Synthesis of 5-(4-Substituted benzyl)-2,4-diaminoquinazolines as Inhibitors of *Candida albicans* Dihydrofolate Reductase

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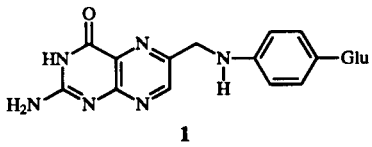
Received May 4, 1995

Several 5-(4-substituted benzyl)-2,4-diaminoquinazolines were prepared as potentially selective inhibitors of *Candida albicans* dihydrofolate reductase. These compounds were synthesized by a novel route, which included as a key step the displacement of a fluoro group in 2,6-difluorobenzonitrile by the anions of ethyl or methyl 4-substituted phenylacetates. The resultant diarylacetates were saponified and decarboxylated to the 2-fluoro-6-(4-substituted phenyl)benzonitriles. Ring closure of these benzonitriles with guanidine carbonate gave the 5-(4-substituted benzyl)-2,4-diaminoquinazolines.

J. Heterocyclic Chem., **32**, 1461 (1995).

Introduction.

One strategy commonly used to develop compounds active against dihydrofolate reductase (DHFR) [1,2], an enzyme that is the target of a number of therapeutic agents such as trimethoprim and methotrexate [3], has been the isosteric replacement of the nitrogen atom(s) in the pyrazine ring of the pterin moiety of folic acid (**1**). Additionally, because of the structural requirement for tight binding in the active site of the enzyme, the 4-oxo group of the pterin moiety is normally replaced by an amino group [2].



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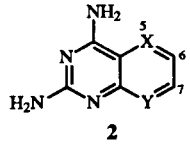

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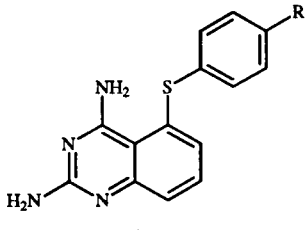
An obvious consequence of isosteric replacement has been the development of methodologies for the synthesis of 2,4-diaminopyridopyrimidines **2** (X = CH, Y = N) and 2,4-diaminoquinazolines **2** (X, Y = CH) which are substituted primarily at the C5 and C6 positions [4,5].

Previous reports on 5-substituted 2,4-diaminoquinazolines have focused on the synthesis of 5-arylthio-2,4-diaminoquinazolines and their potential use as antimalarial agents [5]. Our recent effort in this area was directed toward developing viable antifungal agents through the inhibition of fungal DHFR. In this respect, we found that

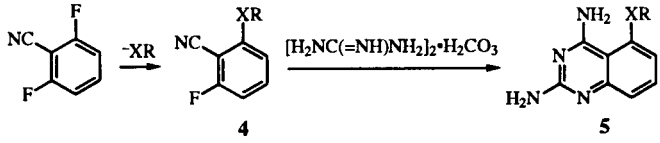


3

5-arylthio-2,4-diaminoquinazolines (**3**) are generally potent and selective inhibitors of *Candida albicans* DHFR [6].

One of our approaches to the synthesis of analogues of **3** was based on the work of Hynes *et al* [7], in which 2,6-difluorobenzonitrile was used as the starting material for the synthesis of 5-substituted 2,4-diaminoquinazolines **5**. As depicted in Scheme I, the key step in their synthesis was the displacement of a fluoro group in 2,6-difluorobenzonitrile by a variety of nucleophiles, including alkylthiolates. Subsequent ring closure of the resultant intermediate **4** with guanidine carbonate gave the desired products **5** .

Scheme I



4 **5**

Using a similar method, we displaced a fluorine atom in 2,6-difluorobenzonitrile by arylthiolates. Cyclization of the resultant intermediate with guanidine carbonate gave compounds **3** in high yield [6].

