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A Novel Method of Synthesis of 2,4-Diamino-6-arylmethylquinazolines Using Palladium(0)-Catalyzed Organozinc Chemistry

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Introduction

Palladium-catalyzed cross-coupling reactions offer a powerful approach to the creation of a carbon−carbon bond between an electrophile C−X (e.g., X = Cl, Br, I, OTf) and an organometallic species C−M (e.g., M = Li, Mg, Zn, B, Si).[1] Organozinc reagents are extremely useful in this context because they can tolerate a wide range of functionality in the electrophilic partner.[2] A large number of organozinc reagents are available commercially as standardized solutions in THF or can prepared easily from organic halides and a highly reactive grade of metallic zinc ("Rieke zinc"),[3] which is likewise commercially available. Thus, organozinc reagents in combination with palladium reagents are advantageous in the synthesis of complex molecules containing multiple functional groups, such as natural products. Of particular note are that the reaction requires only a catalytic amount of palladium and that, in contrast to the Heck reaction, the saturated carbon−carbon is generated directly, without the need to first reduce a double or triple bond. Thus, palladium-catalyzed cross-coupling reactions using organozinc reagents are expected to enjoy increasing popularity in organic synthesis and medicinal chemistry.

Piritrexim (**1**),[4] a lipophilic inhibitor of the key metabolic enzyme dihydrofolate reductase (DHFR), has been studied intensively as an anticancer drug[5] and, more recently, was identified as a potent inhibitor of the enzyme from *Pneumocystis carinii* (Pc) and *Toxoplasma gondii* (Tg), two opportunistic parasites known to be potentially life-threatening in patients with acquired immunodeficiency syndrome (AIDS).[6] A notable structural feature of **1** is the CH_2 bridge between the two halves of the molecule. This bridge is also present in trimethoprim (**2**),[7] another lipophilic DHFR inhibitor widely used for anti-Pc and anti-Tg prophylaxis and therapy in AIDS patients, usually in combination with a sulfa drug to enhance the efficacy.[8] Two other members of this class that have been used clinically against these infections are pyrimethamine (**3**),[7,9] in which the two halves of the molecule are linked without a CH_2 bridge, and trimetrexate (**4**),[10,11] which contains a CH_2NH bridge. In addition to the fact that it contains a longer bridge, **4** differs from **1** in being a quinazoline as opposed to a pyrido[2,3-*d*]pyrimidine. The structures of these four prototypical examples of clinically active lipophilic antifolates are shown in Figure 1.

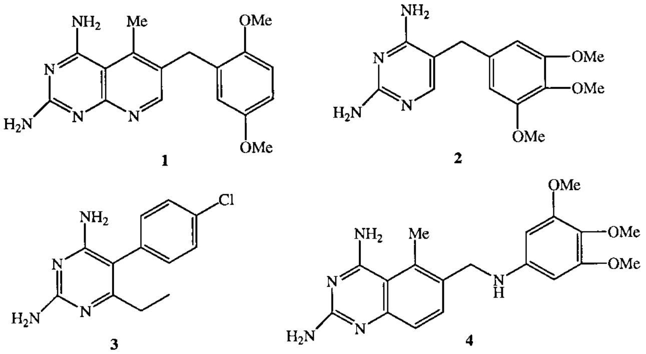

Figure 1. Structures of piritrexim (**1**), trimethoprim (**2**), pyrimethamine (**3**), and trimetrexate (**4**).

Although there are a number of examples in the literature of lipophilic DHFR inhibitors in which the fused 2,4-diaminopyrimidine ring system and the aryl side chain are separated by a short O or S bridge, as in **5** and **6**,[12,13] the only quinazoline antifolates described to date in which this bridge is CH_2 are the 5,6,7,8-tetrahydro derivatives **7**.[14] In the present paper, we report a novel and remarkably straightforward method of synthesis of analogues of **7** in which the B-ring is aromatic.

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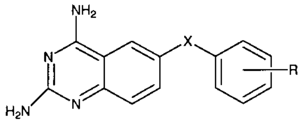
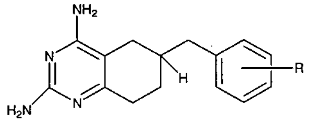
The key step in the synthesis of these compounds, which to our knowledge have not been described previously, is a palladium-catalyzed cross-coupling reaction between 2-amino-5-iodobenzonitrile and arylmethylzinc halides without protection of the amino group. Ring closure of the resulting aminonitriles by heating them with chloroformamidine hydrochloride under previously described dry-fusion conditions[15,16] yielded the fully aromatic analogues **8**.



