Pergamon

Tetrahedron 57 (2001) 9635–9648

TETRAHEDRON

Reformatsky reactions with *N*-arylpyrrolidine-2-thiones: synthesis of tricyclic analogues of quinolone antibacterial agents

Joseph P. Michael,* Charles B. de Koning, Gladys D. Hosken and Trevor V. Stanbury

Molecular Sciences Institute, School of Chemistry, University of the Witwatersrand, P.O. Wits 2050, South Africa

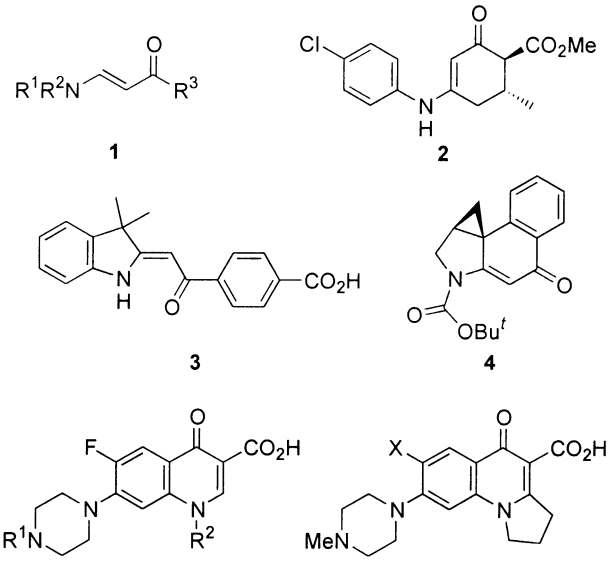
Received 6 July 2001; revised 21 August 2001; accepted 13 September 2001

Abstract—A convenient synthesis of 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acids, tricyclic analogues of the quinolone antibiotics, is described. Key steps in the route are a novel zinc-mediated Reformatsky reaction between diethyl bromomalonate and *N*-arylpyrrolidine-2-thiones **18**, and cyclisation of the resulting diethyl pyrrolidinylidenemalonate intermediates **19** in polyphosphoric acid. The products proved to be devoid of biological activity. © 2001 Elsevier Science Ltd. All rights reserved.

1. Introduction

Enaminones,[1] the basic structure of which is shown in **1**, are versatile intermediates for the synthesis of heterocycles.[2] A less well recognised property of substructure **1** is its ability to serve as a pharmacophore.[3,4] Examples of biologically active enaminones include the anticonvulsant **2**,[4] the 2-alkylideneindole **3**, which has anti-inflammatory potential,[5] and the fused polycyclic compound **4**, a synthetic analogue of the duocarmycin class of antitumour agents.[6] However, the most important chemotherapeutic agents to contain an embedded enaminone component are without doubt the quinolone antibacterials.[7,8] In particular, the fluorinated quinolones, representative examples of which include ciprofloxacin (**5**), norfloxacin (**6**) and pefloxacin (**7**), are amongst the most effective broad-spectrum oral antibacterial agents developed to date. Ciprofloxacin, for instance, is used worldwide for treating genitourinary, gastrointestinal, respiratory and skin infections, as well as sexually transmitted diseases. The fluoroquinolones are especially effective against Gram-negative bacteria, DNA synthesis in which is inhibited by the drugs' ability to corrupt the activities of DNA gyrase and topoisomerase IV, inducing these essential enzymes to kill cells by generating high levels of double-stranded DNA breaks.[9,10] Furthermore, newer compounds are being developed with promising activity against Gram-positive bacteria, anaerobes and mycobacteria,[11–13] as well as antitumour activity.[14] Even though literally thousands of quinolones have been synthesised for biological evaluation, the search for improved quinolone drugs continues, driven by the need for enhanced performance, broader efficacy, novel interventions and problems with bacterial resistance.

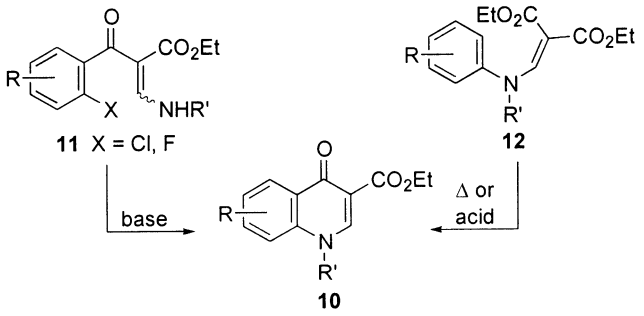
Structure–activity relationships for the quinolone antibacterials, summarised in a classic review by Albrecht,[15] and updated several times since then,[11,16–18] have highlighted, among other factors, the importance of the carboxylic acid at C-3, as well as a small hydrophobic substituent on nitrogen (N-1), typically an ethyl or cyclopropyl group. Although substituents at C-2 invariably render the compounds inactive, a short bridge of two or three atoms between N-1 and C-2 seldom compromises activity. The bridge may include nitrogen, sulphur or oxygen.[19] The all-carbon bridged pyrrolo[1,2-*a*]quinolinone **8**, a pefloxacin analogue, has a minimal inhibitory concentration (MIC) of 0.78 μg ml^{-1} against *Staphylococcus*



Keywords: thiolactams; Reformatsky reaction; enaminones; quinolones.

* Corresponding author. Tel.: +27-11-717-6753; fax: +27-11-339-7967; e-mail: jmichael@aurum.chem.wits.ac.za

PII: S0040-4020(01)00964-4



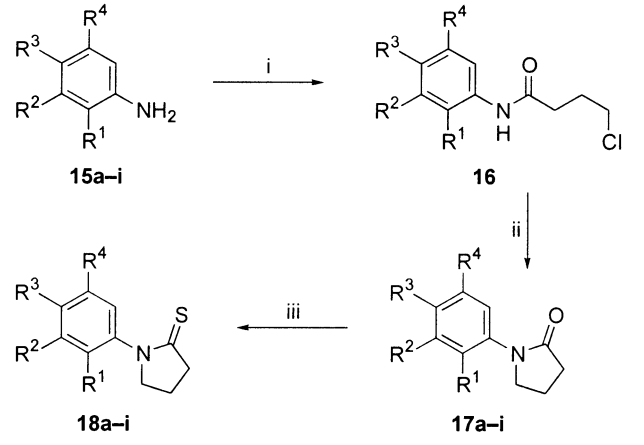
Scheme 1. Standard routes to 4-quinolone-3-carboxylates.

aureus CMX686B, and 1.56 μg ml^{-1} against *Escherichia coli*.[20] This compound also includes two structural features that seem to be obligatory for high biological activity: a fluorine substituent at C-6, and a cyclic amine at C-7. A related compound, **9**, has also demonstrated activity against a wide range of microorganisms.[21]

As part of our continuing investigations into the use of enaminones (vinylogous amides, vinylogous urethanes and related systems) as precursors for alkaloids and other nitrogen-containing heterocycles,[22] we have explored a new synthetic route to tricyclic analogues of the quinolone antibacterials. In this paper we describe a flexible synthesis of several 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acids that allows for easy variation in the nature, number and position of substituents on the aromatic ring, as well as providing access to the active compound **8** itself. Some preliminary results were reported in a prior communication.[23]

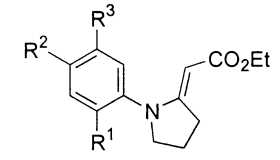
2. Results and discussion

Two principal strategies, both proceeding via enaminone intermediates, have been reported for the construction of the quinolin-4-one nucleus of the quinolone antibacterials (Scheme 1).[24] In the route developed by chemists at Bayer AG,[25,26] the quinolone nucleus **10** is formed by base-induced cyclisation of 2-(2-halobenzoyl)-3-aminoacrylates **11**. The alternative route employs a thermal or acid-catalysed Gould–Jacobs cyclisation[27] of anilinomethylene-malonates **12**. This cyclisation is essentially a modification of the classical Conrad–Limpach synthesis of 4-quinolones from anilines and acetoacetic esters.[28] Our chosen route to the tricyclic targets was based on our prior experience with *N*-aryl-2-pyrrolidinylideneacetates such as **13**,[29] which we had previously prepared either by Eschenmoser sulphide contraction[30] between *N*-arylpyrrolidine-2-thiones and ethyl bromoacetate, or, more efficiently, by condensation between substituted anilines and ethyl 6-chloro-3-oxo-hexanoate. Ready access to these enaminones dictated the use of the Gould–Jacobs cyclisation for the present work.

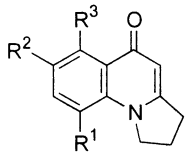


Scheme 2. *Reagents*: i, $Cl(CH_2)_3COCl$, Na_2HPO_4, $CHCl_3$; ii, NaOEt, EtOH; iii, P_2S_5, C_6H_6, ultrasound.

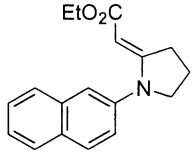
Initial model studies on the 2,5-dimethoxyphenyl substrate **13a** showed that a purely thermal cyclisation at 270°C in medicinal paraffin failed, no doubt because the (*E*)-geometry of the precursor did not permit the close approach of the aryl and ester groups. However, heating **13a** in polyphosphoric acid (PPA) at 150°C for 1.25 h afforded the tricyclic quinolone **14a** in 86% yield. Under the acidic conditions, the somewhat basic vinylogous urethane presumably undergoes protonation, resulting in scrambling of the geometry via an intermediate iminium ion. Similarly, **13b** was cyclised to **14b**, although only in 48% yield. However, under the same conditions the 2,4,5-trimethoxyphenyl substrate **13c** yielded an approximately 1:2 mixture of the expected product **14c′** and compound **14c″**, in which the methoxy substituent *peri* to the carbonyl group had been demethylated to give an intramolecularly hydrogen-bonded phenol.[31] Ethyl 1-(2-naphthyl)-2-pyrrolidinylideneacetate **13d** was cyclised quantitatively to give only **14d**, an interesting product that possesses the nucleus of a 14-azasteroid.



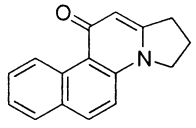
13a $R^1 = R^3 = OMe$; $R^2 = H$
13b $R^1 = R^3 = H$; $R^2 = OMe$
13c $R^1 = R^2 = R^3 = OMe$
13e $R^1 = R^2 = R^3 = H$



14a $R^1 = R^3 = OMe$; $R^2 = H$
14b $R^1 = R^3 = H$; $R^2 = OMe$
14c' $R^1 = R^2 = R^3 = OMe$
14c" $R^1 = R^2 = OMe$; $R^3 = OH$



13d



14d

Extension of these model studies to the synthesis of tricyclic quinolones bearing the pharmacologically crucial carboxylic acid substituent required access to analogues of vinylogous urethanes **13** with two ester substituents rather than one. We envisaged making them by sulphide contraction between diethyl bromomalonate[32] and *N*-arylpyrrolidine-2-thiones, which were in turn prepared from commercially available or easily synthesised anilines **15** in three steps (Scheme 2). Firstly, acylation with 4-chlorobutyryl chloride yielded intermediate *N*-aryl-4-chlorobutanamides **16**, which were cyclised without purification

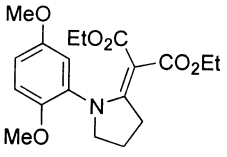
Table 1. Percentage yields for the sequence of conversions **15→17→18→20→22**

Entry	Substituents	Lactam **17**	Thiolactam **18**	Tricyclic ester **20** (over 2 steps)	Tricyclic acid **22**
a	R^1=R^4=OMe, R^2=R^3=H	97	84	49	85
b	R^1=R^2=R^3=R^4=H	80	69	61	91
c	R^1=Me, R^2=R^3=R^4=H	84	76	65	96
d	R^1=R^3=R^4=H, R^2=Me	77	62	20 (**20d**)+44 (**20j**)[a]	87 (**22d**); 89 (**22j**)[a]
e	R^1=R^2=R^4=H, R^3=Me	94	73	64	92
f	R^1=R^2=R^4=H, R^3=OMe	73	66	63	81
g	R^1=R^4=H, R^2–R^3=OCH_2O	81	79	59	69
h	R^1=Br, R^2=R^3=R^4=H	92	92	46	100
i	R^1=R^4=H, R^2=R^3=F	88	83	69	91

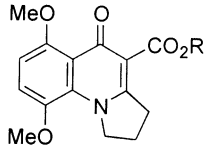
[a] **20j**, **22j**: R^1=R^2=R^3=H, R^4=Me.

to give *N*-arylpyrrolidin-2-ones **17** by treatment with sodium ethoxide in ethanol (a modification of the procedure of Manhas and Jeng[33]). Thionation of lactams **17** with phosphorus pentasulphide in benzene was promoted by sonicating the heterogeneous reaction mixture in an ultrasonic cleaning bath.[34] The yields for the *N*-arylpyrrolidin-2-ones **17a–i** and *N*-arylpyrrolidine-2-thiones **18a–i** prepared in this way are shown in Table 1 (columns 3 and 4). All compounds gave unexceptional spectra except for *N*-(2-bromophenyl)pyrrolidine-2-thione **18h**, the ^{1}H NMR spectrum of which showed two distinct sets of resonances for 5-H, in contrast to the simple triplet observed in all the other cases. The non-equivalence of the two 5-H protons at ambient temperature indicates restricted rotation about the *N*-aryl bond, a consequence of the bulky, mutually *ortho* sulphur and bromine substituents in the system. This compound apparently shows the same kind of atropisomerism that has been documented for other *N*-aryl lactams.[35]

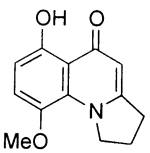
The vinylogous urethane **19a** was chosen as a test case for optimising conditions for Gould–Jacobs cyclisation with a diester precursor. Its preparation in 85% yield by sulphide contraction between thiolactam **18a** and diethyl bromomalonate was straightforward. Under similar conditions to those used for cyclisation of the monoester analogue **13a** (PPA, 140–150°C), the desired quinolone product **20a** was formed, but in a comparatively poor yield of 40%. It appeared that competing reactions at other functional groups were taking their toll, since with careful experimentation, quantities of **21**, the product of *peri*-demethylation and ester hydrolysis and decarboxylation, could be isolated. The addition of **19a** to pre-heated PPA at 193°C followed by stirring for only five minutes gave the carboxylic acid **22a** in 60% yield, indicating that cyclisation and ester hydrolysis



19a



20a R = Et
22a R = H

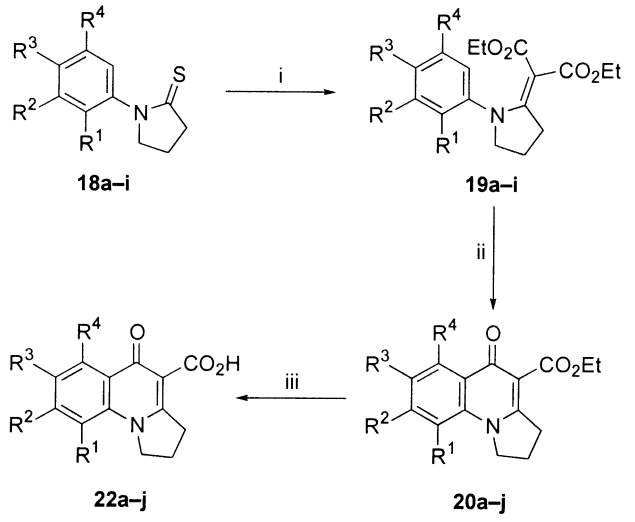


21

precede the demethylation step. Although this is a potentially useful result in view of our ultimate goal, it proved more advantageous to find milder conditions for a general cyclisation protocol. This goal was achieved simply by lowering the reaction temperature to 85–100°C; under these conditions, **19a** was converted into the tricyclic ester **20a** in 75% isolated yield over 45 min.

