Further Studies on the Synthesis of Quinazolines from 2-Fluorobenzonitriles

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Recently, we reported that appropriately substituted 2-fluorobenzonitriles undergo cyclization with guanidine carbonate to afford 2,4-diaminoquinazolines usually in good to excellent yield. This paper describes the preparation of a variety of new 2,4-diaminoquinazolines substituted at positions five or seven. In addition, the reactions of selected 2-fluorobenzonitriles with formamidine acetate or acetamidine acetate were examined. The results obtained demonstrate that the analogous 4-amino- and 2-methyl-4-aminoquinazolines can be prepared by this approach but that the yields are considerably lower than when guanidine carbonate is employed as the cyclization reagent.

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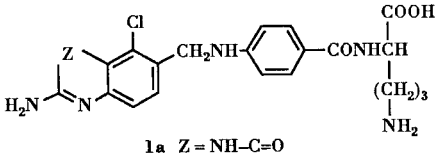
For many years scientists in this laboratory have been involved with the synthesis of new quinazoline analogues of folic acid as potential chemotherapeutic agents. Since many of the target compounds required multistep synthetic sequences, considerable time and effort was devoted to the development of new or improved methods for the preparation of key intermediates. For example, we found that 5-chloro-2,4-diaminoquinazoline could be prepared in greater than 90% yield by the reaction of 2-chloro-6-fluorobenzonitrile with guanidine carbonate in *N*,*N*-dimethylacetamide [1]. This compound had formerly been synthesized *via* a laborious three-step sequence in low overall yield [2]. This innovation facilitated the multistep preparation of N^{α}-(5-chloro-5,8-dideazapteroyl)-L-ornithine, **1a**, a potent and relatively selective inhibitor of the target enzyme folylpolyglutamate synthetase [3]. The 4-amino counterpart of **1a**, N^{α}-(4-amino-4-deoxy-5-chloro-5,8-dideazapteroyl)-L-ornithine, **1b**, which was also elaborated from 5-chloro-2,4-diaminoquinazoline, was found to be the most potent inhibitor of folylpolyglutamate synthetase reported thus far [3]. In a similar vein, the conversion of 2,6-difluorobenzonitrile to 2,4-diamino-5-fluoroquinazoline in excellent yield enabled us to prepare 5-fluoro-5,8-dideazaisoaminopterin and related analogues [4].



1a Z = NH–C=O
b Z = N=C–NH_2

Recently, we reported that the reaction of 2-fluoro-6-trifluoromethylbenzonitrile with guanidine carbonate yielded 2,4-diamino-5-trifluoromethylquinazoline in nearly quantitative yield [5]. Base catalyzed hydrolysis of the 4-amino group then afforded 2-amino-3,4-dihydro-4-oxo-5-trifluoromethylquinazoline in excellent yield [5]. This key intermediate was then employed in the synthesis of 5-trifluoromethyl-5,8-dideazaisofolic acid and 5-trifluoromethyl-5,8-dideazafolic acid [5], which are currently undergoing biological evaluation as potential antitumor agents. In

Scheme I

Synthetic Routes Used to Prepare 2,4-Diaminoquinazolines

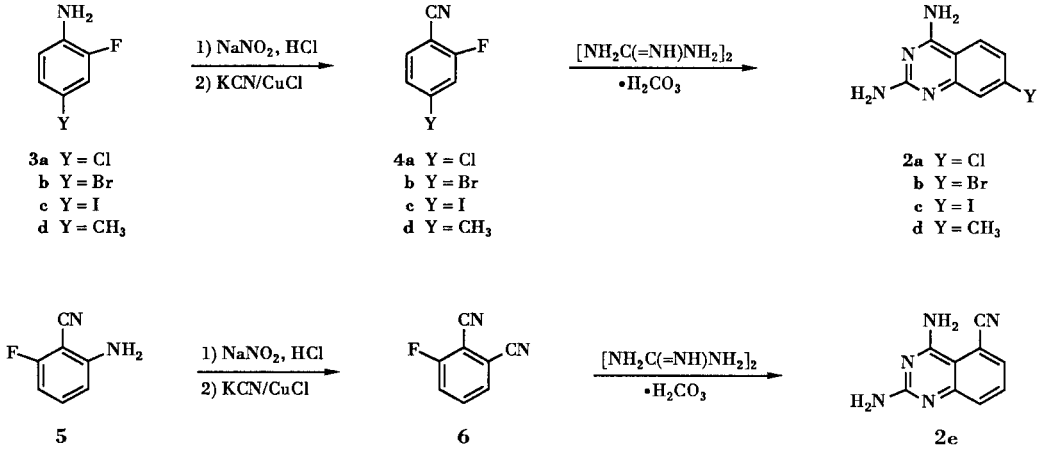
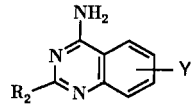


Table 1
Physical and Analytical Data for Quinazolines Prepared from 2-Fluorobenzonitriles



