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Synthesis of brequinar analogue inhibitors of malaria parasite dihydroorotate dehydrogenase

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Abstract—A series of 2-phenyl quinoline-4-carboxylic acid derivatives related to brequinar, an inhibitor of human dihydroorotate dehydrogenase (DHODH), has been prepared and evaluated as inhibitors of DHODH from the malaria parasite *Plasmodium falciparum*. Brequinar was essentially inactive against PfDHODH (IC_{50} 880 μM) whereas several members of the series inhibited PfDHODH. Unexpectedly, replacement of the carboxylic acid required for brequinar to inhibit hDHODH was not essential in the diisopropylamides that inhibited PfDHODH.

1. Introduction

With 300–500 million cases and 1.5–2 million deaths annually, malaria is among three of the principal infectious diseases worldwide (EU-US Summit, 26 June 2004). The treatment and prevention of malaria has traditionally been through the use of chemotherapeutic agents such as chloroquine and fansidar (a sulfadoxine/pyrimethamine combination) however widespread drug resistance has rendered these agents ineffective in many malarious regions of the world. The emergence of drug resistance has highlighted the need for new antimalarial agents and the investigation of novel, exploitable targets within *Plasmodium* parasites.[1] Features of the parasite that differ from the host, such as pyrimidine biosynthesis, offer the best prospects for development of new antimalarial drugs. *Plasmodium* rely completely on de novo pyrimidine synthesis to supply uridine monophosphate (UMP), an essential nucleotide required for growth. Genes encoding all enzymes in the conserved pyrimidine pathway have been identified in the *Plasmodium falciparum* genome but genes encoding enzymes in pyrimidine salvage do not appear to be present.[2] The fourth enzyme in the biosynthetic pathway, dihydroorotate dehydrogenase (DHODH), is located in the mitochondrial membrane where it catalyses the oxidation of dihydroorotate to orotate. Concomitant with dihydroorotate oxidation is electron transfer to ubiquinone (cofactor Q) via a flavin mononucleotide intermediate. DHODH is one of the few targets in *Plasmodium* that has been validated as a drug target.[3] Human cells, in contrast to *Plasmodium*, synthesise and salvage pyrimidines. Leflunomide[4] (Arava™) and brequinar[5] (Fig. 1) are two well-described inhibitors of human dihydroorotate dehydrogenase (hDHODH), although these compounds have different potencies against mouse, rat and hDHODH. In co-crystallisation experiments with brequinar and the active metabolite of leflunomide (A77-1726) with human DHODH,[6] both were found to bind in a common site, that is also believed to be the binding site of the cofactor ubiquinone. DHODH was also originally believed to be the target of the antimalarial drug atovaquone (prescribed as a combination drug Malarone™),[7] an ubiquinone mimic, but it has been shown that its primary site of action is probably due to disruption of electron transport by interaction with the cytochrome BC1 complex.[8] Recently DHODH has also served as the target for development of antimicrobial agents. Inhibitors have been identified that inhibit

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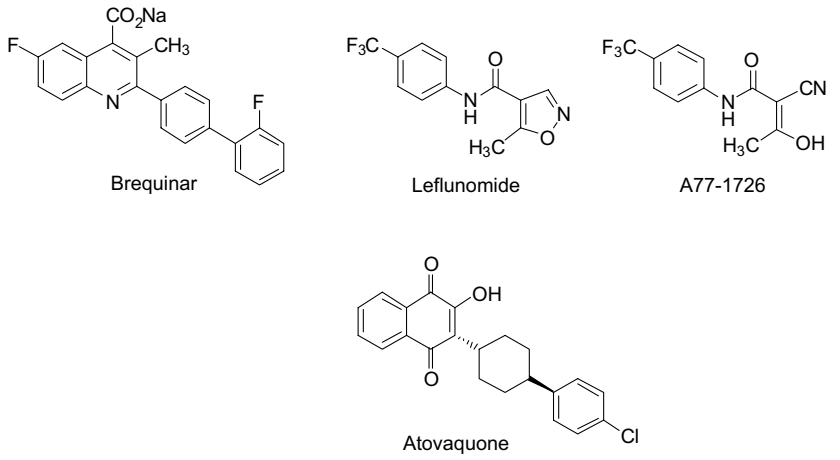


Figure 1.

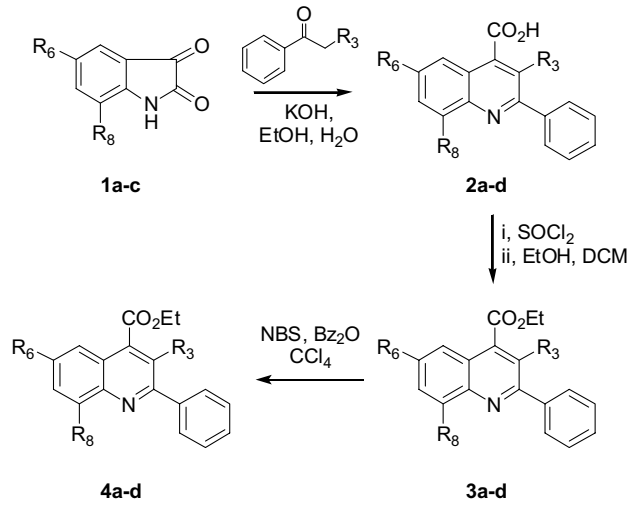
growth of the microorganisms *Helicobacter pylori*[9] and *Enterococcus faecalis*.[10] These are being developed as possible treatments for ulcers and dysentery respectively. In light of the previous research we decided to investigate the synthesis and evaluation of inhibitors of dihydroorotate dehydrogenase from *P. falciparum* (PfDHODH) as potential antimalarial agents, and report herein our preliminary findings.

2. Results

Initially the sensitivity of PfDHODH to brequinar was tested, as this is one the most potent hDHODH inhibitors published.[11] Recombinant protein was expressed from a synthetic PfDHODH gene in which the codon bias has been adjusted to optimise expression in *E. coli*. Expressed PfDHODH and hDHODH are similarly truncated to remove the membrane domains and they contain an amino-terminal histidine tag for ease of purification. Assays for DHODH activity are based on a standard colorimetric assay that measures decreasing absorption in the visible range as a result of reduction of the electron acceptor dichloroindophenol. PfDHODH was significantly less sensitive than hDHODH to inhibition (IC_{50} 880 μM vs 0.01 μM,[12] respectively). This is similar to results with other inhibitors of human DHODH.[13] The basic brequinar skeleton, lacking the 3-methyl and two fluorine atoms, and the parent unsubstituted 2-phenylquinoline-4-carboxylic acid were also prepared but showed no inhibitory activity either at 10 μM.[14] These results indicated that the structure of quinoline-based inhibitors of PfDHODH might need to be significantly different from the brequinar structure. The sequence and structure of PfDHODH indicate that it contains a putative channel analogous to hDHODH although these initial studies suggested it may have substantial alterations (Clardy, J., personal communication). Ironically, the high specificity of brequinar and other DHODH inhibitors for hDHODH may suggest that PfDHODH can be specifically inhibited. Hence we decided to synthesise and test a set of quinolines based upon the 2-phenylquinoline-4-carboxylic acid (PQC) 'core' of brequinar.

In order to evaluate initially as wide a range of derivatives as possible based on the PQC 'scaffold' we proposed a synthetic route involving two classes of key derivatives, namely benzylic bromides and arylaldehydes. We made 3-, 6- and 8-methyl PQC derivatives starting with the classical Sandmeyer isatin synthesis[15] (unless they were available commercially at a reasonable price), followed by base-catalysed Pfitzinger reaction[16] to produce the quinolines **2a**–**d**. Esterification, via the acid chloride, and subsequent free-radical bromination using *N*-bromosuccinimide (NBS) gave the benzylic bromides **4a**–**d** in good yield (Scheme 1 and Table 1).

The 3-, 6- and 8-bromomethyl derivatives of PQC ethyl esters were then reacted with simple nucleophiles, mainly secondary amines but also an alcohol and a thiol, to produce cleanly a variety of derivatives (**5**, **6** and **7**) for which a sub-set was also converted to the corresponding sodium carboxylates **8** (as in brequinar sodium) (Fig. 2 and Table 2). Primary amines reacted with the 3-bromomethyl PQC ethyl ester to give, not unexpectedly, cyclised lactams **9**. Surprisingly moderate activity against PfDHODH was observed with lactam

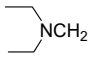
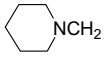
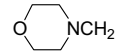
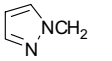
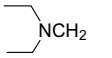
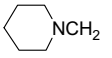
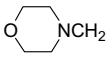
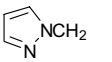
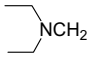
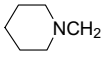
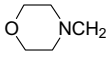
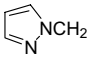


Scheme 1.

Table 1. Key intermediates with 2-phenylquinoline-4-carboxylic acid core

	R_3	R_6	R_8
1a		H	H
1b		CH_3	H
1c		H	CH_3
2a,**3a**	CH_3	H	H
2b,**3b**	H	CH_3	H
2c,**3c**	H	H	CH_3
2d,**3d**	CH_3	CH_3	H
4a	CH_2Br	H	H
4b	H	CH_2Br	H
4c	H	H	CH_2Br
4d	CH_2Br	CH_2Br	H

Table 2. Alkylaminomethyl derivatives of 2-phenylquinoline-4-carboxylic acid

	R_3	R_6	R_8
5a		H	H
5b		H	H
5c **8c**		H	H
5d **8d**		H	H
5e **8e**	H		H
5f **8f**	H		H
5g **8g**	H		H
5h **8h**	H		H
5i **8i**	H	H	
5j **8j**	H	H	
5k **8k**	H	H	
5l **8l**	H	H	
6a X = O **7a** X = S	*p*-$BrC_6H_4XCH_2$	H	H
6a X = O **7a** X = S	H	*p*-$BrC_6H_4XCH_2$	H
6a X = O **7a** X=S	H	H	*p*-$BrC_6H_4XCH_2$

9a and so a few further derivatives were made in this series.

The bromomethyl PQCs **4** were then subjected to further modifications including oxidation to provide a new set of 'building blocks' based upon the aldehyde functional group. The Hass–Bender oxidation,[17] utilizing the nitropropane anion, cleanly gave the 8- and 6-aldehydes **10b** and **10c**, but with 3-bromomethyl PQC **4a** the isolated product was the ethoxy lactone **11** (Scheme 2). This arises from attack of ethoxide on the newly formed aldehyde carbon, followed by attack of the resulting oxyanion on the ethyl ester carbonyl group. The required aldehyde–ester **10a** could however have been obtained by warming **4a** DMSO for 7 min in the presence of $NaHCO_3$.[18] Hydrolysis of the ethoxy lactone **11** to the hydroxy lactone **12** proceeded in quantitative yield, and gave a derivative, which showed modest inhibitory activity against PfDHODH. However, further representative derivatives in this series (**13** and **14**) were inactive. Interestingly, treatment of 3,6-bis(bromomethyl) PQC **4d** with 2.2 equiv of sodium ethoxide and nitropropane gave cleanly the double oxidised compound **15** in 65% yield. This methodology applied to similar heterocycles would seem to hold promise as a way to access versatile, multifunctional scaffolds for combinatorial library construction.

For preparation of further 'building blocks', the synthesis of epoxides was envisaged through the application of sulfur ylide chemistry. However the aldehyde–esters **10b** gave the corresponding epoxide in low yield (20%) even

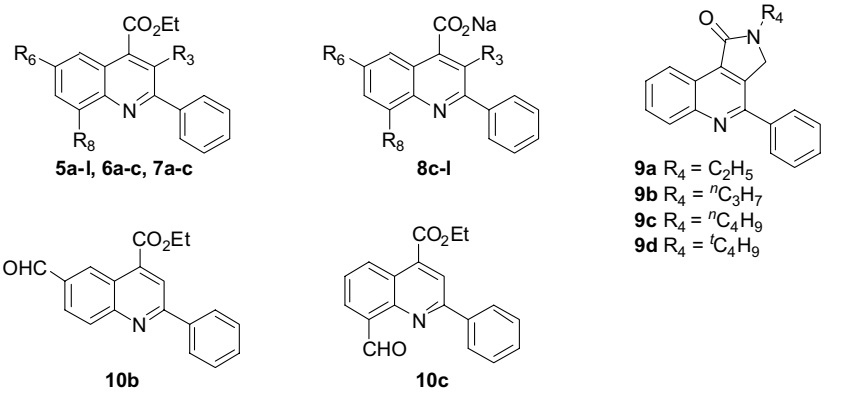
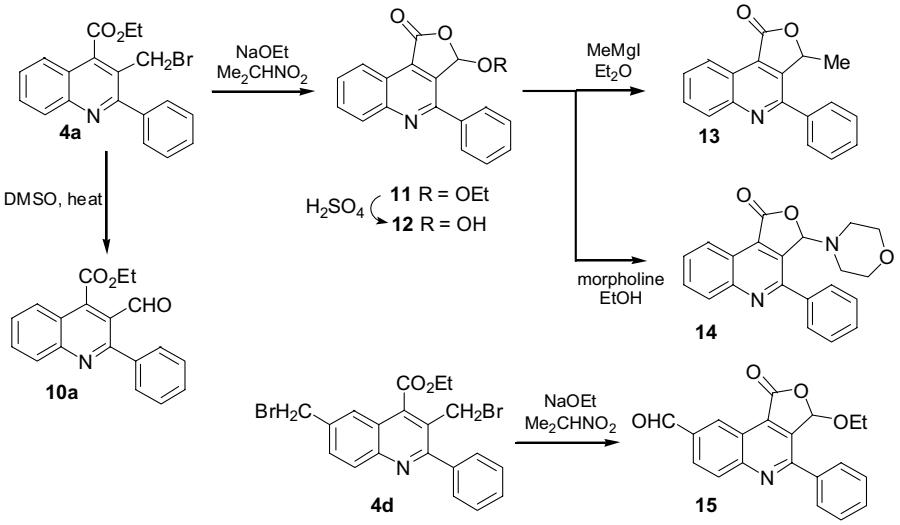


Figure 2.



Scheme 2.

after some effort at optimisation. We surmised that amides would be more stable to the epoxidation reaction conditions than esters. As we knew that some lactams had shown activity (e.g., **9a**) and in brequinar there is both 3- and 6-substitution of the quinoline ring, we prepared the diethyl, dibenzyl and diisopropyl amides **16** of the 3,6-dimethyl PQC acid **2d**. We encountered, however, difficulty in obtaining the range of desired benzylic bromides as the free-radical bromination was not selective. Indeed very complex product mixtures were obtained even with sub-stoichiometric amounts of NBS, which we attributed to the involvement of radical translocation involving the carbon α to the nitrogen.[19] Only with the diisopropylamides of monomethyl derivatives could the bromination be achieved cleanly and in good yield giving **17a** and **17b** (Fig. 3), which were then cleanly converted to the corresponding aldehydes **18a** and **18b** using the Hass–Bender oxidation described previously. In choosing to study amides of **2d**, we had also wondered if selective 6-methyl bromination was possible, given that the 3-methyl group should be more hindered due to the diisopropylamide and phenyl group. However the amide group is essentially perpendicular to the aromatic ring, and does not hinder the 3-methyl group to any great extent. Restricted rotation about the C–Ar bond in derivatives of **17/18a** and **17/18b** led to some interesting stereochemical and mechanistic studies, which we have recently reported in a communication.[20]

Conversion of the amide aldehydes **18** to their corresponding epoxides **19** was, as hoped for, effected cleanly using dimethylsulfonium methylide in *tert*-butanol. ^{1}H NMR showed epoxide **19b**, and derivatives obtained therefrom, to be a 1:1 mixture of diastereoisomeric conformers distinguishable on the NMR timescale due to the restricted rotation about the C_{Ar}–C=O bond. Epoxide **19a** was obtained a mixture of atropisomers (diastereoisomeric conformers with a half-life of 1000 s or more) ranging from about 5 to 6:1.[20]

Epoxides **19a** and **19b** served as precursors to hydroxyethylquinolines through nucleophilic ring opening of the epoxides (Scheme 3). In the case of epoxide **19b**, reaction by heating with secondary amines in ethanol gave the expected 6-(2′-amino-1′-hydroxyethyl)quinolines **20**

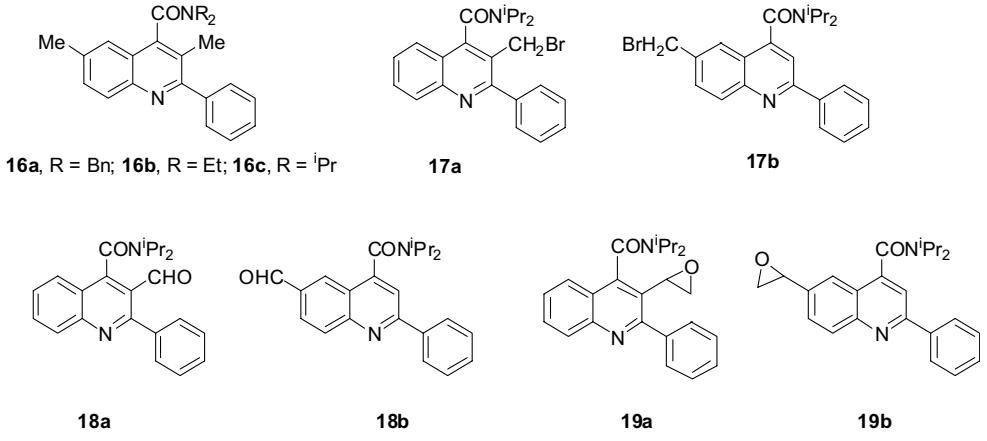
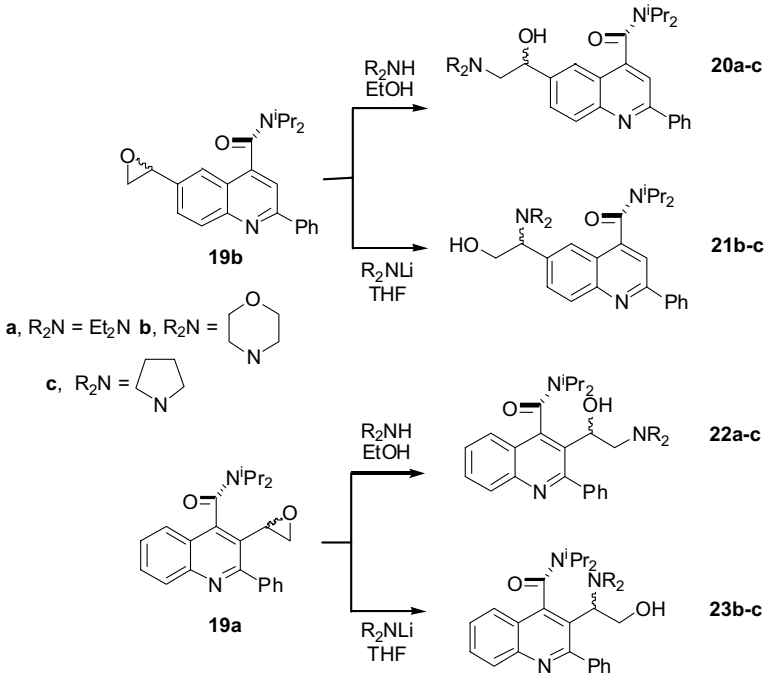


Figure 3.



Scheme 3.

along with the opposite regioisomer **21** as a minor product (~10:1). Reaction of **19b** with lithium amides at room temperature however gave exclusively the regioisomer **21**.[20] Similar results were obtained in the reaction of epoxide **20a** where the reaction with three secondary amines in ethanol gave the amino alcohols **22**, this time exclusively as might be expected due to the increased steric hindrance at the reaction centre. Regioisomers of the amino alcohols (**20/21**; **22/23**) were easily separable by column chromtaography, but clearly the diastereoisomeric conformers were not. Therefore racemic mixtures of **20** and **21** were assayed against PfDHODH, as were mixtures of both enantiomers of the atropisomers of **22** and **23**.

Compounds showing some level of inhibition of PfDHODH (>10% at 10 μM) were tested for a full IC_{50} with enzyme. Inhibition curves were determined for four active compounds **5k**, **12**, **20a** and **20b** (Table 3). They exhibited a range of activities (38–435 μM) but were all substantially more active than brequinar. The active compounds were also tested for their activity against human DHODH. The derivatives were considerably less active against human DHODH than brequinar (IC_{50} values between 38 and 480 μM). As shown in Table 3, two of the derivatives selected for activity against PfDHODH had similar activity or exhibited some preference for inhibiting the parasite versus human DHODH. This supports our hypothesis that inhibitors can be developed that take advantage of differences between the parasite and human DHODH.

