A General Synthesis of 4-Arylaminoquinazoline-2-carbonitriles

Kamal M. El-Shaieb[a], Henning Hopf[b], and Peter G. Jones[c]

[a] Chemistry Department, Faculty of Science, Minia University, El-Minia, Egypt
[b] Institute of Organic Chemistry, Hagenring 30, TU Braunschweig, 38106 Braunschweig, Germany
[c] Institute of Inorganic and Analytical Chemistry, Hagenring 30, TU Braunschweig, 38106 Braunschweig, Germany

Reprint requests to Dr. Kamal M. El-Shaieb. Fax: +2-086-2342601. E-mail: kmelshaieb@yahoo.com

Z. Naturforsch. **2009**, *64b,* 858 – 864; received February 4, 2009

4-Arylaminoquinazoline-2-carbonitriles **5a** – **i** were obtained by a one-step synthesis in moderate to good yield by reacting 2-aminoarylbenzimidamides **3a** – **i** with tetracyanoethylene (TCNE, **4**) in ethyl acetate at r. t. for 4 – 6 h. The structure of the selected benzimidamide **3c** was determined by single crystal X-ray diffraction.

Key words: Aminobenzonitrile, Anilines, Cyanoquinazolines, Tetracyanoethylene

Introduction

Quinazolines are a class of heterocyclic compounds that have attracted much attention within the last decades due to their widespread application and their pharmacological importance [1 – 7]. Quinazolines generally have been obtained from amides or amidines [2, 3, 6, 10]. Although 4-arylaminoquinazoline derivatives have recently been synthesized very simply [6], there has been little progress in the study of their chemical behavior. Certain quinazoline derivatives have been efficiently prepared by condensation of acids [8] or aldehydes [9] with 2-aminoarylbenzimidamide derivatives, produced from fusing primary or secondary amines with nitriles in the presence of $AlCl_3$ as a catalyst [11 – 13]. The synthesized amidines were found to have a wide range of biological activities [14, 15].

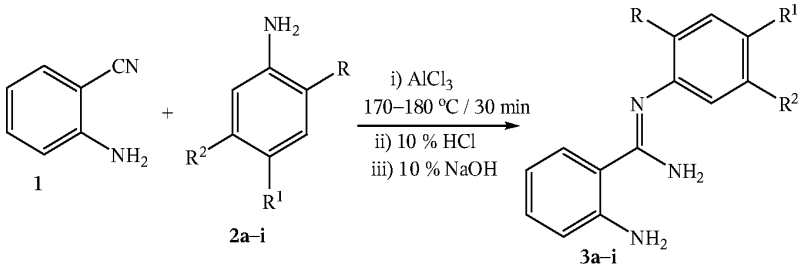
Results and Discussion

Our present work has two main goals: the first one is to improve the yield of the products obtained by the reaction of 2-aminobenzonitrile (**1**) and various aniline derivatives **2a** – **i**. In the method described in the literature [9] the yields of the respective amidines were low, and the applied protocol could not be used to synthesize alkoxy derivatives. This prompted us to synthesize various 2-aminoarylbenzimidamide derivatives **3a** – **i** containing a variety of substituents including alkoxy and dihalo moieties (Scheme 1).

This goal was achieved by diminishing the fusion time from 1 h to 20 – 30 min and lowering the reaction temperature from 200 °C to 170 – 180 °C in addition to using equimolar ratios of the reactants (see Experimental Section). The use of high temperatures and long reaction times together with excess amounts of the catalyst could lead to either formation of stable complexes between catalyst and reactants or polymerization reactions causing a lowering in yield or even absence of products, as in the case of the alkoxy-substituted compounds. Moreover, we noticed that in the literature the ^{1}H NMR data of the starting materials were measured in [D_6]DMSO and [D_6]acetone [9] although we have found that all samples dissolved easily in $CDCl_3$. Furthermore no ^{13}C NMR data have been published for all of the previously obtained samples, a gap which we also wanted to fill. The second aim of our present work was to synthesize 4-arylaminoquinazoline-2-carbonitrile derivatives **5a** – **i**, which could not be obtained by the usual protocol. To achieve this goal we reacted the obtained amidine derivatives with tetracyanoethylene (TCNE, **4**) at r. t. in ethyl acetate for 4 – 6 h (Scheme 2). The target compounds precipitated from the reaction solutions, and the products were collected by filtration and recrystallized from chloroform. This simple and efficient method made several heterocyclic compounds accessible that could not be synthesized by the usual approaches [16 – 22].

