Synthesis of 1,3-Diamino-7,8,9,10-tetrahydropyrido[3,2-*f*]-quinazolines. Inhibitors of *Candida albicans* Dihydrofolate Reductase as Potential Antifungal Agents

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A series of novel 1,3-diamino-7,8,9,10-tetrahydropyrido[3,2-*f*]quinazolines were synthesized starting from 6-amino-5-cyanoquinoline (**4**) . These compounds inhibited *Candida albicans* dihydrofolate reductase with K_i values of ≤ 0.60 n*M*. One analogue exhibited moderate *in vivo* efficacy in a *C. albicans*-infected mouse model.

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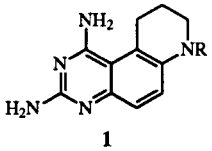
Introduction.

The need for alternative antifungal agents is evidenced by the increase in opportunistic fungal infections, especially among AIDS patients [1-6]. Because of limitations among currently available antifungal agents [7-9], improved drugs having novel mechanisms of action are clearly needed [10].

This report describes the synthesis of a series of novel 1,3-diamino-7,8,9,10-tetrahydropyrido[3,2-*f*]quinazolines **1** and their evaluation as antifungal agents based on the inhibition of fungal dihydrofolate reductase.

Dihydrofolate reductase catalyzes the reduction of dihydrofolic acid to tetrahydrofolic acid, a substrate that is crucial to a number of metabolic pathways, including the biosynthesis of DNA. Inhibition of dihydrofolate reductase causes the cessation of DNA synthesis and can ultimately lead to cell death. Although the enzyme is the target of intervention for a number of well-known drugs such as the antibacterial agent trimethoprim and the anticancer agent methotrexate [11], no clinical antifungal agents based on the inhibition of this enzyme have been reported.

Relatively few dihydrofolate reductase inhibitors have shown *in vitro* antifungal activity [12-14]. However, members of the pyrrolo-2,4-diaminoquinazoline **2** series of inhibitors have shown potent activity against *Candida albicans*. For example, compounds **2a** and **2b** were reported to have *in vitro* activity comparable to that of amphotericin B and flucytosine against 50 *Candida* isolates [12]. The tetrahydropyridoquinazolines **1** were designed as analogues of the pyrroloquinazolines **2**, and as described in this report, compounds **1** generally showed more potent inhibition of *C. albicans* dihydrofolate reductase and were more active as inhibitors of *C. albicans* cell growth than the corresponding members of the pyrroloquinazoline **2** series.



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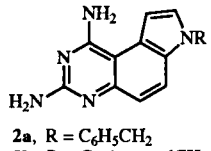
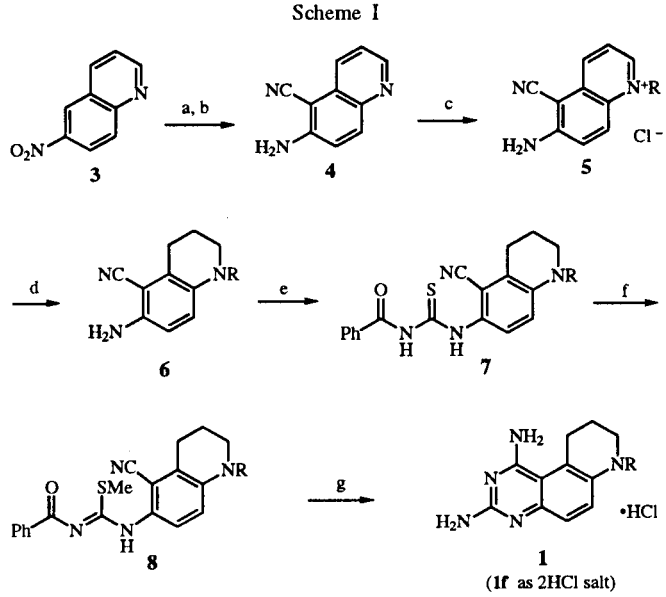


2a, R = $C_6H_5CH_2$
2b, R = CyclopropylCH$_2$

Chemistry.

The synthesis of the desired analogues of **1** is outlined in Schemes I and II.

Scheme I

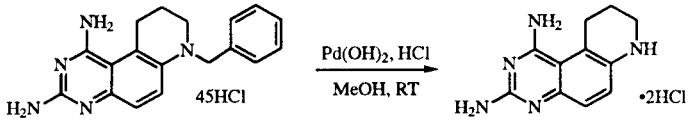


a, R = $C_6H_5CH_2$
b, R = 3,4-$Cl_2C_6H_3CH_2$
c, R = 3,4,5-$(OCH_3)C_6H_2CH_2$
d, R = 1-NaphthylCH$_2$
e, R = 2-NaphthylCH$_2$
f, R = CyclopropylCH$_2$

(a) $NCCH_2CO_2Et$, KOH, DMF; (b) 10% HCl, 20%NaOH; (c) $ArCH_2X$, CH_3CN; (d) H_2, PtO_2, 90% EtOH; (e) PhCONCS, CH_3CN; (f) NaH, DMF, CH_3I; (g) NH_3, methyl cellosolve, HCl.

The synthesis was facilitated by the first step in Scheme I in which 6-amino-5-cyanoquinoline (**4**) was obtained in a regiospecific one-pot conversion from 6-nitroquinoline (**3**) [15]. Intermediate **4** was converted to quinolinium intermediates **5a-f** by refluxing in acetonitrile with the appropriate arylmethyl halides. Subsequent hydrogenation with platinum oxide hydrate as the catalyst [16] led to aminonitriles **6a-f** which were converted to tetrahydropyridoquinazolines **1a-f** using the method of Taylor and Fletcher [17]. This method involved the conversion to thioureas **7a-f** by refluxing **6a-f** in acetonitrile with phenyl isothiocyanate. These thioureas were then methylated with methyl iodide and sodium hydride in DMF to give isothioureas **8a-f**. A solution of these isothioureas in methyl cellosolve in a glass-lined Parr bomb was saturated with ammonia and heated to 140° for 4 hours to furnish the target compounds **1a-f** which were isolated as the hydrochloride salts. As shown in Scheme II, the unsubstituted fused tetrahydropyridine analogue **1g** was obtained in 51% yield from the benzyl derivative **1a** by hydrogenolysis using palladium hydroxide as the catalyst [18].

