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Synthesis of 5-, 6- and 7-substituted-2-aminoquinolines as SH3 domain ligands

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Received 1st April 2005, Accepted 24th May 2005
First published as an Advance Article on the web 13th June 2005

The Src homology 3 (SH3) domains are small protein–protein interaction domains that mediate a range of important biological processes and are considered valuable targets for the development of therapeutic agents. We have been developing 2-aminoquinolines as ligands for SH3 domains—so far the only reported examples of entirely small-molecule ligands for the SH3 domains. The highest affinity 2-aminoquinolines so far identified are 6-substituted compounds. In this article, the synthesis of several new 2-aminoquinolines, including 5-, 6- and 7-substituted compounds, for Tec SH3 domain ligand binding studies is presented. As a part of the synthetic investigation, the utility of different methods for the synthesis of 2-aminoquinolines was explored and potentially powerful methods were identified for the synthesis of 2-aminoquinolines with diverse functionality. Of the compounds prepared, the 5-substituted-2-aminoquinolines generally bound with similar affinities to unsubstituted 2-aminoquinoline, whilst the 7-substituted compounds generally bound with similar or lower affinity than unsubstituted 2-aminoquinoline. However, the 6-substituted-2-aminoquinolines generally bound with significantly higher affinity than unsubstituted 2-aminoquinoline. In addition, one 6-substituted-*N*-benzylated-2-aminoquinoline was also tested for SH3 binding and some evidence for the formation of additional contacts at other regions of the SH3 domain was found. These results provide new and useful SAR information that should greatly assist with the challenge of developing high affinity small-molecule ligands for the SH3 domains.

Introduction

The Src homology 3 (SH3) domains are small, non-catalytic protein modules that bind to proline-rich peptide sequences and mediate a range of important biological processes. These domains are involved in protein–protein interactions that lead to the development of large protein complexes, which mediate signalling pathways within a cell, controlling important processes such as gene expression and cell proliferation.[1,2] Because the deregulation of events involving SH3 domains is known to be associated with human diseases including cancer and osteoporosis, the SH3 domains have been appealing targets for the development of potential therapeutics. A number of approaches for research into high affinity SH3 domain ligands have been reported, including the development of peptide ligands with non-peptide binding elements,[3,4] or 'peptoid' ligands that contain non-natural *N*-substituted amino acids.[5,6] These studies led to the development of ligands with enhanced affinity and selectivity over native ligands. However, because they are peptide ligands, they are poor candidates for drug development. Until recently, no examples of small-molecule ligands for SH3 domains had been reported. In our laboratory, we have been using the SH3 domain from the mouse Tec kinase enzyme as a model system for structure based drug design. Recently we reported the discovery that 2-aminoquinolines (for example **1–5** as illustrated in Fig. 1A) bind to the Tec SH3 domain, with weak to moderate affinity.[7] SAR information, in conjunction with NMR chemical shift perturbation experiments and site directed mutagenesis with the Tec SH3 protein were used to characterise the binding of 2-aminoquinolines to the Tec SH3 domain and a model for the mechanism of the binding was developed, involving two highly conserved residues in the proline-rich peptide binding site. In this model, π–π stacking occurs between the ring systems of the ligand and the side-chain of tryptophan 215 (W215)

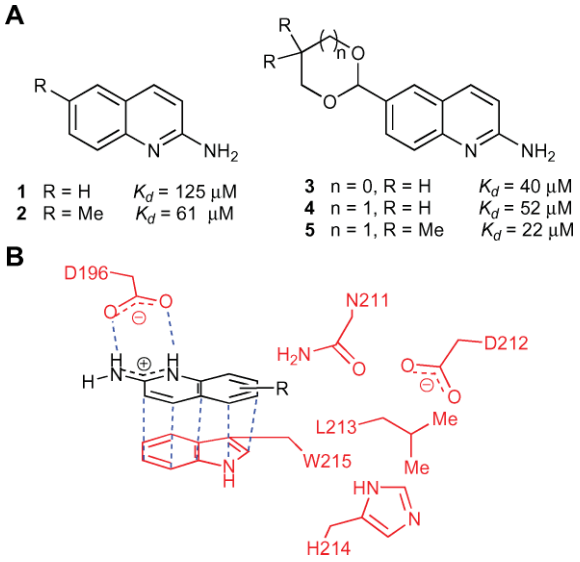


Fig. 1 (A) The structures and equilibrium binding dissociation constants (K_ds) of some 2-aminoquinolines previously tested[7] for Tec SH3 binding. (B) Model for the mechanism of 2-aminoquinoline–Tec SH3 domain binding and regions adjacent to the 2-aminoquinoline binding site, predicted to make contacts with 5-, 6- or 7-position substituents.

and a salt bridge is formed between the protonated ligand and a proximal aspartate residue (D196) on the SH3 domain (Fig. 1B). Of the 2-aminoquinolines so far tested for binding to the Tec SH3 domain, the highest affinity ligands (**3–5** in Fig. 1A), with equilibrium binding dissociation constants (K_d) in the 20–50 μM range, were 6-substituted-2-aminoquinolines that contained bulky lipophilic functionality attached to the quinoline

DOI:10.1039/b504498g

platform. It was thus concluded that a new lipophilic contact was formed between the substituent and residues adjacent to the 2-aminoquinoline binding site on the SH3 domain (Fig. 1B).

In this article, we report the synthesis and binding studies with the Tec SH3 domain of a range of new 2-aminoquinolines with substitution at either the 5-, 6- or 7-position of the quinoline ring. These include the equivalent 5- and 7-positional isomers of ligands **3** and **4**, which have already been reported (Fig. 1A), in addition to several new derivatives in the 5-, 6- and 7-position with more hydrophilic functionality. Similar to the synthesis of the 6-substituted-2-aminoquinolines,[7] the general approach used here was the synthesis of 2-chloroquinolines with the desired ring-functionality in place and conversion of these into 2-aminoquinolines, using the method of Kóródi,[8] involving acetamide as the amination reagent, at near reflux temperature. However, as part of the current investigations, some limitations of the Kóródi method were uncovered and these will also be discussed. In order to overcome these limitations, alternative approaches for the conversion of 2-chloroquinolines into 2-aminoquinolines were explored and the results from these studies are also presented. The binding of all the new ligands with the Tec SH3 domain is then reported and the new SAR information obtained is discussed. Of key importance in this investigation is a comparison of ligand affinities between the 5-, 6- and 7-position isomers synthesised here and previously.

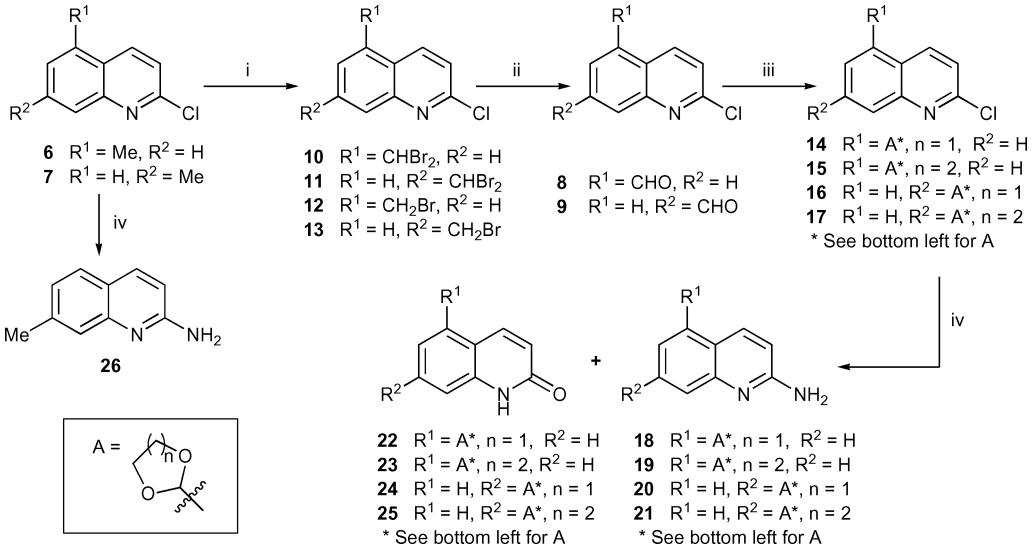
Results and discussion

Synthesis of 5- and 7-subsituted-2-aminoquinolines with lipophilic functionality

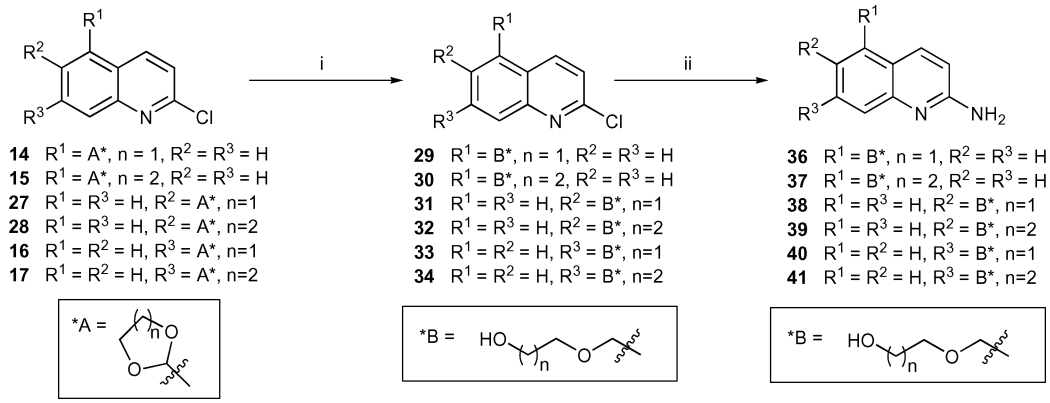
The synthesis of 2-chloro-5-methylquinoline **6** and 2-chloro-7-methylquinoline **7** as an unseparated mixture has been reported, starting from 3-methylcinnamanilide.[9] In a similar fashion to the previous syntheses of 6-substituted-2-aminoquinolines,[7] it was anticipated that the 5- and 7-methylquinoline derivatives could be functionalised by the same approach, provided that the 5- and 7-isomers could be separated. Using fractional crystallisation, a pure sample of **7** but not **6** was obtained. However, it was envisaged that aldehydes **8** and **9** (Scheme 1) might have significantly greater differences in their physical properties and hence be amenable to separation using silica gel chromatography. Thus, the mixture of **6** and **7** obtained *via* the method of Johnston *et al*.[9] (*ca.* 1 : 2 of **6**/**7**) was treated with two eq. of NBS and a catalytic amount of benzoyl peroxide and heated at reflux in benzene, as illustrated in Scheme 1, in an adaption of the method of Newman and Lee.[10] The crude material isolated from this reaction was purified by chromatography on silica gel and the major isolate was a mixture of 2-chloro-5-dibromomethylquinoline **10** and 2-chloro-7-dibromomethylquinoline **11** in 73% yield. A small amount of the corresponding 5- and 7-bromomethyl products **12** and **13** as an impure mixture was also isolated. The mixture of **10** and **11** was subsequently treated with hexamethylenetetraamine in aq. ethanol with heating at reflux, again according to the method of Newman and Lee,[10] to afford a mixture of aldehydes **8** and **9**. Following chromatography on silica gel, both aldehydes **8** and **9** were isolated in pure forms in 29% and 37% yields, respectively. Each of **8** and **9** were subsequently converted into both dioxolane and dioxane acetals **14**–**17** in moderate to good yields (51–79%) by treatment with the appropriate diols in the presence of a catalytic amount of *p*-toluenesulfonic acid and heating at reflux in benzene (Scheme 1). 2-Chloroquinolines **14**–**17** were then converted into 2-aminoquinolines **18**–**21** in moderate to good yields (43–73%) according to the method of Kóródi,[8] involving treatment with acetamide at near reflux temperature in the presence of potassium carbonate (Scheme 1). Consistent with previous observations,[7,8] small amounts (~10%) of the corresponding quinolin-2(1*H*)-ones **22**–**25** were also isolated from the amination reactions. The purified sample of 2-chloro-7-methylquinoline **7** was also converted into 2-amino-7-methylquinoline **26** using the method of Kóródi, however the quinoline-2(1*H*)-one by-product was not isolated in this case (Scheme 1).

Synthesis of 5-, 6- and 7-subsituted-2-aminoquinolines with more hydrophilic functionality—acyclic alcohols

In order to continue the exploration of the SH3 domain binding surface at regions adjacent to the 2-aminoquinoline binding site, 5-, 6- and 7-substituted-2-aminoquinolines with more hydrophilic functionality were also sought. As a step towards obtaining such compounds, it was decided to pursue the conversion of cyclic acetals **14**–**17** prepared above, in addition to **27** and **28** reported previously,[7] into acyclic alcohols as potential amination precursors. Thus, the ring opening conditions for cyclic acetals reported by Daignault and Eliel[11] were adapted with **14**–**17**, **27** and **28** (Scheme 2), involving reduction of the cyclic acetals with lithium aluminium hydride, in the presence of aluminium chloride, in THF at reflux temperature. This led to the synthesis of alcohols **29**–**34** in good to excellent yields (67–97%). In the case of alcohol **30**, a small amount (9%) of the corresponding 3,4-dihydroquinolin-2(1*H*)-one product **35** was also isolated. It was thought that **35** arose due to reduction of the C(3)–C(4) bond, the likeliness of which is considerably increased by the

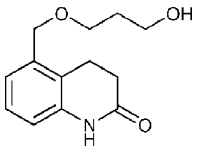


Scheme 1 *Reagents and conditions*: (i) NBS, $(PhCO_2)_2$, benzene, Δ; (ii) hexamethylenetetraamine, ethanol–water, Δ; (iii) $HOCH_2(CH_2)_nOH$, *p*-TosOH–H_2O, benzene, Δ; (iv) $AcNH_2$, K_2CO_3, ~200 °C.



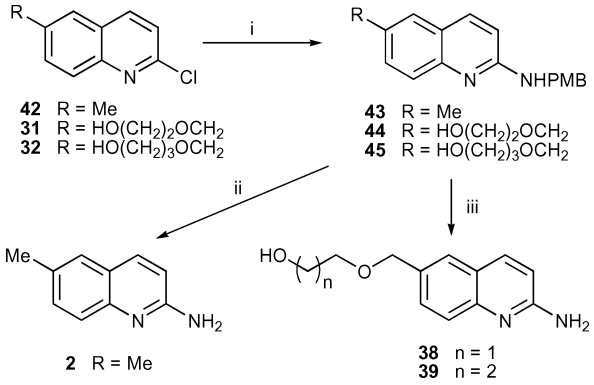
Scheme 2 *Reagents and conditions*: (i) $AlCl_3$, $LiALH_4$, THF, Δ; (ii) (**29**, **30**, **33** and **34**) 1). $AcNH_2$, K_2CO_3, ~200 °C, 2). NaOH, H_2O, Δ; (**31** and **32**) $AcNH_2$, K_2CO_3, ~200 °C.

formation of a complex between the acetal oxygen atoms and aluminium hydride, a possible intermediate in the ring opening process. The proximity of this complex to C(4) of the quinoline ring may then result in reduction in the case of the 5-substituted quinoline only. The 2-chloro substituent was then hydrolysed during workup, to form the 3,4-dihydroquinolin-2(1*H*)-one.



2-Chloroquinolines **29–34** were all converted into 2-aminoquinolines **36–41** using the method of Kóródi (Scheme 2), however the yields in these cases were less than satisfactory (3–15%) and a number of by-products, including the corresponding quinolin-2(1*H*)-ones and others that were not identified, were formed during the reaction. In these cases, only the 2-aminoquinolines were isolated from the crude product mixtures. The use of polar solvents in the reaction workups led to products contaminated with acetamide. In some cases, the excess acetamide was decomposed by treatment with aq. sodium hydroxide at reflux prior to workup and the yields were slightly improved. These results clearly highlight the incompatibility of the Kóródi amination method with 2-chloroquinolines that contain a polar functionality.

