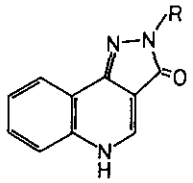
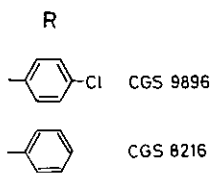
SYNTHESIS OF HETEROCYCLIC COMPOUNDS ISOSTERICALLY RELATED TO PYRAZOLO[4,3-*c*]QUINOLINES AS BENZODIAZEPINE RECEPTOR LIGANDS

Hirohisa Shindo,* Toshio Fujishita, Takashi Sasatani, Nobuo Chomei, and Susumu Takada
Shionogi Research Laboratories, Shionogi & Co., Ltd., Fukushima-ku, Osaka 553, Japan

Abstract — Fused pyridine and pyrimidine derivatives have been synthesized which are isosterically related to pyrazolo[4,3-*c*]quinolines with the high affinity to the benzodiazepine receptor.

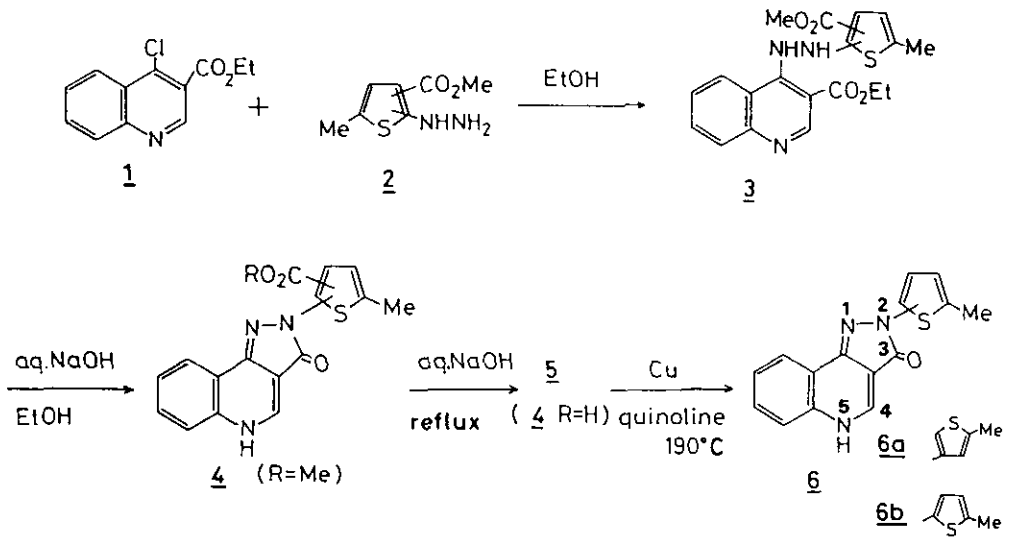
Benzodiazepines are important therapeutic agents which have been extensively studied.[1] Recently, a number of synthetic compounds with a diverse ring system have been found to have an affinity to the benzodiazepine receptors.[2,3] These non-benzodiazepines serve as important tools for studying the physiological properties and structural requirements of the recognition site of the receptor itself. Representative of the non-benzodiazepines is the series of pyrazolo[4,3-*c*]quinoline derivatives such as CGS 8216 and CGS 9896, which have very high affinity for receptors and different intrinsic activities.[3] We have reported that thienylpyrazolo[4,3-*c*]quinolines **6a** and **6b**, having the high affinity for the receptors, exhibit inverse agonist and agonist activities, respectively.[4] In addition, **6a** was shown to enhance performance in learning and memory tasks in animal models.[5] These findings led us to synthesize other heterocyclic compounds with analogous ring systems and screen them for benzodiazepine binding affinity. Here we report the synthesis and the binding affinity of fused pyridine and pyrimidine derivatives which contain at least two nitrogen atoms and one phenyl substituent corresponding to those of 2-substituted pyrazolo[4,3-*c*]-





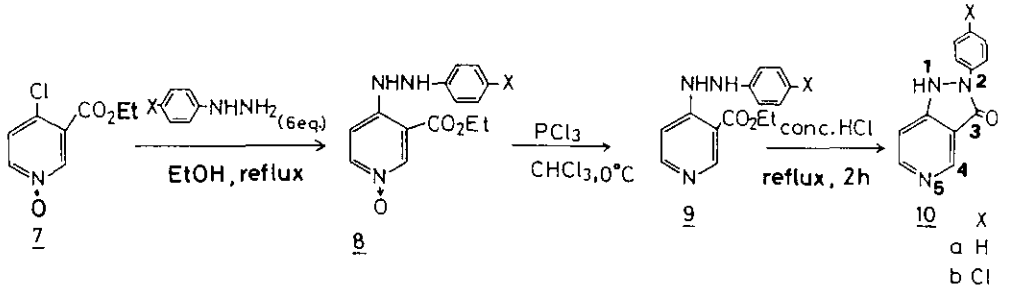
quinolines. The general routes of synthesis of pyrazolo[4,3-c]quinolin-3-ones have been described as outlined in Scheme I.[4] Treatment of ethyl 4-chloroquinoline-3-carboxylate 1 with hydrazinothiophene-carboxylates 2 gave the condensed products 3, which were cyclized to afford the compounds 4. Compounds 4 were hydrolyzed to give acids 5. Decarboxylation of 5 provided pyrazolo[4,3-c]quinolin-3-ones 6.[6]

Scheme I



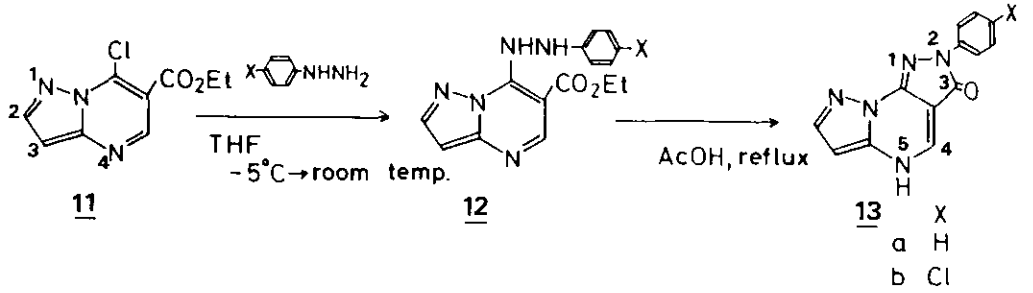
Pyrazolo[4,3-c]pyridin-3-ones 10

In literature,[7] 4-chloronicotinic acid or its N-oxide is used as the key intermediate for the synthesis of 1-substituted pyrazolo[4,3-c]pyridines. When ethyl 4-chloronicotinate N-oxide 7[8] reacted with phenyl-hydrazines, the condensed products 8 were obtained. The nmr spectrum ($CDCl_3$) of 8 showed characteristic broad signals for two NH protons, suggesting that the reaction occurred on N-2 of phenylhydrazines. The compounds 8 were readily reduced to 9 with PCl_3, followed by treatment with hydrochloric acid for conversion into the new compounds 10.[6]