A mechanism proposed for the formation of compounds **5a** – **i** is shown in Scheme 3. The aromatic amino group attacks an olefinic carbon atom

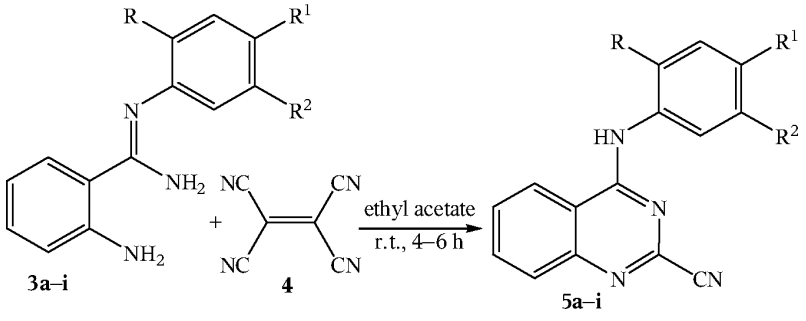
0932–0776 / 09 / 0700–0858 $ 06.00



1 2a–i 3a–i

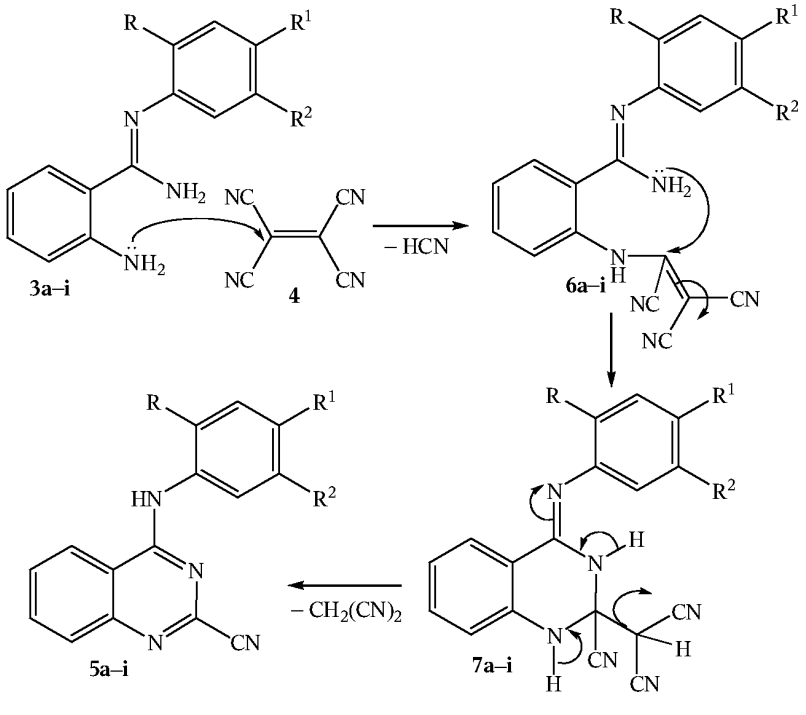
a, R = R^1 = R^2 = H
b, R = R^2 = H, R^1 = CH_3
c, R = R^2 = H, R^1 = Cl
d, R = R^2 = H, R^1 = Br
e, R^1 = R^2 = H, R = I
f, R^1 = H, R = R^2 = CH_3
g, R^1 = H, R = R^2 = Cl
h, R = R^1 = H, R^2 = OCH_3
i, R = R^2 = H, R^1 = OCH_3

Scheme 1. Synthesis of 2-aminoarylbenzimidamides **3a – i**.



3a–i 4 5a–i

Scheme 2. Synthesis of 4-arylaminoquinazoline-2-carbonitriles **5a – i**.



3a–i 4 6a–i 7a–i 5a–i

Scheme 3. Rational pathway for the formation of compounds **5a – i**.

of TCNE first, thus releasing one equivalent of HCN. Subsequently the amidine amino group attacks the same olefinic carbon atom. This leads to the formation of the intermediates **7**, which lose a malononitrile molecule and rearrange to products **5a – i**.

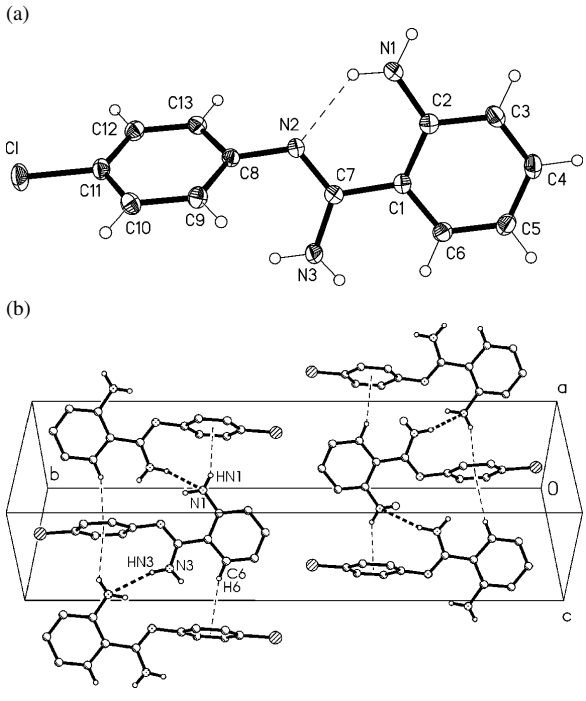


Fig. 1. (a) Molecular structure of compound **3c** in the crystal (displacement ellipsoids at the 50 % probability level); (b) packing diagram of compound **3c** (see text).