Table 3. IC_{50} values for selected inhibitors of *P. falciparum* and human DHODH

Compound	IC_{50} (μM)	
	PfDHODH	hDHODH
Brequinar	888	0.01[12]
5k	38	38
12	162	80
20a	435	335
20b	160	480

Lead compounds identified in the preliminary screen were tested for antiplasmodial activity in a standard microtitre growth assay, utilising the incorporation of ^{3}H-hypoxanthine as a marker of parasite viability. Compound concentrations were tested in a range of 0.01–100 μM in individual incubations in triplicate.[21] Inhibitor efficacy was assessed using comparisons of concentrations causing 50% inhibition of parasite growth, as shown in Figure 4. The compounds were active against *P. falciparum* growth in the micromolar range with **20a** the most active compound (IC_{50} 0.9 μM). The compounds were also tested against a strain of *P. falciparum* that is resistant to chloroquine and mefloquine (W2mef). Naturally, all the brequinar analogues prepared contain a quinoline ring and as such are closely related to chloroquine. This quinoline-based drug is the most used antimalarial drug worldwide and is now suffering from the rampant rise of resistant parasites, but there was no appreciable difference detected between the drug-sensitive and drug-resistant strains in their sensitivity to **5k**, **12**, **20a** and **20b**.

3. Discussion

The set of quinoline derivatives in this study revealed some which were found to be inhibitors of PfDHODH (Table 3). We had also prepared and tested the related 2-(*p*-aminophenyl)quinoline-4-carboxylic acid,[22] but this was inactive. This is not unexpected as the PfDHODH ubiquinone channel is likely to be hydrophobic as in

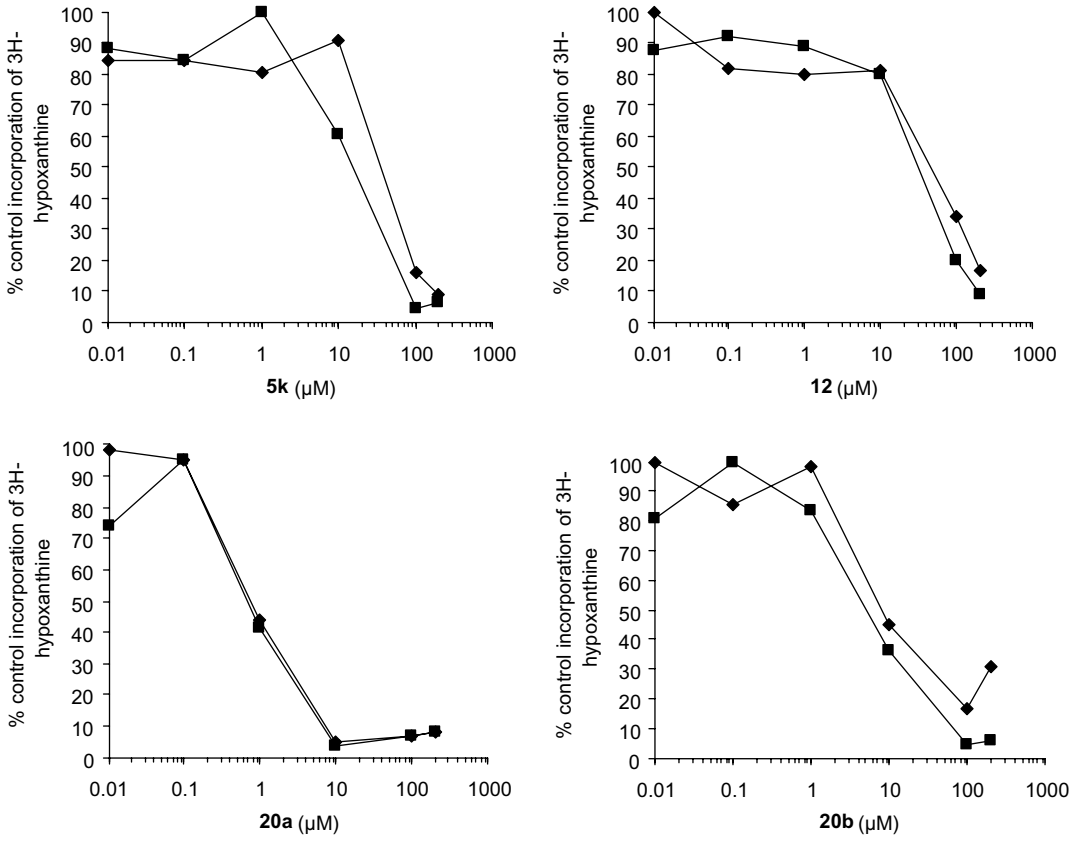


Figure 4. Dose–response plots of the antiplasmodial activity of selected compounds against *P. falciparum* strains 3D7 (♦) and W2 mef (■).

human DHODH, and the amino group will be charged at physiological pH. Although many members of this first set of derivatives were not significantly active **5k** inhibited PfDHODH with an IC_{50} of 38 μM. Primary amines reacted with the 3-bromomethyl PQC ethyl ester **4a** to yield cyclised lactams of which the *N*-ethyl derivative **9a** exhibited some inhibitory activity. This indicates that the carboxylate may not be essential for inhibitory activity against the parasite enzyme (in contrast to hDHODH), though only derivatives with small aliphatic groups attached to the lactam nitrogen appeared to have any detectable activity at 10 μM. Of the amino alcohol series (**20**–**23**) only derivatives **20a** and **20b** showed some level of activity at concentrations tested. Derivative **20b** however showed selective inhibition of PfDHODH and, given that it was tested as a mixture of enantiomers, it may well be that the activity of one isomer would be greater than the 160 μM found. However, as the IC_{50} values determined were quite modest we did not consider the preparation of single enantiomers of these products to be pressing at this time.

Compounds active in inhibiting PfDHODH were also active against drug-sensitive and chloroquine- and mefloquine-resistant parasites. Although there are differences between the inhibition of PfDHODH and sensitivity of parasites, this cannot be readily explained as inhibition of heme polymerisation, analogous to chloroquine, because the compounds are similarly active against CQ-sensitive and CQ-resistant *P. falciparum* strains and there is not significant antagonism in combination treatments with an inhibitor of heme degradation (data not shown). Differences between results with enzyme and parasite growth are most likely due to assay differences soluble recombinant enzyme and membrane-bound mitochondrial protein. Although the inhibition of the parasites roughly correlates with effects on DHODH, unexpectedly the IC_{50} values for the parasites are lower than the enzyme levels. This may be due to differences between in vitro assay conditions and in vivo activity. The recombinant enzyme is soluble with its membrane-binding domain cleaved, and assays are performed in aqueous conditions with a synthetic coenzyme Q as an electron acceptor whereas in vivo the enzyme is bound to the inner mitochondrial membrane and utilises an extended coenzyme Q. Alternatively the inhibitors are concentrated in the parasite or the compounds interact with heme metabolism in the parasites due to π–π stacking of the quinoline.

4. Conclusions

Starting with a skeletal structure of the inhibitor brequinar, that binds in a channel in hDHODH but does not inhibit PfDHODH, several compounds that inhibit PfDHODH were identified from a set of quinoline derivatives. The amino alcohol **20b** shows moderate selective inhibition against the plasmodial versus human enzyme, compared to the specificity of the starting compound brequinar, although the necessity of high selectivity for the parasite enzyme is debatable since high potency

human DHODH inhibitors are in clinical use. This demonstrates that parasite-specific inhibitors can be identified and will serve as a template for the design of more potent, specific derivatives that can be tested against growing parasites. Observation that amides (and lactams) of 2-phenylquinoline 4-carboxylic acids can have micromolar activity contrasts the results found for brequinar. The positive results for **20a**,**b** and lactams such as **9a** indicate that derivatives can bind in a completely different orientation to that of brequinar or that they bind at a different site. Differentiating these possibilities will probably require X-ray data for PfDHODH,[23] co-crystallisation studies in addition to full kinetic analysis and modelling of the enzyme.

5. Experimental

Diethyl ether and THF, used as reaction solvents, were dried over and distilled from sodium wire before use. Ethanol was dried over and distilled from magnesium turnings, and DCM was dried over and distilled from calcium hydride. All other solvents and reagents were used as purchased. Reactions were monitored by thin layer chromatography using aluminium-backed plates coated with silica gel (60 F_{254} Merck), and purification of products by column chromatography was accomplished using silica gel 60 (200–400 mesh) from a variety of suppliers. Spectra were recorded using a JEOL Lambda 400 spectrometer for ^{1}H NMR spectra, either a Perkin–Elmer 880 spectrophotometer or Perkin–Elmer 1000 Fourier Transform (FT-IR) spectrophotometer for IR, and either a Finnigan-MAT 1020 GC/MS or a QP5050A Shimadzu GC/MS spectrometer for mass spectra. Elemental analysis was carried out using a Fisons EA 1108 CHN machine, and in some cases vanadium pentoxide was added to aid combustion. Melting points were measured using a Gallenkamp melting point apparatus in open capillaries and are not corrected.

5.1. 5-Methyl-1*H*-indole-2,3-dione (1b)

To chloral hydrate (22.74 g, 0.138 mol) in water (300 mL) was added sodium sulfate (130 g, 0.92 mol), a solution of *p*-toluidine (13.5 g, 0.125 mol) in water (75 mL) and concentrated hydrochloric acid (12.8 g), and a solution of hydroxylamine hydrochloride (27.45 g, 0.395 mol) in water (125 mL). The mixture was heated under reflux for 1–2 min before being cooled rapidly in an ice/salt bath. The crude product was filtered and washed with cold water. The resulting solid was dissolved in 1.5 M sodium hydroxide solution (100 mL), filtered to remove any insoluble impurities and acidified with 2 M hydrochloric acid. The precipitate was filtered, washed with cold water and dried in vacuo to yield the isonitrosoacetanilide (13.66 g, 61%) as a pale brown solid. Mp 158–160 °C (lit.[15] 162 °C); δ_H (400 MHz; $CDCl_3$): 2.32 (3H, s, CH_3), 7.13 (2H, d, Ar–*H*), 7.43 (1H, s, C*H*=N), 7.49 (2H, d, Ar–*H*), 8.62 (1H, s, NO*H*), 11.72 (1H, s, N*H*). The isonitrosoacetanilide (13.6 g, 0.076 mol) was added to concentrated sulfuric acid (70 mL) in portions over 30–35 min keeping the temperature between 50 and 60 °C. The reaction was warmed to 70–75 °C for 10 min before being cooled to room temperature. The solution was added to ice/water (230 mL) and the resulting precipitate filtered and washed with cold water until free of acid. The crude product was recrystallised from three times its weight of acetic acid, washed with cold water and dried in vacuo (P_2O_5) to yield the title compound (9.06 g, 74%) as dark red crystals. Mp 182–184 °C (lit.[24] 184 °C); δ_H (400 MHz; $CDCl_3$): 2.33 (3H, s, C*H*$_3$), 6.83 (1H, d, Ar–*Hc*), 7.37 (1H, dd, Ar–*Hb*), 7.42 (1H, s, Ar–*Ha*), 8.29 (1H, s, N*H*); *m*/*z* 161 (M+, 45), 133 (100), 104 (75), 78 (35).

5.2. 7-Methyl-1*H*-indole-2,3-dione (1c)

Using the same method as above, chloral hydrate (22.74 g, 0.138 mol) in water (300 mL), sodium sulfate (105 g, 0.76 mol), a solution of *o*-toluidine (13.5 g, 0.125 mol) in water (75 mL) and concentrated hydrochloric acid (12.8 g) and a solution of hydroxylamine hydrochloride (27.45 g, 0.395 mol) in water (125 mL) were heated at reflux for 1–2 min. The isonitrosoacetanilide (13.0 g, 59%) was obtained as a light brown solid. Mp 119–121 °C (lit.[15] 121 °C). Using the same method as for the synthesis of methylisatin (**1b**), the isonitrosoacetanilide (22.0 g, 0.12 mol) was added to concentrated sulfuric acid (100 mL). The crude product was filtered, washed with cold water until free of acid and dried in vacuo (P_2O_5) to yield the title compound (13.82 g, 69%) as a pale orange solid. Mp 266–268 °C (lit.[25] 270–273 °C); δ_H (400 MHz; $CDCl_3$): 2.25 (3H, s, C*H*$_3$), 6.97 (1H, t, Ar–*Hb*), 7.34 (2H, d, Ar–*Ha* + Ar–*Hc*), 10.98 (1H, s, N*H*); *m*/*z* 161 (M+, 35), 133 (30), 104 (100), 78 (35).

5.3. 3-Methyl-2-phenyl-quinoline-4-carboxylic acid (2a)

Potassium hydroxide (110.85 g, 1.98 mol) in water (225 mL) was added dropwise to isatin (**1a**) (48.54 g, 0.33 mol) in ethanol (540 mL) over 15 min. Propiophenone (44.28 g, 0.33 mol) was added and the reaction was heated under reflux for 18 h, cooled to room temperature and solvent removed in vacuo. The resulting solid was dissolved in water, washed with diethyl ether (3×150 mL), cooled in ice/water and acidified with acetic acid. The crude product was filtered and recrystallised from acetic acid. After washing with cold diethyl ether (3×100 mL) and drying in vacuo (P_2O_5) the title compound (71.6 g, 82%) was obtained as a white solid. Mp 294–297 °C (lit.[26] 306 °C); δ_H (400 MHz; $CDCl_3$): 2.44 (3H, s, C*H*$_3$), 7.54 (6H, m, 5Ar–*H* + Ar–*Hb* or Ar–*Hc*), 7.72 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.89 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz), 8.08 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.5 Hz); IR (KBr) ν_{max} 1711, 1295, 1245, 769, 725; *m*/*z* 262 (M+, 100), 217 (20), 108 (15).

5.4. 6-Methyl-2-phenyl-quinoline-4-carboxylic acid (2b)

Using the same method as for the synthesis of carboxylic acid (**2a**), potassium hydroxide (62.9 g, 1.12 mol) in water (135 mL), methylisatin (**1b**) (30.0 g, 0.186 mol) in ethanol (300 mL) and acetophenone (22.36 g, 0.186 mol) were heated under reflux for 18 h. After

addition of the acetic acid the crude product was washed with cold diethyl ether (100 mL) and dried in vacuo (P_2O_5) to yield the title compound as an off white solid (44.0 g, 90%). Mp 225–227 °C (lit.[27] 228 °C); δ_H (400 MHz; $CDCl_3$): 2.60 (3H, s, C*H*$_3$), 7.51 (3H, m, 3Ar–*H*), 7.63 (1H, dd, Ar–*Hc*, J_{cb} 1.7 Hz, J_{cd} 8.5 Hz), 8.16 (1H, d, Ar–*Hd*, J_{dc} 8.5 Hz), 8.20 (2H, m, 2Ar–*H*), 8.51 (1H, s, Ar–*Ha*), 8.62 (1H, s, Ar–*Hb*); IR (KBr) ν_{max} 1713, 1599, 1413, 1379, 1155; *m*/*z* 263 (M+, 80), 218 (100), 108 (25).

5.5. 8-Methyl-2-phenyl-quinoline-4-carboxylic acid (2c)

Using the same method as for the synthesis of carboxylic acid (**2a**), potassium hydroxide (16.69 g, 0.298 mol) in water (36 mL), 7-methylisatin (**1c**) (8.0 g, 4.96×10^{-2} mol) in ethanol (80 mL) and acetophenone (5.96 g, 4.96×10^{-2} mol) were heated under reflux for 18 h. After addition of the acetic acid the crude product was washed with cold diethyl ether (100 mL) and dried in vacuo (P_2O_5) to yield the title compound as an off white solid (10.2 g, 78%). Mp 244–247 °C (lit.[28] 250 °C); δ_H (400 MHz; $CDCl_3$): 2.80 (3H, s, C*H*$_3$), 7.54 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.67 (1H, d, Ar–*Hd*, J_{dc} 7.1 Hz), 8.31 (2H, m, Ar–*H*), 8.38 (1H, s, Ar–*Ha*), 8.41 (1H, d, Ar–*Hb*, J_{bc} 9.3 Hz); IR (KBr) ν_{max} 2926, 1699, 1271, 764; *m*/*z* 263 (M+, 100), 218 (25), 204 (10).

5.6. 3,6-Dimethyl-2-phenyl-quinoline-4-carboxylic acid (2d)

Using the same method as for the synthesis of carboxylic acid (**2a**), potassium hydroxide (16.69 g, 0.298 mol) in water (36 mL), 5-methylisatin (**1b**) (8.0 g, 4.96×10^{-2} mol) in ethanol (80 mL) and propiophenone (6.64 g, 4.96×10^{-2} mol) were heated under reflux for 18 h. After addition of the acetic acid the crude product was washed with cold diethyl ether (100 mL) and dried in vacuo (P_2O_5) to yield the title compound as an off white solid (10.0 g, 73%). Mp >300 °C; δ_H (400 MHz; $CDCl_3$): 2.39 (3H, s, C*H*$_3$), 2.60 (3H, s, C*H*$_3$), 7.46 (6H, m, Ar–*H*), 7.74 (1H, s, 7Ar–*H*), 7.87 (1H, d, Ar–*H*); IR (KBr) ν_{max} 1709, 1293, 1247, 764, 725; *m*/*z* 277 (M+, 70), 276 (100), 230 (25), 114 (40).

5.7. 3-Methyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (3a)

Thionyl chloride (200 mL) was added drop wise to carboxylic acid (**2a**) (30.0 g, 0.114 mol) and the reaction heated under reflux in a N_2 atmosphere for 3 h. This was cooled to room temperature and the thionyl chloride removed in vacuo. The last traces of thionyl chloride were removed with diethyl ether (2100 mL) to leave the acid chloride as a yellow solid. Triethylamine (46.1 g, 0.456 mol) in ethanol (250 mL) was added drop wise to the acid chloride and the reaction was stirred at room temperature for 18 h. Ice/water (300 mL) was added, the product was extracted into DCM (3×200 mL) and the organic layer dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was purified by column chromatography [DCM > DCM–ethyl acetate (6:1)] and dried in vacuo (P_2O_5) to yield the title compound (24.0 g, 73%) as a yellow oil. R_f 0.30 [DCM]; δ_H (400 MHz; $CDCl_3$): 1.49 (3H, t, O–CH_2C*H*$_3$), 2.87 (3H, s, C*H*$_3$), 4.59 (2H, q, O–C*H*$_2$–CH_3), 7.51 (6H, m, 5Ar–*H* + Ar–*Hb* or Ar–*Hc*), 7.70 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.75 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz), 8.15 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 7.8 Hz); IR (KBr) ν_{max} 2987, 1725 (ester), 1228, 1058, 762, 706; *m*/*z* 291 (M+, 95), 262 (100), 215 (20).

5.8. 6-Methyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (3b)

Using the same method as for the synthesis of ethyl ester (**3a**), carboxylic acid (**2b**) (13 g, 4.9×10^{-2} mol) was heated at reflux in thionyl chloride (100 mL) for 3 h. The acid chloride stirred at room temperature with triethylamine (19.8 g, 0.196 mol) in ethanol (150 mL) for 3 h. The crude product, which crystallised on standing was filtered, washed with cold ethanol (2×30 mL) and dried in vacuo (P_2O_5) to yield the title compound (10.4 g, 73%) as a white solid. R_f 0.62 [DCM–hexane (2:1)]; Mp 72–73 °C (lit.[28] 74–76 °C); δ_H (400 MHz; $CDCl_3$): 1.50 (3H, t, O–CH_2C*H*$_3$), 2.59 (3H, s, C*H*$_3$), 4.54 (2H, q, O–C*H*$_2$–CH_3), 7.51 (3H, m, 3Ar–*H*), 7.60 (1H, dd, Ar–*Hc*, J_{cb} 1.7 Hz, J_{cd} 8.5 Hz), 8.12 (1H, d, Ar–*Hd*, J_{dc} 8.5 Hz), 8.18 (2H, m, 2Ar–*H*), 8.35 (1H, s, Ar–*Ha*), 8.51 (1H, s, Ar–*Hb*); IR (KBr) ν_{max} 1705 (ester), 1373, 1235; *m*/*z* 291 (M+, 15), 262 (10), 218 (100), 203 (25), 189 (10), 115 (80), 103 (95).

