

Synthesis of 2-(2-Aminophenyl)-4-arylquinazoline Derivatives by Reaction of 2-Aminoarylbenzimidamides with Isatoic Anhydride

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Z. Naturforsch. **2009**, *64b*, 945–951; received April 30, 2009

A series of 2-(2-aminophenyl)-4-arylquinazoline derivatives (**5a–j**), with various 4-substituents, have been synthesized by one-pot cyclization in 66–79 % yield by heating 2-aminoarylbenzimidamides **3a–j** with isatoic anhydride (**4**). The high yield and simplified workup procedure, in addition to the neutral reaction conditions, are the main advantages of our approach. The structure of the product **5e** was further confirmed by single-crystal X-ray structure analysis.

Key words: Aminoarylbenzimidamides, Cycloaddition, Isatoic Anhydride, Quinazolines

Introduction

Quinazoline derivatives constitute an important class of heterocyclic compounds; they form a large number of products with a broad spectrum of biological activities, such as hypnotic, antibacterial, anticancer, analgesic, antiallergic, anticonvulsant, antimalarial, antidiabetic, and other effects [1–7]. For this reason their synthesis has received considerable attention. Quinazoline derivatives can be prepared by heating isatoic anhydride with diamines [8] or by condensing 2-aminobenzimidamides with aldehydes [9,10]. Recently, quinazoline derivatives have been obtained by heating 2-aminobenzamides with aldehydes [11], or by heating isatoic anhydride with azomethines [12] or aldehydes in the presence of ammonium acetate [13]. Heterocyclization of aminobenzimidamides with isatoic anhydride, however, has been largely overlooked.

Results and Discussion

2-Aminoarylbenzimidamides **3a–j** used in this study were made in good yields by treatment of 2-aminobenzonitrile (**1**) with aniline derivatives **2a–i** in the presence of aluminum chloride as a catalyst (Scheme 1) and were fully characterized by spectral as well as X-ray structural analyses [14].

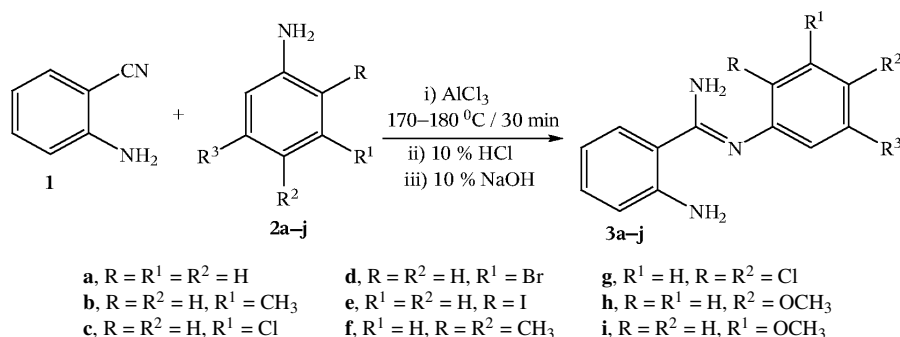
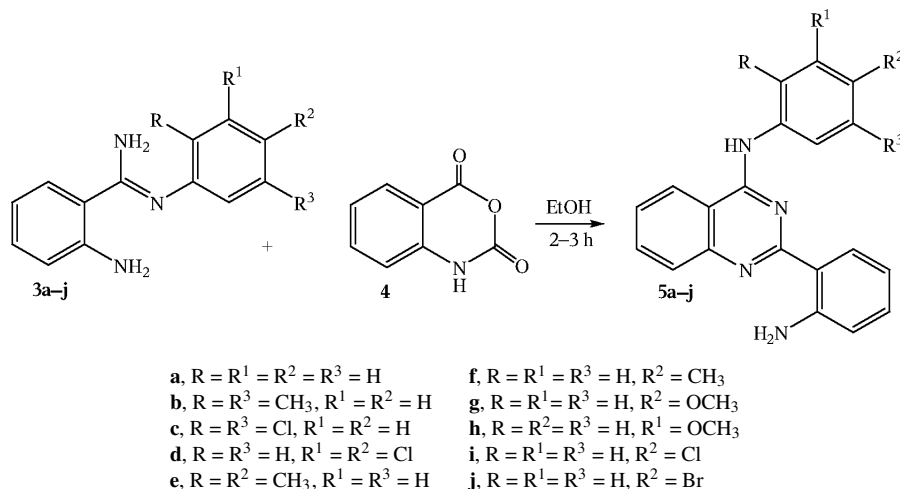
High yields of 2-aminoarylbenzimidamides **3a–j** were obtained by using equimolar ratios of the reactants at 170–180 °C [14]. Most of the known syn-

theses of quinazoline derivatives, such as those using various catalysts such as Yb(OTf)₃ [15], Nafion-H [16], Bi(TFA)₃-FeCl₃ [17], silica gel/FeCl₃ [18], La(NO₃)₃·6H₂O [19], and KAl(SO₄)₂·12H₂O [20] require either reflux for several hours in a large volume of solvent, or the use of an expensive catalyst. Continuing our work on the synthesis of 2,4-disubstituted quinazoline derivatives, in this report we describe the reaction of 2-aminobenzimidamides **3a–j** with isatoic anhydride (**4**) as a simple approach for 2,4-disubstituted quinazolines. We found that heating equimolar ratios of 2-aminoarylbenzimidamides **3a–j** with isatoic anhydride (**4**) in absolute ethanol for 2–3 h yielded 2-(2-aminophenyl)-4-arylquinazoline derivatives **5a–j** in 66–79 % yield (Scheme 2).