Scheme II



Biological Results.

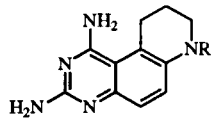
The inhibitory activities of tetrahydropyridoquinazolines **1a-g** against *C. albicans* and human dihydrofolate reductase, as well as against *C. albicans* cell growth are listed in Table 1. For comparison, a series of similarly substituted pyrroloquinazolines **2a-e** were synthesized, using existing procedures [19]. These pyrroloquinazolines were established to be inhibitors of *C. albicans* DHFR, and their *in vitro* activities are also summarized in Table 1.

As indicated in Table 1, substituted tetrahydropyridoquinazolines **1a-f** were at least 10-fold more active than the unsubstituted **1g**. Among the substituted series, **1b-c** were more active than the naphthylmethyl-substituted **1d-e**. The hydrophobic substituents of these compounds presumably bind in the large lipophilic cavity found in the dihydrofolate reductase active site, similar to the observed binding of the dimethoxybenzyl group of piritrexim in its complex with *Pneumocystis carinii* dihydrofolate reductase [20].

In general, among similarly substituted analogues, tetrahydropyridoquinazolines **1** were more active against the *C. albicans* enzyme than pyrroloquinazolines **2**. The only noted exception was the enzyme activity of the 2-naphthylmethyl analogue **2d**, which in the pyrroloquinazoline series was the most active compound against *C. albicans* dihydrofolate reductase. This compound was about 10-fold more active than the similarly substituted **1e**.

Table 1

Inhibition of Dihydrofolate Reductase and *C. albicans* Cells by Tetrahydropyrido-2,4-diaminoquinazolines **1a-g** and Pyrrolo-2,4-diaminoquinazolines **2a-e** [18]



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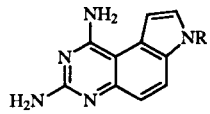

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Compound No.	R	Dihydrofolate reductase K_i (n*M*) [a] *C. albicans*	Human	*C. albicans* MIC (mg/ml) [a]
1a	$C_6H_5CH_2$	0.075	0.0018	0.1
1b	3,4-$Cl_2C_6H_3CH_2$	0.016	0.0030	0.1
1c	3,4,5-$(OCH_3)C_6H_3CH_2$	0.013	<0.001	0.25
1d	1-NaphthylCH_2	0.16	0.0030	0.05
1e	2-NaphthylCH_2	0.20	0.0025	0.02
1f	CyclopropylCH_2	0.60	0.010	0.02
1g	H	5.2	0.037	0.1
2a	$C_6H_5CH_2$	0.11	0.004	0.25
2b	3,4,5-$(OCH_3)C_6H_3CH_2$	0.23	0.38	6.2
2c	1-NaphthylCH_2	0.20	0.0020	3.1
2d	2-NaphthylCH_2	0.016	<0.0010	0.25
2e	H	23	1.0	1

[a] See reference [27] for protocols for the biological assays.

No correlation was found between *C. albicans* cell growth inhibition and enzyme activity for compounds **1**. For example, the weakest enzyme inhibitor, compound **1g**, showed a minimum inhibitory concentration value against the *C. albicans* cells comparable to that of the most active enzyme inhibitor **1c**. The minimum inhibitory concentration values for these tetrahydropyridoquinazolines were in general much lower than those exhibited by the pyrroloquinazoline **2a-e** series. For instance, the value for **1c** was 25-fold lower than that of the corresponding **2b**. Likewise, compound **1d** showed a minimum inhibitory concentration value which was 60 times lower than that shown by the similarly substituted **2c**.

Although compounds **1a-g** were potent against human dihydrofolate reductase (Table 1) and might thus lead to folate-related toxicities *in vivo*, the potential utility of **1a-g** as antifungal agents lie in the fact that such toxic effects can be minimized through the co-administration of leucovorin (5-formyltetrahydrofolate). Furthermore, mammalian cells are known to possess an active transport mechanism for the uptake of leucovorin [21]. *C. albicans*, however, lacks such a mechanism and has to acquire folates through *de novo* synthesis [22]. Leucovorin can minimize folate-related host toxicities and has been used to alleviate myelosuppression [23] induced by the non-selective dihydrofolate reductase inhibitor trimetrexate without affecting its efficacy in the treatment of *P. carinii* pneumonia among AIDS patients [24-25]. As shown in

Table 2, the folate-related cytotoxic effects of compound **1a** on epidermoid adenocarcinoma KB3-1 cell line was significantly reversed by leucovorin. The same levels of leucovorin had no effect on the susceptibility of fungal cells to compound **1a**.

Table 2.

The Cytotoxic Effects of Tetrahydropyridoquinazoline **1a** on Epidermoid Adenocarcinoma KB3-1 Cell Line in the Presence of Leucovorin

Compound +/- Leucovorin	KB3-1 Cell Line EC_{50} (n*M*)
1a	4.2
1a + 10 m*M* Leucovorin	450
1a + 100 m*M* Leucovorin	700

Finally, compound **1a** was found to be moderately efficacious without visible side-effects in immunosuppressed mice with *Candida* nephritis. Compound **1a** was administered intraperitoneally twice-daily on days 1 and 2 at 20 mg/kg with 200 mg/kg of sulfamethoxazole. On day 3, **1a** had reduced the *Candida* burden in the kidney from 6.68 log colony-forming units in the controls to 5.86 log colony-forming units in the treated animals (6.5-fold). Sulfamethoxazole alone showed no activity in this model.

In summary, we have employed a novel synthetic method allowing for entry into tetrahydropyrido-2,4-diaminoquinazolines **1**. Analogues of **1** were potent, non-selective inhibitors of *C. albicans* dihydrofolate reductase, and they also inhibited *C. albicans* cell growth. When compared with similarly substituted pyrrolo-2,4-diaminoquinazolines **2**, analogues of **1** generally were more active against the *C. albicans* enzyme and were more potent in their ability to inhibit *C. albicans* cell growth. Leucovorin attenuated the cytoxocity of inhibitor **1a** without reducing its antifungal activity. In *C. albicans*-infected mice, compound **1a** in combination with sulfamethoxazole was found to be moderately active with no visible signs of adverse side-effects.

