# Synthesis of Some Novel Halogenated 2,4-Diaminoquinazolines



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Three new 2,4-diaminoquinazolines, the 5,6-difluoro, 6,7-difluoro and 7,8-difluoro isomers were prepared by the reaction of the requisite trifluorobenzonitrile and guanidine carbonate. Surprisingly, 2,3,6-trifluorobenzonitriles gave 2,4-diamino-5,6-difluoroquinazoline exclusively as determined by high resolution nuclear magnetic resonance spectroscopy. On the other hand, 3-amino-2,6-difluorobenzonitrile on reaction with guanidine carbonate yielded only 5-fluoro-2,4,8-triaminoquinazoline. This compound was subsequently converted to 8-chloro-2,4-diamino-5-fluoroquinazoline using the Sandmeyer procedure. The nitration of 2,4-diamino-8-fluoroquinazoline occurred exclusively at position six yielding 2,4-diamino-8-fluoro-6-nitroquinazoline, which upon reduction with stannous chloride afforded 8-fluoro-2,4,6-triaminoquinazoline. In a similar fashion 7-fluoro-2,4-diaminoquinazoline underwent nitration at position six and was then reduced to give 7-fluoro-2,4,6-triaminoquinazoline. Finally, both of these triaminoquinazolines were converted to the 6-chloro derivatives under Sandmeyer conditions to yield 6-chloro-2,4-diamino-8-fluoroquinazoline and 6-chloro-2,4-diamino-7-fluoroquinazoline, respectively.

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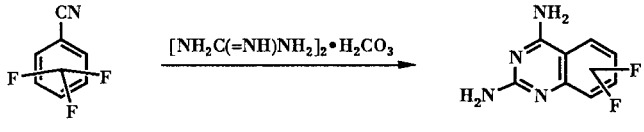
In this laboratory we have been attempting to identify new inhibitors of dihydrofolate reductase (DHFR) which display selectivity for the mycobacterial enzyme *versus* the human enzyme. Initially, these efforts were directed toward the improved chemotherapy of leprosy (*Mycobacterium leprae*), while more recently emphasis has been placed upon species of the *Mycobacterium avium* complex (MAC). Infections due to MAC are quite common in AIDS patients and are extremely difficult to treat with existing drugs. Recently, we reported the inhibitory activities of a wide variety of 2,4-diaminoquinazolines bearing simple substituents on the aromatic ring against human DHFR obtained from the WIL2 fibroblast cell line [1]. For halogenated derivatives inhibitory potency followed the order 5,6 > 5 > 6 > 7 or 8. In order to extend these studies, 2,4-diaminoquinazolines having other ring substitution patterns were required. This paper describes the synthesis of a variety of new halogenated 2,4-diaminoquinazolines with particular emphasis being placed upon fluorine. It should be noted that each of the isomeric monofluorinated 2,4-diaminoquinazolines has been prepared previously by the reaction of the requisite difluorobenzonitrile and guanidine carbonate in *N,N*-dimethylacetamide [2].

As shown in Scheme I three isomeric trifluorobenzonitriles **2a-c** underwent the standard cyclization with guanidine carbonate to yield the isomeric difluoro-2,4-diaminoquinazolines **1a-c** in moderate yields. It is interesting that in the case of 2,3,6-trifluorobenzonitrile, **2a**, which could give either the 5,6- or 5,8-difluoroquinazoline, only 2,4-diamino-5,6-difluoroquinazoline, **1a**, was isolated as demonstrated by its high resolution nuclear magnetic resonance spectrum. It appears that the 6-fluorine of **2a** is a better leaving group than the 2-fluorine by virtue of being *para* to the fluorine located at position 3. However, the reaction of 2,6-difluoro-3-nitrobenzonitrile, **3**, with guanidine carbonated under the same conditions failed to produce either of the expected 2,4-diaminoquinazolines and a complex reaction mixture was obtained. Compound **3** was reduced with stannous chloride to afford 3-amino-2,6-difluorobenzonitrile, **4**, as indicated in Scheme II. This compound was then reacted with guanidine carbonate to yield 5-fluoro-2,4,8-triaminoquinazoline, **1d**, which contained none of its known isomer, 5-fluoro-2,4,6-triaminoquinazoline [3]. The structure of **1d** was confirmed by its independent preparation from 2,4-diamino-5-fluoro-8-nitroquinazoline [3] by catalytic hydrogenation. The regioselectivity of this cyclization reaction may be the result of the deactivating effect of the electron donating *para* amino group upon the 6-fluorine atom. However, it is also possible that the departure of the 2-fluorine atom is facilitated by a neighboring group effect involving hydrogen bonding from the 3-amino group. Next, 5-fluoro-2,4,8-triaminoquinazoline, **1d**, was converted to the new 8-chloro-2,4-diamino-5-fluoroquinazoline, **1e**, under Sandmeyer conditions.