The formation of the products **5a–j** can be rationalized according to the pathway shown in Scheme 3.

With regard to the reaction mechanism, we propose that the condensation reaction begins with a decarboxylation of **4** to the *ortho*-quinoid intermediate **6**. This iminoketene can subsequently be attacked by **3a–j** yielding intermediates **7**, which could cyclize to **8** by loss of water. Two hydrogen shift processes would finally lead to the formation of **5**, the driving force being largely provided by rearomatization.

The structures of the products **5a–j** were fully characterized and elucidated on the basis of spectral and analytical data. The structure of the selected example **5e** was further confirmed by X-ray structural analysis, as shown in Fig. 1. The bicyclic system is essentially

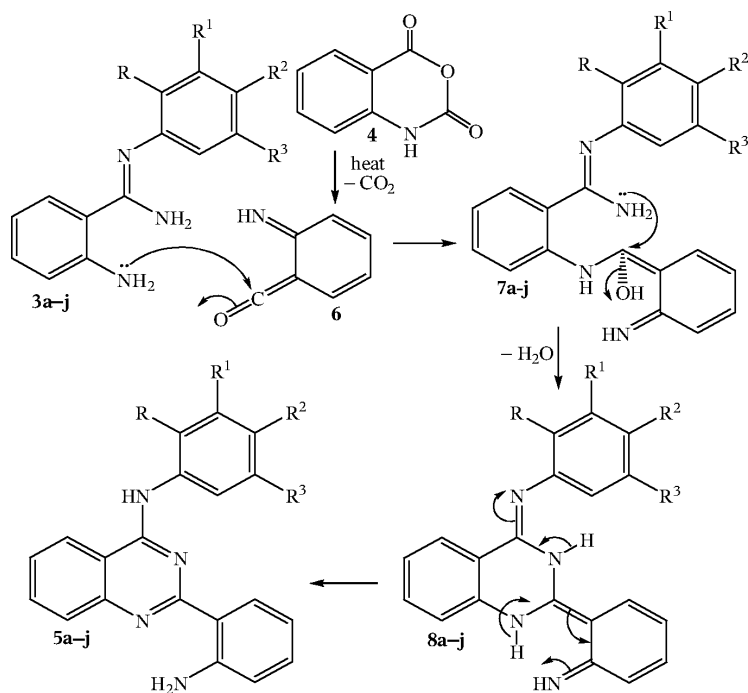
Scheme 1. Synthesis of 2-aminoarylbenzimidamides **3a-j**.Scheme 2. Reaction of 2-aminoarylbenzimidamides **3a-j** with isatoic anhydride (**4**).

planar (mean deviation 0.05 Å) and subtends angles of 13° and 63° to the rings C11–16 and C22–26, respectively. The near-coplanarity to C11–16 is connected with the intramolecular hydrogen bond N18···N1. The other two NH functions form intermolecular hydrogen bonds N18···N3' and N19···N1', which serve to connect the molecules to layers parallel to the crystallographic *yz* plane.

The detailed spectral data are given in the Experimental Section, and only the salient features are discussed here.

The IR spectra of compounds **5a-j** show, besides the absorption at $\nu = 1617-1605\text{ cm}^{-1}$ corresponding to the C=N group, three distinguishable absorptions in the range $\nu = 3489-3211\text{ cm}^{-1}$ related to both NH and NH₂ groups. The protons of these groups resonate in the ¹H NMR spectrum at $\delta = 10.50-7.00\text{ ppm}$. Taking **5j** as an example, its ¹H NMR spectrum ex-

hibits two doublets at $\delta = 7.89$ and 7.66 ppm with coupling constants $\approx 8.90\text{ Hz}$ corresponding to the 1,4-disubstituted aromatic moiety (H-19,23 and H-20,22); 8-H displays a doublet at $\delta = 8.29\text{ ppm}$ with $J = 8.29\text{ Hz}$, and the protons H-16,15,14,13 appear as multiplets at $\delta = 7.63-7.57, 7.17-7.11, 6.79-6.76, 6.64-6.58\text{ ppm}$, respectively. The rest of the aromatic protons resonate in the ¹H NMR spectrum as one doublet of doublets at $\delta = 8.32-8.29\text{ ppm}$ ($J = 1.51, 8.06\text{ Hz}$) and one doublet at $\delta = 7.86\text{ ppm}$ ($J = 3.80\text{ Hz}$) related to 5-H and 6,7-H, respectively. The ¹³C NMR spectrum exhibits twenty distinct resonances in agreement with the quinazoline derivative **5j**. Twelve of them are secondary, and the rest are quaternary carbon atoms. Two of the quaternary carbon atoms resonate at $\delta = 161.14$ and 156.81 ppm characteristic for C-4 and C-2, respectively; C-11 appears at $\delta = 113.12\text{ ppm}$, and the four secondary 1,4-disubstituted aromatic car-



