Synthetic Routes to the Carcinogen IQ and Related 3H-Imidazo[4,5-f]quinolines

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2-Amino-3-methyl-3H-imidazo[4,5-f]quinoline (IQ, 1a) and four new IQ homologues, viz. its 7-methyl, 8-methyl, 9-methyl and 7,9-dimethyl derivatives 1c–1f, have been conveniently synthesized from the appropriate 6-methoxyquinolines 3 rather than from the previously used less reactive and less available 6-haloquinolines. The 7-methyl, 9-methyl and 7,9-dimethyl derivatives were also prepared by radical methylation of 1a. Synthetic routes to 1 and the related compounds 11–14 via the corresponding thioureas 6 were also investigated. Compounds 1 and their analogues 6–14, modified at position 2, will be used in structure–activity studies.

Around 1980, 2-amino-3-methyl-3H-imidazo[4,5-f]quinoline (1a, IQ),[1] its homologue 1b (MeIQ)[2] and the closely related imidazoquinoxaline 2b (MeIQx)[3] were isolated from heated fish or meat and identified by spectral data and chemical synthesis. Later, 2a was isolated from a heated mixture of meat and creatine,[4] while two higher homologues of 2b were obtained from a heated mixture of an amino acid, a sugar and creatinine.[5–7] The so-called IQ compounds 1 and 2 belong to a group of strongly mutagenic heterocyclic amines, present in our environment. As far as has been investigated, these amines are also carcinogenic.[8]
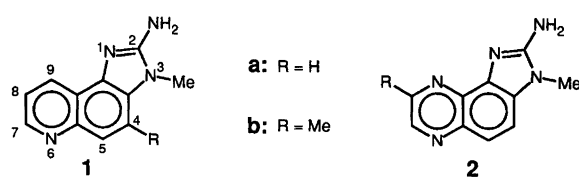
In order to establish relationships between biological activity and molecular structure, a number of substances related to 1 and 2 have been synthesized and their mutagenic activities investigated.[9] In some of these IQ analogues, the substitution pattern of the imidazo moiety has been changed.[2,10–13] Alternatively, the pyridine nitrogen in 1 has been moved[14] or replaced by a methine group.[12] The number and positions of C-methyl groups have also been varied. Thus, all C-methyl derivatives of 2a have been prepared[15] and their mutagenic activities measured.[16] By contrast, 1b and its 5-methyl isomer[2,10] are the only known C-methyl derivatives of 1a.

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The present paper describes the synthesis of four new methyl derivatives of 1a (Scheme 1). Several analogues of 1a (and of its homologues 1b and 1c), modified at position 2, have also been prepared, originally in the hope of finding an alternative to cyanogen bromide for construction of the imidazole ring (Schemes 2 and 3).

Results and discussion

A reasonable synthesis of 1a and 1b starts from the appropriate 6-chloroquinoline.[17] In a similar way, 1a was prepared from 6-bromoquinoline.[18] We used essentially the former method[17] but preferred to start from the more available and reactive 6-methoxyquinolines (3 in Scheme 1). Among these, 3a and 3c were commercially available, while 3d–3f were prepared from p-anisidine through the Doebner–von Miller reaction.[19–21]

The 6-methoxy-5-nitroquinolines 4 were obtained by nitration of 3. Compounds 4a and 4e had been prepared previously[22] in a similar way. Unlike 6-chloroquinolines,[17] compounds 3 yielded the 5-nitro derivatives 4 exclusively; no 8-nitro isomer could be detected in the 1H NMR spectra of the crude products. This is probably due to the electron-releasing effect of the methoxy group. For the same reason, the nitration could be carried out under milder conditions than previously;[17] potassium nitrate and concentrated sulfuric acid, instead of fuming nitric and sulfuric acids.

The methoxy group in 4a, 4c or 4d was readily replaced by methylamine in refluxing ethanol to give the respective 6-methylamino-5-nitroquinoline 5a, 5c or 5d. The reaction time could be shortened from ca. 5 to 2 h by refluxing in 2-methoxyethanol, but this decreased the yield by
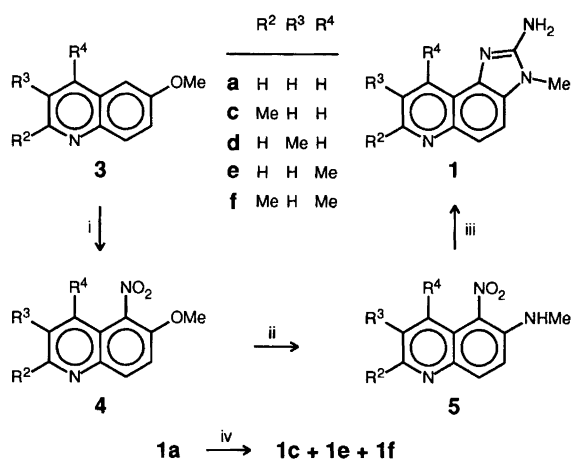
Scheme 1. Syntheses of the title compounds (with cyanogen bromide). i, KNO_3–H_2SO_4, 0 °C, 10 min; ii, $MeNH_2$–EtOH, reflux, 5 h; iii, H_2–Raney-Ni–EtOH, r.t., 30 min, then BrCN–MeCN–EtOH, r.t., overnight; iv, 70 % aq. Me_3COOH–$FeSO_4$–1 M H_2SO_4, r.t., 24 h.

5–10 %. Compound 5c had been prepared previously[23] in a similar way from 6-iodo-2-methyl-5-nitroquinoline. The methoxy group in quinoline 4e or 4f was much harder to replace by methylamine. After refluxing for several days in 2-methoxyethanol, only a minor part of the starting material had been consumed. This was probably due to steric inhibition of resonance by the 4-methyl group, which twisted the nitro group out of the quinoline plane, hence decreasing its activating power. However, 4e and 4f did react with ethanolic methylamine in a pressure bomb (75 min at 150°C).