In order to prepare the isomeric 6-chloro-7-fluoro and 6-chloro-8-fluoroquinazolines, **1h** and **1k**, a different synthetic approach was employed as depicted in Scheme III.

Scheme I

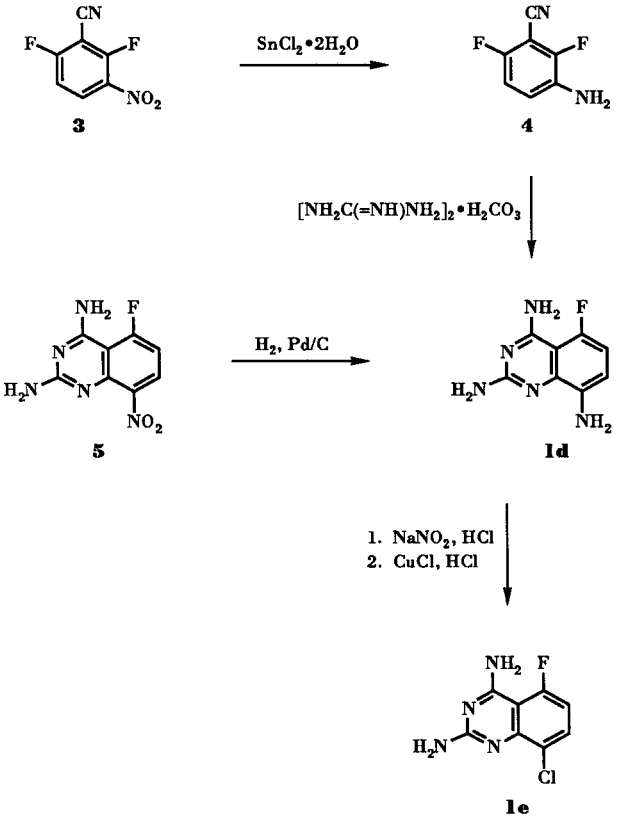
Synthesis of Difluorinated 2,4-Diaminoquinazolines




**2a** 2,3,6-$F_3$ **1a** 5,6-$F_2$
**2b** 2,4,5-$F_3$ **1b** 6,7-$F_2$
**2c** 2,3,4-$F_3$ **1c** 7,8-$F_2$

Scheme II

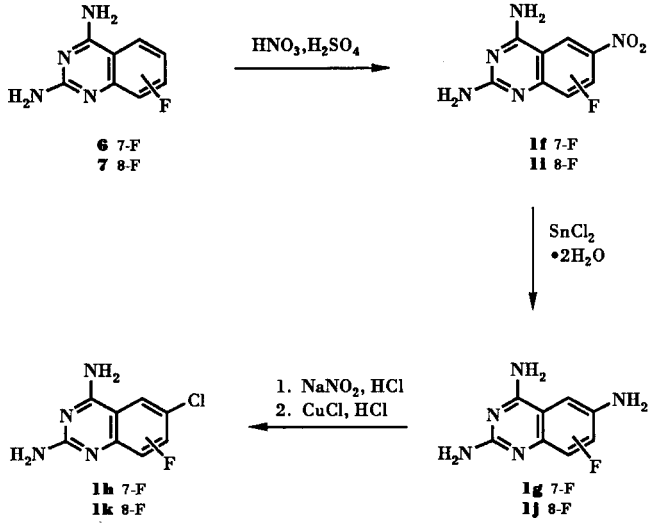
Synthetic Route to 8-Chloro-2,4-diamino-5-fluoroquinazoline




The nitration of 2,4-diamino-7-fluoroquinazoline, **6**, [2] yielded 2,4-diamino-6-nitro-7-fluoroquinazoline, **1f**, as the sole isolated product. This compound was then reduced to give 7-fluoro-2,4,6-triaminoquinazoline, **1g**, using stannous chloride or catalytic hydrogenation. The new 6-chloro-2,4-diamino-7-fluoroquinazoline, **1h**, was obtained from

Scheme III

Synthesis of 6-Chloro-2,4-diamino-7-fluoroquinazoline and 6-Chloro-2,4-diamino-8-fluoroquinazoline




**1g** by diazotization followed by treatment with cuprous chloride. An analogous three step synthetic sequence was then conducted beginning with 2,4-diamino-8-fluoroquinazoline, **7**, [2] resulting in 6-chloro-2,4-diamino-8-fluoroquinazoline, **1k**, which was obtained in reasonable overall yield as shown in Scheme III. It can be concluded then that the nitration of either **6** or **7** occurs exclusively at position six as determined by high resolution nuclear magnetic resonance spectroscopy. However, the nitration of 2,4-diamino-5-fluoroquinazoline was recently reported to yield a mixture of the 6-nitro and 8-nitro isomers in an approximate ratio of 2:1 [3]. It should also be noted that the nitration of 2,4-diamino-7-methylquinazoline apparently occurred at position six, although the product was not characterized unequivocally [7].