Scheme 3. Rational pathway for the formation of the products **5a–j**.

bon atoms (C-20,22,19,23) resonate at $\delta = 131.31$, 124.31 ppm. The IR, ¹H NMR and ¹³C NMR spectra of **5i** are similar to those of **5j** (see Experimental Section). Both mass spectra and elemental analyses confirm the molecular formulae of the products **5a–j**.

Conclusion

New heterocyclic systems, which might possess interesting biological properties, have been synthesized. Herein we report a simple and efficient one-pot synthesis of 2-(2-aminophenyl)-*N*-arylquinazolin-4-amine derivatives under mild conditions with good yield. In all cases the reaction of two components proceeded rapidly to afford the corresponding desired products.

The structure of the selected example **5e** was elucidated by single X-ray structural analysis. The mechanism of formation of the obtained products **5a–j** has been rationalized.

Experimental Section

Starting materials

All reagents were purchased from Alfa Aesar, Fluka, Acros, and Aldrich companies and were used without further purification. 2-Aminoarylbenzimidamide derivatives **3a–j** were prepared according to ref. [14]. Melting points were

measured in capillary tubes without corrections using a Büchi 530 melting point apparatus. IR spectra were run as KBr discs using a Bruker Tensor 27 instrument. The NMR spectra were recorded on a Bruker AM 400 MHz spectrometer with TMS as internal standard; the coupling constants are given in Hz. The mass spectra (EI, 70 eV) were performed using a Finnigan MAT 8430 spectrometer.

Reactions of 2-aminoarylbenzimidamides **3a–j** with isatoic anhydride (**4**)

General procedure

In a three-necked flask fitted with a reflux condenser a solution of 0.25 mmol of 2-aminoarylbenzimidamides **3a–j** in 15 mL of absolute ethanol was added dropwise under nitrogen to a solution of 0.25 mmol of isatoic anhydride (**4**) in 20 mL of absolute ethanol at r.t. The reaction mixture was heated under gentle reflux for 2–3 h. The progress of the reaction was monitored by TLC, and after completion, the mixture was cooled to r.t. The solvent was removed under reduced pressure, and the residue was purified by silica gel chromatography using ethyl acetate / *n*-pentane (3 : 1) as the eluent to give the desired products as off-white to yellow solids in 66–79 % yield.

2-(2-Aminophenyl)-*N*-phenylquinazolin-4-amine (**5a**)

Colorless solid, 55 mg (70 %), m.p. 179–181 °C. – IR (film): $\nu = 3489, 3354, 3263$ (NH, NH₂), 1676, 1611

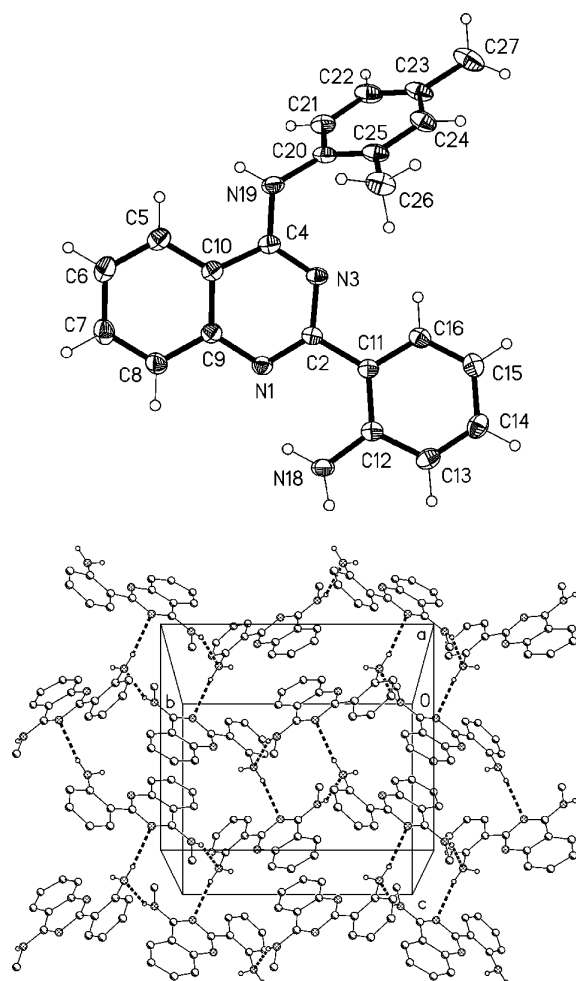


Fig. 1. Crystal and molecular structure of compound **5e**. Above: ellipsoid representation (50 % level) of the molecular structure. Below: packing diagram showing the layers formed by hydrogen bonds of the type N–H···N (xylol groups are reduced to the *ipso* carbon atoms for clarity).