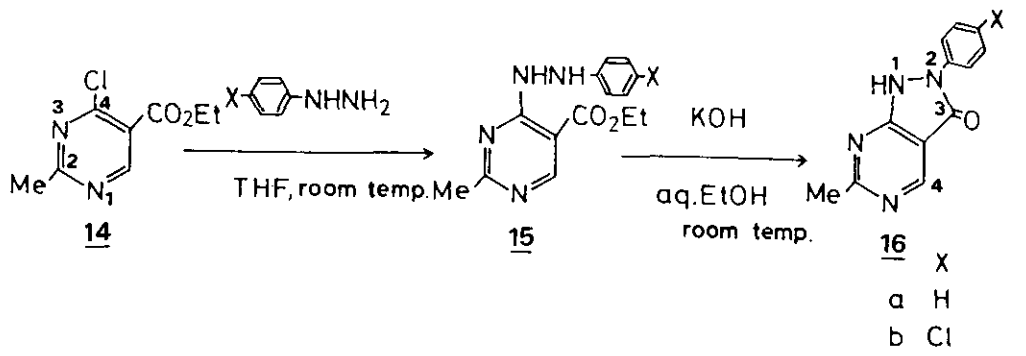
Dipyrazolo[1,5-*a*:4',3'-*e*]pyrimidin-3-ones **13**

The title compounds **13** were synthesized from ethyl 7-chloropyrazolo[1,5-*a*]pyrimidine-6-carboxylate **11** as a starting material.[9] Since **11** is an unstable compound, phenylhydrazines were added to a THF solution of **11** at −5°C, and the mixture was gradually warmed to room temperature to give the products **12**. Dipyrazolo[1,5-*a*:4',3'-*e*]pyrimidin-3-ones **13**[6] were obtained by heating of **12** in acetic acid.



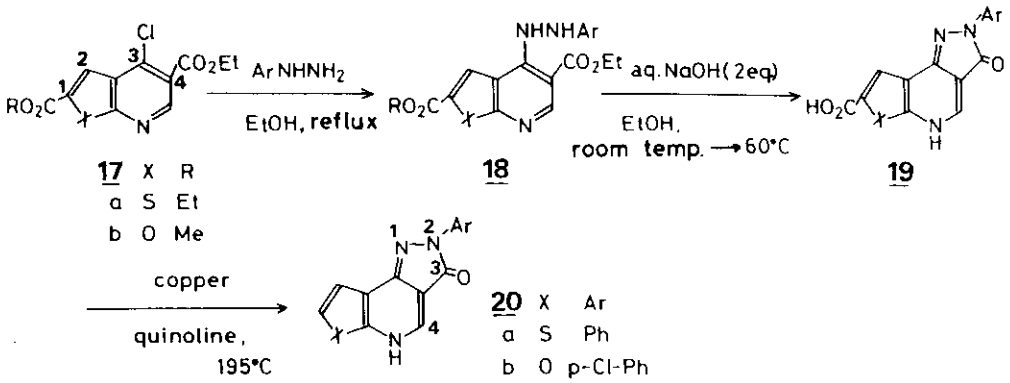
Pyrazolo[3,4-*d*]pyrimidin-3-ones **16**

Treatment of ethyl 4-chloro-2-methylpyrimidine-5-carboxylate **14**[10] with phenylhydrazines provided expected products **15**, which were cyclized by the reaction with KOH in aqueous ethanol, followed by treatment with tartaric acid to afford cyclized compounds **16**.[6]



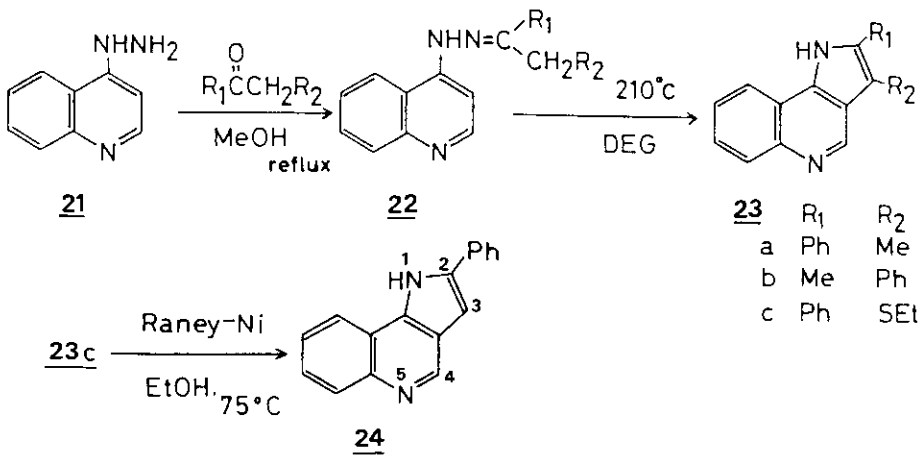
Pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridin-3-one **20a** and Furo[2,3-*b*]pyrazolo[3,4-*d*]pyridin-3-one **20b**

The targeted compounds **20** were synthesized from **17a** or **17b** as described in the literature.[11] The reaction of the compounds **17** with phenylhydrazines in refluxing ethanol gave the corresponding compounds **18**. Treatment of **18** with two equivalents of aq. NaOH gave acids **19a** and **19b**. Decarboxylation of **19** with copper in quinoline provided the compounds **20**.[6]