5 : X = O
6 : X = S
8 : X = CH2



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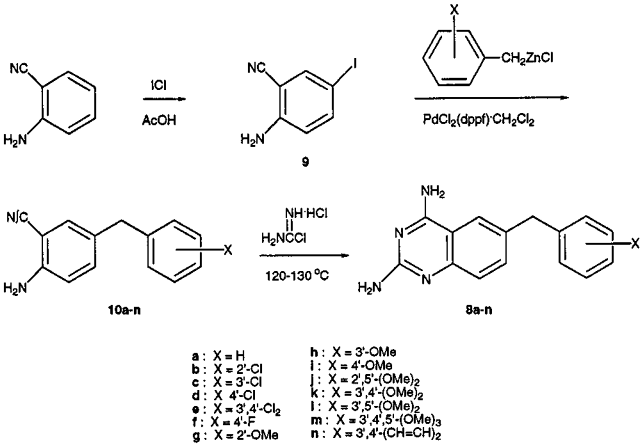
As shown in Scheme 1, iodination of 2-aminobenzonitrile with iodine monochloride in glacial AcOH at room temperature occurred regioselectively at the para position to give 2-amino-5-iodobenzonitrile (**9**) in 65% yield as reported by others.[17] When a catalytic amount (0.1 mmol) of the commercially available reagent [1,1′-bis(diphenylphosphino)ferrocene]dichloropalladium(II)•CH_2Cl_2 [(DPPF)-$PdCl_2$•H_2Cl_2][18] was added to a THF solution of the organozinc halide (5 mmol), a deep yellow color formed after only a few minutes. Upon addition of a solution of **9** (2 mmol) in THF, followed by heating under reflux for another 30 min, TLC showed the cross-coupling reaction to be complete. The resulting amino nitriles **10a**−**n** were purified by column chromatography on silica gel, and their identity and purity were established from their ^{1}H NMR spectra, which contained the expected singlet at approximately δ 3.8, along with OMe, NH_2, and aromatic proton peaks consistent with assigned structures.

Scheme 1



Ring closure of **10a**−**n** to form **8a**−**n** was performed by heating with chloroformamidine hydrochloride under conditions we have used in our laboratory in the past, which involve heating a finely ground mixture of the reactants in an open pear-shaped flask, without solvent, at 120−130 °C for 20 min.[15] The resultant melt is allowed to congeal at room temperature and is taken up in MeOH. Addition of $CHCl_3$ causes precipitation of byproducts arising from thermally induced self-condensation/polymerization of chloroformamidine hydrochloride.[19] The MeOH−$CHCl_3$ filtrate at this stage contains the HCl salt of the diaminoquinazoline as well as the salt of a second product believed to be a noncyclized amidinonitrile intermediate.[15] As noted earlier,[15] further heating under high vacuum is sometimes required in order to drive the ring closure to completion, and the exact reaction conditions may vary depending on the reactivity of the amino nitrile.

^{1}H NMR spectra of **8a**−**n** showed the expected signals for a 2,4-diamino-6-arylmethylquinazoline, among which were a singlet at approximately δ 3.9 for H-5 and doublets at approximately δ 7.1 (J = 8.4−8.8 Hz) and δ 7.3 (J = 8.4−8.8 Hz) for H-8 and H-7, respectively. Signals for the other aromatic protons had chemical shifts and coupling constants in agreement with the nature and location of the substituents on the benzyl ring. The identity of each final product was also confirmed by microchemical analysis and mass spectrometry.

Yields in the cross-coupling reaction to form the amino nitriles **10a**−**n** ranged from 43 to 69%, with an average of 55%. Yields in the ring-closure reaction to form quinazolines **8a**−**n** ranged from 37 to 60%, with an average of 47%. Thus, even though the palladium catalyst, solvent, and temperature were not individually optimized in the cross-coupling reaction and the overall yield from 2-aminobenzonitrile did not exceed 25%, the obvious merit of this synthesis is that it involved only two steps.

In summary, the findings reported here suggest that this simple and potentially versatile method may lend itself to the synthesis of a large variety of previously unknown DHFR inhibitors in which an arylmethyl group is linked directly to the 2,4-diaminoheterocyclic moiety via a CH_2 bridge. Studies along these lines are ongoing in our laboratory.

Experimental Section

IR spectra were obtained on a Perkin-Elmer model 781 double-beam-recording spectrophotometer. Only peaks with wavenumbers greater than 1400 cm^{-1} are reported. ^{1}H NMR spectra were recorded at 200 MHz on a Varian VX200 instrument or at 400 MHz on a Varian VX400 instrument. TLC analyses were performed on Whatman MK6F silica gel plates with UV illumination at 254 nm. Column chromatography was performed on Baker 7024 flash silica gel (40 μm particle size). Melting points were measured in Pyrex capillary tubes in a Mel-Temp ′"Electrothermal"′ apparatus (Fisher Scientific, Pittsburgh, PA) and are not corrected. Mass spectra in the electron-impact (EI) or fast-atom-bombardment (FAB) mode were obtained by staff of the Dana-Farber Cancer Institute Molecular Biology Core

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Facility. The palladium catalyst [1,1′-bis(diphenylphosphino)-ferrocene]dichloropalladium(II)·CH_2Cl_2 and other chemicals, including Rieke-grade active zinc as a suspension in dry THF, were purchased from Aldrich, Milwaukee, WI. Solutions of 3,4-dichlorobenzylzinc chloride, 2,5-dimethoxybenzylzinc chloride, and 3,4,5-trimethoxybenzylzinc chloride in dry THF were prepared and used essentially as described in the literature for other organozinc reagents[3] and were used immediately. Other organozinc reagents, supplied as 0.5 M solutions in THF in ‴“Sure-Seal”‴ bottles, were purchased from Aldrich. The THF used in the zinc cross-coupling reactions was freshly distilled from Na benzophenone ketyl under a dry N_2 atmosphere. Chloroformamidine hydrochloride was prepared from cyanamide in ethereal HCl as described.[17] The amino nitrile intermediates were checked thoroughly for purity by ^1H NMR and TLC ($R_f = 0.24-0.32$ on silica gel using 2:1 hexane$-CH_2Cl_2$), but elemental analyses were obtained only for the quinazoline final products. Elemental analyses were performed by Robertson Laboratories, Madison, NJ, and were within ±0.4% of theoretical values.