Sulphide contraction of the remaining eight *N*-arylpyrrolidine-2-thiones **18b–i** with diethyl bromomalonate gave variable results, in line with our prior observation of capricious sulphide contractions with *N*-arylated thiolactams.[29] After fruitless exploration of alternative routes to enaminones **19** involving condensation of thioiminium salts with diethyl malonate,[36] or reaction of diethyl diazomalonate with the thiolactams in the presence of rhodium(II) acetate,[37,38] we turned to a unique thiocarbonyl version of the Reformatsky reaction that we had previously reported for preparing the vinylogous urethane **13e** from ethyl bromoacetate, *N*-phenylpyrrolidine-2-thione **18b** and zinc–copper couple.[29] We had initially been deterred from re-exploring this option by the subsequent failure of other workers to achieve similar reactions with thiocarbonyl compounds other than thiocarbonates, dithioesters and thioketones.[39] However, when we attempted a zinc-mediated condensation of diethyl bromomalonate with pyrrolidine-2-thiones **18b–i**, we observed smooth conversion into the desired products **19b–i** provided that four equivalents each of activated zinc and the bromomalonate were used, and that iodine (0.2 equiv.) was used as an activator (Scheme 3).[40] While the products were easily isolated (aqueous work-up and chromatography on silica gel; ca. 65–100% yields) and characterised by NMR spectroscopy, they could never be obtained entirely free of a malonate-derived impurity (ca. 10%). They were thus used in the cyclisation step without rigorous purification. A noteworthy feature of the NMR spectra for the products, recorded in deuteriated chloroform, is that both the ^{1}H and ^{13}C signals for the ester groups, particularly those for the methylene groups, were very broad and poorly resolved at ambient temperature. Rotation about the *N*-aryl bond is no doubt impeded by the introduction of a very bulky substituent at C-2, so that conformational equilibration is too slow for resolution of signals on the NMR spectroscopic time scale.

The slightly contaminated vinylogous urethanes **19** were cyclised by heating in polyphosphoric acid at 100°C to give the pyrrolo[1,2-*a*]quinolones **20** in overall yields of 46–69% based on the thiolactams **18** (Table 1, column 5).

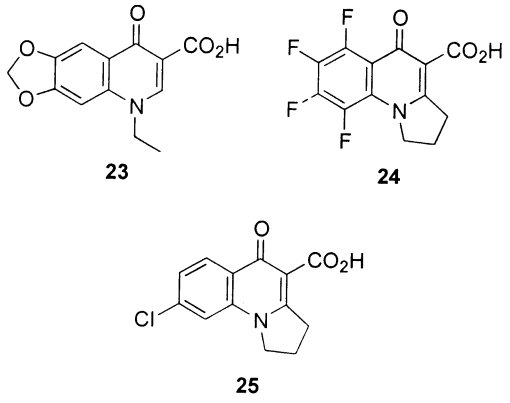


Scheme 3. *Reagents*: i, $BrCH(CO_2Et)_2$ (4 equiv.), Zn (4 equiv.), I_2 (0.2 equiv.), THF, reflux; ii, PPA, 85–100°C; iii, NaOH, H_2O, reflux, then HCl.

With the *m*-tolyl substrate **19d**, Gould–Jacobs cyclisation occurred both *ortho* and *para* to the methyl group to yield product **20d** (20%) and its regioisomer **20j** (44%). In two other cases in which isomers could possibly be formed (**19g**, **19i**), cyclisation was regiospecific. The syntheses of the tricyclic quinolonecarboxylic acids **22** were completed by hydrolysis of esters **20** with hot aqueous sodium hydroxide solution, followed by precipitation of the free acids with concentrated hydrochloric acid. It should be noted that **22g** is an analogue of oxolinic acid (**23**), a clinically prescribed quinolone antibacterial.

7,8-Difluoro-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acid (**22i**) was itself transformed into the hydrochloride salt of the biologically active pefloxacin analogue **8** by heating with excess *N*-methylpiperazine (65°C, 48 h), followed by treatment with hydrochloric acid (27% yield). Compound **22i** is thus a potentially valuable precursor for other amine-substituted pyrrolo-[1,2-*a*]quinolinone analogues of clinically useful quinolone antibiotics.

When the quinolonecarboxylic acids **22a–j** were evaluated for biological activity against two fungi (*Aspergillus niger*, *Candida albicans*) and three bacterial cultures (*Pseudomonas aeruginosa*, *S. aureus*, *E. coli*), they showed insignificant activity even at concentrations of 10^{-2} M in DMSO solution. This result, while disappointing, is in line with the findings of pharmacological tests on the handful of 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylic acids reported in the literature, apart from **8** and **9**; the tetrafluoro compound **24** was ineffective against several bacteria (*P. aeruginosa*, *E. coli*, *Proteus vulgaris*),[41] and the chloro compound **25** was inactive against a range of fungi and bacteria.[21]



3. Experimental

3.1. General methods

All solvents used for reactions and preparative chromatography were distilled. Chloroform and carbon tetrachloride were dried by passage through a short column of basic alumina. THF and diethyl ether were distilled from Na/benzophenone, dichloromethane, acetonitrile, DMF and triethylamine from CaH_2, and benzene and toluene from Na. Commercially available chemicals were used as received. Melting points, recorded on a Reichert hot-stage microscope apparatus, are uncorrected. TLC was performed on aluminium-backed Alugram Sil G/UV_{254} plates pre-coated with 0.25 mm silica gel 60. Column chromatography was carried out on Macherey–Nagel Kieselgel 60, particle size 0.063–0.200 mm (conventional columns) or Macherey–Nagel Kieselgel 60, particle size 0.040–0.063 mm (flash columns). FTIR spectra were recorded on Bruker Vector 22 or Bruker IFS 25 spectrometers. NMR spectra were recorded on Bruker AC-200 (200.13 MHz for ^1H, 50.32 MHz for ^{13}C) or Bruker DRX 400 (400.132 MHz for ^1H, 100.625 MHz for ^{13}C) spectrometers. $CDCl_3$ was used as solvent unless otherwise stated, and TMS as internal standard. DEPT and CH-correlated spectra were routinely used for assignment of signals, supplemented where necessary by nOe, decoupling and correlation experiments. Chemical shifts are reported on the δ scale, and J values are given in Hz. High-resolution mass spectra were recorded at 70 eV on a VG 70 SEQ mass spectrometer with a MASPEC II data system.

3.2. General procedure for cyclisation of ethyl 2-(1-arylpyrrolidin-2-ylidene)acetates 13 with PPA

The appropriate ethyl 2-(1-arylpyrrolidin-2-ylidene)acetate **13**[29] (0.24–0.9 mmol scale) was added to PPA (ca. 20 g per g of precursor), pre-heated to 150°C, and the mixture was stirred for 1.25 h before being cooled to room temperature. H_2O was added, the solution was made basic with concentrated aq. NH_3 solution, and extracted several times with CH_2Cl_2. The combined extracted were dried ($MgSO_4$), filtered and evaporated in vacuo to yield essentially pure 2,3-dihydropyrrolo[1,2-*a*]quinolin-5(1*H*)-ones **14**. The following compounds were prepared in this way.

3.2.1. 6,9-Dimethoxy-2,3-dihydropyrrolo[1,2-*a*]quinolin-5(1*H*)-one (14a). According to the general procedure, **14a** (52 mg, 86%) was obtained from ethyl 2-[1-(2,5-dimethoxyphenyl)pyrrolidin-2-ylidene]acetate (**13a**)[29] (71 mg, 0.24 mmol); cream needles, mp 80–82°C (from CH_2Cl_2–hexane); R_f 0.17 (MeOH–benzene 1:9); ν_{max}/cm^{-1}

($CHCl_3$) 1633 (s), 1595 (s), 1577 (s), 1490 (s), 1263 (s); δ_H (200 MHz, $CDCl_3$) 6.99 (1H, d, J=8.9 Hz; 8-H), 6.64 (1H, d, J=8.9 Hz, 7-H), 6.17 (1H, t, J=0.9 Hz, 4-H), 4.68 (2H, t, J=7.1 Hz, 1-H), 3.89 (3H, s, OCH_3 at C-6; nOe with signal at δ 6.6.4), 3.83 (3H, s, OCH_3 at C-9; nOe with signals at δ 6.99 and 4.68), 2.95 (2H, td, J=7.8 and 0.9 Hz, 3-H), 2.15 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H); δ_C (50 MHz; $CDCl_3$) 178.4 (C=O), 154.8 (C-3a), 154.5 (C-6), 143.3 (C-9), 133.2 (C-9a), 118.5 (C-5a), 113.9 (C-8), 107.7 (C-4), 104.5 (C-7), 56.8 (O*C*H_3 at C-9), 56.7 (O*C*H_3 at C-6), 56.0 (C-1), 30.6 (C-3), 22.2 (C-2). HRMS Found: M^+, 245.1052. $C_{14}H_{15}NO_3$ requires M, 245.1052.

3.2.2. 7-Methoxy-2,3-dihydropyrrolo[1,2-*a*]quinolin-5(1*H*)-one (14b). According to the general procedure, **14b** (94 mg, 48%) was obtained from ethyl 2-[1-(4-methoxyphenyl)-pyrrolidin-2-ylidene]acetate (**13b**)[29] (238 mg, 0.91 mmol); beige powder, mp 150–155°C; R_f 0.19 (MeOH–benzene 1:9); ν_{max}/cm^{-1} ($CHCl_3$) 1625 (m), 1608 (s), 1570 (s), 1498 (s); δ_H (200 MHz; $CDCl_3$) 7.80 (1H, t, J=1.7 Hz, 6-H), 7.23 (2H, d, J=1.7 Hz, 8-H, 9-H), 6.20 (1H, t, J= 0.9 Hz, 4-H), 4.22 (2H, t, J=7.3 Hz, 1-H), 3.92 (3H, s, OCH_3), 3.13. (2H, td, J=7.8 and 0.9 Hz, 3-H), 2.33 (2H, quintet with fine coupling, J=ca. 7.4 Hz, 2-H); δ_C (50 MHz; $CDCl_3$) 177.4 (C=O), 156.0 and 154.4 (C-3a, C-7), 133.2 (C-9a), 126.8 (C-5a), 122.2 and 117.0 (C-8, C-9), 105.8 (C-6), 103.9 (C-4), 55.7 (O*C*H_3), 50.2 (C-1), 31.4 (C-3), 20.8 (C-2). HRMS Found: M^+, 215.0942. $C_{13}H_{13}NO_2$ requires M, 215.0946.

3.2.3. 6,7,9-Trimethoxy-2,3-dihydropyrrolo[1,2-*a*]quinolin-5(1*H*)-one (14c′) and 6-hydroxy-7,9-dimethoxy-2,3-dihydropyrrolo[1,2-*a*]quinolin-5(1*H*)-one (14c″). According to the general procedure, **14c′** and **14c″** were obtained as an inseparable mixture (210 mg, ca. 1:2 ratio) from ethyl 2-[1-(2,4,5-trimethoxyphenyl)pyrrolidin-2-ylidene]acetate (**13c**)[29] (282 mg, 0.88 mmol). NMR spectroscopic signals ascribable to **14c′**: δ_H (200 MHz; $CDCl_3$) 6.82 (1H, s, 8-H), 6.21 (1H, s, 4-H), 4.68 (2H, t, J=7.0 Hz, 1-H), 3.93, 3.89 and 3.86 (9H, 3×s, 3×OCH_3), 2.98 (2H, t, J=7.8 Hz, 3-H), 2.22 (2H, br quintet, J=ca. 7.6 Hz); δ_C(50 MHz; $CDCl_3$) 176.9 (C=O), 155.3 (C-3a), 105.6 (C-4), 103.0 (C-8), 56.3 (C-1), 30.8 (C-3), 22.0 (C-2). NMR spectroscopic signals ascribable to **14c″**: δ_H (200 MHz; $CDCl_3$) 14.82 (OH), 6.83 (1H, s, 8-H), 5.98 (1H, s, 4-H), 4.68 (2H, t, J=7.0 Hz, 1-H), 3.92 and 3.84 (6H, 2×s, 2×OCH_3), 3.01 (2H, t, J=7.8 Hz, 3-H), 2.22 (2H, br quintet, J=ca. 7.6 Hz, 2-H); δ_C(50 MHz; $CDCl_3$) 182.1 (C=O), 157.4 (C-3a), 105.6 (C-4), 103.0 (C-8), 55.8 (C-1), 31.2 (C-3), 21.6 (C-2). Other signals in the ^{13}C NMR spectrum of the mixture were at δ 148.4, 145.89, 144.9, 141.2, 139.8, 124.7, 114.3 (aromatic C), 57.8, 57.6, 57.2 and 56.6 (O*C*H_3).