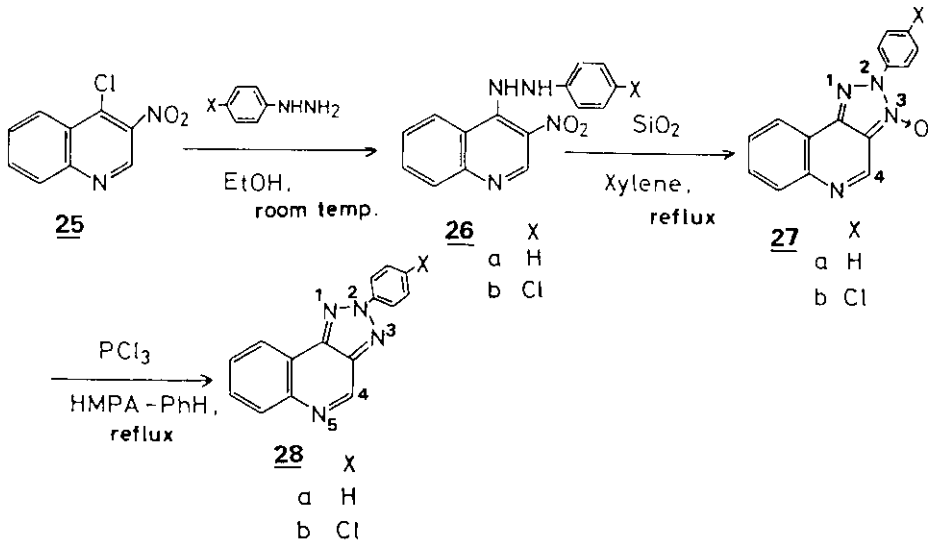
Pyrrolo[3,2-c]quinolines 23 and 24

Although derivatives of pyrrolo[3,2-c]quinoline have been previously reported in the literature,[12] the derivatives with the aromatic substituent at 2-position have not been reported. Reaction of 4-hydrazinoquinoline 21, obtained from 4-chloroquinoline, with the appropriate carbonyl compounds gave the hydrazones 22. Thermally induced Fischer indole cyclization of 22 gave the compounds 23[6] in a good yield. The compound 24 was obtained by desulfurization of 23c with Raney-nickel in ethanol.



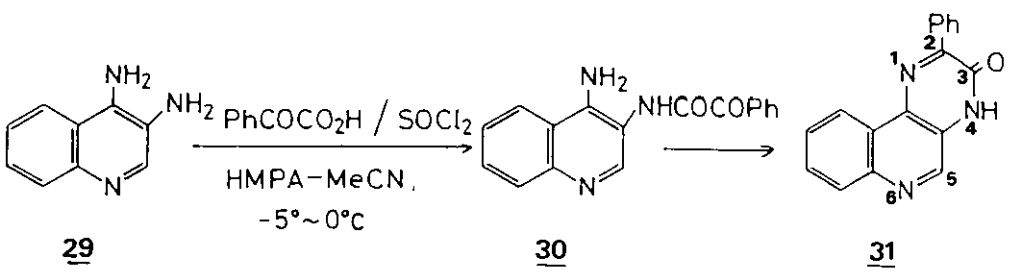
1,2,3-Triazolo[4,5-c]quinolines 28

According to the literature,[13] 4-chloro-3-nitroquinoline 25 was treated with phenylhydrazines to give the condensed products 26, which were cyclized in the presence of SiO_2 in xylene under reflux temperature to the compounds 27. When the N-oxides 27 were reduced by PCl_3 in HMPA-benzene, new products 28 were obtained.

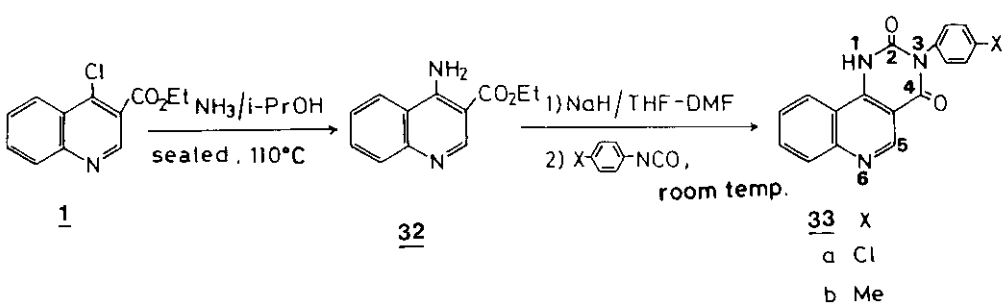


Pyrazino[2,3-c]quinolin-3-one 31

Reaction of 3,4-diaminoquinoline **29** with phenylglyoxylic acid activated by $SOCl_2$ in HMPA-MeCN gave **30**, which was cyclized without purification to give **31**,[6] a compound having the new ring system.



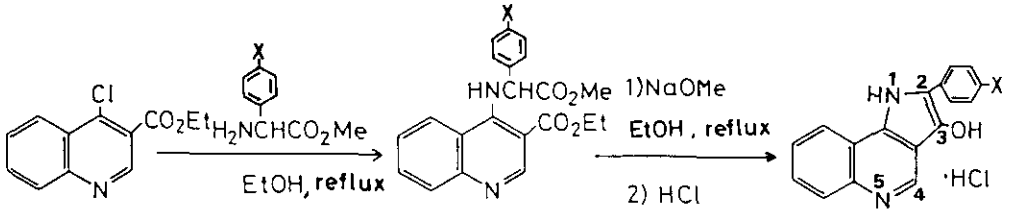
Pyrimidino[5,4-c]quinolin-2,4-diones 33



4-Amino-3-ethoxycarbonylquinoline **32**, obtained by amination of **1**, was treated with NaH in THF and DMF and then with a solution of phenyl isocyanates in THF to give products **33**[6] having the new ring system in a good yield.

3-Hydroxypyrrolo[3,2-c]quinolines **35**

An ethanol solution of **1** and methyl 2-arylglycinate was heated at reflux temperature, giving the condensed products **34** in a reasonable yield. Heating **34** at reflux temperature for 20 min, followed by treatment with the diluted hydrochloric acid, gave cyclized compounds **35** as HCl salts. Isolation of the free bases of **35** failed due to their instability.



1 **34** **35** X: a H, b Cl

The results of binding assay of these compounds are summarized in Table 1.