In most syntheses of IQ compounds, the 2-aminoimidazole moiety has been formed by the reaction of cyanogen bromide with a 5,6-diamino-quinoline[1,2,17,24] or -quinoxaline.[3,15] In the synthesis of 1a and 1b,[17] the requisite diamines were obtained by reduction of the respective nitroamines 5a and 5b (Schemes 1 and 2), and 1c–1f were now prepared from 5c–5f in the same way. The reduction was carried out with Raney nickel–hydrogen.[17] (Reduction with sodium dithionite was more time consuming but gave approximately the same yield, cf. the synthesis of 6 below.) The diamines were not isolated but cyclized directly to 1c–1f.

We also prepared 1c, 1e and 1f through radical methylation of 1a with *tert*-butyl hydroperoxide and iron(II) sulfate.[5] The amount of these reagents, the reaction time and temperature were varied, but the product was always a mixture of 1c, 1e, 1f and much unchanged 1a. As the desired compounds 1c, 1e and 1f had to be obtained from such mixtures by semipreparative HPLC, this method was limited to small-scale (< 10 mg) syntheses.

Although cyanogen bromide may convert a suitable diamine into a desired IQ compound in a single step, it is highly toxic. Ziv *et al.*[25] considered its use in the synthesis of 1a hazardous and unreliable, and suggested an alternative four-step route. We have used their approach to prepare 1a–1c from the respective nitroamines 5a–5c

(Scheme 2). Thus, the imidazole ring was formed by reaction of the crude 5,6-diaminoquinoline intermediate with carbon disulfide rather than cyanogen bromide.[25] The resulting thioureas 6 were converted into their S-methyl derivatives 7, which were oxidized to the sulfones 8. The key step was the nucleophilic displacement of the methylsulfonyl (mesyl) group from 8 by an amino group to give 1.[25]

This route differed from that of Ziv *et al.*[25] mainly because the *N*-methyl group of the final products 1 was already present in the starting material 5 at the desired position. As Ziv *et al.*[25] introduced the *N*- and *S*-methyl groups simultaneously, their crude products 7, 8 and 1 were contaminated by the 1-methyl isomers. A few minor differences may also be mentioned. The nitroamines 5 were reduced with sodium dithionite,[26] which appeared to result in a purer product than hydrogenation.[17] Secondly, the thioureas 6 were S-methylated with iodomethane in strong alkali.

In addition to the three-step route from 6 to 1 via 7 and 8, we also investigated the two-step routes in Scheme 2 via the sulfonic acids 9 or the chlorine compounds 10. The acids 9 were obtained first, along with some by-products, by permanganate oxidation of 6 in acetic acid, essentially as described for the oxidation of 7 to 8.[25] The acids were isolated with some difficulty as their potassium salts. Substitution of hydrogen peroxide for the permanganate led to complete desulfurization. We are currently investigating the scope of this reaction and will report the results elsewhere. Finally, the acids 9 were obtained easily and in high purity by oxidation with hydrogen peroxide in strong aqueous alkali, followed by acidification. The 2-sulfonic acids of imidazole[27] and benzimidazole[28] have been prepared previously by essentially the same procedure. The acids 9a–9c were very hygroscopic, and satisfactory elemental analyses were obtained only from the freshly dried acids. No doubt the acids occur as zwitter ions (inner salts), resulting in low volatility. Accordingly, 9a–9c gave mass spectra on fast atom bombardment (FAB) but not on either electron impact (EI) or on chemical ionization with ammonia as the reagent gas. Moreover, the IR spectra of 9a–9c resembled those of aromatic sulfonic acid salts,[29] which often show bands near 1230, 1190, 1130 and 1040 cm^{-1}. Thus, 9a–9c showed strong bands at ca. 1235 and 1045 cm^{-1}, but their absorption between these bands was less prominent.

Compounds 10 were prepared from 6 by treatment with thionyl chloride in phosphoryl chloride.[30] Without phosphoryl chloride, no reaction occurred. Several attempts to chlorinate 6 with disulfur dichloride[31] yielded complex mixtures containing no 10.

Compounds 8–10 were first aminolysed to 1 with sodium amide in liquid ammonia as described for 8a.[25] Good yields (60–75%) of 1 were obtained from 8 but only moderate yields (35–40%) from 9 or 10. We then tried aqueous ammonia. At reflux temperature, no reaction occurred, but on prolonged heating at 170°C in a
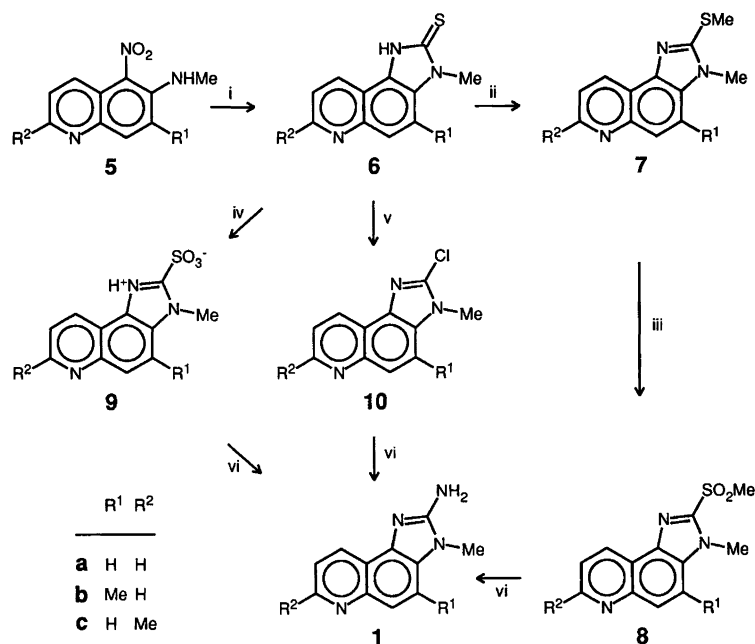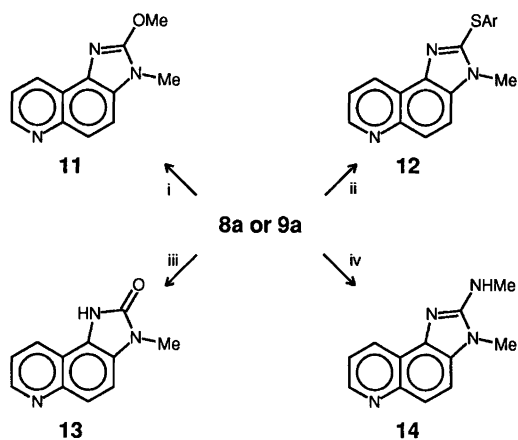
Scheme 2. Syntheses of the title compounds via thioureas. i, $Na_2S_2O_4$–MeOH–25 % aq. NH_3, reflux, 3.5 h, then CS_2–MeOH, reflux, 5 h; ii, MeI–1 M KOH–EtOH, reflux, 8 h; iii, aq. $KMnO_4$–AcOH, r.t., 2 h; iv, 30 % H_2O_2–1 M KOH, r.t., overnight, then aq. HCl; v, $SOCl_2$–$POCl_3$, reflux, 8–48 h; vi, $NaNH_2$–liq. NH_3, reflux, 3–6 h or NH_3–EtOH, 150 °C, 5 h.