(C=N), 1570, 1513 cm^{-1} (C=C). – ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 9.90 (s, 1 H, NH), 8.00–7.72 (m, 4 H), 7.62–7.56 (m, 1 H), 7.42 (s, 2 H, NH_2), 7.31–7.05 (m, 3 H), 6.93–6.76 (m, 2 H), 6.71–6.53 (m, 3 H). – ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): δ = 167.33 (C-4), 157.01 (C-2), 151.25 (C-9), 149.96 (C-12), 139.16 (C-18), 134.37 (CH, C-7), 133.84 (CH, C-20), 133.03 (CH, C-22), 130.50 (CH, C-14), 128.44 (CH, C-5), 127.38 (CH, C-8), 126.07 (CH, C-13), 125.34 (CH, C-19), 123.75 (CH, C-23), 122.90 (CH, C-6), 122.57 (CH, C-21), 117.62 (C-10), 116.43 (CH, C-16), 114.62 (CH, C-15), 113.09 (C-11). – MS (EI, 70 eV): m/z (%) = 312 (80) $[\text{M}]^+$, 311 (100) $[\text{M}-1]^+$, 294 (8) $[\text{M}-\text{NH}_3]^+$, 270 (2), 237 (30) $[\text{M}-\text{Ph}]^+$, 220 (18) $[\text{M}-\text{PhNH}_2]^+$, 194 (56), 178 (4), 166 (16), 156 (12), 139 (8), 119 (26), 102

(10), 92 (28), 77 (20). – $\text{C}_{20}\text{H}_{16}\text{N}_4$ (312.37): calcd. C 76.90, H 5.16, N 17.94; found C 76.67, H 5.11, N 17.70.

2-(2-Aminophenyl)-N-(2,5-dimethylphenyl)quinazolin-4-amine (5b)

Pale-yellow solid, 63 mg (74 %), m. p. 123–124 $^\circ\text{C}$. – IR (film): ν = 3459, 3369, 3292 (NH, NH_2), 1682, 1612 (C=N), 1568, 1553 cm^{-1} (C=C). – ^1H NMR (400 MHz, CDCl_3): δ = 8.34–8.29 (dd, 1 H, J = 1.61, 8.05 Hz), 7.79–7.72 (m, 2 H), 7.64–7.57 (m, 1 H), 7.51 (br, s, 1 H, NH), 7.33–7.25 (m, 1 H), 7.19–7.03 (m, 2 H), 6.89–6.82 (m, 1 H), 6.65–6.57 (m, 3 H), 4.83 (br, s, 2 H, NH_2), 2.24 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3). – ^{13}C NMR (100 MHz, CDCl_3): δ = 162.29 (C), 157.94 (C), 149.55 (C), 136.98 (C), 136.73 (C), 134.46, 133.24 (CH), 131.66 (2 CH), 130.96 (CH), 129.68 (CH), 128.93 (CH), 127.01 (CH), 126.47 (CH), 125.97 (CH), 121.22 (CH), 120.15 (C), 117.55 (C), 116.69 (CH), 113.50 (C), 21.52 (CH_3), 18.81 (CH_3). – MS (EI, 70 eV): m/z (%) = 340 (68) $[\text{M}]^+$, 324 (4) $[\text{M}-\text{NH}_2]^+$, 309 (18) $[\text{M}-\text{CH}_3+\text{NH}_2]^+$, 294 (10), 272 (20), 245 (12), 220 (16), 192 (16), 166 (12), 155 (34), 141 (8), 118 (16), 92 (20), 75 (12). – $\text{C}_{22}\text{H}_{20}\text{N}_4$ (340.42): calcd. C 77.62, H 5.92, N 16.46; found C 77.39, H 5.90, N 16.26.