Table 1. In vitro binding affinity to benzodiazepine receptors

Compound	Ki (nM)	Compound	Ki (nM)
CGS 8216	0.22	**23a**	1300
6a	0.32	**23b**	>10000
10a	1400	**24**	280
10b	740	**28a**	>10000
13a	4100	**28b**	>10000
13b	1500	**31**	550
16a	180	**33a**	>10000
16b	110	**33b**	>10000
20a	8.7	**35a**	240
20b	3400	**35b**	380

In comparison with pyrazolo[4,3-c]quinolines such as CGS 8216 and **6a**, all compounds synthesized here showed relatively the low affinities to the receptors. However, some of the compounds (**16a**, **16b**, **20a**, **24**, **35a** and **35b**) showed the affinity comparable or superior to that of chlordiazepoxide (Ki = 202 nM), which is one of the minor tranquilizers. Removal of the benzene ring of the pyrazolo[4,3-c]quinoline significantly reduced the affinity (**10a,b**), while replacement of the benzene ring with a thiophene ring retained the

affinity (**20a**). Interestingly, similar replacement with a furan ring caused remarkable lowering of the affinity (**20b**). Pyrroloquinolines (**24** and **35**) exhibited the moderate affinities.

EXPERIMENTAL

Unless otherwise noted, all reactions were carried out under an atmosphere of nitrogen. Melting points were determined on a Yanagimoto micro melting point apparatus and were uncorrected. Nmr spectra were recorded on a Varian EM-390 spectrometer. Chemical shifts are given in parts per million relative to tetramethylsilane as the internal standard. Elemental analyses were performed by the analytical department of Shionogi Research Laboratories. Mass spectra were obtained by using Hitachi M-68 spectrometer.

Ethyl 4-(2-Phenylhydrazino)nicotinate 1-oxide (**8a**)

To a stirred solution of ethyl 4-chloronicotinate N-oxide **7** (200 mg, 1 mmol) in EtOH (10 ml) was added phenylhydrazine (645 mg, 6 mmol) and the solution was refluxed for 2 h. After removal of EtOH in vacuo, the residue was poured into water and extracted with $CHCl_3$. The organic solution was dried over $MgSO_4$ and concentrated in vacuo. The resulting residue was purified by column chromatography (SiO_2, eluted with $CHCl_3$:MeOH = 15:1) to give **8a** (175 mg, 64%) as an oil. Nmr ($CDCl_3$) δ 1.36 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.33 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.53 (br, 1H, NH), 6.71-7.30 (m, 6H), 7.94 (m, 1H, H-5), 8.65 (d, 1H, J = 7 Hz, H-2), 9.25 (br, 1H, NH). MS m/z: 273 (M^+).

Ethyl 4-[2-(4-Chlorophenyl)hydrazino]nicotinate 1-oxide (**8b**)

The same procedure as above was employed. Yield 62%. Nmr ($CDCl_3$) δ 1.37 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.36 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.91 (br, 1H, NH), 6.73 and 7.17 (ABq, 4H, J = 8 Hz), 7.09 (d, 1H, J = 7 Hz, H-5), 7.96 (m, 1H, H-6), 8.66 (d, 1H, J = 2 Hz, H-2), 9.30 (br, 1H, NH). MS m/z: 309 ($M^+ + 2$), 307 (M^+).

Ethyl 4-(2-Phenylhydrazino)nicotinate (**9a**)

To a solution of **8a** (704 mg, 2.6 mmol) in $CHCl_3$ (9 ml) was added dropwise a solution of PCl_3 (0.67 ml, 7.8 mmol) in $CHCl_3$ (2 ml) at 0°C. After stirring at 0°C for 30 min, the mixture was diluted with ice water and neutralized with 5 N NaOH at 0°C. The mixture was extracted with $CHCl_3$. The extract was washed with water, and dried ($MgSO_4$), and evaporated in vacuo. The solid was crystallized from EtOH to afford **9a** (420 mg, 66%). Mp 224-226°C. Nmr ($CDCl_3$) δ 1.38 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.34 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 5.93 (br, 1H, NH), 6.63-8.27 (m, 7H), 8.93 (s, 1H, H-2), 9.29 (br, 1H, NH). Anal. calcd for $C_{14}H_{15}N_3O_2$: C, 65.36; H, 5.88; N, 16.33. Found: C, 65.01; H, 6.12; N, 16.25.

Ethyl 4-[2-(4-Chlorophenyl)hydrazino]nicotinate (**9b**)

The same procedure as above was employed. Yield 50%, mp 111-114°C. Nmr ($CDCl_3$) δ 1.37 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.35 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.40 (br, 1H, NH), 6.66-7.30 (m, 5H), 8.28 (m, 1H,

H-6), 8.95 (s, 1H, H-2), 9.33 (br, 1H, NH). Anal. calcd for $C_{14}H_{14}N_3O_2Cl$: C, 57.64; H, 4.84; N, 14.40. Found: C, 57.38; H, 4.95; N, 14.34.

2,3-Dihydro-2-phenyl-1*H*-pyrazolo[4,3-c]pyridin-3-one (10a)

9a (139 mg, 0.5 mmol) in conc. hydrochloric acid (5 ml) was heated to 100°C and held at this temperature for 2 h. The reaction mixture was poured into ice water, neutralized with cold aqueous NaOH (5%), and extracted with EtOAc. The extract was washed with water, and dried ($MgSO_4$). The solvent was removed under reduced pressure. The resulting solid was subsequently purified by column chromatography (SiO_2, eluted with $CHCl_3$:MeOH = 25:1) to give **10a** (45 mg, 42%). Mp 276-278°C. Nmr (DMSO-d_6) δ 6.95-8.30 (m, 5H), 7.00 and 7.53 (each 1H, d, J = 8 Hz, H-6 or H-7), 8.57 (s, 1H, H-4). Anal. calcd for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.22; H, 4.38; N, 19.70.

2-(4-Chlorophenyl)-2,3-dihydro-1*H*-pyrazolo[4,3-c]pyridin-3-one (*10b*)

The same procedure as above was employed. Yield 68%, mp >300°C. Nmr (DMSO-d_6) δ 7.02 and 7.57 (each d, 1H, J = 8 Hz, H-6 or H-7), 7.47 and 8.29 (ABq, 4H, J = 9 Hz, ArH), 8.61 (s, 1H, H-4). Anal. calcd for $C_{12}H_8N_3OCl$: C, 58.67; H, 3.28; N, 17.10. Found: C, 58.50; H, 3.01; N, 16.98.