Typical Procedure. Synthesis of 2,4-Diamino-6-benzylquinazoline (8a): Step 1. A solution of iodine monochloride (16.7 g, 0.1 mol) in glacial AcOH (30 mL) was added dropwise over 15 min to a stirred solution of 2-aminobenzonitrile (11.8 g, 0.1 mol) in glacial AcOH (125 mL) at room temperature. The mixture was stirred for 3 h and then poured into H_2O (1000 mL). The resulting pinkish-brown solid was filtered, washed with H_2O, and dried in vacuo. Crystallization from 9:1 cyclohexane−toluene gave 2-amino-5-iodobenzonitrile (**9**) as translucent plates (14.9 g, 64%): mp 85−86 °C (lit.[17] mp 85−86 °C); ^1H NMR ($CDCl_3$) δ 7.60 (d, $J = 1.6$ Hz, 1H, H-6), 7.57 (dd, $J = 9.2$, 1.6 Hz, 1H, H-4), 6.53 (d, $J = 9.2$ Hz, 1H, H-3), 4.45 (br s, 2H, NH_2). The product was used directly in the next reaction (Step 2).

Step 2. (DPPF)$PdCl_2$·CH_2Cl_2 (82 mg, 0.1 mmol) was added to 0.5 M benzylzinc bromide in dry THF (10 mL, calculated to contain 5 mmol), and the mixture was stirred at room temperature for 5 min under N_2. A solution of **9** (488 mg, 2 mmol) in dry THF (2 mL) was then added, and the reaction mixture was heated under reflux and monitored by TLC (silica gel, 2:1 CH_2Cl_2−hexanes). After 30 min, the reaction was quenched by addition of saturated aqueous NH_4Cl (10 mL) followed by addition of saturated aqueous Na_2EDTA (10 mL), and stirring was continued for another 30 min. The brown mixture was extracted several times with CH_2Cl_2, and the combined extracts were washed with brine, dried over Na_2SO_4, and evaporated to dryness under reduced pressure. The residue was purified by chromatography on silica gel (2:1 CH_2Cl_2−hexanes) to obtain **10a** as a white powder (210 mg, 51%): mp 68−69 °C; ^1H NMR (DMSO-d_6) δ 3.75 (s, 2H, CH_2), 5.85 (br s, 2H, NH_2), 6.70 (d, $J = 8$ Hz, 1H, H-3), 7.13−7.26 (m, 7H, aromatic protons).

Step 3. A finely ground mixture of **10a** (60 mg, 0.29 mmol) and chloroformamidine hydrochloride (132 mg, 1.16 mmol) was placed in a 10 mL pear-shaped flask, which was immersed in an oil bath and triturated continuously with a glass rod while being heated to 120 °C (internal temperature) under a gentle stream of N_2 as described.[15] After 20 min, the reaction mixture was cooled to room temperature, the resulting glassy solid was dissolved in MeOH (0.75 mL), and the solution was diluted with $CHCl_3$ (12 mL) and chilled at 0 °C for 1 h. The solid precipitate was collected, washed with $CHCl_3$, and discarded. This solid consisted mainly of byproducts arising from self-condensation of the chloroformamidine, whereas the pooled filtrates contained the HCl salt of the desired product, along with a variable amount of the salt of the intermediate noncyclized amidinonitrile. To ensure complete ring closure, excess i-Pr_2NH (0.5 mL) was added to the filtrate to neutralize the acid, the mixture was concentrated to dryness on a rotary evaporator, and the solid residue was heated for 1.5 h at 70 °C under high vacuum (0.1 Torr). The crude product was then dissolved in boiling MeOH, and the solution was treated with a small amount of decolorizing carbon (Darco) and hot filtered through a bed of Celite. When the filtrate became cool, it was basified to pH 10 with ammonia, and the precipitate was collected. Recrystallization from MeOH−H_2O afforded **8a** as a white crystalline solid (32 mg, 44%): mp 220−222 °C; MS m/z 251.4, calcd 251.3 (M + 1); IR (KBr) ν 3340, 3170, 1620, 1570, 1510, 1450, 1400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.92 (s, 2H, CH_2), 5.84 (br s, 2H, 2-NH_2), 7.13 (d, $J = 8.6$ Hz, 1H, H-8), 7.16−7.35 (m, ca. 6H, H-7 and other aromatic protons), 7.89 (s, 1H, H-5). In contrast to the majority of the other diaminoquinazolines described below, the hydrogens on the 4-NH_2 group apparently gave a signal at ca. δ 7.2 that was too broad to be observed. Anal. Calcd for $C_{15}H_{15}N_4$·$0.3H_2O$: C, 70.46; H, 5.75; N, 22.16. Found: C, 70.20; H, 5.42; N, 22.28.

2-Amino-5-(2′-chlorobenzyl)benzonitrile (10b). Compound **10b** was obtained from **9** (488 mg, 2 mmol) and 2-chlorobenzylzinc chloride (0.5 M in THF, 10 mL, 5 mmol) by the same method as **10a**: white powder (272 mg, 62%); mp 79−80 °C; ^1H NMR ($CDCl_3$) δ 3.96 (s, 2H, CH_2), 4.79 (br s, 2H, NH_2), 6.69 (d, $J = 8.8$ Hz, 1H, H-3), 7.12−7.19 (m, 5H, aromatic protons), 7.20 (s, 1H, H-6).