The structure of the products **3a – i** and **5a – i** were elucidated by using the usual spectroscopic methods such as IR and NMR spectroscopy. Moreover, the structure of the benzimidamide **3c** was further confirmed by single crystal X-ray methods (Fig. 1a). The double bond N2=C7 has been identified by its length of 1.299(2) Å, and all hydrogens of the NH_2 groups were freely refined. The interplanar angle between the planes (C1-7, N1-3) and (C8-13, N2, Cl) is 63°. An intramolecular hydrogen bond N1–HN1B···N2 (H···N 1.99(2) Å) is observed. The molecules are connected in the direction [10$\bar{1}$] by the rather long classical hydrogen bond N3–HN3A···N1 (H···N 2.57(2) Å) and by the H···π interactions HN1A···Cent(C8 – 13) and H6···Cent(C8 – 13), both 2.76 Å (Fig. 1b). The chains are connected in the third dimension by the interaction H10···Cent(C1 – 6) 2.59 Å (not shown in the Figure).

The IR spectra of these products showed two absorption peaks at 3343 – 3375 and 2251 – 2200 cm^{-1} which are characteristic for NH and CN, respectively. The carbon atoms of the cyano groups resonated at 115.03 – 115.70 ppm. Furthermore, the ^{1}H NMR spectrum revealed, in addition to the aromatic protons, a peak at 7.34 – 10.37 ppm originating from the NH protons. Finally, the mass spectra showed the molecular ion peaks in accordance with the products **5a – i**.

Conclusion

On the basis of the above experimental results, it is concluded that a series of 4-arylaminoquinazoline-2-carbonitriles have been synthesized for the first time by a one-step protocol at r. t. in moderate to good yields.

Experimental Section

Starting materials

All reagents were purchased from Alfa Aesar, Fluka and Aldrich companies and were used without further purification. The melting points were measured in capillary tubes without corrections using a Büchi 530 melting point apparatus. 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) were performed using a Finnigan MAT 8430 spectrometer. IR spectra were run as KBr discs using a Bruker Tensor 27 instrument.

*Synthesis of compounds **3a – i***

General procedure

0.01 mol of 2-aminobenzonitrile (**1**) was fused with 0.01 mol of the aniline derivative (**2a – i**) to form a homogeneous solution. Then 0.01 mol of anhydrous $AlCl_3$ was added, and the reaction mixture was heated at 170 – 180 °C for 20 – 30 min. 10 % aqueous HCl solution was added, and the mixture was heated for 5 min. The resulting solution was filtered while hot into a conical flask containing 10 % aqueous NaOH solution. The colorless precipitate that formed was collected by filtration under suction, washed with water until the filtrate was neutral, and left to dry at r. t. overnight to give the 2-aminoarylbenzimidamide products **3a – i** in 50 – 65 % yield.

*(Z)-2-Amino-N′-phenylbenzimidamide (**3a**)*

1.26 g (60 %), m. p. 140 – 141 °C (lit. [9]: m. p. 146 – 148 °C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.77 (br. s, 2 H, NH_2), 6.00 (br. s, 2 H, NH_2), 6.67 – 6.72 (m, 2 H), 6.97 – 7.06 (m, 2 H), 7.07 – 7.11 (m, 1 H), 7.16 – 7.21 (m, 1 H), 7.33 – 7.46 ppm (m, 3 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.47 (C), 116.59 (CH), 117.16 (CH), 121.83 (2 CH), 123.13 (CH), 127.27 (CH), 129.57 (2 CH), 131.14 (CH), 147.96 (C), 148.91 (C), 155.76 ppm (C).

*(Z)-2-Amino-N′-p-tolylbenzimidamide (**3b**)*

1.45 g (64 %), m. p. 145 – 147 °C (lit. [9]: m. p. 152 – 153 °C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H,

CH_3), 4.77 (br. s, 2H, NH_2), 6.01 (br. s, 2 H, NH_2), 6.68 – 6.71 (m, 2 H), 6.88 – 6.91 (m, 2 H), 7.15 – 7.20 (m, 3 H), 7.40 – 7.43 ppm (dd, J = 1.46, 7.88 Hz, 1 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.82 (CH_3), 116.55 (CH), 116.63 (C), 117.12 (CH), 121.63 (2 CH), 127.27 (CH), 130.13 (2 CH), 131.04 (CH), 132.46 (C), 146.18 (C), 147.95 (C), 155.89 ppm (C).

*(Z)-2-Amino-N′-(4-chlorophenyl)benzimidamide (**3c**)*

1.30 g (53 %), m. p. 149 – 151 °C (lit. [9]: m.p. 161 – 162 °C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.80 (br. s, 2 H, NH_2), 5.94 (br. s, 2 H, NH_2), 6.67 – 6.75 (m, 2 H), 6.90 – 6.95 (m, 2 H), 7.20 – 7.23 (m, 1 H), 7.30 – 7.35 (m, 2 H), 7.40 – 7.43 ppm (dd, J = 1.44, 7.88 Hz, 1 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.17 (CH), 116.19 (C), 116.67 (CH), 117.22 (CH), 123.25 (2 CH), 127.25 (CH), 128.30 (C), 129.08 (C), 129.61 (2 CH), 131.34 (CH), 147.42 (C), 147.89 (C), 156.12 ppm (C).