In an effort to expand our search for selective antifungal agents which act by the inhibition of fungal DHFR, we synthesized 5-(4-substituted benzyl)-2,4-diaminoquinazolines **6** since they are close analogues of the *C. albicans* DHFR-selective inhibitors **3**. To our knowledge, a viable synthetic route to **6** has not been previously reported; the closest examples in the literature are the synthesis of 5-[2-(2-naphthyl)ethyl]-2,4-diaminoquinazoline [5] and of 5-methyl-2,4-diaminoquinazoline [8]. Both compounds were derived from the condensation of the appropriately 6-substituted anthranilonitrile with formamidine chloride [5], cyanamide or guanidine [8]. While it is conceivable that **6** could be obtained from the cyclization of the appro-

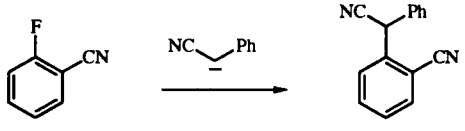
priate 6-(4-substituted benzyl)anthranilonitrile, the latter intermediate would have to be obtained through elaborate synthesis [5].

In this paper, we report a facile and high-yielding synthesis of **6** from 2,6-difluorobenzonitrile. This method should be equally useful for the synthesis of other 5-arylmethyl-2,4-diaminoquinazolines.

Chemistry.

We envisioned that the anion of an acidic methylene group (X = $^-$CH) in Scheme I would be able to selectively displace one fluoro group in 2,6-difluorobenzonitrile, similar to displacement by arylthiolates described above. Cyclization of the resultant intermediate **4** with guanidine or its equivalent would thus give the desired products **5**.

The reaction of the anion of an acidic methylene group with an activated halobenzene has been reported in the literature. 2-Fluorobenzonitrile, for example, reacts with the anion of phenylacetonitrile to give a high yield of arylphenylacetonitrile **7** [9].



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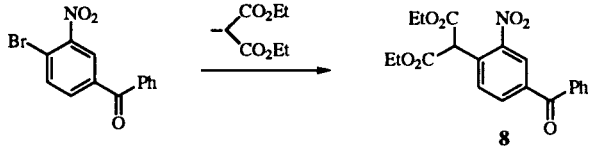
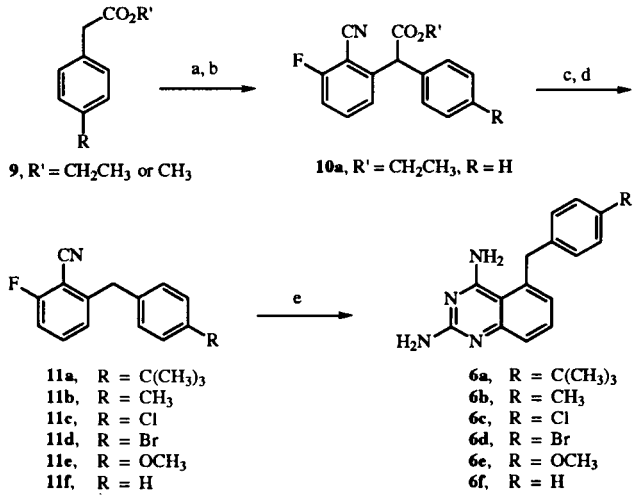
The reaction of 4-bromo-3-nitrobenzophenone with the anion of diethylmalonate results in the displacement of the bromo group to give malonate **8** [10]. In both cases, the halogen substituents were activated by a neighboring electron-withdrawing group.



8

As shown in Scheme II, our synthesis began with the reaction of the anions of methyl or ethyl 4-substituted phenylacetate **9** with excess 2,6-difluorobenzonitrile at -25° in tetrahydrofuran. This led to the displacement of one fluoro group in 2,6-difluorobenzonitrile to give diarylacetate esters **10**. In order to minimize proton transfer from the acidic methinyl proton in **10** to the anion of **9**, 2,6-difluorobenzonitrile and **9** were simultaneously added to a solution of the base, lithium bis(trimethylsilyl)amide, in tetrahydrofuran. Diarylacetate ester **10a** was isolated for characterization. Otherwise, **10** was saponified directly and decarboxylated with 1,8-diazabicyclo-[5.4.0]undec-7-ene [11] to give 2-fluoro-6-(4-substituted benzyl)benzonitriles **11a-f**. These benzonitriles were cyclized with guanidine carbonate in *N,N*-dimethylacetamide [7] to afford high yields of 5-(4-substituted benzyl)-2,4-diaminoquinazolines **6a-f**.

