Synthesis of some novel azido- and tetrazoloquinoline-3-carbonitriles and their conversion into 2,4-diaminoquinoline-3-carbonitriles

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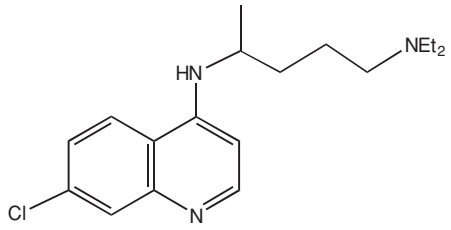
Quinoline-3-carbonitriles carrying amino groups at the 2- and/or 4-position have been prepared *via* the corresponding azido- or tetrazolo-quinolines, through the intermediacy of phosphazenes.

Keywords: quinolines and fused quinolines, azides, fused tetrazoles, phosphazenes

Many quinolines have biological activity as antimalarials,[1-3] for example, chloroquine. Recently, Boland and his co-workers have reported[4] that this important antimalarial drug has lost much of its value because of the widespread emergence of chloroquine-resistant *Plasmodium falciparum* strains. The search for new antimalarial drugs is therefore an active area of investigation. The public health importance of malaria can be gauged by the reported estimates that it is responsible for more than 300 million clinical cases and 1 million deaths each year.[5,6]



Chloroquine

Continuing our research into the synthesis of novel amino-heterocyclic compounds of expected biological activity,[7-12] we report here the synthesis of hitherto unreported 2,4-diaminoquinoline-3-carbonitriles that can be structurally compared to analogous compounds of known antimalarial activity,[1-6] in the hope that they may show similar effects.

Reduction of organic azides to the corresponding primary amines can be achieved by using a variety of reducing agents such as $LiAlH_4$,[13] catalytic hydrogenation,[14-16] sodium borohydride/phase-transfer catalyst,[17] transfer hydrogenation,[18] triethylphosphite,[19] electrolysis[20] and sodium borohydride in tetrahydrofuran.[21] The use of these reagents has some disadvantages, in that sensitive substituents can be attacked, or the reduction may fail when the azide group exists in the isomeric ring-closed tetrazolo form. In addition, some of these methods are not chemoselective and require drastic conditions. On the other hand, using the Staudinger reaction,[22] the reduction can be carried out chemoselectively[23] under mild reaction conditions, and the obtained products are formed in good yields. Consequently, this reaction has been applied in the present investigation to synthesize for the first time novel 4-amino- and 2,4-diaminoquinoline-3-carbonitriles by reduction of azido- and tetrazolo[1,5-*a*]quinoline-3-carbonitriles, *via* the formation of phosphazene intermediates, in excellent yields. To the best of our knowledge, the synthesis of 4-amino- and 2,4-diamino-quinoline-3-carbonitriles from azido- and tetrazolo[1,5-*a*]quinoline-3-carbonitriles has not so far been reported.

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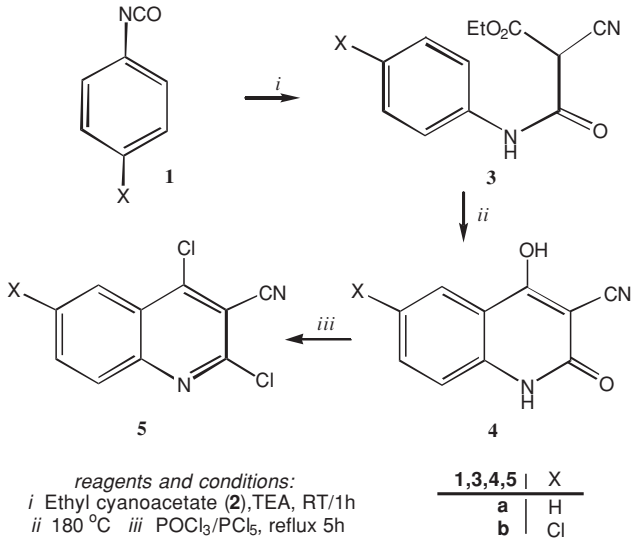


Scheme 1

As depicted in Scheme 1, the required key intermediates **5a,b** were obtained in three steps. Reaction of phenyl isocyanates **1a,b** with an equimolar amount of ethyl cyanoacetate **2** at room temperature gave the intermediate cyanomalonamic acid esters **3a,b**.[24-26] When these were heated in 1,2-dichlorobenzene at reflux temperature they underwent intramolecular cyclisation to give the hydroxyquinolinones **4a,b**.[24-27] Chlorination of **4a,b** with a mixture of $POCl_3/PCl_5$ afforded the corresponding chloroquinolines **5a,b**.