2-(2-Aminophenyl)-N-(2,5-dichlorophenyl)quinazolin-4-amine (5c)

Colorless solid, 66 mg (69 %), m. p. 243–245 $^\circ\text{C}$. – IR (film): ν = 3474, 3410, 3352 (NH, NH_2), 1659, 1602 (C=N), 1572, 1513 cm^{-1} (C=C). – ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 10.27 (s, 1 H, NH), 8.75–8.72 (dd, 1 H, J = 0.98, 8.41 Hz, 8-H), 8.55 (d, 1 H, J = 7.46 Hz, 5-H), 8.25–8.22 (dd, 1 H, J = 1.61, 8.06 Hz, 6-H), 8.02–7.97 (m, 1 H, 7-H), 7.90 (d, 1 H, J = 2.55 Hz, 19-H), 7.73 (d, 1 H, J = 8.65 Hz, 22-H), 7.53–7.49 (dd, 1 H, J = 2.54, 8.61 Hz, 21-H), 7.50–7.46 (m, 1 H, 16-H), 7.36 (m, 1 H, 14-H), 7.13–7.08 (m, 1 H, 15-H), 6.88–6.79 (m, 1 H, 13-H), 6.56 (s, 2 H, NH_2). – ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): δ = 167.74 (C-4), 159.97 (C-2), 150.23 (C-20), 148.25 (C-23), 140.15 (C-9), 137.04 (C-12), 132.60 (CH, C-7), 131.48 (CH, C-21), 131.07 (CH, C-22), 129.44 (CH, C-19), 128.07 (C-18), 127.62 (CH, C-14), 126.92 (CH, C-5), 123.00 (CH, C-8), 122.28 (CH, C-13), 119.90 (CH, C-6), 116.94 (CH, C-16), 115.19 (C-10), 114.99 (CH, C-15), 113.03 (C-11). – MS (EI, 70 eV): m/z (%) = 384 (8) $[\text{M}+4]^+$, 382 (42) $[\text{M}+2]^+$, 380 (78) $[\text{M}]^+$, 364 (4) $[\text{M}-\text{NH}_2]^+$, 329 (10) $[\text{M}-\text{Cl}+\text{NH}_2]^+$, 294 (12), 272 (24), 245 (12), 220 (16), 192 (16), 166 (12), 155 (34), 141 (8), 118 (16), 92 (20), 75 (12). – $\text{C}_{20}\text{H}_{14}\text{Cl}_2\text{N}_4$ (381.26): calcd. C 63.01, H 3.70, Cl 18.60, N 14.70; found C 62.82, H 3.63, Cl 18.34, N 14.53.

2-(2-Aminophenyl)-N-(3,4-dichlorophenyl)quinazolin-4-amine (5d)

Colorless solid, 64 mg (67 %), m. p. 203–205 $^\circ\text{C}$. – IR (film): ν = 3340, 3367, 3208 (NH, NH_2), 1667, 1610 (C=N),

1568, 1548, 1511 cm^{-1} (C=C). – ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 9.97 (s, 1 H, NH), 8.51 (d, 1 H, J = 8.27 Hz, 19-H), 8.42 (d, 1 H, J = 2.40 Hz, 22-H), 8.34–8.29 (dd, 1 H, J = 1.50, 8.10 Hz, 18-H), 7.87–7.83 (m, 2 H), 7.47 (br, s, 2 H, NH_2), 7.23–7.14 (m, 2 H), 6.86–6.82 (m, 2 H), 6.64–6.56 (m, 2 H). – ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): δ = 160.98 (C), 156.59 (C), 150.09 (C), 149.51 (C), 139.53 (C), 133.37 (CH), 131.08 (C), 130.68 (CH), 130.33 (CH), 130.25 (CH), 127.54 (CH), 125.71 (CH), 124.73 (C), 123.27 (CH), 122.84 (CH), 121.79 (CH), 117.33 (C), 116.54 (CH), 114.69 (CH), 113.66 (C). – MS (EI, 70 eV): m/z (%) = 384 (10) $[\text{M}]^{+4}$, 382 (52) $[\text{M}]^{+2}$, 380 (86) $[\text{M}]^{+}$, 364 (4) $[\text{M}-\text{NH}_2]^{+}$, 330 (30) $[\text{M}-(\text{Cl}+\text{NH}_2)]^{+}$, 294 (4), 261 (24), 245 (12), 220 (6), 192 (10), 166 (12), 155 (24), 141 (18), 118 (16), 92 (12), 75 (8). – $\text{C}_{20}\text{H}_{14}\text{Cl}_2\text{N}_4$ (381.26): calcd. C 63.01, H 3.70, Cl 18.60, N 14.70; found C 62.78, H 3.67, Cl 18.39, N 14.46.

2-(2-Aminophenyl)-N-(2,4-dimethylphenyl)quinazolin-4-amine (5e)