5.9. 8-Methyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (3c)

Using the same method as for the synthesis of ethyl ester (**3a**), carboxylic acid (**2c**) (20 g, 7.6×10^{-2} mol) was heated at reflux in thionyl chloride (150 mL) for 3 h. The acid chloride was stirred at room temperature in ethanol (200 mL) and triethylamine (23.06 g, 0.228 mol) for 3 h. The crude product was purified through a pad of silica [DCM > DCM–ethyl acetate (1:1)] and dried in vacuo to give the title compound (16.8 g, 76%) as an off white solid. R_f 0.84 [DCM]; Mp 70–72 °C (lit.[28] 72 °C); δ_H (400 MHz; $CDCl_3$): 1.50 (3H, t, O–CH_2C*H*$_3$), 2.91 (3H, s, C*H*$_3$), 4.53 (2H, q, O–C*H*$_2$–CH_3), 7.53 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.60 (1H, d, Ar–*Hd*, J_{dc} 7.1 Hz), 8.28 (2H, m, 2Ar–*H*), 8.38 (1H, s, Ar–*Ha*), 8.53 (1H, d Ar–*Hb*, J_{bc} 8.3 Hz); IR (KBr) ν_{max} 1731 (ester), 1251, 1205, 1100, 772; *m*/*z* 291 (M+, 100), 263 (60), 218 (25), 109 (35).

5.10. 3,6-Dimethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (3d)

Using the same method as for the synthesis of ethyl ester (**3a**), carboxylic acid (**2d**) (3.57 g, 1.28×10^{-2} mol) was heated at reflux in thionyl chloride (30 mL) for 3 h. The acid chloride was stirred at room temperature in ethanol (30 mL) and triethylamine (3.88 g, 3.84×10^{-2} mol) for 18 h. The crude product was purified through a pad of silica [DCM > DCM–ethyl acetate (1:1)] and dried in vacuo (P_2O_5) to give the title compound (3.5 g, 89%) as an off white solid. R_f 0.49 [DCM–ethyl acetate (19:1)]; Mp 102–104 °C; δ_H

(400 MHz; $CDCl_3$): 1.49 (3H, t, O–CH_2 CH_3), 2.39 (3H, s, CH_3), 2.54 (3H, s, CH_3), 4.59 (2H, q, O–CH_2–CH_3), 7.48 (7H, m, 7Ar–*H*), 8.02 (1H, d, Ar–*H*); IR (KBr) ν_{max} 1728 (ester), 1288, 1228; *m/z* 305 (M+, 55), 277 (100), 230 (55), 217 (50), 115 (40).

5.11. 3-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (4a)

Carbon tetrachloride (300 mL) was added to ethyl ester (**3a**) (23.17 g, 7.95×10^{-2} mol), NBS (15.57 g, 8.75×10^{-2} mol) and benzoyl peroxide (1.93 g, 7.95×10^{-3} mol). The reaction was heated under reflux in a N_2 atmosphere in the presence of a heat lamp for 12 h, cooled to room temperature and insoluble succinimide filtered off. The filtrate was collected and the solvent removed in vacuo to give the crude product. This was recrystallised from ethanol and dried in vacuo (P_2O_5) to yield the title compound (23.7 g, 81%) as fine white needles. R_f 0.70 [hexane–ethyl acetate (2:1)]; Mp 118–122 °C; (Found: C, 61.79%; H, 4.35%; N, 3.77%. $C_{19}H_{16}NO_2Br$ requires: C, 61.63%; H, 4.36%; N, 3.78%); δ_H (400 MHz, $CDCl_3$): 1.54 (3H, t, O–CH_2C*H*$_3$), 4.66 (2H, q, O–C*H*$_2$–CH_3), 4.69 (2H, s, C*H*$_2$Br), 7.52 (3H, m, 3Ar–*H*), 7.62 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.70 (2H, m, 2Ar–*H*), 7.78 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.87 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz), 8.16 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz); δ_C (100 MHz, $CDCl_3$): 14.39, 27.48, 62.64, 123.48, 124.93, 125.90, 127.93, 128.63, 128.76, 129.01, 130.05, 130.81, 139.34, 140.89, 147.50, 159.94, 166.86; IR (KBr) ν_{max} 1727 (ester), 1236, 770, 702; *m/z* 371 (M+, 15), 369 (M+, 15), 290 (95), 262 (100), 216 (85), 108 (45).

5.12. 6-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (4b)

Using the same method as for the synthesis of benzylic bromide (**4a**), ethyl ester (**3b**) (7.95 g, 2.7×10^{-2} mol) was heated at reflux in carbon tetrachloride (150 mL) with NBS (5.34 g, 3.0×10^{-2} mol) and benzoyl peroxide (0.7 g, 2.8×10^{-3} mol) for 4 h. The crude product was recrystallised from ethanol and dried in vacuo (P_2O_5) to yield the title compound (7.16 g, 72%) as fine white needles. R_f 0.69 [hexane–ethyl acetate (3:1)]; Mp 107–108 °C; (Found: C, 61.38%; H, 4.20%; N, 3.69%. $C_{19}H_{16}NO_2Br$ requires: C, 61.63%; H, 4.36%; N, 3.78%); δ_H (400 MHz, $CDCl_3$): 1.51 (3H, t, O–CH_2C*H*$_3$), 4.55 (2H, q, O–C*H*$_2$–CH_3), 4.71 (2H, s, C*H*$_2$Br), 7.53 (3H, m, 3Ar–*H*), 7.80 (1H, dd, Ar–*Hc*, J_{cb} 1.8 Hz, J_{cd} 8.5 Hz), 8.20 (3H, m, 2Ar–*H* + Ar–*Hd*), 8.41 (1H, s, Ar–*Ha*), 8.80 (1H, d, Ar–*Hb*, J_{bc} 1.8 Hz); δ_C (100 MHz, $CDCl_3$): 14.43, 33.64, 62.11, 120.78, 123.95, 125.53, 127.62, 129.04, 130.04, 131.01, 135.94, 137.31, 138.48, 148.86, 157.26, 166.11; IR (KBr) ν_{max} 2983, 1726 (ester), 1253, 1158, 1034; *m/z* 371 (M+, 10), 369 (M+, 10), 290 (100), 262 (30), 216 (15), 108 (15).

5.13. 8-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (4c)

Using the same method as for the synthesis of benzylic bromide (**4a**), ethyl ester (**3c**) (16.0 g, 5.5×10^{-2} mol) was heated at reflux in carbon tetrachloride (200 mL) with NBS (10.75 g, 6.0×10^{-2} mol) and benzoyl peroxide (1.38 g, 5.7×10^{-3} mol) for 4 h. The crude product was recrystallised from ethanol and dried in vacuo (P_2O_5) to yield the title compound (7.16 g, 72%) as fine white solid. R_f 0.65 [hexane–ethyl acetate (3:1)]; Mp 83–85 °C; (Found: C, 61.39%; H, 4.28%; N, 4.00%. $C_{19}H_{16}NO_2Br$ requires: C, 61.63%; H, 4.36%; N, 3.78%); δ_H (400 MHz, $CDCl_3$): 1.50 (3H, t, O–CH_2-CH_3), 4.54 (2H, q, O–CH_2–CH_3), 5.33 (2H, s, CH_2Br), 7.53 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.87 (1H, dd, Ar–*Hd*, J_{dc} 7.1 Hz, J_{db} 1.0 Hz), 8.32 (2H, m, 2Ar–*H*), 8.41 (1H, s, Ar–*Ha*), 8.71 (1H, dd, Ar–*Hb*, J_{bc} 8.6 Hz, J_{bd} 1.2 Hz); IR (KBr) ν_{max} 1725 (ester), 1244, 1204, 766; *m/z* 371 (M+, 25), 369 (M+, 25), 290 (100), 262 (45), 108 (20).

5.14. 6-Bromomethyl-3-methyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester, 3,6-bis-bromomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (4d) and 3-bromomethyl-6-dibromomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester

Using the same method as for the synthesis of benzylic bromide (**4a**), ethyl ester (**3d**) (1.0 g, 3.28×10^{-3} mol) was heated at reflux in carbon tetrachloride (50 mL) with NBS (0.87 g, 4.91×10^{-3} mol) and benzoyl peroxide (0.08 g, 3.28×10^{-4} mol) for 4 h. Column chromatography [DCM–hexane (1:2) > (5:1)] was used to obtain the title compounds.

*6-Bromomethyl-3-methyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester, 3,6-bis-bromomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (***4d***)*: colourless oil (0.15 g, 12%); R_f 0.22 [DCM–hexane (6:1)]; δ_H (400 MHz, $CDCl_3$): 1.50 (3H, t, O–CH_2C*H*$_3$), 2.43 (3H, s, CH_3), 4.60 (2H, q, O–C*H*$_2$–CH_3), 4.66 (2H, s, CH_2Br), 7.51 (5H, m, 5Ar–*H*), 7.72 (2H, m, 2Ar–*H*), 8.13 (1H, d, Ar–*H*); IR (KBr) ν_{max} 1732 (ester), 1231, 1204; *m/z* 385 (M+, 10), 383 (M+, 10), 306 (M, 100), 304 (100), 276 (30), 230 (30); (**4d**); white solid (0.85 g, 56%); R_f 0.44 [DCM–hexane (6:1)]; Mp 120–122 °C; (Found: C, 51.69%; H, 3.43%; N, 2.82%. $C_{20}H_{17}NO_2Br_2$ requires: C, 51.86%; H, 3.70%; N, 2.82%); δ_H (400 MHz, $CDCl_3$): 1.55 (3H, t, O–CH_2C*H*$_3$), 4.66 (2H, s, CH_2Br), 4.68 (2H, q, O–C*H*$_2$–CH_3), 4.69 (2H, s, C*H*$_2$Br), 7.52 (3H, m, 3Ar–*H*), 7.68 (2H, m, 2Ar–*H*), 7.80 (1H, dd, Ar–*Hb*, J_{ba} 2.2 Hz, J_{bc} 8.8 Hz), 7.84 (1H, d, Ar–*Ha*, J_{ab} 2.2 Hz), 8.14 (1H, d, Ar–*H*, J_{cb} 8.8 Hz); δ_C (100 MHz, $CDCl_3$): 14.39, 27.29, 32.92, 62.81, 123.27, 124.73, 126.60, 128.66, 128.71, 129.12, 130.83, 131.79, 137.47, 139.14, 140.67, 147.17, 160.49, 166.55; IR (KBr) ν_{max} 1725 (ester), 1288, 1236, 696; *m/z* 465 (M+, 5), 463 (M+, 10), 461 (M+, 5), 384 (100), 382 (100), 275 (45), 230 (65), 149 (55).

3-Bromomethyl-6-dibromomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester: white solid (0.25 g, 14%); R_f 0.58 [DCM–hexane (6:1)]; Mp 136–138 °C; (Found: C, 44.48%; H, 2.97%; N, 2.62%. $C_{20}H_{16}NO_2Br_3$ requires: C, 44.32%; H, 2.98%; N, 2.58%); δ_H (400 MHz, $CDCl_3$): 1.56 (3H, t, O–CH_2C*H*$_3$), 4.68 (2H, q, O–C*H*$_2$–CH_3), 4.69 (2H, s, C*H*$_2$Br), 6.81 (1H, s, C*H*Br$_2$), 7.53 (3H,

m, 3Ar–*H*), 7.68 (2H, m, 2Ar–*H*), 7.91 (1H, d, Ar–*Ha*, J_{ab} 2.2 Hz), 8.07 (1H, dd, Ar–*Hb*, J_{ba} 2.2 Hz, J_{bc} 8.9 Hz), 8.20 (1H, d, Ar–*Hc*, J_{cb} 8.9 Hz); δ_C (100 MHz, $CDCl_3$): 14.41, 27.08, 40.19, 62.94, 121.56, 122.46, 127.23, 128.67, 128.70, 129.25, 129.78, 131.30, 138.93, 140.89, 141.05, 147.63, 161.25, 166.28; IR (KBr) ν_{max} 3445, 1720 (ester), 1289, 1232, 701, 674; *m/z* 545 (M+), 543 (M+), 541 (M+), 539 (M+), 462 (100), 354 (20), 308 (25), 228 (25).

5.15. 3-Diethylaminomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (5a)

Diethylamine (0.59 g, 8.1×10^{-3} mol) was added to benzylic bromide (**4a**) (1.5 g, 4.05×10^{-3} mol) in toluene (20 mL) and the reaction stirred at room temperature for 24 h. The insoluble amine salt was removed by filtration, the solvent removed in vacuo and the resulting oil taken up in DCM (50 mL). This was washed with saturated NaCl solution (2×30 mL) and dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was purified by column chromatography [DCM > DCM–ethyl acetate (19:1)] and dried in vacuo (P_2O_5) to yield the title compound (1.22 g, 82%) as a white crystalline solid. R_f 0.23 [DCM]; Mp 48–50 °C; (Found: C, 76.43%; H, 7.47%; N, 7.67%. $C_{23}H_{26}N_2O_2$ requires: C, 76.21%; H, 7.23%; N, 7.73%); δ_H (400 MHz, $CDCl_3$): 0.83 (6H, t, $2 \times$ N–CH_2–CH_3), 1.47 (3H, t, O–CH_2–CH_3), 2.41 (4H, q, $2 \times$ N–CH_2–CH_3), 3.76 (2H, s, quinoline–CH_2–N), 4.49 (2H, q, O–CH_2–CH_3), 7.47 (5H, m, 5Ar–*H*), 7.57 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.71 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.88 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz), 8.14 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz); δ_C (100 MHz, $CDCl_3$): 10.43, 14.34, 45.59, 53.03, 61.19, 124.08, 124.40, 127.19, 128.27, 128.33, 129.09, 129.29, 129.49, 129.85, 140.08, 140.62, 146.95, 160.49, 168.10; IR (KBr) ν_{max} 2974, 1732 (ester), 1217, 764; *m/z* 362 (M+, 10), 333 (100), 287 (50), 262 (50), 216 (55), 86 (50).

5.16. 2-Phenyl-3-piperdin-1-ylmethyl-quinoline-4-carboxylic acid ethyl ester (5b)

Using the same method as for the synthesis of amine (**5a**), piperidine (0.69 g, 8.1×10^{-3} mol) and benzylic bromide (**4a**) (1.5 g, 4.05×10^{-3} mol) in toluene (20 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (19:1)] and drying in vacuo (P_2O_5) gave the title compound (1.35 g, 88%) as a white solid. R_f 0.19 [DCM]; Mp 110–112 °C; (Found: C, 76.69%; H, 7.26%; N, 7.29%. $C_{24}H_{26}N_2O_2$ requires: C, 76.98%; H, 7.00%; N, 7.48%); δ_H (400 MHz, $CDCl_3$): 1.34 (2H, s, N–(CH_2–CH_2)$_2$–CH_2), 1.45 (4H, quintet, $2 \times$ N–CH_2–CH_2), 1.48 (3H, t, O–CH_2–CH_3), 2.24 (4H, s (broad), $2 \times$ N–CH_2–CH_2), 3.64 (2H, s, quinoline–CH_2–N), 4.53 (2H, q, O–CH_2–CH_3), 7.47 (5H, m, 5Ar–*H*), 7.57 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.71 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.92 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz), 8.14 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz); IR (KBr) ν_{max} 2937, 1727 (ester), 1214, 1177, 765; *m/z* 374 (M+, 30), 345 (100), 289 (50), 260 (70), 216 (100).

5.17. 3-Morpholin-4-ylmethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (5c)

Using the same method as for the synthesis of amine (**5a**), morpholine (1.41 g, 1.62×10^{-2} mol) and benzylic bromide (**4a**) (3.0 g, 8.1×10^{-3} mol) in toluene (40 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (4:1)] and drying in vacuo (P_2O_5) gave the title compound (2.5 g, 83%) as a white solid. R_f 0.15 [DCM]; Mp 102–104 °C; (Found: C, 73.41%; H, 6.54%; N, 7.46%. $C_{23}H_{24}N_2O_3$ requires: C, 73.38%; H, 6.43%; N, 7.44%); δ_H (400 MHz, $CDCl_3$): 1.50 (3H, t, O–CH_2–CH_3), 2.31 (4H, t, $2 \times$ N–CH_2–CH_2–O), 3.58 (4H, t, $2 \times$ N–CH_2–CH_2–O), 3.71 (2H, s, quinoline–CH_2–N), 4.54 (2H, q, O–CH_2–CH_3), 7.48 (5H, m, 5Ar–*H*), 7.59 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.74 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.91 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 7.8 Hz), 8.15 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.5 Hz); δ_C (100 MHz, $CDCl_3$): 14.38, 53.04, 57.49, 61.61, 66.76, 123.91, 124.38, 127.03, 127.46, 128.37, 128.48, 129.08, 129.85, 129.93, 139.89, 140.35, 147.11, 160.60, 167.93; IR (KBr) ν_{max} 2807, 1734 (ester), 1216, 1113, 781; *m/z* 376 (M+, 15), 347 (20), 289 (25), 260 (35), 216 (100).

5.18. 2-Phenyl-3-pyrazol-1-ylmethylquinoline-4-carboxylic acid ethyl ester (5d)

Using the same method as for the synthesis of amine (**5a**), pyrazole (0.36 g, 5.4×10^{-3} mol) and benzylic bromide (**4a**) (1.0 g, 2.7×10^{-3} mol) in toluene (15 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (19:1)] and drying in vacuo (P_2O_5) gave the title compound (0.97 g, 73%) as a colourless oil. R_f 0.40 [DCM–ethyl acetate (19:1)]; δ_H (400 MHz, $CDCl_3$): 1.35 (3H, t, O–CH_2–CH_3), 4.44 (2H, q, O–CH_2–CH_3), 5.49 (2H, s, quinoline–CH_2–N), 6.15 (1H, t, Ar–*Hf*), 7.08 (1H, d, Ar–*He* or Ar–*Hg*, J_{ef} or J_{gf} 2.4 Hz), 7.44 (6H, m, 5Ar–*H* + Ar–*He* or Ar–*Hg*), 7.62 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.79 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.85 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz), 8.19 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz); IR (KBr) ν_{max} 3449, 1730 (ester), 1284, 1224, 763; *m/z* 357 (M+, 10), 284 (100), 260 (35), 216 (35).

5.19. 6-Diethylaminomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (5e)

Using the same method as for the synthesis of amine (**5a**), diethylamine (0.32 g, 4.32×10^{-3} mol) and benzylic bromide (**4b**) (0.8 g, 2.16×10^{-3} mol) in toluene (15 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [hexane > hexane–ethyl acetate (3:1)] and drying in vacuo (P_2O_5) gave the title compound (0.6 g, 77%) as a white solid. R_f 0.19 [hexane–ethyl acetate (3:1)]; Mp 63–65 °C; (Found: C, 76.08%; H, 7.47%; N, 7.69%. $C_{23}H_{26}N_2O_2$ requires: C, 76.21%; H, 7.23%; N, 7.73%); δ_H (400 MHz, $CDCl_3$): 1.09 (6H, t, $2 \times$ N–CH_2–CH_3), 1.51 (3H, t, O–CH_2–CH_3), 2.59 (4H, q, $2 \times$ N–CH_2–CH_3), 3.78 (2H, s, quinoline–CH_2–N), 4.55

(2H, q, O–CH_2–CH_3), 7.51 (3H, m, 3Ar–*H*), 7.84 (1H, dd, Ar–*Hc*, J_{cb} 2.0 Hz, J_{cd} 8.8 Hz), 8.18 (3H, m, 2Ar–*H* + Ar–*Hd*), 8.36 (1H, s, Ar–*Ha*), 8.62 (1H, d, Ar–*Hb*, J_{bc} 2.0 Hz); IR (KBr) ν_{max} 2974, 2971, 1725 (ester), 1244, 1152, 1035; *m/z* 362 (M+, 10), 347 (20), 290 (100), 262 (40), 217 (15).