The 2,4-dichloroquinoline-3-carbonitriles **5a,b** have been successfully employed in reaction sequences aimed at the synthesis of new aminoquinoline-3-carbonitriles. Kinetic studies indicate that the chlorine atom in position 4 of 2,4-dichloroquinolines is about twice as reactive towards nucleophiles as that at the 2-position.[28] Consequently, the reactive chlorine atom in position 4 of **5a**[29] can readily be displaced by nucleophiles. So the conversions of 4-chloroquinolines into 4-aminoquinolines *via* 4-azidoquinolines was examined. Reacting dichloroquinoline **5a**, for example, with an equimolar amount of sodium azide in DMF at room temperature gave a monoazido-chloroquinoline which proved to be the expected 4azido-2-chloroquinoline-3-carbonitrile **6**. The structure of **6** was supported by its IR spectrum which showed the presence of an azide absorption at 2120 cm^{-1}. The 4-monoazide **6** was converted into 4-(triphenylphosphoranylideneamino)quinoline-3-carbonitrile **7** by reaction with triphenylphosphane *via* the Staudinger reaction. Hydrolysis with aqueous acetic acid produced in one step the 4-amino-2(1*H*)-quinolones **8**. The structure of **8** was established on the basis of elemental analysis and spectral data (see Experimental

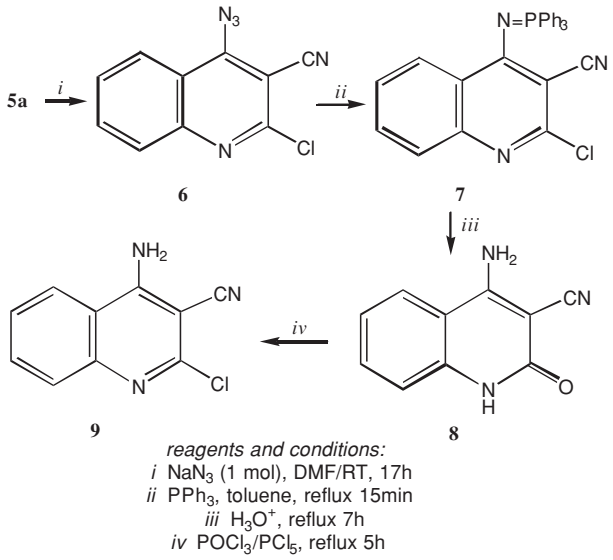
section). Chlorination of compound **8** with $POCl_3/PCl_5$ gave the corresponding aminoquinoline **9**[10] in good yield. An examination of other possible routes to the 4-aminoquinoline-3-carbonitriles **8** shows that the three step sequence *via* the phosphazene **7** is a superior method. 4-Aminoquinoline-3-carbonitriles **8** cannot be prepared by direct amination due to numerous competing side reactions.

Next we examined the conversion of 2,4-dichloroquinolines into 2,4-diaminoquinolines *via* tetrazolo[1,5-*a*]quinolines. Substitution of the chlorine atoms at C-2 and C-4 of **5a,b** with a 2 molar excess of sodium azide at room temperature yielded the 5-azidotetrazolo[1,5-*a*]quinoline-4-carbonitriles **10a,b**, in which the two azido groups are present in two different tautomeric forms. Reacting **10a**, as example, with triphenylphosphane in toluene at room temperature yielded the corresponding phosphazene **14**, which was hydrolysed by acetic acid/water (5:1) to give the corresponding 5-amino-tetrazolo[1,5-*a*]quinoline-4-carbonitrile **15**. Compound **15** can also be obtained by the hydrogenation of the open chain azide moiety at C-5 in **10a** using palladium as catalyst. The tetrazolo moiety (the "masked azide") is not attacked in this reaction. The amines **15** prepared by both pathways were identical in all physical and spectroscopic data. Attempted reduction of the tetrazolo moiety of **10a,b** or **15** by catalytic hydrogenation failed to yield the corresponding 2,4-diaminoquinolines **12a,b**. The influence of solvent on the hydrogenation was studied; different protic and aprotic solvents were tried but no reduction occurred. Other reducing reagents, such as sodium dithionite or zinc dust, were also tried but the reduction of **10a,b** or **15** to the amines **12a,b** was still unsuccessful.