At this point, an alternative method for the synthesis of 2-aminoquinolines from 2-chloroquinolines was sought. As there are well known methods for the mild de-protection of 4-methoxybenzyl ethers with either DDQ[12] or cerium(IV)-ammonium nitrate,[13] the use of 4-methoxybenzylamine as an alternative nucleophile was investigated as a means of introducing a protected amino group at C(2). Using 2-chloro-6-methylquinoline **42** as a model (prepared according to literature[14,15] methods), treatment with 4-methoxybenzylamine at *ca.* 130 °C for 30 h resulted in isolation of pure **43** in 94% yield following workup and chromatography (Scheme 3). De-protection with either DDQ[12] or cerium(IV)ammonium nitrate[13] was unsuitable when applied to the 4-methoxybenzylamine **43**, however when **43** was treated with trifluoromethanesulfonic acid at rt by adapting the method of Anderson and Morris,[16] the primary amine **2** was afforded in 95% yield. The conversion of 2-chloroquinolines **31** and **32** to 2-(4-methoxybenzylamino)-quinolines **44** and **45** also proceeded in high yield (98% and 93% respectively) and protection of the hydroxyl groups of the starting materials was not necessary. The de-protection of **45** was tested using trifluoromethanesulfonic acid under similar conditions used for the successful de-protection of **43** to **2**, however only low recovery of an insoluble material was observed when tested with **45**. But when **45** was stirred in trifluoroacetic acid at *ca.* 50 °C by adapting the method of Ford *et al.*,[17] the

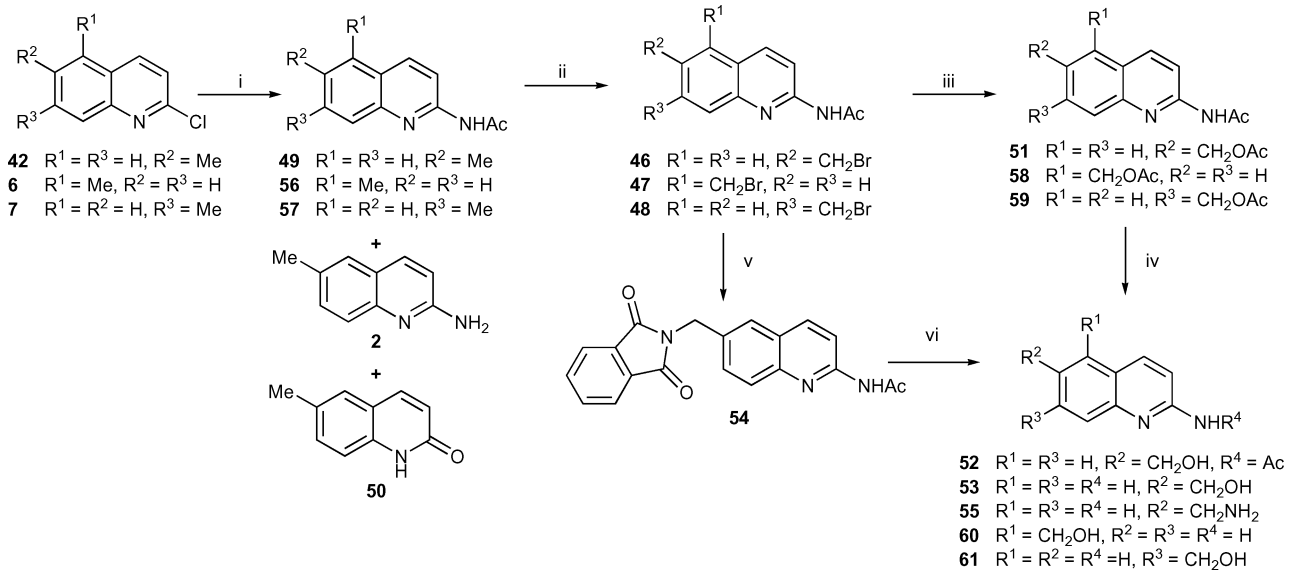


Scheme 3 *Reagents and conditions*: (i) 4-methoxybenzylamine ($PMBNH_2$), *ca.* 130 °C, 30 h; (ii) TfOH, rt, 48 h; (iii) TFA, *ca.* 50 °C, 1 h.

conversion of **45** to the primary 2-aminoquinoline **39** proceeded after 1 h and, following chromatography, pure **39** was isolated in 59% yield. This improved method was also used for the synthesis of **38** in two steps from **31** with similar success (98% yield for amination and 69% yield for de-protection).

Synthesis of 5-, 6- and 7-subsituted-2-aminoquinolines with simple hydrophilic functionality—towards covergent synthesis

As a step towards the development of a more convergent synthetic approach for the preparation of 5-, 6- and 7-substituted-2-aminoquinolines, it was anticipated that bromomethyl-2-acetamidoquinolines such as **46–48** (Scheme 4) might be useful 'key intermediates'. To test this approach, a one step conversion of 2-chloro-6-methylquinoline **42** to the 2-acetamidoquinoline derivative **49** was employed, involving treatment of **42** with a large excess of acetamide in the presence of potassium carbonate and heating at reflux overnight (Scheme 4) according to the method of Watanabe *et al.*[18] This transformation proceeds under similar conditions to the method of Kóródi[8] for the synthesis of 2-aminoquinolines from 2-chloroquinolines (as in Scheme 1and Scheme 2), however the method of Watanabe and coworkers involves a larger excess of acetamide and a much longer reaction time. The precise mechanism of both of these conversions is unclear, however thin layer chromatography indicated that the 2-aminoquinoline forms first in both cases, consistent with the reaction times (1–2 h) for the method of Kóródi. By continuing the reaction overnight (as in the method of Watanabe *et al.*), the 2-acetamidoquinoline then forms. When this reaction was tested on a small scale (0.25 g of **42**), acetamide **49** was isolated in 68% yield after workup and purification, consistent with the literature. However, the ^1H NMR spectrum of the crude isolate indicated that a small amount of both the 2-aminoquinoline **2** and quinolin-2(1*H*)-one **50** was also present in the mixture.



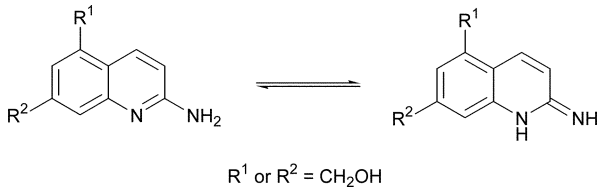
Scheme 4 *Reagents and conditions* (i) $AcNH_2$, K_2CO_3, Δ, 16 h; (ii) NBS, $(PhCO_2)_2$, benzene, Δ; (iii) AcOK, DMF, *ca.* 80 °C; (iv) (**51**) K_2CO_3, MeOH, rt; (**58** and **59**) K_2CO_3, MeOH, *ca.* 50 °C; (v) potassium phthalimide, DMF, *ca.* 80 °C; (vi) NaOH–H_2O, Δ.

When the reaction was repeated on a large scale (7.54 g of **42**), acetamide **49** was isolated in 39% yield and quinolin-2(1*H*)-one **50** was produced in 31% yield, but none of the 2-aminoquinoline was observed. It was thus concluded that this reaction is difficult to control on such a large scale.

Acetamide **49** was then treated with a slight excess of NBS and a catalytic amount of benzoyl peroxide in benzene at reflux (Scheme 4) to produce the bromomethyl derivative **46** in 56% yield following workup and purification. To test the utility of **46** in substitution chemistry, **46** was treated with two eq. of potassium acetate in DMF with heating at *ca.* 80 °C, to form the acetate derivative **51** in 87% yield. It was anticipated that 6-hydroxymethyl-2-acetamidoquinoline **52** may also be a useful intermediate within a convergent synthetic approach. Thus, a selective de-acetylation method for **51** was sought. Treatment of **51** with 0.5 eq. of potassium carbonate in methanol at rt led to the formation of the hydroxymethyl derivative **52** in 72% yield, however the entirely deacetylated 2-aminoquinoline **53** was also obtained in 20% yield (Scheme 4). As a means of producing the corresponding aminomethyl derivative, the bromomethyl derivative **46** was treated with potassium phthalimide in DMF at *ca.* 80 °C overnight to produce the phthalimide derivative **54** in 81% yield (Scheme 4). In this case, the aminomethyl derivative **55** was obtained by treating **54** with aq. sodium hydroxide at reflux (Scheme 4). Amine **55** was formed in *ca.* 50% yield, however the product contained approximately 5% of the hydroxymethyl derivative **53** as an unexpected by-product in the reaction, as judged by ^{1}H NMR. The formation of this by-product was thought to occur because the resonance donating effect of the 2-amino group (after hydrolysis of the acetamide) led to the displacement of the phthalimide to form an activated intermediate. Attack by hydroxide then resulted in the formation of **53**. This material was sufficiently pure (>95% by NMR) to be used in the ligand binding experiments without any further purification.

Using the same approach as described above, the mixture of 2-chloro-5-methylquinoline **6** and 2-chloro-7-methylquinoline **7** was also converted to the corresponding 2-acetamidoquinoline mixture of **56** and **57**, respectively, in 52% yield (Scheme 4). The mixture of **56** and **57** was subsequently converted into the corresponding bromomethyl mixture of **47** and **48**, respectively, in 46% yield, prior to conversion into the mixture of acetates **58** and **59** (Scheme 4). At this point, partial separation of the 5- and 7-positional isomers was possible by chromatography: pure **58** was isolated in 32% yield, together with a *ca.* 19 : 1 mixture of **59** : **58** (as judged by ^{1}H NMR spectroscopy) in 26% yield. An additional 10% recovery of a *ca.* 4 : 1 mixture of **59** : **58** was also obtained. Acetates **58** and **59** were subsequently converted into the corresponding hydroxymethyl-2-aminoquinolines **60** and **61**, respectively, again using potassium carbonate in methanol, however in these cases the temperature was raised to *ca.* 50 °C and one eq. of potassium carbonate was used. Using this approach, **58** was converted into the 2-aminoquinoline **60** in 93% yield, and the *ca.* 19 : 1 mixture of **59** : **58** was converted into the corresponding mixture of **61** : **60** in 88% yield, from which isolation of pure **61** was possible in 44% yield, after chromatography.

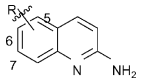
A common feature of the acetamide derivatives prepared (**46–49**, **51**, **52**, **54** and **56–59**) was the observation of significant line broadening of the signal for C(3)H in the ^{1}H NMR spectra. This is attributed to a relatively slow rotational exchange on the NMR timescale of the N–C bond of the acetamide group. Additionally, in the ^{13}C NMR spectrum of the amines **60** and **61** the signals for both C(3) and C(8) are significantly broadened. This is most likely due to tautomerism between the amino and imino forms of these quinolines as illustrated below.



Binding studies of 5-, 6- and 7-substituted-2-aminoquinolines with the Tec SH3 domain

All the 2-aminoquinolines, for which the synthesis was described above, were tested for binding to the Tec SH3 domain using either fluorescence polarisation (FP)[19] peptide displacement assays and/or NMR chemical shift perturbation experiments, using uniformly ^{15}N-labelled Tec SH3 protein. In the FP assay, the ability of the small-molecule ligand to compete with a fluorescently labelled proline-rich peptide (fluorescein–βA-RRPPPPIPPE–CO_2H, hereafter referred to as **PRP-1**) for binding to the Tec GST–SH3 fusion protein was measured. The use of this approach in the current ligand binding studies has been previously reported[7] and leads to the calculation of the concentration of small-molecule ligand at which 50% displacement of **PRP-1** (EC_{50}) from the SH3 domain occurs. With the NMR chemical shift perturbation experiments, the ability of the small-molecule ligand to bind the SH3 domain

Table 1 Binding constants of 5-, 6- and 7-substituted-2-aminoquinolines with the Tec SH3 domain, as studied by either fluorescence polarisation peptide displacement or NMR chemical shift perturbation experiments



	5-Position		6-Position			7-Position	
R	Compound	EC_{50}/μM[a]	Compound	EC_{50}/μM[a]	K_d/μM[b]	Compound	K_d/μM[b]
	**18**	249 ± 39	**3**	34 ± 5[c]	40 ± 8[c]	**20**	207 ± 48
	**19**	269 ± 83	**4**	26 ± 6[c]	52 ± 16[c]	**21**	439 ± 101
$HO(CH_2)_2OCH_2$	**36**	238 ± 82	**38**	40 ± 8	38 ± 9	**40**	176 ± 44
$HO(CH_2)_3OCH_2$	**37**	254 ± 40	**39**	51 ± 4	—	**41**	182 ± 21
$HOCH_2$	**60**	76 ± 11[d]	**53**	71 ± 9	—	**61**	195 ± 34
Me	—	—	**2**	75 ± 15[c]	61 ± 6[c]	**26**	369 ± 93
H			**1**	160 ± 36[c]	125 ± 24[c]		

[a] Quoted values are mean ± standard deviation over three replicate experiments. [b] Quoted values are mean ± standard deviation over residues where ^{1}H (H–N) chemical shift changes of the SH3 domain were at least 0.1 ppm at or near saturation binding of ligand. [c] As reported in Inglis *et al.*[7] [d] Determined by NMR chemical shift perturbation experiments; quoted value is mean ± standard deviation over residues where ^{1}H (H–N) chemical shift changes of the SH3 domain were at least 0.1 ppm at or near saturation binding of ligand.

was measured by recording Heteronuclear Single Quantum Coherence (HSQC)[20] experiments with uniformly ^{15}N-labelled SH3 protein, in the presence of the small-molecule ligand. As reported previously,[7] equilibrium binding dissociation constants (K_ds) were obtained using this approach.

The 5-substituted-2-aminoquinolines **18** and **19** with bulky lipophilic functionality competed for binding with **PRP-1** for the SH3 domain with approximately eight-fold reduced affinity relative to the equivalent 6-position ligands **3** and **4** (EC_{50}'s *ca.* 250 μM for **18** and **19** and *ca.* 30 μM for **3** and **4**,[7] Table 1). In the case of the corresponding 7-position ligands, the 5-membered acetal **20** bound the SH3 domain with approximately five-fold reduced affinity relative to the 6-position ligand **3**[7] (K_ds 207 μM and 40 μM for **20** and **3**, respectively, Table 1), whilst the 6-membered acetal **21** bound with even lower affinity (K_d = 439 μM), approximately eight-fold lower than the corresponding 6-position ligand **4** (K_d = 52 μM).[7] Of the 2-aminoquinolines **36**–**41** with more hydrophilic and flexible substituents, the 6-position ligands **38** and **39** displayed the highest affinity (EC_{50}'s *ca.* 45 μM; Fig. 2, Table 1), whilst the corresponding 5-substituted (**36** and **37**) and 7-substituted compounds (**40** and **41**) all bound with similar affinities (EC_{50}'s *ca.* 200 μM for **36** and **37**, Fig. 2a; K_ds *ca.* 180 μM for **40** and **41**, Table 1). Of the hydroxymethyl derivatives **53**, **60** and **61**, the 5- and 6-positional isomers bound the SH3 domain with similar affinities (EC_{50} = 71 μM for **53**, K_d = 76 μM for **60**, Fig. 1B, Table 1), whilst the 7-position compound bound with approximately two and a half-fold lower affinity (K_d = 195 μM, Table 1). 2-Amino-7-methylquinoline **26** bound the SH3 domain with approximately six-fold reduced affinity (K_d = 369 μM) relative to the corresponding 6-position ligand (K_d = 61 μM).[7] The 6-aminomethyl-2-aminoquinoline derivative **55** competed for binding with **PRP-1** with an EC_{50} of 102 μM, whilst the 6-substituted-2-(4-methoxybenzyl)aminoquinoline **45** bound the SH3 domain with K_d = 81 μM (Table 2).

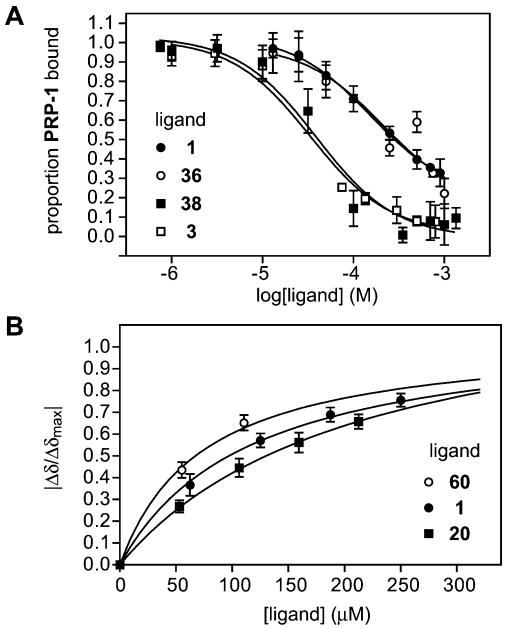
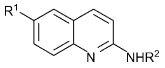


Fig. 2 Tec SH3 domain–5-, 6- and 7-substituted-2-aminoquinolines binding studies. (A) Isotherms obtained from independent experiments for competition of fluorescently labelled proline-rich peptide **PRP-1** by **36** and **38** synthesised here and **1** and **3** previously reported[7] for comparison, from Tec GST–SH3 fusion protein using fluorescence polarisation assay. (B) Isotherms obtained from independent experiments, represented as the mean of the normalised change in chemical shift of residues involved in binding of ligands **20** and **60**, and **1** previously reported[7] for comparison, as determined with NMR chemical shift perturbation experiments.

Discussion

With the exception of **60**, a general trend is evident, indicating that substituents at the 5-position of the 2-aminoquinoline platform (ligands **18**, **19**, **36** and **37**), regardless of their chemical properties, do not appear to make any additional contacts with the SH3 domain surface and thus the affinities of these ligands are not significantly different to that of 2-aminoquinoline **1**. This is consistent with the prediction that substituents at the 5-position would be directed away from the protein surface. In the case of **60**, the mechanism that mediates the *ca.* two-fold improvement in affinity of this ligand relative to 2-aminoquinoline is unclear. It is possible that a weak, entropically unfavourable hydrogen bond is made with a hydrophilic residue on the protein surface. However, inspection of regions adjacent to where **60** sits on the SH3 domain structure according to the ligand binding model, does not provide obvious insight into how this hydrogen bond is mediated. In addition, it seems unlikely that the same interaction(s) that mediates the improvement in affinity of the similar 6-substituted ligands **2** and **53** is responsible for the improvement observed for **60**, because a significantly different and potentially less than optimal orientation of the quinoline

Table 2 Binding studies of additional 2-aminoquinolines



R^1, R^2		EC_{50}/μM[a]	K_d/μM[b]
H, H	**1**	160 ± 36[c]	125 ± 24[c]
H_2NCH_2, H	**55**	102 ± 17	—
$HO(CH_2)_3OCH_2$, $CH_2C_6H_4$-*p*-OMe	**45**	—	81 ± 10
H, Me	**62**	—	380 ± 40[c]

[a] Quoted values are mean ± standard deviation over three replicate experiments. [b] Quoted values are mean ± standard deviation over residues where ^{1}H (H–N) chemical shift changes of the SH3 domain were at least 0.1 ppm at or near saturation binding of ligand. [c] As reported in Inglis *et al*.[7]

ring would be expected for the 5-position substituent to make the same contact(s).

On the other hand, substituents at the 6-position are clearly well placed for the formation of new contacts with the SH3 domain, as evidenced by all the 6-substituted ligands presented here binding with a higher affinity than 2-aminoquinoline **1**. In the case of ligands **38** and **39**, the improvement in affinity was approximately three to four-fold relative to the binding of 2-aminoquinoline **1**. Furthermore, the affinities of **38** and **39** are not substantially different to those of their 'parent' cyclic acetal ligands **3** and **4** (Table 1). This suggests that **38** and **39** make similar and/or additional contacts with the SH3 domain to **3** and **4**. The formation of hydrogen bonds between the hydroxyl groups of **38** or **39** with hydrophilic residues on the SH3 domain possibly mediates the improvement in the affinities of these ligands relative to **1**, however entropic costs associated with hydrogen bond formation, due to the high flexibility of the substituents on **38** and **39**, do not result in optimal affinity. In the case of the 6-hydroxymethyl and 6-aminomethyl derivatives **53** and **55**, their affinities are similar to 2-amino-6-methylquinoline **2** (EC_{50}s = 71, 102 and 75 μM for **53**, **55** and **2**,[7] respectively, Table 1 and Table 2) suggesting that a small lipophilic contact mediates the improvement in affinity in these cases.