Scheme II



(a) LiN(SiMe$_3$)$_2$/THF; (b) 2,6-difluorobenzonitrile; (c) NaOH/MeOH/-H$_2$O; (d) DBU, heat; (e) guanidine carbonate/DMAC/150°C/5 h

Biological Results

Table 1 lists the activities of compounds **6a-f** against *C. albicans* and human DHFR as well as their *in vitro* antifungal activities which are expressed by the minimum inhibitory concentration (MIC) values against *C. albicans* cell growth. For comparison with 5-arylthio-2,4-diaminoquinazolines **3** [6], we synthesized a set of compounds **6a-f** having 4-substituents that can be found in the **3** series. The enzyme activities and selectivity of the corresponding phenylthio analogues **3** are included in Table 1.

In general, there was at least a 5-fold decrease in potency against both the *C. albicans* and human enzymes compared to similarly substituted quinazolines **3**. Only the unsubstituted **6f** retained similar potency to that of its 5-arylthio counterpart **3a**. Compound **6a** was the least potent against *C. albicans* DHFR, in contrast to its arylthio counterpart **3b**, which was the most potent against the *C. albicans* enzyme.

In spite of the fact that **6a-f** showed weaker activity against both *C. albicans* and human DHFR than the **3** series, they were selective for the *C. albicans* enzyme. Three compounds, **6b, c** and **e**, showed selectivity indices greater than 100. The degree of selectivity was, however, different for similarly substituted analogues of **3** and **6**. For example, **6a** was some 3-fold less selective than **3b** for the *C. albicans* enzyme.

Finally, the weaker enzyme activities of **6a-f** than those of **3** were also reflected in the weaker *in vitro C. albicans* cell activities as shown by the MIC values. The unsubsti-

Table 1

Inhibition of Dihydrofolate Reductase and *in vitro* Antifungal Activity of 5-(4-Substituted benzyl)-2,4-diaminoquinazolines **6a-f** and 5-Arylthio-2,4-diaminoquinazolines **3a-f** [a]

Compound No.	R	DHFR I_{50} (μM) *C. albicans*	DHFR I_{50} (μM) Human	Selectivity (Human/*C. albicans* DHFR I_{50})	*C. albicans* MIC (μg/ml)
6a	$C(CH_3)_3$	1.1	82.0	75	>25
6b	CH_3	0.15	21.0	140	—
6c	Cl	0.16	17.0	106	1.6
6d	Br	0.3	14.0	47	1.6
6e	OCH_3	0.12	22.4	187	3.1
6f	H	0.06	1.6	29	0.4
3a	$C(CH_3)_3$	0.008	2.0	250	0.1
3b	CH_3	0.023	0.94	41	0.25
3c	Cl	0.03	2.1	70	0.5
3d	Br	0.03	3.1	103	0.25
3e	OCH_3	0.02	3.5	175	0.25
3f	H	0.03	0.62	18	0.05

[a] See reference [6].

tuted **6f** was the only compound that showed a *C. albicans* MIC value comparable to that of unsubstituted **3f**.

Conclusion.

A novel method was developed for the synthesis of 5-(4-substituted benzyl)-2,4-diaminoquinazolines **6** and, by extension, other 5-arylmethyl-2,4-diaminoquinazolines using 2,6-difluorobenzonitrile. The present series of inhibitors were less potent than their 5-arylthio counterparts **3** against *C. albicans* and human DHFR. The degree of selectivity for the *C. albicans* enzyme was also different from that of series **3**. The reason for the difference is not understood, although one can surmise that because of the difference between the bond angles of a methylene and a sulfur atom, the mode of binding for these two sets of compounds in the active site of the enzyme might be different.

EXPERIMENTAL

General.

The protocols for the biological assays followed that reported in reference [6].