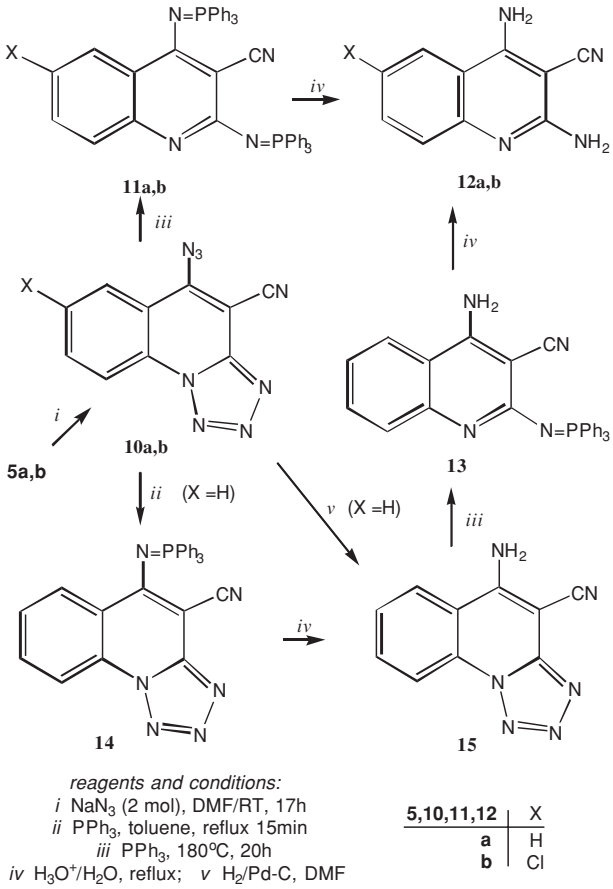
In an attempt to synthesise 2,4-diaminoquinoline-3-carbonitrile **12a**[30], as example, from the tetrazoloquinolines **15**, we investigated the ring opening of the tetrazolo ring in **15** by reaction with triphenylphosphane to give the corresponding open chain phosphazene **13**. Refluxing aminoquinoline **15** with triphenylphosphane in bromobenzene, high stability was observed and no phosphazene **13** was isolated, even upon heating for extended periods. Therefore we repeated the reaction in a solvent of (some 20°) higher boiling point than bromobenzene, *viz.* 1,2-dichlorobenzene. Heating **15** with triphenylphosphane in 1,2-dichlorobenzene at reflux temperature afforded the phosphazene **13**, which could be hydrolysed to 2,4-diaminoquinoline-3-carbonitrile **12a** (Scheme 3). Alternatively, 2,4-diaminoquinolines **12a,b** could also be obtained by refluxing 5-azido-tetrazolo[1,5-*a*]quinoline-4-carbonitriles **10a,b** with a two-molar excess of triphenylphosphane in 1,2-dichlorobenzene to produce the bis-iminophosphoranes **11a,b**, followed by hydrolysis in aqueous acetic acid.

In a further investigation of the scope of the Staudinger reaction to synthesise new aminoquinoline-3-carbonitriles, we studied the conversion of 4-chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbonitrile to the corresponding 4-amine *via* the azide. Thus, chlorination of the 4-hydroxyquinolinone **16**[31] with $POCl_3/PCl_5$ gave the 4-chloroquinoline **17**, which reacted with an equimolar amount of sodium azide to give the corresponding 4-azidoquinolinone **18**. The reaction of **18** with triphenylphosphane in toluene at reflux temperature led to the formation of the phosphazene **19**. Hydrolysis by refluxing in aqueous acetic acid afforded the desired 4-aminoquinolone **20**, in good yield.