5.20. 2-Phenyl-6-piperdin-1-ylmethyl-quinoline-4-carboxylic acid ethyl ester (5f)

Using the same method as for the synthesis of amine (**5a**), piperidine (0.37 g, 4.32×10^{-3} mol) and benzylic bromide (**4b**) (0.8 g, 2.16×10^{-3} mol) in toluene (15 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [hexane > hexane–ethyl acetate (1:1)] and drying in vacuo (P_2O_5) gave the title compound (0.65 g, 80%) as a white solid. R_f 0.21 [hexane–ethyl acetate (3:1)]; Mp 93–95 °C; (Found: C, 76.69%; H, 7.23%; N, 7.47%. $C_{24}H_{26}N_2O_2$ requires: C, 76.98%; H, 7.00%; N, 7.48%); δ_H (400 MHz, $CDCl_3$): 1.46 (2H, m, N–(CH_2–CH_2)$_2$–CH_2), 1.51 (3H, t, O–CH_2–CH_3), 1.60 (4H, quintet, 2 × N–CH_2–CH_2), 2.45 (4H, s (broad), 2 × N–CH_2–CH_2), 3.68 (2H, s, quinoline–CH_2–N), 4.55 (2H, q, O–CH_2–CH_3), 7.51 (3H, m, 3Ar–*H*), 7.82 (1H, dd, Ar–*Hc*, J_{cb} 1.7 Hz, J_{cd} 8.5 Hz), 8.18 (3H, m, 2Ar–*H* + Ar–*Hd*), 8.36 (1H, s, Ar–*Ha*), 8.60 (1H, d, Ar–*Hb*, J_{bc} 1.7 Hz); IR (KBr) ν_{max} 2930, 1715 (ester), 1230, 1153, 1037, 696; *m/z* 374 (M+, 15), 291 (100), 262 (80), 245 (20), 217 (25).

5.21. 6-Morpholin-4-ylmethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (5g)

Using the same method as for the synthesis of amine (**5a**), morpholine (0.38 g, 4.32×10^{-3} mol) and benzylic bromide (**4b**) (0.8 g, 2.16×10^{-3} mol) in toluene (15 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [hexane–ethyl acetate (3:1) > ethyl acetate] and drying in vacuo (P_2O_5) gave the title compound (0.7 g, 88%) as a white solid. R_f 0.16 [hexane–ethyl acetate (3:1)]; Mp 86–88 °C; (Found: C, 73.09%; H, 6.60%; N, 7.39%. $C_{23}H_{24}N_2O_3$ requires: C, 73.38%; H, 6.43%; N, 7.44%); δ_H (400 MHz, $CDCl_3$): 1.51 (3H, t, O–CH_2–CH_3), 2.52 (4H, t, 2 × N–CH_2–CH_2–O), 3.71 (2H, s, quinoline–CH_2–N), 3.74 (4H, t, 2 × N–CH_2–CH_2–O), 4.55 (2H, q, O–CH_2–CH_3), 7.51 (3H, m, 3Ar–*H*), 7.82 (1H, dd, Ar–*Hc*, J_{cb} 1.7 Hz, J_{cd} 8.6 Hz), 8.18 (3H, m, 2Ar–*H* + Ar–*Hd*), 8.37 (1H, s, Ar–*Ha*), 8.64 (1H, d, Ar–*Hb*, J_{bc} 1.7 Hz); IR (KBr) ν_{max} 2821, 1728 (ester), 1240, 1155, 1116; *m/z* 376 (M+, 15), 291 (100), 262 (70), 245 (30), 217 (20).

5.22. 2-Phenyl-6-pyrazol-1-ylmethylquinoline-4-carboxylic acid ethyl ester (5h)

Using the same method as for the synthesis of amine (**5a**), pyrazole (0.29 g, 4.32×10^{-3} mol) and benzylic bromide (**4b**) (0.8 g, 2.16×10^{-3} mol) in toluene (15 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [hexane–ethyl acetate (3:1) > (1:1)] and drying in vacuo (P_2O_5) gave the title compound (0.97 g, 73%) as a white solid. R_f 0.15 [hexane–ethyl acetate (3:1)]; Mp 70–72 °C; δ_H (400 MHz, $CDCl_3$): 1.48 (3H, t, O–CH_2–CH_3), 4.53 (2H, q, O–CH_2–CH_3), 5.56 (2H, s, quinoline–CH_2–N), 6.34 (1H, t, Ar–*Hc*), 7.54 (6H, m, 6Ar–*H*), 8.19 (3H, m, 3Ar–*H*), 8.40 (1H, s, Ar–*Ha*), 8.62 (1H, d, Ar–*Hb*); IR (KBr) ν_{max} 3399, 1712 (ester), 1246, 1143, 755; *m/z* 357 (M+, 100), 328 (70), 290 (50), 262 (40), 216 (25).

5.23. 8-Diethylaminomethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (5i)

Using the same method as for the synthesis of amine (**5a**), diethylamine (0.20 g, 2.7×10^{-3} mol) and benzylic bromide (**4c**) (0.5 g, 1.35×10^{-3} mol) in toluene (10 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [hexane–ethyl acetate (3:1) > (1:2)] and drying in vacuo (P_2O_5) gave the title compound (0.41 g, 84%) as a pale yellow oil. R_f 0.22 [hexane–ethyl acetate (3:1)]; δ_H (400 MHz, $CDCl_3$): 1.12 (6H, t, 2 × N–CH_2–CH_3), 1.50 (3H, t, O–CH_2–CH_3), 2.69 (4H, q, 2 × N–CH_2–CH_3), 4.43 (2H, s, quinoline–CH_2–N), 4.54 (2H, q, O–CH_2–CH_3), 7.55 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.98 (1H, d, Ar–*Hd*, J_{dc} 7.1 Hz), 8.27 (2H, m, 2Ar–*H*), 8.37 (1H, s, Ar–*Ha*), 8.56 (1H, d, Ar–*Hb*, J_{bc} 7.3 Hz); IR (KBr) ν_{max} 2976, 1730 (ester), 1241, 1201, 1097, 770; *m/z* 362 (M+), 333 (20), 291 (100), 262 (40).

5.24. 2-Phenyl-8-piperdin-1-ylmethyl-quinoline-4-carboxylic acid ethyl ester (5j)

Using the same method as for the synthesis of amine (**5a**), piperidine (0.23 g, 2.7×10^{-3} mol) and benzylic bromide (**4c**) (0.5 g, 1.35×10^{-3} mol) in toluene (15 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [hexane–ethyl acetate (3:1) > (1:1)] and drying in vacuo (P_2O_5) gave the title compound (0.41 g, 80%) as a pale yellow oil. R_f 0.22 [hexane–ethyl acetate (3:1)]; δ_H (400 MHz, $CDCl_3$): 1.46 (2H, m, N–(CH_2–CH_2)$_2$–CH_2), 1.50 (3H, t, O–CH_2–CH_3), 1.64 (4H, quintet, 2 × N–CH_2–CH_2), 2.59 (4H, s (broad), 2 × N–CH_2–CH_2), 4.37 (2H, s, quinoline–CH_2–N), 4.54 (2H, q, O–CH_2–CH_3), 7.55 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.91 (1H, d, Ar–*Hd*, J_{dc} 6.1 Hz), 8.28 (2H, m, 2Ar–*H*), 8.38 (1H, s, Ar–*Ha*), 8.58 (1H, d, Ar–*Hb*, J_{bc} 7.6 Hz); IR (KBr) ν_{max} 2926, 1723 (ester), 1247, 1195, 1088; *m/z* 374 (M+), 345, 331, 303, 291 (100), 263 (30), 218 (15).

5.25. 8-Morpholin-4-ylmethyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (5k)

Using the same method as for the synthesis of amine (**5a**), morpholine (0.24 g, 2.7×10^{-3} mol) and benzylic bromide (**4c**) (0.5 g, 1.35×10^{-3} mol) in toluene (10 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [hexane–ethyl acetate (3:1) > (1:2)] and drying in vacuo (P_2O_5) gave the title compound (0.41 g, 80%) as a white solid. R_f 0.15 [hexane–ethyl acetate (3:1)];

Mp 69–71 °C; δ_H (400 MHz, $CDCl_3$): 1.51 (3H, t, O–CH_2–CH_3), 2.66 (4H, t, 2 × N–CH_2–CH_2–O), 3.77 (4H, t, 2 × N–CH_2–CH_2–O), 4.40 (2H, s, quinoline–CH_2–N), 4.55 (2H, q, O–CH_2–CH_3), 7.54 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.91 (1H, dd, Ar–*Hd*, J_{dc} 7.1 Hz, J_{db} 1.3 Hz), 8.27 (2H, m, 2Ar–*H*), 8.39 (1H, s, Ar–*Ha*), 8.61 (1H, dd, Ar–*Hb*, J_{bc} 8.6 Hz, J_{bd} 1.3 Hz); IR (KBr) ν_{max} 3436, 1720 (ester), 1231, 1197, 1114, 1092, 769; *m*/*z* 376 (M+), 347, 291 (100), 275 (15), 263 (50), 218 (20).

5.26. 2-Phenyl-8-pyrazol-1-ylmethylquinoline-4-carboxylic acid ethyl ester (5l)

Using the same method as for the synthesis of amine (**5a**), pyrazole (0.18 g, 2.7×10^{-3} mol) and benzylic bromide (**4c**) (0.8 g, 1.35×10^{-3} mol) in toluene (10 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (19:1)] and drying in vacuo (P_2O_5) gave the title compound (0.39 g, 81%) as a white solid. R_f 0.31 [DCM]; Mp 128–130 °C; (Found: C, 73.69%; H, 5.41%; N, 11.72%. $C_{22}H_{19}N_3O_2$ requires: C, 73.93%; H, 5.36%; N, 11.76%); δ_H (400 MHz, $CDCl_3$): 1.50 (3H, t, O–CH_2–CH_3), 4.54 (2H, q, O–CH_2–CH_3), 6.17 (2H, s, quinoline–CH_2–N), 6.26 (1H, t, Ar–*He*), 7.42 (1H, dd, Ar–*Hd*, J_{dc} 7.1 Hz, J_{db} 1.2 Hz), 7.55 (6H, m, 5Ar–*H* + Ar–*Hc*), 8.27 (2H, m, 2Ar–*H*), 8.44 (1H, s, Ar–*Ha*), 8.67 (1H, dd, Ar–*Hb*, J_{bc} 8.6 Hz, J_{bd} 1.2 Hz); IR (KBr) ν_{max} 3428, 2978, 1722 (ester), 1247, 1200, 760; *m*/*z* 357 (M+, 50), 356 (50), 328 (100), 277 (10), 249 (15), 204 (15).

5.27. 3-(4-Bromophenoxymethyl)-2-phenyl-quinoline-4-carboxylic acid ethyl ester (6a)

Benzylic bromide (**4b**) (0.5 g, 1.35×10^{-3} mol), 4-bromophenol (0.26 g, 1.49×10^{-3} mol) and potassium carbonate (0.41 g, 2.97×10^{-3} mol) in DMF (10 mL) were stirred at room temperature for 24 h. Water (50 mL) was added and the product extracted into DCM (2 × 30 mL). The organic layer was washed with saturated NaCl solution (2 × 30 mL) and dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was purified by column chromatography [hexane–ethyl acetate (3:1)] and dried in vacuo (P_2O_5) to yield the title compound (0.5 g, 81%) as a white solid. R_f 0.51 [hexane–ethyl acetate (3:1)]; Mp 122–124 °C; (Found: C, 64.73%; H, 4.38%; N, 2.69%. $C_{25}H_{20}NO_3Br$ requires: C, 64.95%; H, 4.36%; N, 3.03%); δ_H (400 MHz, $CDCl_3$): 1.33 (3H, t, O–CH_2–CH_3), 4.44 (2H, q, O–CH_2–CH_3), 5.17 (2H, s, quinoline–CH_2–N), 6.71 (2H, d, Ar–*Hf*, J_{fe} 8.8 Hz), 7.34 (2H, d, Ar–*He*, J_{ef} 8.8 Hz), 7.49 (3H, m, 3Ar–*H*), 7.63 (3H, m, 2Ar–H + Ar–*Hb* or Ar–*Hc*), 7.79 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.93 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 9.1 Hz), 8.20 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz); δ_C (100 MHz, $CDCl_3$): 14.27, 62.29, 65.66, 113.79, 116.48, 123.49, 124.36, 124.83, 127.82, 128.66, 129.06, 129.18, 129.99, 130.67, 132.41, 139.45, 141.02, 147.79, 157.24, 159.70, 167.18; IR (KBr) ν_{max} 1728 (ester), 1487, 1474, 1231 (ether), 819; *m*/*z* 463 (M+), 461 (M+), 290 (100), 262 (85), 217 (45).

5.28. 6-(4-Bromophenoxymethyl)-2-phenyl-quinoline-4-carboxylic acid ethyl ester (6b)

Using the same method as for the synthesis of ether (**6a**), benzylic bromide (**4b**) (0.5 g, 1.35×10^{-3} mol) gave the title compound (0.5 g, 81%) as a white solid. R_f 0.62 [hexane–ethyl acetate (3:1)]; Mp 131–133 °C; (Found: C, 64.68%; H, 4.44%; N, 3.16%. $C_{25}H_{20}NO_3Br$ requires: C, 64.95%; H, 4.36%; N, 3.03%); δ_H (400 MHz, $CDCl_3$): 1.50 (3H, t, O–CH_2–CH_3), 4.54 (2H, q, O–CH_2–CH_3), 5.26 (2H, s, quinoline–CH_2–N), 6.92 (2H, d, Ar–*Hf*, J_{fe} 9.3 Hz), 7.40 (2H, d, Ar–*He*, J_{ef} 9.3 Hz), 7.54 (3H, m, 3Ar–*H*), 7.83 (1H, dd, Ar–*Hc*, J_{cb} 2.0 Hz, J_{cd} 8.7 Hz), 8.21 (2H, m, 2Ar–*H*), 8.25 (1H, d, Ar–*Hd*, J_{dc} 8.7 Hz), 8.42 (1H, s, Ar–*Ha*), 8.81 (1H, d, Ar–*Hb*, J_{bc} 2.0 Hz); δ_C (100 MHz, $CDCl_3$): 14.48, 62.09, 70.39, 113.52, 116.93, 120.69, 123.99, 124.01, 127.62, 129.08, 129.18, 129.94, 130.95, 132.50, 135.96, 136.28, 138.85, 149.18, 157.10, 157.89, 166.41; IR (KBr) ν_{max} 1724 (ester), 1484, 1229 (ether), 1170, 1145, 821; *m*/*z* 463 (M+), 461 (M+), 290 (100), 262 (25), 217 (10).

5.29. 8-(4-Bromophenoxymethyl)-2-phenyl-quinoline-4-carboxylic acid ethyl ester (6c)

Using the same method as for the synthesis of ether (**6a**), benzylic bromide (**4c**) (0.5 g, 1.35×10^{-3} mol) gave the title compound (0.5 g, 81%) as a white solid. R_f 0.74 [hexane–ethyl acetate (3:1)]; Mp 99–100 °C; (Found: C, 64.65%; H, 4.47%; N, 3.23%. $C_{25}H_{20}NO_3Br$ requires: C, 64.95%; H, 4.36%; N, 3.03%); δ_H (400 MHz, $CDCl_3$): 1.51 (3H, t, O–CH_2–CH_3), 4.56 (2H, q, O–CH_2–CH_3), 5.93 (2H, s, quinoline–CH_2–N), 6.97 (2H, d, Ar–*Hf*, J_{fe} 9 Hz), 7.30 (2H, d, Ar–*He*, J_{ef} 9 Hz), 7.54 (3H, m, 3Ar–*H*), 7.62 (1H, dd, Ar–*Hc*, J_{cb} 8.4 Hz, J_{cd} 7.0 Hz), 7.90 (1H, d, Ar–*Hd*, J_{dc} 7.0 Hz), 8.22 (2H, m, 2Ar–*H*), 8.44 (1H, s, Ar–*Ha*), 8.68 (1H, d, Ar–*Hb*, J_{bc} 8.7 Hz); δ_C (100 MHz, $CDCl_3$): 14.44, 61.99, 66.85, 113.03, 116.95, 119.78, 123.81, 125.01, 127.42, 127.51, 127.79, 128.95, 129.94, 132.34, 135.44, 136.42, 138.58, 146.32, 155.35, 158.22, 166.37; IR (KBr) ν_{max} 1712 (ester), 1491, 1342, 1251, 1232 (ether), 818, 770; *m*/*z* 463 (M+, 5), 461 (M+, 5), 290 (100), 262 (25), 217 (10).

5.30. 3-(4-Bromophenylsulfanylmethyl)-2-phenyl-quinoline-4-carboxylic acid ethyl ester (7a)

Triethylamine (0.27 g, 2.7×10^{-3} mol) was added to benzylic bromide (**4a**) (0.5 g, 1.3510^{-3} mol) dissolved in THF (10 mL) and cooled to 0 °C before the addition of 4-bromothiophenol (0.25 g, 1.35×10^{-3} mol). The reaction was stirred at room temperature for 2 h and diethyl ether (20 mL) added. The organic layer was washed with water (15 mL), saturated NaCl solution (15 mL) and dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was triturated with diethyl ether and then dried in vacuo to yield the title compound (0.53 g, 82%) as a white solid. R_f 0.48 [hexane–ethyl acetate (3:1)]; Mp 108–110 °C; (Found: C, 62.96%; H, 4.27%; N, 3.09%; S, 6.54%. $C_{25}H_{20}NO_2SBr$ requires: C, 62.76%; H, 4.21%; N, 2.93%; S, 6.70%); δ_H (400 MHz, $CDCl_3$): 1.47 (3H, t, O–CH_2–CH_3), 4.35 (2H, s, quinoline–

CH_2–N), 4.56 (2H, q, O–CH_2–CH_3), 6.97 (2H, d, Ar–*Hf*, J_{fe} 8.4 Hz), 7.29 (2H, d, Ar–*He*, J_{ef} 8.4 Hz), 7.46 (3H, m, 3Ar–*H*), 7.52 (2H, m, 2Ar–H), 7.62 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.75 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.89 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz), 8.16 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz); δ_C (100 MHz, $CDCl_3$): 14.34, 34.78, 62.39, 121.23, 123.59, 124.73, 125.77, 127.75, 128.48, 128.72, 128.98, 130.00, 130.23, 132.04, 132.43, 134.75, 139.74, 140.17, 147.07, 160.49, 167.31; IR (KBr) ν_{max} 1728 (ester), 1476, 1221, 1092, 1007, 701; *m*/*z* 479 (M+, 35), 477 (35), 290 (80), 262 (100), 216 (60).

5.31. 6-(4-Bromo-phenylsulfanylmethyl)-2-phenyl-quinoline-4-carboxylic acid ethyl ester (7b)

Using the same method as for the synthesis of thioether (**7a**), benzylic bromide (**4b**) (0.5 g, 1.35×10^{-3} mol) gave the title compound (0.55 g, 85%) as a white solid. R_f 0.31 [hexane–DCM (2:1)]; Mp 138–140 °C; (Found: C, 62.82%; H, 4.12%; N, 2.96%; S, 6.59%. $C_{25}H_{20}NO_2SBr$ requires: C, 62.76%; H, 4.21%; N, 2.93%; S, 6.70%); δ_H (400 MHz, $CDCl_3$): 1.49 (3H, t, O–CH_2–CH_3), 4.28 (2H, s, quinoline–CH_2–N), 4.52 (2H, q, O–CH_2–CH_3), 7.18 (2H, d, Ar–*Hf*, J_{fe} 8.4 Hz), 7.35 (2H, d, Ar–*He*, J_{ef} 8.4 Hz), 7.53 (3H, m, 3Ar–*H*), 7.74 (1H, dd, Ar–*Hc*, J_{cb} 2.0 Hz, J_{cd} 8.7 Hz), 8.17 (3H, m, 2Ar–*H* + Ar–*Hd*), 8.38 (1H, s, Ar–*Ha*), 8.57 (1H, d, Ar–*Hb*, J_{bc} 2.0 Hz); δ_C (100 MHz, $CDCl_3$): 14.42, 39.91, 61.97, 120.56, 120.89, 123.88, 125.12, 127.51, 129.00, 129.81, 130.77, 130.90, 132.02, 132.26, 134.81, 135.64, 136.87, 138.82, 148.70, 156.78, 166.27; IR (KBr) ν_{max} 1725 (ester), 1252, 1146, 1088; *m*/*z* 479 (M+, 10), 477 (M+, 10), 290 (100), 262 (30).