Scheme IV

Cyclization of 2-Fluoro-6-nitrobenzonitrile

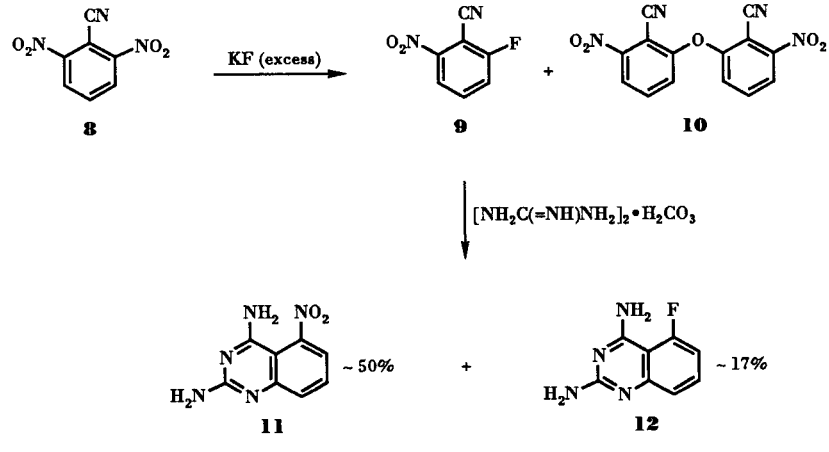
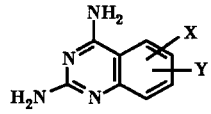


Table 1

Physical and Analytical Data for New 2,4-Diaminoquinazolines



| Compound No. | X | Y | Reaction Time, Hours | Method | Yield % | MS m/e | Emperical Formula | Analyses %, Calcd./Found C | H | N |
|---|---|---|---|---|---|---|---|---|---|---|
| **1a** | 5-F | 6-F | 5 | A | 84 | 196 | $C_8H_6F_2N_4$ | 48.98 | 3.08 | 28.56 |
| | | | | | | | | 49.10 | 3.13 | 28.50 |
| **1b** | 6-F | 7-F | 5 | A | 66 | 196 | $C_8H_6F_2N_4$ | 48.98 | 3.08 | 28.56 |
| | | | | | | | | 49.03 | 3.09 | 28.50 |
| **1c** | 7-F | 8-F | 6 | A | 62 | 196 | $C_8H_6F_2N_4$ | 48.98 | 3.08 | 28.56 |
| | | | | | | | | 49.02 | 3.10 | 28.47 |
| **1d** | 5-F | 8-$NH_2$ | 7 | A | 74 | 193 | $C_8H_8FN_5$ | 49.73 | 4.17 | 36.25 |
| | | | | | | | | 49.68 | 4.17 | 36.23 |
| **1e** | 5-F | 8-Cl | 4.5 | D | 63 | 212 | $C_8H_6ClFN_4$ | 45.19 | 2.84 | 26.35 |
| | | | | | | | | 45.39 | 2.86 | 26.16 |
| **1f** | 6-$NO_2$ | 7-F | 5 | B | 82 | 223 | $C_8H_6FN_5O_2$ | 43.06 | 2.71 | 31.38 |
| | | | | | | | | 43.32 | 2.89 | 31.12 |
| **1g** | 6-$NH_2$ | 7-F | 6 | C | 73 | 193 | $C_8H_8FN_5$ | 49.74 | 4.17 | 36.25 |
| | | | | | | | | 49.84 | 4.25 | 36.04 |
| **1h** | 6-Cl | 7-F | 4 | D | 39 | 212 | $C_8H_6ClFN_4$ | 45.19 | 2.84 | 26.35 |
| | | | | | | | | 45.42 | 2.96 | 26.13 |
| **1i** | 6-$NO_2$ | 8-F | 4 | B | 79 | 223 | $C_8H_6FN_5O_2 \cdot 0.25H_2O$ | 42.20 | 2.88 | 30.76 |
| | | | | | | | | 42.04 | 2.77 | 30.59 |
| **1j** | 6-$NH_2$ | 8-F | 4 | - | 53 | 193 | $C_8H_8FN_5$ | 49.74 | 4.17 | 36.25 |
| | | | | | | | | 49.65 | 4.24 | 36.59 |
| **1k** | 6-Cl | 8-F | 2 | D | 59 | 212 | $C_8H_6ClFN_4$ | 45.19 | 2.85 | 26.35 |
| | | | | | | | | 44.96 | 2.95 | 26.19 |