*(Z)-2-Amino-N′-(4-bromophenyl)benzimidamide (**3d**)*

1.53 g (53 %), m. p. 159 – 161 °C (lit. [9]: m. p. 167 – 168 °C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (br. s, 2 H, NH_2), 5.94 (br. s, 2 H, NH_2), 6.67 – 6.72 (m, 2 H), 6.86 – 6.90 (m, 2 H), 7.17 – 7.22 (m, 1 H), 7.39 – 7.48 ppm (m, 3 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.96 (C), 116.14 (C), 116.68 (CH), 117.24 (CH), 123.73 (2 CH), 127.25 (CH), 131.37 (CH), 132.57 (2 CH), 147.92 (C), 147.94 (2 C), 156.02 ppm (C).

*(Z)-2-Amino-N′-(2-iodophenyl)benzimidamide (**3e**)*

Deep-brown solid, 1.51 g (45 %), m. p. 140 – 143 °C. – IR (film): ν = 3448, 3319 (NH_2), 1619 (C=N), 1568 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.78 (br. s, 2 H, NH_2), 5.96 (br. s, 2 H, NH_2), 6.46 – 6.67 (m, 4 H), 7.31 – 7.36 (m, 1 H), 7.44 – 7.50 ppm (m, 3 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.77 (CH), 117.09 (CH), 121.98 (CH), 122.14 (CH), 123.27 (CH), 124.38 (CH), 127.34 (CH), 129.69 (CH), 131.21 (C), 133.16 (C), 139.60 (C), 148.83 (C), 156.13 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 339 (4), 338 (20), 337 (100), 320 (28), 310 (6), 236 (84), 211 (42), 193 (26), 166 (20), 139 (8), 92 (68), 65 (40), 57 (18), 44 (14). – $C_{13}H_{12}IN_3$ (337.17): calcd. C 46.31, H 3.59, N 12.46; found C 46.19, H 3.54, N 12.28.

*(Z)-2-Amino-N′-(2,5-dimethylphenyl)benzimidamide (**3f**)*

Pale-brown solid, 1.30 g (54 %), m. p. 49 – 51 °C. – IR (film): ν = 3463, 3365, 3304, 3216 (NH_2), 1627 cm^{-1} (C=N). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.10 (s, 3 H, CH_3), 2.25 (CH_3), 4.64 (br. s, 2 H, NH_2), 6.08 (br. s, 2 H, NH_2), 6.62 – 6.70 (m, 3 H), 6.79 – 6.82 (d, J = 7.68 Hz, 1 H), 7.10 – 7.13 (d, J = 7.65 Hz, 1 H), 7.16 – 7.20 (d, J = 1.41 Hz, 1 H), 7.41 – 7.43 ppm (dd, J = 1.40, 7.66 Hz, 1 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.58 (CH_3), 21.00 (CH_3), 116.46 (CH), 117.12 (CH), 121.89 (CH), 123.97 (CH), 126.11 (C), 127.25 (CH), 130.69 (CH), 131.04 (CH), 136.57 (2 C), 147.26 (C), 148.14 (C), 154.95 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 239 (100), 224 (50), 206 (10), 195 (8), 180 (4), 145 (4), 121 (70), 106 (30), 92 (18), 77 (14), 65 (12). – $C_{15}H_{17}N_3$ (239.32): calcd. C 75.28, H 7.16, N 17.56; found C 75.02, H 7.11, N 17.25.

*(Z)-2-Amino-N′-(2,5-dichlorophenyl)benzimidamide (**3g**)*

Colorless solid, 1.81 g (65 %), m. p. 76 – 77 °C. – IR (film): ν = 3470, 3368, 3320, 3076 (NH_2), 1626 (C=N), 1576 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 4.82 (br. s, 2 H, NH_2), 5.86 (br. s, 2 H, NH_2), 6.63 – 6.67 (m, 1 H), 6.96 – 7.02 (dd, J = 2.48, 8.49 Hz, 1 H), 7.05 (d, J = 2.44 Hz, 1 H), 7.17 – 7.22 (m, 1 H), 7.37 – 7.44 ppm (m, 2 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.63 (CH), 117.20 (CH), 118.76 (C), 123.19 (CH), 124.07 (CH), 127.44 (CH), 130.13 (C), 130.98 (CH), 131.63 (CH), 133.06 (C), 147.65 (C), 148.14 (C), 156.47 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 283 (12), 281 (62), 279 (100), 262 (40), 244 (80), 227 (10), 200 (8), 192 (12), 143 (4), 109 (8), 92 (36), 75 (4), 65 (20). – $C_{13}H_{11}Cl_2N_3$ (280.15): calcd. C 55.73, H 3.96, N 15.00; found C 55.57, H 3.91, N 14.82.