5.32. 8-(4-Bromo-phenylsulfanylmethyl)-2-phenyl-quinoline-4-carboxylic acid ethyl ester (7c)

Using the same method as for the synthesis of thioether (**7a**), benzylic bromide (**4c**) (0.5 g, 1.35×10^{-3} mol) gave the title compound (0.55 g, 85%) as a white solid. R_f 0.74 [hexane–ethyl acetate (3:1)]; Mp 105–107 °C; (Found: C, 62.82%; H, 4.13%; N, 3.09%; S, 6.54%. $C_{25}H_{20}NO_2SBr$ requires: C, 62.76%; H, 4.21%; N, 2.93%; S, 6.70%); δ_H (400 MHz, $CDCl_3$): 1.50 (3H, t, O–CH_2–CH_3), 4.55 (2H, q, O–CH_2–CH_3), 4.90 (2H, s, quinoline–CH_2–N), 7.21 (2H, d, Ar–*Hf*, J_{fe} 8.6 Hz), 7.30 (2H, d, Ar–*He*, J_{ef} 8.4 Hz), 7.53 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.67 (1H, d, Ar–*Hd*, J_{dc} 7.3 Hz), 8.24 (2H, m, 2Ar–*H*), 8.42 (1H, s, Ar–*Ha*), 8.63 (1H, dd, Ar–*Hb*, J_{bc} 8.7 Hz, J_{bd} 1.4 Hz); δ_C (100 MHz, $CDCl_3$): 14.47, 35.27, 62.05, 119.85, 120.21, 124.27, 125.11, 127.37, 127.57, 129.00, 129.88, 129.95, 131.81, 131.83, 136.46, 136.70, 136.77, 138.76, 147.00, 155.39, 166.55; IR (KBr) ν_{max} 1723 (ester), 1474, 1245, 1206, 1092, 770; *m*/*z* 479 (M+, 60), 477 (M+, 60), 446 (10), 444 (10), 290 (100), 262 (60).

5.33. Sodium 3-morpholin-4-ylmethyl-2-phenyl-quinoline-4-carboxylate (8c)

Ester (**5c**) (0.25 g, 6.64×10^{-4} mol) and sodium hydroxide (0.027 g, 6.64×10^{-4} mol) were stirred in dioxane (5 mL) and water (2.5 mL) at room temperature for 2 h, then the reaction solvent was removed in vacuo. The resulting solid was filtered, washed with diethyl ether (10 mL) and dried in vacuo (P_2O_5) to yield the title compound (0.20 g, 81%) as a white solid. δ_H (400 MHz, DMSO): 2.14 (4H, t, 2 × N–CH_2–CH_2–O), 3.28 (4H, t, 2 × N–CH_2–CH_2–O), 3.47 (2H, s, quinoline–CH_2–N), 7.39 (3H, m, 3Ar–*H*), 7.46 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.59 (2H, m, 2*Ar*–*H*), 7.62 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.84 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz), 7.94 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz).

5.34. Sodium 2-phenyl-3-pyrazol-1-ylmethylquinoline-4-carboxylate (8d)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5d**) (0.49g, 1.37×10^{-3} mol) gave the title product (0.35 g, 73%) was obtained as a white solid. δ_H (400 MHz, DMSO): 5.47 (2H, s, quinoline–CH_2–N), 6.10 (1H, t, Ar–*Hf*), 7.25 (1H, d, Ar–*He* or Ar–*Hg*, J_{ef} or J_{gf} 2.2 Hz), 7.32 (1H, d, Ar–*He* or Ar–*Hg*, J_{ef} or J_{gf} 2.2 Hz), 7.44 (5H, m, 5Ar–*H*), 7.76 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.91 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.94 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz), 8.12 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz).

5.35. Sodium 6-diethylaminomethyl-2-phenyl-quinoline-4-carboxylate (8e)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5e**) (0.25 g, 6.9×10^{-4} mol) gave the title product (0.2 g, 83%) was obtained as a pale yellow solid. δ_H (400 MHz, DMSO): 0.99 (6H, t, 2 × N–CH_2–CH_3), 2.49 (4H, q, 2 × N–CH_2–CH_3), 3.65 (2H, s, quinoline–CH_2–N), 7.49 (3H, m, 3Ar–*H*), 7.65 (1H, dd, Ar–*Hc*, J_{cb} 1.9 Hz, J_{cd} 8.7 Hz), 7.93 (1H, d, Ar–*Hd*, J_{dc} 8.7 Hz), 7.99 (1H, s, Ar–*Ha*), 8.19 (2H, m, 2Ar–*H*), 8.54 (1H, d, Ar–*Hb*, J_{bc} 1.9 Hz).

5.36. Sodium 2-phenyl-6-piperdin-1-ylmethyl-quinoline-4-carboxylate (8f)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5f**) (0.34 g, 9.08×10^{-4} mol) gave the title product (0.3 g, 90%) was obtained as a white solid. δ_H (400 MHz, DMSO): 1.39 (2H, m (broad), N–(CH_2–CH_2)$_2$–CH_2), 1.50 (4H, quintet, 2 × N–CH_2–CH_2), 2.35 (4H, s (broad), 2 × N–CH_2–CH_2), 3.55 (2H, s, quinoline–CH_2–N), 7.49 (3H, m, 3Ar–*H*), 7.63 (1H, dd, Ar–*Hc*, J_{cb} 2.0 Hz, J_{cd} 8.7 Hz), 7.93 (1H, d, Ar–*Hd*, J_{dc} 8.7 Hz), 7.98 (1H, s, Ar–*Ha*), 8.19 (2H, m, 2Ar–*H*), 8.52 (1H, d, Ar–*Hb*, J_{bc} 2.0 Hz).

5.37. Sodium 6-morpholin-4-ylmethyl-2-phenyl-quinoline-4-carboxylate (8g)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5g**) (0.25 g, 6.64×10^{-4} mol) gave the title product (0.2 g, 83%) was obtained as a white solid. δ_H (400 MHz, DMSO): 2.39 (4H, t (broad), 2 × N–CH_2–CH_2–O), 3.58 (4H, t, 2 × N–CH_2–CH_2–O), 3.59 (2H, s, quinoline–CH_2–N), 7.49 (3H, m, 3Ar–*H*), 7.65 (1H,

dd, Ar–*Hc*, J_{cb} 2.0 Hz, J_{cd} 8.7 Hz), 7.94 (1H, d, Ar–*Hd*, J_{dc} 8.7 Hz), 7.99 (1H, s, Ar–*Ha*), 8.19 (2H, m, Ar–*H*), 8.56 (1H, d, Ar–*Hb*, J_{bc} 2.0 Hz).

5.38. Sodium 2-phenyl-6-pyrazol-1-ylmethylquinoline-4-carboxylate (8h)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5h**) (0.25 g, 6.64×10^{-4} mol) gave the title product (0.2 g, 83%) was obtained as a white solid. δ_H (400 MHz, DMSO): 5.48 (2H, s, quinoline–CH_2–N), 6.27 (1H, t, Ar–*Hc*), 7.49 (5H, m, 5Ar–*H*), 7.85 (1H, d, Ar–*H*), 7.92 (1H, d, Ar–*H*), 7.99 (1H, s, Ar–*Ha*), 8.19 (2H, m, 2Ar–*H*), 8.64 (1H, d, Ar–*Hb*).

5.39. Sodium 8-diethylaminomethyl-2-phenyl-quinoline-4-carboxylate (8i)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5i**) (0.28 g, 7.73×10^{-4} mol) gave the title product (0.23 g, 83%) was obtained as a white solid. δ_H (400 MHz, DMSO): 1.03 (6H, t, 2 × N–CH_2–CH_3), 2.58 (4H, q, 2 × N–CH_2–CH_3), 4.29 (2H, s, quinoline–CH_2–N), 7.49 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.77 (1H, d, Ar–*Hd*, J_{dc} 6.4 Hz), 8.01 (1H, s, Ar–*Ha*), 8.24 (2H, m, 2Ar–*H*), 8.52 (1H, d, Ar–*Hb*, J_{bc} 7.6 Hz).

5.40. Sodium 2-phenyl-8-piperdin-1-ylmethyl-quinoline-4-carboxyate (8j)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5j**) (0.37 g, 9.88×10^{-4} mol) gave the title product (0.31 g, 85%) was obtained as a white solid. δ_H (400 MHz, DMSO): 1.40 (2H, m, N–(CH_2–CH_2)$_2$–CH_2), 1.53 (4H, quintet, 2 × N–CH_2–CH_2), 3.55 (4H, s, 2 × N–CH_2–CH_2), 4.20 (2H, s, quinoline–CH_2–N), 7.49 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.70 (1H, d, Ar–*Hd*, J_{dc} 6.6 Hz), 7.99 (1H, s, Ar–*Ha*), 8.24 (2H, m, 2Ar–*H*), 8.52 (1H, d, Ar–*Hb*, J_{bc} 8.6 Hz).

5.41. Sodium 8-morpholin-4-ylmethyl-2-phenyl-quinoline-4-carboxylate (8k)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5k**) (0.25 g, 6.64×10^{-4} mol) gave the title product (0.21 g, 85%) was obtained as a white solid. δ_H (400 MHz, DMSO): 2.52 (4H, t, 2 × N–CH_2–CH_2–O), 3.60 (4H, t, 2 × N–CH_2–CH_2–O), 4.24 (2H, s, quinoline–CH_2–N), 7.49 (4H, m, 3Ar–*H* + Ar–*Hc*), 7.72 (1H, d, Ar–*Hd*, J_{dc} 6.1 Hz), 7.98 (1H, s, Ar–*Ha*), 8.25 (2H, m, 2Ar–*H*), 8.53 (1H, d, Ar–*Hb*, J_{bc} 7.0 Hz).

5.42. Sodium 2-phenyl-8-pyrazol-1-ylmethylquinoline-4-carboxylate (8l)

Using the same method as for the synthesis of carboxylate salt (**8c**), ester (**5l**) (0.28 g, 7.83×10^{-4} mol) gave the title product (0.24 g, 87%) was obtained as a white solid. δ_H (400 MHz, DMSO): 6.04 (2H, s, quinoline–CH_2–N), 6.25 (1H, t, Ar–*H*), 7.15 (1H, d, Ar–*H*), 7.47 (5H, m, 5Ar–*H*), 7.85 (1H, s, Ar–*H*), 8.04 (1H, s, Ar–*Ha*), 8.29 (2H, d, 2Ar–*H*), 8.60 (1H, d, Ar–*H*).

5.43. 2-Ethyl-4-phenyl-2,3-dihydropyrrolo[3,4-*c*]quinolin-1-one (9a)

Using the same method as for the synthesis of amine (**5a**), ethylamine (0.24 g, 5.4×10^{-3} mol) and benzylic bromide (**4a**) (1.0 g, 2.7×10^{-3} mol) in toluene (30 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (19:1)] and drying in vacuo (P_2O_5) gave the title compound (0.7 g, 90%) as a white solid. R_f 0.47 [DCM–ethyl acetate (19:1)]; Mp 149–151 °C; (Found: C, 79.05%; H, 5.89%; N, 9.44%. $C_{19}H_{16}N_2O$ requires: C, 79.14%; H, 5.59%; N, 9.72%); δ_H (400 MHz, $CDCl_3$): 1.35 (3H, t, CH_2–CH_3), 3.79 (2H, t, N–CH_2–CH_3), 4.68 (2H, s, quinoline–CH_2–N), 7.54 (3H, m, 3Ar–*H*), 7.70 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.81 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.91 (2H, m, 2Ar–*H*), 8.26 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.5 Hz), 9.17 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz); δ_C (100 MHz, $CDCl_3$): 13.76, 37.21, 49.47, 122.79, 123.58, 127.92, 128.28, 128.96, 129.53, 129.56, 130.02, 133.23, 136.25, 138.57, 148.33, 153.53, 167.70; IR (KBr) ν_{max} 1695 (amide), 1458, 1250, 776, 707; *m*/*z* 288 (M+, 100), 273 (20), 259 (45), 216, (40), 108 (30).

5.44. 2-Propyl-4-phenyl-2,3-dihydropyrrolo[3,4-*c*]quinolin-1-one (9b)

Using the same method as for the synthesis of amine (**5a**), propylamine (0.32 g, 5.4×10^{-3} mol) and benzylic bromide (**4a**) (1.0 g, 2.710^{-3} mol) in toluene (30 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (19:1)] and drying in vacuo (P_2O_5) gave the title compound (0.7 g, 86%) as a white solid. R_f 0.49 [DCM–ethyl acetate (19:1)]; Mp 118–119 °C; (Found: C, 79.31%; H, 6.10%; N, 9.38%. $C_{20}H_{18}N_2O$ requires: C, 79.44%; H, 6.00%; N, 9.27%); δ_H (400 MHz, $CDCl_3$): 1.00 (3H, t, CH_2–CH_3), 1.77 (2H, sextet, CH_2–CH_2–CH_3), 3.69 (2H, t, N–CH_2–CH_2), 4.67 (2H, s, quinoline–CH_2–N), 7.55 (3H, m, 3Ar–*H*), 7.70 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.81 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.91 (2H, m, 2Ar–*H*), 8.26 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz), 9.17 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz); IR (KBr) ν_{max} 1693 (amide), 1458, 1247, 779, 705; *m*/*z* 302 (M+, 60), 273 (100), 216 (80), 122 (20).

5.45. 2-Butyl-4-phenyl-2,3-dihydropyrrolo[3,4-*c*]quinolin-1-one (9c)

Using the same method as for the synthesis of amine (**5a**), *n*-butylamine (0.4 g, 5.4×10^{-3} mol) and benzylic bromide (**4a**) (1.0 g, 2.710^{-3} mol) in toluene (30 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (19:1)] and drying in vacuo (P_2O_5) gave the title compound (0.7 g, 82%) as a white solid. R_f 0.57 [DCM–ethyl acetate (19:1)]; Mp 120–122 °C; (Found: C, 79.54%; H, 6.58%; N, 8.87%. $C_{21}H_{20}N_2O$ requires: C, 79.72%; H, 6.37%; N, 8.86%); δ_H (400 MHz, $CDCl_3$): 0.98 (3H, t, CH_2–CH_3), 1.43 (2H, sextet, CH_2–CH_2–CH_3), 1.72 (2H, quintet, N–CH_2–CH_2), 3.73 (2H,

t, N–CH_2–CH_2), 4.67 (2H, s, quinoline–CH_2–N), 7.55 (3H, m, 3Ar–*H*), 7.70 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.81 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.91 (2H, m, 2Ar–*H*), 8.26 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.5 Hz), 9.17 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz); δ_C (100 MHz, $CDCl_3$): 13.80, 20.20, 30.72, 42.30, 50.12, 122.81, 123.62, 127.91, 128.32, 128.95, 129.54, 129.60, 130.00, 133.27, 136.16, 138.60, 148.34, 153.42, 167.93; IR (KBr) ν_{max} 2933, 1694 (amide), 1460, 1235, 777, 688; *m*/*z* 316 (M+, 100), 273 (80), 216 (60), 122 (15).

5.46. 2-*tert*-Butyl-4-phenyl-2,3-dihydropyrrolo[3,4-*c*]-quinolin-1-one (9d)

Using the same method as for the synthesis of amine (**5a**), *tert*-butylamine (0.4 g, 5.4×10^{-3} mol) and benzylic bromide (**4a**) (1.0 g, 2.7×10^{-3} mol) in toluene (30 mL) were stirred at room temperature for 24 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (19:1)] and drying in vacuo (P_2O_5) gave the title compound (0.7 g, 82%) as a white solid. R_f 0.49 [DCM–ethyl acetate (19:1)]; Mp 158–160 °C; (Found: C, 79.43%; H, 6.62%; N, 8.91%. $C_{21}H_{20}N_2O$ requires: C, 79.72%; H, 6.37%; N, 8.86%); δ_H (400 MHz, $CDCl_3$): 1.65 (9H, s, C(CH_3)$_3$), 4.73 (2H, s, quinoline–CH_2–N), 7.55 (3H, m, 3Ar–*H*), 7.68 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.79 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.90 (2H, m, 2Ar–*H*), 8.25 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz), 9.18 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz); IR (KBr) ν_{max} 2972, 1673 (amide), 1231, 776, 699; *m*/*z* 316 (25), 301, (100), 260 (40), 231 (30), 216 (60), 204 (25), 136 (20).

5.47. 3-Formyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (10a)

DMSO (17 mL) was sonicated for 30 min, benzylic bromide (**4a**) (1.0 g, 2.7×10^{-3} mol) and sodium hydrogen carbonate (1.87 g, 2.23×10^{-2} mol) were added and the reaction heated at 100 °C for 7 min. This was cooled in an ice/water bath, saturated NaCl solution (100 mL) added and the product extracted into diethyl ether (3×50 mL). The organic phase was washed with saturated NaCl solution (2×35 mL) and dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was purified by column chromatography [DCM–hexane (2:1) > DCM] and dried in vacuo (P_2O_5) to yield the title compound (0.6 g, 73%) as a colourless oil. R_f 0.36 [DCM]; δ_H (400 MHz, $CDCl_3$): 1.47 (3H, t, O–CH_2CH_3), 4.64 (2H, q, O–CH_2–CH_3), 7.55 (3H, m, 3Ar–*H*), 7.67 (3H, m, 2Ar–*H* + Ar–*Hb* or Ar–*Hc*), 7.88 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.93 (1H, d, Ar–*Ha* or Ar–*Hb*, J_{ab} or J_{dc} 8.6 Hz), 8.22 (1H, d, Ar–*Ha* or Ar–*Hb*, J_{ab} or J_{dc} 8.5 Hz), 10.10 (1H, s, C*H*O); IR (KBr) ν_{max} 1726 (ester), 1693, 1584, 1246, 1167; *m*/*z* 305 (M+, 15), 276 (30), 260 (15), 231 (30), 204 (100), 75 (30).

5.48. 6-Formyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (10b)

Using the same method as for the synthesis of (**11**), 2-nitropropane (2.54 g, 3.02×10^{-2} mol), sodium (0.546 g, 2.38×10^{-2} mol) in ethanol (25 mL) and benzylic bromide (**4b**) (8.0 g, 2.16×10^{-2} mol) in ethanol (60 mL) were warmed in a N_2 atmosphere for 3 h. The crude product that crystallised was filtered, washed with cold ethanol and dried in vacuo (P_2O_5) to yield the title compound (4.8 g, 73%) as fine yellow needles. R_f 0.55 [hexane–ethyl acetate (3:1)]; Mp 107–108 °C; (Found: C, 74.45%; H, 5.09%; N, 4.68%. $C_{19}H_{15}NO_3$ requires: C, 74.74%; H, 4.95%; N, 4.59%); δ_H (400 MHz, $CDCl_3$): 1.54 (3H, t, O–CH_2CH_3), 4.59 (2H, q, O–CH_2–CH_3), 7.56 (3H, m, 3Ar–*H*), 8.28 (4H, m, 2Ar–*H* + Ar–*Hc* + Ar–*Hd*), 8.52 (1H, s, Ar–*Ha*), 9.35 (1H, d, Ar–*Hb*, J_{bc} 1.7 Hz), 10.23 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$): 14.40, 62.35, 121.14, 123.72, 126.64, 127.73, 129.12, 130.55, 131.54, 132.44, 135.10, 136.84, 138.15, 151.87, 159.40, 165.75, 191.89; IR (KBr) ν_{max} 1723 (ester), 1695 (aldehyde), 1588, 1251, 1146; *m*/*z* 305 (M+, 75), 276 (10), 233 (100), 204 (35), 176 (10), 102 (25).

5.49. 8-Formyl-2-phenyl-quinoline-4-carboxylic acid ethyl ester (10c)

Using the same method as for the synthesis of (**11**), 2-nitropropane (1.27 g, 1.51×10^{-2} mol), sodium (0.273 g, 1.19×10^{-2} mol) in ethanol (14 mL) and benzylic bromide (**4c**) (4.0 g, 1.08×10^{-2} mol) in ethanol (40 mL) were warmed in a N_2 atmosphere for 3 h. The crude product that crystallised was filtered, washed with cold ethanol and dried in vacuo (P_2O_5) to yield the title compound (3.0 g, 91%) as fine yellow needles. R_f 0.50 [hexane–ethyl acetate (3:1)]; Mp 116–118 °C; (Found: C, 74.51%; H, 4.94%; N, 4.54%. $C_{19}H_{15}NO_3$ requires: C, 74.74%; H, 4.95%; N, 4.59%); δ_H (400 MHz, $CDCl_3$): 1.53 (3H, t, O–CH_2CH_3), 4.58 (2H, q, O–CH_2–CH_3), 7.56 (3H, m, 3Ar–*H*), 7.76 (1H, t, Ar–*Hc*), 8.29 (2H, m, 2Ar–*H*), 8.38 (1H, dd, Ar–*Hb* or Ar–Hd, J_{bc} or J_{dc} 7.1 Hz, J_{bd} or J_{db} 1.5 Hz), 8.52 (1H, s, Ar–*Ha*), 9.06 (1H, dd, Ar–*Hb* or Ar–Hd, J_{bc} or J_{dc} 8.6 Hz, J_{bd} or J_{db} 1.5 Hz), 11.66 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$): 14.40, 62.27, 120.31, 124.01, 127.29, 127.56, 129.10, 129.57, 130.49, 131.91, 136.44, 138.13, 148.51, 157.13, 166.00, 192.75; IR (KBr) ν_{max} 1727 (ester), 1685 (aldehyde), 1595, 1556, 1236, 1064, 697; *m*/*z* 305 (M+), 277 (100), 249 (60), 204 (65).