In an attempt to shed additional light upon the mechanism of the guanidine carbonate cyclization of *ortho*-fluorobenzonitriles, we endeavored to prepare 2-fluoro-6-nitrobenzonitrile, **9**, as shown in Scheme IV. The reaction of 2,6-dinitrobenzonitrile, **8**, with anhydrous potassium fluoride in *N,N*-dimethylformamide was found to give **9** invariably accompanied by side reaction products. In spite of the use of an 8-fold excess of potassium fluoride and the potential nitrite ion scavenger, phthalic anhydride [4], the formation of a significant amount of di(2-cyano-3-nitrophenyl) ether, **10**, occurred. The cyclization of 2-fluoro-6-nitrobenzonitrile, **9**, with guanidine carbonate gave a mixture of the known compounds 2,4-diamino-5-nitroquinazoline, **11**, and 2,4-diamino-5-fluoroquinazoline, **12**, [2] in an approximate ratio of 3:1. Compound **11** had a melting point which was in agreement with the literature value [5]. These results indicate that in this instance fluorine is a better leaving group than the nitro group.

## EXPERIMENTAL

Melting points were determined on a Mel-temp apparatus and are uncorrected. Elemental analyses were performed by Atlantic Microlabs, Inc., Norcross, GA. Solvation due to water was confirmed by the presence of a broad peak centered at *ca* $\delta$ 3.4 ppm in the $^1$H nmr spectrum which was transformed into a sharp singlet (DOH) by addition of deuterium oxide. All intermediates and target compounds were free of significant impurities on tlc using silica gel media (Kodak — 13181) or (Baker 1B2-F). Column chromatographic separations were performed on Baker silica gel (60-200 mesh). The $^1$H and $^{19}$F nmr spectra were obtained using 300 MHz (Bruker AM-300) or 400 MHz (Varian VXR-400) instruments. The $^1$H chemical shifts are presented in parts per million downfield from tetramethylsilane as the internal standard and the relative peak areas are given to the nearest whole number. The $^{19}$F chemical shifts are presented in parts per million relative to fluorotrichloromethane as the standard. The electron impact mass spectra were obtained off probe using a Finnigan 4521 spectrometer and fast atom bombardment mass spectra (FAB) were obtained on a Finnigan MAT 212 spectrometer using argon bombardment. Unless stated otherwise all mass spectra were determined by electron impact. The 2,6-dinitrobenzonitrile was prepared by the method of Beck [6]. 2,3,6-, 2,4,5-and 2,3,4-Trifluorobenzonitriles were obtained from Aldrich Chemical Co., while 2,6-difluoro-3-nitrobenzonitrile was purchased from Lancaster Synthesis, Inc.

3-Amino-2,6-difluorobenzonitrile (**4**).

A mixture of concentrated hydrochloric acid (82 ml) and glacial

acetic acid (28 ml) was stirred and cooled in ice bath under nitrogen. To this solution stannous chloride dihydrate (20 g, 0.089 mole) was added in one portion. After stirring the reaction mixture at 0° for five minutes, 2,6-difluoro-3-nitrobenzonitrile (5 g, 0.027 mole) was added during a twenty minute period. The reaction mixture was stirred at 0° for 30 minutes and then for 18 hours at ambient temperature. The mixture was poured onto crushed ice (200 ml) and the resulting white suspension was basified with concentrated ammonium hydroxide to *p*H 9. After cooling the suspension in an ice bath for 8 hours, the precipitate was collected by filtration, washed with water and dried under vacuum at 40°. This material was extracted successively with tetrahydrofuran (2 x 200 ml) and methanol (1 x 200 ml). The extracts were combined and evaporated under reduced pressure and the residual off-white solid was purified by column chromatography on silica gel eluting with 50% *n*-hexane in tetrahydrofuran to afford 3.17 g (76%) of an off-white solid, tlc (tetrahydrofuran:*n*-hexane, 6:4), mp 103-104°; $^1$H nmr (DMSO-$d_6$): 300 MHz $\delta$ 5.56 (br s, 2H, 3-$NH_2$), 7.05-7.15 (m, 2H, 4-H, 5-H); $^{19}$F nmr (DMSO-$d_6$): 300 MHz $\delta$ -48.59 to -48.47 (m, 6-F), -51.61 to -51.51 (m, 2-F); ms: (EI) (m/e) 154 ($M^+$).

*Anal.* Calcd. for $C_7H_4F_2N_2$: C, 54.55; H, 2.62; N, 18.18. Found: C, 54.59; H, 2.63; N, 18.24.

2-Fluoro-6-nitrobenzonitrile (**9**) and Di-(2-cyano-3-nitrophenyl) Ether (**10**).