*(Z)-2-Amino-N′-(3-methoxyphenyl)benzimidamide (**3h**)*

Yellowish brown solid, 0.920 g (38 %), m. p. 35 – 37 °C. – IR (film): ν = 3461, 3367, 3224, 3216 (NH_2), 1605 (C=N), 1571 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.78 (s, 3H, OCH_3), 4.82 (br. s, 2 H, NH_2), 5.95 (br. s, 2 H, NH_2), 6.54 – 6.57 (m, 1 H), 6.59 – 6.62 (m, 1 H), 6.63 – 6.66 (m, 1 H), 6.67 – 6.72 (m, 2 H), 7.14 – 7.20 (m, 1 H), 7.22 – 7.27 (m, 1 H), 7.38 – 7.42 ppm (dd, J = 1.34, 7.90 Hz, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.32 (OCH_3), 107.40 (CH), 109.13 (CH), 114.17 (CH), 116.71 (CH), 117.23 (CH), 127.43 (CH), 130.41 (CH), 131.24 (CH), 147.81 (C), 150.18 (C), 155.86 (C), 160.72 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 241 (100), 240 (40), 224 (20), 209 (4), 195 (4), 181 (4), 154 (4), 147 (12), 133 (20), 113 (4), 94 (36), 92 (28), 77 (18), 65 (16). – $C_{14}H_{15}N_3O$ (241.30): calcd. C 69.69, H 6.27, N 17.41; found C 69.48, H 6.24, N 17.24.

*(Z)-2-Amino-N′-(4-methoxyphenyl)benzimidamide (**3i**)*

Brown solid, 1.14 g (47 %), m. p. 139 – 140 °C. – IR (film): ν = 3484, 3435, 3381 (NH_2), 1611 (C=N), 1573, 1535 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.80 (s, 3 H, OCH_3), 4.79 (br. s, 2 H, NH_2), 6.02 (br. s, 2 H, NH_2), 6.76 – 6.65 (m, 2 H), 6.92 (s, 4 H), 7.22 – 7.15 (m, 1 H), 7.43 – 7.39 ppm (dd, J = 1.24, 7.77 Hz, 1 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.51 (OCH_3), 114.90

(2 CH), 116.55 (CH), 117.12 (CH), 122.67 (2 CH), 127.27 (CH), 131.02 (CH), 147.92 (C), 155.67 (C), 156.29 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 241 (66), 224 (18), 209 (12), 196 (4), 181 (6), 147 (6), 133 (8), 123 (74), 108 (100), 92 (20), 80 (12), 65 (16), 53 (10), 44 (22). – $C_{14}H_{15}N_3O$ (241.30): calcd. C 69.69, H 6.27, N 17.41; found C 69.51, H 6.26, N 17.28.

*Reactions of **3a – i** with tetracyanoethylene (TCNE)*

General procedure

One mmol of 2-aminoarylbenzimidamides **3a – i** was dissolved in 10 mL of dry ethyl acetate, and this solution was added to a solution of 2 mmol of tetracyanoethylene (**4**) in 10 mL of dry ethyl acetate; the color of the reaction mixture changed from yellow to yellowish red. The reaction mixture was stirred at r. t. for 4 – 6 h. The colorless to yellow solid that precipitated was collected by filtration and was recrystallized from chloroform to give 4-arylaminoquinazoline-2-carbonitriles **5a – i** in 57 – 73 % yield.

*4-(Phenylamino)quinazoline-2-carbonitrile (**5a**)*

Yellow solid, 175 mg (71 %), m. p. 84 – 85 °C. – IR (film): ν = 3374 (NH), 2200 (CN), 1613 (C=N), 1566 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.21 – 7.28 (m, 1 H), 7.42 – 7.48 (m, 2 H), 7.68 – 7.73 (m, 2 H), 7.75 – 7.80 (m, 2 H), 7.88 – 7.93 (m, 1 H), 7.95 (br. s, 1 H, NH), 7.96 – 8.01 ppm (m, 1H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.13 (C), 116.64 (C), 120.46 (CH), 121.78 (2 CH), 125.42 (CH), 129.21 (CH), 129.25 (2 CH), 129.52 (CH), 134.09 (CH), 137.13 (C), 140.60 (C), 149.45 (C), 157.57 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 246 (40), 254 (100), 236 (4), 218 (8), 192 (4), 166 (4), 139 (2), 123 (4), 104 (8), 102 (6), 96 (8), 77 (12), 66 (4), 51 (8), 41 (4). – $C_{15}H_{10}N_4$ (246.27): calcd. C 73.16, H 4.09, N 22.75; found C 72.97, H 4.11, N 22.63.

*4-(p-Tolylamino)quinazoline-2-carbonitrile (**5b**)*

Colorless solid, 160 mg (62 %), m. p. 130 – 131 °C. – IR (film): ν = 3363 (NH), 2201 (CN), 1608 (C=N), 1564 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 7.23 – 7.26 (m, 2 H), 7.35 (br. s, 1 H, NH), 7.61 – 7.64 (m, 2 H), 7.68 – 7.72 (m, 1 H), 7.87 – 7.95 ppm (m, 3 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.99 (CH_3), 115.14 (C), 116.68 (C), 120.48 (CH), 121.93 (2 CH), 129.08 (CH), 129.48 (CH), 129.76 (2 CH), 133.96 (CH), 134.52 (C), 135.34 (C), 140.76 (C), 149.44 (C), 157.63 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 260 (44), 259 (100), 244 (12), 232 (8), 205 (4), 192 (4), 154 (6), 129 (12), 116 (8), 102 (12), 91 (8), 77 (6), 51 (6), 44 (8). – $C_{16}H_{12}N_4$ (260.30): calcd. C 73.83, H 4.65, N 21.52; found C 73.62, H 4.64, N 21.33.