In summary: the results obtained in this work represent convenient synthetic strategies for the construction of 4-amino-and 2,4-diaminoquinoline-3-carbonitriles, of potential biological interest and obtainable only with difficulty otherwise. The azide group can be reduced successfully to the corresponding amino function using the Staudinger reaction, in the presence of cyano, chloride and carbonyl groups, which



Scheme 2

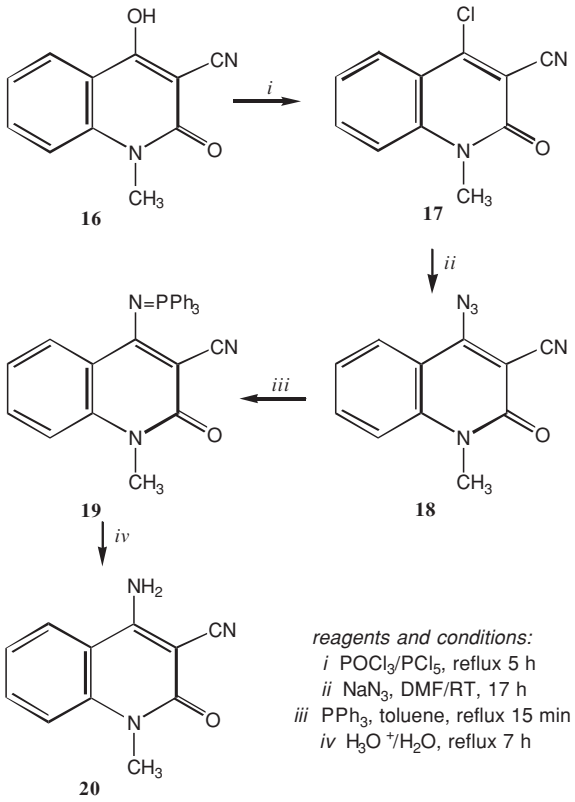


Scheme 3

are normally sensitive to other reduction conditions. Moreover, tetrazolo[1,5-*a*]quinolines ("masked" α-azidoazines) can also be converted successfully into the corresponding primary amines in excellent yields by this strategy.

Experimental

All m.p.s were measured on a Gallenkamp melting point apparatus. IR spectra were recorded (KBr) on a Perkin Elmer 298 spectrophotometer. ^{1}H NMR spectra were measured in d_6-DMSO with Varian XL-200 (90 MHz) and Varian Gemini-200 (200 MHz) spectrometers using TMS as internal standard; the chemical shifts are expressed as



Scheme 4

(δ) values (ppm). Microanalyses were performed on a Carlo Erba C, H, N-Automatic 1106 instrument at the Institute of Organic Chemistry, Karl-Franzens University, Graz, Austria. All reactions were monitored by TLC, carried out on 0.2 mm silica gel 60 F-254 (Merck) plates using UV light for detection. Compounds **4a** and **5a** were prepared according to references 24, 26 and 32, 33, respectively.

6-Chloro-4-hydroxy-2-oxo-1,2-dihydroquinoline-3-carbonitrile (**4b**): A suspension of **3b**[25] (3g, 11.25 mmol) in 1,2-dichlorobenzene (40 ml) was refluxed for 1h. After cooling to room temperature, the resulting solid product was collected by filtration, dried and recrystallised from dioxan to give **4b** as yellow crystals (1.80 g, 73%) (Lit.[27] yield 72%); m.p. 309–310 °C. IR: ν_{max} 3200–2700 (NH), 2260 (CN), 1665 (CO) cm^{-1}. ^1H NMR: Δ = 7.25-7.65 (m, 2Ar–H), 8.15 (d, *J* = 8Hz, 1Ar–H), 11.20 (br s, 1H, NH). Found: C, 54.48; H, 2.25; Cl, 15.80; N, 12.61. Calcd. for $C_{10}H_5ClN_2O_2$ (220.65): C, 54.43; H, 2.28; Cl, 16.09; N, 12.70 %.