Additional consideration is required to rationalise the observations made with the 7-position ligands. Given that 2-amino-7-methylquinoline **26** binds the SH3 domain with an approximately three-fold reduced affinity relative to 2-aminoquinoline **1**, this suggests that the simple substituent of **26** is poorly accommodated in the region adjacent to the 2-aminoquinoline binding site and a steric penalty leads to the reduction in affinity. However, the similar affinity of the 7-substituted-5-membered cyclic acetal derivative **20** with 2-aminoquinoline **1** (Table 1) suggests that the bulky lipophilic substituent of **20** is better accommodated than the smaller substituent of **26** and thus a new lipophilic and/or hydrophilic contact is made at this region, but an overall improvement in affinity relative to **1** is not observed as there are entropic penalties for the SH3 domain associated with accommodating the substituent of **20**. In the case of the equivalent 6-membered cyclic acetal **21**, an approximately three-fold reduction in affinity relative to 2-aminoquinoline **1** is observed, suggesting that the larger size of this substituent is poorly accommodated at the binding site relative to **20**. In the case of ligands **40**, **41** and **61** with more hydrophilic and flexible substituents, the affinities again are not substantially different to 2-aminoquinoline and are similar to the 5-membered cyclic acetal **20**. Hence the apparent steric clashes that lead to the reduced affinity of the 7-methyl ligand **26** and the 6-membered acetal **21** are off-set for all the other 7-position ligands. These results suggest that the oxygen atom(s) attached to the benzylic carbon atom of the 7-position ligands may mediate the improvement in affinities observed by way of a non-ideal hydrogen bond. For the 5-membered cyclic acetal **20**, the steric clash observed with the smaller 5-membered acetal is compensated for by the formation of a hydrogen bond, but in the case of the larger 6-membered acetal of **21** the steric violations are too great and hence the level of compensation gained through hydrogen bond formation is reduced. In a similar fashion, the 7-position ligands **40** and **41** may also make a non-ideal hydrogen bond, however less steric penalties are observed in these cases due to the high flexibility of the alkyl functionality attached to the benzylic oxygen atoms. Given that the affinity of hydroxymethyl derivative **61** is similar to the ligands **40** and **41**, this suggests that the alkyl chains of **40** and **41** do not make any additional interactions with the protein. Despite these observations, a general conclusion that can be made about the 7-substituted-2-aminoquinolines is that substitution at this position is not well tolerated. This is consistent with the prediction that substituents at this position would be directed into the protein surface and would therefore potentially lead to steric clashes.

The affinity of the 6-substituted 2-(4-methoxybenzyl)amino-quinoline derivative **45** (K_d = 81 μM, Table 2) indicates that an approximately two-fold reduction in affinity has occurred compared with the related primary amines **38** and **39** (EC_{50}s **38** and **39** *ca.* 45 μM, K_d **38** = 38 μM, Table 1). This is consistent with the observation that the *N*-methylated-2-aminoquinoline derivative **62** bound the SH3 domain with approximately three-fold reduced affinity[7] relative to 2-aminoquinoline **1**. However, the reduction in affinity in the case of **45** is less severe than in the case of the *N*-methylated compound **62**, suggesting that additional contacts between the substituent at the 6-position of the ligand and the protein surface residues have been made. Furthermore, it may be concluded that the reduction in affinity in the case of the *N*-benzyl substituent of ligand **45**, is less severe than may have been expected from substitution of the amino group with a methyl group alone. Thus, it may also be concluded that additional contacts are made between surface residues on the other side of the 2-aminoquinoline binding site and the 4-methoxybenzyl motif attached to the amino group of **45**. Additional support for this is found by consideration of the [^{1}H,^{15}N] HSQC spectra of the SH3 domain, where an unusual exchange process is observed in the presence of ligand **45**. For the majority of the ligands studied in this work, fast exchange processes on the NMR timescale have been observed in the [^{1}H,^{15}N] HSQC spectra of the SH3 domain. In some cases however, intermediate exchange processes were observed,[7] as evidenced by the complete loss of, or substantial drops in, intensity of the ^{1}H (H–N) cross-peaks for some residues at or near the 2-aminoquinoline binding site, at concentrations of ligand less than one molar eq. (see for **38** in Fig. 3A). Prior to the testing of compound **45**, all examples of the intermediate exchange observation were dependent on the concentration of the ligand; at equimolar to excess levels of the ligand, fast exchange characteristics were again observed (Fig. 3A). But in the case of **45**, the intermediate exchange observation for many protein residues was observed at all ligand concentrations, even when a large excess of ligand was present. Specifically, in the case of the indole ^{1}H (H–N) of the side-chain of tryptophan 215 (W215ε1), a residue central to the ligand-binding site (Fig. 1B), the signal was not observed at any ligand concentration (Fig. 3B). This suggests that the exchange process for ligand **45** is closer to slow exchange than fast exchange on the NMR timescale, possibly a result of a reduction in the off-rate constant k_{off}. This apparent reduction in k_{off} may in turn be a consequence the formation of multiple contacts between the ligand and the protein, providing some evidence for the formation of new contacts between the 4-methoxybenzyl motif of the ligand and regions adjacent to where this motif sits in the ligand-binding site. However, an overall higher affinity ligand is not obtained in this case, possibly due to an accompanying reduction in the on-rate constant k_{on}. This may in turn be a consequence of the benzyl substituent on the amino group of **45** leading to entropic costs associated with salt bridge formation with D196.

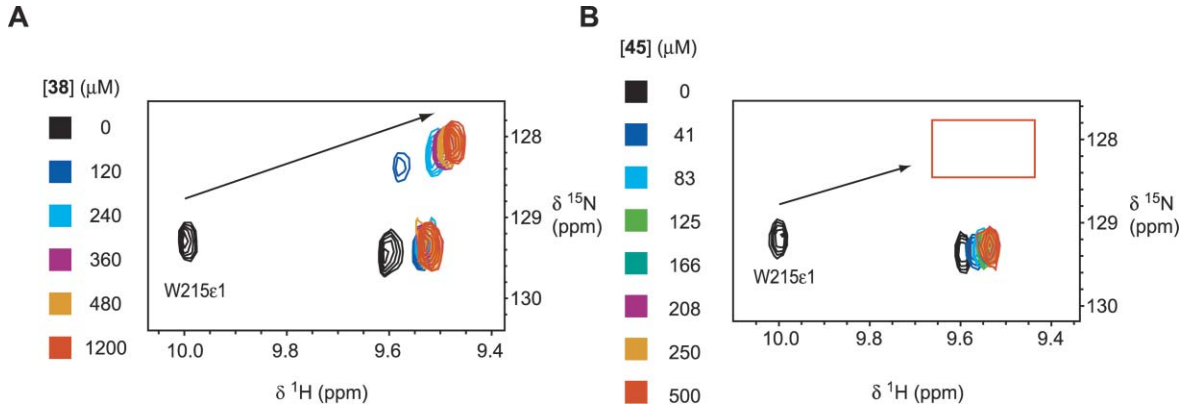


Fig. 3 Comparison of HSQC spectra of the Tec SH3 domain in the presence of ligands **38** and **45**, which exhibit intermediate exchange properties on the NMR timescale. (A) Overlaid HSQC spectra in the presence of intermediate exchange ligand **38**, recorded with a 240 μM sample of the uniformly ^{15}N-labelled SH3 protein. (B) As for (A), using intermediate exchange ligand **45**, with a 125 μM sample of the uniformly ^{15}N-labelled SH3 protein. The red box indicates the region of the spectrum where the signal for W215ε1 is normally observed at saturation binding of ligand [compare with **38** in (A)].

However, ligand **45** and others presented in this report remain unsuitable for the determination of the 3D structure of the ligand when bound to the SH3 domain, as ligands that bind in slow exchange on the NMR timescale are necessary for this. Slow exchange allows sufficient time for inter-molecular nuclear Overhauser effect build-up and transfer between the ligand and the protein, from which structure calculations are possible. Thus, confirmation of the binding modes of the ligands discussed here with a structure is not yet possible.

Conclusions

In this report, a significant extension of the initial work on the synthesis of 6-substituted-2-aminoquinolines for Tec SH3 domain binding studies[7] has been presented. Key synthetic advancements include the preparation of several 5- and 7-substituted-2-aminoquinolines. The mixture of 2-chloro-5-methylquinoline **6** and 2-chloro-7-methylquinoline **7** prepared according to the method of Johnston *et al*.[9] was converted into the 2-chloro-5-formylquinoline **8** and 2-chloro-7-formylquinoline **9**, which could be separated using silica gel chromatography, and these precursors were subsequently used for the preparation of several 5- and 7-substituted-2-aminoquinolines for ligand binding studies. In addition, new methodology for the synthesis of 2-aminoquinolines from 2-chloroquinolines was explored. This led to the development of methods for the synthesis of 5-, 6- and 7-substituted-2-aminoquinolines with a range of functionality. Of particular interest is the conversion of 2-chloroquinolines into 2-(4-methoxybenzyl)amines and their subsequent de-benzylation with trifluoroacetic acid. With additional exploratory research to establish milder reaction conditions for the amination reaction, this approach may lead to the development of powerful new methods for the synthesis of 2-aminoquinolines with diverse functionality. In addition, the utility of 'key intermediates', such as the bromomethyl-2-acetamidoquinolines **46**–**48**, in a convergent synthetic strategy also requires additional exploration.

The SAR information provided by testing all the ligands presented here provides new and useful information about the 2-aminoquinoline–Tec SH3 domain binding event. With the exception of the 5-substituted ligand **60**, of all the 5-, 6- and 7-substituted-2-aminoquinolines reported here, only the 6-substituted compounds bound the SH3 domain with an improvement in affinity. It may be concluded that functionality at the 5-position does not make any interactions with the SH3 domain as these ligands bind with similar affinity to 2-aminoquinoline **1**. It may also be concluded that addition of new functionality at the 7-position of the quinoline ring generally leads to unfavourable interactions between the ligand and the protein surface. Thus, the 6-position of the 2-aminoquinoline platform remains the best prospect for development of optimal interactions with regions on the SH3 domain surface adjacent to the 5-, 6- or 7-position of the quinoline ring. The highest affinity ligands discovered in this work (*eg*. ligand **38**, K_d = 38 μM), bound with comparable affinity to the highest affinity ligands previously reported.[7] However, no further improvements in affinities were obtained. Thus further work into the development of 6-substituted-2-aminoquinolines as Tec SH3 domain ligands, potentially leading to optimal ligands, and with more drug-like properties, is required. In addition, further investigation into formation of contacts on the other side of the quinoline ring, similar to those suggested by the binding of the 2-(4-methoxybenzyl)aminoquinoline **45**, would also be beneficial.

Experimental

Ligand binding studies

The testing of binding of compounds for Tec SH3 domain binding, using either the fluorescence polarisation (FP) peptide displacement assays or the NMR chemical shift perturbation experiments, were performed according to protocols previously described.[7]

Chemistry: general

All solvents were distilled, dried and stored according to standard procedures.[21] Melting points were determined using a Kofler hot-stage apparatus equipped with a Reichart microscope and values are uncorrected. Infrared spectra were recorded on an ATI Mattson Genesis FTIR spectrometer either as nujol mulls or as liquid films between sodium chloride plates. ^{1}H and ^{13}C NMR spectra were recorded on either a Varian Gemini-2000 spectrometer (^{1}H: 200.13 MHz, ^{13}C: 50.32 MHz or ^{1}H: 300.13 MHz, ^{13}C: 74.47 MHz), or a Varian INOVA 600 spectrometer (^{1}H: 599.842 MHz, ^{13}C: 150.842 MHz). The Varian INOVA 600 spectrometer was fitted with a ^{1}H{^{13}C/^{15}N} inverse triple resonance PFG probe with z-axis gradients. Spectra were recorded as solutions in $CDCl_3$ [tetramethylsilane ($\delta_H = 0.0$) or $CDCl_3$ ($\delta_C = 77.7$) as internal references], d_6-acetone [$\delta_H = 2.05$, $\delta_C = 29.9$ as internal references], d_6-DMSO [$\delta_H = 2.50$, $\delta_C = 39.5$ as internal references] or d_4-methanol [$\delta_H = 3.31$, $\delta_C = 49.2$ as internal references]. Chemical shift values are given on the δ scale quoted in parts per million, followed by the integration, multiplicity, coupling constant J (given in Hz) and assignment. The following abbreviations have been used: s, singlet; d, doublet; t, triplet; q, quartet; quin, quintet; m, multiplet; br, broad. Multiplicity marked with a dagger (†), is indicative of a broadened signal due to unresolved J coupling(s). ^{13}C signals

for new compounds were assigned from heteronuclear multiple quantum correlation (HMQC) and heteronuclear multiple bond correlation (HMBC) experiments. Flash chromatography was performed using Scharlau Silica Gel 60, 230–400 mesh. Thin layer chromatography (TLC) was performed on aluminium backed silica gel 60 plates (Merck) and were visualised under UV light (254 nm) or by staining with a $KMnO_4$–K_2CO_3 solution. Electron impact (EI) mass spectra were recorded using a Vacuum Generators ZAB 2HF mass spectrometer. High resolution mass spectrometry was performed at Monash University (Victoria, Australia) or the University of Tasmania (Tasmania, Australia). Elemental analyses were performed at the University of Otago (Dunedin, New Zealand).

Sources of compounds

Compounds **6** and **7** were prepared as a *ca.* 1 : 2 mixture according to a literature procedure.[9] Compounds **27**,[7] **28**[7] and **42**[14,15] were also prepared according to literature methods.

A pure sample of **7** was obtained by fractional crystallisation of the **6–7** mixture with aq. methanol to afford **7** as white crystals, mp 83–84 °C (lit.,[22] 83–84 °C); ν_{max}(nujol)/cm^{-1} 1621, 1595 and 1541; δ_H(200 MHz; $CDCl_3$) 2.55 [3 H, s, C(7)Me], 7.30 [1 H, d, *J* 8.6, C(3)H], 7.38 [1 H, dd, $J_{6,8}$ 1.6 $J_{5,6}$ 8.2, C(6)H], 7.69 [1 H, d, $J_{5,6}$ 8.2, C(5)H], 7.79 [1 H, dd, $J_{6,8}$ 1.6 $J_{4,8}$ 0.8, C(8)H], 8.03 [1 H, dd, $J_{4,8}$ 0.8 $J_{3,4}$ 8.4, C(4)H].

2-Chloro-5-formylquinoline 8/2-chloro-7-formylquinoline 9. The **6–7** mixture‡ (2.50 g, 14.1 mmol), *N*-bromosuccinimide (5.00 g, 28.2 mmol) and benzoyl peroxide (0.34 g, 1.41 mmol) were heated at reflux in benzene (10 mL) for 15 h. After cooling, the benzene was removed and the residue was filtered through silica gel using dichloromethane as eluant. Following purification by column chromatography on silica gel (4 : 1 dichloromethane–hexane), a mixture of the dibrominated products **10** and **11** (2.89 g, 73%) (R_f 0.54) was isolated, in addition to a small amount of a *ca.* 5 : 1 mixture of monobrominated/dibrominated products (**12** and **13**)/(**10** and **11**) (R_f 0.43).

‡ Prior to the reaction, the **6–7** mixture was partially purified by filtration through silica gel using dichloromethane as eluant.

10/11: δ_H(200 MHz; $CDCl_3$) 6.81 [1 H, s, C(7*)$CHBr_2$], 7.16 [1 H, s, C(5)$CHBr_2$], 7.43 [1 H, d, $J_{3,4}$ 8.4, C(3*)H], 7.56 [1 H, d, $J_{3,4}$ 8.9, C(3)H], 7.67 [1 H, t, $J_{6,7}$ and $J_{7,8}$ 8.0, C(7)H], 7.82 [1 H, d, $J_{6,7}$ 8.0, C(6)H], 7.88 [2 H, m, C(5*, 6*)H], 8.05 [1 H, d, $J_{4,8}$ 0.8, C(8*)H], 8.08–8.13 [2 H, m, C(4*, 8)H], 8.87 [1 H, d, $J_{3,4}$ 8.9, C(4)H]; *m*/*z* (EI) 332.8541 ($C_{10}H_6{}^{79}Br_2{}^{35}ClN$ requires 332.8555), 256 (100%).

* Refers to **11**.

12/13: δ_H(200 MHz; $CDCl_3$) 4.65 [1 H, s, C(5)CH_2Br], 4.87 [1 H, s, C(7*)CH_2Br], 7.34–7.70 [m, C(Ar)H], 7.76–7.86 [m, C(Ar)H], 7.97–8.10 [m, C(Ar)H], 8.42 [1 H, dd, *J* 0.8 *J* 8.8, C(4* or 8)H]; *m*/*z* (EI) 257 (M$^{+\cdot}$ [$^{79}Br^{37}Cl$], 8), 256 (M$^{+\cdot}$ [$^{79}Br^{37}Cl$]–H, 14), 255 (M$^{+\cdot}$ [$^{79}Br^{35}Cl$], 5), 254 (M$^{+\cdot}$ [$^{79}Br^{35}Cl$]–H, 4) 192 (20), 178 (M$^{+\cdot}$ [$^{79}Br^{37}Cl$]–Br, 30), 176 (M$^{+\cdot}$ [$^{79}Br^{35}Cl$]–Br, 100), 163 (36), 128 (39).

* Refers to **13**.

The mixture of **10** and **11** prepared above (2.80 g, 8.35 mmol) was treated with hexamethylenetetraamine (3.51 g, 25.1 mmol) in 50% aq. ethanol (10 mL) with heating at reflux for 2.5 h. After cooling, concentrated hydrochloric acid (1.5 mL) was added and the mixture was heated at reflux for a further 30 min. After cooling, brine (10 mL) was added and the mixture was extracted with dichloromethane (3 × 15 mL). The combined extracts were dried (Na_2SO_4) and the solvent was removed. The residue was chromatographed on silica gel using 4 : 1 dichloromethane–hexane as eluant to provide the pure title compound **8** (0.460 g, 29%) (R_f 0.34) as white crystals, mp 144–146 °C (from aq. ethanol). In addition, the pure title compound **9** (0.590 g, 37%) (R_f 0.19) was also isolated as a white solid, mp 130–133 °C.