3.2.4. 2,3-Dihydrobenzo[*f*]pyrrolo[1,2-*a*]quinolin-11(1*H*)-one (14d). According to the general procedure, **14d** (64 mg, 100%) was obtained from ethyl 2-[1-(2-naphthyl)pyrrolidin-2-ylidene]acetate (**13d**)[29] (77 mg, 0.27 mmol); white powder, mp 260–262°C; R_f 0.25 (MeOH–benzene 1:9); ν_{max}/cm^{-1} ($CHCl_3$) 1637 (s), 1610 (m), 1560 (s), 1515 (m), 1483 (m), 1466 (s); δ_H (200 MHz; $CDCl_3$; signals assigned by extensive decoupling experiments) 10.51 (1H, dm, J=8.7 and ca. 1.2 Hz, 10-H), 7.92 (1H, d with fine coupling, J=9.5 Hz, 6-H), 7.85 (1H, dd, J=8.0 and 1.6 Hz, 7-H), 7.74 (1H, ddd, J=8.7, 7.0 and 1.6 Hz, 9-H), 7.57 (1H, ddd, J=8.0, 7.0 and 1.2 Hz, 8-H), 7.28 (1H, d, J=9.5 Hz, 5-H), 6.38 (1H, t, J=0.9 Hz, 12-H), 4.24 (2H, t, J=7.3 Hz, 3-H), 3.08 (2H, td, J=7.8 and 0.9 Hz, 1-H), 2.30 (2H, br quintet, J=ca. 7.5 Hz, 2-H); δ_C (50 MHz; $CDCl_3$) 179.7 (C=O), 151.9 (C-12a), 138.6 (C-4a), 133.3 (C-7), 131.4 and 129.4 (C-6a, C-10a), 128.3 (C-9), 127.8 (C-6), 127.1 (C-10), 125.6 (C-8), 117.9 (C-10b), 115.1 (C-5), 109.2 (C-12), 51.0 (C-3), 30.6 (C-1), 20.5 (C-2). HRMS Found, M^+, 235.0997. $C_{16}H_{13}NO$ requires M, 235.0997.

3.3. General procedure for the preparation of *N*-aryl-pyrrolidin-2-ones 17

The appropriate aniline **15** (24–66 mmol scale) was added to a stirred suspension of Na_2HPO_4 (ca. 2 equiv.) in anhydrous $CHCl_3$ (50–85 cm^3). Once the aniline had dissolved, an equimolar quantity of 4-chlorobutyryl chloride was added in portions. An exothermic reaction occurred, with formation of a milky solution. Stirring was maintained under N_2 for 2–22 h. Filtration of the inorganic solids through a Celite® pad followed by concentration of the filtrate in vacuo afforded the crude intermediate *N*-aryl-4-chlorobutyramide **16**. This product was added to a solution of sodium ethoxide in ethanol (prepared from 7.8 equiv. of Na metal per equivalent of substrate; concentration ca. 1 g per 17 cm^3 EtOH). The mixture was stirred at room temperature under N_2 for between 35 min and 18 h and was then acidified with concentrated HCl. Removal of the solvent under reduced pressure yielded a crude residue. H_2O (100 cm^3) was added, and the organic material was extracted with CH_2Cl_2 (3×50 cm^3). The extracts were combined, dried ($MgSO_4$) and concentrated in vacuo to yield the crude product. Column chromatography on silica gel with 10–50% EtOAc–hexane mixtures gave the desired *N*-arylpyrrolidin-2-ones **17**. Nine compounds were prepared by this general procedure (yields in Table 1). The physical properties, ^1H and ^{13}C NMR spectroscopic data for the following six agree with those published in the literature: *N*-(2,5-dimethoxyphenyl)pyrrolidin-2-one (**17a**),[42] *N*-phenyl-pyrrolidin-2-one (**17b**),[42] *N*-(2-methylphenyl)pyrrolidin-2-one (**17c**),[42] *N*-(3-methylphenyl)pyrrolidin-2-one (**17d**),[42] *N*-(4-methylphenyl)pyrrolidin-2-one (**17e**),[42] *N*-(4-methoxyphenyl)pyrrolidin-2-one (**17f**).[43] Data for the remaining three compounds are given below.

3.3.1. *N*-(3,4-Methylenedioxyphenyl)pyrrolidin-2-one (17g). According to the general procedure, **17g** was obtained from 3,4-methylenedioxyaniline **15g**[44] (81% over 2 steps); cream powder, mp 84–86°C; R_f 0.37 (EtOAc–hexane 1:1); ν_{max}/cm^{-1} (KBr) 1686 (s), 1609 (m), 1491 (s), 1375 (s), 1345 (s), 1313 (s), 1265 (s), 1210 (s), 1032 (s), 930 (s), 872 (s), 793 (s); δ_H (200 MHz; $CDCl_3$) 7.30 (1H, d, J=2.0 Hz, arom 2-H), 6.85 (1H, dd, J=8.4, 2.0 Hz, arom 6-H), 6.77 (1H, d, J=8.4 Hz, arom 5-H), 5.94 (2H, s, OCH_2O), 3.79 (2H, t, J=7.0 Hz, 5-H), 2.57 (2H, t, J= 7.6 Hz, 3-H), 2.17 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 173.9 (C=O), 147.6 and 144.4 (arom C-3, C-4), 133.7 (arom C-1), 113.1, 107.7 and 102.6 (arom C-2, C-5, C-6), 101.2 (O*C*H_2O); 49.4 (C-5), 32.4 (C-3), 17.8 (C-4); *m/z* (EI) 205 (M^+, 34%), 150

(100). HRMS Found: M^+, 205.0752. $C_{11}H_{11}NO_3$ requires M, 205.0739.

3.3.2. *N*-(2-Bromophenyl)pyrrolidin-2-one (17h). According to the general procedure, **17h** was obtained from 2-bromoaniline **15h** (92% over 2 steps); off-white powder, mp 55–56°C (lit.[33] 54.5–55°C); R_f 0.29 (EtOAc–hexane 1:1); δ_H (200 MHz; $CDCl_3$) 7.65 (1H, dd, J=7.9 and 1.5 Hz, arom 3-H), 7.41–7.16 (3H, m, arom H), 3.77 (2H, t, J=6.9 Hz, 5-H), 2.58 (2H, t, J=7.9 Hz, 3-H), 2.24 (2H, quintet with fine coupling, J=ca. 7.3 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 174.8 (C=O), 137.9 (arom C-1), 133.6, 129.6, 129.4 and 128.5 (arom C-3, C-4, C-5, C-6), 122.2 (arom C-2), 50.0 (C-5), 31.0 (C-3), 19.1 (C-4).

3.3.3. *N*-(3,4-Difluorophenyl)pyrrolidin-2-one (17i). According to the general procedure, **17i** was obtained from 3,4-difluoroaniline **15i** (88% over 2 steps); off-white powder, mp 53.5–55°C; R_f 0.40 (EtOAc–hexane 1:1); ν_{max}/cm^{-1} (KBr) 1686 (s), 1518 (s), 1396 (s), 1335 (m), 1277 (m), 1213 (m), 1181 (m), 1130 (m), 869 (m), 819 (m), 781 (m); δ_H (200 MHz; $CDCl_3$) 7.69 (1H, ddd, J=2.5, 7.5 and 12.7 Hz, arom 6-H), 7.27–7.03 (2H, m, arom 2-H, 5-H), 3.80 (2H, t, J=7.0 Hz, 5-H), 2.59 (2H, t, J=7.9 Hz, 3-H); 2.16 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 174.2 (C=O), 149.8 (dd, $^2J_{CF}$=13.3 Hz, $^1J_{CF}$=246.8 Hz, arom C-3 or C-4), 146.8 (dd, $^2J_{CF}$=12.9 Hz, $^1J_{CF}$=245.8 Hz, arom C-3 or C-4), 136.0 (d, $^4J_{CF}$=ca. 3.6 Hz, arom C-1), 116.0 (d, $^2J_{CF}$=17.4 Hz, arom C-2 or C-5), 115.0 (dd, $^4J_{CF}$=3.6 Hz, $^3J_{CF}$=5.8 Hz, arom C-6), 109.3 (d, $^2J_{CF}$=21.9 Hz, arom C-2 or C-5), 48.6 (C-5), 32.5 (C-3), 17.6 (C-4); *m/z* (EI) 197 (M^+, 47%), 142 (100), 113 (13). HRMS Found: M^+, 197.0660. $C_{10}H_9NO$ requires M, 197.0652.

3.4. General procedure for the preparation of *N*-aryl-pyrrolidine-2-thiones 18

The appropriate *N*-arylpyrrolidin-2-one **17** (9–23 mmol scale) was dissolved in benzene (concentration ca. 1 g per 10 cm^3) with the aid of an ultrasonic cleaning bath. Phosphorus pentasulphide (ca. 0.6 equiv.) was added in portions to the mixture, and ultrasonic irradiation was maintained for 2–22 h. The reaction was monitored by TLC until the starting material had been consumed. The reaction mixture was filtered, and the residue was copiously washed with boiling benzene (200 cm^3). The combined organic phases were evaporated under reduced pressure, and the crude product was purified by chromatography on silica gel with EtOAc–hexane mixtures. Nine *N*-arylpyrrolidine-2-thiones **18** were obtained (yields in Table 1). The physical properties, ^1H and ^{13}C NMR spectroscopic data for the following three agree with those published in the literature: *N*-(2,5-dimethoxyphenyl)pyrrolidine-2-thione (**18a**),[29] *N*-phenylpyrrolidine-2-thione (**18b**),[29] *N*-(4-methoxyphenyl)pyrrolidine-2-thione (**18f**).[29] Data for the remaining six compounds are given below.

3.4.1. *N*-(2-Methylphenyl)pyrrolidine-2-thione (18c). According to the general procedure, **18c** (3.34 g, 76%) was obtained from *N*-(2-methylphenyl)pyrrolidin-2-one (**17c**) (4.00 g, 22.8 mmol); colourless solid, mp 115–116°C (from EtOAc); R_f 0.59 (EtOAc–hexane 1:1); ν_{max}/cm^{-1} (KBr) 1638 (m), 1617 (m), 1489 (s), 1458 (m), 1435 (m), 1415 (m), 1301 (s), 1147 (m), 1113 (m), 770 (s); δ_H (200 MHz; $CDCl_3$) 7.31–7.23 (3H, m, arom H), 7.18–7.08 (1H, m, arom H), 3.93 (2H, t, J=7.2 Hz, 5-H), 3.17 (2H, t, J=7.9 Hz, 3-H), 2.24 (2H, quintet with fine coupling, J=ca. 7.4 Hz, 4-H), 2.22 (3H, s, CH_3); δ_C (50 MHz; $CDCl_3$) 202.5 (C=S), 139.1 and 134.4 (arom C-1, C-2), 130.9, 128.4, 126.9, 125.8 (arom C-3, C-4, C-5, C-6), 58.1 (C-5), 44.8 (C-3), 20.8 (C-4), 17.2 (*C*H_3). Anal. Found: C, 68.96; H, 6.85; N, 7.36. $C_{11}H_{13}NS$ requires C, 69.07; H, 6.85; N, 7.32%.

3.4.2. *N*-(3-Methylphenyl)pyrrolidine-2-thione (18d). According to the general procedure, **18d** (2.23 g, 62%) was obtained from *N*-(3-methylphenyl)pyrrolidin-2-one (**17d**) (3.28 g, 18.7 mmol); pale yellow solid, mp 97–98°C (from EtOAc–hexane); R_f 0.67 (EtOAc–hexane 1:1); ν_{max}/cm^{-1} (KBr) 1638 (m), 1610 (m), 1589 (m), 1485 (s), 1464 (m), 1444 (m), 1416 (m), 1327 (m), 1298 (s), 1267 (m), 1136 (m), 804 (s), 696 (s); δ_H (200 MHz; $CDCl_3$) 7.33–7.27 (3H, m, arom H), 7.15–7.10 (1H, m, arom H), 4.07 (2H, t, J=7.2 Hz, 5-H), 3.20 (2H, t, J=7.9 Hz, 3-H), 2.37 (3H, s, CH_3), 2.19 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 202.4 (C=S), 140.3 and 138.8 (arom C-1, C-3), 128.7, 128.3, 125.3 and 121.9 (arom C-2, C-4, C-5, C-6), 58.7 (C-5), 46.0 (C-3), 21.1 (*C*H_3), 20.4 (C-4). Anal. Found: C, 68.96; H, 6.80; N, 7.36. $C_{11}H_{13}NS$ requires C, 69.07; H, 6.85; N, 7.32%.

3.4.3. *N*-(4-Methylphenyl)pyrrolidine-2-thione (18e). According to the general procedure, **18e** (3.20 g, 73%) was obtained from *N*-(4-methylphenyl)pyrrolidin-2-one (**17e**) (4.00 g, 22.8 mmol); pale yellow solid, mp 88–91°C; R_f 0.76 (EtOAc–hexane 1:1); ν_{max}/cm^{-1} (KBr) 1638 (m), 1617 (m), 1514 (s), 1482 (s), 1464 (s), 1447 (s), 1418 (m), 1408 (m), 1312 (s), 1295 (s) 1260 (s), 1140 (s), 1107 (m), 1044 (m), 1020 (m), 835 (s), 560 (s); δ_H (200 MHz; $CDCl_3$) 7.38 (2H, d, J=8.4 Hz, arom H), 7.22 (2H, d, J=8.4 Hz, arom H), 4.05 (2H, t, J=7.2 Hz, 5-H), 3.18 (2H, t, J=7.9 Hz, 3-H), 2.35 (3H, s, CH_3), 2.18 (2H, quintet with fine coupling, J=7.6 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 202.1 (C=S), 137.6 and 137.2 (arom C-1, C-4), 129.3 and 124.4 (arom C-2, C-3, C-5, C-6), 58.5 (C-5), 45.9 (C-3), 20.8 (*C*H_3), 20.2 (C-4). HRMS Found: M^+, 191.0765. $C_{11}H_{13}NS$ requires M, 191.0769.