pressure bomb, moderate to good yields of 1 were obtained from 8–10. However, hydrolysis to the urea derivative (13 in Scheme 3 or a homologue) was a serious side reaction. In the final experiments, 8–10 were heated at 150°C for 5 h with ethanolic ammonia in a pressure bomb. Good yields (72–78%) of 1 were obtained from 8, 9 or their potassium salts. The yields of 1 from 10 were slightly lower (65–69%). The acids 9 were easier to purify than the chlorine compounds 10. For these reasons, we preferred the route from 6 to 1 via the sulfonic acids 9 to that via the chlorine compounds 10. The route via the

Scheme 3. Nucleophilic substitution on sulfone 8a or sulfonic acid 9a. Ar = p-tolyl. i, MeONa–MeOH, reflux, 1 h; ii, ArSNa–EtOH–reflux, 2 h; iii, 1 M NaOH–Me_2SO, reflux, 24 h; iv, $MeNH_2$–EtOH, 150 °C, 4 h.

sulfides 7 and sulfones 8[25] was one step longer but otherwise convenient.

The reactions shown in Scheme 2 made available a number of IQ analogues, modified at position 2. As expected, the mesyl group in 8 and the sulfonate group in 9 were fairly good leaving groups in nucleophilic substitutions. This was exploited for the preparation of some additional IQ analogues in good yields from 8a or 9a (Scheme 3). Thus, 11–13 were obtained in reactions with the appropriate, strongly nucleophilic anions, while 14 was prepared by treatment with ethanolic methylamine at 150°C. This synthesis of 14 is superior to that previously reported.[12] On the other hand, 8a and 9a failed to react with cyanide or azide ions, even on heating in dimethyl sulfoxide at 150°C for 24 h.

Experimental

General methods. Reactions at high pressure were performed in a 23 ml Parr 4749 Teflon-coated pressure bomb. Flash liquid chromatography (FC) was performed on silica gel (230–400 mesh ASTM, Merck). HPLC separations were performed using Waters Associates equipment with an 0.8 × 10 cm column model RCM. 40% methanol in a 10 mM H_3PO_4–NaOH buffer (pH 7.3) was used as the mobile phase. The flow rate was 1 ml min^{-1}. All reactions and purifications were monitored by TLC with UV detection on aluminium sheets coated with silica gel 60 F_{254} (Merck). All evaporations were performed at reduced pressure below 40°C. Melting points are uncorrected and were determined on a Mettler FP5 or FP62

instrument. The IR spectra were obtained on a Perkin-Elmer FT-IR 1760X spectrometer. The ^{1}H NMR spectra were obtained on a Varian VXR-400 spectrometer at 20°C, and referenced to the solvent (CHCl$_3$ 7.26, Me$_2$CO 2.04 or Me$_2$SO 2.49 ppm). Coupling constants *J* are given in Hz and without sign. The mass spectra of the sulfonic acids **9a–9c** were recorded on a JEOL JMS-SX/SX102A instrument, with direct insertion, 10 keV positive FAB ionization, xenon as the neutral beam and 3-nitrobenzyl alcohol as the matrix. The other mass spectra were obtained on a Finnigan 4021 instrument, with direct insertion, 70 eV EI ionization and an ion source temperature of 200°C. Ions containing minor isotopes are not listed.

Materials. Unless otherwise stated, these were commercial samples. All organic solvents were either freshly distilled or of *p.a.* quality. The ethanol was 95%. Solvent mixtures are defined by volume ratios (v/v). 6-Methoxy-3-methylquinoline (**3d**),[21] 6-methoxy-4-methylquinoline (**3e**)[20] and 6-methoxy-2,4-dimethylquinoline (**3f**)[19] were prepared from *p*-anisidine through the Doebner–von Miller reaction. The crude products **3d–3f** were used directly in the preparation of **4d–4f** without any purification. 7-Methyl-6-methylamino-5-nitroquinoline (**5b**) was prepared from 4-chloro-*m*-toluidine in three steps.[17]

Syntheses according to Scheme 1

6-Methoxy-5-nitroquinolines **4**: *general procedure.* The appropriate 6-methoxyquinoline **3** (30 mmol) was added dropwise to concentrated sulfuric acid (40 ml) with stirring and cooling in ice. Potassium nitrate (4.4 g, 45 mmol) was added in one portion with continued stirring and cooling. After 10 min, the reaction was complete according to TLC (CHCl$_3$–EtOAc 1:1), and the mixture was poured onto ice (200 g). To the ice slurry, was added dropwise 25% aqueous ammonia, so that the temperature remained below 5°C. After addition of ca. 90 ml (pH ca. 2), a light yellow product precipitated. It was filtered off, washed with plenty of cool water and crystallized from aqueous ethanol.