A mixture of 19.3 g (0.10 mole) of 2,6-dinitrobenzonitrile, 14.8 g (0.10 mole) of phthalic anhydride and 46.8 g (0.80 mole) of anhydrous potassium fluoride in 200 ml of *N,N*-dimethylformamide was heated at 57° under argon for 21 hours. The mixture was added to 1 ℓ of 5% sodium bicarbonate and this solution was then extracted with chloroform (3 x 200 ml). The extract was washed with water (2 x 200 ml), dried over magnesium sulfate containing charcoal, filtered, and then concentrated under reduced pressure. Water (400 ml) was added to the residue to yield a solid which was separated by filtration, washed with chilled water and extracted with ethyl ether. The ethyl ether insoluble solid was separated by filtration and recrystallized from 2-methoxyethanol:water, 1:1, to yield 1.0 g of **10** as light tan crystals, tlc (chloroform), mp 226-228° (preliminary softening); ms: (FAB) (m/e) 311 $(M + 1)^+$.

*Anal.* Calcd. for $C_{14}H_6N_4O_5$: C, 54.20; H, 1.95; N, 18.06. Found: C, 54.33; H, 1.90; N, 18.02.

The ether extract was concentrated under reduced pressure to give an oil, which yielded a yellow crystalline solid upon the addition of *n*-hexane. This product was dissolved in benzene and traces of insoluble solid were removed by filtration. The solvent was removed under reduced pressure, and the residual product was dried under vacuum at room temperature for 12 hours to yield 8.5 g (51%) of light yellow crystals, tlc (benzene), mp 69-71°; $^1$H nmr (DMSO-$d_6$): 400 MHz $\delta$ 8.02-8.08 (m, 2H, 3-H, 5-H), 8.29 (dd, 1H, 5-H, J = 7.57 Hz, J = 1.99 Hz); $^{19}$F nmr (DMSO-$d_6$): 400 MHz $\delta$ -24.22 to -24.32 (m, 2-F); ms: (EI) (m/e) 166 ($M^+$).

*Anal.* Calcd. for $C_7H_3FN_2O_2$: C, 50.61; H, 1.82; F, 11.43; N, 16.87. Found: C, 50.45; H, 1.82; F, 11.20; N, 16.83.

Method A for Preparing Compounds **1a-1d**, **11** and **12**.

2,4-Diamino-5,6-difluoroquinazoline (**1a**).

A mixture of 1.0 g (0.006 mole) of 2,3,6-trifluorobenzonitrile and 2.30 g (0.013 mole) of guanidine carbonate in 50 ml of *N,N*-dimethylacetamide was heated at 135° under nitrogen for 5 hours. The reaction mixture was then evaporated under reduced pressure and the residual light brown product was dried under vacuum at 80° for 4 hours. This product was suspended in cold water and the *p*H was adjusted to 8.5 with concentrated ammonium hydroxide. After cooling, the precipitate was collected by filtration and washed successively with cold water (2 x 10 ml), diethyl ether (2 x 25 ml), *n*-pentane (2 x 25 ml) and dried under vacuum at 70° for 2 hours. This product was purified by column chromatography on silica gel eluting with 30% *n*-hexane in tetrahydrofuran to yield chromatographically pure product, tlc (tetrahydrofuran:*n*-hexane, 8:2). Recrystallization from tetrahydrofuran:*n*-hexane, 3:2 afforded 1.045 g (84%) of an off-white crystalline product, mp 256-257°; $^1$H-nmr (DMSO-$d_6$): 300 MHz $\delta$ 6.49 (br s, 2H, 2-$NH_2$), 6.67-6.75 (m, 1H, 8-H), 6.93 (br s, 1H, 4-NH), 7.28-7.36 (ddd, 1H, 7-H, J = 10.69 Hz, J = 8.79 Hz, J = 4.92 Hz), 7.54 (br s, 1H, 4-NH); $^{19}$F nmr (DMSO-$d_6$): 300 MHz $\delta$ -39.69 to -39.83 (ddd, 1F, 6-F, J = 20.71 Hz, J = 11.52 Hz, J = 4.79 Hz), -56.42 to -56.54 (ddd, 5-F, J = 20.49 Hz, J = 10.68 Hz, J = 3.44 Hz).

2,4-Diamino-6,7-difluoroquinazoline (**1b**).

This compound was obtained from **2b** as a yellow solid. Chromatography on silica gel using gradient elution with ethyl acetate followed by 2% increments of *N,N*-dimethylformamide until a 9:1 mixture of ethyl acetate and *N,N*-dimethylformamide was reached, gave a light yellow product, pure by tlc (ethyl acetate: *N,N*-dimethylformamide, 9:1). Recrystallization from ethyl acetate:benzene, 1:1 afforded an off-white crystalline powder, mp 172-173°; $^1$H nmr (DMSO-$d_6$): $\delta$ 5.92 (br s, 4H, 2-$NH_2$, 4-$NH_2$), 6.85 (dd, 1H, 5-H or 8-H, J = 6.95 Hz, J = 11.81 Hz), 7.56 (dd, 1H, 5-H or 8-H, J = 6.51 Hz, J = 10.62 Hz); $^{19}$F nmr (DMSO-$d_6$): 400 MHz $\delta$ -34.08 to -34.19 (m, 6-F or 7-F), -48.74 to -48.84 (m, 6-F or 7-F).