3.4.4. *N*-(3,4-Methylenedioxyphenyl)pyrrolidine-2-thione (18g). According to the general procedure, **18g** (1.57 g, 79%) was obtained from *N*-(3,4-methylenedioxyphenyl)-pyrrolidin-2-one (**17g**) (1.84 g, 9.0 mmol); colourless spars, mp 143–144°C (from $CHCl_3$–hexane); R_f 0.68 (EtOAc–hexane 1:1); ν_{max}/cm^{-1} (KBr) 1506 (s), 1492 (s), 1301 (s), 1256 (s), 1039 (s), 932 (s), 830 (s); δ_H (200 MHz; $CDCl_3$) 7.00–6.99 (1H, m, arom H), 6.86–6.85 (2H, m, arom H), 6.01 (2H, s, OCH_2O), 4.05 (2H, t, J=7.3 Hz, 5-H), 3.21 (2H, t, J=7.9 Hz, 3-H), 2.22 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 202.8 (C=S), 147.8 and 146.8 (arom C-3, C-4), 134.3 (arom C-1) 118.4, 108.2 and 106.6 (arom C-2, C-5, C-6), 101.6 (O*C*H_2O), 59.1 (C-5), 45.9 (C-3), 20.5 (C-4); *m/z* (EI) 221 (M^+, 66%), 220 (100). HRMS Found: M^+, 221.0495. $C_{11}H_{11}NO_2S$ requires M, 221.0511.

3.4.5. *N*-(2-Bromophenyl)pyrrolidine-2-thione (18h).

According to the general procedure, **18h** (2.94 g, 92%) was obtained from *N*-(2-bromophenyl)pyrrolidin-2-one (**17h**) (3.00 g, 12.5 mmol); colourless needles, mp 122–123°C (from EtOAc–hexane); ν_{max}/cm^{-1} (KBr) 1638 (m), 1617 (m), 1486 (s), 1435 (s), 1420 (s), 1327 (s), 1292 (s), 1265 (s), 1142 (s), 1061 (m), 1029 (m), 760 (s), 714 (m); R_f 0.63 (EtOAc–hexane 1:1); δ_H (200 MHz; $CDCl_3$) 7.73–7.66 (1H, m, arom H), 7.48–7.23 (3H, m, arom H), 4.30–3.80 (2H, br m, 5-H), 3.21 (2H, t, *J*=7.8 Hz, 3-H), 2.32 (2H, quintet with fine coupling, *J*=ca. 7.6 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 204.3 (C=S), 139.6 (arom C-1), 133.7, 130.1, 129.0 and 128.7 (arom C-3, C-4, C-5, C-6), 121.0 (arom C-2), 57.5 (C-5), 44.9 (C-3), 21.3 (C-4). Anal. Found: C, 47.07; H, 3.90; N, 5.55. $C_{10}H_{10}BrNS$ requires C, 46.89; H, 3.93; N, 5.47%.

3.4.6. *N*-(3,4-Difluorophenyl)pyrrolidine-2-thione (18i). According to the general procedure, **18i** (2.71 g, 83%) was obtained from *N*-(3,4-difluorophenyl)pyrrolidin-2-one (**17i**) (3.02 g, 15.3 mmol); colourless powder, mp 95–97°C (from $CHCl_3$–hexane); R_f 0.59 (EtOAc–hexane 1:1); ν_{max}/cm^{-1} (KBr) 1609 (s), 1560 (s), 1512 (s), 1430 (s), 1304 (s), 1280 (s), 1137 (s), 1111 (s), 882 (m), 828 (m), 772 (s); δ_H (200 MHz; $CDCl_3$) 7.57–7.46 (1H, m, arom 6-H), 7.29–7.15 (2H, m, arom 2-H, 5-H), 4.10 (2H, t, *J*=7.3 Hz, 5-H), 3.21 (2H, t, *J*=7.9 Hz, 3-H), 2.24 (2H, quintet with fine coupling, *J*=ca. 7.5 Hz, 4-H); δ_C (50 MHz; $CDCl_3$) 203.4 (C=S), 149.7 (dd, $^2J_{CF}$=13.4 Hz, $^1J_{CF}$=249.4 Hz, arom C-3 or C-4), 148.9 (dd, $^2J_{CF}$=12.4 Hz, $^1J_{CF}$=249.7 Hz, arom C-3 or C-4), 136.5 (dd, $^4J_{CF}$=3.5 Hz, $^3J_{CF}$=7.8 Hz, arom C-1), 121.1 (dd, $^4J_{CF}$=3.8 Hz, $^3J_{CF}$=6.3 Hz, arom C-6), 117.3 (d, $^2J_{CF}$=18.1 Hz, arom C-2 or C-5), 114.7 (d, $^2J_{CF}$=19.8 Hz, arom C-2 or C-5), 58.4 (C-5), 46.1 (C-3), 20.3 (C-4); *m/z* (EI) 213 (M^+, 63%), 212 (100), 142 (22), 113 (18). HRMS Found: M^+, 213.0419. $C_{10}H_9F_2NS$ requires M, 213.0424.

3.5. Diethyl [1-(2,5-dimethoxyphenyl)pyrrolidin-2-ylidene]malonate (19a)

A solution of *N*-(2,5-dimethoxyphenyl)pyrrolidine-2-thione (**18a**) (314 mg, 1.32 mmol) and diethyl bromomalonate (374 mg, 1.57 mmol) in CH_2Cl_2 (5 cm^3) was stirred at rt for 47 h, at which time TLC indicated complete salt formation. Triphenylphosphine (410 mg, 1.56 mmol) was added, forming an orange solution. After 10 min, triethylamine (0.33 cm^3, 2.33 mmol, 1.8 equiv.) was added, and stirring was continued for a further 68 h. The solvent was removed from the dark red solution in vacuo, and the crude orange-brown solid (1.03 g) was purified by column chromatography on silica gel, eluting with CH_2Cl_2 followed by EtOAc–hexane (7:3). The title compound **19a** (407 mg, 85%) was obtained as a pale yellow solid, mp 119–120°C (from EtOAc–hexane); R_f 0.43 (EtOAc–hexane 1:1); ν_{max}/cm^{-1} (KBr) 1712 (s), 1674 (s), 1551 (s), 1515 (s), 1446 (m), 1323 (m), 1285 (s), 1228 (s), 1104 (s), 1050 (m), 807 (m); δ_H (200 MHz; $CDCl_3$) 6.88–6.74 (2H, m, arom 3-H, 4-H), 6.69 (1H, d, *J*=2.6 Hz, arom 6-H), 4.20–3.90 and 4.05–3.90 (4H, overlapping v br s and dt, *J*=9.7 and 6.9 Hz, $CO_2CH_2CH_3$ and 5-H), 3.83 (3H, s, OCH_3), 3.74 (3H, s, OCH_3), 3.60–3.20 and 3.55–3.25 (4H, overlapping v br s and m, $CO_2CH_2CH_3$ and 3-H), 2.10 (2H, quintet with fine coupling, *J*=ca. 7.6 Hz, 4-H), 1.25–1.00 (6H, v br s, 2×$CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 167.3 (C-2), 163.8 (2×C=O), 153.2 and149.1 (arom C-2, C-5), 130.3 (arom C-1), 114.0, 113.2 and 112.9 (arom C-3, C-4, C-6), 92.7 (N–C=C), 59.6 (br s, 2×$CO_2CH_2CH_3$), 56.1 and 55.7 (C-5, OCH_3); 34.3 (C-3), 21.5 (C-4), 14.0 (br s, 2×$CO_2CH_2CH_3$). HRMS Found: M^+, 363.1701, $C_{19}H_{25}NO_6$ requires M, 363.1682. Anal. Found: C, 62.71; H, 7.08; N, 3.85. $C_{19}H_{25}NO_6$ requires C, 62.80; H, 6.93; N, 3.85%.

3.6. Cyclisation of diethyl *N*-[1-(2,5-dimethoxyphenyl)-pyrrolidin-2-ylidene]malonate (19a) in polyphosphoric acid

3.6.1. 6-Hydroxy-9-methoxy-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinolin-5-one (21). Diethyl [1-(2,5-dimethoxyphenyl)pyrrolidin-2-ylidene]malonate (**19a**) (105 mg, 0.29 mmol) was added to PPA (10 g) pre-heated to 160°C. After 75 min of stirring, the mixture was allowed to cool and diluted with H_2O (20 cm^3) and diethyl ether (50 cm^3). The organic material was extracted with diethyl ether (2×20 cm^3), dried (Na_2SO_4), and the solvent was removed under reduced pressure, yielding a crude solid (0.04 g). Recrystallisation gave the title compound **21** (11 mg, 17%) as a yellow powder, mp 196–197°C (from EtOH–hexane); R_f 0.49 (MeOH–EtOAc 1:3); ν_{max}/cm^{-1} (KBr) 3416 (br, OH), 1638 (s), 1580 (m), 1559 (m), 1506 (s), 1485 (m), 1267 (s), 1071 (m), 1158 (m), 841 (s); δ_H (200 MHz; $CDCl_3$) 14.62 (1H, s, Ar O*H*) 6.94 (1H, d, *J*=8.8 Hz, 7-H or 8-H), 6.53 (1H, d, *J*=8.8 Hz, 7-H or 8-H), 6.02 (1H, s, 4-H), 4.68 (2H, t, *J*=7.3 Hz, 1-H), 3.78 (3H, s, OCH_3), 3.00 (2H, t, J_2=7.9 Hz, 3-H), 2.20 (2H, quintet with fine coupling, *J*=ca. 7.6 Hz, 2-H); δ_C (50 MHz; $CDCl_3$) 181.8 (C=O), 157.7 and 155.7 (C-3a, C-9), 140.4 and 130.6 (C-5a, C-9a), 116.8, 108.2 and 103.6 (C-4, C-7, C-8), 114.0 (C-6), 57.2 and 55.9 (C-1, OCH_3), 31.1 (C-3), 21.6 (C-2); *m/z* (EI) 231 (M^+, 32%), 217 (17), 216 (100, M^+-CH_3). HRMS Found: M^+, 231.0894. $C_{13}H_{13}NO_3$ requires M, 231.0895.

3.6.2. 6,9-Dimethoxy-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylic acid (22a). Diethyl [1-(2,5-dimethoxyphenyl)pyrrolidin-2-ylidene]malonate (**19a**) (199 mg, 0.55 mmol) was added to PPA (4.00 g) pre-heated to 193°C. After 5 min of stirring the mixture was allowed to cool for 5 min. H_2O (5 cm^3) was added dropwise over 10 min, and the solution was neutralized with aqueous NH_3 (36%). A white precipitate formed. The mixture was extracted with CH_2Cl_2 (3×50 cm^3), and the combined extracts were washed with water (3×50 cm^3). The organic phase was dried (Na_2SO_4) and the solvent removed in vacuo to yield the carboxylic acid **22a** (0.047 g, 60%) as a yellow amorphous solid (vide infra for characterisation).

3.7. General procedure for the preparation of diethyl (1-arylpyrrolidin-2-ylidene)malonates 19 by Reformatsky reaction

A solution of diethyl bromomalonate[32] (4 equiv.) in dry THF (5–10 cm^3) was added in portions over 30 min to a mixture of Zn powder (4 equiv., dried beforehand by heating at 150°C for at least 1 h) and I_2 (ca. 0.2 equiv.) in boiling THF (5–10 cm^3) under an atmosphere of dry N_2 gas. The appropriate *N*-arylpyrrolidine-2-thione **18** (1–6.8 mmol scale) was added as a solid in one portion, and an additional

quantity of THF (5–10 cm^3) was used to ensure quantitative transfer. The mixture was heated under reflux for 1–1.5 h. After cooling, aqueous K_2CO_3 solution (50%, 20–40 cm^3) was added, and stirring was maintained for up to 2 h. The aqueous phase was extracted with diethyl ether, and the extracts were copiously washed with aqueous KI solution (10%). The organic phase was dried ($MgSO_4$) and evaporated in vacuo. The crude residue was purified by chromatography on silica gel using CH_2Cl_2 as eluant followed by EtOAc–hexane mixtures (1:9–1:1). The diethyl (1-arylpyrrolidin-2-ylidene)malonates **19**, obtained as orange oils or semi-solids after chromatography, retained an inseparable malonate-derived contaminant (^1H NMR spectroscopic signals at δ 4.4–4.1 and 1.4–1.2 ppm). The products were therefore used in the next reaction without further purification, but their NMR spectra were recorded, as detailed below. The following nine compounds were prepared by this procedure:

3.7.1. Diethyl [1-(2,5-dimethoxyphenyl)pyrrolidin-2-ylidene]malonate (19a). According to the general procedure, **19a** (1.16 g, impure) was obtained from *N*-(2,5-dimethoxyphenyl)pyrrolidine-2-thione (**18a**) (1.00 g, 4.21 mmol) and diethyl bromomalonate (4.03 g, 16.9 mmol); characterisation as described above.

3.7.2. Diethyl (1-phenylpyrrolidin-2-ylidene)malonate (19b). According to the general procedure, **19b** (392 mg, impure) was obtained from *N*-phenylpyrrolidine-2-thione (**18b**) (247 mg, 1.39 mmol) and diethyl bromomalonate (1.33 g, 5.56 mmol); R_f 0.64 (EtOAc–hexane 1:1); δ_H (200 MHz; $CDCl_3$) 7.39–7.15 (5H, m, arom H), 4.30–3.95 (2H, v br s, $CO_2CH_2CH_3$), 3.82 (2H, t, J=7.2 Hz, 5-H), 3.60–3.25 and 3.36 (4H, overlapping br s and t, J=7.9 Hz, $CO_2CH_2CH_3$ and 3-H), 2.12 (2H, quintet with fine coupling, J=7.5 Hz, 4-H), 1.35–0.95 (6H, v br s, 2×$CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 167.3 (C-2), 163.7 (2×C=O), 142.3 (arom C-1), 129.1, 126.5 and 124.8 (arom C), 89.0 (*N*–C=C), 59.7 (br s, 2×$CO_2CH_2CH_3$), 57.9 (C-5), 34.8 (C-3), 21.0 (C-4), 14.1 (br s, 2×$CO_2CH_2CH_3$). HRMS Found: M^+, 303.1479. $C_{17}H_{21}NO_4$ requires M, 303.1471.