8: (found: C, 62.4; H, 2.95; N, 7.3%. $C_{10}H_6ClNO$ requires C, 62.7; H, 3.15; N, 7.3%); ν_{max}(nujol)/cm^{-1} 1693 (CO), 1606, 1583 and 1565; δ_H(600 MHz, $CDCl_3$) 7.57 [1 H, d, $J_{3,4}$ 9.0, C(3)H], 7.91 [1 H, dd, $J_{6,7}$ 7.2 $J_{7,8}$ 8.4, C(7)H], 8.06 [1 H, dd, $J_{6,8}$ 1.2 $J_{6,7}$ 7.2, C(6)H], 8.26 [1 H, ddd, $J_{4,8}$ 0.6 $J_{6,8}$ 1.2 $J_{7,8}$ 8.4, C(8)H], 9.56 [1 H, dd, $J_{4,8}$ 0.6 $J_{3,4}$ 9.0, C(4)H], 10.32 [1H, s, C(5)CHO]; δ_C(150 MHz, $CDCl_3$) 124.41 [C(4a)], 124.94 [C(3)], 129.55 [C(7)], 131.57 [C(5)], 135.23 [C(8)], 136.47 [C(4)], 136.92 [C(6)], 148.14 [C(8a)], 151.89 [C(2)], 192.73 [CO]; *m*/*z* (EI) 193 (M$^{+\cdot}$ [^{37}Cl], 33), 192 (M$^{+\cdot}$ [^{37}Cl]–H, 48), 191 (M$^{+\cdot}$ [^{35}Cl], 100), 190 (M$^{+\cdot}$ [^{35}Cl]–H, 91), 164 (15), 162 (43), 127 (27).

9: (found: C, 62.4; H, 3.05; N, 7.25%. $C_{10}H_6ClNO$ requires C, 62.7; H, 3.15; N, 7.3%); ν_{max}(nujol)/cm^{-1} 1684 (CO), 1587 and 1555; δ_H(600 MHz, $CDCl_3$) 7.53 [1 H, d, $J_{3,4}$ 8.4, C(3)H], 7.94 [1 H, d, $J_{5,6}$ 8.4, C(5)H], 8.06 [1 H, dd, $J_{6,8}$ 1.6 $J_{5,6}$ 8.4, C(6)H], 8.18 [1 H, dd, $J_{4,8}$ 0.6 $J_{4,5}$ 8.4, C(4)H], 8.46 [1 H, dt, $J_{CHO,8} = J_{4,8}$ 0.6 $J_{6,8}$ 1.6 C(8)H], 10.22 [1 H, d, *J* 0.6, C(7)CHO]; δ_C(150 MHz, $CDCl_3$) 123.80 [C(6)], 124.83 [C(3)], 128.77 [C(5)], 130.25 [C(4a)], 133.92 [C(8)], 137.68 [C(7)], 138.72 [C(4)], 147.56 [C(8a)], 152.06 [C(2)], 191.53 [CO]; *m*/*z* (EI) 193 (M$^{+\cdot}$ [^{37}Cl], 35), 192 (M$^{+\cdot}$ [^{37}Cl]–H, 48), 191 (M$^{+\cdot}$ [^{35}Cl], 100), 190 (M$^{+\cdot}$ [^{35}Cl]–H, 89), 164 (16), 162 (43), 127 (27).

General procedure for acetal formation

The formyl compound (**8** or **9**), the diol (1.1–2 eq.) and *p*-toluenesulfonic acid monohydrate (0.05–0.1 eq.) were heated at reflux in benzene (~4 mL mmol^{-1} aldehyde) using a Dean Stark apparatus until thin layer chromatography indicated that all the starting material had been consumed. After cooling, the benzene was removed under a reduced pressure and the residue was taken up into dichloromethane, washed twice with water and once with brine, dried (Na_2SO_4) and the solvent was removed. The residue was then chromatographed on silica gel using dichloromethane as eluant to afford the analytically pure product.

2-Chloro-5-(1,3-dioxolan-2-yl)quinoline 14. 2-Chloro-5-formylquinoline **8** (0.70 mg, 3.65 mmol) was treated with ethylene glycol (0.45 g, 7.30 mmol) and *p*-toluenesulfonic acid monohydrate (0.021 g, 0.11 mmol) in 10 mL of benzene as described above. Following workup and chromatography, the title compound **14** (0.68 g, 79%) (R_f 0.31) was isolated, mp 100–103 °C. (Found: C, 61.4; H, 4.15; N, 5.85%. $C_{12}H_{10}ClNO_2$ requires C, 61.15; H, 4.3; N, 5.95%); ν_{max}(nujol)/cm^{-1} 1613, 1594 and 1568; δ_H(200 MHz, $CDCl_3$) 4.15–4.21 [4 H, m, C(4′, 5′)H], 6.34 [1 H, s†, C(2′)H], 7.43 [1 H, d, $J_{3,4}$ 9.0, C(3)H], 7.72 [1 H, dd, $J_{6,7}$ 7.2 $J_{7,8}$ 7.8, C(7)H], 7.80 [1 H, ddd, $J_{2',6}$ 0.6 $J_{6,8}$ 1.8 $J_{6,7}$ 7.2, C(6)H], 8.04 [1 H, ddd, $J_{4,8}$ 0.8 $J_{6,8}$ 1.8 $J_{7,8}$ 7.8, C(8)H], 8.55 [1 H, dd, $J_{4,8}$ 0.8 $J_{3,4}$ 9.0, C(4)H]; δ_C(150 MHz, $CDCl_3$) 65.51 [C(4′, 5′)], 101.92 [C(2′)], 122.22 [C(3)], 124.73 [C(4a)], 124.77 [C(6)], 129.77 [C(7)], 129.91 [C(8)], 133.84 [C(5)], 135.89 [C(4)], 148.27 [C(8a)], 150.55 [C(2)]; *m*/*z* (EI) 237 (M$^{+\cdot}$ [^{37}Cl], 8), 235 (M$^{+\cdot}$ [^{35}Cl], 22), 163 (9), 165 (3).

2-Chloro-5-(1,3-dioxan-2-yl)quinoline 15. 2-Chloro-5-formylquinoline **8** (0.60 g, 3.13 mmol) was treated with 1,3-propanediol (0.48 g, 6.26 mmol) and *p*-toluenesulfonic acid monohydrate (0.018 g, 0.939 mmol) in 9 mL of benzene as described above. Following workup and chromatography the title compound **15** (0.59 g, 73%) (R_f 0.16) was isolated, mp 101–103 °C. (Found: C, 62.55; H, 4.75; N, 5.55%. $C_{13}H_{12}ClNO_2$ requires C, 62.55; H, 4.85; N, 5.6%); ν_{max}(nujol)/cm^{-1} 1590 and 1570; δ_H(600 MHz, $CDCl_3$) 1.53 [1 H, dtt, $J_{4'eq,5'eq}$ 1.3 $J_{4'ax,5'eq}$ 2.6 $J_{5'ax,5'eq}$ 13.7, C(5′)H_{eq}], 2.34 [1 H, dtt, $J_{4'eq,5'ax}$ 5.0 $J_{4'ax,5'ax}$ 12.5 $J_{5'ax,5'eq}$ 13.7, C(5′)H_{ax}], 4.05–4.10 [2 H, m, C(4′, 6′)H], 4.32–4.35 [2 H, m, C(4′, 6′)H], 5.91 [1 H, s†, C(2′)H], 7.39 [1 H, d, $J_{3,4}$ 9.0, C(3)H], 7.69 [1 H, dd, $J_{6,7}$ 7.2 $J_{7,8}$ 8.2, C(7)H], 7.72 [1 H, ddd, $J_{2',6}$ 0.8 $J_{6,8}$ 1.6 $J_{6,7}$ 7.2, C(6)H], 8.01 [1 H, ddd, $J_{4,8}$ 0.8 $J_{6,8}$ 1.6 $J_{7,8}$ 8.2, C(8)H], 8.69 [1 H, dd, $J_{4,8}$ 0.8 $J_{3,4}$ 9.0, H(4)]; δ_C(150 MHz, $CDCl_3$) 25.73 [C(5′)], 67.66 [C(4′, 6′)], 101.33 [C(2′)], 122.01[C(3)], 124.32 [C(4a)], 125.46 [C(6)], 129.68 [C(7)], 129.81 [C(8)], 134.50 [C(5)], 136.67 [C(4)], 148.31 [C(8a)], 150.40 [C(2)]; *m*/*z* (EI) 251 (M$^{+\cdot}$

[^{37}Cl], 21), 249 ($M^{+\cdot}$ [^{35}Cl], 63), 192 (19), 190 (52), 165 (19), 163 (63).

2-Chloro-7-(1,3-dioxolan-2-yl)quinoline 16. 2-Chloro-7-formylquinoline **9** (0.60 g, 3.13 mmol) was treated with ethylene glycol (0.39 g, 6.26 mmol) and *p*-toluenesulfonic acid monohydrate (0.018 g, 0.939 mmol) in 9 mL of benzene as described above. Following workup and chromatography, the title compound **16** (0.38 g, 51%) (R_f 0.14) was isolated, mp 88–90 °C. (Found: C, 60.85; H, 4.1; N, 5.75%. $C_{12}H_{10}ClNO_2$ requires C, 61.15; H, 4.3; N, 5.95%); ν_{max}(nujol)/cm^{-1} 1590 and 1566; δ_H(200 MHz, $CDCl_3$) 4.06–4.22 [4 H, m, C(4′, 5′)H], 6.02 [1 H, s†, C(2′)H], 7.41 [1 H, d, $J_{3,4}$ 8.8, C(3)H], 7.68 [1 H, dd†, $J_{6,8}$ 1.6 $J_{5,6}$ 8.4, C(6)H], 7.85 [1 H, d, $J_{5,6}$ 8.4 Hz, C(5)H], 8.10–8.14 [2 H, m, C(4, 8)H]; δ_C(50 MHz, $CDCl_3$) 65.6 [C(4′, 5′)], 103.3 [C(2′)], 122.9 [C(3)], 125.2 [C(6)], 126.8 [C(8)], 127.2 [C(4a)], 128.0 [C(5)], 138.7 [C(4)], 140.0 [C(7)], 147.7 [C(8a)], 151.2 [C(2)]; *m/z* (EI) 237 ($M^{+\cdot}$ [^{37}Cl], 23) 235 ($M^{+\cdot}$ [^{35}Cl], 70), 192 (11), 190 (28), 165 (27), 163 (100).

2-Chloro-7-(1,3-dioxan-2-yl)quinoline 17. 2-Chloro-7-formylquinoline **9** (0.60 g, 3.13 mmol) was treated with 1,3-propanediol (0.48 g, 6.26 mmol) and *p*-toluenesulfonic acid monohydrate (0.018 g, 0.939 mmol) in 9 mL of benzene as described above. Following workup and chromatography, the title compound **17** (0.47 g, 60%) (R_f 0.15) was isolated, mp 134–136 °C. (Found: C, 62.8; H, 4.75; N, 5.55%. $C_{12}H_{10}ClNO_2$ requires C, 62.55; H, 4.85; N, 5.6%); ν_{max}(nujol)/cm^{-1} 1626, 1588 and 1565; δ_H(600 MHz, $CDCl_3$) 1.49 [1 H, dtt, $J_{4'eq,5'eq}$ 1.2 $J_{4'ax,5'eq}$ 2.4 $J_{5'ax,5'eq}$ 13.2, C(5′)H_{eq}], 2.26 [1 H, dtt, $J_{4'eq,5'ax}$ 4.8 $J_{4'ax,5'ax}$ 12.6 $J_{5'ax,5'eq}$ 13.2, C(5′)H_{ax}], 4.02–4.07 [2 H, m, C(4′, 6′)H], 4.29–4.32 [2 H, m, C(4′, 6′)H], 5.67 [1 H, s†, C(2′)H], 7.37 [1 H, d, $J_{3,4}$ 8.4, C(3)H], 7.72 [1 H, dd†, $J_{6,8}$ 1.2 $J_{5,6}$ 8.4, C(6)H], 7.81 [1 H, d, $J_{5,6}$ 8.4, H(5)], 8.07 [1 H, dd, $J_{4,8}$ 0.6 $J_{3,4}$ 8.4, C(4)H], 8.12 [1 H, dd†, $J_{4,8}$ 0.6 $J_{6,8}$ 1.2, C(8)H]; δ_C(150 MHz, $CDCl_3$) 25.70 [C(5′)], 67.40 [C(4′, 6′)], 100.87 [C(2′)], 122.57 [C(3)], 124.92 [C(6)], 126.24 [C(8)], 126.83 [C(4a)], 127.62 [C(5)], 138.58 [C(4)], 141.16 [C(7)], 147.52 [C(8a)], 150.78 [C(2)]; *m/z* (EI) 251 ($M^{+\cdot}$ [^{37}Cl], 32), 249 ($M^{+\cdot}$ [^{35}Cl], 100), 192 (29), 190 (64), 165 (20), 163 (60).

General procedure for amination of 2-chloroquinolines according to the method of Kóródi[8]

The 2-chloroquinoline (1 eq.) was treated with acetamide (20 eq.) and potassium carbonate (5 eq.) at ~200 °C until thin layer chromatography (9 : 1 dichloromethane–ethanol) indicated the reaction was complete (~1–2 h). After cooling, water was added to the residue and the aqueous layer was extracted three times with chloroform. The combined organic extracts were washed with brine, dried (Na_2SO_4) and the solvent was removed. Unless otherwise indicated, the residues were chromatographed over silica gel using 9 : 1 dichloromethane–ethanol as eluant to afford the pure 2-aminoquinolines. In most cases, the accompanying quinolin-2(1*H*)-ones were also isolated.

2-Amino-5-(1,3-dioxolan-2-yl)quinoline 18. 2-Chloro-5-(1,3-dioxolan-2-yl)quinoline **14** (0.20 g, 0.849 mmol) was treated with acetamide (1.0 g, 17.0 mmol) and potassium carbonate (0.59 g, 4.25 mmol) as described above. Following workup and chromatography, the title compound **18** (0.079 g, 43%) (R_f 0.23) was isolated, mp 170–178 °C. In addition, the by-product 5-(1,3-dioxolan-2-yl)quinolin-2(1*H*)-one **22** (0.036 g) (R_f 0.50) was also isolated in an impure form.

18: ν_{max}(nujol)/cm^{-1} 3446 and 3301 (NH), 1652, 1610, 1570 and 1518; δ_H(600 MHz, $CDCl_3$) 4.10–4.21 [4 H, m, C(4′, 5′)H], 4.97 [2 H, br s, NH_2], 6.29 [1 H, s†, C(2′)H], 6.76 [1 H, d, $J_{3,4}$ 9.0, C(3)H], 7.49 [1 H, ddd, $J_{2',6}$ 0.6 $J_{6,8}$ 1.2 $J_{6,7}$ 7.2, C(6)H], 7.54 [1 H, dd, $J_{7,8}$ 8.4 $J_{6,7}$ 7.2, C(7)H], 7.68 [1 H, ddd, $J_{4,8}$ 0.6 $J_{6,8}$ 1.2 $J_{7,8}$ 8.4, C(8)H], 8.32 [1 H, dd, $J_{4,8}$ 0.6 $J_{3,4}$ 9.0, C(4)H]; δ_C(150 MHz, $CDCl_3$) 65.24 [C(4′, 5′)], 102.30 [C(2′)], 111.61 [C(3)], 120.84 [C(6)], 121.17 [C(4a)], 127.18 [C(8)], 129.15 [C(7)], 133.39 [C(5)], 134.94 [C(4)], 147.41 [C(8a)], 156.38 [C(2)]; *m/z* (EI) 216.0896 ($C_{12}H_{12}N_2O_2$ requires 216.0899), 172 (11), 171 (16), 144 (100), 143 (18).

22: δ_H(200 MHz, $CDCl_3$) 4.08–4.24 [4 H, m, C(4′, 5′)H], 6.21 [1 H, s†, C(2′)H], 6.76 [1 H, d, $J_{3,4}$ 10.0, C(3)H], 7.41–7.50 [3 H, m, C(6, 7, 8)H], 8.27 [1 H, d, $J_{3,4}$ 10.0, C(4)H], 12.19 [1 H, br s, NH].

2-Amino-5-(1,3-dioxan-2-yl)quinoline 19. 2-Chloro-5-(1,3-dioxan-2-yl)quinoline **15** (0.200 g, 0.801 mmol) was treated with acetamide (0.950 g, 16.0 mmol) and potassium carbonate (0.550 g, 4.01 mmol) as described above. After workup and chromatography, the title compound **19** (0.135 g, 73%) (R_f 0.16) was isolated, mp 186–210 °C. In addition, the by-product 5-(1,3-dioxan-2-yl)quinolin-2(1*H*)-one **23** (0.028 g, 15%) (R_f 0.41) was isolated, mp >230 °C.

19: (found: C, 67.9; H, 6.0; N, 12.0%. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.15; N, 12.15%); ν_{max}(nujol)/cm^{-1} 3458 and 3316 (NH), 1654, 1618, 1572 and 1522; δ_H(200 MHz, $CDCl_3$) 1.52 [1 H, dtt, $J_{4'eq,5'eq}$ 1.4 $J_{4'ax,5'eq}$ 2.6 $J_{5'ax,5'eq}$ 13.4, C(5′)H_{eq}], 2.20 [1 H, dtt, $J_{4'eq,5'ax}$ 5.2 $J_{4'ax,5'ax}$ 12.0 $J_{5'ax,5'eq}$ 13.4, C(5′)H_{ax}], 4.02–4.27 [4 H, m, C(4′, 6′)H], 5.84 [1 H, br s, NH], 5.92 [1 H, s†, C(2′)H], 6.85 [1 H, d, $J_{3,4}$ 9.2, C(3)H], 7.34 [1 H, ddd, $J_{2',6}$ 0.4 $J_{6,8}$ 1.8 $J_{6,7}$ 7.0, C(6)H], 7.43 [1 H, dd, $J_{7,8}$ 8.2 $J_{6,7}$ 7.0, C(7)H], 8.12 [1 H, ddd, $J_{4,8}$ 0.6 $J_{6,8}$ 1.8 $J_{7,8}$ 8.2, C(8)H], 8.07 [1 H, dd, $J_{4,8}$ 0.6 $J_{3,4}$ 9.2, C(4)H]; δ_C(50 MHz, $CDCl_3$) 25.9 [C(5′)], 67.7 [C(4′, 6′)], 101.9 [C(2′)], 111.5 [C(3)], 120.7 [C(4a)], 121.6 [C(6)], 127.1 [C(8)], 129.1 [C(7)], 134.2 [C(5)], 135.7 [C(4)], 147.5 [C(8a)], 156.3 [C(2)]; *m/z* (EI) 230 ($M^{+\cdot}$, 100), 172 (48), 171 (24), 144 (60), 143 (25).