6-Methoxy-5-nitroquinoline (**4a**). Yield 3.9 g (63%), m.p. 103–105°C (lit.[22] 105–106°C). The ^{1}H NMR and mass spectral data were in accordance with those reported.[22]

6-Methoxy-2-methyl-5-nitroquinoline (**4c**). Yield 5.2 g (79%), m.p. 97–99°C. Anal. C$_{11}$H$_{10}$N$_2$O$_3$: C, H, N. ^{1}H NMR (CDCl$_3$): δ 2.74 (2-Me, s), 4.06 (OMe, s), 7.41 (3-H, d, *J* 8.8), 7.54 (7-H, d, *J* 9.4), 7.97 (4-H, d, *J* 8.8), 8.17 (8-H, d, *J* 9.4). MS, *m/z* (% rel. int.): 218 (*M*, 100), 188 (8), 171 (11), 160 (33), 142 (48).

6-Methoxy-3-methyl-5-nitroquinoline (**4d**). Yield 5.5 g (84%), m.p. 140–141°C. Anal. C$_{11}$H$_{10}$N$_2$O$_3$: C, H, N. ^{1}H NMR (CDCl$_3$): δ 2.54 (3-Me, s), 4.07 (OMe, s), 7.50 (7-H, d, *J* 9.0), 7.81 (4-H, m), 8.22 (8-H, d, *J* 9.0), 8.72

(2-H, d, *J* 1.9). MS, *m/z* (% rel. int.): 218 (*M*, 100), 188 (12), 171 (12), 160 (27), 142 (36).

6-Methoxy-4-methyl-5-nitroquinoline (**4e**). Yield 4.7 g (72%), m.p. 114–115°C (lit.[22] 114–116°C). The ^{1}H NMR and mass spectral data were in accordance with those reported.[22]

6-Methoxy-2,4-dimethyl-5-nitroquinoline (**4f**). Yield 5.1 g (73%), m.p. 98–99°C. Found: C 61.6; H 4.7; N 12.0. Calc. for C$_{12}$H$_{12}$N$_2$O$_3$: C 62.1; H 5.2; N 12.1. ^{1}H NMR (CDCl$_3$): δ 2.54 (4-Me, s), 2.66 (2-Me, s), 4.02 (OMe, s), 7.17 (3-H, s), 7.50 (7-H, d, *J* 9.5), 8.14 (8-H, d, *J* 9.5). MS, *m/z* (% rel. int.): 232 (*M*, 100), 215 (64), 185 (18), 171 (29), 156 (39).

6-Methylamino-5-nitroquinolines **5**: *general procedure A.* The appropriate 6-methoxy-5-nitroquinoline **4** (2.5 mmol) was refluxed in ethanol (10 ml), while 40% aqueous methylamine (1.2 g, 15 mmol) was added dropwise through a dropping funnel extending below the liquid surface. After 5 h, the reaction was complete according to TLC (EtOAc–CHCl$_3$ 1:1). The mixture was then poured onto ice. The orange product was filtered off and recrystallized from methanol.

6-Methylamino-5-nitroquinoline (**5a**). Yield 0.44 g (86%), identical (m.p., TLC, ^{1}H NMR) with a sample prepared from 6-chloroquinoline.[17]

2-Methyl-6-methylamino-5-nitroquinoline (**5c**). Yield 0.35 g (65%). A second crystallization of the evaporation residue from the mother liquor raised the yield to 0.51 g (94%), m.p. 168–169°C (lit.[23] 167.5–168°C). ^{1}H NMR [(CD$_3$)$_2$CO]: δ 2.59 (2-Me, s), 3.25 (NMe, d, *J* 5.1), 7.46 (3-H, d, *J* 8.8), 7.54 (7-H, d, *J* 9.5), 8.00 (8-H, d, *J* 9.5), 8.89 (NH, br s), 8.90 (4-H, d, *J* 8.8). MS, *m/z* (% rel. int.): 217 (*M*, 100), 200 (13), 170 (41), 143 (34), 115 (68).

3-Methyl-6-methylamino-5-nitroquinoline (**5d**). Yield 0.46 g (84%). M.p. 182.5–183.5°C. Anal. C$_{11}$H$_{11}$N$_3$O$_2$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$CO]: δ 2.55 (3-Me, s), 3.30 (NMe, d, *J* 4.9), 7.54 (7-H, d, *J* 9.5), 8.08 (8-H, dd, *J* 9.5 and 0.9), 8.57 (2-H, d, *J* 1.8), 8.83 (4-H, m), 8.89 (NH, br s). MS, *m/z* (% rel. int.): 217 (*M*, 100), 200 (12), 170 (38), 144 (25), 115 (51).

General procedure B. The appropriate 6-methoxy-5-nitroquinoline **4** (2.5 mmol) was dissolved in 33% ethanolic methylamine (10 ml). The solution was heated at 150°C for 75 min in a pressure bomb. After cooling, the reaction mixture was evaporated to dryness and the residue crystallized from aqueous ethanol.

4-Methyl-6-methylamino-5-nitroquinoline (**5e**). Yield 0.35 g (65%), m.p. 135–136°C. Anal. C$_{11}$H$_{11}$N$_3$O$_2$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$CO]: δ 2.40 (4-Me, s), 3.22 (NMe, d, *J* 4.9), 7.24 (NH, br s), 7.38 (3-H, d, *J* 4.6), 7.56 (7-H,

d, J 9.5), 8.08 (8-H, d, J 9.5), 8.58 (2-H, d, J 4.6). MS, m/z (% rel. int.): 217 (M, 100), 200 (46), 182 (41), 171 (50), 156 (50).

2,4-Dimethyl-6-methylamino-5-nitroquinoline (*5f*). Yield 0.38 g (65%), m.p. 154.5–155°C. Anal. $C_{12}H_{13}N_3O_2$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$CO]: δ 2.36 (4-Me, s), 2.60 (2-Me, s), 3.20 (NMe, d, J 4.9), 7.12 (NH, br s), 7.28 (3-H, s), 7.51 (7-H, d, J 9.4), 8.00 (8-H, d, J 9.4). MS, m/z (% rel. int.): 231 (M, 100), 214 (28), 196 (23), 185 (47), 170 (33).