2,4-Diamino-7,8-difluoroquinazoline (**1c**).

This compound was prepared from **2c** and isolated as a tan solid. Column chromatography on silica gel using gradient elution with ethyl acetate followed by 2% increments of *N,N*-dimethylformamide until a 9:1 mixture of ethyl acetate and *N,N*-dimethylformamide was reached afforded an off-white crystalline powder, pure by tlc (ethyl acetate:*N,N*-dimethylformamide, 9:1); mp 295-296°; $^1$H nmr (DMSO-$d_6$): 400 MHz $\delta$ 6.38 (br s, 2H, 2-$NH_2$), 6.95-7.04 (m, 1H, 6-H), 7.46 (br s, 2H, 4-$NH_2$), 7.80-7.85 (m, 1H, 5-H); $^{19}$F nmr (DMSO-$d_6$): 400 MHz $\delta$ -54.72 to -54.83 (m, 2F, 7-F, 8-F).

5-Fluoro-2,4,8-triaminoquinazoline (**1d**).

This compound was obtained from 3-amino-2,6-difluorobenzonitrile (**4**) as a brown crystalline powder. Chromatography on silica gel using gradient elution with ethyl acetate followed by 5% increments of *N,N*-dimethylformamide until a 8:2 mixture of ethyl acetate and *N,N*-dimethylformamide was reached afforded a light brown crystalline product, pure by tlc (ethyl acetate: *N,N*-dimethylformamide, 9:1), mp 184-185°; $^1$H nmr (DMSO-$d_6$): 300 MHz $\delta$ 5.06 (br s, 2H, 8-$NH_2$), 6.09 (br s, 2H, 2-$NH_2$), 6.51-6.64 (m, 2H, 6-H, 7-H), 6.71 (br s, 1H, 4-NH), 7.27 (br s, 1H, 4-NH); $^{19}$F nmr (DMSO-$d_6$): 300 MHz $\delta$ -51.60 (dd, 5-F, J = 11.79 Hz, J = 5.35 Hz).

2,4-Diamino-5-nitroquinazoline (**11**) and 2,4-Diamino-5-fluoroquinazoline (**12**).

These two compounds were obtained from 2-fluoro-6-nitrobenzonitrile (**9**) as a dark orange-red solid mixture. This crude product was purified by chromatography on silica gel eluting with 20% *n*-hexane in tetrahydrofuran to afford two separated crystalline products, both pure by tlc (tetrahydrofuran:*n*-hexane, 8:2). 2,4-Diamino-5-nitroquinazoline was isolated as a dark-red crystalline powder, mp 236-237° (lit [5] mp 237-239°); $^1$H nmr (DMSO-$d_6$): 400 MHz $\delta$ 6.44 (br s, 2H, 2-$NH_2$), 6.76 (br s, 2H, 4-$NH_2$), 7.46-7.51 (m, 2H, 6-H, 8-H), 7.59 (dd, 1H, 7-H, $J_1 \cong J_2$ = 7.92 Hz); ms: (EI) (m/e) 205 ($M^+$).

2,4-Diamino-5-fluoroquinazoline was isolated as an off-white crystalline product which was identified by comparing its $^1$H nmr spectrum with $^1$H nmr spectrum of the authentic sample [2], mp 252-253° (lit [2] mp 249-251°).

Method B for Preparing Compounds **1f** and **1i**.

2,4-Diamino-7-fluoro-6-nitroquinazoline (**1f**).

A mixture of 90% nitric acid (3 ml) and 98% sulfuric acid (3 ml) was stirred and cooled in an ice bath under nitrogen. To this solution was added portionwise 2,4-diamino-7-fluoroquinazoline **6** [2] (0.411 g, 0.002 mole) during a twenty minute period. After stirring the reaction mixture at 0° for 15 minutes, the ice bath was removed and the yellow solution was stirred at room temperature for 5 hours. After this period the reaction mixture was poured onto crushed ice (50 ml). The light yellow suspension was stirred at 0° while being basified with concentrated ammonium hydroxide to *p*H 8.5. After cooling the suspension for 12 hours, the precipitate was collected by filtration, washed with chilled water and dried under vacuum at 70° to yield an orange crystalline product. Chromatography on silica gel using gradient elution with ethyl acetate followed by 2% increments of *N,N*-dimethylformamide until a 9:1 mixture of ethyl acetate and *N,N*-dimethylformamide was reached gave 0.42 g (82%) of an orange crystalline powder, pure by tlc (ethyl acetate:*N,N*-dimethylformamide, 9:1), mp 350-352°; $^1$H nmr (DMSO-$d_6$): 300 MHz $\delta$ 6.89 (br s, 2H, 2-$NH_2$), 6.98 (d, 1H, 8-H, J = 13.88 Hz), 7.90 (br s, 2H, 4-$NH_2$), 9.04 (d, 1H, 5-H, J = 8.63 Hz); $^{19}$F nmr (DMSO-$d_6$): 300 MHz $\delta$ -38.95 (dd, 7-F, J = 13.48 Hz, J = 8.23 Hz).