Pale-yellow solid, 65 mg (76 %), m.p. 155–157 °C. – IR (film): ν = 3431, 3376, 3226 (NH, NH_2), 1684, 1611 (C=N), 1574, 1504 cm^{-1} (C=C). – ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 9.71 (s, 1 H, NH), 8.52 (d, 1 H, J = 8.09 Hz, 8-H), 8.22 (d, 1 H, J = 7.00 Hz, 5-H), 7.81 (d, 1 H, J = 3.71 Hz, 22-H), 7.77–7.73 (m, 1 H, 7-H), 7.57–7.49 (m, 1 H, 6-H), 7.33 (d, 1 H, J = 7.88 Hz, 19-H), 7.26–7.21 (m, 1 H, 20-H), 7.15 (d, 1 H, J = 7.73 Hz, 16-H), 7.10 (br, s, 2 H, NH_2), 6.81 (d, 1 H, J = 8.47 Hz, 14-H), 6.75–6.70 (m, 1 H, 15-H), 6.60–6.46 (m, 1 H, 13-H), 2.35 (s, 3 H, CH_3), 2.12 (s, 3 H, CH_3). – ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): δ = 167.36 (C-4), 161.38 (C-2), 158.21 (C-9), 151.29 (C-12), 149.91 (C-18), 135.34 (C-10), 134.55 (C-23), 133.83 (CH, C-7), 131.09 (CH, C-14), 130.66 (CH, C-5), 130.53 (CH, C-8), 128.22 (CH, C-13), 127.26 (CH, C-6), 126.75 (C-21), 122.94 (CH, C-20), 117.77 (CH, C-19), 116.45 (CH, C-22), 114.62 (CH, C-16), 112.77 (CH, C-15), 108.93 (C-11), 20.60 (CH_3), 17.88 (CH_3). – MS (EI, 70 eV): m/z (%) = 341 (30) $[\text{M}]^{+1}$, 340 (100) $[\text{M}]^{+}$, 324 (8) $[\text{M}-\text{NH}_2]^{+}$, 309 (30) $[\text{M}-(\text{CH}_3+\text{NH}_2)]^{+}$, 294 (6), 272 (40), 245 (2), 220 (16), 192 (16), 166 (12), 155 (34), 141 (8), 118 (16), 92 (20), 75 (12). – $\text{C}_{22}\text{H}_{20}\text{N}_4$ (340.42): calcd. C 77.62, H 5.92, N 16.46; found C 77.41, H 5.87, N 16.28.

2-(2-Aminophenyl)-N-p-tolylquinazolin-4-amine (5f)

Colorless solid, 62 mg (76 %), m.p. 159–160 °C. – IR (film): ν = 3357, 3287, 3211 (NH, NH_2), 1608 (C=N), 1573, 1552, 1511 cm^{-1} (C=C). – ^1H NMR (400 MHz, $[\text{D}_6]\text{DMSO}$): δ = 9.77 (s, 1 H, NH), 8.51 (d, 1 H, J = 8.33 Hz, 8-H), 8.33–8.30 (dd, 1 H, J = 1.59, 8.07 Hz, 5-H), 7.87–7.81 (m, 2 H, 6,7-H), 7.73 (d, 2 H, J = 8.40 Hz, 20,22-H), 7.58–7.53 (m, 1 H, 16-H), 7.36 (br, s, 2 H, NH_2), 7.26 (d, 2 H, J = 8.26 Hz, 19,23-H), 7.14–7.09 (m, 1 H, 14-H),

6.77–6.74 (dd, 1 H, J = 1.01, 8.17 Hz, 15-H), 6.61–6.54 (m, 1 H, 13-H), 2.35 (s, 3 H, CH_3). – ^{13}C NMR (100 MHz, $[\text{D}_6]\text{DMSO}$): δ = 161.30 (C-4), 157.05 (C-2), 150.01 (C-9), 149.51 (C-12), 136.56 (C-18), 133.06 (CH, C-7), 132.91 (CH, C-14), 130.87 (CH, C-5), 130.48 (CH, C-8), 128.97 (2 CH, C-20,22), 127.44 (CH, C-13), 125.36 (CH, C-6), 122.90 (CH, C-16), 122.69 (2 CH, C-19,23), 117.68 (C-21), 116.42 (C-10), 114.60 (CH, C-15), 113.11 (C-11), 20.57 (CH_3). – MS (EI, 70 eV): m/z (%) = 326 (100) $[\text{M}]^{+}$, 325 (86) $[\text{M}-1]^{+}$, 309 (4) $[\text{M}-\text{NH}_3]^{+}$, 232 (8) $[\text{M}-\text{PhNH}_2]^{+}$, 220 (12), 208 (48), 192 (16), 180 (8), 163 (16), 129 (4), 118 (16), 102 (4), 92 (16), 75 (12). – $\text{C}_{21}\text{H}_{18}\text{N}_4$ (326.39): calcd. C 77.28, H 5.56, N 17.17; found C 77.02, H 5.51, N 16.94.