2-Amino-3-methylimidazoquinolines **1**: general procedure, cf. Ref. 17. The appropriate 6-methylamino-5-nitroquinoline **5** (1.00 mmol) was dissolved in ethanol (35–40 ml). Raney nickel (1 teaspoonful) was added, and the solution was hydrogenated under ambient conditions. After ca. 30 min, the calculated amount of hydrogen (73 ml), had been absorbed, and TLC (MeOH–CHCl$_3$ 1:10) indicated complete reaction. The catalyst was quickly filtered off by suction through filter aid under a nitrogen atmosphere. A 5.0 M solution (0.40 ml) of cyanogen bromide in acetonitrile was immediately added to the filtrate. This was stirred under nitrogen overnight, after which all intermediate diamine had been consumed according to TLC (same system as above). The solution was treated with 25% aqueous ammonia (1 ml) and evaporated onto silica gel. FC (MeOH–CHCl$_3$ 1:5) and crystallization from 1-butanol–toluene yielded **1**, m.p. > 300°C.

2-Amino-3,7-dimethyl-3H-imidazo[4,5-f]quinoline (*1c*). Yield 89 mg (42%). Anal. $C_{12}H_{12}N_4$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$SO]: δ 2.60 (7-Me, s), 3.61 (3-Me, s), 6.51 (NH$_2$, br s), 7.29 (8-H, d, J 8.4), 7.45 (5-H, d, J 8.8), 7.62 (4-H, d, J 8.8), 8.41 (9-H, d, J 8.4). MS, m/z (% rel. int.): 212 (M, 100), 197 (35), 184 (14), 170 (16).

2-Amino-3,8-dimethyl-3H-imidazo[4,5-f]quinoline (*1d*). Yield 100 mg (47%). Anal. $C_{12}H_{12}N_4$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$SO]: δ 2.47 (8-Me, s), 3.61 (3-Me, s), 6.44 (NH$_2$, br s), 7.51 (5-H, dd, J 8.9 and 0.4), 7.60 (4-H, d, J 8.9), 8.30 (9-H, dd, J 2.2 and 0.4), 8.56 (7-H, d, J 2.2). MS, m/z (% rel. int.): 212 (M, 100), 197 (27), 184 (13), 170 (15), 106 (21).

2-Amino-3,9-dimethyl-3H-imidazo[4,5-f]quinoline (*1e*). Yield 83 mg (39%). Anal. $C_{12}H_{12}N_4$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$SO]: δ 3.03 (9-Me, s), 3.63 (3-Me, s), 6.49 (NH$_2$, br s), 7.18 (8-H, d, J 4.0), 7.55 (4-H, d, J 8.7), 7.68 (5-H, d, J 8.7), 8.52 (7-H, d, J 4.0). MS, m/z (% rel. int.): 212 (M, 100), 211 (38), 197 (47), 184 (14), 170 (15).

2-Amino-3,7,9-trimethyl-3H-imidazo[4,5-f]quinoline (*1f*). Yield 61 mg (27%). Anal. $C_{13}H_{14}N_4$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$SO]: δ 2.53 (7-Me, s), 2.97 (9-Me, s), 3.60 (3-Me, s), 6.41 (NH$_2$, br s), 7.07 (8-H, s), 7.46 (4-H, d, J 8.8), 7.60 (5-H, d, J 8.8). MS, m/z (% rel. int.): 226 (M, 100), 225 (24), 211 (18), 194 (8), 184 (12).

Radical methylation of **1a**, cf. Ref. 5. Compound **1a** (99 mg, 0.50 mmol) was dissolved in 1 M sulfuric acid (34 ml). Iron(II) sulfate (0.36 g) and 70% aqueous tert-butyl hydroperoxide (6.5 ml, 50 mmol) were added with cooling in ice. After 30 min, the ice bath was removed, and the reaction mixture was left at room temperature with vigorous stirring for 24 h. The reaction mixture was then washed with ether (3 × 25 ml), adjusted to pH 9 with 25% ammonia and extracted with chloroform (5 × 10 ml). A small part of the combined extracts was evaporated to dryness. Semi-preparative HPLC of the residue yielded **1a**, **1c**, **1e** and **1f** in the approximate ratio 50:5:15:30, identical (TLC, ^{1}H NMR) with samples prepared from **5**. With equimolar amounts of **1a** and tert-butyl hydroperoxide, **1c** was the main product.

Syntheses according to Scheme 2

Thioureas **6**: general procedure, cf. Ref. 26. The appropriate 6-methylamino-5-nitroquinoline **5** (6.0 mmol) was dissolved in methanol (50 ml) and 25% aqueous ammonia (3 ml). Sodium dithionite (3.4 g, 20 mmol) was added portionwise to the refluxing solution for 30 min. The mixture was refluxed for another 3 h, until TLC (MeOH–MeCN–PhMe, 1:1:3) showed no **5**. The sodium salts were filtered off as a white precipitate and washed with hot methanol (3 × 10 ml). Carbon disulfide (10 ml, 165 mmol) was added to the combined filtrates, which were then heated to reflux. After 5 h, all diamine had reacted according to TLC. The solution was cooled to room temperature and evaporated to dryness. The residue was crystallized from ethanol, yielding **6** as colourless needles, m.p. > 300°C. The IR spectrum showed virtually no absorption at 2500–2600 cm^{-1} (S–H).

1,3-Dihydro-3-methylimidazo[4,5-f]quinoline-2-thione (*6a*). Yield 0.98 g (76%). Anal. $C_{11}H_9N_3S$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$SO]: δ 3.77 (Me, s), 7.61 (8-H, dd, J 8.4 and 4.2), 7.86 (5-H, dd, J 9.0 and 0.7), 7.90 (4-H, d, J 9.0), 8.71 (9-H, ddd, J 8.4, 1.7 and 0.7), 8.87 (7-H, dd, J 4.2 and 1.7), 13.76 (1-H, s). MS, m/z (% rel. int.): 215 (M, 100), 200 (5), 182 (40), 173 (16), 155 (7).