Chloroquinoline-3-carbonitriles **5b**, **9** *and* **17**; *general procedure*
A mixture of hydroxyquinoline (**4b**, **8** or **16**) (5 mmol), PCl_5 (2.09 g, 10 mmol) and $POCl_3$ (10 ml) was heated at reflux temperature for 5 h. The excess of $POCl_3$ was distilled *in vacuo* and the residue was treated with cold H_2O. After neutralisation with cold dilute KOH the resulting solid product that formed was collected by filtration, washed well with H_2O, dried, and finally recrystallised from 1, 2-dichloroethane to afford the corresponding chloroquinoline (**5b, 9** and **17**, respectively).

2,4,6-Trichloroquinoline-3-carbonitrile (**5b**): Yellowish crystals (1.10 g, 85%), m.p. 165–166 °C. IR: ν_{max} 2240 cm^{-1} (CN). Found: C, 46.30; H, 1.17; Cl, 41.40; N, 10.79. Calcd. for $C_{10}H_3Cl_3N_2$ (257.63): C, 46.62; H, 1.17; Cl, 41.34; N, 10.87 %.

4-Amino-2-chloroquinoline-3-carbonitrile (**9**): Colourless crystals (0.99g, 97%), m.p. 303-305 °C. (Lit.[10] yield: 92%, m.p. 305-307 °C).

4-Chloro-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbonitrile (**17**): Colourless crystals (1.03 g, 94%), m.p. 212–213 °C. IR: ν_{max} 2240 (CN), 1645 (CO) cm^{-1}. Found: C, 60.65; H, 3.25; Cl, 16.12; N, 12.81. Calcd. for $C_{11}H_7ClN_2O$ (218.68): C, 60.41; H, 3.23; Cl, 16.23; N, 12.81 %.

4-Azidoquinoline-3-carbonitriles **6, 18** *and 5-azidotetrazolo[1, 5-a]quinoline-4-carbonitriles* **10a,b**: *general procedure*
NaN_3 (0.146 g, 2.24 mmol) was added to a stirred solution of chloroquinoline **5a** or **17** (2.24 mmol) in DMF (15 ml). Stirring was continued for a further 17h at r.t. and the solution was then poured into H_2O. The precipitated solid product was collected by filtration, washed with H_2O, dried, and finally recrystallised from MeOH to afford the corresponding azidoquinoline **6** or **18**. Using the same procedure, compounds **10a,b** were prepared from compounds **5a,b** (2.24 mmol) and NaN_3 (0.292 g, 4.48 mmol) in DMF.

4-Azido-2-chloroquinoline-3-carbonitrile (**6**): Colourless crystals (0.48 g, 93%), m.p. 136–138 °C (dec). IR: ν_{max} 2220 (CN), 2120 (N_3) cm^{-1}. Found: C, 52.30; H, 1.81; Cl, 15.40; N, 30.70. Calcd. for $C_{10}H_4ClN_5$ (229.66): C, 52.29; H, 1.75; Cl, 15.46; N, 30.49 %.

5-Azidotetrazolo[1,5-a]quinoline-4-carbonitrile (**10a**): Yellow crystals (0.45 g, 85%); m.p. 190 °C (dec). IR: ν_{max} 2240 (CN), 2130 (N_3) cm^{-1}. Found: C, 51.05; H, 1.87; N, 47.75. Calcd. for $C_{10}H_4N_8$ (236.18): C, 50.85; H, 1.71; N, 47.44 %.

5-Azido-7-chloro-tetrazolo[1,5-a]quinoline-4-carbonitrile (**10b**): Violet crystals (0.46 g, 76%); m.p. 192 °C (dec.). Because of the poor stability of this compound, satisfactory spectroscopic and elemental analysis could not be obtained and it was used without delay in the next reaction.

4-Azido-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbonitrile (**18**): Yellowish crystals (0.485 g, 96%), m.p. 172–173 °C (dec). IR: ν_{max} 2240 (CN), 2140 (N_3), 1640 (CO) cm^{-1}. Found: C, 58.93; H, 3.05; N, 31.28. Calcd. for $C_{11}H_7N_5O$ (225.20): C, 58.66; H, 3.13; N, 31.10 %.