5.50. 3-Ethoxy-4-phenyl-3*H*-furo[3,4-*c*]quinolin-1-one (11)

2-Nitropropane (2.54 g, 3.02×10^{-2} mol) was added to sodium (0.546 g, 2.38×10^{-2} mol) in ethanol (25 mL) to form a white gelatinous precipitate. This was added to benzylic bromide (**4a**) (8.0 g, 2.16×10^{-2} mol) in ethanol (60 mL) and the reaction was warmed in a N_2 atmosphere for 3 h, cooled to room temperature and the solvent removed in vacuo. The resulting solid was taken up in DCM (100 mL), washed with water (30 mL) and saturated NaCl solution (30 mL) and dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was purified by column chromatography [DCM] and dried in vacuo (P_2O_5) to yield the title compound (4.9 g, 74%) as a yellow crystalline solid. R_f 0.48 [hexane–ethyl acetate (3:1)]; Mp 129–131 °C; (Found: C, 74.52%; H, 4.87%; N, 4.48%.

$C_{19}H_{15}NO_3$ requires: C, 74.74%; H, 4.95%; N, 4.59%); δ_H (400 MHz, $CDCl_3$): 1.17 (3H, t, O–CH_2CH_3), 3.80 (1H, double quartet, O–CH*H*–CH_3), 3.98 (1H, double quartet, O–C*H*H–CH_3), 6.70 (1H, s, O–C*H*–O), 7.54 (3H, m, 3Ar–*H*), 7.77 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.90 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.98 (2H, m, 2Ar–*H*), 8.31 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz), 8.93 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz); δ_C (100 MHz, $CDCl_3$): 14.85, 66.67, 102.17, 121.66, 123.63, 128.74, 128.88, 129.26, 129.84, 130.02, 131.27, 131.45, 137.33, 137.69, 149.56, 154.50, 167.93; IR (KBr) ν_{max} 1780 (lactone), 1339 (ether), 1106, 943, 773; *m*/*z* 305 (M+, 95), 276 (30), 261 (100), 232 (45), 204 (85).

5.51. 3-Hydroxy-4-phenyl-3*H*-furo[3,4-*c*]quinolin-1-one (12)

Concentrated hydrochloric acid (10 mL) was added to lactone (**11**) (2.0 g, 6.55×10^{-3} mol) and heated under reflux for 15 min. The reaction was cooled to room temperature and water (100 mL) added. The crude product was filtered, washed with diethyl ether and dried in vacuo (P_2O_5) to yield the title compound (1.8 g, 100%) as a pale yellow solid. R_f 0.22 [hexane–ethyl acetate (3:1)]; Mp 270–273 °C; (Found: C, 73.35%; H, 4.14%; N, 5.03%. $C_{17}H_{11}NO_3$ requires: C, 73.64%; H, 4.00%; N, 5.05%); δ_H (400 MHz, DMSO): 7.32 (1H, s, O–C*H*–O), 7.56 (3H, m, 3Ar–*H*), 7.87 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.98 (1H, t, Ar–*Hb* or Ar–*Hc*), 8.10 (2H, m, 2Ar–*H*), 8.19 (1H, s (broad), O*H*), 8.28 (1H, d, Ar–*Ha* or Ar–*Hb*, J_{ab} or J_{dc} 8.0 Hz), 8.79 (1H, d, Ar–*Ha* or Ar–*Hb*, J_{ab} or J_{dc} 8.3 Hz); δ_C (100 MHz, DMSO): 98.40, 121.11, 122.86, 128.69, 129.09, 129.53, 129.74, 129.92, 130.48, 131.50, 137.36, 140.06, 148.50, 154.00, 167.99; IR (KBr) max 3209, 2497, 1783 (lactone), 1647, 1121; *m*/*z* 277 (M+, 35), 249 (10), 220 (10), 204 (100), 102 (40).

5.52. 3-Methyl-4-phenyl-3*H*-furo[3,4-*c*]quinolin-1-one (13)

Methyl iodide (2.05 g, 1.44×10^{-2} mol) in diethyl ether (7.5 mL) was added to magnesium (0.35 g, 1.44×10^{-2} mol) in diethyl ether (2.5 mL). This Grignard reagent was added drop wise to lactol (**12**) (0.5 g, 1.8×10^{-3} mol) in THF (10 mL) at −78 °C. The reaction was allowed to warm to room temperature and stirred for 18 h. Hydrochloric acid (2 M) was added and the product extracted into ethyl acetate (2×30 mL). This was washed with sodium metabisulfite (30 mL) and dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was purified by column chromatography [DCM–hexane (4:1)] and dried in vacuo (P_2O_5) to yield the title compound (0.37 g, 75%) as a pale yellow solid. R_f 0.58 [DCM]; Mp 121–123 °C; (Found: C, 78.34%; H, 4.81%; N, 4.82%. $C_{18}H_{13}NO_2$ requires: C, 78.53%; H, 4.76%; N, 5.09%); δ_H (400 MHz, $CDCl_3$): 1.36 (3H, d, CH–C*H*$_3$) 6.13 (1H, q, C*H*–CH_3), 7.56 (3H, m, 3Ar–*H*), 7.77 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.82 (2H, m, 2Ar–*H*), 7.88 (1H, t, Ar–*Hb* or Ar–*Hc*), 8.31 (1H, d, Ar–*Ha* or Ar–*Hb*, J_{ab} or J_{dc} 8.6 Hz), 8.96 (1H, d, Ar–*Ha* or Ar–*Hb*, J_{ab} or J_{dc} 8.3 Hz); δ_C (100 MHz, $CDCl_3$): 18.64, 77.79, 122.13, 123.31, 128.39, 129.17, 129.21, 129.27, 129.95, 130.85, 138.11, 143.75, 148.68, 153.94, 169.44; IR (KBr) ν_{max} 1772 (lactone), 1124, 782, 726; *m*/*z* 275 (M+, 90), 246 (75), 230 (60), 218 (100), 204 (75).

5.53. 3-Morpholin-4-yl-4-phenyl-3*H*-furo[3,4-*c*]quinolin-1-one (14)

Lactol (**12**) (0.1 g, 3.6×10^{-4} mol) was heated under reflux in morpholine (5 mL) for 4 h. The reaction was cooled and the solvent removed in vacuo. The crude product was purified by column chromatography [DCM–ethyl acetate (19:1)] and dried in vacuo (P_2O_5) to yield the title compound (0.12 g, 100%) as a colourless oil. R_f 0.41 [DCM–ethyl acetate (19:1)]; δ_H (400 MHz, $CDCl_3$): 2.67 (2H, m, $2 \times$ N–C*H*H–CH_2–O), 3.23 (2H, m, $2 \times$ N–CH_2–CH*H*–O), 3.29 (2H, m, $2 \times$ N–CH_2–C*H*H–O), 6.62 (1H, s, O–C*H*–N), 7.54 (3H, m, 3Ar–*H*), 7.76 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.82 (2H, m, 2Ar–*H*), 7.88 (1H, t, Ar–*Hb* or Ar–*Hc*), 8.29 (1H, d, Ar–*Ha* or Ar–*Hb*, J_{ab} or J_{dc} 8.6 Hz), 8.97 (1H, d, Ar–*Ha* or Ar–*Hb*, J_{ab} or J_{dc} 8.6 Hz); *m*/*z* 346 (M+, 50), 259 (40), 218 (100), 204 (35).

5.54. 3-Ethoxy-1-oxo-4-phenyl-1,3-dihydro-furo[3,4-*c*]-quinoline-8-carbaldehyde (15)

Using the same method as for the synthesis of lactone (**11**), 2-nitropropane (0.25 g, 3.02×10^{-3} mol), sodium (0.57 g, 2.37×10^{-3} mol) in ethanol (6 mL) and benzylic bromide (**4d**) (0.5 g, 1.08×10^{-3} mol) in ethanol (15 mL) were warmed in a N_2 atmosphere for 3 h. The crude product was purified by column chromatography [DCM–hexane (9:1)] and dried in vacuo (P_2O_5) to yield the title compound (0.23 g, 65%) as a pale yellow solid. R_f 0.23 [DCM–hexane (9:1)]; Mp 190–192 °C; (Found: C, 71.92%; H, 4.56%; N, 4.07%. $C_{20}H_{15}NO_4$ requires: C, 72.06%; H, 4.54%; N, 4.20%); δ_H (400 MHz, $CDCl_3$): 1.20 (3H, t, O–CH_2 C*H*$_3$), 3.87 (1H, double quartet, O–CH*H*–CH_3), 4.03 (1H, double quartet, O–C*H*H–CH_3), 6.76 (1H, s, O–C*H*–O), 7.59 (3H, m, 3Ar–*H*), 8.03 (2H, m, 2Ar–*H*), 8.39 (2H, m, 2Ar–*H*), 9.41 (1H, d, Ar–*Ha*), 10.30 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$): 14.78, 67.01, 77.31, 102.29, 121.21, 128.05, 128.82, 128.97, 129.61, 130.49, 131.12, 132.53, 136.00, 137.04, 138.21, 151.85, 157.11, 167.36, 191.27; IR (KBr) ν_{max} 1780 (lactone), 1700 (aldehyde), 1333 (ether); *m*/*z* 333 (M+, 85), 304 (30), 289 (100), 260 (35), 230 (60), 204 (50).

5.55. 3,6-Dimethyl-2-phenyl-quinoline-4-carboxylic acid dibenzylamide (16a)

Thionyl chloride (30 mL) was added drop wise to carboxylic acid (**2d**) (3.57 g, 1.28×10^{-2} mol) and the reaction heated under reflux in a N_2 atmosphere for 3 h. The reaction was cooled to room temperature and the thionyl chloride removed in vacuo. The last traces of thionyl chloride were removed with diethyl ether (2×50 mL) to leave the acid chloride as a yellow solid, which was dissolved in DCM (50 mL). This was added drop wise to dibenzylamine (5.05 g, 2.56×10^{-2} mol) in DCM (50 mL). The reaction was stirred at room temperature for 3 h. Saturated sodium hydrogen carbonate (30 mL)

was added. The organic layer was dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was recrystallised from ethanol, washed with cold ethanol and dried in vacuo (P_2O_5) yield the title compound (4.8 g, 82%) as a white solid. R_f 0.32 [DCM–ethyl acetate (19:1)]; Mp 230–232 °C; δ_H (400 MHz; CD_2Cl_2): 2.30 (3H, s, C*H*$_3$), 2.45 (3H, s, C*H*$_3$), 4.15 (1H, d, N–CH*H*–Ph, *J* 15.6 Hz (*gem*)), 4.22 (1H, d, N–C*H*H–Ph, *J* 15.6 Hz (*gem*)), 4.82 (1H, d, N–CH*H*–Ph, *J* 14.2 Hz (*gem*)), 4.97 (1H, d, N–C*H*H–Ph, *J* 14.2 Hz (*gem*)), 7.00 (2H, m, 2Ar–*H*), 7.27 (3H, m, 3Ar–*H*), 7.62 (12H, m, 12Ar–*H*), 8.00 (1H, d, Ar–*H*); IR (KBr) ν_{max} 1622 (amide), 1455, 1233, 700; *m*/*z* (EI, relative intensity) 456 (M+, 15), 441 (18), 365 (20), 231 (45), 217 (65).

5.56. 3,6-Dimethyl-2-phenyl-quinoline-4-carboxylic acid diethylamide (16b)

Using the same method as for the synthesis of amide (**16b**), carboxylic acid (**2d**) (2.25 g, 8.0×10^{-3} mol) was refluxed in thionyl chloride (30 mL) for 3 h. The acid chloride in DCM (30 mL) was added to diethylamine (1.17 g, 1.6×10^{-2} mol) in DCM (30 mL) and stirred at room temperature for 3 h. Purification of the crude product by column chromatography [DCM–ethyl acetate (19:1) > (1:1)] and drying in vacuo (P_2O_5) gave the title compound (2.2 g, 87%) as a white solid. R_f 0.16 [hexane–ethyl acetate (3:1)]; Mp 205–207 °C; δ_H (400 MHz; $CDCl_3$): 0.99 (3H, t, N–CH_2–C*H*$_3$), 1.39 (3H, t, N–CH_2–C*H*$_3$), 2.36 (3H, s, C*H*$_3$), 2.51 (3H, s, C*H*$_3$), 3.13 (2H, q, N–C*H*$_2$–CH_3), 3.40 (1H, m, N–CH*H*–CH_3), 3.84 (1H, m, N–C*H*H–CH_3), 7.48 (7H, m, 7Ar–*H*), 8.02 (1H, d, Ar–*H*); IR (KBr) ν_{max} 3445, 1636 (amide), 1474, 1438; *m*/*z* (EI, relative intensity) 332 (M+, 30), 317 (35), 260 (60), 230 (95), 217 (100), 128 (35).

5.57. 3,6-Dimethyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (16c)

Using the same method as for the synthesis of amide (**16a**), carboxylic acid (**2d**) (2.25 g, 8.0×10^{-3} mol) was refluxed in thionyl chloride (30 mL) for 3 h. The acid chloride in DCM (30 mL) was added to diisopropylamine (1.62 g, 1.6×10^{-2} mol) in DCM (30 mL) and heated under reflux for 3 h. Purification of the crude product by column chromatography [DCM–ethyl acetate (19:1) > (1:1)] and drying in vacuo (P_2O_5) gave the title compound (2.0 g, 70%) as a white solid. R_f 0.17 [DCM–ethyl acetate (19:1)]; Mp 209–211 °C; δ_H (400 MHz; $CDCl_3$): (Found: C, 79.81%; H, 7.64%; N, 7.67%. $C_{24}H_{28}N_2O$ requires: C, 79.96%; H, 7.83%; N, 7.77%); 1.06 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.14 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.68 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.79 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 2.37 (3H, s, C*H*$_3$), 2.52 (3H, s, C*H*$_3$), 3.58 (1H, m, N–C*H*–$(CH_3)_2$), 3.65 (1H, m, N–C*H*–$(CH_3)_2$), 7.50 (7H, m, 7Ar–*H*), 8.01 (1H, d, Ar–*H*); δ_C (100 MHz, $CDCl_3$): 17.37, 20,43, 20.70, 20.95, 21.00, 21.84, 46.32, 51.20, 123.11, 123.57, 123.72, 128.13, 128.27, 128.86, 129.38, 131.37, 136.78, 140.75, 142.75, 145.01, 159.94, 167.86; IR (KBr) ν_{max} 2980, 1633 (amide), 1450, 1318; *m*/*z* (EI, relative intensity) 360 (M+, 40), 345 (25), 317 (20), 260 (90), 231 (100), 216 (80).

5.58. 3-Methyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (precursor to 17a)

Thionyl chloride (140 mL) was added drop wise to carboxylic acid (**2a**) (15.0 g, 2.7×10^{-2} mol) and the reaction heated under reflux in a N_2 atmosphere for 3 h. The reaction was cooled to room temperature and the thionyl chloride removed in vacuo. The last traces of thionyl chloride were removed with diethyl ether (250 mL) to leave the acid chloride as a yellow solid, which was dissolved in DCM (150 mL). This was added drop wise to diisopropylamine (11.5 g, 0.114 mol) in DCM (150 mL). The reaction was stirred at room temperature for 3 h. Saturated sodium hydrogen carbonate (100 mL) was added. The organic layer was dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (6:1)] and drying in vacuo (P_2O_5) gave the title compound (14 g, 71%) as a white solid. R_f 0.37 [DCM–ethyl acetate (19:1)]; Mp 130–132 °C; (Found: C, 79.72%; H, 7.65%; N, 8.02%. $C_{23}H_{26}N_2O$ requires: C, 79.73%; H, 7.56%; N, 8.08%); δ_H (400 MHz; $CDCl_3$): 1.06 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.15 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.68 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.78 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 2.39 (3H, s, C*H*$_3$), 3.58 (1H, m, N–C*H*–$(CH_3)_2$), 3.65 (1H, m, N–C*H*–$(CH_3)_2$), 7.50 (6H, m, 5Ar–*H* + Ar–*Hb* or Ar–*Hc*), 7.68 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.75 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz), 8.12 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz); δ_C (100 MHz, $CDCl_3$): 17.33, 20.34, 20.61, 20.89, 20.97, 46.29, 51.22, 123.54, 123.79, 124.16, 126.91, 128.25, 128.76, 129.09, 129.63, 140.56, 143.37, 146.32, 160.84, 167.57; IR (KBr) ν_{max} 2976, 1636 (amide), 1447, 1316; *m*/*z* 346 (M+, 20), 331 (15), 303 (20), 260 (10), 246 (70), 217 (100).

5.59. 3-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (17a)

Using the same method as for the synthesis of benzylic bromide (**4a**), the requisite amide (see above) (5.0 g, 1.44×10^{-2} mol) was heated in carbon tetrachloride (150 mL) with NBS (2.83 g, 1.59×10^{-2} mol) and benzoyl peroxide (0.34 g, 1.44×10^{-3} mol) for 3 h. The crude product was purified by column chromatography [DCM > DCM–ethyl acetate (19:1)] and dried in vacuo (P_2O_5) to yield the title compound (4.75 g, 78%) as a white solid. R_f 0.44 [DCM–ethyl acetate (19:1)]; Mp 141–144 °C; (Found: C, 64.98%; H, 6.10%; N, 6.57%. $C_{23}H_{25}N_2OBr$ requires: C, 64.94%; H, 5.92%; N, 6.59%); δ_H (400 MHz; $CDCl_3$): 1.07 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.28 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.70 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.79 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 3.56 (1H, m, N–C*H*–$(CH_3)_2$), 3.69 (1H, m, N–C*H*–$(CH_3)_2$), 4.57 (1H, d, CH*H*Br, *J* 10.7 Hz *gem*), 4.72 (1H, d, C*H*HBr, *J* 10.7 Hz *gem*), 7.51 (3H, m, 3Ar–*H*), 7.58 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.68 (2H, m, 2Ar–*H*), 7.75 (1H, m, Ar–*Hb* or Ar–*Hc*), 7.83 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz), 8.17 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.0 Hz); δ_C (100 MHz, $CDCl_3$): 20.53, 20.60, 21.00, 21.24, 27.87, 46.81, 51.14, 123.40, 124.47, 125.31, 127.35, 128.50, 128.76, 128.82, 129.99, 130.75, 139.69,

144.92, 147.34, 161.14, 166.19; IR (KBr) ν_{max} 2982, 1629 (amide), 1442, 771; *m/z* 427 (M+, 20), 425 (M+, 20), 345 (50), 301 (35), 244 (35), 217 (100).

5.60. 6-Methyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (precursor to 17b)

Using the same method as for the synthesis of amide above, carboxylic acid (**2b**) (16.0 g, 6.1×10^{-2} mol) was heated at reflux in thionyl chloride (160 mL) for 3 h. The acid chloride in DCM (150 mL) was added to diisopropylamine (12.34 g, 0.12 mol) in DCM (150 mL) and heated under reflux for 3 h. Purification of the crude product by column chromatography [DCM > DCM–ethyl acetate (3:1)] and drying in vacuo (P_2O_5) gave the title compound (16 g, 76%) as a white solid. R_f 0.6 [DCM–ethyl acetate (19:1)]; Mp 180–182 °C; (Found: C, 79.46%; H, 7.31%; N, 8.15%. $C_{23}H_{26}N_2O$ requires: C, 79.73%; H, 7.56%; N, 8.08%); δ_H (400 MHz; $CDCl_3$): 1.08 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.11 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.68 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.74 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 2.53 (3H, s, C*H*$_3$), 3.63 (2H, m, 2 × N–C*H*–$(CH_3)_2$), 7.51 (5H, m, 5Ar–*H*), 7.66 (1H, s, Ar–*Ha*), 8.08 (1H, d, Ar–*H*, *J* 9.0 Hz), 8.14 (2H, m, 2Ar–*H*); δ_C (100 MHz, $CDCl_3$): 20.75, 20.78, 20.80, 20.85, 33.26, 46.48, 51.38, 114.96, 123.17, 124.70, 127.63, 127.68, 128.99, 129.03, 129.84, 130.94, 131.13, 136.46, 139.08, 145.20, 148.25, 157.77, 167.57; IR (KBr) ν_{max} 2964, 1635 (amide), 1438, 1357, 702; *m/z* 346 (M+, 30), 246 (100), 218 (55), 203 (15).