1,3-Dihydro-3,4-dimethylimidazo[4,5-f]quinoline-2-thione (*6b*). Yield 0.99 g (72%). Anal. $C_{12}H_{11}N_3S$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$SO]: δ 2.85 (4-Me, s), 4.05 (3-Me, s), 7.52 (8-H, dd, J 8.4 and 4.2), 7.61 (5-H, s), 8.68 (9-H, dd, J 8.4 and 1.7), 8.81 (7-H, dd, J 4.2 and 1.7), 13.86 (1-H, s). MS, m/z (% rel. int.): 229 (M, 100), 214 (9), 196 (56), 142 (9), 115 (32).

1,3-Dihydro-3,7-dimethylimidazo[4,5-f]quinoline-2-thione (*6c*). Yield 1.02 g (74%). Anal. $C_{12}H_{11}N_3S$: C, H, N. ^{1}H NMR [(CD$_3$)$_2$SO]: δ 2.65 (7-Me, s), 3.75 (3-Me, s), 7.50 (8-H, d, J 8.5), 7.76 (5-H, d, J 8.8), 7.82 (4-H, d, J 8.8), 8.59 (9-H, d, J 8.5), 13.65 (1-H, s). MS, m/z (% rel. int.): 229 (M, 100), 214 (8), 196 (42), 187 (10), 115 (28).

Sulfides 7 *(Scheme 2): general procedure.* A solution of iodomethane (0.71 g, 5.0 mmol) in ethanol (10 ml) was added dropwise for a period of 3 h to a refluxing suspension of the appropriate thiourea 6 (5.0 mmol) in ethanol (50 ml) and aqueous 1 M potassium hydroxide (6 ml). After another 5 h, TLC (EtOAc–CHCl₃ 1:1) indicated complete reaction. The reaction mixture was cooled to room temperature, diluted with water (50 ml), evaporated to ca. 50 ml and left overnight at 4°C. The product was collected and crystallized from aqueous ethanol, to yield 7 as white crystals.

3-Methyl-2-methylthio-3H-imidazo[4,5-f]quinoline (7a). Yield 1.08 g (94%), m.p. 127–128°C. Anal. $C_{12}H_{11}N_3S$: C, H, N. MS, m/z (% rel. int.): 229 (M, 71), 214 (13), 196 (100), 182 (18), 170 (30). The ¹H NMR spectral data were in accordance with those reported.[25]

3,4-Dimethyl-2-methylthio-3H-imidazo[4,5-f]quinoline (7b). Yield 1.08 g (89%), m.p. 163–165°C. Anal. $C_{13}H_{13}N_3S$: C, H, N. ¹H NMR (CDCl₃): δ 2.86 (SMe, s), 2.87 (4-Me, s), 4.04 (3-Me, s), 7.42 (8-H, dd, J 8.2 and 4.3), 7.61 (5-H, d, J 0.9), 8.83 (7-H, dd, J 4.3 and 1.9), 8.86 (9-H, ddd, J 8.2, 1.9 and 0.9). MS, m/z (% rel. int.): 243 (M, 74), 228 (13), 210 (100), 196 (19), 184 (22).

3,7-Dimethyl-2-methylthio-3H-imidazo[4,5-f]quinoline (7c). Yield 1.14 g (94%), m.p. 148–149°C. Anal. $C_{13}H_{13}N_3S$: C, H, N. ¹H NMR (CDCl₃): δ 2.77 (7-Me, s), 2.84 (SMe, s), 3.80 (3-Me, s), 7.38 (8-H, d, J 8.5), 7.60 (4-H, d, J 9.0), 7.84 (5-H, dd, J 9.0 and 0.7), 8.80 (9-H, dd, J 8.5 and 0.7). MS, m/z (% rel. int.): 243 (M, 63), 228 (13), 211 (13), 210 (100), 196 (15), 184 (22).

Sulfones 8: *general procedure.* The appropriate sulfide 7 (3.0 mmol) was dissolved in glacial acetic acid (15 ml). A solution of potassium permanganate (0.71 g, 4.5 mmol) in water (30 ml) was added dropwise and with stirring within 5 min. After 2 h, the reaction was complete according to TLC (MeCN–MeOH–PhMe 1:1:3). Solid sodium hydrogen sulfite (<0.2 g) was added, until the purple colour was discharged. The reaction mixture was extracted with chloroform (3 × 50 ml). The combined extracts were washed with aqueous sodium hydrogen carbonate (100 ml), dried over anhydrous magnesium sulfate and evaporated to dryness. Crystallization of the residue from aqueous ethanol yielded 8 as light-yellow crystals.

3-Methyl-2-methylsulfonyl-3H-imidazo[4,5-f]quinoline (8a). Yield 0.60 g (76%), m.p. 226–227°C. Anal. $C_{12}H_{11}N_3O_2S$: C, H, N. MS, m/z (% rel. int.): 261 (M, 100), 198 (65), 182 (45), 170 (56), 155 (19). The ¹H NMR spectral data were in accordance with those reported.[25]

3,4-Dimethyl-2-methylsulfonyl-3H-imidazo[4,5-f]quinoline (8b). Yield 0.59 g (72%), m.p. 258–260°C. Anal. $C_{13}H_{13}N_3O_2S$: C, H, N. ¹H NMR (CDCl₃): δ 2.91 (4-Me, s), 3.64 (3-Me, s), 4.47 (SMe, s), 7.50 (8-H, dd, J 8.3

and 4.3), 7.80 (5-H, s), 8.82 (9-H, dd, J 8.3 and 1.8), 8.91 (7-H, dd, J 4.3 and 1.8). MS, m/z (% rel. int.): 275 (M, 100), 212 (36), 196 (43), 184 (35), 171 (14).

3,7-Dimethyl-2-methylsulfonyl-3H-imidazo[4,5-f]quinoline (8c) Yield 0.61 g (74%), m.p. 190–192°C. Anal. $C_{13}H_{13}N_3O_2S$: C, H, N. ¹H NMR (CDCl₃): δ 2.80 (7-Me, s), 3.60 (3-Me, s), 4.25 (SMe, s), 7.48 (8-H, d, J 8.4), 7.73 (4-H, d, J 9.2), 8.06 (5-H, dd, J 9.2 and 0.7), 8.81 (9-H, dd, J 8.4 and 0.7). MS, m/z (% rel. int.): 275 (M, 100), 212 (56), 196 (49), 184 (57).