2-Amino-5-(3′-chlorobenzyl)benzonitrile (10c). Compound **10c** was obtained from **9** (488 mg, 2 mmol) and 3-chlorobenzylzinc chloride (0.5 M in THF, 10 mL, 5 mmol) by the same method as **10a**: white powder (269 mg, 55%); mp 84.5−85.5 °C; ^1H NMR ($CDCl_3$) δ 3.82 (s, 2H, CH_2), 4.30 (br s, 2H, NH_2), 7.02 (d, $J = 8.4$ Hz, 1H, H-3), 7.12−7.22 (m, 5H, aromatic protons).

2-Amino-5-(4′-chlorobenzyl)benzonitrile (10d). Compound **10d** was obtained from **9** (488 mg, 2 mmol) and 4-chlorobenzylzinc chloride (0.5 M in THF, 10 mL, 5 mmol) by the same method as **10a**: white powder (243 mg, 59%); mp 91.5−93 °C; ^1H NMR (DMSO-d_6) δ 3.79 (s, 2H, CH_2), 5.87 (br s, 2H, NH_2), 6.68 (d, $J = 8.0$ Hz, 1H, H-3), 7.11 (d, $J = 8.0$ Hz, 1H, H-4), 7.18 (d, $J = 8.4$ Hz, 2H, H-2′ and H-6′), 7.20 (s, 1H, H-6), 7.29 (d, $J = 8.4$ Hz, 2H, H-3′ and H-5′).

2-Amino-5-(3′,4′-dichlorobenzyl)benzonitrile (10e). A suspension of active Zn metal in THF (0.76 M, 6.3 mL calculated to contain 4.8 mmol or a 20% theoretical excess) was placed in a thoroughly dried three-necked flask that was flushed continuously with a gentle stream of dry N_2. A solution of 3,4-dichlorobenzyl chloride (790 mg, 4 mmol) in dry THF (2 mL) was then added slowly to the flask at room temperature, and the reaction mixture was stirred at 68 °C for 10 h and left to stand for 3 h to allow the excess Zn metal to settle to the bottom. The dark-brown solution of organozinc reagent was transferred via a cannula using gentle N_2 pressure into another three-necked flask, to which was then added dropwise at room temperature a solution of **9** (244 mg, 1 mmol) in dry THF (1 mL) followed by a single portion of (DPPF)$PdCl_2$·CH_2Cl_2 (41 mg, 0.05 mmol). Standard workup similar to that used for **10a** afforded **10e** as a pale-yellow powder (172 mg, 65%): mp 104−107 °C; ^1H NMR ($CDCl_3$) δ 3.80 (s, 2H, CH_2), 4.35 (br s, 2H, NH_2), 6.68 (d, $J = 8.4$ Hz, 1H, H-3), 6.97 (dd, $J = 8.0$, 2.0 Hz, 1H, H-6′), 7.11 (s, $J = 8.4$ Hz, H-4), 7.16 (s, 1H, H-6), 7.22 (d, $J = 2.0$ Hz, 1H, H-2′), 7.35 (d, $J = 8.0$ Hz, 1H, H-5′).

2-Amino-5-(4′-fluorobenzyl)benzonitrile (10f). Compound **10f** was obtained from **9** (488 mg, 2 mmol) and 4-fluorobenzylzinc chloride (0.5 M in THF, 10 mL, 5 mmol) by the same method as **10a**: pale-yellow powder (275 mg, 51%); mp 105−107 °C; ^1H NMR ($CDCl_3$) δ 3.82 (s, 2H, CH_2), 4.32 (br, 2H, NH_2), 6.68 (d, $J = 8.8$ Hz, 1H, H-3), 6.96−7.00 (m, 2H, H-3′ and H-5′), 7.08−7.14 (m, 3H, H-4, H-2′, and H-6′), 7.17 (s, 1H, H-6).

2-Amino-5-(2′-methoxybenzyl)benzonitrile (10g). Compound **10g** was obtained from **9** (610 mg, 2.5 mmol) and 2-methoxybenzylzinc chloride (0.5 M in THF, 10 mL, 5 mmol) by the same method as **10a**: white powder (364 mg, 61%); mp 77.5−78.5 °C; ^1H NMR ($CDCl_3$) δ 3.81 (s, 3H, OMe), 3.82 (s, 2H, CH_2), 4.25 (br s, 2H, NH_2), 6.64 (d, $J = 8.0$ Hz, 1H, H-3), 6.85−6.88 (m, 2H, H-3′ and H-5′), 7.06 (d, $J = 7.2$ Hz, 1H, H-6′), 7.18−7.23 (m, 3H, H-4′, H-4, and H-6).

2-Amino-5-(3′-methoxybenzyl)benzonitrile (10h). Compound **10h** was obtained from **9** (488 mg, 2 mmol) and 3-methoxybenzylzinc chloride (0.5 M in THF, 10 mL, 5 mmol) by the same method as **10a**: white powder (274 mg, 49%); mp 81−82 °C; ^1H NMR ($CDCl_3$) δ 3.81 (s, 2H, OMe), 3.82 (s, 2H, CH_2), 4.25 (br s, NH_2), 6.67 (d, $J = 8.0$ Hz, 1H, H-3), 6.68 (s, 1H, H-2′), 6.72−6.77 (m, 2H, H-4′ and H-6′), 7.15 (d, $J = 8.0$ Hz, 1H, H-4), 7.19 (s, 1H, H-6), 7.22 (t, $J = 7.6$ Hz, 1H, H-5′).