5.61. 6-Bromomethyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (17b)

Using the same method as for the synthesis of benzylic bromide (**4a**), the requisite amide (see above) (10.16 g, 2.9×10^{-2} mol) was heated in carbon tetrachloride (150 mL) with NBS (5.74 g, 3.2×10^{-2} mol) and benzoyl peroxide (0.7 g, 2.9910^{-3} mol) for 3 h. The crude product was purified by column chromatography [DCM > DCM–ethyl acetate (4:1)] and dried in vacuo (P_2O_5) to yield the title compound (10.7 g, 87%) as a white solid. R_f 0.34 [hexane–ethyl acetate (3:1)]; Mp 188–190 °C; (Found: C, 65.14%; H, 5.97%; N, 6.34%. $C_{23}H_{25}N_2OBr$ requires: C, 64.94%; H, 5.92%; N, 6.59%); δ_H (400 MHz; $CDCl_3$): 1.11 (6H, t, 2 × CH–C*H*$_3$), 1.69 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.76 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 3.60 (1H, m, N–C*H*–$(CH_3)_2$), 3.68 (1H, m, N–C*H*–$(CH_3)_2$), 4.61 (1H, d, CH*H*Br, *J* 10.5 Hz *gem*), 4.69 (1H, d, C*H*HBr, *J* 10.5 Hz *gem*), 7.52 (3H, m, 3Ar–*H*), 7.71 (1H, s, Ar–*Ha*), 7.75 (1H, dd, Ar–*Hc*, J_{cb} 2.0 Hz, J_{cd} 8.8 Hz), 7.81 (1H, d, Ar–*Hb*, J_{bc} 2.0 Hz), 8.15 (3H, m, 2Ar–*H* + Ar–*Hd*); IR (KBr) ν_{max} 1629 (amide), 1444, 1355, 1315; *m/z* 426 (M+, 25), 424 (M+, 25), 383 (5), 381 (55), 345 (90), 326 (55), 324 (55), 246 (100), 217 (60).

5.62. 3-Formyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (18a)

Using the same method as for the synthesis of lactone (**11**), 2-nitropropane (2.35 g, 2.8×10^{-2} mol), sodium (0.50 g, 2.2×10^{-2} mol) in ethanol (25 mL) and benzylic bromide (**17a**) (8.5 g, 2.0×10^{-2} mol) in ethanol (36 mL) were warmed in a N_2 atmosphere for 3 h. The crude product was washed with cold ethanol and dried in vacuo (P_2O_5) to yield the title compound (6.7 g, 93%) as a white solid. R_f 0.42 [DCM–ethyl acetate (19:1)]; Mp 138–140 °C; δ_H (400 MHz; $CDCl_3$): 1.04 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.19 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.79 (6H, m, 2CH–C*H*$_3$), 3.46 (1H, m, N–C*H*–$(CH_3)_2$), 3.69 (1H, m, N–C*H*–$(CH_3)_2$), 7.54 (3H, m, 3Ar–*H*), 7.65 (3H, m, 2Ar–*H* + Ar–*Hb* or Ar–*Hc*), 7.87 (1H, t, Ar–*Hb* or Ar–*Hc*), 8.01 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz), 8.20 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.5 Hz), 10.10 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$): 19.79, 20.10, 20.93, 20.97, 46.62, 51.69, 122.62, 123.39, 126.45, 127.90, 128.76, 129.51, 130.09, 130.28, 132.58, 138.34, 146.44, 149.53, 160.63, 166.25, 191.05; IR (KBr) ν_{max} 2980, 1639 (amide), 1551, 1447, 1353; *m/z* 360 (M+, 10), 317 (85), 275 (80), 260 (60), 232 (50), 204 (80), 100 (100).

5.63. 6-Formyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (18b)

Using the same method as for the synthesis of lactone (**11**), 2-nitropropane (1.61 g, 1.8×10^{-2} mol), sodium (0.327 g, 1.4×10^{-2} mol) in ethanol (14 mL) and benzylic bromide (**17b**) (5.5 g, 1.3×10^{-2} mol) in ethanol (20 mL) were warmed in a N_2 atmosphere for 3 h. The crude product was purified by column chromatography [DCM–ethyl acetate (5:1)] and dried in vacuo (P_2O_5) to yield the title compound (4.0 g, 85%) as a white solid. R_f 0.27 [hexane–ethyl acetate (3:1)]; Mp 176–178 °C; (Found: C, 76.36%; H, 6.78%; N, 7.77%. $C_{23}H_{24}N_2O_2$ requires: C, 76.64%; H, 6.71%; N, 7.77%); δ_H (400 MHz; $CDCl_3$): 1.09 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.16 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.69 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.77 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 3.61 (1H, m, N–C*H*–$(CH_3)_2$), 3.69 (1H, m, N–C*H*–$(CH_3)_2$), 7.54 (3H, m, 3Ar–*H*), 7.80 (1H, s, Ar–*Ha*), 8.20 (3H, m, 2Ar–*H* + Ar–*Hc*), 8.29 (1H, d, Ar–*Hd*, J_{dc} 8.5 Hz), 8.32 (1H, d, Ar–*Hb*, J_{bc} 2.0 Hz), 10.15 (1H, s, C*H*O); δ_C (100 MHz, $CDCl_3$): 20.75, 20.84, 20.87, 46.67, 51.46, 115.37, 123.03, 127.51, 127.81, 129.08, 130.38, 130.42, 131.49, 134.46, 138.57, 146.50, 151.30, 159.83, 167.00, 191.10; IR (KBr) ν_{max} 1690, 1630 (amide), 1450, 1355, 1313; *m/z* 360 (M+, 25), 317 (20), 260 (100), 232 (35), 204 (30).

5.64. 3-Oxiranyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (19a)

Potassium *tert*-butoxide (4.1 g, 3.65×10^{-2} mol) and trimethylsulfonium iodide (8.15 g, 4.0×10^{-2} mol) were stirred in *tert*-butanol (200 mL) under a N_2 atmosphere at 30 °C for 20 min. Arylaldehyde (**18a**) (6.0 g, 1.66×10^{-2} mol) was added and the reaction stirred for a further 30 min. Diethyl ether (100 mL) and water (200 mL) were then added, the diethyl ether layer collected, washed with saturated NaCl solution (100 mL) and dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The product was filtered, washed with cold diethyl ether and dried in vacuo (P_2O_5) to yield the title compound (4.8 g, 78%)

as a 5:1 mixture of atropisomers. White solid. R_f 0.21 [DCM–ethyl acetate (19:1)]; Mp 150–152 °C; (Found: C, 77.29%; H, 7.27%; N, 7.78%. $C_{24}H_{26}N_2O_2$ requires: C, 76.98%; H, 7.00%; N, 7.48); δ_H (400 MHz; $CDCl_3$, major atropisomer): 0.99 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.21 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.68 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.74 (3H, d, CH–C*H*$_3$, *J* 7.1 Hz), 3.00 (1H, dd, CHOCH*H*, *J* 4.2 Hz, *J* 6.4 Hz), 3.29 (1H, dd, CHOC*H*H, *J* 2.7 Hz, *J* 6.4 Hz), 3.48 (1H, m, N–C*H*–$(CH_3)_2$), 3.62 (1H, m, N–C*H*–$(CH_3)_2$), 3.89 (1H, dd, C*H*OCH$_2$, *J* 2.7 Hz, *J* 4.2 Hz), 7.49 (3H, m, 3Ar–*H*), 7.55 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.70 (3H, m, 2Ar–H + Ar–*Hb* or Ar–*Hc*), 7.87 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.6 Hz), 8.14 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 7.5 Hz); δ_C (100 MHz, $CDCl_3$): 19.42, 19.56, 20.79, 20.84, 46.28, 51.00, 51.42, 51.61, 123.49, 124.06, 124.70, 127.21, 128.52, 128.90, 129.19, 129.80, 130.00, 140.01, 141.45, 147.17, 159.39, 166.64; *m*/*z* 374 (M+, 5), 359 (10), 331 (50), 274 (100), 259 (65), 246 (55), 230 (25), 217 (85).

5.65. 6-Oxiranyl-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (19b)

Using the same method as for the synthesis of epoxide (**19a**), arylaldehyde (**18b**) (1.0 g, 2.77×10^{-3} mol), potassium *tert*-butoxide (0.68 g, 6.09×10^{-3} mol) and trimethylsulfonium iodide (1.36 g, 6.65×10^{-3} mol) were stirred in *tert*-butanol (50 mL) at 30 °C for 30 min. The crude product was purified by column chromatography [DCM > DCM–ethyl acetate (4:1)] and dried in vacuo (P_2O_5) to yield the title compound (0.7 g, 67%) as a 1:1 mixture of rotamers. White solid; R_f 0.43 [DCM–ethyl acetate (19:1)]; Mp 195–197 °C; δ_H (400 MHz; $CDCl_3$, mixture of rotamers (1:1)): 1.11 (6H, m, 2 × CH–C*H*$_3$), 1.16 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.69 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.75 (3H, dd, CH–C*H*$_3$), 2.85 (0.5H, dd, CHOCH*H*, *J* 2.5 Hz, *J* 5.4 Hz), 2.88 (0.5H, dd, CHOCH*H*, *J* 2.5 Hz, *J* 5.4 Hz), 3.22 (1H, m, CHOC*H*H), 3.62 (2H, m, 2 × N–C*H*–$(CH_3)_2$), 4.01 (1H, m, C*H*OCH$_2$), 7.51 (3.5H, m, 3Ar–*H* + 0.5Ar–*Hc*), 7.64 (0.5H, dd, Ar–Hc, J_{cb} 2.0 Hz, J_{cd} 8.7 Hz), 7.69 (0.5H, s, Ar–*Ha*), 7.70 (0.5H, s, Ar–*Ha*), 7.71 (0.5H, d, Ar–*Hb*, J_{bc} 2.0 Hz), 7.81 (0.5H, d, Ar–*Hb*–*Hb*, J_{bc} 2.0 Hz), 8.15 (3H, m, 2Ar–*H* + Ar–*Hd*); δ_C (100 MHz, $CDCl_3$): 20.60, 20.76, 20.79, 20.83, 20.86, 20.91, 46.46, 46.49, 51.23, 51.33, 51.36, 51.59, 52.17, 52.42, 114.88, 114.92, 121.00, 122.37, 123.10, 123.22, 126.51, 127.60, 127.81, 128.97, 129.73, 130.54, 130.83, 136.53, 136.65, 139.18, 144.94, 145.08, 148.52, 148.62, 157.38, 167.69, 167.73; IR (KBr) ν_{max} 1633 (amide), 1443, 1350, 1315, 835, 698; *m*/*z* 374 (M+, 40), 331 (15), 274 (100), 246 (40), 217 (30).

5.66. 6-(2-Diethylamino-1-hydroxy-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (20a) and 6-(1-diethylamino-2-hydroxy-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (21a)

Epoxide (**19b**) (0.2 g, 5.34×10^{-4} mol) and diethylamine (0.078 g, 1.07×10^{-3} mol) were heated at reflux in ethanol (5 mL) for 2 h. The solvents were removed in vacuo and the crude products were purified by column chromatography [ethyl acetate > ethyl acetate–methanol (9:1)] and dried in vacuo (P_2O_5). (**21a**); white solid (0.2 g, 83%); R_f 0.25 [ethyl acetate–methanol (2:1)]; Mp 149–152 °C; (Found: C, 74.87%; H, 8.21%; N, 9.45%. $C_{28}H_{37}N_3O_2$ requires: C, 75.13%; H, 8.33%; N, 9.39%); δ_H (400 MHz; $CDCl_3$, mixture of rotamers (1:1)): 1.10 (12H, m, 2 × CH–C*H*$_3$ + 2 × N–CH$_2$–C*H*$_3$), 1.69 (3H, dd, CH–C*H*$_3$), 1.75 (3H, dd, CH–C*H*$_3$), 2.51 (1H, t, CH(OH)–CH*H*), 2.62 (2H, m, N–C*H*$_2$–CH$_3$), 2.75 (3H, m, N–CH$_2$–CH$_3$ + CH(OH)–C*H*H), 3.62 (2H, m, 2 × N–C*H*–$(CH_3)_2$), 4.81 (1H, t, C*H*(OH)–CH$_2$), 7.50 (3H, m, 3Ar–*H*), 7.67 (0.5H, dd, Ar–*Hc*, J_{cb} 1.7 Hz, J_{cd} 8.7 Hz), 7.69 (0.5H, s, Ar–*Ha*), 7.71 (0.5H, s, Ar–Ha), 7.78 (0.5H, d, Ar–Hb, 1.7 Hz), 7.82 (0.5H, dd, Ar–Hc, J_{cb} 1.7 Hz, J_{cd} 8.7 Hz), 7.94 (0.5H, d, Ar–Hb, 1.7 Hz), 8.15 (3H, m, 2Ar–*H* + Ar–*Hd*); *m*/*z* 447 (M+), 416, 361, 317, 260, 86 (100); (**20b**); pale yellow oil (0.017 g, 7%); R_f 0.32 [ethyl acetate–methanol (9:1)]; δ_H (400 MHz; $CDCl_3$, mixture of rotamers (1:1)): 1.07 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.13 (9H, m, CH–C*H*$_3$ + 2 × N–CH$_2$–C*H*$_3$), 1.69 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 1.72 (3H, dd, CH–C*H*$_3$), 2.35 (2H, m, N–C*H*$_2$–CH$_3$), 2.80 (2H, m, N–C*H*$_2$–CH$_3$), 3.64 (2H, m, 2 × N–C*H*–$(CH_3)_2$), 3.76 (1H, m), 4.02 (1H, m), 4.15 (1H, m), 7.51 (3H, m, 3Ar–*H*), 7.63 (2H, m, 2Ar–*H*), 7.70 (1H, d, Ar–*H*), 8.15 (3H, m, 3Ar–*H*); *m*/*z* 447 (M+), 430, 416 (100), 374 (5), 358 (5), 259 (5).

5.67. 6-(1-Hydroxy-2-morpholin-4-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (20b) and 6-(2-hydroxy-1-morpholin-4-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (21b)

Epoxide (**19b**) (0.2 g, 5.34×10^{-4} mol) and morpholine (0.093 g, 1.07×10^{-3} mol) were heated at reflux in ethanol (5 mL) for 2 h. The solvents were removed in vacuo and the crude products were purified by column chromatography [ethyl acetate > ethyl acetate–methanol (9:1)] and dried in vacuo (P_2O_5). (**20b**); white solid (0.2 g, 83%); R_f 0.44 [ethyl acetate–methanol (9:1)]; Mp 109–111 °C; δ_H (400 MHz; $CDCl_3$, mixture of rotamers (1:1)): 1.10 (6H, m, 2 × CH–C*H*$_3$), 1.68 (3H, dd, CH–C*H*$_3$), 1.75 (3H, t, CH–C*H*$_3$, *J* 6.7 Hz), 2.54 (3H, m (broad), 2 × N–CH*H*–CH$_2$–O + CH(OH)–CH*H*), 2.65 (1H, m, CH(OH)–C*H*H), 2.80 (2H, m (broad), 2 × N–C*H*H–CH$_2$–O), 3.58 (2H, m, 2 × N–C*H*–$(CH_3)_2$), 3.79 (4H, m, 2 × N–CH$_2$–C*H*$_2$–O), 4.94 (1H, t, C*H*(OH)–CH$_2$), 7.52 (3H, m, 3Ar–*H*), 7.65 (0.5H, dd, Ar–*Hc*, J_{cb} 1.7 Hz, J_{cd} 8.7 Hz), 7.69 (0.5H, s, Ar–*Ha*), 7.71 (0.5H, s, Ar–*Ha*), 7.78 (0.5H, d, Ar–*Hb*, J_{bc} 1.7 Hz), 7.81 (0.5H, dd, Ar–*Hc*, J_{cb} 1.7 Hz, J_{cd} 8.7 Hz), 7.96 (0.5H, d, Ar–*Hb*, J_{bc} 1.7 Hz), 8.17 (3H, m, 2Ar–*H* + Ar–*Hd*); *m*/*z* 461 (M+), 416, 362, 260, 233, 204, 100 (100). (**21b**); white solid (0.02, 8%); R_f 0.63 [ethyl acetate–methanol (9:1)]; Mp 176–178 °C; (Found: C, 72.57%; H, 7.65%; N, 9.24%. $C_{28}H_{35}N_3O_3$ requires: C, 72.86%; H, 7.64%; N, 9.10%); δ_H (400 MHz; $CDCl_3$, mixture of rotamers (1:1)): 1.07 (3H, t, CH–C*H*$_3$), 1.13 (3H, dd, CH–C*H*$_3$), 1.69 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.73 (3H, d, CH–C*H*$_3$, *J* 6.5 Hz), 2.50 (2H, m (broad), 2 × N–CH*H*–CH$_2$–O), 2.60 (2H, m (broad), 2 × N–C*H*H–CH$_2$–O), 3.71 (7H, m, 2 × N–CH$_2$–C*H*$_2$–O + 2 × N–C*H*–$(CH_3)_2$ + 1H), 3.83 (1H, m), 4.02 (1H,

m), 7.51 (3H, m, 3Ar–*H*), 7.67 (3H, m, 3Ar–*H*), 8.17 (3H, m, 3Ar–*H*); δ_C (100 MHz, $CDCl_3$): 20.53, 20.68, 20.75, 46.33, 50.24, 50.48, 51.19, 60.97, 61.44, 65.81, 67.16, 70.43, 70.66, 114.67, 122.90, 122.97, 124.03, 124.19, 127.54, 128.90, 129.65, 130.18, 130.94, 135.67, 136.28, 139.10, 144.93, 145.02, 148.13, 148.19, 157.36, 157.45; IR (KBr) ν_{max} 1631 (amide), 1611, 1449, 1361, 1116; *m*/*z* 461 (M+), 430 (100), 388 (5), 372 (5), 302 (5).