Compound No.	R_2	Y	Reaction Time, Hours	Method	Yield %	MS m/e	Emperical Formula	Analyses %, Calcd./Found C	H	N
2a	NH_2	7-Cl	10	B	58	194	$C_8H_7ClN_4$	49.37	3.63	28.79
								49.40	3.65	28.83
2b	NH_2	7-Br	6	B	59	239	$C_8H_7BrN_4$	40.19	2.95	23.43
								40.05	2.97	23.29
2c	NH_2	7-I	8	B	65	286	$C_8H_7IN_4$	33.59	2.47	19.58
								33.73	2.66	19.65
2d	NH_2	7-CH_3	6	B	63	174	$C_9H_{10}N_4$	62.05	5.79	32.16
								61.89	5.69	31.98
2e	NH_2	5-CN	4	B	51	185	$C_9H_7N_5$	58.37	3.81	37.82
								58.11	4.03	37.61
2f	CH_3	5-Cl	7.5	C	53	193	$C_9H_8ClN_3$	55.83	4.16	21.70
								55.96	4.17	21.80
2g	H	5-Cl	12	D	51	179	$C_8H_6ClN_3$	53.50	3.37	23.40
								53.58	3.37	23.34
2h	CH_3	5-F	7	E	27	177	$C_9H_8FN_3$ •0.15 H_2O	60.08	4.62	23.36
								60.16	4.49	23.33
2i	H	5-F	7.5	D	54	163	$C_8H_6FN_3$	58.89	3.71	25.76
								58.63	3.50	25.54
2j	CH_3	5-CF_3	7.5	E	29	227	$C_{10}H_8F_3N_3$	52.86	3.56	18.50
								52.65	3.48	18.30
2k	H	5-OCH_2CF_3	8	D	60	243	$C_{10}H_8F_3N_3O$	49.39	3.32	17.28
								49.46	3.34	17.21
2l	CH_3	5-OCH_2CF_3	10	G	30	257	$C_{11}H_{10}F_3N_3O$	51.37	3.92	16.34
								51.38	3.93	16.30
2m	CH_3	5-$OCH_2CF_2CF_3$	10	G	23	307	$C_{12}H_{10}F_5N_3O$	46.91	3.28	13.68
								47.17	3.36	13.51
2n	CH_3	5-$OCH_2(CF_2)_2CF_3$	10	G	29	357	$C_{13}H_{10}F_7N_3O$	43.71	2.82	11.76
								43.85	2.83	11.69

this paper we report the synthesis of five new 2,4-diaminoquinazolines from 2-fluorobenzonitriles having substituents at positions five or seven. In addition, the reactions of selected 2-fluorobenzonitriles with formamidine acetate or acetamidine acetate demonstrate that 4-aminoquinazolines and 2-methyl-4-aminoquinazolines can also be prepared *via* this approach.

For the past several years, we have been attempting to develop selective inhibitors of the dihydrofolate reductases from opportunistic microorganisms such as *Pneumocystis carinii* [6]. Several prototype 2,4-diaminoquinazolines having substituents at position seven were required for these studies. Therefore, the 7-Cl, 7-Br, 7-I and 7-CH_3 derivatives **2a-d** were synthesized as shown in Scheme I. The commercially available anilines, **3a-d**, were converted to the corresponding 2-fluorobenzonitriles, **4a-d**, under Sandmeyer conditions. The requisite 2,4-diaminoquinazolines were then obtained in respectable yields by heating these nitriles with guanidine carbonate in *N,N*-dimethylacetamide. It should be noted that 7-chloro-2,4-diaminoquinazoline, **2a**, and 2,4-diamino-7-methylquinazoline, **2d**, have been reported previously, having been prepared from the requisite anthranilonitriles in significantly lower yields [7]. The properties of these new analogues are presented in Table 1.

The presence of a cyano function at position five of the quinazoline nucleus should prove to be valuable for the introduction of novel substituents at this position. Therefore, the synthesis of 5-cyano-2,4-diaminoquinazoline, **2e**, was conducted as shown in Scheme I. The key intermediate, 3-fluorophthalonitrile, **6**, was prepared from 2-amino-6-fluorobenzonitrile, **5**, [1] using the Sandmeyer reaction. This route to **6** represents a considerable improvement over the earlier method, which involved making diethyl 3-fluorophthalate and then proceeding to the dinitrile through the diamide [8]. Compound **6** was then reacted with guanidine carbonate to provide the target compound **2e** in moderate yield.