Ethyl 7-(2-Phenylhydrazino)pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (12a)

To a solution of ethyl 7-chloropyrazolo[1,5-a]pyrimidine-6-carboxylate 11 (1.93 g, 8.6 mmol) in THF (40 ml) at −5°C was added phenylhydrazine (1.85 g, 17.1 mmol). The reaction mixture was stirred for 1 h at room temperature. The resulting precipitate was removed by filtration and the filtrate was concentrated in vacuo. The residue was poured into water and extracted with EtOAc. The organic phase was dried ($MgSO_4$) and concentrated in vacuo. The residue, purified by column chromatography (SiO_2, eluted with n-hexane:EtOAc = 2:1), gave **12a** (1.40 g, 55%). Mp 95-96°C. Nmr ($CDCl_3$) δ 1.40 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.37 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.40 (d, 1H, J = 2 Hz, H-3), 6.67-7.33 (m, 5H), 7.95 (d, 1H, J = 2 Hz, H-2), 8.68 (s, 1H, H-5), 8.91 (br, 1H, NH), 10.7 (br, 1H, NH). Anal. calcd for $C_{15}H_{15}N_5O_2$: C, 60.60; H, 5.09, N, 23.56. Found: C, 60.62; H, 5.17; N, 23.48.

Ethyl 7-[2-(4-Chlorophenyl)hydrazino]pyrazolo[1,5-*a*]pyrimidine-6-carboxylate (12b)

The same procedure as above was employed. Yield 81%, mp 127-128°C. Nmr ($CDCl_3$) δ 1.40 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.41 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.43 (d, 1H, J = 2 Hz, H-3), 6.82 and 7.15 (ABq, 4H, J = 9 Hz), 7.98 (d, 1H, J = 2 Hz, H-2), 8.72 (s, 1H, H-5), 8.88 (br, 1H, NH), 10.7 (br, 1H, NH). Anal. calcd for $C_{15}H_{14}N_5O_2Cl$: C, 54.31; H, 4.25; N, 21.11. Found: C, 54.34; H, 4.04; N, 21.05.

2,5-Dihydro-2-phenyl-3*H*-dipyrazolo[1,5-*a*:4',3'-*e*]pyrimidin-3-one (13a)

A solution of **12a** (1.0 g, 3.4 mmol) in AcOH (10 ml) was heated at reflux for 4 h. The resulting precipitate, collected by filtration and washed with EtOH, afforded **13a** (775 mg, 92%). Mp >300°C. Nmr (DMSO-d_6) δ 6.47 (d, 1H, J = 2 Hz, H-6), 7.01-7.57 (m, 3H), 7.97-8.30 (m, 2H), 8.05 (d, 1H, J = 2 Hz, H-7), 8.73 (s, 1H, H-4). Anal. calcd for $C_{13}H_9N_5O$: C, 62.15; H, 3.61; N, 27.87. Found: C, 62.04; H, 3.65; N, 27.88.

2-(4-Chlorophenyl)-2,5-dihydro-3*H*-dipyrazolo[1,5-*a*:4',3'-*e*]pyrimidin-3-one (13b)

The same procedure as above was employed. Yield 93%, mp >300°C. Nmr (DMSO-d_6) δ 6.50 (d, 1H, J = 2 Hz, H-6), 7.45 and 8.15 (ABq, 4H, J = 9 Hz), 8.05 (d, 1H, J = 2 Hz, H-7), 8.75 (s, 1H, H-4). Anal. calcd for $C_{13}H_8N_5OCl$: C, 54.64; H, 2.82; N, 24.51. Found: C, 54.96; H, 3.12; N, 24.50.

Ethyl 2-Methyl-4-(2-phenylhydrazino)pyrimidine-5-carboxylate (15a)

To a solution of ethyl 4-chloro-2-methylpyrimidine-5-carboxylate (14) (3.2 g, 16 mmol) in THF (75 ml) was added a solution of phenylhydrazine (3.45 g, 33 mmol) in THF (10 ml). This was stirred for 8 h at room temperature. The reaction mixture was concentrated in vacuo. The residue was poured into water, extracted with $CHCl_3$, and dried ($MgSO_4$). Removal of the solvent left **15a** (2.24 g, 52%). Mp 181-182°C. Nmr ($CDCl_3$) δ 1.40 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 2.50 (s, 3H, $-CH_3$), 4.40 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.63 (d, 1H, J = 5 Hz, NH), 6.78-7.40 (m, 5H), 8.83 (s, 1H, H-6), 9.57 (d, 1H, J = 5 Hz, NH). Anal. calcd for $C_{14}H_{16}N_4O_2$: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.68; H, 5.72; N, 20.50.

Ethyl 4-[2-(4-Chlorophenyl)hydrazino]-2-methylpyrimidine-5-carboxylate (15b)

The same procedure as above was employed. Yield 50%, mp 123-124°C. Nmr ($CDCl_3$) δ 1.38 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 2.47 (s, 3H, $-CH_3$), 4.37 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.60 (d, 1H, J = 6 Hz, NH), 6.80 and 7.17 (ABq, 4H, J = 8 Hz), 8.81 (s, 1H, H-6), 9.52 (d, 1H, J = 6 Hz, NH). Anal. calcd for $C_{14}H_{15}N_4O_2Cl$: C, 54.82; H, 4.93; N, 18.26. Found: C, 54.78; H, 5.10; N, 18.27.

2,3-Dihydro-6-methyl-2-phenyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (16a)

To a solution of **15a** (1.48 g, 5.4 mmol) in EtOH (100 ml) was added a solution of KOH (420 mg, 7.5 mmol) in water (2 ml). After stirring for 2 h at room temperature, the mixture was concentrated in vacuo. The residue was dissolved in water (30 ml), and then acidified with a solution of tartaric acid (750 mg) in water (5 ml). The resulting crystals were collected and washed with water, EtOH and EtOAc, giving **16a** (980 mg, 80%). Mp >300°C. Nmr (DMSO-d_6) δ 2.42 (s, 3H, $-CH_3$), 6.97-7.53 (m, 5H), 8.60 (s, 1H, H-4). Anal. calcd for $C_{12}H_{10}N_4O$: C, 63.71; H, 4.46; N, 24.76. Found: C, 63.88; H, 4.18; N, 24.79.

2-(4-Chlorophenyl)-2,3-dihydro-6-methyl-1*H*-pyrazolo[3,4-*d*]pyrimidin-3-one (16b)

The same procedure as above was employed. Yield 84%, mp >300°C. Nmr (DMSO-d_6) δ 2.43 (s, 3H, CH_3), 7.45 and 8.18 (ABq, 4H, J = 8 Hz), 8.68 (s, 1H, H-4). Anal. calcd for $C_{12}H_9N_4OCl$: C, 55.29; H, 3.48; N, 21.49. Found: C, 55.02; H, 3.36; N, 21.47.