3.7.3. Diethyl [1-(2-methylphenyl)pyrrolidin-2-ylidene]malonate (19c). According to the general procedure, **19c** (1.68 g, impure) was obtained from *N*-(2-methylphenyl)pyrrolidine-2-thione (**18c**) (1.00 g, 5.22 mmol) and diethyl bromomalonate (5.00 g, 20.9 mmol); R_f 0.41 (EtOAc–hexane 1:1); δ_H (200 MHz; $CDCl_3$) 7.24–7.09 (4H, m, arom H), 4.25–3.90 (2H, v br s, $CO_2CH_2CH_3$), 3.75–3.53 (2H, m, 5-H); 3.45–3.20 and 3.37 (4H, overlapping v br s and t, J=7.6 Hz, $CO_2CH_2CH_3$ and 3-H), 2.23 (3H, s, Ar–CH_3); 2.23–2.07 (2H, m, 4-H); 1.35–0.95 (6H, v br s, 2×$CO_2CH_2CH_3$); δ_H (200 MHz; toluene-d_8) 7.10–6.85 (4H, m, arom H), 4.20–4.05 (2H, br m, $CO_2CH_2CH_3$), 3.45–3.25 and 3.23 (4H, overlapping br m and td, J=7.9 and 1.1 Hz, $CO_2CH_2CH_3$ and 3-H), 3.15 (2H, m, 5-H), 1.46 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 4-H), 1.05 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), 0.92 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 167.0 (C-2), 163.2 (2×C=O), 139.6 and 135.9 (arom C-1, C-2), 130.8, 127.9, 127.6 and 126.6 (arom C), 92.5 (*N*–C=C), 59.5 (v br s, 2×$CO_2CH_2CH_3$), 57.1 (C-5), 34.2 (C-3), 21.6 (C-4), 17.6 (Ar–CH_3), 13.9 (v br s, 2×$CO_2CH_2CH_3$). HRMS Found: M^+, 317.1625. $C_{18}H_{23}NO_4$ requires M, 317.1627.

3.7.4. Diethyl [1-(3-methylphenyl)pyrrolidin-2-ylidene]malonate (19d). According to the general procedure, **19d** (1.89 g, impure) was obtained from *N*-(3-methylphenyl)pyrrolidine-2-thione (**18d**) (1.31 g, 6.82 mmol) and diethyl bromomalonate (6.53 g, 27.3 mmol); R_f 0.33 (EtOAc–hexane 3:7); δ_H (200 MHz; $CDCl_3$) 7.18–7.28 (1H, m, arom 6-H), 7.02–6.97 (3H, m, arom 2-H, 3-H, 4-H), 4.35–4.00 (2H, v br s, $CO_2CH_2CH_3$), 3.81 (2H, t, J=7.1 Hz, 5-H), 3.60–3.25 and 3.35 (4H, overlapping v br s and t, J=7.6 Hz, $CO_2CH_2CH_3$ and 3-H), 2.33 (3H, s, Ar–CH_3), 2.17–2.04 (2H, m, 4-H), 1.25–1.00 (6H, v br s, 2×$CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 167.3 (C-2) 163.5 (2×C=O), 142.2 (arom C-1), 138.9 (arom C-3), 128.9, 127.1, 125.2 and 121.7 (arom C), 93.2 (*N*–C=C); 59.7 (br s, 2×$CO_2CH_2CH_3$), 57.8 (C-5), 34.8 (C-3), 21.2 and 20.9 (C-4 and Ar–CH_3), 14.0 (br s, 2×$CO_2CH_2CH_3$). HRMS Found: M^+, 317.1634. $C_{18}H_{23}NO_4$ requires M, 317.1627.

3.7.5. Diethyl [1-(4-methylphenyl)pyrrolidin-2-ylidene]malonate (19e). According to the general procedure, **19e** (840 mg, impure) was obtained from *N*-(4-methylphenyl)pyrrolidine-2-thione (**18e**) (497 mg, 2.60 mmol) and diethyl bromomalonate (2.50 g, 10.5 mmol); R_f 0.29 (EtOAc–hexane 3:7); δ_H (200 MHz; $CDCl_3$) 7.17–7.04 (4H, m, arom 2H), 4.35–4.10 (2H, v br m, $CO_2CH_2CH_3$), 3.95–3.70 and 3.79 (4H, overlapping v br m and t, J=7.1 Hz, $CO_2CH_2CH_3$ and 5-H), 3.35 (2H, t, J=7.8 Hz, 3-H), 2.32 (3H, s, Ar–CH_3), 2.10 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 4-H), 1.20–1.05 (6H, br m, 2×$CO_2CH_2CH_3$).

3.7.6. Diethyl [1-(4-methoxyphenyl)pyrrolidin-2-ylidene]malonate (19f). According to the general procedure, **19f** (1.48 g, impure) was obtained from *N*-(4-methoxyphenyl)pyrrolidine-2-thione (**18f**) (1.00 g, 4.82 mmol) and diethyl bromomalonate (4.61 g, 19.3 mmol); R_f 0.35 (EtOAc–hexane 1:1); δ_H (200 MHz; $CDCl_3$) 7.12 (2H, d, J=8.9 Hz, arom 2-H, 6-H), 6.89 (2H, d, J=8.9 Hz, arom 3-H, 5-H), 4.35–4.15 (2H, v br s, $CO_2CH_2CH_3$), 3.95–3.60, 3.79 and 3.76 (7H, overlapping v br s, s and t, J=7.2 Hz, $CO_2CH_2CH_3$, OCH_3 and 5-H), 3.34 (2H, t, J=7.8 Hz, 3-H), 2.10 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 4-H), 1.13 (6H, br t, J=ca. 6.9 Hz, 2×$CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 167.1 (C-2), 163.8 (2×C=O), 157.8 (arom C-4), 134.7 (arom C-1), 126.4 (arom C-2, C-6), 114.0 (arom C-3, C-5), 92.1 (N–C=C), 59.5 (br s, 2×$CO_2CH_2CH_3$); 58.2 and 55.2 (C-5, OCH_3), 34.6 (C-3) 20.9 (C-4), 13.9 (br s, 2×$CO_2CH_2CH_3$). HRMS Found: M^+, 333.1566. $C_{18}H_{23}NO_5$ requires M, 333.1576.

3.7.7. Diethyl [1-(3,4-methylenedioxyphenyl)pyrrolidin-2-ylidene]malonate (19g). According to the general procedure, **19g** (735 mg, impure) was obtained from *N*-(3,4-methylenedioxyphenyl)pyrrolidine-2-thione (**18g**) (491 mg, 2.22 mmol) and diethyl bromomalonate (2.16 g, 9.04 mmol); R_f 0.79 (EtOAc); δ_H (200 MHz; $CDCl_3$) 6.78–6.62 (3H, m, arom H), 5.97 (2H, s, OCH_2O), 4.39–3.42 and 3.74 (6H, overlapping v br s and t, J=7.1 Hz, 2×$CO_2CH_2CH_3$ and 5-H), 3.32 (2H, t, J=7.8 Hz, 3-H), 2.09 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 4-H), 1.16

(6H, br t, J=ca. 7.0 Hz, $CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 167.2 (C-2), 163.6 (2×C=O), 147.8 and 146.0 (arom C-3, C-4), 136.1 (arom C-1), 118.7, 108.0 and 106.6 (arom C-2, C-5, C-6), 111.9 (N–C=C), 101.5 (OCH_2O), 59.7 (br s, 2×$CO_2CH_2CH_3$), 58.4 (C-5), 34.7 (C-3), 21.0 (C-4), 14.0 (br s, 2×$CO_2CH_2CH_3$). HRMS Found: M^+, 347.1361. $C_{18}H_{21}NO_6$ requires M, 347.1369.

3.7.8. Diethyl [1-(2-bromophenyl)pyrrolidin-2-ylidene]-malonate (19h). According to the general procedure, **19h** (244 mg, impure) was obtained from *N*-(2-bromophenyl)-pyrrolidine-2-thione (**18h**) (253 mg, 0.99 mmol) and diethyl bromomalonate (930 mg, 3.89 mmol); R_f 0.69 (EtOAc–hexane 1:1); δ_H (200 MHz; $CDCl_3$) 7.62 (1H, dd, J=1.4 and 7.9 Hz, arom 3-H), 7.37–7.12 (3H, m, arom H), 4.19–4.00 and 3.97 (3H, overlapping v br m and dt, J= 9.6 and J=6.5 Hz, $CO_2CH_2CH_3$ and NCH_aH_b), 3.56–3.24, 3.40 and 3.36 (5H, overlapping v br m, dt, J=7.6 and 9.6 Hz, and t with fine coupling, J=ca. 7.7 Hz, $CO_2CH_2CH_3$, NCH_aH_b and 3-H), 2.15 (2H, quintet with fine coupling, J=ca. 7.4 Hz, 4-H), 1.18 and 1.05 (6H, overlapping br t and br t, J=ca. 6.3 and 6.4 Hz, 2×$CO_2CH_2CH_3$).

3.7.9. Diethyl [1-(3,4-difluorophenyl)pyrrolidin-2-ylidene]malonate (19i). According to the general procedure, **19i** (1.26 g, impure) was obtained from *N*-(3,4-difluorophenyl)pyrrolidine-2-thione (**18i**) (0.99 g, 4.65 mmol) and diethyl bromomalonate (4.44 g, 18.6 mmol); δ_H (200 MHz; $CDCl_3$) 7.20–6.92 (3H, m, arom H), 4.36–3.96 (2H, v br s, $CO_2CH_2CH_3$), 3.79 (2H, t, J=7.1 Hz, 5-H), 3.70–3.49 (2H, v br s, $CO_2CH_2CH_3$), 3.33 (2H, t, J= 7.8 Hz, 3-H), 2.13 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 4-H), 1.37–0.93 (6H, v br s, 2×$CO_2CH_2CH_3$).

3.8. General procedure for PPA-induced cyclisation of diethyl (1-arylpyrrolidin-2-ylidene)malonates 19 to ethyl 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylates 20

The malonate-contaminated diethyl (1-arylpyrrolidin-2-ylidene)malonates **19** were dissolved in diethyl ether (3–4 cm^3) and added to PPA (ca. 10 g per g of crude **19**). The stirred mixture was heated at 85–100°C for 1–1.5 h, after which ice and H_2O (ca. 30 cm^3) was added. Stirring was maintained for 0.75 h before the solution was extracted with CH_2Cl_2 (4×40 cm^3). The extracts were dried ($MgSO_4$) before removal of the solvent in vacuo. The crude residue was purified by chromatography on silica gel with hexane–EtOAc mixtures to yield the ten pyrrolo[1,2-*a*]quinolinones **20** described below. Other than in the case of **20a**, the yields cited are over 2 steps, and are based on the amount of *N*-arylpyrrolidine-2-thione **18** used in the previous reaction.

3.8.1. Ethyl 6,9-dimethoxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (20a). According to the general procedure, **20a** (130 mg, 75%) was obtained from pure diethyl [1-(2,5-dimethoxyphenyl)pyrrolidin-2-ylidene]malonate (**19a**) (prepared by sulphide contraction; 199 mg, 0.55 mmol); waxy solid, mp 129–132°C; R_f 0.49 (MeOH–EtOAc 1:3); ν_{max}/cm^{-1} (KBr) 1699 (s), 1630 (s), 1590 (s), 1535 (s), 1366 (m), 1341 (m), 1315 (s), 1258 (s), 1142 (s), 1076 (m), 1022 (m), 960 (m), 827 (m), 810 (m); δ_H (200 MHz; $CDCl_3$) 7.02 (1H, d, J=9.0 Hz, 7-H or 8-H), 6.69 (1H, d, J=9.0 Hz, 7-H or 8-H), 4.69 (2H, t, J=7.3 Hz, 1-H), 4.35 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 3.88 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 3.23 (2H, t, J=7.9 Hz, 3-H), 2.16 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 2-H), 1.37 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 174.7 (quinolone C=O), 166.9 (ester C=O), 157.6, 154.6, 143.0, 131.8, 119.1, 114.9, 111.9 and 106.3 (arom C), 60.4 ($CO_2CH_2CH_3$), 56.8, 56.7 and 56.4 (C-1 and 2×OCH_3), 31.1 (C-3), 21.8 (C-2), 14.2 ($CO_2CH_2CH_3$); *m/z* (EI) 317 (M^+, 30%), 288 (13), 272 (17, $M^+-OCH_2CH_3$), 270 (31), 256 (43), 244 (17, $M^+-CO_2CH_2CH_3$), 243 (100), 242 (18), 215 (18), 214 (14), 200 (10), 185 (10), 115 (14). HRMS Found: M^+, 317.1250. $C_{17}H_{19}NO_5$ requires M, 317.1263. The yield of the same product prepared via malonate-contaminated diethyl [1-(2,5-dimethoxyphenyl)-pyrrolidin-2-ylidene]malonate (**19a**) was 49% over 2 steps from thiolactam **18a**.