23: ν_{max}(nujol)/cm^{-1} 3410 (NH), 1691 (CO), 1659 and 1598; δ_H(200 MHz, $CDCl_3$) 1.42–2.04 [1 H, m, C(5′)H_{eq}], 2.05–2.30 [1 H, m, C(5′)H_{ax}], 4.04–4.28 [4 H, m, C(4′, 6′)H], 5.93 [1 H, s†, C(2′)H], 6.50 [1 H, d, $J_{3,4}$ 10.0, C(3)H], 7.30–7.51 [3 H, m, C(6, 7, 8)H], 8.36 [1 H, d†, $J_{3,4}$ 10.0, C(4)H], 11.95 [1H, br s, NH]; δ_C(50 MHz, $CDCl_3$) 25.8 [C(5′)], 67.7 [C(4′, 6′)], 101.4 [C(2′)], 117.1 [C(4a)], 117.3 [C(8)], 121.3 [C(6)], 121.5 [C(3)], 130.1 [C(7)], 135.2 [C(5)], 138.4 [C(4)], 139.0 [C(8a)], 163.4 [C(2)]; *m/z* (EI) 231.0895 ($C_{13}H_{13}NO_3$ requires 231.0895), 173 (67), 172 (64), 145 (48), 144 (20).

2-Amino-7-(1,3-dioxolan-2-yl)quinoline 20. 2-Chloro-7-(1,3-dioxolan-2-yl)quinoline **16** (0.200 g, 0.849 mmol) was treated with acetamide (1.00 g, 17.0 mmol) and potassium carbonate (0.590 g, 4.25 mmol) as described above. Following workup and chromatography, the title compound **20** (0.114 g, 62%) (R_f 0.14) was isolated, mp 159–169 °C. In addition, the by-product 7-(1,3-dioxolan-2-yl)quinolin-2(1*H*)-one **24** (0.022 g, 12%) (R_f 0.36) was also isolated, mp 195–200 °C.

20: (found: C, 66.45; H, 5.5; N, 12.7%. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 12.95%); ν_{max}(nujol)/cm^{-1} 3453 and 3311 (NH), 1644, 1628, 1565 and 1515; δ_H(200 MHz, $CDCl_3$) 3.96–4.16 [4 H, m, C(4′, 5′)H], 5.85 [1 H, s†, C(2′)H], 5.94 [2 H, br s, NH_2], 6.87 [1 H, d, $J_{3,4}$ 9.0, C(3)H], 7.27 [1 H, ddd, $J_{2',6}$ 0.6 $J_{6,8}$ 1.6 $J_{5,6}$ 8.4, C(6)H], 7.62–7.66 [2 H, m, C(5, 8)H], 7.91 [1 H, d†, $J_{3,4}$ 9.0, C(4)H]; δ_C(50 MHz, $CDCl_3$) 65.6 [C(4′, 5′)], 103.9 [C(2′)], 112.3 [C(3)], 120.9 [C(6)], 124.1 [C(4a)], 124.2 [C(8)], 128.0 [C(5)], 138.1 [C(4)], 140.0 [C(7)], 147.3 [C(8a)], 157.4 [C(2)]; *m/z* (EI) 216 ($M^{+\cdot}$, 15), 171 (4), 144 (21), 143 (4).

24: ν_{max}(nujol)/cm^{-1} 3447 (NH), 1656 (CO), 1608 and 1555; δ_H(200 MHz, $CDCl_3$) 4.03–4.20 [4 H, m, C(4′, 5′)H], 5.90 [1 H, s†, C(2′)H], 6.71 [1 H, d, $J_{3,4}$ 9.4, C(3)H], 7.34 [1 H, dd†, $J_{6,8}$ 1.6 $J_{5,6}$ 8.0, C(6)H], 7.45 [1 H, d†, $J_{6,8}$ 1.6, C(8)H], 7.58 [1 H, d, $J_{5,6}$ 8.0, C(5)H], 7.80 [1 H, d†, $J_{3,4}$ 9.4, C(4)H], 11.26 [1 H, br s, NH]; δ_C(50 MHz, $CDCl_3$) 65.7 [C(4′, 5′)], 103.2 [C(2′)], 114.4 [C(8)], 120.7 [C(4a)], 121.2 [C(6)], 121.9 [C(3)], 128.3 [C(5)], 138.4 [C(8a)], 141.0 [C(4)], 141.4 [C(7)], 164.3 [C(2)]; *m/z* (EI) 217.0739 ($C_{12}H_{11}NO_3$ requires 217.0739), 173 (35), 172 (36), 145 (100).

2-Amino-7-(1,3-dioxan-2-yl)quinoline 21. 2-Chloro-7-(1,3-dioxan-2-yl)quinoline **17** (0.200 g, 0.801 mmol) was treated

with acetamide (1.00 g, 17.0 mmol) and potassium carbonate (0.550 g, 4.01 mmol) as described above. Following workup and chromatography, the title compound **21** (0.134 g, 73%) (R_f 0.16) was isolated, mp 175–196 °C. In addition the by-product 7-(1,3-dioxan-2-yl)quinolin-2(1*H*)-one **25** (0.022 g, 12%) (R_f 0.47) was also isolated, mp 196–204 °C.

21: (found: C, 67.8; H, 6.15; N, 12.15%. $C_{13}H_{14}N_2O_2$ requires C, 67.8; H, 6.15; N, 12.15%); ν_{max}(nujol)/cm^{-1} 3458 and 3291 (NH), 1641, 1626, 1566 and 1518; δ_H(600 MHz, $CDCl_3$) 1.46 [1 H, dtt, $J_{4'eq,5'eq}$ 1.2 $J_{4'ax,5'eq}$ 2.4 $J_{5'ax,5'eq}$ 13.8, C(5′)H_{eq}], 2.25 [1 H, dtt, $J_{4'eq,5'ax}$ 4.8 $J_{4'ax,5'ax}$ 12.6 $J_{5'ax,5'eq}$ 13.8, C(5′)H_{ax}], 4.00–4.04 [2 H, m, C(4′, 6′)H], 4.27–4.30 [2 H, m, C(4′, 6′)H], 5.19 [2 H, br s, NH_2], 5.61 [1 H, s†, C(2′)H], 6.72 [1 H, d, $J_{3,4}$ = 9.0, C(3)H], 7.43 [1 H, dd†, $J_{6,8}$ 1.2 $J_{5,6}$ 8.4, C(6)H], 7.61 [1 H, d, $J_{5,6}$ 8.4, C(5)H], 7.76 [1 H, dd†, $J_{4,8}$ 0.6 $J_{6,8}$ 1.2, C(8)H], 7.85 [1 H, dd, $J_{4,8}$ 0.6 $J_{3,4}$ 9.0, C(4)H]; δ_C(150 MHz, $CDCl_3$) 25.78 [C(5′)], 67.38 [C(4′, 6′)], 101.50 [C(2′)], 112.08 [C(3)], 120.63 [C(6)], 123.18 [C(8)], 123.49 [C(4a)], 127.68 [C(5)], 138.18 [C(4)], 140.46 [C(7)], 146.28 [C(8a)], 156.88 [C(2)]; *m/z* (EI) 230 ($M^{+\cdot}$, 94), 172 (100), 171 (49), 144 (81), 143 (39).

25: ν_{max}(nujol)/cm^{-1} 3436 (NH), 1669 (CO), 1611 and 1557; δ_H(600 MHz, $CDCl_3$) 1.48 [1 H, dtt, $J_{4'eq,5'eq}$ 1.2 $J_{4'ax,5'eq}$ 2.4 $J_{5'ax,5'eq}$ 13.2, C(5′)H_{eq}], 2.25 [1 H, dtt, $J_{4'eq,5'ax}$ 4.8 $J_{4'ax,5'ax}$ 12.6 $J_{5'ax,5'eq}$ 13.2, C(5′)H_{ax}], 4.00–4.04 [2 H, m, C(4′, 6′)H], 4.28–4.31 [2 H, m, C(4′, 6′)H], 5.59 [1 H, s†, C(2′)H], 6.75 [1 H, d, $J_{3,4}$ 9.6, C(3)H], 7.39 [1 H, dd†, $J_{6,8}$ 1.2 $J_{5,6}$ 8.4, C(6)H], 7.53 [1 H, d†, $J_{6,8}$ 1.2, C(8)H], 7.58 [1 H, d, $J_{5,6}$ 8.4, C(5)H], 7.83 [1 H, d†, $J_{3,4}$ 9.6, C(4)H], 12.01 [1H, br s, NH]; δ_C(150 MHz, $CDCl_3$) 25.67 [C(5′)], 67.42 [C(4′, 6′)], 100.65 [C(2′)], 114.05 [C(8)], 120.23 [C(4a)], 120.81 [C(6)], 121.27 [C(3)], 127.89 [C(5)], 137.98 [C(8a)], 141.05 [C(4)], 141.62 [C(7)], 164.17 [C(2)]; *m/z* (EI) 231.0894 ($C_{13}H_{13}NO_3$ requires 231.0895), 173 (84), 172 (96), 145 (56), 144 (29).

2-Amino-7-methylquinoline 26. 2-Chloro-7-methylquinolone **7** (0.200 g, 1.13 mmol) was treated with acetamide (1.33 g, 22.6 mmol) and potassium carbonate (0.780 g, 5.65 mmol) as described above. Following workup and chromatography the title compound **26** (0.110 g, 61%) (R_f 0.18) was isolated, mp 131–135 °C (from water) (lit.,[23] 134–135 °C). ν_{max}(nujol)/cm^{-1} 3435 and 3301 (NH), 1651, 1624, 1608, 1563 and 1515; δ_H(200 MHz, $CDCl_3$) 2.47 [1 H, s, C(7)Me], 5.04 [2H, br s, NH_2], 6.63 [1 H, d, $J_{3,4}$ 8.8, C(3)H], 7.08 [1 H, dd, $J_{6,8}$ 1.6 $J_{5,6}$ 8.4, C(6)H], 7.45 [1 H, dd, $J_{4,8}$ 0.6 $^4J_{6,8}$ 1.6, C(8)H], 7.49 [1 H, d, $J_{5,6}$ 8.4, C(5)H], 7.79 [1 H, dd, $J_{4,8}$ 0.6 $J_{3,4}$ 8.8, C(4)H]; δ_C(50 MHz, $CDCl_3$) 22.0 [C(7)Me], 110.9 [C(3)], 121.7 [C(4a)], 124.9 [C(6)], 125.4 [C(8)], 127.3 [C(5)], 138.0 [C(4)], 140.2 [C(7)], 147.9 [C(8a)], 157.3 [C(2)].

General procedure for acetal reduction to form acyclic alcohols

Aluminium chloride (2.1 eq.) was placed in an oven-dried round-bottomed flask under a nitrogen atmosphere at *ca.* 0 °C, and dry THF (~1 mL mmol^{-1} $AlCl_3$) was added. The mixture was stirred at *ca.* 0 °C until a uniform suspension was obtained before the careful addition of lithium aluminium hydride (1.2 eq.), portion-wise over 5 min. Stirring was continued at *ca.* 0 °C for 30 min, before the acetal (1 eq.) dissolved in dry THF (~3 mL mmol^{-1} acetal) was added drop-wise over 10 min. The mixture was then stirred at rt for 15 min, before heating at reflux until the reaction was complete (~3–4 h), as judged by TLC. After cooling, the mixture was added cautiously and portion-wise to ice (~30 g mmol^{-1} of acetal) with stirring and stirring was continued until the evolution of gas had ceased. Concentrated sulfuric acid (~0.4 mL mmol^{-1} acetal) was then added and stirring was continued for 15 min. The THF was removed under a reduced pressure and the remaining aqueous solution was extracted with dichloromethane (3 ×). The combined organic layers were washed with brine (1 ×), dried (Na_2SO_4) and the solvent was removed to afford the crude alcohol. Purified products were obtained following chromatography on silica gel.

2-Chloro-5-[(2-hydroxyethoxy)methyl]quinoline 29. The general procedure described above was used with aluminium chloride (0.715 g, 5.36 mmol) in dry THF (4 mL), lithium aluminium hydride (0.116 g, 3.06 mmol) and acetal **14** (0.600 g, 2.55 mmol) dissolved in dry THF (7.2 mL). Following workup, sufficiently pure title compound **29** (0.580 g, 96%) was isolated. A portion was chromatographed using 3 : 1 dichloromethane–ethyl acetate as eluant (R_f 0.26), to afford analytically pure **29**, mp 58–60 °C. (Found: C, 60.35; H, 5.15; N, 5.85%. $C_{12}H_{12}ClNO_2$ requires C, 60.65; H, 5.1; N, 5.9%); ν_{max}(nujol)/cm^{-1} 3306 (OH), 1674, 1613, 1592 and 1572; δ_H(200 MHz, $CDCl_3$) 2.78 [1 H, br s, OH], 3.58–3.78 [4 H, m, C(1, 2)H], 4.91 [2 H, s, C(5′)CH_2], 7.35 [1 H, d, $J_{3',4'}$ 8.8, C(3′)H], 7.49 [1 H, dd, $J_{6',8'}$ 1.2 $J_{6',7'}$ 7.0, C(6′)H], 7.62 [1 H, dd, $J_{6',7'}$ 7.0 $J_{7',8'}$ 8.4, C(7′)H], 7.94 [1 H, ddd, $J_{4',8'}$ 0.6 $J_{6',8'}$ 1.2 $J_{7',8'}$ 8.4, C(8′)H], 8.39 [1 H, dd, $J_{4',8'}$ 0.6 $J_{3',4'}$ 8.8, C(4′)H]; δ_C(50 MHz, $CDCl_3$) 61.6 [C(2)], 71.0 [C(1)], 71.7 [C(5′)CH_2], 122.2 [C(3′)], 125.5 [C(4a′)], 127.3 [C(6′)], 128.9 [C(8′)], 129.9 [C(7′)], 134.3 [C(5′)], 135.8 [C(4′)], 148.1 [C(8a′)], 150.5 [C(2′)]; *m/z* (EI) 239 ($M^{+\cdot}$ [^{37}Cl], 15), 237 ($M^{+\cdot}$ [^{35}Cl], 44), 194 (34), 192 (100), 178 ($M^{+\cdot}$ [^{37}Cl] − $HO(CH_2)_2O$, 26), 176 ($M^{+\cdot}$ [^{35}Cl] − $HO(CH_2)_2O$, 81).

2-Chloro-5-[(3-hydroxypropoxy)methyl]quinoline 30. The general procedure described above was used with aluminium chloride (1.14 g, 8.52 mmol) in dry THF (6.4 mL), lithium aluminium hydride (0.183 g, 4.82 mmol) and acetal **15** (1.00 g, 4.02 mmol) dissolved in dry THF (12 mL). Following workup, the residue was chromatographed using ethyl acetate as eluant to afford pure **30** (0.680 g, 67%) (R_f 0.47) as an oil. In addition, the by-product 5-[3-(hydroxypropoxy)methyl]-3,4-dihydroquinolin-2(1*H*)-one **35** (0.087 g, 9%) (R_f of 0.17) was also isolated, mp 97–100 °C.

30: ν_{max}(nujol)/cm^{-1} 3392 (OH), 1612, 1591 and 1568; δ_H(200 MHz, $CDCl_3$) 1.86 [2 H, quin, *J* 5.8, C(2)H], 2.66 [1H, br s, OH], 3.68 [2 H, t, *J* 5.8, C(1)H], 3.73 [2 H, t, *J* 5.8, C(3)H], 4.88 [2 H, s, C(5′)CH_2], 7.40 [1 H, d, $J_{3',4'}$ 8.8, C(3′)H], 7.51 [1 H, dd, $J_{6',8'}$ 0.8 $J_{6',7'}$ 7.0, C(6′)H], 7.65 [1 H, dd, $J_{6',7'}$ 7.0 $J_{7',8'}$ 8.4, C(7′)H], 7.96 [1 H, dd†, $J_{6',8'}$ 0.8 $J_{7',8'}$ 8.4, C(8′)H], 8.40 [1 H, d†, $J_{3',4'}$ 8.8, C(4′)H]; δ_C(150 MHz, $CDCl_3$) 32.16 [C(2)], 60.85 [C(3)], 68.75 [C(1)], 71.00 [C(5′)CH_2], 122.26 [C(3′)], 125.49 [C(4a′)], 127.33 [C(6′)], 128.91 [C(8′)], 129.93 [C(7′)], 134.26 [C(5′)], 135.67 [C(4′)], 148.20 [C(8a′)], 150.52 [C(2′)]; *m/z* (EI) 251.0706 ($C_{13}H_{14}ClNO_2$ requires 251.0713), 194 (39), 192 (100), 178 (33), 176 (89).