The 4-substituted phenylacetic acid esters used herein were either commercially available or were prepared from commercially available acids by treatment with thionyl chloride in methanol [5]. 2,6-Difluorobenzonitrile was obtained from Lancaster Synthesis, and 1.0 *N* lithium bis(trimethylsilyl)-amide/tetrahydrofuran was purchased from Aldrich Chemical Company. Melting points were determined on a Thomas Hoover melting point apparatus and are uncorrected. The ^1H 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. Reactions were followed by silica gel thin layer chromatography or by gas chromatography using an HP-5890 Series II gas chromatograph equipped with an HP-3396 Series II integrator.

Ethyl 2-(2-Cyano-3-fluorophenyl)-2-phenylacetate (**10a**).

A cooled (-40°) solution of 1.0 *N* lithium bis(trimethylsilyl)amide in tetrahydrofuran (11 ml, 11 mmoles) under nitrogen was treated dropwise with a mixture of ethyl phenylacetate (0.82 g, 5 mmoles) and 2,6-difluorobenzonitrile (0.83 g, 6 mmoles) in anhydrous tetrahydrofuran at a rate that kept the reaction temperature below -25°. The reaction mixture was then allowed to warm to room temperature over 0.5 hour and was stirred for one hour. Additional 2,6-difluorobenzonitrile (0.28 g, 2 mmoles) was introduced and the mixture was stirred for 18 hours. This reaction mixture was then added into a rapidly stirred ice-cold mixture of saturated aqueous sodium bicarbonate (50 ml) and methylene chloride (75 ml). The organic layer was separated. The aqueous solution was extracted with methylene chloride (2 x 25 ml). The combined organic solution was dried over sodium sulfate and concentrated *in vacuo*. The resultant residue was taken up in methylene chloride and filtered through a pad of alumina with methylene chloride as the eluent. The filtrate was concentrated *in vacuo*, and the residue was recrystallized from cold methylene chloride/hexane (two crops) to afford 1.27 g (90%) of **10a** as a white solid; mp 65-67°; ^1H nmr (deuteriochloroform): δ 7.55 (q, 1H), 7.35 (s, 5H), 7.34 (t, 1H), 7.12 (t, 1H), 5.40 (s, 1H), 4.25 (m, 2H), 1.28 (t, 3H); ms: (CI), m/z 284 ($M+H^+$, 100), 210 ($M-CO_2Et+H^+$, 50).

Anal. Calcd. for $C_{17}H_{14}FNO_2$: C, 72.07; H, 4.98; N, 4.94. Found: C, 72.11; H, 4.97; N, 4.90.

2-(4-*tert*-Butylbenzyl)-6-fluorobenzonitrile (**11a**).

A 250 ml 3-neck round-bottomed flask under nitrogen was charged with 1.0 *N* lithium bis(trimethylsilyl)amide in tetrahydrofuran (55 ml, 55 mmoles) and cooled to -40°. A solution of methyl 4-*tert*-butylphenylacetate (4.54 g, 22 mmoles) and 2,6-difluorobenzonitrile (4.17 g, 30 mmoles) in anhydrous tetrahydrofuran (25 ml) was then added dropwise at a rate that kept the reaction temperature below -25°. The reaction mixture was allowed to reach room temperature; then it was stirred for one hour and treated with additional 2,6-difluorobenzonitrile (1.4 g, 10 mmoles). Stirring was continued for 18 hours. Aqueous sodium hydroxide (1.0 *N*, 50 ml) was added, followed by methanol (25 ml), and the solution was stirred for 2.5 hours. The mixture was added to ice water (250 ml), and the aqueous solution was washed with ether (2 x 100 ml) and acidified to *p*H 3 with 6*N* hydrochloric acid (*ca.* 25 ml). The solution was extracted with toluene (3 x 150 ml) mixed with 5 ml of 2-propanol for each extract. The combined toluene extracts were washed with water (200 ml), dried (sodium sulfate), and partially concentrated to 100 ml volume. This solution was treated with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 3.8 g, 25 mmoles) and heated to 90° for 2.5 hours. The solution was cooled, treated with 2*N* hydrochloric acid (50 ml), and extracted with toluene (100 ml). The toluene solution was washed with water (100 ml) and saturated sodium bicarbonate (100 ml), dried (sodium sulfate), and concentrated *in vacuo*. The resultant residue was taken up in methylene chloride and filtered through a short pad of alumina with methylene chloride as the eluent.