*4-(4-Chlorophenylamino)quinazoline-2-carbonitrile (**5c**)*

Yellow crystals, 159 mg (57 %), m. p. 208 – 210 °C. – IR (film): ν = 3357 (NH), 2205 (CN), 1601 (C=N), 1568 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, [D_6]DMSO): δ = 7.51 – 7.55 (m, 2 H), 7.81 – 7.85 (m, 3 H), 7.87 – 7.90 (m, 1 H), 7.90 – 7.93 (m, 1 H), 7.99 – 8.03 (m, 1 H), 8.65 (d, *J* = 8.45 Hz, 1 H), 10.37 ppm (br. s, 1 H, NH). – ^{13}C NMR (100 MHz, [D_6]DMSO): δ = 115.50 (C), 116.82 C), 123.40 (CH), 124.70 (2 CH), 128.12 (CH), 128.60 (2 CH), 128.73 (C), 129.11 (C), 134.48 (CH), 136.98 (C), 139.78 (C), 148.85 (C), 158.27 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 281 (60), 280 (68), 279 (100), 252 (8), 244 (30), 219 (4), 217 (8), 204 (4), 192 (8), 190 (6), 164 (6), 140 (8), 122 (8), 111 (12), 102 (18), 96 (14), 84 (8), 75 (16), 51 (8). – $C_{15}H_9ClN_4$ (280.72): calcd. C 64.18, H 3.23, N 19.96, Cl 12.63; found C 63.88, H 3.19, N 19.75, Cl 12.31.

*4-(4-Bromophenylamino)quinazoline-2-carbonitrile (**5d**)*

Colorless crystals, 179 mg (55 %), m. p. 176 – 177 °C. – IR (film): ν = 3343 (NH), 2251 (CN), 1611 (C=N), 1599 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 10.37 (br. s, 1 H, NH), 8.61 – 8.63 (d, *J* = 7.70 Hz, 1 H), 7.96 – 8.03 (m, 1 H), 7.89 – 7.93 (m, 1 H), 7.82 – 7.86 (m, 1 H), 7.75 – 7.79 (m, 2 H), 7.64 – 7.68 ppm (m, 2 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 115.51 (C), 116.80 (C), 116.88 (C), 123.39 (CH), 125.02 (2 CH), 128.12 (CH), 129.12 (CH), 131.52 (2 CH), 134.49 (CH), 137.41 (C), 139.75 (C), 148.85 (C), 158.22 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 325 (100), 298 (2), 281 (4), 244 (40), 217 (6), 192 (8), 155 (6), 132 (4), 122 (18), 102 (14), 90 (10), 75 (8), 50 (4), 41 (12). – $C_{15}H_9BrN_4$ (325.17): calcd. C 55.41, H 2.79, Br 24.57, N 17.23; found C 55.26, H 2.76, N 17.04.

*4-(2-Iodophenylamino)quinazoline-2-carbonitrile (**5e**)*

Brown solid, 153 mg (41 %), m. p. 89 – 90 °C. – IR (film): ν = 3366 (NH), 2200 (CN), 1613 (C=N), 1593 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.94 – 7.00 (m, 1 H), 7.44 – 7.53 (m, 2 H), 7.71 – 7.78 (m, 1 H), 7.89 – 7.92 (m, 2 H), 7.94 – 8.98 (m, 2 H), 8.13 ppm (br. s, 1 H, NH). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 111.92 (C), 120.65 (CH), 121.77 (C), 123.08 (CH), 129.37 (CH), 129.67 (CH), 129.77 (CH), 134.38 (CH), 137.48 (C), 138.18 (C), 139.11 (CH), 134.48 (CH), 136.98 (C), 139.78 (C), 149.54 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 372 (40), 371 (78), 320 (20), 245 (100), 218 (8), 192 (8), 166 (6), 139 (4), 122 (4), 96 (8), 63 (4), 51 (6). – $C_{15}H_9IN_4$ (372.17): calcd. C 48.41, H 2.44, N 15.05; found C 48.29, H 2.41, N 14.89.

*4-(2,5-Dimethylphenylamino)quinazoline-2-carbonitrile (**5f**)*

Colorless crystals, 125 mg (46 %), m. p. 172 – 173 °C. – IR (film): ν = 3345 (NH), 2244 (CN), 1618 (C=N), 1588 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.30 (s, 3 H, CH_3), 2.39 (s, 3 H, CH_3), 7.05 (d, 1 H, *J* = 7.74 Hz),

7.20 (d, J = 7.65 Hz, 1 H), 7.40 (s, 1H), 7.58 (br. s, 1 H, NH), 7.66 – 7.70 (m, 1 H), 7.90 – 7.96 (m, 2 H), 7.98 – 8.01 ppm (m, 1 H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 17.70 (CH_3), 21.15 (CH_3), 115.09 (C), 116.62 (C), 120.52 (CH), 125.44 (CH), 127.61 (CH), 128.75 (C), 129.01 (CH), 129.58 (CH), 130.80 (CH), 133.97 (CH), 134.91 (C), 136.86 (C), 149.60 (C), 158.34 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 274 (50), 259 (100), 248 (20), 244 (10), 230 (6), 205 (8), 192 (4), 164 (4), 137 (14), 129 (12), 120 (18), 103 (16), 65 (4), 51 (8), 41 (10). – $C_{17}H_{14}N_4$ (274.33): calcd. C 74.43, H 5.14, N 20.42; found C 74.28, H 5.16, N 20.30.