5.68. 6-(1-Hydroxy-2-pyrrolidin-1-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (20c) and 6-(2-hydroxy-1-pyrrolodin-1-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (21c)

Epoxide (**19b**) (0.2 g, 5.34×10^{-4} mol) and pyrrolidine (0.076 g, 1.07×10^{-3} mol) were heated at reflux in ethanol (5 mL) for 2 h. The solvents were removed in vacuo and the crude products were purified by column chromatography [ethyl acetate–methanol (2:1) > methanol] and dried in vacuo (P_2O_5). (**20c**); white solid (0.2 g, 83%); R_f 0.29 [ethyl acetate–methanol (2:1)]; Mp 166–168 °C; (Found: C, 75.18%; H, 7.94%; N, 9.51%. $C_{28}H_{35}N_3O_2$ requires: C, 75.47%; H, 7.92%; N, 9.43%); δ_H (400 MHz; $CDCl_3$, mixture of rotamers (1:1)): 1.10 (6H, m, 2 × CH–C*H*$_3$), 1.68 (3H, dd, CH–C*H*$_3$), 1.74 (3H, dd, CH–C*H*$_3$), 1.83 (4H, m, 2 × N–CH$_2$–C*H*$_2$), 2.60 (3H, m, 2 × N–CH*H*–CH$_2$ + CH(OH)–CH*H*), 2.82 (3H, m, 2 × N–C*H*H–CH$_2$ + CH(OH)–C*H*H), 3.62 (2H, m, 2 × N–C*H*–(CH$_3$)$_2$), 4.97 (1H, m, C*H*(OH)–CH$_2$), 7.50 (3H, m, 3Ar–*H*), 7.69 (1.5H, m, Ar–*Ha* + Ar–*Hc*), 7.79 (0.5H, d, Ar–*Hb*, J_{bc} 2.0 Hz), 7.83 (0.5H, dd, Ar–*Hc*, J_{cb} 2.0 Hz, J_{cd} 9.0 Hz), 7.94 (0.5H, d, Ar–*Hb*, J_{bc} 2.0 Hz), 8.16 (3H, m, 2Ar–*H* + Ar–*Hd*); δ_C (100 MHz, $CDCl_3$): 20.49, 20.60, 20.71, 20.76, 23.65, 46.30, 51.22, 51.29, 53.83, 63.49, 63.84, 70.30, 70.60, 114.60, 120.88, 121.54, 122.92, 123.05, 127.49, 128.22, 128.49, 128.85, 129.48, 129.88, 130.30, 139.11, 139.28, 141.32, 141.60, 144.99, 145.15, 147.98, 148.21, 156.95, 167.90; *m*/*z* 445 (M+), 411, 361, 260, 233, 204 (100), 84 (100). (**21c**); white solid (0.025 g, 10%); R_f 0.27 [ethyl acetate–methanol (4:1)]; Mp 169–171 °C; (Found: C, 75.29%; H, 8.01%; N, 9.74%. $C_{28}H_{35}N_3O_2$ requires: C, 75.47%; H, 7.92%; N, 9.43%); δ_H (400 MHz; $CDCl_3$, mixture of rotamers (1:1)): 1.07 (3H, dd, CH–C*H*$_3$), 1.11 (3H, d, CH–C*H*$_3$, *J* 6.5 Hz), 1.68 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 1.73 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 1.75 (4H, m (broad), 2 × N–CH$_2$–C*H*$_2$), 2.57 (4H, m (broad), 2 × N–C*H*$_2$–CH$_2$), 3.63 (3H, m, 2 × N–C*H*–(CH$_3$)$_2$ + 1*H*), 3.91 (2H, m), 7.51 (3H, m, 3Ar–*H*), 7.75 (3H, m, 3Ar–*H*), 8.16 (3H, m, 3Ar–*H*); δ_C (100 MHz, $CDCl_3$): 20.58, 20.76, 20.82, 23.21, 46.35, 51.10, 51.23, 51.55, 64.03, 64.69, 69.43, 70.06, 114.65, 122.89, 122.97, 123.96, 124.04, 127.57, 128.92, 129.59, 130.16, 130.19, 130.72, 130.99, 138.27, 138.92, 139.29, 144.99, 145.10, 148.15, 148.21, 157.21, 158.28, 167.79; *m*/*z* 445 (M+), 430, 414 (100), 372 (5), 356 (5).

5.69. 6-(2-Hydroxy-1-morpholin-4-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (21b)

n-Butyl lithium (1.34 mL, 2.14×10^{-3} mol) was added to morpholine (0.37 g, 4.27×10^{-3} mol) in THF (10 mL) at 0 °C. This was stirred for 10 min and a further 30 min at room temperature. Epoxide (**19b**) (0.4 g, 1.07×10^{-3} mol) in THF (10 mL) was added drop wise and stirred for 30 min at room temperature. Water (20 mL) was added, THF removed in vacuo and the product extracted into DCM (2 × 30 mL). This was washed with saturated NaCl solution (30 mL) and dried over magnesium sulfate prior to filtration and removal of the solvent in vacuo. The crude product was purified by column chromatography [ethyl acetate > ethyl acetate–methanol (9:1)] and dried in vacuo (P_2O_5) to yield the title compound (0.42 g, 86%) as a 1:1 mixture of rotamers (spectroscopic data detailed above).

5.70. 6-(2-Hydroxy-1-pyrrolodin-1-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (21c)

Using the same method as for the synthesis of β-amino alcohol (**21b**), epoxide (**19b**) (0.2 g, 5.34×10^{-4} mol), *n*-butyl lithium (0.67 mL, 1.07×10^{-3} mol) and pyrrolidine (0.15 g, 2.14×10^{-3} mol) in THF (5 mL) were stirred for 30 min. The crude product was purified by column chromatography [ethyl acetate > ethyl acetate–methanol (4:1)] and dried in vacuo (P_2O_5) to yield the title compound (0.21 g, 89%) as a 1:1 mixture of rotamers (spectroscopic data detailed above).

5.71. 3-(2-Diethylamino-1-hydroxyl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (22a)

Epoxide (**19a**) (0.2 g, 5.34×10^{-4} mol) and diethylamine (0.078 g, 1.07×10^{-3} mol) were heated at reflux in ethanol (5 mL) for 16 h. The solvents were removed in vacuo and the crude product was purified by column chromatography [DCM–ethyl acetate (19:1) > (4:1) > ethyl acetate] and dried in vacuo (P_2O_5) to yield the title compound (0.21 g, 86%) as a 5:1 mixture of atropisomers. Colourless oil; R_f 0.19 [ethyl acetate–methanol (9:1)]; δ_H (400 MHz; $CDCl_3$, major atropisomer): 0.89 (6H, t, 2 × N–CH$_2$C*H*$_3$), 0.99 (3H, d, CH–C*H*$_3$, *J* 6.6 Hz), 1.21 (3H, d, CH–C*H*$_3$, *J* 6.5 Hz), 1.61 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.76 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 2.33 (5H, m, 2 × N–C*H*$_2$–CH$_3$ + CH(OH)–CH*H*), 3.07 (1H, t, CH(OH)–C*H*H), 3.58 (2H, m, 2 × N–C*H*–(CH$_3$)$_2$), 4.90 (1H, d, C*H*(OH)–CH$_2$), 7.45 (5H, m, Ar–*H*), 7.53 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.69 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.95 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.5 Hz), 8.10 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.5 Hz); *m*/*z* 447 (M+), 429, 416, 375, 361, 347, 317.

5.72. 3-(1-Hydroxy-2-morpholin-1-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (22b)

Epoxide (**19a**) (0.2 g, 5.34×10^{-4} mol) and morpholine (0.093 g, 1.07×10^{-3} mol) were heated at reflux in ethanol (5 mL) for 4 h. The solvents were removed in vacuo and the crude product was purified by column chromatography [DCM–ethyl acetate (2:1) > ethyl acetate] and dried in vacuo (P_2O_5) to yield the title compound (0.22 g, 90%) as a 5:1 mixture of atropisomers. White solid; R_f 0.59 [ethyl acetate]; Mp 176–178 °C; (Found: C, 72.89%; H, 7.90%; N, 9.32%. $C_{28}H_{35}N_3O_3$ requires: C,

72.86%; H, 7.64%; N, 9.10%); δ_H (400 MHz; $CDCl_3$, major atropisomer): 1.00 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 1.21 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 1.61 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 1.76 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 2.25 (2H, s (broad), 2 × N–CH*H*–CH$_2$–O), 2.35 (3H, m (broad), 2 × N–C*H*H–CH$_2$–O + CH(OH)–CH*H*), 3.15 (1H, t, CH(OH)–C*H*H), 3.54 (1H, m, N–C*H*–(CH$_3$)$_2$), 3.62 (5H, m, N–C*H*–(CH$_3$)$_2$ + 2 × N–CH$_2$–C*H*$_2$–O), 5.00 (1H, d (broad), C*H*(OH)–CH$_2$), 7.44 (5H, m, 5Ar–*H*), 7.55 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.70 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.93 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.5 Hz), 8.10 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.3 Hz); δ_C (100 MHz, $CDCl_3$): 19.29, 19.41, 20.63, 20.68, 46.12, 51.48, 53.00, 63.33, 66.39, 67.02, 124.48, 124.67, 126.91, 128.36, 128.39, 128.43, 128.67, 129.73, 129.89, 140.61, 143.08, 146.90, 159.89, 168.19; *m*/*z* 461 (M+, 5), 361 (20), 260 (40), 232 (10), 204 (25), 100 (100).

5.73. 3-(1-Hydroxy-2-pyrrolidin-1-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (22c)

Epoxide (**19a**) (0.2 g, 5.34×10^{-4} mol) and pyrrolidine (0.076 g, 1.07×10^{-3} mol) were heated at reflux in ethanol (5 mL) for 4 h. The solvents were removed in vacuo and the crude product was purified by column chromatography [DCM–ethyl acetate (19:1) > (4:1) > ethyl acetate] and dried in vacuo (P_2O_5) to yield the title compound (0.20 g, 82%) as a 5:1 mixture of atropisomers. White solid; R_f 0.18 [ethyl acetate–methanol (4:1)]; Mp 164–166 °C; (Found: C, 75.17%; H, 7.72%; N, 9.26%. $C_{28}H_{35}N_3O_2$ requires: C, 75.47%; H, 7.92%; N, 9.43%); δ_H (400 MHz; $CDCl_3$, major atropisomer): 0.99 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.20 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.62 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.67 (4H, m (broad), 2 × N–CH$_2$–C*H*$_2$), 1.76 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 2.24 (3H, m (broad), 2 × N–CH*H*–CH$_2$ + CH(OH)–CH*H*), 2.48 (2H, m, 2 × N–C*H*H–CH$_2$), 3.38 (1H, t, CH(OH)–C*H*H), 3.55 (1H, m, N–C*H*–(CH$_3$)$_2$), 3.62 (1H, m, N–C*H*–(CH$_3$)$_2$), 4.99 (1H, m, C*H*(OH)–CH$_2$), 7.45 (5H, m, 5Ar–*H*), 7.54 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.70 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.94 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz), 8.10 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz); δ_C (100 MHz, $CDCl_3$): 15.33, 19.34, 19.51, 20.66, 20.72, 23.66, 46.13, 51.47, 53.35, 61.22, 65.88, 68.46, 124.55, 124.80, 126.80, 128.29, 128.79, 129.71, 129.76, 140.79, 143.00, 146.88, 160.11, 168.18; *m*/*z* 446 (M+), 411, 260, 233, 204 (60), 84 (100).

5.74. 3-(2-Hydroxy-1-morpholin-4-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (23b)

Using the same method as for the synthesis of β-amino alcohol (**21b**), epoxide (**19a**) (0.2 g, 5.34×10^{-4} mol), *n*-butyl lithium (0.67 mL, 1.07×10^{-3} mol) and morpholine (0.19 g, 2.14×10^{-3} mol) in THF (5 mL) were stirred for 1 h. The crude product was purified by column chromatography [DCM–ethyl acetate > ethyl acetate] and dried in vacuo (P_2O_5) to yield the title compound (0.22 g, 90%) as a 1.25:1 mixture of atropisomers. White solid, R_f 0.6 [DCM–ethyl acetate (1:1)]; Mp 141–143 °C; δ_H (400 MHz; $CDCl_3$, major atropisomer): 1.10 (3H, d, CH–C*H*$_3$, *J* 6.4 Hz), 1.20 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.70 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 1.79 (3H, d, CH–C*H*$_3$, *J* 7.0 Hz), 2.24 (4H, m (broad), 2 × N–C*H*$_2$–CH$_2$–O), 3.22 (2H, m (broad), 2 × N–CH$_2$–CH*H*–O), 3.34 (2H, m (broad), 2 × N–CH$_2$–C*H*H–O), 3.55 (1H, m, N–C*H*–(CH$_3$)$_2$), 3.69 (2H, m, N–C*H*–(CH$_3$)$_2$ + 1*H*), 3.85 (1H, q), 4.02 (1H, m), 7.42 (5H, m, 5Ar–*H*), 7.57 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.72 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.78 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz), 8.15 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz); δ_C (100 MHz, $CDCl_3$): 20.58, 20.67, 20.78, 22.04, 47.07, 51.73, 52.28, 65.14, 66.56, 70.75, 123.00, 124.62, 127.19, 127.52, 127.65, 128.36, 130.05, 130.08, 143.32, 143.79, 146.56, 161.00, 169.07; *m*/*z* 443 (M+, 25, –H$_2$O), 430 (70), 388 (100), 315 (25), 231 (50).

5.75. 3-(2-Hydroxy-1-pyrrolidin-1-yl-ethyl)-2-phenyl-quinoline-4-carboxylic acid diisopropylamide (23c)

Using the same method as for the synthesis of β-amino alcohol (**21b**), epoxide (**19a**) (0.2 g, 5.34×10^{-4} mol), *n*-butyl lithium (0.67 mL, 1.07×10^{-3} mol) and pyrrolidine (0.15 g, 2.14×10^{-3} mol) in THF (5 mL) were stirred for 1 h. The crude products were purified by column chromatography [DCM–ethyl acetate (9:1) > ethyl acetate] and dried in vacuo (P_2O_5) to yield the title compound as a 1.3:1 mixture of atropisomers. Major atropisomer of (**23c**); white solid (0.11 g, 46%); R_f 0.58 [DCM–ethyl acetate (1:1)]; Mp 179–181 °C; (Found: C, 75.36%; H, 8.06%; N, 9.76%. $C_{28}H_{35}N_3O_2$ requires: C, 75.47%; H, 7.92%; N, 9.43%); δ_H (400 MHz; $CDCl_3$): 1.03 (3H, d, CH–C*H*$_3$, *J* 6.5 Hz), 1.20 (3H, d, CH–C*H*$_3$, *J* 6.5 Hz), 1.54 (4H, m (broad), 2 × N–CH$_2$–C*H*$_2$), 1.67 (3H, d, CH–C*H*$_3$, *J* 7.0 Hz), 1.76 (3H, d, CH–C*H*$_3$, *J* 6.8 Hz), 2.14 (2H, m (broad), 2 × N–CH*H*–CH$_2$), 2.38 (2H, m, 2 × N–C*H*H–CH$_2$), 3.52 (1H, m, N–C*H*–(CH$_3$)$_2$), 3.70 (1H, m, N–C*H*–(CH$_3$)$_2$), 3.88 (2H, m), 4.16 (1H, t), 7.44 (3H, m, 3Ar–*H*), 7.54 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.61 (2H, m, 2Ar–*H*), 7.71 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.88 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz), 8.13 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz); *m*/*z* 427 (M+, 25, –H$_2$O), 414 (100), 328 (20), 313 (50), 231 (40), 216 (30). Minor atropisomer of (**23c**); colourless oil (0.09 g, 36%); R_f 0.17 [ethyl acetate]; δ_H (400 MHz; $CDCl_3$): 1.10 (3H, d, CH–C*H*$_3$, *J* 6.5 Hz), 1.20 (3H, d, CH–C*H*$_3$, *J* 6.5 Hz), 1.39 (4H, m, 2 × N–CH$_2$–C*H*$_2$), 1.69 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 1.76 (3H, d, CH–C*H*$_3$, *J* 6.7 Hz), 2.16 (2H, m, 2 × N–CH*H*–CH$_2$), 2.27 (2H, m, 2 × N–C*H*H–CH$_2$), 3.59 (1H, m, N–C*H*–(CH$_3$)$_2$), 3.70 (2H, m, N–C*H*–(CH$_3$)$_2$ + 1H), 3.94 (1H, m), 4.19 (1H, m, (broad)), 7.34 (3H, m, 3Ar–*H*), 7.42 (2H, m, 2Ar–*H*), 7.55 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.71 (1H, t, Ar–*Hb* or Ar–*Hc*), 7.78 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz), 8.15 (1H, d, Ar–*Ha* or Ar–*Hd*, J_{ab} or J_{dc} 8.4 Hz).

5.76. Expression and purification of human DHODH and PfDHODH

PfDHODH and human DHODH protein expression was carried out in SØ6745 *E. coli* cells (pyrD-defective strain kindly provided by K.F. Jensen, University of Copenhagen) transformed with the human or *P. falciparum* DHODH gene fused to a His$_6$-tag in the pRSET

expression vector (Invitrogen). Both constructs were kindly provided by Professor J. Clardy (Harvard Medical School, USA). The over-expressed enzyme has a molecular mass of ~45 kDa and lacks a 168 amino acid hydrophobic membrane associated domain from the N-terminus. Cells were grown in LB medium, supplemented with 20 μg/mL uracil, 50 μg/mL ampicillin, 50 μg/mL methicillin, 30 μg/mL kanamycin and 34 μg/mL chloramphenicol (Sigma, Poole, UK), to an A_{600} nm of 0.6–0.8, and induced with 0.8 mM isopropyl β-D-thiogalactopyranoside (Sigma, Poole, UK) for 15–18 h. Cells were harvested by centrifugation at 5000*g* for 10 min at 4 °C and then frozen at −70 °C. Frozen cell pellets were resuspended in lysis buffer (50 mM NaH_2PO_4, 300 mM NaCl, 10 mM imidazole, adjusted to pH 8.0 with NaOH) containing 15 μg/mL protease inhibitor cocktail (Sigma, Poole, UK), consisting of aprotinin, bestatin, E-64, leupeptin and pepstatin-A, 1 mg/mL lysozyme (Sigma, Poole, UK), and 2.5 mM dihydroorotate (DHO, Sigma, Poole, UK). The suspension was sonicated on ice using six 20-s bursts at 200–300 W. The lysate was then centrifuged at 15,000*g* for 30 min at 4 °C. The supernatant recovered by centrifugation was loaded onto a nickel agarose resin (Qiagen, Crawley, UK), which had been equilibrated with wash buffer (50 mM NaH_2PO_4, 300 mM NaCl, 20 mM imidazole, adjusted to pH 8.0 with NaOH), at a ratio of 10 mL per 1.5 mL pure matrix. The supernatant was left to bind for 20 min at 4 °C and removed following centrifugation. Wash buffer was then added to the matrix at a ratio of 5–10 mL per mL matrix. Following centrifugation, the supernatant was discarded and the process was repeated twice. Elution buffer (50 mM NaH_2PO_4, 300 mM NaCl, 250 mM imidazole, adjusted to pH 8.0 with NaOH) was then added at twice the volume of the matrix. The suspension was left for 5 min at 4 °C, and the supernatant was recovered and frozen in liquid nitrogen, before being stored at −70 °C. Protein content was quantified spectrophotometrically using the Bradford protein assay (Bio-Rad, Hemel Hempstead, UK).

5.77. DHODH activity: quantification and inhibition

DHODH activity was determined colourimetrically using 2,6-dichloroindophenol (DCIP). In this assay DCIP acts as the final electron acceptor reoxidising ubiquinone. Its reduction is measured spectrophotometrically as a decrease in absorbance at 600 nm ($\varepsilon = 18.8\ mM^{-1}cm^{-1}$). All DHODH assays contained 1 μg DHODH, 0.06 mM DCIP, 150 mM KCl, 50 mM Tris/HCl and saturating concentrations of synthetic cofactor CoQ_0 (100 μM) and dihydroorotate (DHO; 200 μM). Changes in absorbance were measured over 3 min on a SpectraMAX 340pc plate reader and data were analysed using SOFTmax® PRO software (Molecular Devices, Wokingham, UK). Compounds were tested against PfDHODH at 10 μM. The activity of four compounds from this initial screen, **5k**, **23**, **20a** and **20b**, was quantified against PfDHODH and human DHODH at concentrations between 0.01 and 200 μM. Inhibition curves were generated as percentage of the rate of DCIP reduction in control reactions.

5.78. Parasite growth inhibition assays

Lead compounds (**5k**, **12**, **20a** and **20b**) were tested for antiplasmodial activity against two strains of *P. falciparum*, NF54 3D7 and W2 mef (a chloroquine- and mefloquine-resistant strain) utilising the incorporation of ^{3}H-hypoxanthine as a marker of parasite viability. Isolates were cultured in freshly washed pooled human O+ red blood cells (British Transfusion Service) and hypoxanthine-free RPMI 1640 medium supplemented with 5.96 g/L HEPES buffer and 3.60 g/L glucose (Gibco, Paisley, UK), 42 mL/L 5% sterile filtered sodium bicarbonate and 10% pooled, sterile heat-inactivated human O+ serum (British Transfusion Service). Cultures were incubated in low oxygen (1% oxygen, 3% carbon dioxide, 96% nitrogen), and maintained at 37 °C. Parasite growth inhibition assays were carried out in 96-well microtitre plates. Parasites were aliquoted and serial dilutions of stock compounds (10 mM in DMSO) were added with final added haematocrit of 2.5% and parasitaemia of 0.5% in 1200 μL complete medium. Plates were incubated for 48 h under low oxygen concentration at 37 °C with agitation after 24 h. ^{3}H-hypoxanthine was added at an activity of 1 μCi/well in 20 μL complete medium. Plates were frozen at −20 °C after 24 h. Lysates were harvested with Tomtec Harvester 96® cell harvester (Tomtec, Banbury, UK) onto Wallac 1450 MicroBeta™ glass fibre filtermats (PerkinElmer®, Beaconsfield, UK). Filters were quantified using the Wallac MicroBeta™ 1450 Trilux liquid scintillation counter. Inhibition curves were generated as a percentage of the activity of control groups that received 0 μM of each compound.

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