The filtrate was concentrated *in vacuo* to afford 5.19 g (88%) of **11a** as a white solid, mp 65.0-66.5° (hexane); ^{1}H nmr (deuteriochloroform): δ 7.40-7.55 (m, 1H), 7.34 (d, 2H,J = 8 Hz), 7.18 (d, 2H, J = 8 Hz), 7.00-7.10 (m, 2H), 4.17 (s, 2H), 1.31 (s, 9H); ms: (CI), m/z 268 (m+H$^+$, 80), 212 (m-(*t*-bu)+H$^+$, 100).

Anal. Calcd. for $C_{18}H_{18}FN$: C, 80.87; H, 6.79; N, 5.24. Found: C, 80.76; H, 6.81; N, 5.23.

2-Fluoro-6-(4-methylbenzyl)benzonitrile (**11b**).

The procedure for the preparation of **11a** was followed using ethyl 4-methylphenylacetate (3.92 g, 22 mmoles) as the starting ester. The crude product was filtered through alumina (eluted with methylene chloride) and the filtrate was concentrated *in vacuo* to afford 3.81 g (77%) of **11b** as a white solid, mp 67-68° (hexane); ^{1}H nmr (deuteriochloroform): δ 7.40-7.50 (m, 1H), 7.13 (s, 4H), 7.00-7.10 (m, 2H), 4.15 (s, 2H), 2.32 (s, 3H); ms: (CI), m/z 226 (m+H$^+$, 100).

Anal. Calcd. for $C_{15}H_{12}FN$: C, 79.98; H, 5.37; N, 6.22. Found: C, 79.99; H, 5.40; N, 6.16.

2-(4-Chlorobenzyl)-6-fluorobenzonitrile (**11c**).

The procedure for the preparation of **11a** was followed using methyl 4-chlorophenylacetate (4.06 g, 22 mmoles) as the starting ester. The crude product was filtered through alumina (eluted with methylene chloride) and the filtrate was concentrated *in vacuo* to afford 4.31 g (80%) of **11c** as a white solid, mp 94.5-95.5° (hexane); ^{1}H nmr (deuteriochloroform): δ 7.45-7.55 (m, 1H), 7.28 (d, 2H, J = 8 Hz), 7.16 (d, 2H, J = 8 Hz), 7.00-7.10 (m, 2H), 4.16 (s, 2H); ms: (CI), m/z 246 (m+H$^+$, 100).

Anal. Calcd. for $C_{14}H_9ClFN$: C, 68.44; H, 3.69; N, 5.70. Found: C, 68.40; H, 3.65; N, 5.69.

2-(4-Bromobenzyl)-6-fluorobenzonitrile (**11d**).

The procedure for the preparation of **11a** was followed using methyl 4-bromophenylacetate (5.04 g, 22 mmoles) as the starting ester. The crude product was filtered through alumina (eluted with methylene chloride) and the filtrate was concentrated *in vacuo* to afford 5.30 g (83%) of **11d** as a white solid, mp 114-115° (hexane); ^{1}H nmr (deuteriochloroform): δ 7.45-7.55 (m, 1H), 7.44 (d, 2H, J = 8 Hz), 7.11 (d, 2H, J = 8 Hz), 7.00-7.10 (m, 2H), 4.14 (s, 2H); ms: (CI), m/z 290 (m+H$^+$, 100).

Anal. Calcd. for $C_{14}H_9BrFN$: C, 57.96; H, 3.13; N, 4.83. Found: C, 57.87; H, 3.09; N, 4.81.

2-Fluoro-6-(4-methoxybenzyl)benzonitrile (**11e**).