Sulfonic acids 9: *general procedure, cf. Ref. 27.* The appropriate thiourea 6 (5.0 mmol) was dissolved in 1 M potassium hydroxide (10 ml). The solution was treated with 30% hydrogen peroxide (2.0 ml, 20 mmol) in one portion and left at 20°C overnight. As TLC (MeOH–MeCN–PhMe 1:1:3) showed no more 6, concentrated hydrochloric acid was added dropwise, until the solution became faintly yellow (pH ca. 6). After brief cooling in ice, the free acid 9 separated as colourless crystals, m.p. >300°C. Recrystallization from aqueous ethanol was hardly necessary. The ¹H NMR signal from the acidic proton coalesced with that from the solvent moisture.

3-Methyl-3H-imidazo[4,5-f]quinoline-2-sulfonic acid (9a). Yield 1.17 g of the monohydrate (83%). Anal. $C_{11}H_9N_3O_3S·H_2O$: C, H, N. IR (KBr): 1235 (s), 1045 (s) cm⁻¹. ¹H NMR [(CD₃)₂SO]: δ 4.06 (Me, s), 7.97 (8-H, dd, J 8.5 and 4.7), 8.12 (5-H, d, J 9.2), 8.33 (4-H, d, J 9.2), 9.14 (9-H, dd, J 4.7 and 1.5), 9.31 (7-H, d, J 8.5). MS, m/z: 264 (M + H).

3,4-Dimethyl-3H-imidazo[4,5-f]quinoline-2-sulfonic acid (9b). Yield 1.29 g (93%). Anal. $C_{12}H_{11}N_3O_3S$: C, H, N. IR (KBr): 1232 (s), 1041 (s) cm⁻¹. ¹H NMR [(CD₃)₂SO]: δ 2.96 (4-Me, s), 4.41 (3-Me, s), 7.76 (5-H, s), 7.90 (8-H, dd, J 8.4 and 4.9), 9.06 (7-H, d, J 4.9), 9.27 (9-H, d, J 8.4). MS, m/z: 278 (M + H).

3,7-Dimethyl-3H-imidazo[4,5-f]quinoline-2-sulfonic acid (9c). Yield 1.20 g (87%). Anal. $C_{12}H_{11}N_3O_3S$: C, H, N. IR (KBr): 1253 (s), 1215 (s), 1048 (s) cm⁻¹. ¹H NMR [(CD₃)₂SO]: δ 2.87 (7-Me, s), 4.16 (3-Me, s), 7.92 (8-H, d, J 8.4), 8.00 (4-H, d, J 9.2), 8.30 (5-H, d, J 9.2), 9.27 (9-H, d, J 8.4). MS, m/z: 278 (M + H).

2-Chloro-3-methylimidazoquinolines 10: *general procedure, cf. Ref. 30.* Thionyl chloride (0.40 ml, 5.5 mmol) was added in one portion to a refluxing solution of the appropriate thiourea 6 (5.0 mmol) in phosphoryl chloride (25 ml). When TLC (CHCl₃–EtOAc–AcOH 20:20:1) indicated complete reaction, the mixture was poured onto ice (200 g), washed with chloroform (3 × 50 ml) and made alkaline with 25% aqueous ammonia. The light-brown precipitate was filtered off and crystallized from aqueous ethanol.

2-Chloro-3-methyl-3H-imidazo[4,5-f]quinoline (**10a**). Reaction time 48 h, yield 0.70 g (64%), m.p. 174–175°C. Found: C 60.9; H 4.0; N 18.5. Calc. for $C_{11}H_8ClN_3$: C 60.7; H 3.7; N 19.3. ^1H NMR ($CDCl_3$): δ 3.93 (Me, s), 7.54 (8-H, dd, *J* 8.3 and 4.3), 7.69 (4-H, d, *J* 9.1), 8.02 (5-H, dd, *J* 9.1 and 0.8), 8.87 (9-H, ddd, *J* 8.3, 1.7 and 0.8), 8.93 (7-H, dd, *J* 4.3 and 1.7). MS, *m/z* (% rel. int.): 217 (*M*, 100), 202 (6), 182 (6), 141 (18).

2-Chloro-3,4-dimethyl-3H-imidazo[4,5-f]quinoline (**10b**). Reaction time 24 h, yield 0.72 g (62%), m.p. 188–190°C. Anal. $C_{13}H_{10}ClN_3$: C, H, N. ^1H NMR ($CDCl_3$): δ 2.89 (4-Me, s), 4.15 (3-Me, s), 7.46 (8-H, dd, *J* 8.3 and 4.3), 7.70 (5-H, d, *J* 0.8), 8.81 (9-H, ddd, *J* 8.3, 1.7 and 0.8), 8.87 (7-H, dd, *J* 4.3 and 1.7). MS, *m/z* (% rel. int.): 231 (*M*, 100), 216 (15), 196 (14), 180 (6).

2-Chloro-3,7-dimethyl-3H-imidazo[4,5-f]quinoline (**10c**). Reaction time 8 h, yield 0.69 g (60%), m.p. 173–175°C. Anal. $C_{13}H_{10}ClN_3$: C, H, N. ^1H NMR ($CDCl_3$): δ 2.78 (7-Me, s), 3.91 (3-Me, s), 7.43 (8-H, d, *J* 8.3), 7.64 (4-H, d, *J* 9.0), 7.94 (5-H, d, *J* 9.0), 8.76 (9-H, d, *J* 8.3). MS, *m/z* (% rel. int.): 231 (*M*, 100), 216 (16), 196 (10), 115 (21).