EXPERIMENTAL

General.

The protocols for the biological assays followed that reported in reference [27].

Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. ^{1}H nmr spectra were recorded on a Varian XL-300 NMR spectrometer. Mass spectral data were obtained from Oneida Research Services. Microanalyses were provided by Atlantic Microlab. All commercial reagents were used without further purification. DMF was dried over 4 Å molecular sieves. 6-Amino-5-cyanoquinoline (**4**) was prepared according to a procedure described in reference [15].

6-Amino-5-cyano-1-benzylquinolinium Bromide (**5a**).

To an opaque brown mixture of **4** (338.4 g, 2.0 moles) in acetonitrile (3400 ml) at 80°, benzyl bromide (286 ml, 2.4 moles) was added over a 10 minute period. The resultant mixture was maintained at reflux (83°) overnight from which the product precipitated. The product was filtered, washed with additional acetonitrile (1500 ml) and vacuum dried at 40° for four days to afford 588 g (86%) of **5a**, mp 198-200°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 6.33 (s, 2H, CH_2Ph), 7.3-7.5 (m, 5H, aromatic), 7.41 (d, 1H, aromatic), 7.43 (br s, 2H, NH_2), 8.2-8.3 (m, 1H, aromatic), 8.50 (d, 1H, aromatic), 8.88 (d, 1H, aromatic), 9.44 (d, 1H, aromatic); ms: (CI) m/z 260 (M-Br, 6), 170 (M-CH_2Ph, 100).

Anal. Calcd. for $C_{17}H_{14}N_3Br$: C, 60.02; H, 4.15; N, 12.35; Br, 23.49. Found: C, 59.96; H, 4.15; N, 12.30; Br, 23.48.

6-Amino-1-benzyl-5-cyano-1,2,3,4-tetrahydroquinoline (**6a**).

A 40° dark red solution of **5a** (70 g, 0.21 mole) in a 2.5:1 ethanol/water mixture cooled to room temperature and a slurry of platinum oxide hydrate (4.0 g, 6% w/w) was charged into a glass-lined 2-liter Parr bomb and hydrogenated at 48° and 50 psi over a 4-hour period. The reaction mixture was slurried with 15 g of celite and filtered through a pad of celite which was then washed with water (500 ml). The combined filtrate/wash was basified with 1*N* sodium hydroxide (*ca* 150 ml) to *p*H 10, stirred for 30 minutes, filtered, washed with water (100 ml) and vacuum dried to give 33.2 g (61%) of **6a** as a ruddy red powder; mp 122-124°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-1.95 (m, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.20 (t, 2H, CH_2), 4.35 (s, 2H, CH_2Ph), 5.13 (br s, 2H, NH_2), 6.5 (d, 1H, aromatic), 6.7 (d, 1H, aromatic), 7.15-7.35 (m, 5H, aromatic).

Anal. Calcd. for $C_{17}H_{17}N_3$: C, 77.54; H, 6.51; N, 15.96. Found: C, 77.37; H, 6.53; N, 15.89.

1-Benzoyl-3-(1-benzyl-5-cyano-1,2,3,4-tetrahydroquinolinyl)-thiourea (**7a**).

To a 55° solution of **6a** (10 g, 0.038 mole) in acetonitrile (40 ml) under nitrogen, benzoyl isothiocyanate (6.2 ml, 0.046 mole) was added and the resultant mixture heated to reflux (110-140°) where it was maintained for 30 minutes. The thick yellow-green mixture was spontaneously cooled to room temperature and filtered. The isolated solid was washed with acetonitrile (25 ml) followed by hexane (50 ml) and then vacuum dried at room temperature to give 14.12 g (87%) of **7a** as a gold solid, mp 186-188°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.75-2.25 (m, 2H, CH_2), 2.90 (unresolved t, 2H, CH_2), 3.4 (unresolved t, 2H, CH_2), 4.58 (br s, 2H, CH_2Ph), 6.63 (unresolved d, 1H, aromatic), 7-7.38 (m, 6H, aromatic), 7.38-7.75 (m, 3H, aromatic), 7.75-8 (m, 2H, aromatic), 11.7 (br s, 1H, NH), 12.29 (br s, 1H, NH); ms: (CI) m/z 427 ($M+H^+$, 5), 338 (M-CH_2Ph, 9), 306 (34), 291 (12), 274 (13), 273 (17), 264 (20), 228 (9), 215 (26), 214 (10), 173 (68), 172 (20), 122 (100), 105 (50).

Anal. Calcd. for $C_{25}H_{22}N_4SO$: C, 70.40; H, 5.20; N, 13.14; S, 7.52. Found: C, 70.27; H, 5.26; N, 13.09; S, 7.44.

1-Benzoyl-3-(1-benzyl-5-cyano-1,2,3,4-tetrahydroquinolinyl)-*S*-methylisothiourea (**8a**).

To a stirring room temperature suspension of sodium hydride (3.32 g, 0.083 mole) in *N,N*-dimethylformamide (310 ml) was added **7a** (rinsed in with an additional 25 ml of *N,N*-dimethylformamide) and the resultant mixture was stirred at room temperature for 30 minutes. The resultant red solution was cooled

externally to 5° and a solution of methyl iodide (12 ml, 0.188 mole) in *N,N*-dimethylformamide (52 ml) was added dropwise over a 5 minute period. External cooling was removed and the reaction mixture was stirred under nitrogen at ambient temperature overnight. The mixture was concentrated *in vacuo* to a residue which was slurried in methanol (60 ml) at 0° for 30 minutes and filtered. The isolated solid was washed with cold methanol (25 ml), followed by hexane (2 x 25 ml) and vacuum dried to give 29.54 g (89%) of **8a** as a yellow powder, mp 177-179° dec; ^{1}H nmr (deuteriochloroform): 0.87-1.25 (m, 2H, CH_2), 2.0 (unresolved t, 2H, CH_2), 2.48 (unresolved t, 2H, CH_2), 3.5 (s, 2H, CH_2Ph), 5.62 (d, 1H, aromatic), 6.0 (d, 1H, aromatic), 6.0-6.5 (m, 8H, aromatic), 7.0-7.5 (m, 2H, aromatic), 12.5 (br s, 1H, NH); ms: (CI) m/z 463 (M+23, 3), 320 (M-PhCONH, 100), 305 (40), 262 (14), 173 (25), 105 (55).