Diethyl 4-(2-Phenylhydrazino)thieno[2,3-*b*]pyridine-2,5-dicarboxylate (18a)

A solution of **17a** (350 mg, 1.1 mmol) and phenylhydrazine (133 mg, 1.3 mmol) in EtOH (5 ml) was refluxed. After 1 h, the reaction mixture was concentrated in vacuo, then poured into water, and extracted with EtOAc. The EtOAc solution was washed with water, and dried ($MgSO_4$). The resulting solid was recrystallized from EtOH to give **18a** (410 mg, 97%); mp 126-129°C. Nmr (DMSO-d_6) δ 1.35 and 1.42 (each

t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.36 and 4.39 (each q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.77-7.38 (m, 6H), 8.74 (m, 1H, H-3), 9.00 (m, 1H, H-6).

Ethyl Methyl 4-[2-(4-Chlorophenyl)hydrazino]furo[2,3-*b*]pyridine-2,5-dicarboxylate (18b)

The same procedure as above was employed. Yield 90%, mp 186-188°C. Nmr (DMSO-d_6) δ 1.49 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 3.87 (s, 3H, CO_2CH_3), 4.36 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.15 (br, 1H, NH), 6.81 and 7.20 (ABq, 2H, J = 9 Hz), 7.78 (s, 1H, H-3), 8.90 (s, 1H, H-6), 10.10 (br, 1H, NH).

7-Carboxy-2,5-dihydro-2-phenyl-3*H*-pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridin-3-one (19a)

To a solution of **18a** (405 mg, 1.1 mmol) in EtOH (5 ml) was added 1 N aq. NaOH (1.3 ml), and this was stirred at room temperature. After 1 h, additional 1 N aq. NaOH was added to the solution, followed by heating at 60°C for 40 min. The reaction mixture was acidified with AcOH (1 ml), and the resulting solid was collected by filtration and washed several times with EtOH to give **19a** (267 mg, 78%). Nmr (DMSO-d_6) δ 7.10-7.55 (m, 3H), 8.05-8.23 (m, 3H), 8.78 (s, 1H, H-4).

7-Carboxy-2-(4-chlorophenyl)-2,5-dihydro-3*H*-furo[2,3-*b*]pyrazolo[3,4-*d*]pyridin-3-one (19b)

The same procedure as above was employed. Yield 85%, mp 276-278°C. Nmr (DMSO-d_6) δ 7.54-7.96 (m, 4H), 7.66 (s, 1H, H-8), 8.70 (s, 1H, H-4). Anal. calcd for $C_{15}H_8N_3O_4Cl\cdot 3/4H_2O$: C, 52.49; H, 2.79; N, 12.24. Found: C, 52.21; H, 2.99; N, 12.20.

2,5-Dihydro-2-phenyl-3*H*-pyrazolo[3,4-*d*]thieno[2,3-*b*]pyridin-3-one (20a)

A mixture of **19a** (500 mg, 1.6 mmol) and copper powder (150 mg) in quinoline (10 ml) was stirred at 195°C for 1 h. The copper was removed by filtration and the filtrate was partitioned between ether and aq. NaOH. The separated aqueous layer was acidified with AcOH and the resulting precipitate was filtered, washed with water, and dried to obtain **20a** (384 mg, 87%). Mp 293-294°C. Nmr (DMSO-d_6) δ 7.14-7.73 (m, 5H, ArH), 8.13-8.25 (m, 2H), 8.70 (s, 1H, H-4). Anal. calcd for $C_{14}H_9N_3OS\cdot 1/2H_2O$: C, 60.86; H, 3.65; N, 15.21. Found: C, 61.06; H, 3.79; N, 15.12.

2-(4-Chlorophenyl)-2,5-dihydro-3*H*-furo[2,3-*b*]pyrazolo[3,4-*d*]pyridin-3-one (20b)

The same procedure as above was employed. Yield 48%, mp 253-225°C. Nmr (DMSO-d_6) δ 7.06-7.19 (br, 1H, H-8), 7.57-7.98 (m, 4H), 8.11 (d 1H, J = 3 Hz, H-7), 8.60 (br, 1H, H-4). Anal. calcd for $C_{14}H_8N_3O_2Cl\cdot 3/4H_2O$: C, 56.20; H, 3.20; N, 14.04. Found: C, 56.38; H, 3.11; N, 13.93.

General procedure for 1*H*-pyrrolo[3,2-*c*]quinoline (23)

A mixture of 4-hydrazinoquinoline **21** (2.0 mmol) and the appropriate ketone derivatives (2.2 mmol) in MeOH (6 ml) was refluxed for 2 h, and concentrated in vacuo. The resulting hydrazone, without purification, was refluxed in diethylene glycol (5 ml) for 30 min - 1 h under argon. The cooled mixture was poured into water, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried ($MgSO_4$) and concentrated in vacuo to afford the crude **23**, which was purified by column chromatography (SiO_2, eluted with $CHCl_3$:MeOH = 30:1) to give **23**.

3-Methyl-2-phenyl-1*H*-pyrrolo[3,2-c]quinoline (**23a**)

Yield 56%, mp 295-300°C (from EtOH). Nmr (DMSO-d_6) δ 2.55 (s, 3H, CH_3), 7.43-7.88 (m, 7H), 7.99-8.15 (m, 1H), 8.53-8.68 (m, 1H), 9.16 (s, 1H, H-4), 12.33 (br, 1H, NH). Anal. calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.73; H, 5.61; N, 10.81.

2-Methyl-3-phenyl-1*H*-pyrrolo[3,2-c]quinoline (**23b**)

Yield 39%, mp >300°C (from EtOH). Nmr (DMSO-d_6) δ 2.57 (s, 3H, CH_3), 7.25-7.70 (m, 7H), 7.93-8.10 (m, 1H), 8.30-8.43 (m, 1H), 9.05 (s, 1H, H-4), 12.4 (br, 1H, NH). Anal. calcd for $C_{18}H_{14}N_2$: C, 83.69; H, 5.46; N, 10.84. Found: C, 83.72; H, 5.64; N, 10.74.