3.8.2. Ethyl 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (20b). According to the general procedure, **20b** (218 mg) was obtained from malonate contaminated diethyl (1-phenylpyrrolidin-2-ylidene)malonate (**19b**) (392 mg); 61% over 2 steps from *N*-phenylpyrrolidine-2-thione (**18b**); colourless spars, mp 141–142°C (from $CHCl_3$–hexane) (lit.[45] 140–142°C); R_f 0.18 (EtOAc); ν_{max}/cm^{-1} (KBr) 1692 (s), 1621 (s), 1599 (s), 1535 (s), 1502 (m), 1488 (m), 1462 (m), 1204 (m), 1151 (s), 1082 (m), 1035 (m), 767 (s); δ_H (200 MHz; $CDCl_3$) 8.30 (1H, dd, J=1.6 and J=8.1 Hz, 6-H), 7.52 (1H, td, J=1.6 and 7.2 Hz, 8-H), 7.27 (1H, td, J=0.9 and 7.6 Hz, 7-H), 7.16 (1H, d, J=8.4 Hz, 9-H), 4.34 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.17 (2H, t, J=7.5 Hz, 1-H), 3.36 (2H, t, J=7.9 Hz, 3-H), 2.28 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H), 1.39 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 174.4 (quinolone C=O), 166.1 (ester C=O), 159.5 (C-3a), 137.3 (C-9a), 131.9 (C-8), 126.7 (C-6), 126.5 (C-5a), 124.0 (C-7), 115.6 (C-9), 108.8 (C-4), 60.1 ($CO_2CH_2CH_3$), 50.5 (C-1), 33.0 (C-3), 20.0 (C-2), 14.2 ($CO_2CH_2CH_3$); *m/z* (EI) 257 (M^+, 16%), 212 (32, $M^+-OCH_2CH_3$), 186 (14), 185 (100, $M^+-CO_2C_2H_4$). HRMS Found: M^+, 257.1040. $C_{15}H_{15}NO_3$ requires M, 257.1052.

3.8.3. Ethyl 9-methyl-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylate (20c). According to the general procedure, **20c** (0.917 g) was obtained from malonate contaminated diethyl [1-(2-methylphenyl)pyrrolidin-2-ylidene]malonate (**19c**) (1.679 g); 65% over 2 steps from thiolactam **18c**; cream needles, mp 137–138°C (from $CHCl_3$–hexane); R_f 0.25 (EtOAc); ν_{max}/cm^{-1} (KBr) 1715 (m), 1699 (s), 1616 (s), 1586 (s), 1549 (m), 1489 (m), 1421 (m), 1146 (s), 1106 (m), 1035 (m), 771 (m), 747 (m); δ_H (200 MHz; $CDCl_3$) 8.33 (1H, dd, J=1.7 and 7.8 Hz, 6-H), 7.36–7.31 (1H, m, 8-H), 7.18 (1H, t, J=7.8 Hz, 7-H), 4.65 (2H, t, J=7.3 Hz, 1-H), 4.38 (2H, q, J=7.2 Hz, $CO_2CH_2CH_3$), 3.34 (2H, t, J=7.9 Hz, 3-H), 2.76 (3H, s, Ar–CH_3), 2.23 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 2-H), 1.40 (3H, t, J=7.2 Hz, $CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 174.5 (quinolone C=O), 166.7 (ester C=O), 160.5 (C-3a), 138.3 (C-9a), 136.7 (C-8), 128.7 (C-9), 126.1 (C-6), 125.5 (C-5a), 124.3 (C-7), 109.5 (C-4), 60.6 ($CO_2CH_2CH_3$), 55.8 (C-1), 32.1 (C-3), 23.7 (Ar–CH_3), 21.9 (C-2), 14.4 ($CO_2CH_2CH_3$); *m/z* (EI) 271 (M^+, 18%), 226 (28, $M^+-OCH_2CH_3$), 200 (15), 199 (100,

$M^+-CO_2C_2H_4$). HRMS Found: M^+, 271.1200. $C_{16}H_{17}NO_3$ requires M, 271.1208.

3.8.4. Ethyl 8-methyl-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylate (20d) and ethyl 6-methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (20j). According to the general procedure, **20d** (373 mg) and **20j** (808 mg) were obtained from malonate-contaminated diethyl [1-(3-methylphenyl)pyrrolidin-2-ylidine]malonate (**19d**) (1.888 g); 20 and 44% yields, respectively, over 2 steps from thiolactam **18d**. Compound **20j**: colourless needles, mp 148–149°C (from $CHCl_3$–hexane); R_f 0.33 (acetone–CH_2Cl_2 1:9); ν_{max}/cm^{-1} (KBr) 1717 (s), 1599 (s), 1540 (s), 1497 (s), 1439 (m), 1419 (m), 1367 (m), 1283 (m), 1204 (s), 1134 (s), 1024 (m), 814 (m), 786 (m), 758 (s), 755 (m); δ_H (200 MHz; $CDCl_3$) 7.46 (1H, t, J=7.9 Hz, 8-H), 7.14–7.09 (2H, m, 7-H, 9-H), 4.39 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.22 (2H, t, J=7.5 Hz, 1-H), 3.45 (2H, t, J=7.9 Hz, 3-H), 2.96 (3H, s, Ar–CH_3), 2.33 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H), 1.40 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), δ_C (50 MHz; $CDCl_3$) 177.5 (quinolone C=O), 166.8 (ester C=O), 157.8 (C-3a), 142.6 (C-6), 139.5 (C-9a), 131.3 (C-8), 127.7 (C-7), 125.3 (C-5a), 113.6 (C-9), 111.0 (C-4), 60.6 ($CO_2CH_2CH_3$), 51.3 (C-1), 32.8 (C-3), 24.0 (Ar–CH_3), 20.4 (C-2), 14.5 ($CO_2CH_2CH_3$); *m/z* 271 (M^+, 34%), 226 (14, $M^+-OCH_2CH_3$), 198 (17), 197 (100, $M^+-CO_2C_2H_4$), 169 (11). HRMS Found: M^+, 271.1205. $C_{16}H_{17}NO_3$ requires M, 271.1208. Compound **20d**: light brown powder, mp 165–168°C; R_f 0.15 (acetone–CH_2Cl_2 1:9); ν_{max}/cm^{-1} (KBr) 1707 (s), 1686 (s), 1604 (s), 1560 (m), 1528 (s), 1476 (m), 1221 (m), 1193 (m), 1150 (m), 1091 (m), 1033 (m), 803 (s); δ_H (200 MHz; $CDCl_3$) 8.21 (1H, d, J=8.2 Hz, 6-H), 7.10 (1H, dd, J=0.8 and 8.2 Hz, 7-H), 6.96 (1H, s, 9-H), 4.35 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.19 (2H, t, J=7.5 Hz, 1-H), 3.39 (2H, t, J=7.9 Hz, 3-H), 2.43 (3H, s, Ar–CH_3), 2.29 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H), 1.39 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$), δ_C (50 MHz; $CDCl_3$) 174.6 (quinolone C=O), 166.4 (ester C=O), 159.5 (C-3a), 143.0, 137.6 and 124.6 (C-5a, C-8, C-9a), 126.9 and 125.7 (C-6, C-7), 115.5 (C-9), 108.8 (C-4), 60.3 ($CO_2CH_2CH_3$), 50.6 (C-1), 33.1 (C-3), 21.8 (C-2), 20.1 (Ar–CH_3), 14.3 ($CO_2CH_2CH_3$); *m/z* (EI) 271 (M^+, 14%), 226 (26, $M^+-OCH_2CH_3$), 200 (17), 199 (100). HRMS Found: M^+, 271.1201. $C_{16}H_{17}NO_3$ requires M, 271.1208.

3.8.5. Ethyl 7-methyl-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylate (20e). According to the general procedure, **20e** (454 mg) was obtained from malonate-contaminated diethyl [1-(4-methylphenyl)pyrrolidin-2-ylidene]malonate (**19e**) (840 mg); 64% over 2 steps from thiolactam **18e**; pale yellow amorphous solid, mp 175–179°C; R_f 0.23 (EtOAc); ν_{max}/cm^{-1} (KBr) 1703 (s), 1629 (s), 1603 (s), 1506 (s), 1186 (s), 1167 (s), 1098 (s), 1033 (m), 806 (s); δ_H (400 MHz; $CDCl_3$) 8.17 (1H, d, J=1.4 Hz, 6-H), 7.40 (1H, dd, J=1.4 and 8.5 Hz, 8-H), 7.15 (1H, d, J=8.5 Hz, 9-H), 4.37 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.22 (2H, t, J=7.5 Hz, 1-H), 3.45 (2H, t, J=7.9 Hz, 3-H), 2.43 (3H, s, Ar–CH_3), 2.34 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H), 1.40 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 174.4 (quinolone C=O), 166.3 (ester C=O), 159.0 (C-3a), 135.4, 137.6 and 126.5 (C-5a, C-7, C-9a), 133.2 and 126.3 (C-6, C-8), 115.6 (C-9), 108.5 (C-4), 60.1 ($CO_2CH_2CH_3$), 50.6 (C-1), 33.0 (C-3), 20.8 (C-2), 20.0 (Ar–CH_3), 14.2 ($CO_2CH_2CH_3$); *m/z* (EI) 271 (M^+, 18%), 226 (26, $M^+-OCH_2CH_3$), 200 (15), 199 (100). HRMS Found: M^+, 271.1198. $C_{16}H_{17}NO_3$ requires M, 271.1208.

3.8.6. Ethyl 7-methoxy-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylate (20f). According to the general procedure, **20f** (0.878 g) was obtained from malonate-contaminated diethyl [1-(4-methoxyphenyl)pyrrolidin-2-ylidene]malonate (**19f**) (1.475 g); 63% over 2 steps from thiolactam **18f**; pale yellow amorphous solid, mp 175–176.5°C; R_f 0.12 (EtOAc); ν_{max}/cm^{-1} (KBr) 2976 (m), 1717 (s), 1600 (s), 1582 (s), 1540 (s), 1506 (s), 1427 (m), 1387 (m), 1347 (m), 1266 (m), 1204 (s), 1151 (s), 1044 (s), 1026 (s), 815 (s), 625 (m); δ_H (200 MHz; $CDCl_3$) 7.75 (1H, s, 6-H), 7.15 (2H, d, J=1.3 Hz, 8-H, 9-H), 4.36 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.20 (2H, t, J=7.5 Hz, 1-H), 3.87 (3H, s, OCH_3), 3.42 (2H, t, J=7.9 Hz, 3-H), 2.30 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 2-H), 1.40 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 174.1 (quinolone C=O), 166.5 (ester C=O), 158.4 and 156.6 (C-3a, C-7), 132.0 and 128.1 (C-5a, C-9a), 122.0, 117.3 and 106.9 (C-6, C-8, C-9), 108.0 (C-4), 60.2 ($CO_2CH_2CH_3$), 55.5 (OCH_3), 50.9 (C-1), 32.1 (C-3), 20.1 (C-2), 14.3 ($CO_2CH_2CH_3$); *m/z* (EI) 287 (M^+, 35%), 242 (26, $M^+-OCH_2CH_3$), 241 (12), 242 (12), 216 (17), 215 (100, $M^+-CO_2C_2H_4$), 214 (21, $M^+-CO_2CH_2CH_3$). HRMS Found: M^+, 287.1169. $C_{16}H_{17}NO_4$ requires M, 287.1158.

3.8.7. Ethyl 7,8-methylenedioxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (20g). According to the general procedure, **20g** (395 mg) was obtained from malonate-contaminated diethyl [1-(3,4-methylenedioxyphenyl)pyrrolidin-2-ylidene]malonate (**19g**) (735 mg); 59% over 2 steps from thiolactam **18g**; beige powder, mp 242–246°C; R_f 0.12 (EtOAc); ν_{max}/cm^{-1} (KBr) 1686 (s), 1628 (m), 1584 (s), 1539 (s), 1506 (s), 1467 (s), 1242 (s), 1191 (m), 1098 (m), 1081 (m), 1036 (m), 932 (m), 806 (m); δ_H (200 MHz; $CDCl_3$) 7.67 (1H, br s, 6-H), 6.64 (1H, br s, 9-H), 6.08 (2H, br s, OCH_2O), 4.36 (2H, br q, J=7.0 Hz, $CO_2CH_2CH_3$), 4.18 (2H, br t, J=7.1 Hz, 1-H), 3.44 (2H, br t, J=7.6 Hz, 3-H), 2.32 (2H, br quintet, J=ca. 7.4 Hz, 2-H), 1.40 (3H, br t, J=7.0 Hz, $CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 173.5 (quinolone C=O), 166.7 (ester C=O), 158.1 (C-3a), 151.9 and 145.8 (C-7, C-8), 134.7 (C-9a), 122.7 (C-5a), 108.6 (C-4), 104.2 and 102.1 (C-6, C-9), 95.4 (OCH_2O), 60.5 ($CO_2CH_2CH_3$), 51.4 (C-1), 33.1 (C-3), 20.3 (C-2), 14.4 ($CO_2CH_2CH_3$); *m/z* (EI) 301 (M^+, 21%), 256 (26, $M^+-OCH_2CH_3$), 230 (15), 229 (100, $M^+-CO_2C_2H_4$). HRMS Found: M^+, 301.0936. $C_{16}H_{15}NO_5$ requires M, 301.0950.

3.8.8. Ethyl 9-bromo-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylate (20h). According to the general procedure, **20h** (153 mg) was obtained from malonate-contaminated diethyl [1-(2-bromophenyl)pyrrolidin-2-ylidene]malonate (**19h**) (244 mg); 46% over 2 steps from thiolactam **18h**; light brown amorphous solid, mp 175–178°C; R_f 0.43 (EtOAc); ν_{max}/cm^{-1} (KBr) 1699 (s), 1622 (s), 1585 (m), 1535 (m), 1481 (m), 1421 (m), 1218 (m), 1147 (m), 1077 (m), 1039 (m); δ_H (200 MHz; $CDCl_3$) 8.40 (1H, dd, J=1.6 and 7.9 Hz, 6-H), 7.80 (1H,

dd, J=1.7 and 7.6 Hz, 8-H), 7.12 (1H, t, J=7.8 Hz, 7-H), 4.92 (2H, t, J=7.3 Hz, 1-H), 4.37 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 3.36 (2H, t, J=7.9 Hz, 3-H), 2.25 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 2-H), 1.40 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); δ_C (50 MHz; $CDCl_3$) 173.2 (quinolone C=O), 165.9 (ester C=O), 161.1 (C-3a), 139.2 (C-8), 136.8, 129.9, 110.2 and 108.0 (C-4, C-5a, C-9, C-9a), 127.3 and 124.9 (C-6, C-7), 60.6 ($CO_2CH_2CH_3$), 56.4 (C-1), 32.0 (C-3), 21.8 (C-2), 14.2 ($CO_2CH_2CH_3$); m/z (EI) 335 (M^+, 12%), 292 (19), 290 ($M^+-OCH_2CH_3$, 20), 271 (19), 266 (10), 265 (77), 264 (15), 263 (79), 226 (26), 200 (14), 199 (100), 154 (18). HRMS Found: M^+, 335.0143. $C_{15}H_{14}BrNO_3$ requires M, 335.0157.