Anal. Calcd. for $C_{26}H_{24}N_4SO$: C, 70.88; H, 5.49; N, 12.72; S, 7.28. Found: C, 70.77; H, 5.51; N, 12.79; S, 7.33.

1,3-Diamino-7-benzyl-7,8,9,10-tetrahydropyrido[3,2-*f*]quinazoline Hydrochloride (**1a**).

A solution of **8a** (29.0 g, 0.066 mole) in methyl cellosolve was cooled to subambient temperature and saturated with anhydrous ammonia in a 1 liter round-bottomed flask under nitrogen. The saturated solution was transferred to a 2 liter glass-lined Parr bomb which was sealed and heated to 140° for 4 hours. The reaction mixture was removed from the bomb (cooled to -78° in a dry ice/acetone bath prior to opening) and reduced *in vacuo* to a gold solid. The residue was dissolved in 50° ethanol (870 ml), treated with 1.15*M* ethanolic hydrochloric acid (225 ml, 0.259 mole) and stirred at room temperature for 3 hours. The solid was filtered, washed with ethanol (*ca* 25 ml) and dried under vacuum at 45° to give 16.5 g (73%) of **1a** as a yellow powder. Concentration of the filtrate/wash to one-tenth of its original volume and re-treatment with ethanolic hydrochloric acid (40 ml, 0.046 mole) afforded additional 2.5 g (11%) of **1a**, mp 318-320° dec (water); ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.0 (m, 2H, CH_2), 3.2 (t, 2H, CH_2), 3.4 (t, 2H, CH_2), 4.6 (s, 2H, CH_2Ph), 7.0-7.2 (m, 2H, aromatic), 7.2-7.3 (m, 5H, aromatic), 7.4 (br s, 2H, NH_2), 7.6 (br s, 1H, NH), 8.8 (br s, 1H, NH), 12.4 (br s, 1H, NH); ms: (CI) m/z 306 ($M+H^+$, 100).

Anal. Calcd. for $C_{18}H_{20}N_5Cl$: C, 63.24; H, 5.90; N, 20.49; Cl, 10.37. Found: C, 63.21; H, 5.98; N, 20.37; Cl, 10.35.

6-Amino-5-cyano-1-(3,4-dichlorobenzyl)quinolinium Chloride (**5b**).

A suspension of **4** (5 g, 0.63 mole) in acetonitrile was heated to aid dissolution. The resultant solution was cooled to room temperature. To this was added α,3,4-trichlorotoluene (4.9 ml, 0.35 mole). The resultant mixture was refluxed for 11 days. The precipitate was collected by filtration and washed with ethyl acetate to give 7.32 g (68%) of **5b** as a yellow powder. The filtrate was further refluxed with 1.62 ml of α,3,4-trichlorotoluene for 7 days to yield an additional crop of 3.10 g (29%) of **5b**. Without further purification, this **5b** intermediate was used in the following reaction.

6-Amino-1-(3,4-dichlorobenzyl)-5-cyano-1,2,3,4-tetrahydroquinoline (**6b**).

The procedure for the preparation of **6a** was followed using **5b** (1 g, 0.027 mole), platinum oxide hydrate (0.06 g), and hydrogen (10.5 psi). After purification by flash column chromatography [28] on silica gel with 30% ethyl acetate in hexane as the eluent, 0.18 g (19%) of **6b** was obtained as a yellow powder, mp 128-129°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.0 (m, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.15 (t, 2H, CH_2), 4.32 (s, 2H, CH_2Ph), 5.13 (br s, 2H, NH_2), 6.45 (d, 1H, aromatic), 6.65 (d, 1H, aromatic), 7.2 (dd, 1H, J = 8, 2 Hz, aromatic), 7.45 (d, 1H, J = 2 Hz), 7.55 (d, 1H, J = 8 Hz, aromatic); ms: (CI): m/z 332 ($M+H^+$, 100).

Anal. Calcd. for $C_{17}H_{15}N_3Cl_2$•0.1EtOH: C, 61.33; H, 4.67; N, 12.47; Cl, 21.05. Found: C, 61.27; H, 4.58; N, 12.45; Cl, 20.89.

1-Benzoyl-3-[1-(3,4-dichlorobenzyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]thiourea (**7b**).

The procedure for the preparation of **7a** was followed using **6b** (0.5 g, 0.017 mole) and benzoyl isothiocyanate (0.32 g, 0.02 mole). This resulted in 0.74 g (91%) of **7b** as a yellow powder; mp 204-206°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.1 (m, 2H, CH_2), 3.2 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 4.55 (s, 2H, CH_2Ph), 6.7 (d, 1H, aromatic), 7.15-7.3 (m, 2H, aromatic), 7.4-7.7 (m, 5H, aromatic), 8 (d, 2H, aromatic), 11.7 (br s, 1H, NH), 12.25 (br s, 1H, NH); ms: (CI) m/z 332 (100), 122 (23), 181 (17), 164 (12), 105 (16).

Anal. Calcd. for $C_{25}H_{20}N_4Cl_2OS$: C, 60.61; H, 4.07; N, 11.31; Cl, 14.31; S, 6.47. Found: C, 60.88; H, 4.15; N, 11.53; Cl, 14.66; S, 6.51.

1-Benzoyl-3-[1-(3,5-dichlorobenzyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]-*S*-methylisothiourea (**8b**).

The procedure for the preparation of **8a** was followed using **7b** (0.72 g, 1.5 mmoles), 60% oil-dispersed sodium hydride (0.064 g, 1.61 mmoles), and methyl iodide (0.52 g, 3.65 mmoles). After purification by flash column chromatography on silica gel with 50% ethyl acetate in hexane, 0.59 g (79%) of **8b** was obtained as a yellow solid; mp 157-158°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.9-2.1 (m, 2H, CH_2), 2.8-3.0 (m, 2H, CH_2), 3.35-4.0 (m, 2H, CH_2), 4.5 (br s, 2H, CH_2Ph), 6.7 (d, 1H, aromatic), 6.95 (br s, 1H, NH), 7.2 (d, 1H, aromatic), 7.35-7.7 (m, 6H, aromatic), 7.95 (br s, 2H, aromatic); ms: (CI) m/z 376 (25), 374 (35), 336 (12), 334 (67), 332 (100).