35: (found: C, 66.55; H, 7.35; N, 5.65%. $C_{13}H_{15}NO_3$ requires C, 66.35; H, 7.3; N, 5.95%); ν_{max}(nujol)/cm^{-1} 3316 and 3195 and 3144 (NH), 1706 (CO), 1659 and 1598; δ_H(200 MHz, $CDCl_3$) 1.86 [2 H, quin, *J* 5.8, C(2)H], 2.58–3.02 [5 H, m, C(3′, 4′)H and OH], 3.64 [2 H, t, *J* 5.8, C(1)H], 3.76 [2 H, t, *J* 5.8, C(3)H], 4.50 [2 H, s, C(5′)CH_2], 6.83 [1 H, dd, $J_{6',8'}$ 1.2 $J_{6',7'}$ 7.8, C(6′)H], 6.99 [1 H, dd, $J_{6',8'}$ 1.2 $J_{7',8'}$ 7.4, C(8′)H], 7.13 [1 H, dd, $J_{7',8'}$ 7.4 $J_{6',7'}$ 7.8, C(7′)H], 9.47 [1 H, br s, NH]; δ_C(50 MHz, $CDCl_3$) 21.6 [C(4′)], 30.4 [C(3′)], 32.4 [C(2)], 61.3 [C(3)], 69.1 [C(1)], 71.4 [C(5′)CH_2], 116.0 [C(8′)], 122.7 [C(4a′)], 124.2 [C(6′)], 127.3 [C(7′)], 135.7 [C(5′)], 137.9 [C(8a′)], 172.3 [C(2′)]; *m/z* (EI) 235 ($M^{+\cdot}$, 30), 176 (18), 159 (100).

2-Chloro-6-[(2-hydroxyethoxy)methyl]quinoline 31. The general procedure described above was used with aluminium chloride (0.988 g, 7.41 mmol) in dry THF (6 mL), lithium aluminium hydride (0.161 g, 4.24 mmol) and acetal **27** (0.832 g, 3.53 mmol) dissolved in dry THF (11 mL) with heating at reflux for 5 h. Following workup and chromatography using 3 : 1 dichloromethane–ethyl acetate as eluant, pure **31** (0.621 g, 74%) (R_f 0.20) was isolated as fluffy white crystals, mp 51–53 °C. (Found: C, 60.4; H, 5.05; N, 5.85%. $C_{12}H_{12}ClNO_2$ requires C, 60.65; H 5.1; N, 5.9%); ν_{max}(nujol)/cm^{-1} 3332 (OH), 1586, 1565 and 1499; δ_H(300 MHz, $CDCl_3$) 2.17 [1 H, br s, OH], 3.65–3.68 [2 H, m, AA′ portion of AA′BB′, C(1)H], 3.80–3.83 [2 H, m, BB′ portion of AA′BB′, C(2)H], 4.73 [2 H, s, C(6′)CH_2], 7.38 [1 H, d, $J_{3',4'}$ 8.9, C(3′)H], 7.70 [1 H, dd, $J_{5',7'}$ 1.5 $J_{7',8'}$ 8.5, C(7′)H], 7.77

[1 H, s†, C(5′)H)], 8.00 [1 H, d, $J_{7',8'}$ 8.5, C(8′)H], 8.08 [1 H, d, $J_{3',4'}$ 8.9, C(4′)H]; δ_C(75 MHz, $CDCl_3$) 62.6 [C(2)], 72.5 [C(1)], 73.4 [C(6′)CH_2], 123.3 [C(3′)], 126.4 [C(5′)], 127.3 [C(4a′)], 129.5 [C(8′)], 130.8 [C(7′)], 137.8 [C(6′)], 139.4 [C(4′)], 148.2 [C(8a′)], 151.4 [C(2′)]; *m/z* (EI) 239 ($M^{+\cdot}$ [^{37}Cl], 8), 237 ($M^{+\cdot}$ [^{35}Cl], 24), 194 (8), 192 (24), 178 ($M^{+\cdot}$ [^{37}Cl] − $HO(CH_2)_2O$, 40), 176 ($M^{+\cdot}$ [^{35}Cl] − $HO(CH_2)_2O$, 100).

2-Chloro-6-[(3-hydroxypropoxy)methyl]quinoline 32. The general procedure described above was used with aluminium chloride (1.06 g, 7.99 mmol) in dry THF (6 mL), lithium aluminium hydride (0.173 g, 4.56 mmol) and acetal **28** (0.95 g, 3.80 mmol) dissolved in dry THF (12 mL) with heating at reflux for 5 h. Following workup and chromatography using 3 : 1 dichloromethane–ethyl acetate as eluant, pure **32** (0.735 g, 77%) (R_f 0.20) was isolated as a white fluffy solid, mp 58–60 °C. (Found: C, 62.1; H, 5.55; N, 5.65%. $C_{13}H_{14}ClNO_2$ requires C, 62.05; H, 5.6; N, 5.55%); ν_{max}(nujol)/cm^{-1} 3307 (OH), 1585, 1562 and 1502; δ_H(600 MHz, $CDCl_3$) 1.91 [2 H, quin, *J* 6.0, C(2)H], 2.21 [1 H, br s, OH], 3.72 [2 H, t, *J* 6.0, C(1)H], 3.81 [2 H, t, *J* 6.0, C(3)H], 4.69 [2 H, s, C(6′)CH_2], 7.38 [1 H, d, $J_{3',4'}$ 8.4, C(3′)H], 7.69 [1 H, dd, $J_{5',7'}$ 1.8 $J_{7',8'}$ 8.4, C(7′)H], 7.76 [1 H, s†, C(5′)H], 8.00 [1 H, d, $J_{7',8'}$ 8.4, C(8′)H], 8.08 [1 H, d, $J_{3',4'}$ 8.4, C(4′)H]; δ_C(150 MHz, $CDCl_3$) 32.9 [C(2)], 62.2 [C(3)], 70.2 [C(1)], 73.3 [C(6′)CH_2], 123.2 [C(3′)], 126.2 [C(5′)], 127.3 [C(4a′)], 129.3 [C(8′)], 130.9 [C(7′)], 138.0 [C(6′)], 139.6 [C(4′)], 148.0 [C(8a′)], 151.2 [C(2′)]; *m/z* (EI) 253 ($M^{+\cdot}$ [^{37}Cl], 8), 251 ($M^{+\cdot}$ [^{35}Cl], 22), 194 (30), 192 (100), 178 ($M^{+\cdot}$ [^{37}Cl] − $HO(CH_2)_3O$, 28), 176 ($M^{+\cdot}$ [^{35}Cl] − $HO(CH_2)_3O$, 68).

2-Chloro-7-[(2-hydroxyethoxy)methyl]quinoline 33. The general procedure described above was used with aluminium chloride (0.715 g, 5.36 mmol) in dry THF (4 mL), lithium aluminium hydride (0.116 g, 3.06 mmol) and acetal **16** (0.600 g, 2.55 mmol) dissolved in dry THF (7.2 mL). Following workup sufficiently pure title compound **33** (0.585 g, 97%) was isolated. A portion was chromatographed using 3 : 1 dichloromethane–ethyl acetate as eluant (R_f 0.26) to afford purified **33** as an oil. ν_{max}(nujol)/cm^{-1} 3369 (OH), 1627, 1589, 1560 and 1500; δ_H(200 MHz, $CDCl_3$) 2.88 [1 H, br s, OH], 3.63–3.84 [4 H, m, C(1, 2)H], 4.74 [2 H, s, C(7′)CH_2], 7.34 [1 H, d, *J* 8.4, C(3′)H], 7.53 [1 H, dd, $J_{6',8'}$ 1.4 $J_{5',6'}$ 8.4, C(6′)H], 7.76 [1 H, d, $J_{5',6'}$ 8.4, C(5′)H], 7.93 [1 H, d†, $J_{6',8'}$ 1.4, C(8′)H], 8.05 [1 H, d†, $J_{3',4'}$ 8.4, C(4′)H]; δ_C(50 MHz, $CDCl_3$) 61.9 [C(2)], 72.0 [C(1)], 72.7 [C(7′)CH_2], 122.3 [C(3′)], 126.3 [C(4a′)], 126.5 [C(6′, 5′)], 127.8 [C(8′)], 138.7 [C(4′)], 141.3 [C(7′)], 147.9 [C(8a′)], 150.9 [C(2′)]; *m/z* (ESI) 238.0633 ([$C_{12}H_{13}{}^{35}ClNO_2$ + H]$^+$ requires 238.0635); (EI) 194 (31), 192 (100), 178 (29), 176 (83).

2-Chloro-7-[(3-hydroxypropoxy)methyl]quinoline 34. The general procedure described above was used with aluminium chloride (1.14 g, 8.52 mmol) in dry THF (6.4 mL), lithium aluminium hydride (0.183 g, 4.82 mmol) and acetal **17** (1.00 g, 4.02 mmol) dissolved in dry THF (12 mL). Following workup and chromatography using 3 : 1 dichloromethane–ethyl acetate as eluant pure **34** (0.710 g, 70%) (R_f 0.22) was isolated as an oil. ν_{max}(nujol)/cm^{-1} 3391 (OH), 1628, 1590 and 1567; δ_H(200 MHz, $CDCl_3$) 1.92 [2 H, quin, *J* 6.0, C(2)H], 3.66–3.72 [3 H, m, C(1)H and OH], 3.82 [2 H, t, *J* 6.0, C(3)H], 4.66 [2 H, s, C(7′)CH_2], 7.28 [1 H, d, $J_{3',4'}$ 8.6, C(3′)H], 7.47 [1 H, dd, $J_{6',8'}$ 1.2 $J_{5',6'}$ 8.6, C(6′)H], 7.70 [1 H, d, $J_{5',6'}$ 8.6, C(5′)H], 7.88 [1 H, d†, $J_{6',8'}$ 1.2, C(8′)H], 8.00 [1 H, d†, $J_{3',4'}$ 8.6, C(4′)H]; δ_C(50 MHz, $CDCl_3$) 32.2 [C(2)], 59.4 [C(3)], 68.0 [C(1)], 71.9 [C(7′)CH_2], 121.6 [C(3′)], 125.3 [C(4a′)], 125.9 [C(5′ or 6′)], 125.6 [C(5′ or 6′)], 127.3 [C(8′)], 138.4 [C(4′)], 141.3 [C(7′)], 147.1 [C(8a′)], 150.2 [C(2′)]; *m/z* (EI) 251.0713 ($C_{13}H_{14}{}^{35}ClNO_2$ requires 251.0713), 194 (32), 192 (100), 178 (33), 176 (79).

General procedure for the synthesis of 2-aminoquinolines 36–41 using the method of Kóródi[8]

The same procedure for the amination method of Kóródi as described above was used. Unless otherwise specified, at the completion of the reaction, the cooled reaction mixture was added to a solution of 10% sodium hydroxide (~15 mL mmol^{-1} 2-chloroquinoline), and was heated at reflux for a further 3 h. After cooling, the aqueous mixture was extracted with 3 : 1 chloroform–isopropanol (3 ×), the combined organic extracts were dried (Na_2SO_4) and then the solvent was removed. The pure amines were obtained following chromatography on silica gel using 3 : 1 dichloromethane–ethanol as eluant.

2-Amino-5-[(2-hydroxyethoxy)methyl]quinoline 36. 2-Chloro-5-[(2-hydroxyethoxy)methyl]quinoline **29** (0.350 g, 1.47 mmol) was treated with acetamide (1.74 g, 29.4 mmol) and potassium carbonate (1.02 g, 7.35 mmol) as described above. After workup and chromatography, the title compound **36** (0.020 g, 6%) (R_f 0.25) was isolated, mp 145–149 °C. ν_{max}(nujol)/cm^{-1} 3382 and 3337 and 3215 (OH and/or NH), 1658, 1614, 1573 and 1511; δ_H(200 MHz, CD_3OD) 3.57–3.72 [4 H, m, C(1, 2)H], 4.89 [2 H, s, C(5′)CH_2], 6.87 [1 H, d, $J_{3',4'}$ 9.2, C(3′)H], 7.26 [1 H, dd, $J_{6',8'}$ 3.0 $J_{6',7'}$ 5.4, C(6′)H], 7.44–7.51 [2 H, m, C(7′, 8′)H], 8.31 [1 H, d†, $J_{3',4'}$ 9.2, H(4′)]; δ_C(50 MHz, CD_3OD) 62.4 [C(2)], 72.3 [C(1)], 72.9 [C(5′)CH_2], 113.5 [C(3′)], 123.0 [C(4′a)], 124.7 [C(6′)], 125.8 [C(8′)], 130.5 [C(7′)], 136.1 [C(5′)], 136.8 [C(4)], 148.0 [C(8′a)], 157.8 [C(2′)]; *m/z* (EI) 218.1045 ($C_{12}H_{14}N_2O_2$ requires 218.1055), 173 (10), 158 (51), 157 (100).

2-Amino-5-[(3-hydroxypropoxy)methyl]quinoline 37. 2-Chloro-5-[(3-hydroxypropoxy)methyl]quinoline **30** (0.100 g, 0.397 mmol) was treated with acetamide (0.469 g, 7.94 mmol) and potassium carbonate (0.275 g, 1.99 mmol) as described above. After workup and chromatography, the title compound **37** (0.014 g, 15%) (R_f 0.16) was isolated, mp 93–95 °C. ν_{max}(nujol)/cm^{-1} 3453 and 3327 and 3154 (OH and/or NH), 1676, 1648, 1570 and 1512; δ_H(200 MHz, $CDCl_3$) 1.85 [2 H, quin, *J* 5.8, C(2)H], 2.72 [1 H, br s, OH], 3.67 [2 H, t, *J* 5.8, C(1)H], 3.74 [2 H, t, *J* 5.8, C(3)H], 4.84 [2 H, s, C(5′)CH_2], 5.18 [2 H, br s, NH_2], 6.77 [1 H, d, $J_{3',4'}$ 9.2, C(3′)H], 7.22 [1 H, d†, $J_{6',7'}$ 7.0, C(6′)H], 7.49 [1 H, dd, $J_{6',7'}$ 7.0 $J_{7',8'}$ 8.4, C(7′)H], 7.64 [1 H, d†, $J_{7',8'}$ 8.4, C(8′)H], 8.21 [1 H, d†, $J_{3',4'}$ 9.2, C(4′)H]; δ_C(50 MHz, $CDCl_3$) 32.5 [C(2)], 61.6 [C(3)], 69.1 [C(1)], 71.6 [C(5′)CH_2], 112.0 [C(3′)], 122.1 [C(4′a)], 124.1 [C(6′)], 126.2 [C(8′)], 129.6 [C(7′)], 134.2 [C(5′)], 135.3 [C(4′)], 147.3 [C(8′a)], 156.7 [C(2′)]; *m/z* (EI) 232.1200 ($C_{13}H_{16}N_2O_2$ requires 232.1212), 173 (34), 158 (100), 157 (85).

2-Amino-6-[(2-hydroxyethoxy)methyl]quinoline 38. 2-Chloro-6-[(2-hydroxyethoxy)methyl]quinoline **31** (0.122 g, 0.513 mmol) was treated with acetamide (0.606 g, 10.3 mmol) and potassium carbonate (0.355 g, 2.57 mmol) as described above. After cooling, saturated brine (20 mL) was added to the residue, and the resulting mixture was extracted with 3 : 1 chloroform–isopropanol (3 × 10 mL), dried (Na_2SO_4) and the solvent was removed. The residue was purified by preparative thin layer chromatography over two silica gel plates, using 3 : 1 dichloromethane–ethanol as eluant with successive developments, to afford the title compound **38** (0.003 g, 3%) as a white solid [characterisation for **38** is provided below, for its synthesis from the 2-(4-methoxybenzylamino)quinoline derivative **44**].

2-Amino-6-[(3-hydroxypropoxy)methyl]quinoline 39. 2-Chloro-6-[(3-hydroxypropoxy)methyl]quinoline **32** (0.125 g, 0.497 mmol) was treated with acetamide (0.586 g, 9.93 mmol) and potassium carbonate (0.343 g, 2.48 mmol) as described above. After cooling, some of the excess acetamide was removed by sublimation under a reduced pressure (oil bath temperature *ca.* 80 °C at 0.02 mm) for 1 h. The residue was resuspended in methanol (6 mL), filtered and the solvent was removed. The residue was purified once by column chromatography

and subsequently by preparative thin layer chromatography using 3 : 1 dichloromethane–ethanol as eluant, to afford the title compound **39** (0.003 g, 3%) as a while solid [characterisation for **39** is provided below, for its synthesis from the 2-(4-methoxybenzylamino)quinoline derivative **45**].

2-Amino-7-[(2-hydroxyethoxy)methyl]quinoline 40. 2-Chloro-7-[(2-hydroxyethoxy)methyl]quinoline **33** (0.350 g, 1.47 mmol) was treated with acetamide (1.74 g, 29.4 mmol) and potassium carbonate (1.02 g, 7.35 mmol) as described above. After workup and chromatography the title compound **40** (0.040 g, 13%) (R_f 0.19) was isolated, mp 135–138 °C. ν_{max}(nujol)/cm^{-1} 3408 and 3332 and 3205 (OH and/or NH), 1621, 1560 and 1517; δ_H(200 MHz, $CDCl_3$) 3.58–3.76 [4 H, m, C(1, 2)H], 4.67 [2 H, s, C(7′)CH_2], 6.80 [1 H, d, $J_{3',4'}$ 8.8, C(3′)H], 7.25 [1 H, dd, $J_{6',8'}$ 1.6 $J_{5',6'}$ 8.2, C(6′)H], 7.51 [1 H, dd, $J_{4',8'}$ 0.8 $J_{6',8'}$ 1.6, C(8′)H], 7.62 [1 H, d, J 8.2, C(5′)H], 7.91 [1 H, dd, $J_{4',8'}$ 0.8 $J_{3',4'}$ 8.8, C(4′)H]; δ_H(50 MHz, $CDCl_3$) 62.0 [C(2)], 71.8 [C(1)], 73.3 [C(7′)CH_2], 111.9 [C(3′)], 122.5 [C(6′)], 123.1 [C(4′a)], 124.4 [C(8′)], 127.9 [C(5′)], 138.2 [C(4′)], 140.2 [C(7′)], 147.3 [C(8′a)], 157.3 [C(2′)]; m/z (EI) 218.1055 ($C_{12}H_{14}N_2O_2$ requires 218.1055), 173 (12), 158 (100), 157 (99).