3.8.9. Ethyl 7,8-difluoro-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylate (20i). According to the general procedure, **20i** (0.944 g) was obtained from malonate-contaminated diethyl [1-(3,4-difluorophenyl)pyrrolidin-2-ylidene]malonate (**19i**) (1.258 g); 69% over 2 steps from thiolactam **18i**; colourless needles, mp 184–185°C (from EtOAc–hexane); R_f 0.34 (EtOAc); ν_{max}/cm^{-1} (KBr) 1717 (s), 1710 (s), 1610 (s), 1545 (m), 1491 (s), 1303 (m), 1191 (m), 1095 (m), 1083 (s); δ_H (400 MHz; $CDCl_3$) 8.11 (1H, dd, $^3J_{6,F}$=8.7 Hz and $^2J_{6,F}$=10.5 Hz, 6-H), 7.10 (1H, dd, $^3J_{8,F}$=6.2 Hz and $^2J_{8,F}$=10.6 Hz, 8-H), 4.37 (2H, q, J=7.1 Hz, $CO_2CH_2CH_3$), 4.23 (2H, t, J=7.5 Hz, 1-H), 3.49 (2H, t, J=7.9 Hz, 3-H), 2.38 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H), 1.39 (3H, t, J=7.1 Hz, $CO_2CH_2CH_3$); δ_C (100 MHz; $CDCl_3$) 173.2 (quinolone C=O), 166.0 (ester C=O), 160.2 (C-3a), 153.3 (dd, $^2J_{CF}$=15.2 Hz and $^1J_{CF}$=256.1 Hz, C-7 or C-8), 148.1 (dd, $^2J_{CF}$=13.3 Hz and $^1J_{CF}$=250.0 Hz, C-7 or C-8), 134.6 (d, $^3J_{CF}$=9.5 Hz, C-9a), 124.0 (C-5a), 115.1 (d, $^2J_{CF}$=18.7 Hz, C-6 or C-9), 109.3 (C-4), 104.6 (d, $^2J_{CF}$=21.9 Hz, C-6 or C-9), 60.7 ($CO_2CH_2CH_3$), 51.3 (C-1), 33.2 (C-3), 20.4 (C-2), 14.3 ($CO_2CH_2CH_3$); m/z (EI) 293 (M^+, 15%), 248 ($M^+-OCH_2CH_3$, 33), 222 (15), 221 (100), 220 ($M^+-CO_2CH_2CH_3$, 10), 69 (18), 41 (11), 28 (23). HRMS Found: M^+, 293.0858. $C_{15}H_{13}F_2NO_3$ requires M, 293.0863.

3.9. General procedure for the preparation of 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acids 22 from esters 20

A mixture of the appropriate ethyl 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate **20** (0.15–1.50 mmol scale) and aqueous 1M NaOH solution (10–20 cm^3) was heated to 80–100°C, and maintained in this temperature range for 1 h. The reaction mixture was allowed to cool, and then acidified to pH ca. 4 with concentrated HCl. The precipitate that formed was filtered and washed with copious quantities of with water. Drying in a desiccator yielded essentially pure 5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylic acids **22**. The products could be recrystallised from DMF for microanalysis, but owing to their generally poor solubility in other organic solvents, NMR spectra were recorded on the sodium salts (prepared in situ in $NaOD/D_2O$ solution) in all cases other than **22a**. The following 10 compounds were prepared by the general procedure.

3.9.1. 6,9-Dimethoxy-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylic acid (22a). According to the general procedure, **22a** (180 mg, 85%) was obtained from ethyl 6,9-dimethoxy-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylate (**20a**) (232 mg, 0.73 mmol); colourless needles, mp 257–259°C decomp. (from DMF); ν_{max}/cm^{-1} (KBr) 3412 (br, OH), 1699 (s), 1612 (m), 1546 (s), 1419 (m), 1314 (m), 1266 (m), 1150 (m), 1084 (m), 820 (m); δ_H (200 MHz; $CDCl_3$) 16.38 (1H, s, CO_2H), 7.20 (1H, d, J=9.1 Hz, 7-H or 8-H), 6.86 (1H, d, J=9.1 Hz, 7-H or 8-H), 4.88 (2H, t, J=7.6 Hz, 1-H), 3.97 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 3.71 (2H, t, J=8.1 Hz, 3-H), 2.25 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H); δ_C (50 MHz; $CDCl_3$) 179.6 (quinolone C=O), 170.5 (CO_2H), 167.6, 163.5, 154.5, 143.3, 131.1, 116.5 (C-7 or C-8), 107.3 (C-7 or C-8), 106.2, 57.8, 57.0 and 56.7 (C-1, 2× OCH_3), 33.2 (C-3), 21.5 (C-2). Anal. Found: C, 62.00; H, 5.20; N, 4.81. $C_{15}H_{15}NO_5$ requires C, 62.28; H, 5.23; N, 4.84%.

3.9.2. 5-Oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acid (22b). According to the general procedure, **22b** (195 mg, 91%) was obtained from ethyl 5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (**20b**) (240 mg, 0.93 mmol); white powder, mp 258–259°C decomp. (from DMF) (lit.[45] 252–254°C); ν_{max}/cm^{-1} (KBr) 3411 (br, OH), 1708 (s), 1598 (s), 1535 (s), 1458 (s), 1173 (m), 1282 (m), 972 (m), 777 (s); δ_H (400 MHz; D_2O/NaOD) 7.99 (1H, d, J=8.1 Hz, 6-H), 7.46 (1H, t, J=ca. 7.7 Hz, 8-H), 7.26 (1H, t, J=ca. 7.6 Hz, 7-H), 7.10 (1H, d, J=8.4 Hz, 9-H), 4.04 (2H, t, J=7.3 Hz, 1-H), 3.23 (2H, t, J=7.8 Hz, 3-H), 2.25 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 2-H); δ_C (100 MHz; D_2O/NaOD) 175.7 and 174.6 (2×C=O), 156.4 (C-3a), 138.2 (C-9a), 133.1, 125.9, 125.6 (C-5a), 125.0, 119.0 (C-4), 117.4, 52.2 (C-1), 32.6 (C-3), 21.0 (C-2). Anal. Found: C, 68.05; H, 4.89; N, 6.12. $C_{13}H_{11}NO_3$ requires C, 68.11; H, 4.84; N, 6.11%.

3.9.3. 9-Methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylic acid (22c). According to the general procedure, **22c** (344 mg, 96%) was obtained from ethyl 9-methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (**20c**) (399 mg, 1.47 mmol); colourless needles, mp 297–298°C (from DMF); ν_{max}/cm^{-1} (KBr) 3413 (br, OH), 1711 (s), 1599 (s), 1542 (s), 1514 (m), 1488 (s), 1463 (m), 1416 (m), 1276 (w), 1110 (w), 976 (2), 796 (m); δ_H (200 MHz; D_2O/NaOD) 7.98 (1H, d, J=7.7 Hz, 6-H), 7.26–7.10 (2H, m, 7-H, 8-H), 4.57 (2H, br t, J=7.1 Hz, 1-H), 3.18 (2H, t, J=7.8 Hz, 3-H), 2.49 (3H, s, Ar–CH_3), 2.22 (2H, quintet with fine coupling, J=ca. 7.4 Hz, 2-H); δ_C (50 MHz; D_2O/NaOD) 177.0 and 176.0 (2×C=O), 166.4, 159.2, 140.9, 138.9, 129.8, 129.2, 126.7, 126.5, 121.1, 59.2 (C-1), 33.7 (C-3), 25.4 (Ar–CH_3), 24.3 (C-2); m/z (EI) 243 (M^+, 28%), 224 (10), 200 (15), 199 (100, M^+-CO_2), 198 (10), 171 (14), 170 (13). HRMS Found: M^+, 243.0911. $C_{14}H_{13}NO_3$ requires M, 243.0895. Anal. Found: C, 68.87; H, 5.43; N, 5.59. $C_{14}H_{13}NO_3$ requires C, 69.12; H, 5.39; N, 5.76%.

3.9.4. 8-Methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylic acid (22d). According to the general procedure, **22d** (104 mg, 87%) was obtained from ethyl 8-methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (**20d**) (133 mg, 0.49 mmol); beige powder, mp 272–273°C decomp. (from DMF); ν_{max}/cm^{-1}

(KBr) 3443 (br, OH), 1693 (s), 1622 (m), 1601 (s), 1520 (s), 1438 (s), 1286 (m), 1097 (m), 960 (w), 809 (s); δ_H (400 MHz; D_2O/NaOD) 8.02 (1H, d, J=8.4 Hz, 6-H), 7.23 (1H, d, J=8.4 Hz, 7-H), 7.18 (1H, s, 9-H), 4.23 (2H, t, J=7.4 Hz, 1-H), 3.28 (2H, t, J=7.8 Hz, 3-H), 2.40 (3H, s, Ar–CH_3), 2.33 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H); δ_C (50 MHz; D_2O/NaOD) 177.3 and 176.6 (2×C=O), 167.6, 157.9, 146.6, 140.5, 128.7, 127.7, 125.3, 120.6, 118.8, 54.0 (C-1), 34.3 (C-3), 23.6 and 22.9 (Ar–CH_3, C-2); m/z (EI) 243 (M^+, 14%), 200 (15), 199 (100, M^+-CO_2), 198 (13), 170 (12). HRMS Found: M^+, 243.0890. $C_{14}H_{13}NO_3$ requires M, 243.0895.

3.9.5. 7-Methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylic acid (22e). According to the general procedure, **22e** (165 mg, 92%) was obtained from ethyl 7-methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (**20e**) (199 mg, 0.73 mmol); off-white powder, mp 244–245°C; ν_{max}/cm^{-1} (KBr) 3413 (br, OH), 1718 (s), 1600 (s), 1536 (s), 1463 (s), 1287 (m), 812 (m); δ_H (400 MHz; D_2O/NaOD) 7.90 (1H, s with fine coupling, 6-H), 7.45 (1H, dd, J=1.7 and 8.6 Hz, 8-H), 7.24 (1H, d, J=8.6 Hz, 9-H), 4.20 (2H, t, J=7.5 Hz, 1-H), 3.26 (2H, t, J=7.9 Hz, 3-H), 2.41 (3H, s, Ar–CH_3), 2.31 (2H, quintet with fine coupling, J=ca. 7.7 Hz, 2-H); δ_C (100 MHz; D_2O/NaOD) 175.3 and 174.9 (2×CO), 167.0, 155.9, 136.7, 135.6, 134.8, 125.7, 125.3, 119.0, 117.5, 52.3 (C-1), 32.6 (C-3), 21.2 and 21.1 (Ar–CH_3, C-2). Anal. Found: C, 69.43; H, 5.51; N, 5.84. $C_{14}H_{13}NO_3$ requires C, 69.12; H, 5.39; N, 5.76%.

3.9.6. 7-Methoxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylic acid (22f). According to the general procedure, **22f** (160 mg, 81%) was obtained from ethyl 7-methoxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylate (**20f**) (219 mg, 0.76 mmol); white powder, mp 225–227°C (from DMF); ν_{max}/cm^{-1} (KBr) 3423 (br, OH), 1712 (s), 1601 (s), 1537 (s), 1481 (s), 1459 (s), 1282 (s), 1234 (m), 1024 (m), 814 (m); δ_H (400 MHz; D_2O/NaOD) 7.40 (1H, d, J=2.6 Hz, 6-H), 7.22 (1H, d, J=9.2 Hz, 9-H), 7.12 (1H, dd, J=2.6 and 8.6 Hz, 8-H), 4.18 (2H, t, J=7.4 Hz, 1-H), 3.83 (3H, s, OCH_3), 3.25 (2H, t, J=7.8 Hz, 3-H), 2.29 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 2-H); δ_C (50 MHz; D_2O/NaOD) 176.5 and 176.4 (2×C=O), 169.5, 158.2, 157.0, 135.2, 128.6, 124.6, 121.1, 120.1, 107.7, 58.2 (OCH_3), 54.2 (C-1), 34.3 (C-3), 22.8 (C-2). Anal. Found: C, 64.93; H, 5.05; N, 5.44. $C_{14}H_{13}NO_4$ requires C, 64.86; H, 5.06; N, 5.40%.

3.9.7. 7,8-Methylenedioxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acid (22g). According to the general procedure, **22g** (82 mg, 69%) was obtained from ethyl 7,8-methylenedioxy-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylic acid (**20g**) (132 mg, 0.44 mmol); white powder, mp >315°C (from DMF); ν_{max}/cm^{-1} (KBr) 3462 (br, OH), 1702 (s), 1626 (s), 1551 (s), 1498 (s), 1438 (s), 1279 (s), 1243 (s), 1105 (m), 1028 (s), 927 (m), 812 (m); δ_H (400 MHz; D_2O/NaOD) 7.46 (1H, s, 6-H), 6.91 (1H, s, 9-H), 6.09 (2H, s, OCH_2O), 4.28 (2H, t, J=7.4 Hz, 1-H), 3.27 (2H, t, J=7.8 Hz, 3-H), 2.35 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 2-H); δ_C (100 MHz; D_2O/NaOD) 175.0 and 174.3 (2×C=O), 167.8, 154.4, 153.0, 146.8, 136.5, 121.6, 118.8, 103.5, 102.9, 96.8, 53.1 (C-1), 32.4 (C-3), 21.3 (C-2); m/z (EI) 273 (M^+, 31%), 254 (12), 229 (100, M^+-CO_2), 228 (M^+-CO_2H), 114 (11). HRMS Found: M^+, 273.0642. $C_{14}H_{11}NO_5$ requires M, 273.0637. Anal. Found: C, 61.43; H, 4.03; N, 4.78. $C_{14}H_{11}NO_5$ requires C, 61.54; H, 4.06; N, 5.13%.