*4-(2,5-Dichlorophenylamino)quinazoline-2-carbonitrile (**5g**)*

Yellow solid, 176 mg (56 %), m. p. 72 – 73 °C. – IR (film): ν = 3398 (NH), 2204 (CN), 1628 (C=N), 1572 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 7.42 – 7.46 (dd, J = 2.51, 8.62 Hz, 1 H), 7.46 – 7.51 (m, 1 H), 7.63 (d, J = 8.64 Hz, 1 H), 7.75 – 7.79 (m, 1 H), 7.82 (d, J = 2.45 Hz, 1 H), 8.33 (d, J = 8.04 Hz, 1 H), 10.57 (s, 1 H), 12.05 ppm (br. s, 1 H, NH). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 109.87 (C), 117.32 (CH), 118.01 (C), 123.77 (CH), 124.45 (CH), 128.18 (CH), 129.03 (CH), 129.13 (C), 130.86 (CH), 131.45 (C), 135.28 (CH), 135.50 (C), 140.21 (C), 156.93 (C), 160.32 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 318 (12), 316 (64), 314 (100), 304 (10), 279 (100), 267 (8), 244 (24), 221 (8), 207 (12), 192 (6), 165 (8), 149 (14), 125 (18), 111 (14), 97 (12), 83 (20), 71 (24), 57 (18). – $C_{15}H_8Cl_2N_4$ (315.16): calcd. C 57.17, H 2.56, N 17.78; found C 56.98, H 2.51, N 17.57.

*4-(3-Methoxyphenylamino)quinazoline-2-carbonitrile (**5h**)*

Deep-red crystals, 141 mg (51 %), m. p. 66 – 67 °C. – IR (film): ν = 3336 (NH), 2199 (CN), 1603 (C=N), 1570 (C=C) cm^{-1}. – ^{1}H NMR (400 MHz, [D$_6$]DMSO): δ = 3.81 (s, 3 H, OCH_3), 6.81 – 6.85 (m, 1 H), 7.36 – 7.40 (m, 1 H), 4.39 – 7.42 (m, 1 H), 7.46 – 7.50 (m, 1 H), 7.80 – 7.84 (m, 1 H), 7.86 – 7.90 (m, 1 H), 7.95 – 8.01 (m, 1 H), 8.62 (d, J = 7.84 Hz, 1 H), 10.22 ppm (br. s, 1 H, NH). – ^{13}C NMR (100 MHz, [D$_6$]DMSO): δ = 55.10 (OCH_3), 108.84 (CH), 110.24 (CH), 115.15 (CH), 115.50 (C), 116.87 (C), 123.34 (CH), 128.04 (CH), 128.91 (CH), 129.37 (CH), 134.26 (CH), 139.17 (C), 139.85 (C), 148.80 (C), 158.21 (C), 159.39 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 276 (40), 275 (100), 260 (28), 245 (8), 232 (20), 204 (4), 179 (6), 165 (64), 158 (8), 129 (4), 116 (8), 102 (6), 84 (12), 77 (8), 43 (14). – $C_{16}H_{12}N_4O$ (276.29): calcd. C 69.55, H 4.38, N 20.28; found C 69.34, H 4.36, N 20.09.

*4-(4-Methoxyphenylamino)quinazoline-2-carbonitrile (**5i**)*

Deep-red solid, 190 mg (69 %), m. p. 90 – 91 °C. – IR (film): ν = 3370 (NH), 2199 (CN), 1602 (C=N), 1578 cm^{-1} (C=C). – ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.75 (s, OCH_3), 6.86 (d, J = 9.06 Hz, 2H), 7.54 (d, J = 9.05 Hz, 2H), 7.66 – 7.61 (m, 2H), 7.74 (br. S, NH_2), 7.88 – 7.83 (m, 2H). – ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.63 (OCH_3), 114.43 (2 CH), 117.51 (C), 120.95 (CH), 124.10 (2 CH), 129.17 (CH), 129.23 (CH), 134.06 (CH), 139.21 (C), 139.59 (C), 149.18 (C), 158.72 (C), 159.33 ppm (C). – MS (EI, 70 eV): *m/z* (%) = 276 (28), 275 (100), 260 (46), 245 (18), 232 (20), 204 (4), 179 (6), 165 (64), 158 (8), 129 (4), 116 (8), 102 (6), 84 (12), 77 (8), 43 (14). – $C_{16}H_{12}N_4O$ (276.29): calcd. C 69.55, H 4.38, N 20.28; found C 69.38, H 4.37, N 20.12.