A great deal of interest has recently been focused on 5,8-dideazafolates modified at position 2. The replacement of the 2-amino group by hydrogen or a small alkyl substituent was often found to enhance cytotoxicity, due at least in part to improved uptake into cells, despite resulting in decreased affinity for the target enzyme, thymidylate synthase [9-11]. Therefore, the reactions of 6-substituted-2-fluorobenzonitriles with formamidine acetate or acetamidine acetate were investigated as a potential means of obtaining precursors for preparing 2-desamino- and 2-desamino-2-methyl-5,8-dideazafolates modified at position five. As shown in Scheme II, the reaction of 2-fluoro-6-chlorobenzonitrile, **7a**, with formamidine acetate gave 4-amino-5-chloroquinazoline, **2g**, in modest yield. This compound has also been prepared by the ammonolysis of 5-chloro-4-fluoroquinazoline [12]. In addition, 2,6-difluorobenzonitrile, **7b**, reacted with formamidine acetate to afford 4-amino-5-fluoroquinazoline, **2i**. The cyclization of **7a** with acetamidine acetate afforded 4-amino-5-chloro-2-methylquinazoline, **2f**, in significantly better yield than was the case using **7b**, which gave 4-amino-5-fluoro-2-methylquinazoline, **2h**, in 27% yield. This reaction was also attempted with 2-fluoro-6-trifluoromethylbenzonitrile, **7c**, under the same conditions as employed with **7b**. The yield of 4-amino-2-methyl-5-trifluoromethylquinazoline, **2j**, was essentially the same as for **2h**.

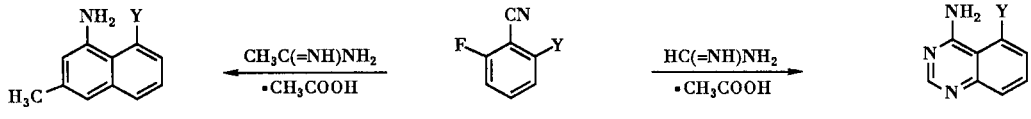
Two new 2-fluoro-6-alkoxybenzonitriles, **8b** and **8c**, were prepared in an analogous fashion to that described earlier for 2-fluoro-6-(2,2,2-trifluoroethoxy)benzonitrile, **8a** [1]. Each of the nitriles reacted with acetamidine acetate to yield the corresponding 5-alkoxy-4-amino-2-methyl quinazolines, **2l-n**, in low yield as shown in Scheme III. Compound **8a** was also reacted with formamidine acetate to yield 4-amino-5-(2,2,2-trifluoroethoxy)quinazoline, **2k**, in 60% yield. The physical properties of these new quinazolines are presented in Table 1. The results obtained demonstrate that 4-amino- and 4-amino-2-methylquinazolines can be obtained directly from the appropriately substituted 2-fluorobenzonitriles. In general the yields obtained are significantly lower than when guanidine carbonate is employed [1]. This may be attributed to the fact that formamidine and acetamidine are considerably less stable thermally than guanidine. On the other hand, the presence of acetic acid liberated by heating these acetate salts may contribute to side reactions resulting in lower yields.

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* δ 3.4 ppm

Scheme II

Synthetic Routes Used to Prepare 4-Amino and 2-Methyl-4-aminoquinazolines



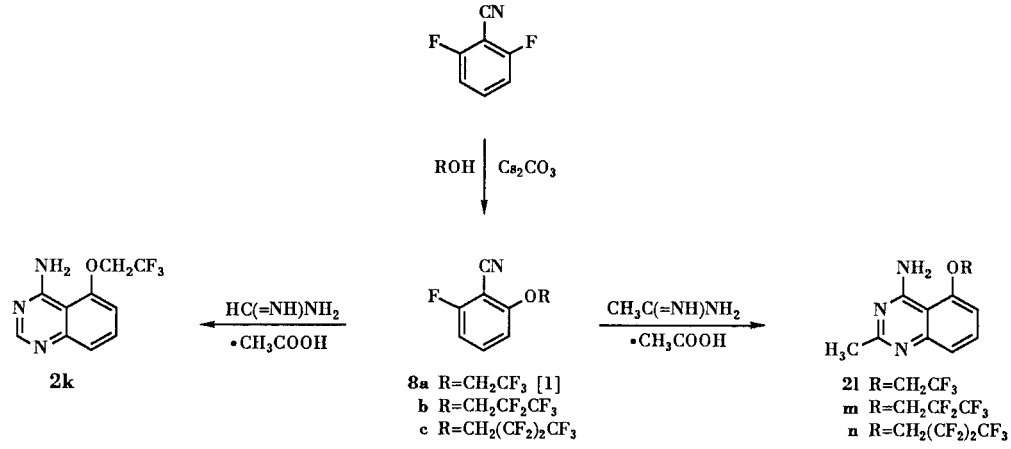
2f Y = Cl
h Y = F
j Y = CF_3

7a Y = Cl
b Y = F
c Y = CF_3

2g Y = Cl
i Y = F

Scheme III

Synthesis of 4-Amino and 2-Methyl-4-aminoquinazolines Bearing Fluoroalkoxy Substituents at Position 5