2,4-Diamino-8-fluoro-6-nitroquinazoline (**1i**).

This compound was obtained from 2,4-diamino-8-fluoroquinazoline, **7**, [2] as a dark orange crystalline solid, which was purified by column chromatography on silica gel using gradient elution with ethyl acetate followed by 2% increments of *N,N*-dimethylformamide until a 9:1 mixture of ethyl acetate and *N,N*-dimethylformamide was reached. Chromatographically pure compound (ethyl acetate:*N,N*-dimethylformamide, 9:1) was recrystallized from benzene:*N,N*-dimethylformamide, 8:2 to afford an orange crystalline powder, mp >350° dec; $^1$H nmr (DMSO-$d_6$): 400 MHz $\delta$ 6.97 (br s, 2H, 2-$NH_2$), 7.90 (br s, 2H, 4-$NH_2$), 8.08 (dd, 1H, 7-H, J = 10.98 Hz, J = 2.48 Hz), 8.96 (dd, 1H, 5-H, J = 2.48 Hz, J = 1.02 Hz); $^{19}$F nmr (DMSO-$d_6$): 400 MHz $\delta$ -45.84 (d, 8-F, J = 11.00 Hz).

Method C for Preparing Compounds **1g** and **1d**.

7-Fluoro-2,4,6-triaminoquinazoline (**1g**).

A mixture of 2,4-diamino-7-fluoro-6-nitroquinazoline (**1f**) (0.63 g, 0.003 mole) and 10% palladium on charcoal (0.248 g) in 2-methoxyethanol (80 ml) was hydrogenated in a low pressure Parr hydrogenator at ambient temperature for 6 hours. After diluting with 2-methoxyethanol (80 ml), the reaction mixture was heated at reflux for 20 minutes, filtered through Celite and the solvent removed under reduced pressure. Trituration of the residual material with *n*-pentane gave a brown solid which was collected by filtration. Chromatography on silica gel using gradient elution with ethyl acetate followed by 5% increments of *N,N*-dimethylformamide until a 8:2 mixture of ethyl acetate and *N,N*-dimethylformamide was reached afforded 0.39 g (73%) of light brown solid, pure by tlc (ethyl acetate:*N,N*-dimethylformamide, 7:3), mp 274-275° dec; $^1$H nmr (DMSO-$d_6$): 300 MHz $\delta$ 4.86 (br s, 2H, 6-$NH_2$), 5.72 (br s, 2H, 2-$NH_2$), 6.85 (d, 1H, 8-H, J = 12.98 Hz), 7.00 (br s, 2H, 4-$NH_2$), 7.19 (d, 1H, 5-H, J = 9.85 Hz); $^{19}$F nmr (DMSO-$d_6$): 300 MHz $\delta$ -39.29 (dd, 7-F, J = 10.15 Hz, J = 12.42 Hz).

5-Fluoro-2,4,8-triaminoquinazoline (**1d**).

This compound was prepared from **5** [3] as a dark brown solid. Chromatography on silica gel using gradient elution with ethyl acetate, followed by 5% increments of *N,N*-dimethylformamide until an 8:2 mixture of ethyl acetate and *N,N*-dimethylformamide was reached, gave a light brown crystalline solid, pure by tlc (ethyl acetate:*N,N*-dimethylformamide, 7:3), mp 185-186°. The $^1$H nmr spectrum of this sample was identical to that which was obtained from the cyclization of **4** with guanidine carbonate (Scheme II).

8-Fluoro-2,4,6-triaminoquinazoline (**1j**).

A mixture of concentrated hydrochloric acid (18 ml) and glacial acetic acid (6 ml) was stirred and cooled in ice bath under nitrogen. To this solution was added in one portion stannous chloride dihydrate (4.2 g, 0.019 mole). The mixture was stirred at 0° for 5 minutes and then 2,4-diamino-8-fluoro-6-nitroquinazoline (**1i**) (1.34 g, 0.006 mole) was added over 20 minutes. After 30 minutes, the reaction mixture was allowed to warm to ambient temperature and stirred for 4 hours. The off-white precipitate was collected by filtration, suspended in cold water and the *p*H was adjusted to 8.5 with concentrated ammonium hydroxide. After cooling the suspension for 12 hours, the precipitate was collected by filtration, washed with chilled water and dried under vacuum at 70° for 2 hours. Chromatography on silica gel, using gradient elution with ethyl acetate followed by 5% increments of *N,N*-dimethylformamide until a 7:3 mixture of ethyl acetate and *N,N*-dimethylformamide was reached, yielded 0.61 g (53%) of brown crystalline product, pure by tlc (ethyl acetate:*N,N*-dimethylformamide, 7:3), mp 300-302° dec; $^1$H nmr (DMSO-$d_6$): 400 MHz $\delta$ 4.94 (br s, 2H, 6-$NH_2$), 5.70 (br s, 2H, 2-$NH_2$), 6.76-6.81 (m, 2H, 5-H, 7-H), 7.00 (br s, 2H, 4-$NH_2$); $^{19}$F nmr (DMSO-$d_6$): 400 MHz $\delta$ -48.92 (d, 8-F, J = 13.1 Hz).