2-Amino-5-(4′-methoxybenzyl)benzonitrile (10i). Compound **10i** was obtained from **9** (488 mg, 2 mmol) and 4-methoxybenzyl chloride (0.5 M in THF, 10 mL, 5.0 mmol) by the same method as **10a**: white powder (239 mg, 43%); mp 72.5−73.5 °C; ^1H NMR ($CDCl_3$) δ 3.79 (s, 5H, CH_2 and OMe), 4.28 (br s, NH_2), 6.66 (d, $J = 8.4$ Hz, 1H, H-3), 6.83 (d, $J = 8.4$ Hz, 2H, H-3′ and H-5′), 7.05 (d, $J = 7.6$ Hz, 2H, H-2′ and H-6′), 7.14 (d, $J = 8.4$ Hz, 1H, H-4), 7.17 (s, 1H, H-6).

2-Amino-5-(2′,5′-dimethoxybenzyl)benzonitrile (10j). 2,5-Dimethoxybenzylzinc chloride was prepared from 2,5-dimethoxybenzyl chloride (746 mg, 4 mmol) and reactive metallic zinc suspension (0.76 M in THF, 6.3 mL, 4.8 mmol). The supernatant was transferred via a cannula into a solution of **9** (366 g, 1.5 mmol) in THF at room temperature, followed by addition of a (DPPF)$PdCl_2 \cdot CH_2Cl_2$ (62 mg, 0.075 mmol) in one portion. After the usual workup, **10j** was obtained as a pale-yellow powder (280 mg, 69%): mp 90−92 °C; ^{1}H NMR ($CDCl_3$) δ 3.74 (s, 3H, OMe), 3.76 (s, 3H, OMe), 3.80 (s, 2H, CH_2), 4.66 (br s, 2H, NH_2), 6.63 (d, J = 2.8 Hz, 1H, H-6′), 6.70 (d, J = 8.4 Hz, 1H, H-3), 6.72 (dd, J = 9.0 Hz, J = 2.8 Hz, 1H, H-4′), 6.80 (d, J = 9.0 Hz, 1H, H-3′), 7.19 (d, J = 8.4 Hz, 1H, H-4), 7.22 (s, 1H, H-6).

2-Amino-5-(3′,4′-dimethoxybenzyl)benzonitrile (10k). Compound **10k** was obtained from **9** (488 mg, 2 mmol) and 3,4-dimethoxybenzylzinc chloride (0.5 M in THF, 10 mL, 5.0 mmol) by the same method as **10a**: yellow oil (247 mg, 46%); ^{1}H NMR ($CDCl_3$) δ 3.79 (s, 2H, CH_2), 3.83 (s, 3H, OMe), 3.86 (s, 3H, OMe), 4.21 (br s, NH_2), 6.65−6.82 (m, 4H, H-3, H-2′, H-5′, and H-6′), 7.15 (d, J = 8.4 Hz, 1H, H-4), 7.17 (s, 1H, H-6).

2-Amino-5-(3′,5′-dimethoxybenzyl)benzonitrile (10l). Compound **10l** was obtained from **9** (244 mg, 1 mmol) and 3,5-dimethoxybenzylzinc chloride (0.5 M in THF, 5 mL, 2.5 mmol) by the same method as **10a**: pale-yellow powder (158 mg, 59%); mp 105−107 °C; ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 8H, CH_2, 3′-OMe, and 5′-OMe), 4.31 (br s, NH_2), 6.29−6.32 (m, 3H, H-2′, H-4′, and H-6′), 6.68 (d, J = 8.2 Hz, 1H, H-3), 7.14 (d, J = 8.2 Hz, 1H, H-4), 7.19 (s, 1H, H-6).

2-Amino-5-(3′,4′,5′-trimethoxybenzyl)benzonitrile (10m). 3,4,5-Trimethoxybenzylzinc chloride was prepared from 3,4,5-trimethoxybenzyl chloride (867 mg, 4 mmol) and reactive metallic zinc suspension (0.76 M in THF, 6.3 mL, 4.8 mmol). The supernatant was transferred via a cannula into a solution of **9** (244 g, 1 mmol) in THF at room temperature, followed by addition of (DPPF)$PdCl_2 \cdot CH_2Cl_2$ (41 mg, 0.05 mmol) in one portion. After the usual workup, **10m** was obtained as a pale-yellow oil (127 mg, 43%): ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 2H, CH_2), 3.81 (s, 6H, 3′-OMe and 5′-OMe), 3.82 (s, 3H, 4′-OMe), 4.28 (br s, NH_2), 6.30 (s, 2H, H-2′ and H-6′), 6.69 (d, J = 8.4 Hz, 1H, H-3), 7.16 (d, J = 8.4 Hz, 1H, H-4), 7.19 (s, 1H, H-6).

2-Amino-5-(2′-naphthylmethyl)benzonitrile (10n). Compound **10n** was obtained from **9** (488 mg, 2 mmol) and 2-naphthylmethylzinc chloride (0.5 M in THF, 10 mL, 5 mmol) by the same method as **10a**: pale-yellow oil (327 mg, 63%); ^{1}H NMR ($CDCl_3$) δ 4.01 (s, 2H, CH_2), 4.35 (br s, NH_2), 6.68 (d, J = 8.0 Hz, 1H, H-3), 7.18 (d, J = 8.0 Hz, 1H, H-4), 7.24 (s, 1H, H-6), 7.45−7.49 (m, 3H, H-4′, H-5′ and H-8′), 7.59 (s, 1H, H-1′), 7.76−7.82 (m, 3H, H-3′, H-6′, and H-7′).