2-(2-Aminophenyl)-N-(4-methoxyphenyl)quinazolin-4-amine (5g)

Brown solid, 60 mg (70 %), m.p. 131–133 °C. – IR (film): ν = 3385, 3277, 3243 (NH, NH_2), 1610 (C=N), 1559, 1535, 1505 cm^{-1} (C=C). – ^1H NMR (400 MHz, CDCl_3): δ = 7.92–7.86 (m, 2 H), 7.77–7.62 (m, 2 H), 7.49–7.42 (m, 1 H), 7.44 (br, s, 1 H, NH), 7.31–7.22 (m, 2 H), 7.01–6.93 (m, 1 H), 6.79–6.62 (m, 4 H), 5.71 (br, s, 2 H, NH_2), 3.73 (s, 3 H, OCH_3). – ^{13}C NMR (100 MHz, CDCl_3): δ = 162.03 (C-4), 151.75 (C-2), 150.39 (C-21), 147.15 (C-9), 140.43 (C-12), 139.52 (C-18), 134.65 (C-10), 133.93 (CH, C-7), 131.19 (2 CH, C-19,23), 127.09 (CH, C-14), 126.40 (CH, C-5), 124.16 (CH, C-8), 122.27 (CH, C-13), 116.63 (2 CH, C-20,22), 116.19 (CH, C-6), 114.78 (CH, C-16), 114.14 (CH, C-15), 109.36 (C-11), 55.70 (OCH_3). – MS (EI, 70 eV): m/z (%) = 342 (62) $[\text{M}]^{+}$, 325 (4) $[\text{M}-\text{NH}_3]^{+}$, 294 (4) $[\text{M}-(\text{NH}_2+\text{OCH}_3)]^{+}$, 251 (6) $[\text{M}-\text{PhNH}_2]^{+}$, 192 (10), 163 (8), 129 (4), 118 (16), 102 (4), 92 (16), 75 (12). – $\text{C}_{21}\text{H}_{18}\text{N}_4\text{O}$ (342.39): calcd. C 73.67, H 5.30, N 16.36; found C 77.43, H 5.23, N 16.12.

2-(2-Aminophenyl)-N-(3-methoxyphenyl)quinazolin-4-amine (5h)

Pale-brown solid, 58 mg (68 %), m.p. 93–95 °C. – IR (film): ν = 3378, 3287, 3253 (NH, NH_2), 1615 (C=N), 1545, 1523, 1500 cm^{-1} (C=C). – ^1H NMR (400 MHz, CDCl_3): δ = 7.79–7.68 (m, 2 H), 7.66–7.60 (m, 2 H), 7.53–7.48 (m, 1 H), 7.47 (br, s, 1 H, NH), 7.31–7.22 (m, 2 H), 7.01–6.93 (m, 1 H), 6.79–6.62 (m, 4 H), 5.73 (br, s, 2 H, NH_2), 3.79 (s, 3 H, OCH_3). – ^{13}C NMR (100 MHz, CDCl_3): δ = 161.32 (C-4), 151.57 (C-2), 151.43 (C-21), 147.61 (C-9), 141.03 (C-12), 139.52 (C-18), 134.65 (C-10), 133.93 (CH, C-7), 131.19 (2 CH, C-19,23), 127.09 (CH, C-14), 126.40 (CH, C-5), 124.16 (CH, C-8), 122.27 (CH, C-13), 116.63 (2 CH, C-20,22), 116.19 (CH, C-6), 114.78 (CH, C-16), 114.14 (CH, C-15), 109.36 (C-11), 55.89 (OCH_3). – MS (EI, 70 eV): m/z (%) = 342 (40) $[\text{M}]^{+}$, 326 (12) $[\text{M}-\text{NH}_2]^{+}$, 296 (4), 250 (8) $[\text{M}-\text{PhNH}_2]^{+}$, 220 (2), 208 (6), 192 (12), 182

(8), 160 (16), 129 (4), 118 (16), 102 (4), 92 (16), 75 (12). – $C_{21}H_{18}N_4O$ (342.39): calcd. C 73.67, H 5.30, N 16.36; found C 77.49, H 5.26, N 16.17.

2-(2-Aminophenyl)-N-(4-chlorophenyl)quinazolin-4-amine (5i)

Colorless solid, 57 mg (66 %), m. p. 195–196 °C. – IR (film): ν = 3352, 3270, 3211 (NH, NH₂), 1607 (C=N), 1571, 1552, 1512 cm⁻¹ (C=C). – ¹H NMR (400 MHz, [D₆]DMSO): δ = 9.93 (s, 1 H, NH), 8.53 (d, 1 H, J = 8.31 Hz, 8-H), 8.32–8.29 (dd, 1 H, J = 1.61, 8.08 Hz, 5-H), 7.93 (d, 2 H, J = 8.90 Hz, 20,22-H), 7.86 (d, 2 H, J = 3.65 Hz, 6,7-H), 7.62–7.57 (m, 1 H, 16-H), 7.51 (d, 2 H, J = 8.88 Hz, 19,23-H), 7.18–7.15 (m, 1 H, 14-H), 7.42 (s, 2 H, NH₂), 6.80–6.76 (dd, 1 H, J = 1.06, 8.20 Hz, 15-H), 6.63–6.57 (m, 1 H, 13-H). – ¹³C NMR (100 MHz, [D₆]DMSO): δ = 161.15 (C-4), 156.87 (C-2), 150.03 (C-9), 149.53 (C-12), 138.22 (C-18), 133.26 (CH, C-7), 130.97 (CH, C-14), 130.46 (CH, C-5), 128.41 (2 CH, C-20,22), 127.50 (C-21), 127.34 (CH, C-8), 125.56 (CH, C-13), 124.01 (2 CH, C-19,23), 122.93 (CH, C-6), 117.48 (C-10), 116.45 (CH, C-16), 114.73 (CH, C-15), 113.09 (C-11). – MS (EI, 70 eV): m/z (%) = 348 (40) [M]⁺, 346 (100) [M]⁺, 330 (2) [M–NH₂]⁺, 254 (4) [M–PhNH₂]⁺, 237 (16), 228 (50), 22 (18), 201 (4), 192 (16), 166 (12), 155 (12), 141 (8), 118 (18), 111 (8), 92 (20), 75 (10). – $C_{20}H_{15}ClN_4$ (346.81): calcd. C 69.26, H 4.36, Cl 10.22, N 16.15; found C 69.03, H 4.33, Cl 9.97, N 15.92.