3-Ethylthio-2-phenyl-1*H*-pyrrolo[3,2-c]quinoline (**23c**)

Yield 40%, mp 226-228°C (from EtOAc). Nmr (DMSO-d_6) δ 1.05 (t, 3H, J = 7 Hz, $SCH_2\underline{CH_3}$), 2.73 (q, 2H, J = 7 Hz, $SC\underline{H_2}CH_3$), 7.41-8.17 (m, 8H), 8.50-8.69 (m, 1H), 9.19 (s, 1H, H-4), 12.8 (br, 1H, NH). Anal. calcd for $C_{19}H_{16}N_2S$: C, 74.97; H, 5.29; N, 9.20. Found: C, 74.79; H, 5.19; N, 9.36.

2-Phenyl-1*H*-pyrrolo[3,2-c]quinoline (**24**)

To a solution of **23c** (180 mg, 0.6 mmol) in MeOH (6 ml)-EtOH (2 ml) was added Raney-Ni (100 mg), and the mixture was stirred at 75°C for 50 min. The reaction mixture was subjected to filtration, and the filtrate was concentrated in vacuo. The resulting solid was purified by column chromatography (SiO_2, eluted with $CHCl_3$:MeOH = 20:1) to afford **24**; yield 68%, mp >300°C (from EtOH). Nmr (DMSO-d_6) δ 7.20-7.72 (m, 6H), 7.90-8.10 (m, 3H), 8.55-8.70 (m, 1H), 9.12 (s, 1H, H-4). Anal. calcd for $C_{17}H_{12}N_2$: C, 83.58; H, 4.95; N, 11.46. Found: C, 83.59; H, 5.07; N, 11.35.

2-Phenyl-1,2,3-triazolo[4,5-c]quinoline-3-oxide (**27a**)

To a stirred suspension of **25** (1.14 g, 5.5 mmol) in EtOH (20 ml) was added phenylhydrazine (1.78 g, 16.5 mmol) at room temperature and this was stirred for 2 h. The resulting crystals **26a** were collected by filtration and washed several times with EtOH. **26a** was suspended in xylene (75 ml) containing SiO_2 (7 g) and heated at 120°C for 10 min. The hot reaction mixture was immediately filtered off and the filtrate was concentrated in vacuo. The resulting solid was purified by column chromatography (SiO_2, eluted with $CHCl_3$:EtOAc = 20:1) to afford **27a** (0.75 g, 52%). Mp 192-194°C. Nmr ($CDCl_3$) δ 7.50-7.90 (m, 5H), 8.05-8.30 (m, 3H), 8.40-8.55 (m, 1H), 8.27 (s, 1H, H-4). Anal. calcd for $C_{15}H_{10}N_4O$: C, 68.69; H, 3.84; N, 21.36. Found: C, 69.04; H, 3.76; N, 21.32.

2-(4-Chlorophenyl)-1,2,3-triazolo[4,5-c]quinoline-3-oxide (**27b**)

The same procedure as above was employed. Yield 80%, mp 235-236°C. Nmr ($CDCl_3$-CD_3OD) δ 7.60 and 8.20 (ABq, 4H, J = 10 Hz), 7.65-8.55 (m, 4H), 9.27 (s, 1H, H-4). Anal. calcd for $C_{15}H_9N_4OCl$: C, 60.72; H, 3.06; N, 18.88. Found: C, 60.54; H, 3.25; N, 18.73.

2-Phenyl-1,2,3-triazolo[4,5-c]quinoline (**28a**)

To a solution of **27a** (730 mg, 2.79 mmol) in benzene (40 ml) and HMPA (4 ml) was added PCl_3 (1.2 ml, 12.0 mmol) at room temperature. The reaction mixture was refluxed for 2.5 h. After removal of benzene in vacuo, the residue was poured into ice water and neutralized with aq. $NaHCO_3$. The resulting precipitate was collected by filtration and washed with water, and then taken up in $CHCl_3$. The organic solution was dried over $MgSO_4$ and concentrated in vacuo to afford the crude **28a**. Purification of **28a** by column chromatography (SiO_2, eluted with $CHCl_3$:EtOAc = 20:1) gave **28a** (660 mg, 96%); mp 179-180°C. Nmr ($CDCl_3$) δ 7.35-7.85 (m, 5H), 8.15-8.60 (m, 4H), 9.50 (s, 1H, H-4). Anal. calcd for $C_{15}H_{10}N_4$: C, 73.16; H, 4.09; N, 22.75. Found: C, 73.31; H, 4.28; N, 22.52.

2-(4-Chlorophenyl)-1,2,3-triazolo[4,5-c]quinoline (28b)

The same procedure as above was employed. Yield 92%, mp 216-217°C. Nmr ($CDCl_3$) δ 7.53 and 8.35 (ABq, 4H, J = 10 Hz), 7.50-7.90 (m, 2H), 8.05-8.55 (m, 2H), 9.47 (s, 1H, H-4). Anal. calcd for $C_{15}H_{10}N_4Cl$: C, 64.18; H, 3.23; N, 19.96. Found: C, 64.22; H, 3.29; N, 19.89.

3,4-Dihydro-2-phenylpyrazino[2,3-c]quinolin-3-one (31)

To a stirred solution of phenylglyoxylic acid (580 mg, 13.90 mmol) in HMPA (10 ml) and CH_3CN (1 ml) was added dropwise $SOCl_2$ (480 mg, 4.0 mmol) at −5-0°C. The solution was stirred at −5°C for 30 min and then **29** (600 mg, 3.8 mmol) was added. The reaction mixture was stirred at 0°C for 4 h and poured into ice water, then neutralized with aq. $NaHCO_3$. The resulting precipitate was collected by filtration and washed several times with water. The precipitate was heated at 100°C in vacuo to afford the cyclized product **31** (950 mg, 92%); mp >300°C. Nmr (DMSO-d_6) δ 7.50-7.90 (m, 5H), 7.95-8.20 (m, 1H), 8.40-8.85 (m, 3H), 9.00 (s, 1H, H-5), 13.1 (br, 1H, NH). Anal. calcd for $C_{17}H_{11}N_3O$: C, 74.71; H, 4.06; N, 15.38. Found: C, 74.93; H, 4.14; N, 15.42.