2k

8a R=CH_2CF_3 [1]
b R=$CH_2CF_2CF_3$
c R=$CH_2(CF_2)_2CF_3$

2l R=CH_2CF_3
m R=$CH_2CF_2CF_3$
n R=$CH_2(CF_2)_2CF_3$

in the ^1H nmr spectrum which was transformed into a sharp singlet (DOH) by addition of deuterium oxide. All intermediates 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). ^1H nmr and ^{19}F nmr spectra were obtained on 90 MHz (Varian EM390), 300 MHz (Bruker AM-300) or 400 MHz (Varian VXR-400) instruments. The ^1H chemical shifts are presented in parts per million downfield from tetramethylsilane as the internal standard and the relative peaks are given to the nearest whole number. The ^{19}F chemical shifts are presented in parts per million relative to fluorotrichloromethane [a] or trifluoroacetic acid [b] as the standards. The electron impact mass spectra were obtained off probe using a Finnigan 4521 and Finnigan 4000 with Teknivent data system (St. Louis, MO.). MS samples of compounds **4a-d** and **6** were subjected to gas chromatography prior to analysis using helium (50 cm/second) through a 30 m x 0.32 mm, 0.25 μm film thickness dimethylsilicone fused-silica column (DB-1, J & W Scientific, Folsom, CA) operated at 130°. 2,6-Difluorobenzonitrile and 2-chloro-6-fluorobenzonitrile were obtained from Fairfield Chemical Co., while 2-fluoro-6-trifluoromethylbenzonitrile was obtained from Accurate Chemical and Scientific Corp.

Method A for Preparing Compounds **4a-d** and **6**.

4-Chloro-2-fluorobenzonitrile (**4a**).

A solution of 19.77 g (0.303 mole) of potassium cyanide in 55 ml of water was added dropwise to a suspension of 7.5 g (0.076 mole) of cuprous chloride in 32 ml of water, whereupon the cuprous chloride entered into solution with considerable evolution of heat. After stirring this mixture at ambient temperature for 30 minutes, the resulting suspension was filtered, the filtrate was covered with 200 ml of benzene and cooled to 0°. While the solution of cuprous cyanide complex was cooling, 5.26 g (0.036 mole) of 4-chloro-2-fluoroaniline was mixed with 130 ml of 2*N* hydrochloric acid and cooled at 0°. A solution of 3.72 g (0.054 mole) of sodium nitrite in 42 ml of water was added dropwise with stirring to the suspension of 4-chloro-2-fluoroaniline hydrochloride, keeping the temperature between 0° and 5° for 20 minutes.

Then the suspension of diazonium salt was covered with 150 ml of toluene and cautiously neutralized at 0° by adding anhydrous sodium carbonate to *p*H 6.5. This solution was slowly added under the surface to the solution of cuprous cyanide complex. After addition the reaction mixture was stirred at 0° for 30 minutes and was allowed to warm to room temperature and stirred for 12 hours. The reaction mixture was filtered and the filtrate transferred to a separatory funnel. The organic phase was successively partitioned with 5% solution of hydrochloric acid (1 x 50 ml), 10% solution of sodium carbonate (1 x 50 ml) and saturated sodium chloride (1 x 80 ml). After drying over magnesium sulfate the organic phase was treated with charcoal and then filtered through Celite. The filtrate was evaporated under reduced pressure and the residual dark brown semisolid product was purified by column chromatography on silica gel. Gradient elution with *n*-hexane followed by 10% increments of chloroform until a 1:1 mixture of chloroform and *n*-hexane was reached, gave 3.48 g (62%) of a brown semisolid product, pure by tlc (chloroform:*n*-hexane, 7:3); ^1H nmr (DMSO-d_6): 400 MHz δ 7.55 (ddd, 1H, 5-H, J = 8.40 Hz, J = 1.93 Hz, J = 0.83 Hz), 7.84 (dd, 1H, 3-H, J = 9.45 Hz, J = 2.01 Hz), 7.99 (dd, 1H, 6-H, J = 8.38 Hz, J = 7.28 Hz); ^{19}F nmr [a] (DMSO-d_6): 400 MHz δ -25.65 (dd, 2-F, J = 7.23 Hz, J = 9.47 Hz); ir: ν C≡N 2242.12 cm^{-1}; ms: (EI) (m/e) 155 $(M)^+$.

4-Bromo-2-fluorobenzonitrile (**4b**).

This compound was obtained as a dark brown semisolid. Chromatography on silica gel eluting with 40% *n*-hexane in chloroform afforded a brown semisolid in 63% yield. This compound was pure by tlc (chloroform:*n*-hexane, 7:3); ms: (EI) (m/e) 200 $(M)^+$.

2-Fluoro-4-iodobenzonitrile (**4c**).

This compound was obtained as a dark brown semisolid. Chromatography on silica gel eluting with 20% *n*-hexane in chloroform afforded a dark brown semisolid in 60% yield, pure by tlc (chloroform:*n*-hexane, 6:4); ms: (EI) (m/e) 247 $(M)^+$.

2-Fluoro-4-methylbenzonitrile (**4d**).

This compound was obtained as a dark brown semisolid, which was purified by column chromatography on silica gel using gradient elution starting with a 1:1 mixture of *n*-hexane and chloroform followed by 5% increments of chloroform until a 7:3 mixture of chloroform and *n*-hexane was reached. Chromatographically pure compound (chloroform:*n*-hexane, 7:3) was obtained as a brown semisolid in 59% yield; ms: (EI) (m/e) 135 $(M)^+$.