Triphenylphosphoranylideneaminoquinolines **7**, **11a**,**b**, **13**, **14** *and* **19**: *general procedure*
A solution of the appropriate azidoquinoline **6**, **10a** or **18** (10 mmol) and triphenylphosphane (2.62 g, 10 mmol) in toluene (20 ml) was heated under reflux for 15 min. The solvent was then removed under reduced pressure and the resulting solid product was collected and recrystallised from DMF to afford 7, 14 and 19, respectively.

For compounds **11a**,**b** and **13**, a solution of the tetrazoloquinolines **10a**,**b** or **15** (10 mmol) and triphenylphosphane (5.24 g, 20 mmol) (in the case of **11a**,**b**) and (2.62 g, 10 mmol) (in the case of **13**) in 1, 2-dichlorobenzene (20 ml) was refluxed for 20h. The reaction mixture was then worked up as described for **7**.

2-Chloro-4-(triphenylphosphoranylideneamino)quinoline-3-carbonitrile (**7**): Colourless crystals (4.45 g, 96%), m.p. 223–224 °C. IR: ν_{max} 2220 cm^{-1} (CN). Found: C, 72.70; H, 4.10; N, 8.92%. Calcd. for $C_{28}H_{19}ClN_3P$ (463.95): C, 72.48; H, 4.13; N, 9.06 %.

2,4-Bis(triphenylphosphoranylideneamino)quinoline-3-carbonitrile (**11a**): Colourless crystals, (4.75 g, 67%), m.p. 266–268 °C. IR: ν = 2200 (CN) cm^{-1}. Found: C, 78.34; H, 4.73; N, 7.94%. Calcd. for $C_{46}H_{34}N_4P_2$ (704.75): C, 78.39; H, 4.86; N, 7.95%.

6-Chloro-2,4-bis(triphenylphosphoranylideneamino)quinoline-3-carbonitrile (**11b**)**:** Colourless crystals (5.85 g, 79%), m.p. 297–298 °C. IR: ν_{max} 2210 cm^{-1} (CN). Found: C, 74.64; H, 4.58; N, 7.43%. Calcd. for $C_{46}H_{33}ClN_4P_2$ (739.24): C, 74.73; H, 4.50; N, 7.58 %.

4-Amino-2-triphenylphosphoranylideneaminoquinoline-3-carbonitrile (**13**): Colourless crystals (4.10 g, 92%), m.p. 299–301 °C. IR: ν_{max} 3480, 3340, 3240 (NH), 2200 (CN) cm^{-1}. ^1H NMR: Δ 7.10 (s, 2H, NH_2), 7.42-8.10 (m, 19Ar–H). Found: C, 75.40; H, 4.98; N, 12. 50. Calcd. for $C_{28}H_{21}N_4P$ (444.47): C, 75.66; H, 4.76; N, 12.60 %.

5-(Triphenylphosphoranylideneamino)tetrazolo[1,5-a]quinoline-4-carbonitrile (**14**): Colourless crystals (4.0 g, 85%), m.p. 238–240 °C. IR: ν_{max} 2210 cm^{-1} (CN). Found: C, 71.59; H, 4.19; N, 17.93%. Calcd. for $C_{28}H_{19}N_6P$ (470.47): C, 71.48; H, 4.07; N, 17.86 %.

1-Methyl-2-oxo-4-(triphenylphosphoranylideneamino)-1,2-dihydroquinoline-3-carbonitrile (**19**): Colourless crystals, (4.35 g, 95%), m.p. 224–226 °C. IR: ν_{max} 2210 (CN), 1630 (CO) cm^{-1} Found: C, 75.90; H, 4.95; N, 9.15. Calcd. for $C_{29}H_{22}N_3OP$ (459.49): C, 75.80; H, 4.83; N, 9.14 %.

Aminoquinoline-3-carbonitriles **8, 12a,b; 15** *and* **20:** *general procedures*
(Route A) A solution of the appropriate phosphazenes **7**, **11a**,**b**; **14** and **19** (2 mmol) in AcOH (80%, 15 ml) was refluxed for 7h (in case of **8**, **15** and **20**) or 17h (in case of preparation of **12a,b** from **11a,b**). The solvent was then removed in vacuum and the resulting solid product was collected by filtration, washed well with MeOH to remove Ph_3PO, dried and recrystallised from DMF.