Anal. Calcd. for $C_{26}H_{22}N_4Cl_2OS$: C, 61.3; H, 4.35; N, 11.00; Cl, 13.92; S, 6.29. Found: C, 61.27; H, 4.38; N, 11.00; Cl, 14.01; S, 6.26.

1,3-Diamino-7-(3,4-dichlorobenzyl)-7,8,9,10-tetrahydropyrido-[3,2-*f*]quinazoline Hydrochloride (**1b**).

The procedure for the preparation of **1a** was followed using **8b** (0.56 g, 1.1 mmoles) dissolved in methyl cellosolve and saturated with ammonia at subambient temperature. This resulted in 0.2 g (43%) of **1b** as a yellow powder, mp 396-398° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.0 (m, 2H, CH_2), 3.2 (t, 2H, CH_2), 3.35 (t, 2H, CH_2), 4.55 (s, 2H, CH_2Ph), 7.1 (s, 2H, aromatic), 7.2 (dd, 1H, J = 8, 2 Hz, aromatic), 7.5 (d, 1H, J = 2 Hz), 7.55 (s, 1H, NH), 7.6 (d, 1H, J = 8 Hz), 8.8 (s, 1H, NH), 12.1 (s, 1H, NH); ms: (CI) m/z 374 (M^++H^+, 100), 376 (73), 378 (13).

Anal. Calcd. for $C_{18}H_{18}N_5Cl_3$•0.2EtOH•0.8H_2O: C, 50.88; H, 4.83; N, 16.12; Cl, 24.49. Found: C, 51.08; H, 4.64; N, 16.07; Cl, 24.33.

6-Amino-5-cyano-1-(3,4,5-trimethoxybenzyl)quinolinium Chloride (**5c**).

The procedure for the preparation of **5a** was followed using **4** (1 g, 5.9 mmoles) and 3,4,5-trimethoxybenzylchloride (1.41 g, 6.5 mmoles). This resulted in 0.93 g of **5c** as a yellow powder which was used without further purification.

6-Amino-1-(3,4,5-trimethoxybenzyl)-5-cyano-1,2,3,4-tetrahydroquinoline (**6c**).

The procedure for the preparation of **6a** was followed using **5c** (0.46 g, 1.19 mmoles), platinum oxide hydrate (0.06 g), and hydrogen (15.2 psi). After purification by flash column chromatography on silica gel with 70% ethyl acetate in hexane, 0.24 g (52%) of **6c** was obtained as a yellow powder, mp 154-155°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.0 (m, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.1-3.2 (m, 2H, CH_2), 3.6 (s, 3H, OCH_3), 3.7 (s, 6H, 2 x OCH_3), 4.25 (s, 2H, CH_2Ph), 5.1 (br s, 2H, NH_2), 6.5 (d, 1H, aromatic), 6.52 (s, 2H, aromatic), 6.75 (d, 1H, aromatic); ms: (CI) m/z 354 (M^++H^+, 100).

Anal. Calcd. for $C_{20}H_{23}N_3O_3$: C, 67.97; H, 6.56; N, 11.89. Found: C, 67.83; H, 6.61; N, 11.71.

1-Benzoyl-3-[1-(3,4,5-trimethoxybenzyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]thiourea (**7c**).

The procedure for the preparation of **7a** was followed using **6c** (0.24 g, 0.68 mmoles) and benzoyl isothiocyanate (0.13 g, 0.82 mmole). This resulted in 0.16 g (47%) of **7c** as a yellow solid, mp 147-149°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.9-2.1 (m, 2H, CH_2), 2.9 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 3.6 (s, 3H, OCH_3), 3.71 (s, 6H, 2 x OCH_3), 4.5 (s, 2H, CH_2Ph), 6.54 (s, 2H, aromatic), 6.8 (d, 1H, aromatic), 7.2 (d, 1H, aromatic), 7.5 (t, 2H, aromatic), 7.62 (t, 1H, aromatic), 8.0 (d, 2H, aromatic), 11.7 (br s, 1H, NH), 12.3 (br s, 1H, NH); ms: (CI) m/z 181 (6), 164 (30), 105 (100).

Anal. Calcd. for $C_{28}H_{28}N_4O_4S$: C, 65.1; H, 5.46; N, 10.84; S, 6.21. Found: C, 64.84; H, 5.73; N, 10.77; S, 6.22.

1-Benzoyl-3-[1-(3,4,5-trimethoxybenzyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]-*S*-methylisothiourea (**8c**).

The procedure for the preparation of **8a** was followed using **7c** (0.44 g, 0.86 mmole), 60% oil-dispersed sodium hydride (0.04 g, 0.94 mmole), and methyl iodide (0.3 g, 2.14 mmoles). After purification by flash column chromatography on silica gel with 70% ethyl acetate in hexane, 0.32 g (69%) of **8c** was obtained as a yellow solid, mp 136-138°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.85-2.1 (m, 2H, CH_2), 2.9 (t, 2H, CH_2), 3.3-3.5 (m, 2H, CH_2), 3.6 (s, 3H, OCH_3), 3.7 (s, 6H, 2 x OCH_3), 4.5 (s, 2H, CH_2Ph), 6.5 (s, 2H, aromatic), 6.75 (br s, 1H, NH), 6.9-7.1 (m, 1H, aromatic), 7.35-7.6 (m, 3H, aromatic), 7.9-8.2 (m, 1H, aromatic); ms: (EI) m/z 531 (M^++H^+, 2), 226 (34), 105 (100).

Anal. Calcd. for $C_{29}H_{30}N_4O_4S$: C, 65.64; H, 5.7; N, 10.56; S, 6.04. Found: C, 65.53; H, 5.72; N, 10.5; S, 5.99.

1,3-Diamino-7-(3,4,5-trimethoxybenzyl)-7,8,9,10-tetrahydropyrido[3,2-*f*]quinazoline Hydrochloride (**1c**).