2-Amino-3-methylimidazoquinolines **1**: *general procedure A, cf. Ref. 25.* A suspension of sodium amide was prepared from sodium (0.4 g, 17 mmol), liquid ammonia (60 ml) and a grain of anhydrous iron(III) chloride. The suspension was stirred and refluxed for 3–6 h with the appropriate compound **8**, **9** or **10** (1.00 mmol). When TLC ($MeOH-CHCl_3$ 1:5) indicated complete reaction, solid ammonium chloride was added to destroy the excess of sodium amide, and the ammonia was allowed to evaporate off. The solid residue was extracted with hot acetone (5 × 25 ml) and then with hot ethanol (5 × 25 ml). The combined extracts were evaporated onto silica gel. FC (same solvent system as above) and crystallization from ethanol–chloroform yielded **1** (59–74% from **8**, 35–39% from **9** and 35–38% from **10**), identical (TLC, ^1H NMR) with a sample prepared from **5**.

General procedure B. A suspension of the appropriate compound **8**, **9** or **10** (1.00 mmol) in 1.5 M ethanolic ammonia (10 ml) was heated at 150°C in a pressure bomb, until TLC ($MeOH-CHCl_3$ 1:5) indicated complete reaction (5 h). The reaction mixture was evaporated onto silica gel and purified as in procedure A, yielding **1** (72–75% from **8**, 74–78% from **9** and 65–69% from **10**), identical (TLC, ^1H NMR) with a sample prepared from **5**.

Syntheses according to Scheme 3

2-Methoxy-3-methyl-3H-imidazo[4,5-f]quinoline (**11**). A solution of sodium methoxide (0.54 g, 10 mmol) in methanol (30 ml) was refluxed with **8a** or **9a** (1.00 mmol). After 1 h, TLC (MeCN–MeOH–PhMe 1:1:3) showed complete reaction, and the mixture was diluted with water

(100 ml). The colourless precipitate was collected and crystallized from aqueous ethanol. The yield of **11** was 183 mg (85%) from **8a** and 179 mg (83%) from **9a**. M.p. 89.0–89.5°C. Found: C 66.9; H 5.4; N 19.1. Calc. for $C_{12}H_{11}N_3O$: C 67.6; H 5.2; N 19.7. ^1H NMR [$(CD_3)_2SO$]: δ 3.69 (3-Me, s), 4.28 (OMe, s), 7.46 (8-H, dd, *J* 8.4 and 4.2), 7.60 (4-H, d, *J* 8.8), 7.90 (5-H, dd, *J* 8.8 and 0.7), 8.80 (9-H, ddd, *J* 8.4, 1.7 and 0.7), 8.86 (7-H, dd, *J* 4.2 and 1.7). MS, *m/z* (% rel. int.): 213 (*M*, 68), 198 (100), 170 (57), 157 (17), 142 (11).

3-Methyl-2-(4-tolylthio)-3H-imidazo[4,5-f]quinoline (**12**). Compound **8a** or **9a** (1.00 mmol) was added in one portion to a refluxing solution of 4-toluenethiol (150 mg, 1.2 mmol) and sodium hydroxide (44 mg, 1.1 mmol) in ethanol (25 ml). After 2 h, the reaction was complete according to TLC (MeCN–MeOH–PhMe 1:1:3). The mixture was poured into water (200 ml) and extracted with chloroform (3 × 50 ml). The combined extracts were dried over anhydrous magnesium sulfate and evaporated to dryness. The residue was crystallized from aqueous ethanol. The yield of yellow **12** was 0.22 g (72%) from **8a** and 0.21 g (69%) from **9a**. M.p. 138.5–139.5°C. Anal. $C_{18}H_{15}N_3S$: C, H, N. ^1H NMR ($CDCl_3$): δ 2.31 (4'-Me, s), 3.86 (3-Me, s), 7.11 (3'-H and 5'-H, br d, *J* 7.9), 7.25 (2'-H and 6'-H, br d, *J* 7.9), 7.54 (8-H, dd, *J* 8.3 and 4.3), 7.67 (4-H, d, *J* 9.2), 8.00 (5-H, dd, *J* 9.2 and 0.8), 8.92 (7-H, dd, *J* 4.3 and 1.8), 9.00 (9-H, ddd, *J* 8.3, 1.8 and 0.8). MS, *m/z* (% rel. int.): 305 (*M*, 100), 272 (16), 212 (19), 170 (10), 105 (72).

1,3-Dihydro-3-methylimidazo[4,5-f]quinolin-2-one (**13**). A mixture of dimethyl sulfoxide (20 ml) and 1 M sodium hydroxide (10 ml) was refluxed with **8a** or **9a** (1.00 mmol). After 24 h, all **8a** had reacted according to TLC (MeCN–MeOH–PhMe 1:1:3). The reaction mixture was diluted with water (200 ml) and extracted with chloroform (3 × 100 ml). The combined extracts were washed, dried and evaporated onto silica gel. FC in the same system as above and crystallization from aqueous ethanol yielded **13**: 135 mg (68%) from **8a** and 149 mg (75%) from **9a**. M.p. > 300°C. Anal. $C_{11}H_9N_3O$: C, H, N. IR (KBr): 1684 (s) cm^{-1} (C=O). Other 2-imidazolones show the amide I band at exactly the same wavenumber.[32] ^1H NMR [$(CD_3)_2SO$]: δ 3.41 (Me, s), 7.50 (8-H, dd, *J* 8.5 and 4.1), 7.70 (4-H, d, *J* 9.0), 7.73 (5-H, dd, *J* 9.0 and 0.7), 8.44 (9-H, ddd, *J* 8.5, 1.7 and 0.7), 8.76 (7-H, dd, *J* 4.1 and 1.7), 11.84 (1-H, br s). MS, *m/z* (% rel. int.): 199 (*M*, 100), 184 (14), 170 (35), 156 (23), 129 (19).

3-Methyl-2-methylamino-3H-imidazo[4,5-f]quinoline (**14**). A solution of **8a** or **9a** (1.00 mmol) in 33% ethanolic methylamine (10 ml) was heated at 150°C for 4 h in a pressure bomb. After cooling, the reaction mixture was evaporated onto silica gel. FC ($MeOH-CHCl_3$ 1:5) and crystallization from aqueous ethanol gave **14** as yellow crystals, m.p. 196–197°C (lit.[12] 197–198°C). The yield

was 176 mg (83%) from **8a** and 182 mg (86%) from **9a**. The ^{1}H NMR and mass spectral data were in accordance with those reported.[12]

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