(Route B) for 2,4-diaminoquinoline-3-carbonitrile (**12a**): A solution of phosphazene **13** (1 mmol) in AcOH (80%, 10 ml) was refluxed for 8h. Then the reaction mixture was worked up as described above for preparation of **12a** from **11a** (*Route A*).

(Route C) for 5-aminotetrazolo[1,5-a]quinoline-4-carbonitrile (**15**): To a solution of **10a** (1g, 4.23 mmol) in DMF (50 ml), palladium on activated carbon (30 mg, 10% Pd) was added. The reaction mixture was stirred under a slow steam of of hydrogen at r.t. for 5h.

The catalyst was removed by filtration and the solvent was evaporated to dryness under reduced pressure. The resulting solid product so formed was collected by filtration and dried.

4-Amino-2-oxo-1,2-dihydroquinoline-3-carbonitrile (**8**): Colourless crystals (0.35 g, 95%), m.p. 321–323 °C. IR: ν_{max} 3380, 3330, 3220 (NH), 2220 (CN), 1660 (CO) cm^{-1}. ^1H NMR: Δ 6.25 (s, 2H, NH_2), 7.35-8.05 (m, 4Ar–H), 11.15 (br s, 1H, NH). Found: C, 64.94; H, 3.87; N, 22.84. Calcd. for $C_{10}H_7N_3O$ (185.18): C, 64.86; H, 3.81; N, 22.69 %.

2,4-Diaminoquinoline-3-carbonitrile (**12a**): Colourless crystals, [0.35 g, 96% (route A), 0.175 g, 95%, route B)]; m.p. 305–307 °C (Lit.[30] yield: 82%, m.p. 303–305 °C). IR: ν_{max} 3420, 3360, 3240 (NH), 2200 (CN) cm^{-1}. ^1H NMR: Δ 6.15 (s, 2H, NH_2), 6.80-7.47 (m, 5H, NH_2 + 3Ar–H), 8.0 (d, *J* = 8Hz, 1Ar–H). Found: C, 65.47; H, 4.41; N, 30.68. Calcd. for $C_{10}H_8N_4$ (184.18): C, 65.20; H, 4.38; N, 30.42 %.

6-Chloro-2,4-diaminoquinoline-3-carbonitrile (**12b**): Colourless crystals (0.35 g, 80%), m.p. 352–353 °C. IR: ν_{max} 3470, 3370, 3260 (NH), 2210 (CN) cm^{-1}. ^1H NMR: Δ 6.40 (s, 2H, NH_2), 6.80-7.43 (m, 4H, NH_2 + 2Ar–H), 8.20 (d, *J* = 8Hz, 1Ar–H). Found: C, 54.66; H, 3.37; Cl, 16.02; N, 25.63%. Calcd. for $C_{10}H_7ClN_4$ (218.68): C, 54.92; H, 3.23; Cl, 16.23; N, 25.62 %.

5-Aminotetrazolo[1,5-a]quinoline-4-carbonitrile (**15**): Colourless crystals [0.375 g, 89% (route A), 0.80 g, 90%(route C)], m.p. 320–321 °C. IR: ν_{max} 3440, 3340, 3230 (NH), 2210 (CN) cm^{-1}. ^1H NMR: Δ 6.40 (s, 2H, NH_2), 7.15–7.55 (m, 3Ar–H), 8.15 (d, *J* = 8Hz, 1Ar–H). Calcd. for $C_{10}H_6N_6$ (210.19): C, 57.14; H, 2.88; N, 39.98. Found: C, 57.16; H, 2.95; N, 39.99 %.

4-Amino-1-methyl-2-oxo-1,2-dihydroquinoline-3-carbonitrile (**20**): Colourless crystals (0.39 g, 98%); m.p. 332-334 °C. IR: ν_{max} 3460, 3420, 3340, 3240 (NH), 2210 (CN), 1670 (CO) cm^{-1}. ^1H NMR: Δ 3.25 (s, 3H, CH_3), 6.35 (s, 2H, NH_2), 7.25–7.50 (m, 3Ar–H), 8.10 (d, *J* = 8Hz, 1Ar–H). Found: C, 66.47; H, 4.66; N, 21.07. Calcd. for $C_{11}H_9N_3O$ (199.20): C, 66.32; H, 4.55; N, 21.09 %.