3-Fluorophthalonitrile (**6**).

This compound was obtained as a dark brown semisolid. Chromatography on silica gel using gradient elution, starting with *n*-hexane, followed by 5% increments of tetrahydrofuran until a 8:2 mixture of *n*-hexane and tetrahydrofuran was reached, gave **6** pure by tlc (tetrahydrofuran:*n*-hexane, 1:1) in 71% yield; ms: (EI) (m/e) 146 $(M)^+$.

Method B for Preparing Compounds **2a-e**.

7-Chloro-2,4-diaminoquinazoline (**2a**).

A mixture of 3.44 g (0.022 mole) of 4-chloro-2-fluorobenzonitrile, **4a**, and 7.97 g (0.044 mole) of guanidine carbonate in 100 ml of *N,N*-dimethylacetamide was heated at 150° under nitrogen for 10 hours. After this period the reaction mixture was evaporated under reduced pressure and the residual dark brown material was dried in high vacuum at 80° for 4 hours. This product was suspended in cold water and *p*H was adjusted to 8.5 with concentrated ammonium hydroxide. After cooling the suspension for 8 hours, the precipitate was collected by filtration and washed successively with cold water (2 x 40 ml), diethyl ether (2 x 40 ml) 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 9:1 mixture of ethyl acetate and *N,N*-dimethylformamide was reached, gave an off-white product pure by tlc (ethyl acetate:*N,N*-dimethylformamide, 8:2). Recrystallization from tetrahydrofuran:*n*-hexane, 10:1, afforded 2.51 g (58%) of white crystalline powder, mp 246-247° (lit [7] mp 229.5-230.5°); ^1H nmr (DMSO-d_6): 400 MHz δ 6.14 (br s, 2H, 2-NH_2), 7.00 (dd, 1H, 6-H, J = 8.65 Hz, J = 2.20 Hz), 7.16 (d, 1H, 8-H, J = 2.16 Hz), 7.36 (br s, 2H, 4-NH_2), 7.97 (d, 1H, 5-H, J = 8.79 Hz).

7-Bromo-2,4-diaminoquinazoline (**2b**).

This compound was obtained from **4b** as an off-white solid which was purified by column chromatography on silica gel eluting with 20% *n*-hexane in tetrahydrofuran to afford chroma-

tographically pure product (tetrahydrofuran:*n*-hexane, 8:2). Recrystallization from tetrahydrofuran:*n*-hexane, 7:1, gave a white crystalline powder, mp 255-256°; ^{1}H nmr (DMSO-d_6): 400 MHz δ 6.16 (br s, 2H, 2-NH_2), 7.13 (dd, 1H, 6-H, J = 8.65 Hz, J = 2.01 Hz), 7.33 (d, 1H, 8-H, J = 2.01 Hz), 7.37 (br s, 2H, 4-NH_2), 7.89 (d, 1H, 5-H, J = 8.75 Hz).

2,4-Diamino-7-iodoquinazoline (**2c**).

This compound was obtained from **4c** as a light brown solid. Chromatography on silica gel with 10% *n*-hexane in tetrahydrofuran as the eluent gave a tan product, pure by tlc (tetrahydrofuran:*n*-hexane, 8:2). Recrystallization from tetrahydrofuran:*n*-hexane, 5:1, afforded a light brown solid, mp 266-267°; ^{1}H nmr (DMSO-d_6): 400 MHz δ 6.10 (br s, 2H, 2-NH_2), 7.28 (dd, 1H, 6-H, J = 8.46 Hz, J = 1.73 Hz), 7.32 (br s, 2H, 4-NH_2), 7.55 (d, 1H, 8-H, J = 1.67 Hz), 7.72 (d, 1H, 5-H, J = 8.46 Hz).

2,4-Diamino-7-methylquinazoline (**2d**).

This compound was obtained from **4d** as a tan solid. Chromatography on silica gel using 10% acetonitrile in tetrahydrofuran as eluent afforded an off-white solid, pure by tlc (tetrahydrofuran:acetonitrile, 9:1). Recrystallization from tetrahydrofuran:*n*-hexane, 5:1, provided an off-white crystalline powder, mp 227-228° (lit [7] mp 226-227°); ^{1}H nmr (DMSO-d_6): 400 MHz δ 2.33 (s, 3H, CH_3), 5.88 (br s, 2H, 2-NH_2), 6.84 (dd, 1H, 6-H, J = 8.24 Hz, J = 1.46 Hz), 6.98 (br s, 1H, 8-H), 7.14 (br s, 2H, 4-NH_2), 7.84 (d, 1H, 5-H, J = 8.24 Hz).

5-Cyano-2,4-diaminoquinazoline (**2e**).