2-(2-Aminophenyl)-N-(4-bromophenyl)quinazolin-4-amine (5j)

Colorless solid, 65 mg (67 %), m. p. 243–245 °C. – IR (film): ν = 3353, 3275, 3211 (NH, NH₂), 1607 (C=N), 1569, 1551, 1510 cm⁻¹ (C=C). – ¹H NMR (400 MHz, [D₆]DMSO): δ = 9.91 (s, 1 H, NH), 8.52 (d, 1 H, J = 8.29 Hz, 8-H), 8.32–8.29 (dd, 1 H, J = 1.51, 8.06 Hz, 5-H), 7.89 (d, 2 H, J = 8.90 Hz, 20,22-H), 7.86 (d, 2 H, J = 3.80 Hz, 6,7-H), 7.66 (d, 2 H, J = 8.87 Hz, 19,23-H), 7.63–7.57 (m, 1 H, 16-H), 7.43 (s, 2 H, NH₂), 7.17–7.11 (m, 1 H, 14-H), 6.79–6.76 (dd, 1 H, J = 1.33, 8.18 Hz, 15-H), 6.64–6.58 (m, 1 H, 13-H). – ¹³C NMR (100 MHz, [D₆]DMSO): δ =

161.14 (C-4), 156.81 (C-2), 150.03 (C-9), 149.52 (C-12), 138.66 (C-18), 133.27 (CH, C-7), 131.31 (2 CH, C-20,22), 130.98 (CH, C-14), 130.46 (CH, C-5), 127.50 (CH, C-8), 125.57 (CH-13), 124.31 (2 CH, C-19,23), 122.92 (CH, C-6), 117.46 (C-21), 116.45 (CH, C-16), 115.39 (C-10), 114.74 (CH, C-15), 113.12 (C-11). – MS (EI, 70 eV): m/z (%) = 392 (90) [M]⁺, 390 (100) [M]⁺, 374 (92) [M–NH₂]⁺, 309 (30) [M–HBr]⁺, 294 (4) [M–PhNH₂]⁺, 272 (40), 245 (2), 220 (16), 192 (16), 166 (12), 155 (34), 141 (8), 118 (16), 92 (20), 75 (12). – $C_{20}H_{15}BrN_4$ (391.26): calcd. C 61.39, H 3.86, N 14.32; found C 61.23, H 3.81, N 14.14.

X-Ray structure determination of 5e

Crystal data: $C_{22}H_{20}N_4$, M_r = 340.42, monoclinic, $P2_1/c$, T = –173 °C, a = 12.2795(3), b = 13.4766(3), c = 11.1640(3) Å, β = 105.739(4)°, V = 1778.22 Å³, Z = 4, $F(000)$ = 720, λ (CuK α) = 1.54184 Å, μ = 0.6 mm⁻¹, D_x = 1.272 g cm⁻³. **Data collection:** A colorless tablet, ca. 0.25 × 0.1 × 0.05 mm³, was mounted in inert oil on a glass fibre and transferred to the cold gas stream of an Oxford Diffraction Nova Atlas diffractometer. Data were recorded to 2θ = 152° and were complete to 145°. **Structure refinement:** The structure was refined using SHELXL-97 [21]. NH hydrogen atoms were refined freely; the methyl group at C26 was refined as an idealized rigid group and that at C27, rotationally disordered, as an idealized hexagon of half-occupied hydrogen positions; other H were included using a riding model. The final $wR2$ (all reflections) was 0.100 for 3681 intensities and 249 parameters, with $R1$ [$I \geq 2\sigma(I)$] = 0.036; S = 1.08, max. $\Delta\rho$ = 0.22 e Å⁻³.

CCDC 726886 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Acknowledgements

Kamal M. El-Shaieb thanks Prof. H. Hopf for the provision of laboratory facilities and valuable discussion, and the Egyptian Government for a post-doctoral fellowship and financial support.

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