*X-Ray structure determination of **3c***

Crystal data: $C_{13}H_{12}ClN_3$, M_r = 245.71, monoclinic, $P2_1/n$, T = −170 °C, a = 5.7795(2), b = 26.6025(10), c = 7.6992(4) Å, β = 96.442(5)°, U = 1176.3 Å^3, Z = 4, $F(000)$ = 512, λ(Cu$K\alpha$) = 1.54184 Å, μ = 2.7 mm^{-1}, D_x = 1.387 g cm^{-3}.

Data collection: A colorless prism of *ca.* 0.35 × 0.1 × 0.1 mm^3 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 = 151° and were 99.9 % complete to 145°.

Structure refinement: The structure was refined using SHELXL-97 [23]. NH hydrogen atoms were refined freely, other H atoms were included using a riding model. The final *wR*2 (all reflections) was 0.084 for 2446 intensities and 170 parameters, with *R*1 [$I \geq 2\sigma(I)$] 0.032; S 1.05, max. $\Delta\rho$ = 0.22 e Å^{-3}.

CCDC 723205 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.

Acknowledgement

Kamal M. El-Shaieb thanks the Egyptian Government for a post-doctoral fellowship and financial support.

[1] S. J. Lee, Y. Konishi, D. T. Yu, T. A. Miskowski, C. M. Riviello, O. T. Macina, M. R. Frierson, K. Kondo, M. Sugitanit, J. C. Sircar, K. M. Blazejewskit, *J. Med. Chem.* **1995**, *38*, 18 – 22.

[2] a) M. Tobe, Y. Isobe, H. Tomizawa, T. Nagasaki, H. Takahashi, T. Fukazawa, H. Hayashi, *Bioorg. & Med. Chem.* **2003**, *11*, 383 – 391; b) W. R. Bowman, M. O. Cloonan, A. J. Fletcher, T. Stein, *Org. Biomol. Chem.* **2005**, *3*, 1460 – 1467.

[3] V. Kumar, G. Bhargava, P. D. Dey, M. P. Mahajan, *Synthesis* **2005**, *18*, 3059– 3062.
[4] A. A. Khalil, S. G. Abdel-Hamid, A. M. Al-Obaid, H. I. El-Subbag, *Arch. Pharm*. **2003**, *336*, 95 – 103.
[5] T. Herget, M. Freitag, M. Morbitzer, R. Kupfer, T. Stamminger, M. Marschall, *Antimicrob. Agents & Chemother*. **2004**, *48*, 4154 – 4162.
[6] S. Madapa, Z. Tusi, A. Mishra, K. Srivastava, S. K. Pandey, R. Tripathi, S. K. Puri, S. Batra, *Bioorg. & Med. Chem*. **2009**, *17*, 222 – 234.
[7] A. E. Wakeling, A. J. Barker, D. H. Davies, D. S. Brown, L. R. Green, S. A. Cartlidge, J. R. Woodburn, *Breast Cancer Res. & Treat*. **1996**, *38*, 67 – 73.
[8] W. Szczepankiewicz, J. Suwinski, *Tetrahedron Lett*. **1998**, *39*, 1785 – 1786.
[9] W. Szczepankiewicz, J. Suwinski, R. Bujok, *Tetrahedron* **2000**, *56*, 9343 – 9349.
[10] D. Shi, L. Rong, J. Wang, Q. Zhuang, X. Wang, H. Hu, *Tetrahedron Lett*. **2003**, *44*, 3199 – 3201.
[11] F. C. Cooper, M. W. Partridge, *Org. Synth*. **1963**, *Coll. Vol. 4*, 769 – 770.
[12] M. W. Patridge, M. F. G. Stefens, *J. Chem. Soc.* **1964**, 3663 – 3669.
[13] M. W. Partridge, S. A. Slorach, H. J. Vipond, *J. Chem. Soc*. **1964**, 3670 – 3673.
[14] D. D. Díaz, M. G. Finn, *Chem. Eur. J*. **2004**, *10*, 303 – 309.
[15] V. G. Granik, *Usp. Khim*. **1983**, *52*, 669 – 703.
[16] K. M. El-Shaieb, *J. Sulf. Chem*. **2007**, *28*, 223 – 229.
[17] A. A. Aly, K. M. El-Shaieb, *J. Chem. Res. (s)* **2007**, 207 – 209.
[18] K. M. El-Shaieb, A. A. Hassan, A. E. Mourad, *Heteroatom* **2004**, *15*, 63 – 66.
[19] A. A. Aly, K. M. El-Shaieb, *Tetrahedron* **2004**, *60*, 3797 – 3802.
[20] A. A. Hassan, A. E. Mourad, K. M. El-Shaieb, A. H. Abou-Zeid, *Z. Naturforsch*. **2004**, *59b*, 910 – 916.
[21] A. A. Hassan, K. M. El-Shaieb, D. Döpp, *Arkivoc* **2005**, *i*, 139 – 149.
[22] K. M. El-Shaieb, A. E. Mourad, A. A. Aly, H. Hopf, *Arkivoc* **2006**, *ii*, 193 – 200.
[23] G. M. Sheldrick, *Acta Cryst*. **2008**, *A64*, 112 – 122.