This product was obtained from **6** as a dark brown solid. Chromatography on silica gel with 10% of *N,N*-dimethylformamide in ethyl acetate as the eluent gave an orange solid, which was pure by tlc (ethyl acetate:*N,N*-dimethylformamide, 9:1). Recrystallization from tetrahydrofuran afforded a white crystalline powder, mp 231-232°; ^{1}H nmr (DMSO-d_6): 400 MHz δ 6.42 (br s, 2H, 2-NH_2), 7.11 (br s, 2H, 4-NH_2), 7.53 (dd, 1H, 8-H, J = 8.09 Hz, J = 1.68 Hz), 7.57 (dd, 1H, 6-H, J = 7.14 Hz, J = 1.65 Hz), 7.62 (dd, 1H, 7-H, J = 8.05 Hz, J = 7.14 Hz); ir: ν C≡N 2214.15 cm^{-1}.

Method C for Preparing Compound **2f**.

4-Amino-5-chloro-2-methylquinazoline (**2f**).

A mixture of 2.50 g (0.016 mole) of 2-chloro-6-fluorobenzonitrile and 3.8 g (0.032 mole) of acetamidine acetate in 100 ml of *N,N*-dimethylacetamide was heated at 145° under nitrogen for 3.5 hours. After the addition of a second portion of acetamidine acetate (3.8 g, 0.032 mole), heating at 145° was continued for 4 hours. Next, the reaction mixture was evaporated under reduced pressure and the residual brown tar was dried under vacuum at 80° for 6 hours. This product was suspended in cold water and the *p*H was adjusted to 8.5 with concentrated ammonium hydroxide. After cooling the suspension for 8 hours, the precipitate was separated by filtration and washed successively with cold water (2 x 25 ml), diethyl ether (2 x 25 ml) and *n*-pentane (2 x 30 ml) and dried under vacuum at 70° for 3 hours. Chromatography on silica gel beginning with a 7:3 mixture of *n*-hexane and tetrahydrofuran followed by increasing tetrahydrofuran in 10% increments until a 1:1 mixture was reached, gave a beige colored powder, pure by tlc (*n*-hexane:tetrahydrofuran, 1:1). Recrystallization from tetrahydrofuran:*n*-hexane, 6:1, afforded 1.66 g (53%) of an off-white crystalline powder, mp 199-200°; ^{1}H nmr (DMSO-d_6): 400 MHz δ 2.42 (s, 3H, CH_3), 7.46 (dd, 1H, 8-H, J = 7.47 Hz, J = 1.28 Hz), 7.55 (dd, 1H, 6-H, J = 8.42 Hz, J = 1.28 Hz), 7.64 (dd, 1H, 7-H, J = 8.38 Hz, J = 7.65 Hz), 7.98 (br s, 2H, 4-NH_2).

Method E for Preparing Compounds **2h-j**.

4-Amino-5-fluoro-2-methylquinazoline (**2h**).

A mixture of 58.97 g (0.424 mole) of 2,6-difluorobenzonitrile, 50.08 g (0.424 mole) of acetamidine acetate and 54.79 g (0.424 mole) of *N,N*-diisopropylethylamine in 200 ml of *N,N*-dimethylacetamide was heated at 120° under nitrogen for 7 hours. After this period the reaction mixture was evaporated under reduced pressure. The residue was suspended in cold water and the *p*H adjusted to 8 with concentrated ammonium hydroxide. After cooling the suspension at 0° for 1 hour, the precipitate was collected by filtration and washed successively with cold water (2 x 25 ml), *n*-hexane (2 x 50 ml), diethyl ether (2 x 50 ml) and petroleum ether (2 x 50 ml). This material was recrystallized from *N,N*-dimethylformamide and dried under vacuum at 65° over phosphorus pentoxide to afford 20.49 g (27%) of yellow crystalline powder, mp 162°, tlc homogeneous (tetrahydrofuran:*n*-hexane, 3:2); ^{1}H nmr (DMSO-d_6): 300 MHz δ 2.41 (s, 3H, CH_3), 7.18 (m, 2H, 7-H + H of 4-NH_2), 7.41 (dd, 1H, 8-H, J = 8.44 Hz, J = 0.86 Hz), 7.68 (m, 1H, 6-H), 7.90 (br s, 1H, H of 4-NH_2); ^{19}F nmr [b] (DMSO-d_6): 300 MHz δ -34.49 (m, 5-F).

4-Amino-2-methyl-5-trifluoromethylquinazoline (**2j**).

This compound was obtained from 2-fluoro-6-trifluoromethylbenzonitrile as a white crystalline solid. It was recrystallized from *N,N*-dimethylformamide and dried in high vacuum at 60° over phosphorus pentoxide to afford a white crystalline product in 29% yield, mp 196-197°, tlc homogeneous (tetrahydrofuran:*n*-hexane, 3:2); ^{1}H nmr (DMSO-d_6): 300 MHz δ 2.43 (s, 3H, CH_3), 7.11 (br s, 2H, 4-NH_2), 7.82-7.94 (m, 3H, 6-H, 7-H, 8-H); ^{19}F nmr [b] (DMSO-d_6): 300 MHz δ -21.24 (s, CF_3).