2-Amino-7-[(3-hydroxypropoxy)methyl]quinoline 41. 2-Chloro-7-[(3-hydroxypropoxy)methyl]quinoline **34** (0.250 g, 0.993 mmol) was treated with acetamide (1.17 g, 19.9 mmol) and potassium carbonate (0.686 g, 4.96 mmol) as described above. After workup and purification once by column chromatography and subsequently by preparative thin layer chromatography using 3 : 1 dichloromethane–ethanol as eluant, the title compound **41** (0.016 g, 7%) (R_f 0.13) was isolated, mp 88–90 °C. ν_{max}(nujol)/cm^{-1} 3463 and 3352 and 3159 (OH and/or NH), 1656, 1616, 1563 and 1517; δ_H(200 MHz, $CDCl_3$) 1.89 [2 H, quin, J 5.8 Hz, C(2)H], 2.50 [1 H, br s, OH], 3.70 [2 H, t, J 5.8, C(1)H], 3.82 [2 H, t, J 5.8, C(3)H], 4.66 [2 H, s, C(7′)CH_2], 5.16 [2 H, br s, NH_2], 6.71 [1 H, d, $J_{3',4'}$ 8.8, C(3′)H], 7.25 [1 H, dd, $J_{6',8'}$ 1.4 $J_{5',6'}$ 8.2, C(6′)H], 7.59–7.63 [2 H, m, C(5′, 8′)H], 7.87 [1 H, d†, $J_{3',4'}$ 8.8, H(4′)]; δ_C(50 MHz, $CDCl_3$) 32.5 [C(2)], 61.1 [C(3)], 69.0 [C(1)], 73.1 [C(7′)CH_2], 112.0 [C(3′)], 122.3 [C(6′)], 122.9 [C(4′a)], 123.7 [C(8′)], 127.9 [C(5′)], 138.2 [C(4′)], 140.5 [C(7′)], 147.0 [C(8′a)], 157.5 [C(2′)]; m/z (EI) 232.1200 ($C_{13}H_{16}N_2O_2$ requires 232.1212), 173 (17), 158 (100), 157 (34).

2-[(4-Methoxybenzyl)amino]-6-methylquinoline 43. 2-Chloro-6-methylquinoline **42** (0.100 g, 0.563 mmol) was stirred in 4-methoxybenzylamine (1.6 mL, 1.69 g, 12.3 mmol) at *ca.* 140 °C for 26 h. The excess 4-methoxybenzylamine was removed under a reduced pressure using a Kugelrohr apparatus and the residue was chromatographed on silica gel using 17 : 3 dichloromethane–ethyl acetate as eluant, to afford the title compound **43** (0.147 g, 94%), mp 55–58 °C. ν_{max}(nujol)/cm^{-1} 3317 (NH), 1613 and 1511; δ_H(600 MHz, $CDCl_3$) 2.42 [3 H, s, C(6)Me], 3.76 [3 H, s, C(4′)OMe], 5.59 [1 H, d, $J_{(1')CH,NH}$ 5.4, C(1′)CH_2], 5.06 [1 H, br s, NH], 6.55 [1 H, d, $J_{3,4}$ 9.3, C(3)H], 6.83–6.86 [2 H, m, AA′ portion of AA′XX′, C(3′, 5′)H], 7.28–7.31 [2 H, m, XX′ portion of AA′XX′, C(2′, 6′)H], 7.33 [1 H, d, $J_{5,7}$ 0.6, C(5)H], 7.35 [1 H, dd, $J_{5,7}$ 0.6 $J_{7,8}$ 8.4, C(7)H], 7.61 [1 H, d, $J_{7,8}$ 8.4, C(8)H], 7.69 [1 H, d, $J_{3,4}$ 9.3, C(4)H]; δ_C($CDCl_3$, 150 MHz) 21.75 [C(6)Me] 45.06 [C(1′)CH_2], 55.90 [C(4′)OMe], 111.88 [C(3)], 114.65 [C(3′, 5′)], 124.05 [C(4a)], 126.43 [C(8)], 127.28 [C(5)], 129.67 [C(2′, 6′)], 132.03 [C(1′)], 132.20 [C(6)], 132.21 [C(7)], 137.62 [C(4)], 146.67 [C(8a)], 156.95 [C(2)], 159.52 [C(4′)]; m/z (ESI) 279.1498 ($[C_{18}H_{18}N_2O + H]^+$ requires 279.1492); (EI) 136 (71), 121 (89).

2-Amino-6-methylquinoline 2. 2-[(4-Methoxybenzyl)amino]-6-methylquinoline **43** (0.029 g, 0.104 mmol) was stirred in trifluoromethanesulfonic acid (1.5 mL, 2.54 g, 17.0 mmol) at rt for 22 h. The mixture was carefully added to saturated sodium bicarbonate (20 mL) and extracted with dichloromethane (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and the solvent was removed to afford the title compound **2** (0.016 g, 95%). δ_H(200 MHz, $CDCl_3$)* 2.45 [3 H, s, C(6)Me], 5.22 [2 H, br s, NH_2], 6.75 [1 H, d, $J_{3,4}$ 8.8, C(3)H], 7.38–7.42 [2 H, m, C(5, 7)H], 7.57 [1 H, d, $J_{7,8}$ 8.8, C(8)H], 7.82 [1 H, $J_{3,4}$ 8.8, C(4)H].

*Data consistent with that presented in the literature.[7]

6-[(2-Hydroxyethoxy)methyl]-2-[(4-methoxybenzyl)amino]-quinoline 44. 2-Chloro-6-[(2-hydroxyethoxy)methyl]quinoline **31** (0.248 g, 1.04 mmol) was stirred in 4-methoxybenzylamine (3 mL, 3.15 g, 23.0 mmol) at *ca.* 140 °C for 30 h. After cooling, the excess 4-methoxybenzylamine was removed under a reduced pressure using a Kugelrohr apparatus and the residue was chromatographed over silica gel using 9 : 1 dichloromethane–ethanol as eluant to afford the title compound **44** (0.347 g, 98%) as a pale orange oil (R_f 0.61) that eventually solidified, mp 85–93 °C. ν_{max}(nujol)/cm^{-1} 3519 and 3311 (OH and/or NH), 1614, 1576, 1537 and 1513; δ_H(300 MHz, $CDCl_3$) 2.46 [1 H, br s. OH], 3.62–3.65 [2 H, m, AA′ portion of AA′BB′, C(1)H], 3.77–3.80 [2 H, m, BB′ portion of AA′BB′, C(2)H], 3.80 [3 H, s, C(4″)OMe], 4.62 [2 H, d, $J_{(1'')CH,NH}$ 4.5, C(1″)CH_2], 4.65 [2 H, s, C(6′)CH_2], 5.65 [1 H, br s, NH], 6.62 [1 H, d, $J_{3',4'}$ 9.0, C(3′)H], 6.85–6.90 [2 H, m, AA′ portion of AA′XX′, C(3″, 5″)H], 7.30–7.34 [2 H, m, XX′ portion of AA′XX′, C(2″, 6″)H], 7.51–7.55 [2 H, m, C(5′, 7′)H], 7.72 [1 H, d, $J_{7',8'}$ 8.1, C(8′)H], 7.81 [1 H, d, $J_{3',4'}$ 9.0, C(4′)H]; δ_C(75 MHz, $CDCl_3$) 46.1 [C(1″)CH_2], 55.9 [C(4″)OMe], 62.5 [C(2)], 72.1 [C(1)], 73.8 [C(6′)CH_2], 112.0 [C(3′)], 114.8 [C(3″, 5″)], 123.6 [C(4a′)], 126.3 [C(8′)], 127.2 [C(5′)], 129.6 [C(2″, 6″)], 130.6 [C(7′)], 131.6 [C(1″)], 132.7 [C(6′)], 138.6 [C(4′)], 147.2 [C(8a′)], 157.2 [C(2′)], 159.7 [C(4″)]; m/z (ESI-TOF) 339.1703 ($[C_{20}H_{22}N_2O_3 + H]^+$ requires 339.1703); (ESI) 339 ($[M + H^+]$, 12); MS/MS (339): 307 (25), 231 (100), 121 (55).

2-Amino-6-[(2-hydroxyethoxy)methyl]quinoline 38. 6-[(2-Hydroxyethoxy)methyl]-2-[(4-methoxybenzyl)amino]quinoline **44** (0.200 g, 0.591 mmol) was stirred in trifluoroacetic acid (3 mL) at *ca.* 60 °C for 1 h when thin layer chromatography indicated that all of the starting material had been consumed. After cooling, the excess trifluoroacetic acid was removed under a reduced pressure and the residue was dried under a high vacuum for an additional 1 h. The residue was resuspended in 10% aq. sodium hydroxide (15 mL) and extracted with 3 : 1 chloroform–isopropanol (4 × 15 mL). The combined organic layers were washed with a 1 : 1 mixture of 10% aq. sodium hydroxide/saturated brine (1 × 60 mL), dried (Na_2SO_4) then the solvent was removed. The residue was then chromatographed over silica gel using 9 : 1 dichloromethane–methanol as eluant to afford the title compound **38** (0.089 g, 69%) (R_f 0.17) as an off-white solid. A portion was re-chromatographed as described above to afford a white solid, mp 120–130 °C. (Found: C, 64.9; H, 6.35; N, 12.55%. $C_{12}H_{14}N_2O_2$ requires C, 66.05; H, 6.45; N, 12.85%); ν_{max}(nujol)/cm^{-1} 3430 and 3311and 3205 (OH and/or NH), 1643, 1625, 1611, 1570, 1507 and 1494; δ_H(300 MHz, d_6-acetone) 2.90 [1 H, br s, OH], 3.55–3.59 [2 H, m, AA′ portion of AA′BB′, C(1)H], 3.67–3.70 [2 H, m, BB′ portion of AA′BB′, C(2)H], 4.61 [2 H, s, C(6′)CH_2], 6.85 [1 H, d, $J_{3',4'}$ 8.9, C(3′)H], 7.47–7.53 [2 H, m, C(7′, 8′)H], 7.60 [1 H, s†, C(5′)H], 7.89 [1 H, d, $J_{3',4'}$ 8.9, C(4′)]; δ_C(75 MHz, d_6-acetone) 62.1 [C(2)], 72.8 [C(1)], 73.5 [C(6′)CH_2], 113.2 [C(3′)], 123.9 [C(4a′)], 126.7 [C(8′)], 127.2 [C(5′)], 130.1 [C(7′)], 133.2 [C(6′)], 138.1 [C(4′)], 148.7 [C(8a′)], 159.2 [C(2′)]; m/z (ESI) 219.1127 ($[C_{12}H_{14}N_2O_2 + H]^+$ requires 219.1128); (EI) 174 (15), 173 (40), 172 (30), 158 ($M^{+\cdot} - HO(CH_2)_2O + H$, 18), 157 ($M^{+\cdot} - HO(CH_2)_2O$, 100).

6-[(3-Hydroxypropoxy)methyl]-2-[(4-methoxybenzyl)amino]-quinoline 45. 2-Chloro-6-[(3-hydroxypropoxy)methyl]quinoline **32** 0.114 g, 0.453 mmol) was stirred in 4-methoxybenzylamine (1.5 mL, 1.58 g, 11.5 mmol) at *ca.* 140 °C for 30 h. After cooling, the excess 4-methoxybenzylamine was removed under a reduced pressure using a Kugelrohr apparatus and the residue was chromatographed over silica gel using 9 : 1 dichloromethane–ethanol as eluant to afford the title compound **45** (0.145 g, 91%) as a pale orange oil (R_f 0.27) that eventually solidified,

mp 85–90 °C. (Found: C, 69.75; H, 7.15; N, 7.7%. $C_{21}H_{24}N_2O_3$ requires C, 71.55; H, 6.85; N, 7.95%); ν_{max}(nujol)/cm^{-1} 3418 and 3296 (OH and/or NH), 1615, 1580, 1536 and 1511; δ_H(300 MHz, $CDCl_3$) 1.88 [2 H, quin, J 5.8, C(2)H], 3.50 [1 H, br s, OH], 3.69 [2 H, t, J 5.8, C(1)H], 3.78–3.81 [5 H, m, C(3)H and C(4″)OMe], 4.60 [2 H, s, C(6′)CH_2], 4.63 [2 H, d, $J_{C(1'')CH,NH}$ 5.3, C(1″)CH_2], 5.82 [1 H, br s, NH], 6.65 [1 H, d, $J_{3',4'}$ 9.0, C(3′)H], 6.85–6.90 [2 H, m, AA′ portion of AA′XX′, C(3″, 5″)H], 7.30–7.35 [2 H, m, XX′ portion of AA′XX′, C(2″, 6″)H], 7.51–7.54 [2 H, m, C(5′, 7′)H], 7.71 [1 H, d, $J_{7',8'}$ 8.4, C(8′)H], 7.82 [1 H, d, $J_{3',4'}$ 9.0, C(4′)H]; δ_C(75 MHz, $CDCl_3$) 32.8 [C(2)], 46.0 [C(1″)CH_2], 55.9 [C(4″)OMe], 62.2 [C(3)], 69.6 [C(1)], 73.7 [C(6′)CH_2], 112.1 [C(3′)], 114.7 [C(3″, 5″)], 123.7 [C(4a′)], 126.8 [C(8′)], 127.0 [C(5′)], 129.7 [C(2″, 6″)], 130.2 [C(7′)], 131.8 [C(1″)], 132.5 [C(6′)], 138.1 [C(4′)], 148.0 [C(8a′)], 157.4 [C(2′)], 159.6 [C(4″)]; m/z (ESI-TOF) 353.1866 ([$C_{21}H_{24}N_2O_3$ + H]$^+$ requires 353.1860); (ESI) 353 ([M + H$^+$], 12); MS/MS (353): 321 (25), 245 (100), 157 (10), 121 (52).

2-Amino-6-[(3-hydroxypropoxy)methyl]quinoline 39. 6-[(3-Hydroxypropoxy)methyl]-2-[(4-methoxybenzyl)amino]quinoline **45** (0.100 g, 0.284 mmol) was stirred in trifluoroacetic acid (1.5 mL) at *ca.* 60 °C for 1 h when thin layer chromatography indicated that all of the starting material had been consumed. The reaction was worked up using the same procedure described for the synthesis of **38** above. Following successive chromatography of the crude product over silica gel using 9 : 1 dichloromethane–methanol as eluant, the title compound **39** (0.039 g, 59%) (R_f 0.13) was isolated as a white solid, mp 118–128 °C. (Found: C, 67.25; H, 7.05; N, 12.05%. $C_{13}H_{16}N_2O_2$ requires C, 67.2; H, 6.95; N, 12.05%); ν_{max}(nujol)/cm^{-1} 3428 and 3311 and 3185 (OH and/or NH), 1640, 1624, 1610, 1567, 1507 and 1483; δ_H(300 MHz, d_6-acetone) 1.80 [2 H, quin, J 6.3, C(2)H], 2.95 [1 H, br s, OH], 3.60 [2 H, t, J 6.3, C(1 or 3)H], 3.65 [2 H, t, J 6.3, C(1 or 3)H], 4.56 [2 H, s, C(6′)CH_2], 5.86 [2 H, br s, NH_2], 6.85 [1 H, d, $J_{3',4'}$ 9.0, C(3′)H], 7.47 [1 H, dd, $J_{5',7'}$ 1.8 $J_{7',8'}$ 8.6, C(7′)H], 7.51 [1 H, d, $J_{7',8'}$ 8.6, C(8′)H], 7.58 [1H, s†, C(5′)H] 7.89 [1 H, d, $J_{3,4}$ 9.0, C(4′)H]; δ_H(75 MHz, d_6-acetone) 33.9 [C(2)], 59.9 [C(3)], 68.3 [C(1)], 73.3 [C(6′)CH_2], 113.4 [C(3′)], 123.7 [C(4a′)], 125.6 [C(8′)], 127.1 [C(5′)], 130.3 [C(7′)], 133.7 [C(6′)], 138.8 [C(4′)], 147.5 [C(8a′)], 159.0 [C(2′)]; m/z (EI) 232 (M$^{+\cdot}$, 50), 174 (6), 173 (55), 158 (M$^{+\cdot}$ − HO$(CH_2)_3$O + H, 40), 157 (M$^{+\cdot}$ − HO$(CH_2)_3$O, 100).

General procedure for synthesis of 2-acetamidoquinolines from 2-chloroquinolines

A mixture of the 2-chloroquinoline (1 eq.), acetamide (~80 eq.) and potassium carbonate (5 eq.) was heated at reflux for 14 h.* After cooling, the mixture was added to water and extracted with dichloromethane (3 ×). The combined organic extracts were washed with water (1 ×) dried (Na_2SO_4) and the solvent was removed. Unless otherwise specified, the residue was purified by filtration through silica gel using 17 : 3 dichloromethane–ethyl acetate as eluant to afford the pure 2-acetamidoquinoline.

*When performing this reaction on a large scale, an air condenser with a large diameter should be used to avoid blockage of the condenser with sublimed acetamide during the reaction.

***N*-(6-Methylquinolin-2-yl)acetamide 49 (small scale).** 2-Chloro-6-methylquinoline **42** (0.250 g, 1.40 mmol) was treated with acetamide (7.07 g, 0.120 mol) and potassium carbonate (0.973 g, 7.04 mmol) for 15 h, as described above. Following workup, the ^{1}H NMR spectrum of the crude product indicated that the title compound **49** was the major product, however a small amount (~15%) of a mixture of the corresponding the 2-aminoquinoline **2** and quinolin-2(1*H*)-one **50** was also present, as evidenced by the presence of diagnostic chemical shifts observed in samples of **2**[7] and **50**[14] prepared by literature methods. The crude product was chromatographed on silica gel using 3 : 1 dichloromethane–ethyl acetate as eluant to afford the pure title compound **49** (0.190 g, 68%) (R_f 0.33) as white crystals, mp 181–184 °C. (Found: C, 72.1; H, 6.1; N, 14.0%. $C_{12}H_{12}N_2O$ requires C, 72.0; H, 6.05; N, 14.0%); ν_{max}(nujol)/cm^{-1} 3240 (NH), 1686, 1661 (CO), 1597, 1577, 1536 and 1490; δ_H(300 MHz, $CDCl_3$) 2.17 [3 H, s, CH_3CO], 2.49 [3 H, s, C(6)Me], 7.48 [1H, dd, $J_{5,7}$ 1.8 $J_{7,8}$ 8.4, C(7)H], 7.53 [1 H, s†, C(5)H], 7.72 [1 H, d, $J_{7,8}$ 8.4, C(8)H], 8.08 [1 H, d, $J_{3,4}$ 8.9, C(4)H], 8.39 [1 H, br d, $J_{3,4}$ 8.9, C(3)H], 9.56 [1 H, br s, NH]; δ_C(75 MHz, $CDCl_3$) 22.0, [C(6)Me], 25.4 [CH_3CO], 115.2 [C(3)], 126.9 [C(4a)], 127.2 [C(5, 8)], 132.9 [C(7)], 135.7 [C(6)], 138.8 [C(4)], 145.2 [C(8a)], 151.3 [C(2)], 170.1 [CO]; m/z (EI) 200 (M$^{+\cdot}$, 35), 159 (10), 158 (M$^{+\cdot}$ − CH_2=C=O, 100), 157 (M$^{+\cdot}$ − CH_2=C=O–H, 30).