Method D for Preparing Compounds **1e**, **1h** and **1k**.

8-Chloro-2,4-diamino-5-fluoroquinazoline (**1e**).

A solution of cuprous chloride (0.62 g, 0.006 mole) in 10 ml concentrated hydrochloric acid was covered with 100 ml of benzene and cooled to 0°. While the solution of cuprous chloride was cooling, 0.8 g (0.004 mole) of 5-fluoro-2,4,8-triaminoquinazoline (**1d**) was mixed with 15 ml of 2*N* hydrochloric acid and cooled at 0°. A solution of 0.43 g (0.006 mole) of sodium nitrite in 6 ml of water was added dropwise with stirring to the suspension

of 5-fluoro-2,4,8-triaminoquinazoline hydrochloride, keeping the temperature between 0° and 5° for 15 minutes. Then the suspension of diazonium salt was slowly added under the surface of the solution of cuprous chloride in concentrated hydrochloric acid. After addition, the reaction mixture was stirred at 0° for 15 minutes, and then allowed to warm to room temperature and stirred for 4.5 hours. The reaction mixture was basified to *p*H 8.5 with concentrated ammonium hydroxide at 0°. After cooling the suspension for 12 hours, the precipitate was collected by filtration, washed with chilled water and dried under vacuum at 70° for 3 hours. Chromatography on silica gel using a gradient elution with a 1:1 mixture of tetrahydrofuran and *n*-hexane, followed by 5% increments of tetrahydrofuran until a 8:2 mixture of tetrahydrofuran and *n*-hexane was reached, gave 0.56 g (63%) of green crystalline product, pure by tlc (tetrahydrofuran:*n*-hexane, 8:2), mp 265-267°; $^1$H nmr (DMSO-$d_6$): 400 MHz δ 6.53 (br s, 2H, 2-$NH_2$), 6.78 (dd, 1H, 6-H, J = 11.35 Hz, J = 8.60 Hz), 6.88 (br s, 1H, 4-NH), 7.62 (br s, 1H, 4-NH), 7.64 (dd, 1H, 7-H, J = 8.56 Hz, J = 5.78 Hz); $^{19}$F nmr (DMSO-$d_6$): δ -31.55 (m, 5-F).

6-Chloro-2,4-diamino-7-fluoroquinazoline (**1h**).

This compound was obtained from **1g** as a dark green solid. Chromatography on silica gel using gradient elution with a 1:1 mixture of tetrahydrofuran and *n*-hexane, followed by 5% increments of tetrahydrofuran until a 8:2 mixture of tetrahydrofuran and *n*-hexane was reached, afforded a yellow green crystalline product, pure by tlc (tetrahydrofuran:*n*-hexane, 8:2), mp 268-270°; $^1$H nmr (DMSO-$d_6$): 400 MHz δ 6.26 (br s, 2H, 2-$NH_2$), 6.42 (br s, 2H, 4-$NH_2$), 7.05 (d, 1H, 8-H, J = 11.35 Hz), 8.27 (d, 1H, 5-H, J = 8.38 Hz); $^{19}$F nmr (DMSO-$d_6$): 400 MHz δ -31.75 (dd, 7-F, J = 11.20 Hz, J = 8.30 Hz).

6-Chloro-2,4-diamino-8-fluoroquinazoline (**1k**).

This compound was obtained from **1j** as a dark green crystalline solid. Chromatography on silica gel using gradient elution with chloroform followed by 5% increments of methanol until a 7:3 mixture of chloroform and methanol was reached, afforded a yellowish-green crystalline powder pure by tlc (ethyl acetate:*N*,*N*-dimethylformamide, 9:1), mp >295° dec; $^1$H nmr (DMSO-$d_6$): 400 MHz δ 6.36 (br s, 2H, 2-$NH_2$), 7.48 (dd, 3H, 7-H + 4-$NH_2$, J = 10.54 Hz, J = 1.79 Hz), 7.96 (d, 1H, 5-H, J = 1.77 Hz); $^{19}$F nmr (DMSO-$d_6$): 400 MHz δ -45.85 (d, 8-F, J = 11.00 Hz).

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