Method D for Preparing Compounds **2g-i** and **2k**.

4-Amino-5-chloroquinazoline (**2g**).

A mixture of 3.0 g (0.019 mole) of 2-chloro-6-fluorobenzonitrile and 3.95 g (0.038 mole) of formamidine acetate in 100 ml of *N,N*-dimethylacetamide was heated at 150° under nitrogen for 10 hours. After this period the reaction mixture was evaporated under reduced pressure and dark brown residual product was dried under vacuum at 80° for 4 hours. This product was suspended in cold water and the *p*H adjusted to 8.5 with concentrated ammonium hydroxide. After cooling the suspension for 8 hours, the precipitate was isolated by filtration and washed successively with chilled water (2 x 25 ml), diethyl ether (2 x 25 ml) and *n*-pentane (2 x 30 ml) and dried under vacuum at 70° for 2 hours. Chromatography on silica gel with 30% tetrahydrofuran in *n*-hexane as the eluent, gave a yellow powder, pure by tlc (*n*-hexane:tetrahydrofuran, 7:3). Recrystallization from tetrahydrofuran:*n*-hexane, 3:1, afforded 1.76 g (51%) of light yellow crystals, mp 217-218°; ^{1}H nmr (DMSO-d_6): 400 MHz δ 7.55 (dd, 1H, 8-H, J = 7.43 Hz, J = 1.51 Hz), 7.64 (dd, 1H, 6-H, J = 8.36 Hz, J = 1.51 Hz), 7.70 (dd, 1H, 7-H, J = 8.40 Hz, J = 7.42 Hz), 8.38 (s, 1H, 2-H).

4-Amino-5-fluoroquinazoline (**2i**).

This compound was obtained from 2,6-difluorobenzonitrile as a brown crystalline powder. Chromatography on silica gel with 40% tetrahydrofuran in *n*-hexane as the eluent and drying under vacuum at 80° for 12 hours gave an off-white crystalline product, pure by tlc (tetrahydrofuran:*n*-hexane, 1:1), mp 204-205°; ^{1}H nmr (DMSO-d_6): 400 MHz δ 7.27 (dd, 1H, 7-H, J = 11.76 Hz, J = 8.06 Hz), 7.50 (d, 1H, 8-H, J = 8.38 Hz), 7.74 (dd, 1H, 6-H, J = 14.46 Hz, J = 8.09 Hz), 7.98 (br s, 2H, 4-NH_2), 8.40 (s, 1H, 2-H); ^{19}F nmr [a] (DMSO-d_6): 400 MHz δ -30.1 (m, 5-F).

4-Amino-5-(2,2,2-trifluoroethoxy)quinazoline (**2k**).

This compound was obtained from 2-fluoro-6-(2,2,2-trifluoroethoxy)benzonitrile [1] as an off-white crystalline solid which was purified by column chromatography on silica gel, using gradient elution, starting with pure chloroform, followed by 1% increments of methanol until a 95:5 mixture of chloroform and methanol was reached. Chromatographically pure compound (tetrahydrofuran:*n*-hexane, 8:2) was recrystallized from ethanol:water, 1:1 and dried under vacuum at 80° for 4 hours to afford 3.01 g (60%) of crystalline product, mp = 227-228°; ^{1}H nmr (DMSO-d_6): 90 MHz δ 4.8-5.2 (m, 2H, CH_2), 7.0-7.9 (m, 5H, 6-H, 7-H, 8-H, + 4-NH_2), 8.30 (s, 1H, 2-H); ^{19}F nmr [a] (DMSO-d_6): 90 MHz δ 72.0 (br s, CF_3).

Method F for Preparing Compounds **8b** and **c**.

2-Fluoro-6-(2,2,3,3,3-pentafluoropropoxy)benzonitrile (**8b**).

A mixture of 1.39 g (0.01 mole) of 2,6-difluorobenzonitrile, 3.89 g (0.025 mole) of pentafluoro-1-propanol and 3.26 g (0.01 mole) of cesium carbonate in 40 ml of *N,N*-dimethylacetamide was stirred at ambient temperature under nitrogen for 48 hours. After this period the reaction mixture was filtered and the filtrate poured on 200 ml of crushed ice and the resulting suspension was maintained at ~6° for 12 hours. The precipitate was collected by filtration and dried under vacuum over phosphorus pentoxide for 24 hours. The crude product was purified by column chromatography, using gradient elution, starting with pure *n*-hexane, followed by 2% increments of chloroform until a 8:2 mixture of *n*-hexane and chloroform was reached. Fractions homogeneous by tlc (tetrahydrofuran:*n*-hexane, 2:8) were pooled and evaporated and the resulting solid was recrystallized from *n*-hexane to afford 2.04 g (76%) of crystalline powder, mp 52-53°; ^{1}H nmr (DMSO-d_6): 90 MHz δ 5.05 (t, 2H, CH_2, J = 9.2 Hz), 7.15 (m, 2H, 4-H, 5-H), 7.75 (m, 1H, 3-H); ^{19}F nmr [a] (DMSO-d_6): 90 MHz δ 83.5 (br s, 3F, CF_3), 107.0 (br s, 1F, 2-F), 123.0 (br s, 2F, CF_2).