With the exception of minor adjustments in the amounts of MeOH and $CHCl_3$ used in the crystallization step, the following 2,4-diaminoquinazolines were prepared from amino nitriles **10b**−**10n** and chloroformamidine hydrochloride as described for **8a** (see above).

2,4-Diamino-6-(2′-chlorobenzylquinazoline (8b). Compound **8b** was obtained from **10b** (180 mg, 0.74 mmol) and chloroformamidine hydrochloride (340 mg, 3 mmol) at 130 °C (internal) for 30 min: white needles (79 mg, 38%); mp 221−222 °C; MS m/z 285.2, calcd 285.8 (M + 1); IR (KBr) ν 3400, 3180, 1610, 1550, 1500, 1430 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.04 (s, 2H, CH_2), 5.88 (br s, 2-NH_2), 7.11 (s, J = 8.0 Hz, 1H, H-8), 7.18 (br s, 4-NH_2), 7.20−7.24 (m, 4H, H-3′, H-4′, H-5′, and H-6′), 7.43 (d, J = 8.0 Hz, 1H, H-7), 7.88 (s, 1H, H-5). Anal. Calcd for $C_{15}H_{13}N_4Cl \cdot 0.3H_2O$: C, 62.09; H, 4.72; N, 19.31; Cl, 12.21. Found: C, 62.40; H, 4.65; N, 19.32; Cl, 11.84.

2,4-Diamino-6-(3′-chlorobenzylquinazoline (8c). Compound **8c** was obtained from **10c** (107 mg, 0.44 mmol) and chloroformamidine hydrochloride (201 mg, 1.76 mmol) at 120 °C for 30 min: white needles (52 mg, 41%); mp 242−243 °C; MS m/z 285.1, calcd 285.8 (M + 1); IR (KBr) ν 3440, 3200, 1620, 1565, 1510, 1470 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.98 (s, 2H, CH_2), 5.92 (br s, 2-NH_2), 7.11 (d, J = 8.4 Hz, 1H, H-8), 7.16−7.27 (m, 4H, H-2′, H-4′, H-5′, and H-6′), 7.21 (br s, 2H, 4-NH_2), 7.34 (d, J = 8.4 Hz, 1H, H-7), 7.88 (s, 1H, H-5). Anal. Calcd for $C_{15}H_{13}N_4Cl \cdot 0.2H_2O$: C, 62.48; H, 4.68; N, 19.43; Cl, 12.29. Found: C, 62.32; H, 4.64; N, 19.38; Cl, 12.56.

2,4-Diamino-6-(4′-chlorobenzyl)quinazoline (8d). Compound **8d** was obtained from **10d** (243 mg, 1 mmol) and chloroformamidine hydrochloride (456 mg, 4 mmol) at 130 °C for 15 min: white needles (107 mg, 37%); mp 224−225 °C; MS m/z 285.1, calcd 285.8 (M + 1); IR (KBr) ν 3340, 3160, 1615, 1565, 1510, 1490, 1450, 1400 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 4.02 (s, 2H, CH_2), 5.89 (br s, 2-NH_2), 7.12 (d, J = 8.8 Hz, 1H, H-8), 7.19 (br s, 2H, 2-NH_2), 7.25 (d, J = 8.4 Hz, 2H, H-2′ and H-6′), 7.32 (d, J = 8.8 Hz, 1H, H-7), 7.34 (d, J = 8.4 Hz, 2H, H-3′ and H-5′), 7.88 (s, 1H, H-5). Anal. Calcd for $C_{15}H_{13}N_4Cl \cdot 0.2H_2O$: C, 62.48; H, 4.68; N, 19.43; Cl, 12.29. Found: C, 62.52; H, 4.56; N, 19.63; Cl, 12.32.

2,4-Diamino-6-(3′,4′-dichlorobenzyl)quinazoline (8e). Compound **8e** was obtained from **10e** (172 mg, 0.65 mmol) and chloroformamidine hydrochloride (298 mg, 2.6 mmol) at 130 °C for 15 min: white needles (78 mg, 37%); mp 150−151 °C; MS m/z 319.2, calcd 319.2 (M + 1); IR (KBr) ν 3310, 3180, 1620, 1560, 1510, 1470, 1445, 1400 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.93 (s, 2H, CH_2), 5.89 (br s, 2H, 2-NH_2), 7.12 (d, J = 8.4 Hz, 1H, H-8), 7.19 (br s, 2H, 4-NH_2), 7.22 (d, J = 8.4 Hz, 1H, H-6′), 7.35 (d, J = 8.4 Hz, 1H, H-7), 7.51 (s, 1H, H-2′), 7.54 (d, J = 7.6 Hz, 1H, H-5′), 7.87 (s, 1H, H-5). Anal. Calcd for $C_{15}H_{12}N_4Cl_2 \cdot 0.1H_2O$: C, 56.13; H, 3.83; N, 17.45; Cl, 22.09. Found: C, 56.21; H, 3.73; N, 17.27; Cl, 21.83.