Ethyl 4-Aminoquinoline-3-carboxylate (32)

A mixture of **1** (1.18 g, 5.0 mmol) and a solution of ammonia in 2-propanol (5% w/v, 15 ml) was heated at 110°C in a sealed steel cylinder. After 3 h, the mixture was diluted with water, and the resulting crystals were filtrated and washed with water and EtOH to afford **32** (889 mg, 82%); mp 209-210°C. Nmr (DMSO-d_6) δ 1.33 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.35 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 7.40-8.00 (m, 3H), 8.36 (br, 2H, $N\underline{H}_2$), 8.40 (d, 1H, J = 7 Hz), 8.94 (s, 1H, H-2). Anal. calcd for $C_{12}H_{12}N_2O_2$: C, 66.65; H, 5.59; N, 12.96. Found: C, 66.48; H, 5.44; N, 12.98.

3-(4-Chlorophenyl)-1,2,3,4-tetrahydropyrimidino[5,4-c]quinolin-2,4-dione (33a)

To a stirred solution of **32** (432 mg, 2 mmol) in THF (8 ml) and DMF (0.5 ml) was added sodium hydride (96 mg, 2.4 mmol, 60% dispersion in mineral oil) at room temperature. After 1 h, a solution of 4-chlorophenyl isocyanate (339 mg, 2.2 mmol) in THF (0.5 ml) was added and stirred for 1 h. The mixture was concentrated in vacuo, and the residue was dissolved in water and filtered. The filtrate was washed with ether and acidified with AcOH. The resulting solid was filtrated and washed with water. Purification of this solid by

column chromatography (SiO_2, eluted with $CHCl_3$:MeOH = 50:1) gave **33a** (440 mg, 68%); mp >300°C. Nmr (DMSO-d_6) δ 7.40-7.70 (m, 4H), 7.70-8.20 (m, 3H), 8.81 (d, 1H, J = 8 Hz), 9.18 (s, 1H, H-5), 12.43 (s, 1H, NH). Anal. calcd for $C_{17}H_{10}N_3O_2Cl$: C, 63.07; H, 3.11; N, 12.98. Found: C, 63.17; H, 3.37; N, 12.95.

1,2,3,4-Tetrahydro-3-(4-methylphenyl)pyrimido[5,4-*c*]quinolin-2,4-dione (**33b**)

The same procedure as above was employed. Yield 72%, mp >300°C. Nmr (DMSO-d_6) δ 2.40 (s, 3H, CH_3), 7.20-7.40 (m, 4H), 7.70-8.20 (m, 3H), 8.80 (d, 1H, J = 8 Hz), 9.17 (s, 1H, H-5), 12.4 (s, 1H, NH). Anal. calcd for $C_{18}H_{13}N_3O_2$: C, 71.27; H, 4.32; N, 13.86. Found: C, 71.47; H, 4.22; N, 13.79.

Ethyl 4-(α-Methoxycarbonylbenzylamino)quinoline-3-carboxylate (**34a**)

A solution of **1** (707 mg, 6 mmol) and 2-phenylglycine methyl ester (918 mg, 6 mmol) in EtOH (3 ml) was heated at reflux for 2 h. The mixture was dissolved in $CHCl_3$ (20 ml). The organic solution was washed with aq. $NaHCO_3$ and water, and dried ($MgSO_4$), and then concentrated. The residue was purified by column chromatography (SiO_2, eluted with benzene:EtOAc = 10:1), giving **34a** (722 mg, 66%); mp 121-124°C. Nmr (DMSO-d_6) δ 1.43 (t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 3.70 (s, 3H, OCH_3), 4.45 (q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 5.76 (d, 1H, J = 8 Hz, benzylic proton), 7.20-8.00 (m, 9H), 9.14 (s, 1H, H-2), 10.05 (d, 1H, J = 8 Hz, NH). Anal. Calcd for $C_{21}H_{20}N_2O_4$: C, 69.22; H, 5.53; N, 7.69. Found: C, 69.47; H, 5.45; N, 7.67.

Ethyl 4-[(α-Methoxycarbonyl-4-chlorobenzyl)amino]quinoline-3-carboxylate (**34b**)

The same procedure as above was employed. Yield 83%, mp 97-98°C. Nmr (DMSO-d_6) δ 1.09 and 1.39 (each t, 3H, J = 7 Hz, $CO_2CH_2C\underline{H}_3$), 4.12 and 4.39 (each q, 2H, J = 7 Hz, $CO_2C\underline{H}_2CH_3$), 6.15 (d, 1H, J = 7 Hz, benzylic proton), 7.38-8.25 (m, 4H), 7.45 (s, 4H), 9.02 (s, 1H, H-2), 9.31 (d, 1H, J = 7 Hz, NH). Anal. calcd for $C_{22}H_{21}N_2O_4Cl$: C, 64.00; H, 5.12; N, 6.78. Found: C, 63.98; H, 5.26; N, 6.82.

3-Hydroxy-2-phenyl-1*H*-pyrrolo[3,2-*c*]quinoline hydrochloride (**35a**)

A solution of **34a** (182 mg, 0.5 mmol) and NaOMe (54 mg, 1 mmol) in EtOH (1 ml) was heated at reflux for 20 min. The cooled mixture was poured into 1 N aq. HCl (1 ml) and the resulting solid was washed with aq. EtOH to give **35a** (100 mg, 68%); mp >300°C. Nmr (DMSO-d_6) δ 7.20-8.40 (m, 8H), 9.10 (m, 1H), 9.76 (s, 1H, H-4), 10.8 (br, 1H), 13.3 (br, 1H). Anal. calcd for $C_{17}H_{13}N_2OCl$: C, 68.80; H, 4.42; N, 9.44. Found: C, 68.59; H, 4.41; N, 9.29.

2-(4-Chlorophenyl)-3-hydroxy-1*H*-pyrrolo[3,2-*c*]quinoline (**35b**)

The same procedure as above was employed. Yield 69%, mp >300°C. Nmr (DMSO-d_6) δ 7.80-8.30 (m, 3H), 7.55 and 8.21 (ABq, 4H, J = 9 Hz), 8.99-9.13 (m, 1H), 9.72 (s, 1H, H-4), 10.9 (br, 1H), 13.4 (br, 1H). Anal. calcd for $C_{17}H_{12}N_2OCl_2 \cdot H_2O$: C, 58.47; H, 4.04; N, 7.98. Found: C, 58.25; H, 4.16; N, 8.02.

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6. The 5-H structure of **6** was supported by its uv spectrum which is similar to that of 5-methyl derivative of **6**. This structure was also confirmed by the X-ray analyses of **6a** and **6b** (unpublished results from M. Shiro et al.). The compounds **10**, **13**, **16**, **23**, **24**, **31**, **33** and **35** have two possible tautomeric structures, one of which is depicted tentatively.
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