2-Fluoro-6-(2,2,3,3,4,4,4-heptafluorobutoxy)benzonitrile (**8c**).

This compound was obtained by the reaction of 2,6-difluorobenzonitrile and heptafluoro-1-butanol as an orange semisolid, which was purified by column chromatography on silica gel, using gradient elution, starting with pure *n*-hexane, followed by 2% increments of chloroform until a 7:3 mixture of hexane and chloroform was reached. Chromatographically pure compound (tetrahydrofuran:*n*-hexane, 2:8) was dried over phosphorus pentoxide for 24 hours to afford a yellow semisolid product, mp 30°; ^{1}H nmr (DMSO-d_6): 90 MHz δ 5.10 (m, 2H, CH_2), 7.20 (m, 2H, 4-H, 5-H), 7.75 (m, 1H, 3-H); ^{19}F nmr [a] (DMSO-d_6): 90 MHz δ 81.0 (br s, 3F, CF_3), 107.0 (br s, 1F, 2-F), 119.5 (br s, 2F, CF_2), 126.5 (br s, 2F, CF_2).

Method G for Preparing Compounds **2l-n**.

4-Amino-2-methyl-5-(2,2,2-trifluoroethoxy)quinazoline (**2l**).

A mixture of 1 g (0.0046 mole) of 2-fluoro-6-(2,2,2-trifluoroethoxy)benzonitrile [1] and 0.82 g (0.0069 mole) of acetamidine acetate in 100 ml of *N,N*-dimethylacetamide was heated at 140° under nitrogen for 5 hours. An additional 1.64 g (0.0314 mole) of acetamidine acetate was added and heating at 140° was continued for 5 hours. After this period the reaction mixture was evaporated under reduced pressure. The solid residue was suspended in cold water and the *p*H was adjusted to 9.0 with concentrated ammonium hydroxide. After cooling the suspension at ~6° for 12 hours the precipitate was collected by filtration, washed with chilled water and dried. The crude product was purified by column chromatography, using gradient elution, starting with pure chloroform, followed by 1% increments of methanol until a 95:5 mixture of chloroform and methanol was reached. Chromatographically pure compound (chloroform:methanol, 9:1) was dried under vacuum, at 100° for 4 hours to afford 0.35 g (30%) of a beige crystalline powder, mp 229-231°; ^{1}H nmr (DMSO-d_6): 90 MHz δ 2.35 (s, 3H, CH_3), 4.95 (q, 2H, CH_2, J = 9 Hz), 6.9-7.9 (m, 5H, 6-H, 7-H, 8-H + 4-NH_2); ^{19}F nmr [a] (DMSO-d_6): 90 MHz δ 72.3 (br s, CF_3).

4-Amino-2-methyl-5-(2,2,3,3,3-pentafluoropropoxy)quinazoline (**2m**).

This compound was obtained from **8b** as an off-white crystalline solid which was purified by column chromatography, using gradient elution, starting with pure chloroform, followed by 10% increments of methanol until a mixture of chloroform:methanol, 8:2 was reached. Chromatographically pure compound (tetrahydrofuran:hexane, 8:2) was dried under vacuum at 100° for 6 hours to give a white crystalline product in 23% yield, mp 166-168°; ^{1}H nmr (DMSO-d_6): 90 MHz δ 2.40 (s, 3H, CH_3), 5.05 (t, 2H, CH_2, J = 9 Hz), 6.85-7.95 (m, 5H, 6-H, 7-H, 8-H + 4-NH_2); ^{19}F nmr [a] (DMSO-d_6): 90 MHz δ 82.8 (br s, 3F, CF_3), 122.3 (br s, 2F, CF_2).

4-Amino-2-methyl-5-(2,2,3,3,4,4,4-heptafluorobutoxy)quinazoline (**2n**).

This compound was obtained from **8c** as a dark beige crystalline powder and was purified by column chromatography on silica gel, using gradient elution, starting with pure chloroform, followed by 1% increments of methanol until a 9:1 mixture of chloroform and methanol was reached. Chromatographically pure compound (tetrahydrofuran:*n*-hexane, 8:2) was dried under vacuum at 80° for 5 hours to afford a light-yellow crystalline powder in 29% yield, mp 145-147°; ^{1}H nmr (DMSO-d_6): 90 MHz δ 2.40 (s, 3H, CH_3), 5.05 (t, 2H, CH_2, J = 10 Hz), 6.85-7.95 (m, 5H, 6-H, 7-H, 8-H + 4-NH_2); ^{19}F nmr [a] (DMSO-d_6): 90 MHz δ 80.5 (br s, 3F, CF_3), 119.4 (br s, 2F, CF_2), 126.7 (br s, 2F, CF_2).

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