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References

1 E.H. Erickson, L. Lappi, T.K. Rice, K.F. Swingle and M.V. Winkl, *J. Med. Chem*., 1978, **21**, 984.
2 L.N. Ferguson, *Chem. Soc. Rev*., 1975, **14**, 289.
3 J.M. Domagala, L.D. Hanna, G.L. Heifetz, M.P. Hutt, T.F. Mich, J.P. Sanchez and M. Solomon, *J. Med. Chem*., 1986, **29**, 394.
4 P.B. Boland, E.M. Lackritz, P.N. Karembe, J.B.O. Were, R. Steketee and C.C. Campbell, *J. Infect. Dis*., 1993, **167**, 932.
5 *W.H.O. Wkly. Epidem. Rec*., 1994, **69**, 309.
6 S.C.Jr. Oaks, V.S. Mitchell and G. W. Pearson, *Malaria: Obstacles and Opportunities*, Institute of Medicine, Washington, DC. 1991.
7 R. Mekheimer, *Pharmazie,* 1994, **49**, 322.
8 R. Mekheimer, *Bull. Soc. Chim. Fr.*, 1994, **131**, 279.
9 R.A. Mekheimer, N.K. Mohamed and K.U. Sadek, *Bull. Chem. Soc. Jpn*., 1997, **70**, 1625**.**
10 R.A. Mekheimer, *Synth. Commun*., 1998, **28**, 3665.
11 R.A. Mekheimer, *Synthesis,* 2001, 103.
12 T. Kappe, A. Pfaffeschlager and W. Stadlbauer, *Synthesis*, 1989, 666.
13 J.H. Boyer, *J. Am. Chem. Soc.,* 1951, **73**, 5865.
14 W.S. Mungall, G.L. Greene, G.A. Heavner and R.L. Letsigner, *J. Org. Chem*., 1975, **40**, 1659.
15 E.D. Nicolaides, R.D. Westland and E.L. Wittle, *J. Am. Chem. Soc*., 1954, **76**, 2887**.**
16 E.J. Corey, K.C. Nicolaou, R.P. Balanson and Y. Machida, *Synthesis,* 1975, 590.
17 F. Rolla, *J. Org. Chem*., 1983, **47**, 4327**.**
18 T. Gartiser, C. Selve and J. Delpuech, *Tetrahedron Lett*., 1983, **24**, 1609**.**
19 A. Koziara, K. O. Pacewicka, S. Zawadzki and A. Zwierzak, *Synthesis,* 1985, 202**.**
20 D. Knittel, *Monatsh. Chem*., 1984, **115**, 523.
21 K. Soai, S. Yokoyama and A. Ookwa, *Synthesis,* 1987, 48.
22 H.M. Staudinger, *Helv. Chim. Acta*, 1919, **2**, 635.
23 M. Vaultier, N. Knozi and R. Carrie, *Tetrahedron Lett*., 1983, **24**, 763.
24 E. Ziegler, H. Junek and A. Metallidis, *Monatsh. Chem*., 1970, **101**, 92.
25 L. Capuano and R. Zander, *Chem. Ber*., 1973, **106**, 3670**.**
26 R.F. Abdulla and P.L. Unger, *Tetrahedron Lett*., 974, 1781 (1).
27 M.M. Sim, C.L. Lee. and A. Ganesan, *Tetrahedron Lett*., 1998, **39**, 6399.
28 W. Steinschiffer and W. Stadlbauer, *J. Prakt. Chem*., 1994, **336**, 311.
29 R. Mekheimer, *Pharmazie,* 1994, **49**, 486.
30 K. Gewald, U. Hain, G. Schwarzer and M. Gruner, *J. Prakt. Chem*., 1992, **334**, 89.
31 G.M. Coppola and G.E. Hardtmann, *J. Heterocyclic Chem*., 1979, **16**, 1605.
32 S. Gabriel, *Chem. Ber*., 1918, **51**, 1500**.**
33 G. Koller, H. Ruppersberg and E. Strang, *Monatsh. Chem*., 1929, **52**, 59.