The procedure for the preparation of **11a** was followed using methyl 4-methoxyphenylacetate (3.97 g, 22 mmoles) as the starting ester. The crude product was filtered through alumina (eluted with methylene chloride) and the filtrate was concentrated *in vacuo* to afford 4.84 g (91%) of **11e** as a white solid, mp 60.5-62.0° (hexane); ^{1}H nmr (deuteriochloroform): δ 7.40-7.50 (m, 1H), 7.16 (d, 2H, J = 9 Hz), 7.00-7.10 (m, 2H), 6.86 (d, 2H, J = 9 Hz), 4.13 (s, 2H), 3.79 (s, 3H); ms: (CI), m/z 242 (m+H$^+$, 100).

Anal. Calcd. for $C_{15}H_{12}FNO$: C, 74.68; H, 5.01; N, 5.81. Found: C, 74.75; H, 5.04; N, 5.81.

2-Benzyl-6-fluorobenzonitrile (**11f**).

The procedure for the preparation of **11a** was followed using ethyl phenylacetate (3.61 g, 22 mmoles) as the starting ester. The crude product was filtered through alumina (eluted with methylene chloride) and the filtrate was concentrated *in vacuo* to afford 3.90 g (84%) of **11f** as a white solid, mp 60-61° (hexane); ^{1}H nmr (deuteriochloroform): δ 7.48 (m, 1H), 7.20-7.40 (m, 5H), 7.06 (m, 2H), 4.20 (s, 2H); ms: (CI), m/z 212 (m+H$^+$, 100).

Anal. Calcd. for $C_{14}H_{10}FN$: C, 79.60; H, 4.77; N, 6.63. Found: C, 79.51; H, 4.80; N, 6.64.

2,4-Diamino-5-(*tert*-butylbenzyl)quinazoline (**6a**).

A mixture of 2-(4-*tert*-butylbenzyl)-6-fluorobenzonitrile (**11a**, 4.01 g, 15 mmoles) and guanidine carbonate (6.49 g, 36 mmoles) in anhydrous *N,N*-dimethylacetamide (50 ml) under nitrogen was heated to 150° for 5 hours. The mixture was evaporated to near dryness, and the residue was taken up in cold water (100 ml). The solid was isolated by filtration, rinsed with cold water, air dried, and recrystallized from 95% ethanol (two crops) to afford 3.98 g (87%) of **6a** as pale tan crystals; mp 236-237°; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.39 (t, 1H, J = 8 Hz), 7.33 (d, 2H, J = 8 Hz), 7.13 (d, 1H, J = 8 Hz), 7.03 (d, 2H, J = 8 Hz), 6.75 (d, 1H, J = 7 Hz), 6.46 (br s, 2H), 5.94 (br s, 2H), 4.41 (s, 2H), 1.25 (s, 9H); ms: (CI), m/z 307 (M+H$^+$, 100).

Anal. Calcd. for $C_{19}H_{22}N_4$: C, 74.48; H, 7.24; N, 18.28. Found: C, 74.50; H, 7.25; N, 18.22.

2,4-Diamino-5-(4-methylbenzyl)quinazoline (**6b**).

The procedure for the preparation of **6a** was followed using 2-fluoro-6-(4-methylbenzyl)benzonitrile (**11b**, 3.38 g, 15 mmoles) and guanidine carbonate (6.50 g, 36 mmoles). This resulted in 3.40 g (86%) of **6b** as a pale tan solid after recrystallization from methanol (two crops), mp 256-258° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.40 (t, 1H, J = 7 Hz), 7.10-7.20 (m, 3H), 7.01 (d, 2H, J = 8 Hz), 6.74 (d, 1H, J = 7 Hz), 6.46 (br s, 2H), 5.96 (br s, 2H), 4.42 (s, 2H), 2.28 (s, 3H); ms: (CI), m/z 265 (M+H$^+$, 100).

Anal. Calcd. for $C_{16}H_{16}N_4$: C, 72.70; H, 6.10; N, 21.20. Found: C, 72.60; H, 6.11; N, 21.11.

2,4-Diamino-5-(4-chlorobenzyl)quinazoline (**6c**).

