz, 1H), 7.21

(d, J = 8.9 Hz, 1H), 7.08 (d, J = 8.9 Hz, 1H), 4.60 (t, J = 5.9 Hz, 2H), 3.53 (t, J = 5.7 Hz, 2H), 3.48 (t, J = 6.2 Hz, 2H), 3.20 (t, J = 6.2 Hz, 2H).

Anal Calcd. for $C_{16}H_{18}N_6S$•2HCl: C, 48.12, H, 5.05, N, 21.04. Found: C, 48.01; H, 5.00; N, 20.80.

N'-[2-[2-Dimethylamino)ethyl]-2*H*-pyrido[3',2':5,6]thiopyrano[4,3,2-*cd*]-indazol-5-yl]-2-oxo-1,2-ethanediamine Trihydrochloride (**62a**).

Following procedure C, **51a** was quantitatively converted into **62a**; ^{1}H nmr (deuterium oxide): δ 8.09 (dd, J = 4.8, 1.6 Hz, 1H), 8.03 (dd, J = 7.9, 1.6 Hz, 1H), 7.33 (d, J = 8.8 Hz, 1H), 7.18 (d, J = 8.8 Hz, 1H), 7.13 (dd, J = 7.9, 4.8 Hz, 1H), 4.71 (t, J = 6.0 Hz, 2H), 4.23 (br s, 2H), 3.79 (t, J = 6.0 Hz, 2H).

Anal. Calcd. for $C_{18}H_{20}N_6OS$•3HCl C, 45.24; H, 4.85; N, 17.59. Found: C, 45.09; H, 5.05; N 17.15

N'-2-[2-(Dimethylamino)ethyl]-2*H*-pyrido[3'4':5,6]thiopyrano-[4,3,2-*cd*]indazol-5-yl-2-oxo-1,2-ethanediamine Trihydrochloride (**63c**).

Treatment of **53c** according to this procedure led to a quantitative yield of **63c**; ^{1}H nmr (deuterium oxide): 9.20 (s, 1H), 8.50 (d, J = 6.5 Hz, 1H), 8.05 (d, J = 6.5 Hz, 1H), 7.50 (d, J = 8.9 Hz, 1H), 7.46 (d, J = 8.9 Hz, 1H), 4.95 (t, J = 5.8 Hz, 2H), 4.22 (br s, 2H), 3.93 (t, J = 5.8 Hz, 2H), 3.10 (s, 6H).

Anal. Calcd. for $C_{18}H_{20}N_6OS$•3HCl C, 45.24, H, 4.85, N, 17.59. Found: C, 45.36, H, 4.71, N, 17.85.

N'[2-[2-(Dimethylamino)ethyl]2*H*-pyrido[3',4':5,6]thiopyrano-[4,3,2-*cd*]-5-yl]-1,2-ethanediamine Trihydrochloride (**64c**).

Following procedure C, **55c** was converted into **64c** (98%); ^{1}H nmr (deuterium oxide): δ 9.01 (s, 1H), 8.39 (d, J = 6.5 Hz, 1H), 7.90 (d, J = 6.5 Hz, 1H), 7.39 (d, J = 8.9 Hz, 1H), 7.27 (d, J = 8.9 Hz, 1H), 4.86 (t, J = 5.9 Hz, 2H), 3.88 (t, J = 5.8 Hz, 2H), 3.62 (t, J = 6.2 Hz, 2H), 3.36 (t, J = 6.2 Hz, 2H), 3.09 (s, 6H).

Anal. Calcd. for $C_{18}H_{22}N_6S$•3HCl•$2H_2O$: C, 44.87; H, 5.65; N, 17.44. Found: C, 44.57; 5,64; N, 17,34.

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