2,4-Diamino-6-(4′-fluorobenzyl)quinazoline (8f). Compound **8f** was obtained from **10f** (150 mg, 0.56 mmol) and chloroformamidine hydrochloride (255 mg, 2.24 mmol) at 120 °C for 30 min: white needles (97 mg, 65%); mp 214−216 °C; MS m/z 269.2, calcd 269.3 (M + 1); IR (KBr) ν 3310, 3180, 1610, 1550, 1500, 1440, 1400 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.93 (s, 2H, CH_2), 5.86 (br, 2-NH_2), 7.08−7.14 (m, 3H, H-3′, H-5′, and H-8), 7.18 (br s, 2H, 4-NH_2), 7.25−7.28 (m, 2H, H-2′ and H-6′), 7.32 (d, J = 8.4 Hz, 1H, H-7), 7.88 (s, 1H, H-5). Anal. Calcd for $C_{15}H_{13}N_4F$: C, 67.15; H, 4.88; N, 20.88; F, 7.08. Found: C, 66.98; H, 5.03; N, 20.81; F, 7.16.

2,4-Diamino-6-(2′-methoxybenzyl)quinazoline (8g). Compound **8g** was obtained from **10g** (190 mg, 0.8 mmol) and chloroformamidine hydrochloride (365 mg, 3.2 mmol) at 120 °C for 20 min: pale-yellow solid (127 mg, 57%); mp 214−215 °C; MS m/z 281.4, calcd 281.3 (M + 1); IR (KBr) ν 3340, 3180, 1610, 1560, 1500, 1450, 1400 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.79 (s, 3H, OMe), 3.89 (s, 2H, CH_2), 6.18 (br s, 2H, 2-NH_2), 6.85 (t, J = 7.2 Hz, 1H, H-5′), 6.96 (d, J = 8.4 Hz, 1H, H-3′), 7.05 (d, J = 7.2 Hz, 1H, H-6′), 7.13 (d, J = 8.4 Hz, 1H, H-8), 7.18 (t, J = 7.6 Hz, 1H, H-4′), 7.34 (d, J = 8.4 Hz, 1H, H-7), 7.43 (br s, 2H, 4-NH_2), 7.89 (s, 1H, H-5). Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.73; N, 19.99. Found: C, 68.34; H, 5.58; N, 20.09.

2,4-Diamino-6-(3′-methoxybenzyl)quinazoline (8h). Compound **8h** was obtained from **10h** (238 mg, 1 mmol) and chloroformamidine hydrochloride (456 mg, 4 mmol) at 120 °C for 20 min: pale-yellow needles (124 mg, 60%); mp 207−209 °C; MS m/z 281.4, calcd 281.3 (M + 1); IR (KBr) ν 3415, 3350, 3110, 1650, 1600, 1550, 1500, 1425 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.71 (s, 3H, OMe), 3.89 (s, 2H, CH_2), 6.03 (br s, 2-NH_2), 6.75 (d, J = 7.2 Hz, 1H, H-4′ or H-6′), 6.80 (d, J = 7.2 Hz, 1H, H-4′ or H-6′), 6.81 (s, 1H, H-2′), 7.13 (d, J = 8.8 Hz, 1H, H-8), 7.19 (t, J = 7.6 Hz, 1H, H-5′), 7.32 (br s, 2H, 4-NH_2), 7.37 (d, J = 8.4 Hz, 1H, H-7), 7.82 (s, 1H, H-5). Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.73; N, 19.99. Found: C, 68.34; H, 5.91; N, 19.91.

2,4-Diamino-6-(4′-methoxybenzyl)quinazoline (8i). Compound **8i** was obtained from **10i** (238 mg, 1 mmol) and chloroformamidine hydrochloride (456 mg, 4 mmol) at 120 °C for 20 min: pale-yellow needles (124 mg, 60%); mp 207−209 °C; MS m/z 281.4, calcd 281.2 (M + 1); IR (KBr) ν 3420, 3340, 3120, 1600, 1560, 1500, 1400 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.70 (s, 3H, OMe), 3.86 (s, 2H, CH_2), 5.87 (br s, 2H, 2-NH_2), 6.84 (d, J = 8.0 Hz, 2H, H-3′ and H-5′), 7.10 (d, J = 8.4, 1H, H-8), 7.14 (d, J = 8.0 Hz, 2H, H-2′ and H-6′), 7.18 (br s, 2H, 4-NH_2), 7.27 (d, J = 8.8 Hz, 1H, H-7), 7.87 (s, 1H, H-5). Anal. Calcd for $C_{16}H_{16}N_4O$: C, 68.55; H, 5.73; N, 19.99. Found: C, 68.62; H, 5.53; N, 20.12.

2,4-Diamino-6-(2′,5′-dimethoxybenzyl)quinazoline (8j). Compound **8j** was obtained from **10j** (120 mg, 0.45 mmol) and chloroformamidine hydrochloride (204 mg, 1.8 mmol) at 120 °C for 20 min: white crystals (65 mg, 46%); mp 190−192 °C; MS m/z 311.2, calcd 311.4 (M + 1); IR (KBr) ν 3360, 3180, 1610, 1560, 1490, 1440, 1400 cm^{-1}; ^{1}H NMR (DMSO-d_6) δ 3.64 (s, 3H, OMe), 3.73 (s, 3H, OMe), 3.85 (s, 2H, CH_2), 5.81 (br s, 2H, 2-NH_2), 6.65 (d, J = 3.2 Hz, 1H, H-6′), 6.73 (dd, J = 9.0, 3.2 Hz, 1H, H-4′), 6.88 (d, J = 9.0 Hz, 1H, H-3′), 7.10 (d, J = 8.6, 1H, H-8), 7.15 (br s, 2H, 4-NH_2), 7.35 (dd, *J* = 8.6, 2.0 Hz, 1H, H-7), 7.84 (d, *J* = 2.0 Hz, 1H, H-5). Anal. Calcd for $C_{17}H_{18}N_4O_2\cdot 0.3H_2O$: C, 64.66; H, 5.94; N, 17.74. Found: C, 64.62; H, 5.71; N, 17.74.