3.9.8. 9-Bromo-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylic acid (22h). According to the general procedure, **22h** (45 mg, 100%) was obtained from ethyl 9-bromo-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (**20h**) (49 mg, 0.15 mmol); colourless needles, mp 265–266°C decomp. (from DMF); ν_{max}/cm^{-1} (KBr) 3413 (br, OH), 1714 (s), 1580 (m), 1528 (m), 1514 (m), 1481 (m), 1458 (m), 1440 (s), 1414 (m), 1094 (m), 784 (m), 745 (w); δ_H (200 MHz; D_2O/NaOD) 8.00 (1H, dd, J=8.1 and 1.2 Hz, 8-H), 7.70 (1H, dd, J=7.6 and 1.2 Hz, 6-H), 7.00 (1H, t, J=ca. 7.9 Hz, 7-H), 5.05–4.50 (m, overlapping 1-H and H_2O), 3.14 (2H, t, J=7.8 Hz, 3-H), 2.18 (2H, quintet with fine coupling, J=ca. 7.4 Hz, 2-H); δ_C (50 MHz; D_2O/NaOD) 176.7 and 176.2 (2×C=O), 169.3, 160.2, 142.1, 139.4, 130.7, 128.4, 127.4, 121.9, 111.2, 60.1 (C-1), 33.8 (C-3), 24.4 (C-2). Anal. Found: C, 50.39; H, 3.03; N, 4.56: $C_{13}H_{10}NO_3Br$ requires C, 50.67; H, 3.27; N, 4.55%.

3.9.9. 7,8-Difluoro-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylic acid (22i). According to the general procedure, (359 mg, 91%) was obtained from ethyl 7,8-difluoro-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylate (**20i**) (439 mg, 1.50 mmol); pale yellow powder, mp 269–270°C decomp. (from DMF); ν_{max}/cm^{-1} (KBr) 3450 (br, OH), 1716 (s), 1608 (s), 1505 (s), 1491 (s), 1480 (s), 1285 (s), 1246 (s), 1104 (m), 973 (m), 930 (m), 813 (m), 786 (s), 606 (m); δ_H (400 MHz; D_2O/NaOD) 7.87 (1H, dd, $J_{6,7\text{-F}}$=11.0 Hz and $J_{6,8\text{-F}}$=8.6 Hz, 6-H), 7.87 (1H, dd, $J_{9,8\text{-F}}$=11.5 Hz and $J_{9,7\text{-F}}$=6.7 Hz, 9-H), 4.27 (2H, t, J=7.5 Hz, 1-H), 3.31 (2H, t, J=7.9 Hz, 3-H), 2.37 (2H, quintet with fine coupling, J=ca. 7.5 Hz, 2-H). Anal. Found: C, 58.76; H, 3.46; N, 5.30: $C_{13}H_9F_2NO_3$ requires C, 58.87; H, 3.42; N, 5.28%.

3.9.10. 6-Methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]-quinoline-4-carboxylic acid (22j). According to the general procedure, **22j** (193 mg, 89%) was obtained from ethyl 6-methyl-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-4-carboxylate (**20j**) (242 mg, 0.89 mmol); white powder, mp 263–264°C decomp. (from DMF); ν_{max}/cm^{-1} (KBr) 3414 (br, OH), 1714 (s), 1599 (s), 1540 (s), 1455 (s), 1277 (s), 1251 (m), 1157 (m), 994 (m), 820 (m), 791 (m), 767 (m); δ_H (400 MHz; D_2O/NaOD) 7.43 (1H, t, J=ca. 7.9 Hz, 8-H), 7.15 (1H, d, J=7.6 Hz, 7-H or 9-H), 7.07 (1H, d, J=8.4 Hz, 7-H or 9-H), 4.17 (2H, t, J=7.4 Hz, 1-H), 3.22 (2H, t, J=7.9 Hz, 3-H), 2.81 (3H, s, Ar–CH_3), 2.30 (2H, quintet with fine coupling, J=ca. 7.6 Hz, 2-H); δ_C (100 MHz; D_2O/NaOD) 178.6 and 175.4 (2×C=O), 166.6, 154.2, 141.2, 140.2, 132.3, 127.7, 124.5, 120.8, 115.5, 52.6 (C-1), 32.0 (C-3), 24.0 (Ar–CH_3), 21.0 (C-2). Anal. Found: C, 69.25; H, 5.37; N, 5.81. $C_{14}H_{13}NO_3$ requires C, 69.12; H, 5.39; N, 5.76%.

3.9.11. 7-Fluoro-8-(4-methylpiperazin-1-yl)-5-oxo-1,2,3,5-tetrahydropyrrolo[1,2-*a*]quinoline-3-carboxylic acid (8). A mixture of 7,8-difluoro-5-oxo-1,2,3,5-tetrahydropyrrolo-[1,2-*a*]quinoline-4-carboxylic acid (**22i**) (87 mg, 0.33

mmol) and *N*-methylpiperazine (2 cm^3) was stirred under a N_2 atmosphere at ca. 65°C for 48 h. Excess *N*-methylpiperazine was removed under reduced pressure to leave a solid yellow residue, to which was added aqueous HCl (0.1 M; 6 cm^3). The solid precipitate was filtered, washed with H_2O (10 cm^3) and dried in a desiccator to yield the hydrochloride salt of the title compound **8** (34 mg, 27%) as a yellow powder, mp >250°C (lit.[20] >250°C); δ_H (200 MHz; CF_3CO_2H) 8.29 (1H, d, $J_{6,F}$=12.4 Hz, 6-H), 7.35 (1H, d, $J_{9,F}$=6.5 Hz, 9-H), 4.93 (2H, br t, *J*=ca. 7.4 Hz, 1-H), 4.27–4.18 (2H, m, NCH_2), 4.11 (2H, br t, *J*=ca. 7.6 Hz, 3-H), 3.96–3.90 (2H, m, NCH_2), 3.75–3.50 (4H, m, NCH_2), 2.11 (2H, br quintet, *J*=ca. 7.3 Hz, 2-H). The NMR spectroscopic data agree with those reported in the literature.[20]

Acknowledgements

We thank the National Research Foundation, Pretoria, the University of the Witwatersrand, and the UK/RSA Science and Technology Fund for providing the funding for this research. We are grateful to Dr P. R. Boshoff (Cape Technikon) and Mrs S. Heiss (University of the Witwatersrand) for mass spectra and NMR spectra, respectively, and to Professor I. Moodley and his staff (Department of Pharmacy, University of the Witwatersrand) for the antimicrobial testing.

References

1. Greenhill, J. V. *Chem. Soc. Rev.* **1977**, *6*, 277–294.
2. Lue, P.; Greenhill, J. V. *Adv. Heterocycl. Chem.* **1996**, *67*, 207–343.
3. Edafiogho, I. O.; Alexander, M. S.; Moore, J. A.; Farrar, V. A.; Scott, K. R. *Curr. Med. Chem.* **1994**, *1*, 159–175.
4. Eddington, N. D.; Cox, D. S.; Roberts, R. R.; Stables, J. P.; Powell, C. B.; Scott, K. R. *Curr. Med. Chem.* **2000**, *7*, 417–436.
5. Dannhardt, G.; Bauer, A.; Nowe, U. *J. Prakt. Chem.* **1998**, *340*, 256–263.
6. Boger, D. L.; Ishizaki, T.; Wysocki, Jr., R. J.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461–6463.
7. *The 4-Quinolones: Anti Bacterial Agents In Vitro*; Crumplin, G. C., Ed.; Springer: London, 1990.
8. Appelbaum, F. C.; Hunter, P. A. *Int. J. Antimicrob. Agents* **2000**, *16*, 5–15.
9. Hooper, D. C. *Drugs* **1993**, *45* (Suppl. 3), 8–14.
10. Anderson, V. E.; Osheroff, N. *Curr. Pharm. Design* **2001**, *7*, 337–353.
11. Gootz, T. D.; Brighty, K. E. *Med. Res. Rev.* **1996**, *16*, 433–486.
12. Bush, K.; Goldschmidt, R. *Curr. Opin. Invest. Drugs* **2000**, *1*, 22–30.
13. Dong, Y.; Drlica, K. *Recent Res. Dev. Antimicrob. Agents Chemother.* **1999**, *3 (Part 2)*, 323–344.
14. Xia, Y.; Yang, Z.-Y.; Morris-Natschke, S. L.; Lee, K.-H. *Curr. Med. Chem.* **1999**, *6*, 179–194.
15. Albrecht, R. *Prog. Drug Res.* **1977**, *21*, 9–104.
16. Mitscher, L. A.; Devasthale, P. V.; Zavod, R. M. In Ref. 7, pp 115–146.
17. Chu, D. T. W.; Fernandes, P. B. *Adv. Drug Res.* **1991**, *21*, 39–144.
18. Asahina, Y.; Ishizaki, T.; Suzue, S. *Prog. Drug Res.* **1992**, *38*, 57–106.
19. Barrett, D.; Sasaki, H.; Kinoshita, T.; Fujikawa, A.; Sakane, K. *Tetrahedron* **1996**, *52*, 8471–8488 and references cited therein.
20. Chu, D. T. W.; Claiborne, A. K. *J. Heterocycl. Chem.* **1987**, *24*, 1537–1539.
21. Glushkov, R. G.; Marchenko, N. B.; Padeiskaya, A. N.; Shipilova, L. D. *Khim.-Farm. Zh.* **1990**, *24*, 24–27 (*Pharm. Chem. J., Engl. Transl.* **1990**, *24*, 460–465); *Chem. Abstr.* **1990**, *113*, 148774.
22. Michael, J. P.; de Koning, C. B.; Gravestock, D.; Hosken, G. D.; Howard, A. S.; Jungmann, C. M.; Krause, R. W. M.; Parsons, A. S.; Pelly, S. C.; Stanbury, T. V. *Pure Appl. Chem.* **1999**, *71*, 979–988.
23. Michael, J. P.; de Koning, C. B.; Stanbury, T. V. *Tetrahedron Lett.* **1996**, *37*, 9403–9406.
24. For a recent survey of synthetic approaches to the quinolone antibacterials, see: Radl, S.; Bouzard, D. *Heterocycles* **1992**, *34*, 2143–2177.
25. Grohe, K. *J. Prakt. Chem.* **1993**, *335*, 397–409.
26. Grohe, K.; Heitzer, H. *Liebigs Ann. Chem.* **1987**, 29–37.
27. Gould Jr., R. G.; Jacobs, W. A. *J. Am. Chem. Soc.* **1939**, *61*, 2890–2895.
28. Conrad, M.; Limpach, L. *Ber.* **1887**, *20*, 944–948.
29. Michael, J. P.; Hosken, G. D.; Howard, A. S. *Tetrahedron* **1988**, *44*, 3025–3036.
30. (a) Roth, M.; Dubs, P.; Götschi, E.; Eschenmoser, A. *Helv. Chim. Acta* **1971**, *54*, 710–734. (b) Shiosaki, K. *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon: Oxford, 1991; Vol. 2, pp. 865–892.
31. For related peri-demethylations, see (a) Fitzpatrick, L.; Sala, T.; Sargent, M. V. *J. Chem. Soc., Perkin Trans. 1* **1980**, 85–89. (b) Carvalho, C. F.; Russo, A. V.; Sargent, M. V. *Aust. J. Chem.* **1985**, *38*, 777–792 and references cited therein.
32. Palmer, C. S.; McWherter, P. W. *Organic Syntheses*, Collect. Vol. 1; Wiley: New York, 1941; pp 245–246.
33. Manhas, M. S.; Jeng, S. J. *J. Org. Chem.* **1967**, *32*, 1246–1248.
34. Raucher, S.; Klein, P. *J. Org. Chem.* **1981**, *46*, 3558–3559.
35. (a) Fujita, M.; Kitagawa, O.; Yamada, Y.; Izawa, H.; Hasegawa, H.; Taguchi, T. *J. Org. Chem.* **2000**, *65*, 1108–1114. (b) Kitagawa, O.; Fujita, M.; Kohriyama, M.; Hasegawa, H.; Taguchi, T. *Tetrahedron Lett.* **2000**, *41*, 8539–8544 and referenced cited therein.
36. Gugelchuk, M. M.; Hart, D. J.; Tsai, Y.-M. *J. Org. Chem.* **1981**, *46*, 3671–3675.
37. Kim, G.; Chu-Moyer, M. Y.; Danishefsky, S. J.; Schulte, G. K. *J. Am. Chem. Soc.* **1993**, *115*, 30–39.
38. Kim, G.; Kang, S.; Keum, G. *Tetrahedron Lett.* **1994**, *35*, 3747–3748.
39. Chandrasekharam, M.; Bhat, L.; Ila, H.; Junjappa, H. *Tetrahedron Lett.* **1993**, *34*, 6439–6442.
40. Korean workers have very recently extended our achievement by devising a more general thiocarbonyl Reformatsky reaction with certain *N*-substituted pyrrolidine-2-thiones, methyl bromoacetate and activated zinc: Lee, H. K.; Kim, J.; Pak, C. S. *Tetrahedron Lett.* **1999**, *40*, 2173–2174.
41. Dannhardt, G.; Bauer, A. *Pharmazie* **1996**, *51*, 805–810.
42. Billing, D. G.; Boeyens, J. C. A.; Denner, L.; du Plooy, K. E.;

Long, G. C.; Michael, J. P. *Acta Crystallogr., Sect. B* **1991**, *47*, 284–288.
43. Billing, D. G.; Boeyens, J. C. A.; Levendis, D. C.; Michael, J. P. *S. Afr. J. Chem.* **1991**, *44*, 75–79.
44. Steck, E. A.; Buck, J. S.; Fletcher, L. T. *J. Am. Chem. Soc.* **1957**, *79*, 4414–4417.
45. Coppola, G. M.; Damon, R. E. *J. Heterocycl. Chem.* **1980**, *17*, 1729–1731.