The procedure for the preparation of **1a** was followed using **8c** (0.53 g, 0.57 mmole) dissolved in methyl cellosolve and saturated with ammonia at subambient temperature. This resulted in 0.12 g (48%) of **1c** as a yellow powder, mp 261-263°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.0 (m, 2H, CH_2), 3.2 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 3.6 (s, 3H, OCH_3), 3.7 (s, 6H, 2 x OCH_3), 4.5 (s, 2H, CH_2Ph), 6.5 (s, 2H, aromatic), 7.1 (s, 2H, aromatic), 7.28 (br s, 2H, NH_2), 7.6 (br s, 1H, NH), 8.8 (br s, 1H, NH), 12.1 (s, 1H, NH); ms: (CI) m/z 396 (M^++H^+, 4), 79 (100), 97 (41).

Anal. Calcd. for $C_{21}H_{26}N_5O_3Cl$•$0.4H_2O$: C, 57.44; H, 6.15; N, 15.95; Cl, 8.07. Found: C, 57.54; H, 6.17; N, 15.81; Cl, 8.04.

6-Amino-5-cyano-1-(1-naphthylmethyl)quinolinium Bromide (**5d**).

The procedure for the preparation of **5a** was followed using **4** (1 g, 5.9 mmoles) and 1-(bromomethyl)naphthalene (1.44 g, 6.5 mmoles). This resulted in 1.25 (54%) g of **5d** as a yellow powder which was used without further purification.

6-Amino-1-(1-naphthylmethyl)-5-cyano-1,2,3,4-tetrahydroquinoline (**6d**).

The procedure for the preparation of **6b** was followed using **5d** (1.25 g, 3.2 mmoles), platinum oxide hydrate (0.08 g), and hydrogen (9 psi). After purification by flash column chromatography on silica gel with 50% ethyl acetate in hexane, 0.37 g (37%) of **6d** was obtained as a yellow powder; mp 151-152°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.0 (m, 2H, CH_2), 2.8 (t, 2H, CH_2), 3.1-3.25 (m, 2H, CH_2), 4.8 (s, 2H, CH_2Ph), 5.1 (br s, 2H, NH_2), 6.45 (d, 1H, aromatic), 6.6 (d, 1H, aromatic), 7.3 (d, 1H, aromatic), 7.4 (t, 1H, aromatic), 7.45-7.6 (m, 2H, aromatic), 7.8 (d, 1H, aromatic), 7.85-8.0 (m, 1H, aromatic), 8.0-8.15 (m, 1H, aromatic); ms: (CI) m/z 314 (M^++H^+, 100%).

Anal. Calcd. for $C_{21}H_{19}N_3$•$0.1H_2O$: C, 80.02; H, 6.14; N, 13.33. Found: C, 80.00; H, 5.91; N, 13.06.

1-Benzoyl-3-[(1-naphthylmethyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]thiourea (**7d**).

The procedure for the preparation of **7a** was followed using **6d** (0.37 g, 1.18 mmoles) and benzoyl isothiocyanate (0.23 g, 1.42 mmoles). This resulted in 0.48 g (85%) of **7d** as a yellow solid, mp 175-178°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2-2.1 (m, 2H, CH_2), 3.0 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 4.05 (s, 2H, CH_2Ph), 6.6 (d, 1H, aromatic), 7.2 (d, 1H, aromatic), 7.25 (d, 1H, aromatic), 7.3-7.7 (m, 7H, aromatic), 7.82 (d, 1H, aromatic), 7.9-8.1 (m, 3H, aromatic); ms: (CI): m/z 356 (39), 314 (100).

Anal. Calcd. for $C_{29}H_{24}N_4OS$: C, 73.08; H, 5.08; N, 11.76; S, 6.73. Found: C, 72.86; H, 5.10; N, 11.7; S, 6.68.

1-Benzoyl-3-[1-(1-naphthylmethyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]-*S*-methylisothiourea (**8d**).

The procedure for the preparation of **8a** was followed using **7d** (0.48 g, 0.98 mmole), 60% oil-dispersed sodium hydride (0.043 g, 1.1 mmoles), and methyl iodide (0.35 g, 2.44 mmoles). After purification by flash column chromatography on silica gel with 50% ethyl acetate in hexane, 0.37 g (78%) of **8d** was obtained as a yellow solid; mp 212-213°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.95-2.1 (m, 2H, CH_2), 2.95 (t, 2H, CH_2), 3.45 (unresolved t, 2H, CH_2), 5.0 (br s, 2H, CH_2Ph), 6.6 (d, 1H, aromatic), 6.95 (br s, 1H, NH), 7.2 (d, 1H, aromatic), 7.3-7.65 (m, 7H, aromatic), 7.8 (d, 1H, aromatic), 7.9-8.1 (m, 4H, aromatic); ms: (CI) m/z 340 (100), 226 (97).

Anal. Calcd. for $C_{30}H_{26}N_4OS$•$0.2H_2O$: C, 72.91; H, 5.38; N, 11.34; S, 6.49. Found: C, 72.84; H, 5.44; N, 11.23; S, 6.47.

1,3-Diamino-7-(1-naphthylmethyl)-7,8,9,10-tetrahydropyrido-[3,2-*f*]quinazoline Hydrochloride (**1d**).

The procedure for the preparation of **1a** was followed using **8d** (0.36 g, 0.73 mmole) dissolved in methyl cellosolve and saturated with ammonia at subambient temperature. This resulted in 0.22 g (78%) of **1d** as a yellow powder, mp 317-318°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.1 (m, 2H, CH_2), 3.2 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 5.0 (s, 2H, CH_2Ph), 6.95 (d, 1H, aromatic), 7.05 (d, 1H, aromatic), 7.2 (d, 1H, aromatic), 7.35 (br s, 2H, NH_2), 7.3-7.5 (m, 1H, aromatic), 7.5-7.7 (m, 3H, aromatic and NH), 7.8 (d, 1H, aromatic), 7.9-8.2 (m, 2H, aromatic), 8.8 (br s, 1H, NH), 12.1 (s, 1H, NH); ms: (CI) m/z 356 (M^++H^+, 100).

Anal. Calcd. for $C_{22}H_{22}N_5Cl$•$0.4EtOH$•$0.2H_2O$: C, 66.16; H, 6.04; N, 16.92; Cl, 8.56. Found: C, 65.97; H, 5.85; N, 16.74; Cl, 8.56.