The procedure for the preparation of **6a** was followed using 2-(4-chlorobenzyl)-6-fluorobenzonitrile (**11c**, 3.44 g, 14 mmoles) and guanidine carbonate (6.31 g, 35 mmoles). This resulted in 2.99 g (86%) of **6c** as a pale tan solid after recrystallization from methanol (two crops), mp 254-256° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.35-7.45 (m, 3H), 7.10-7.20 (m, 3H), 6.73 (d, 1H), 6.53 (br s, 2H), 5.97 (br s, 2H), 4.48 (s, 2H); ms: (CI), m/z 285 (M+H$^+$, 100).

Anal. Calcd. for $C_{15}H_{13}ClN_4$: C, 63.27; H, 4.60; N, 19.68. Found: C, 63.15; H, 4.57; N, 19.62.

2,4-Diamino-5-(4-bromobenzyl)quinazoline (**6d**).

The procedure for the preparation of **6a** was followed using 2-(4-bromobenzyl)-6-fluorobenzonitrile (**11d**, 4.93 g, 17 mmoles) and guanidine carbonate (7.39 g, 41 mmoles). This resulted in 4.30 g (77%) of **6d** as a pale orange solid after recrystallization from methanol/methylene chloride (two crops), mp 255-257° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.49 (d, 2H, J = 8 Hz), 7.38 (t, 1H, J = 7 Hz), 7.13 (d, 1H, J = 7 Hz), 7.05 (d, 2H, J = 8 Hz), 6.71 (d, 1H, J = 7 Hz), 6.50 (br s, 2H), 5.94 (br s, 2H), 4.44 (s, 2H); ms: (CI), m/z 329 (M+H$^+$, 100).

Anal. Calcd. for $C_{15}H_{13}BrN_4$: C, 54.73; H, 3.98; N, 17.02. Found: C, 54.78; H, 4.03; N, 17.10.

2,4-Diamino-5-(4-methoxybenzyl)quinazoline (**6e**).

The procedure for the preparation of **6a** was followed using 2-fluoro-6-(4-methoxybenzyl)benzonitrile (**11e**, 3.62 g, 15 mmoles) and guanidine carbonate (6.50 g, 36 mmoles). This resulted in 3.89 g (92%) of **6e** as a pale tan solid; mp 260-262° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.38 (t, 1H, J = 8 Hz), 7.13 (d, 1H, J = 8 Hz), 7.03 (d, 2H, J = 9 Hz), 6.88 (d, 2H, J = 9 Hz), 6.72 (d, 1H, J = 8 Hz), 6.45 (br s, 2H), 5.93 (br s, 2H), 4.37 (s, 2H), 3.72 (s, 3H); ms: (CI), m/z 281 ($M+H^+$, 100).

Anal. Calcd. for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.40; H, 5.76; N, 20.07.

2,4-Diamino-5-benzylquinazoline (**6f**).

The procedure for the preparation of **6a** was followed using 2-benzyl-6-fluorobenzonitrile (**11f**, 1.06 g, 5 mmoles) and guanidine carbonate (2.16 g, 12 mmoles). This resulted in 1.09 g (87%) of **6f** as amber crystals after recrystallization from methanol/ethanol, mp 256-258° dec; ^{1}H nmr (dimethyl-d_6 sulfoxide): δ 7.30-7.50 (m, 3H)), 7.20 (m, 1H), 7.12 (m, 3H), 6.73 (d, 1H), 6.48 (br s, 2H), 5.96 (br s, 2H), 4.46 (s, 2H); ms: (CI), m/z 251 ($M+H^+$, 100).

Anal. Calcd. for $C_{15}H_{14}N_4$: C, 71.98; H, 5.64; N, 22.38. Found: C, 71.84; H, 5.70; N, 22.27.

Acknowledgements.

The authors extend their thanks to Dr. Lee Kuyper for many fruitful discussions and to Dr. Robert McNutt for his comments. Dr. Gary Martin and his group have provided some of the nmr spectra. We thank Ms. Donna Tabon for drawing the structures, Mr. Allen Jones and Ms. Carol Winkelman for proofreading, and Mr. Randy Carmichael for typing the manuscript.

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