2,4-Diamino-6-(3′,4′-dimethoxybenzyl)quinazoline (8k). Compound **8k** was obtained from **10k** (120 mg, 0.45 mmol) and chloroformamidine hydrochloride (204 mg, 1.8 mmol) at 120 °C for 20 min: white crystals (61 mg, 43%); mp 215−217 °C; MS *m*/*z* 311.2, calcd 311.4 (M + 1); IR (KBr) ν 3350, 3180, 1610, 1550, 1500, 1440, 1400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.70 (s, 3H, OMe), 3.71 (s, 3H, OMe), 3.85 (s, 2H, CH_2), 5.85 (br s, 2H, 2-NH_2), 6.70 (dd, *J* = 8.2 Hz, 1.8 Hz, 1H, H-6′), 6.84 (dd, *J* = 1.8 Hz, 1H, H-2′), 6.86 (d, *J* = 8.2 Hz, 1H, H-5′), 7.11 (d, *J* = 8.6, 1H, H-8), 7.18 (br s, 2H, 4-NH_2), 7.33 (dd, *J* = 8.6 Hz, 1.8 Hz, 1H, H-7), 7.88 (d, *J* = 1.8 Hz, 1H, H-5). Anal. Calcd for $C_{17}H_{18}N_4O_2\cdot 0.3H_2O$: C, 64.66; H, 5.94; N, 17.74. Found: C, 64.35; H, 5.70; N, 17.78.

2,4-Diamino-6-(3′,5′-dimethoxybenzyl)quinazoline (8l). Compound **8l** was obtained from **10l** (120 mg, 0.45 mmol) and chloroformamidine hydrochloride (204 mg, 1.8 mmol) at 120 °C for 20 min: white crystals (57 mg, 41%); mp 230−232 °C; MS *m*/*z* 311.2, calcd 311.4 (M + 1); IR (KBr) ν 3360, 3160, 1610, 1560, 1490, 1450, 1400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.69 (s, 6H, OMe), 3.84 (s, 2H, CH_2), 5.84 (br s, 2H, 2-NH_2), 6.31 (t, *J* = 2.4 Hz, 1H, H-4′), 6.39 (d, *J* = 2.4 Hz, 2H, H-2′ and H-6′), 7.11 (d, *J* = 8.6 Hz, 1H, H-8), 7.17 (br s, 2H, 4-NH_2), 7.34 (dd, *J* = 8.6, 2.0 Hz, 1H, H-7), 7.88 (d, *J* = 2.2 Hz, 1H, H-5). Anal. Calcd for $C_{17}H_{18}N_4O_2$: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.53; H, 5.67; N, 18.12.

2,4-Diamino-6-(3′,4′,5′-trimethoxybenzyl)quinazoline (8m). Compound **8m** was obtained from **10m** (82 mg, 0.28 mmol) and chloroformamidine hydrochloride (125 mg, 1.1 mmol) at 120 °C for 15 min: white crystals (47 mg, 49%); mp 219−221 °C; MS *m*/*z* 341.2, calcd 341.4 (M + 1); IR (KBr) ν 3380, 3180, 1620, 1560, 1500, 1450, 1400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 3.59 (s, 3H, 4′-OMe), 3.71 (s, 6H, 3′-OMe and 5′-OMe), 3.84 (s, 2H, CH_2), 5.83 (br s, 2H, 2-NH_2), 6.54 (s, 2H, H-2′ and H-6′), 7.10 (d, *J* = 8.6 Hz, 1H, H-8), 7.14 (br s, 2H, 4-NH_2), 7.35 (dd, *J* = 8.6, 2.0 Hz, 1H, H-7), 7.88 (s, 1H, H-5). Anal. Calcd for $C_{18}H_{20}N_4O_3\cdot 0.3H_2O$: C, 62.52; H, 6.00; N, 16.20. Found: C, 62.14; H, 5.90; N, 16.13.

2,4-Diamino-6-(2-naphthylmethyl)quinazoline (8n). Compound **8n** was obtained from **10n** (172 mg, 0.66 mmol) and chloroformamidine hydrochloride (300 mg, 2.64 mmol) at 120 °C for 20 min: white crystals (90 mg, 45%); mp 256−257 °C; MS *m*/*z* 301.3, calcd 301.4 (M + 1); IR (KBr) ν 3340, 3180, 1615, 1565, 1510, 1445, 1400 cm^{-1}; ^1H NMR (DMSO-d_6) δ 4.04 (s, 2H, CH_2), 5.86 (br s, 2H, 2-NH_2), 7.09 (d, *J* = 8.2 Hz, 1H, H-8), 7.15 (br s, 2H, 4-NH_2), 7.33−7.46 (m, 4H, H-4′, H-5′, H-8′, and H-7), 7.70 (s, 1H, H-1′), 7.78−7.85 (m, 3H, H-3′, H-6′, and H-7′), 7.93 (d, *J* = 2.0 Hz, 2H, H-5). Anal. Calcd for $C_{19}H_{16}N_4\cdot 0.3H_2O$: C, 74.63; H, 5.47; N, 18.32. Found: C, 74.27; H, 5.37; N, 18.52.

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