6-Amino-5-cyano-1-(2-naphthylmethyl)quinolinium Bromide (**5e**).

The procedure for the preparation of **5a** was followed using **4** (1.0 g, 5.9 mmoles) and 2-(bromomethyl)naphthalene (1.44 g, 6.5 mmoles). This resulted in 1.56 (67%) g of **5e** as a yellow powder which was used without further purification.

6-Amino-1-(2-naphthylmethyl)-5-cyano-1,2,3,4-tetrahydroquinoline (**6e**).

The procedure for the preparation of **6b** was followed using **5e** (1.56 g, 4 mmoles), platinum oxide hydrate (0.1 g), and hydrogen (7 psi). After purification by flash column chromatography on silica gel with 50% ethyl acetate in hexane, 0.53 g (43%) of **6e** was obtained as a yellow powder, mp 151-152°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.0 (m, 2H, CH_2), 2.75 (t, 2H, CH_2), 3.15-3.3 (m, 2H, CH_2), 4.5 (s, 2H, CH_2Ph), 5.1 (br s, 2H, NH_2), 6.45 (d, 1H, aromatic), 6.75 (d, 1H, aromatic), 7.3-7.5 (m, 3H, aromatic), 7.75 (s, 1H, aromatic), 7.75-7.9 (m, 3H, aromatic); ms: (CI) m/z 314 (M^++H^+, 100).

Anal. Calcd. for $C_{21}H_{19}N_3$: C, 80.48; H, 6.11; N, 13.41. Found: C, 80.26; H, 6.29; N, 13.34.

1-Benzoyl-3-[(2-naphthylmethyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]thiourea (**7e**).

The procedure for the preparation of **7a** was followed using **6e** (0.52 g, 1.66 mmoles) and benzoyl isothiocyanate (0.33 g, 2 mmoles). This resulted in 0.78 g (97%) of **7e** as a yellow solid; mp 195-196°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 2.0-2.2 (m, 2H, CH_2), 2.95 (t, 2H, CH_2), 3.5 (t, 2H, CH_2), 4.7 (s, 2H, CH_2Ph), 6.8 (d, 1H, aromatic), 7.2 (d, 1H, aromatic), 7.35-7.55 (m, 5H, aromatic), 7.55-7.7 (m, 1H, aromatic), 7.75 (unresolved s, 1H, aromatic), 7.8-7.95 (m, 4H, aromatic), 7.99 (d, 1H, aromatic); ms: (CI) m/z 356 (30), 314 (100).

Anal. Calcd. for $C_{29}H_{24}N_4OS$: C, 73.08; H, 5.08; N, 11.76; S, 6.73. Found: C, 73.14; H, 5.09; N, 11.74; S, 6.69.

1-Benzoyl-3-[1-(2-naphthylmethyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]-*S*-methylisothiourea (**8e**).

The procedure for the preparation of **8a** was followed using **7e** (0.74 g, 1.56 mmoles), 60% oil-dispersed sodium hydride (0.07 g, 1.7 mmoles), and methyl iodide (0.55 g, 3.9 mmoles). After purification by flash column chromatography on silica gel with 50% ethyl acetate in hexane, 0.59 g (78%) of **8e** was obtained as a yellow solid, mp 120-122°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.9-2.1 (m, 2H, CH_2), 2.9 (t, 2H, CH_2), 3.5 (t, 2H, CH_2), 4.7 (br s, 2H, CH_2Ph), 6.75 (d, 1H, aromatic), 7.0 (br s, 1H, NH), 7.2-7.6 (m, 7H, aromatic), 7.65-7.9 (m, 4H, aromatic), 8.0 (br s, 1H, aromatic); ms: (CI) m/z 340 (100), 226 (90).

Anal. Calcd. for $C_{30}H_{26}N_4OS \cdot 0.3H_2O$: C, 72.64; H, 5.40; N, 11.30; S, 6.46. Found: C, 72.65; H, 5.44; N, 11.24; S, 6.38.

1,3-Diamino-7-(2-naphthylmethyl)-7,8,9,10-tetrahydropyrido-[3,2-*f*]quinazoline Hydrochloride (**1e**).

The procedure for the preparation of **1d** was followed using **8e** (0.56 g, 1.14 mmoles) dissolved in methyl cellosolve and saturated with ammonia at subambient temperature. This resulted in 0.32 g (71%) of **1e** as a yellow powder, mp 303-305°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.1 (m, 2H, CH_2), 3.2 (t, 2H, CH_2), 3.45 (t, 2H, CH_2), 4.78 (s, 2H, CH_2Ph), 7.1 (d, 1H, aromatic), 7.2 (d, 1H, aromatic), 7.3 (br s, 2H, NH_2), 7.3-7.5 (m, 3H, aromatic), 7.6 (br s, 1H, NH), 7.7 (s, 1H, aromatic), 7.7-8 (m, 3H, aromatic), 8.8 (br s, 1H, NH), 12.1 (s, 1H, NH); ms: (CI) m/z 356 (M^++ H^+, 100).

Anal. Calcd. for $C_{22}H_{22}N_5Cl \cdot 0.3H_2O$: C, 66.51; H, 5.73; N, 17.63; Cl, 8.92. Found: C, 66.51; H, 5.76; N, 17.87; Cl, 9.05.

6-Amino-5-cyano-1-(cyclopropylmethyl)quinolinium Bromide (**5f**).

The procedure for the preparation of **5a** was followed using **4** (1.5 g, 8.8 mmoles) and bromomethylcyclopropane (1.69 g, 10.65 mmoles). This resulted in 2 g (74%) of **5f** as a yellow powder which was used without further purification.

6-Amino-1-(cyclopropylmethyl)-5-cyano-1,2,3,4-tetrahydroquinoline (**6f**).

The procedure for the preparation of **6b** was followed using **5f** (2.23 g, 7.34 mmoles), platinum oxide hydrate (0.14 g), and hydrogen (33 psi). After purification by flash column chromatography on silica gel with 50% ethyl acetate in hexane, 0.51 g (32%) of **6f** was obtained as a yellow powder, mp 90-93°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 0.1-0.2 (m, 2H, CH_2), 0.3-0.5 (m, 2H, CH_2), 0.8-1.0 (m, 1H, CH), 1.75-1.95 (m, 2H, CH_2), 2.65 (t, 2H, CH_2), 3.0 (d, 2H, CH_2), 3.15 (t, 2H, CH_2), 5.1 (br s, 2H, NH_2), 6.45 (d, 1H, aromatic), 6.6 (d, 1H, aromatic); ms: (CI) m/z 228 (M^++H^+, 100).

Anal. Calcd. for $C_{14}H_{17}N_3$: C, 73.98; H, 7.54; N, 18.49. Found: C, 73.90; H, 7.56; N, 18.43.

1-Benzoyl-3-[(cyclopropylmethyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]thiourea (**7f**).

The procedure for the preparation of **7a** was followed using **6f** (0.51 g, 2.26 mmoles) and benzoyl isothiocyanate (0.44 g, 2.72 mmoles). This resulted in 0.82 g (93%) of **7f** as a yellow solid, mp 159-161°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 0.1-0.2 (m, 2H, CH_2), 0.2-0.3 (m, 2H, CH_2), 0.9-1.1 (m, 1H, CH), 1.85-2.0 (m, 2H, CH_2), 2.43 (t, 2H, CH_2), 3.3 (d, 2H, CH_2), 3.4 (t, 2H, CH_2), 7.0 (d, 1H, aromatic), 7.3 (d, 1H, aromatic), 7.5 (t, 2H, aromatic), 7.63 (unresolved t, 1H, aromatic), 8.0 (d, 2H, aromatic), 11.7 (s, 1H, NH), 12.3 (s, 1H, NH); ms: (CI) m/z 391 (M^++H^+, 100).

Anal. Calcd. for $C_{22}H_{22}N_4OS$: C, 67.67; H, 5.68; N, 14.35; S, 8.21. Found: C, 67.60; H, 5.73; N, 14.32; S, 8.15.

1-Benzoyl-3-[(cyclopropylmethyl)-5-cyano-1,2,3,4-tetrahydroquinolinyl]-*S*-methylisothiourea (**8f**).

The procedure for the preparation of **8a** was followed using **7f** (0.78 g, 2 mmoles), 60% oil-dispersed sodium hydride (0.09 g, 2.2 mmoles), and methyl iodide (0.71 g, 5 mmoles). After purification by flash column chromatography on silica gel with 40% ethyl acetate in hexane, 0.52 g (62%) of **8f** was obtained as an off-white powder; mp 164-166°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 0.1-0.3 (m, 2H, CH_2), 0.4-0.6 (m, 2H, CH_2), 0.9-1.1 (m, 1H, CH), 1.8-2.0 (m, 2H, CH_2), 2.85 (t, 2H, CH_2), 3.1-3.25 (m, 2H, CH_2), 3.3-3.4 (m, 2H, CH_2), 6.8-7.0 (m, 2H, aromatic), 7.1 (br s, 1H, NH), 7.3-7.6 (m, 3H, aromatic), 7.8-8.2 (m, 2H, aromatic); ms: (CI) m/z 405 (M^++H^+, 100).

Anal. Calcd. for $C_{23}H_{24}N_4OS$: C, 68.29; H, 5.98; N, 13.85; S, 7.93. Found: C, 68.17; H, 6.03; N, 13.81; S, 7.88.

1,3-Diamino-7-(cyclopropylmethyl)-7,8,9,10-tetrahydropyrido-[3,2-*f*]quinazoline dihydrochloride (**1f**).

The procedure for the preparation of **1a** was followed using **8f** (0.43 g, 1.1 mmoles) dissolved in methyl cellosolve and saturated with ammonia at subambient temperature. This resulted in 0.18 g (51%) of **1f** as a beige powder, mp 244-246°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 0.18-0.3 (m, 2H, CH_2), 0.4-0.6 (m,

2H, CH_2), 0.8-1.1 (m, 1H, CH), 1.7-1.9 (m, 2H, CH_2), 3.1 (unresolved t, 2H, CH_2), 3.3 (d, 2H, CH_2), 3.3-3.4 (m, 2H, CH_2), 7.2 (d, 1H, aromatic), 7.4 (d, 1H, aromatic), 7.42 (br s, 2H, NH_2), 7.59 (br s, 1H, NH), 8.8 (br s, 1H, NH), 12.4 (br s, 1H, NH); ms: (CI) m/z 270 (M^++H^+, 100).

Anal. Calcd. for $C_{15}H_{21}N_5Cl_2 \cdot H_2O$: C, 50.01; H, 6.43; N, 19.44; Cl, 19.68. Found: C, 50.1; H, 6.45; N, 19.43; Cl, 19.74.

1,3-Diamino-7,8,9,10-tetrahydropyrido[3,2-*f*]quinazoline Dihydrochloride (**1g**).

A mixture of **1a** (15 g, 0.044 mole) in 3.4 liters of anhydrous methanol was heated to 48°. This solution was cooled and transferred to a 5-liter 3-necked round-bottomed flask equiped with a mechanical stirrer. To this was added ethanolic hydrochloric acid (42 ml, 1.1*M*, 0.048 mole) followed by palladium hydroxide (22.5 g, 150% (w/w)). The flask was sealed, evacuated of air and pressurized with hydrogen. After vigorous stirring for 45 minutes (total hydrogen consumed 7 psi), the round-bottomed flask was flushed with nitrogen. The reaction mixture was filtered through a Supercel bed over a filter paper contained in a fritted glass funnel. The bed was washed with 75 ml of methanol and the combined filtrate/wash was concentrated *in vacuo*. After further drying in a vacuum oven, 10 g (79.5%) of **1g** was obtained as a yellow solid, mp >300° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 1.8-2.0 (m, 2H, CH_2), 3.1-3.3 (m, 4H, 2 x CH_2), 7.23 (d, 1H, aromatic), 7.3 (d, 1H, aromatic), 7.5 (br s, 2H, NH_2), 7.6 (s, 1H, NH), 8.9 (s, 1H, NH), 12.7 (s, 1H); ms: (CI) m/z 216 (M^++H^+, 100).

Anal. Calcd. for $C_{11}H_{15}N_5Cl_2$: C, 45.85; H, 5.25; N, 24.3; Cl, 24.6. Found: C, 45.66; H, 5.27; N, 24.19; Cl, 24.77.

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