***N*-(6-Methylquinolin-2-yl)acetamide 49 (large scale).** 2-Chloro-6-methylquinoline **42** (7.54 g, 0.0424 mol) was treated with acetamide (200 g, 3.4 mol) and potassium carbonate (29.33 g, 0.212 mol) for 14 h as described above. Following workup and filtration through silica gel as described above, the title compound **49** (3.301 g, 39%) (R_f 0.17) was isolated as white crystals (data provided above). The eluant was changed to 9 : 1 dichloromethane–ethanol and the quinolin-2(1*H*)-one by-product **50** (2.215 g, 31%) was also isolated as an orange–brown solid, as evidenced by the presence of diagnostic chemical shifts observed for **50** prepared by a literature method.[14]

***N*-(5-Methylquinolin-2-yl)acetamide 56/*N*-(7-methylquinolin-2-yl)acetamide 57.** A mixture of 2-chloro-5-methylquinoline **6** and 2-chloro-7-methylquinoline **7** (5.00 g, 28 mmol) was treated with acetamide (82.7 g, 1.4 mol) and potassium carbonate (19.3 g, 0.14 mol) for 16 h as described above. Following workup as described above, the residue was filtered through silica gel using 9 : 1 dichloromethane–ethyl acetate as eluant to afford the mixture of the title compounds **56** and **57** (2.92 g, 52%). ν_{max}(nujol)/cm^{-1} 1709, 1661 (CO), 1603 and 1509; δ_H(300 MHz, $CDCl_3$) 2.18 [3 H, s, *CH_3CO], 2.30 [3 H, s, CH_3CO], 2.55 [3 H, s, C(7*)Me], 2.68 [3 H, s, C(5)Me], 7.29–7.33 [2 H, m, C(6, 6*)H], 7.57 [1 H, dd, J 7.1 J 8.5, C(7)H], 7.61 [1 H, d, $J_{4,8}$ 0.6, C(8*)H], 7.67–7.70 [2 H, m, C(5*, 8)H], 8.18 [1 H, dd, $J_{4,8}$ 0.6 $J_{3,4}$ 9.0, C(4*)H], 8.39 [1H, dd, $J_{4,8}$ 0.6 $J_{3,4}$ 9.3, C(4)H], 8.44 [1 H, br d, $J_{3,4}$ 9.0, C(3*)H], 8.51 [1 H, br d, $J_{3,4}$ 9.3, C(3)H], 10.53 [2 H, br s, *NH and NH]; m/z (EI) 200.0958 ($C_{12}H_{12}N_2O$ requires 200.0950), 158 (67).

* Refers to **57**.

***N*-[6-(Bromomethyl)quinolin-2-yl]acetamide 46.** A mixture of *N*-(6-methylquinolin-2-yl)acetamide **49** (1.500 g, 7.5 mmol), *N*-bromosuccinimide (1.47 g, 8.24 mmol), and benzoyl peroxide (0.18 g, 0.75 mmol) was heated at reflux in benzene (10 mL) for 5 h. After cooling, the benzene was removed under a reduced pressure and the residue was dissolved in dichloromethane (50 mL). The dichloromethane solution was washed with 10% $NaHCO_3$ (3 × 50 mL), dried (Na_2SO_4), then the solvent was removed to afford 1.96 g of a light brown solid. Following chromatography over silica gel using 17 : 3 dichloromethane–ethyl acetate as eluant, the title compound **49** (1.175 g, 56%) (R_f 0.26) was afforded as a pale yellow fluffy solid, mp 185–187 °C. (Found: C, 51.9; H, 4.1; N, 9.8%; $C_{12}H_{11}BrN_2O$ requires C, 51.6; H, 3.95; N, 10.05%); ν_{max}(nujol)/cm^{-1} 3190 (NH), 1673 (CO), 1602, 1580, 1540 and 1494; δ_H(300 MHz, $CDCl_3$) 2.25 [3 H, s, CH_3], 4.65 [2 H, s, C(6)CH_2], 7.69 [1 H, dd, $J_{5,7}$ 2.1 $J_{7,8}$ 8.7, C(7)H], 7.78–7.81 [2 H, m, C(5, 8)H], 8.14 [1 H, d, $J_{3,4}$ 9.0, C(4)H], 8.43 [1 H, br d, $J_{3,4}$ 9.0, C(3)H], 8.66 [1 H, br s, NH]; δ_C(75 MHz, $CDCl_3$) 25.6 [CH_3], 33.6 [C(6)CH_2], 115.4 [C(3)], 126.4 [C(5)], 127.4 [C(4a)], 128.3 [C(8)], 132.5 [C(7)], 135.9 [C(6)], 140.5 [C(4)], 144.9 [C(8a)], 152.0 [C(2)], 170.5 [CO]; m/z (EI) 280 (M$^{+\cdot}$ [^{81}Br], 6), 278 (M$^{+\cdot}$ [^{79}Br], 6), 200 (M$^{+\cdot}$ − Br + H, 12), 199 (M$^{+\cdot}$ − Br, 78), 158 (M$^{+\cdot}$ − Br–CH_2=C=O + H, 15), 157 (M$^{+\cdot}$ − Br–CH_2=C=O, 100).

***N*-[5-(Bromomethyl)quinolin-2-yl]acetamide 47/*N*-[7-(bromomethyl)quinolin-2-yl]acetamide 48.** The mixture of *N*-(5-methylquinolin-2-yl)acetamide **56** and *N*-(7-methylquinolin-2-yl)acetamide **57** prepared above (2.55 g, 12.7 mmol), *N*-bromosuccinimide (2.26 g, 12.7 mmol) and benzoyl peroxide (0.310 g, 1.27 mmol) were heated at reflux in benzene (8 mL) for 2.5 h. After cooling, the mixture was filtered, and the filtrate was evaporated under a reduced pressure. The residue was chromatographed through silica gel using 17 : 3 dichloromethane–ethyl acetate as eluant to afford the mixture of the title compounds **47** and **48** (1.64 g, 46%) (R_f 0.24). ν_{max}(nujol)/cm^{-1} 3010 (NH), 1663 (CO), 1639, 1607 and 1580; δ_H(300 MHz, $CDCl_3$) 2.23 [6 H, s, CH_3CO and CH_3CO*], 4.63 [2 H, s, C(7*)CH_2], 4.88 [3 H, s, C(5)CH_2], 7.45–7.49 [2 H, m, C(6*, 6,)H], 7.57 [1 H, dd, *J* 7.2 *J* 8.4, C(7)H], 7.67–7.70 [3 H, m, C(5*, 8*, 8)H], 8.15 [1 H, d, $J_{3,4}$ 8.7, C(4*)H], 8.42–8.55 [3 H, m, C(3*, 3, 4)H], 9.28 [1 H, br s, *NH or NH], 9.37 [1H, br s, *NH or NH]; *m*/*z* (EI) 278.0053 ($C_{12}H_{11}{}^{79}BrN_2O$ requires 278.0055), 238 ($M^{+\cdot}$ [^{81}Br]–CH_2=C=O, 36), 236 ($M^{+\cdot}$ [^{79}Br]–CH_2=C=O, 39), 199 ($M^{+\cdot}$ − Br, 100), 157 ($M^{+\cdot}$ − Br–CH_2=C=O, 65).

* Refers to **48**.

***N*-{[6-(Acetyloxy)methyl]quinolin-2-yl}acetamide 51.** A mixture of *N*-[6-(bromomethyl)quinolin-2-yl]acetamide **46** (0.350 g, 1.25 mmol) and potassium acetate (0.246 g, 2.50 mmol) was stirred in DMF (8 mL) at *ca.* 80 °C for 14 h. After cooling, the mixture was diluted with ethyl acetate (60 mL) and washed with water (3 × 60 mL) and brine (3 × 60 mL). The resulting ethyl acetate solution was dried (Na_2SO_4) then the solvent was removed to afford the title compound **51** (0.282 g, 87%) as a yellow solid. This material could be used for further synthesis without additional purification, however a portion was further purified by silica gel chromatography using 3 : 1 dichloromethane–ethyl acetate as eluant (R_f 0.25) to afford a white solid, mp 140–145 °C. (Found: C; 64.95; H 5.65; N 10.05%. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.45; N, 10.85%); ν_{max}(nujol)/cm^{-1} 3309 (NH), 1699 and 1689 (CO), 1602, 1580 and 1493; δ_H(300 MHz, $CDCl_3$) 2.15 [3 H, s, CH_3CO_2], 2.23 [3 H, s, CH_3CON], 5.26 [2H, s, C(6)CH_2], 7.64 [1 H, dd, $J_{5,7}$ 1.7 $J_{7,8}$ 8.6, C(7)H], 7.77 [1 H, d, $J_{5,7}$ 1.7, C(5)H], 7.81 [1 H, d, $J_{7,8}$ 8.6, C(8)H], 8.17 [1 H, d, $J_{3,4}$ 8.9, C(4)H], 8.44 [1 H, br d, $J_{3,4}$ 8.9, C(3)H], 8.96 [1 H, br s, NH]; δ_C(75 MHz, $CDCl_3$) 21.5 [CH_3CO_2], 25.3 [CH_3CON], 66.4 [C(6)CH_2], 115.5 [C(3)], 126.5 [C(4a)], 127.6 [C(5)], 128.0 [C(8)], 130.6 [C(7)], 133.5 [C(6)], 139.2 [C(4)], 146.6 [C(8a)], 152.2 [C(2)], 170.1 [CH_3CON], 171.4 [CH_3CO_2]; *m*/*z* (EI) 258.1004 ($C_{14}H_{14}N_2O_3$ requires 258.1004), 216 ($M^{+\cdot}$ − CH_2=C=O, 40), 199 ($M^{+\cdot}$ − CH_3CO_2, 5), 174 ($M^{+\cdot}$ − CH_2=C=O–CH_3CO + H, 38), 157 ($M^{+\cdot}$ − CH_3CO_2 –CH_2=C=O, 100).

***N*-{[5-(Acetyloxy)methyl]quinolin-2-yl}acetamide 58/*N*-{[7-(acetyloxy)methyl]quinolin-2-yl}acetamide 59.** The mixture of *N*-[5-(bromomethyl)quinolin-2-yl]acetamide **47** and *N*-[7-(bromomethyl)quinolin-2-yl]acetamide **48** prepared above (0.875 g, 3.13 mmol) was treated with potassium acetate (0.614 g, 6.26 mmol) in DMF (20 mL) with stirring at *ca.* 80 °C for 16 h. After cooling, the reaction mixture was diluted with ethyl acetate (50 mL), and the solution was washed with water (4 × 50 mL) and brine (2 × 50 mL). The organic phase was dried (Na_2SO_4) and the solvent was removed. The residue was chromatographed on silica gel using 4 : 1 dichloromethane–ethyl acetate as eluant to afford the title compound **58** (0.260 g, 32%) (R_f 0.19), mp 140–145 °C. In addition, the title compound **59** (0.210 g, 26%) (R_f 0.15) was isolated as a *ca.* 19 : 1 mixture with **58**, mp 124–126 °C. An additional 0.100 g (10%) of **59–58** as a 4 : 1 mixture was also isolated.

58: (found: C, 65.05; H, 5.45; N, 10.55%. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.45; N, 10.85%); ν_{max}(nujol)/cm^{-1} 3427 and 3213 (NH), 1727 and 1704 (CO), 1671, 1602, 1583 and 1503; δ_H(200 MHz, $CDCl_3$) 2.11 [3 H, s, CH_3CO_2 or CH_3CON], 2.35 [3 H, s, CH_3CO_2 or CH_3CON], 5.52 [2 H, s, C(5)CH_2], 7.50 [1 H, d, $J_{6,7}$ 7.2, C(6)H], 7.63 [1 H, dd, $J_{6,7}$ 7.2 $J_{7,8}$ 8.4, C(7)H], 7.82 [1 H, d, $J_{7,8}$ 8.4, C(8)H], 8.38 [1 H, d, $J_{3,4}$ 9.0, C(4)H], 8.48 [1 H, br d, $J_{3,4}$ 9.0, C(3)H], 9.07 [1 H, br s, NH]; δ_C(50 MHz, $CDCl_3$) 21.0 [CH_3CO_2 or CH_3CON], 24.8 [CH_3CO_2 or CH_3CON], 63.8 [C(5)CH_2], 114.9 [C(3)], 124.8 [C(4a)], 126.6 [C(6)], 128.3 [C(8)], 129.6 [C(7)], 132.2 [C(5)], 134.8 [C(4)], 146.8 [C(8a)], 151.4 [C(2)], 169.7 [CH_3CO_2 or CH_3CON], 170.8 [CH_3CO_2 or CH_3CON]; *m*/*z* (EI) 258 ($M^{+\cdot}$, 45), 216 ($M^{+\cdot}$ − CH_2=C=O, 41), 174 ($M^{+\cdot}$ − CH_2=C=O–CH_3CO + H, 100), 157 ($M^{+\cdot}$ − CH_2=C=O–CH_3CO_2, 52).

59: (found: C, 65.05; H, 5.35; N, 10.65%. $C_{14}H_{14}N_2O_3$ requires C, 65.1; H, 5.45; N, 10.85%); ν_{max}(nujol)/cm^{-1} 3483 and 3198 (NH), 1740 and 1706 (CO), 1666, 1600, 1579, 1535 and 1508; δ_H(200 MHz, $CDCl_3$) 2.15 [3 H, s, CH_3CO_2 or CH_3CON], 2.25 [3 H, s, CH_3CO_2 or CH_3CON], 5.29 [2 H, s, C(7)CH_2], 7.42 [1 H, dd, $J_{6,8}$ 1.2 $J_{5,6}$ 8.2, C(6)H], 7.84 [1 H, s, C(8)H], 7.85 [1 H, d, $J_{5,6}$ 8.2, C(5)H], 8.17 [1 H, d, $J_{3,4}$ 9.0, C(4)H], 8.43 [1 H, br d, $J_{3,4}$ 9.0, C(3)H], 8.80 [1 H, br s, NH]; δ_C(50 MHz, $CDCl_3$) 21.0 [CH_3CO_2 or CH_3CON], 24.8 [CH_3CO_2 or CH_3CON], 65.9 [C(7)CH_2], 114.9 [C(3)], 124.9 [C(8)], 125.8 [C(4a)], 126.0 [C(6)], 128.1 [C(5)], 138.2 [C(7)], 138.6 [C(4)], 146.3 [C(8a)], 151.8 [C(2)], 169.7 [CH_3CO_2 or CH_3CON], 170.8 [CH_3CO_2 or CH_3CON]; *m*/*z* (EI) 258 ($M^{+\cdot}$, 70), 216 ($M^{+\cdot}$ − CH_2=C=O, 41), 174 ($M^{+\cdot}$ − CH_2=C=O–CH_3CO + H, 80), 157 ($M^{+\cdot}$ − CH_2=CvO–CH_3CO_2, 31), 43 (100).

***N*-[6-(Hydroxymethyl)quinolin-2-yl]acetamide 52/2-amino-6-(hydroxymethyl)quinoline 53.** A mixture of *N*-{[6-(acetyloxy)methyl]quinolin-2-yl}acetamide **51** (0.215 g, 0.83 mmol) and potassium carbonate (0.057 g, 0.42 mmol) was stirred in methanol (7 mL) at rt for 2 h. The solvent was removed and the residue was chromatographed over silica gel using 9 : 1 dichloromethane–methanol as eluant to afford **52** (0.130 g, 72%) (R_f 0.31) as a pale yellow solid, mp 170–174 °C. The eluant was changed to 3 : 1 dichloromethane–methanol and **53** (0.029 g, 20%) (R_f 0.31) was also isolated as a white powder, mp 210–220 °C.

52: (found: C, 66.7; H, 5.65; N, 12.95%. $C_{12}H_{12}N_2O_2$ requires C, 66.65; H, 5.6; N, 12.95%); ν_{max}(nujol)/cm^{-1} 3337 (NH), 1701, 1674 (CO), 1599, 1580 and 1493; δ_H(300 MHz, d_6-acetone) 2.26 [3 H, s, CH_3], 4.40 [1 H, t, *J* 5.6, OH], 4.79 [2 H, d, *J* 5.6, C(6)CH_2], 7.66 [1 H, dd, $J_{5,7}$ 1.8 $J_{7,8}$ 8.7, C(7)H], 7.72 [1 H, d, $J_{7,8}$ 8.7, C(8)H], 7.82 [1 H, s†, C(5)H], 8.24 [1 H, d, $J_{3,4}$ 8.9, C(4)H], 8.40 [1 H, br d, $J_{3,4}$ 8.9, C(3)H], 9.66 [1 H, br s, NH]; δ_C(75 MHz, d_6-acetone) 24.6 [CH_3], 64.5 [C(6)CH_2], 115.0 [C(3)], 125.3 [C(5)], 126.8 [C(4a)], 128.2 [C(8)], 129.9 [C(7)], 138.7 [C(6)], 140.1 [C(4)], 147.2 [C(8a)], 152.5 [C(2)], 170.2 [CO]; *m*/*z* (EI) 216 ($M^{+\cdot}$, 75), 174 ($M^{+\cdot}$ − CH_2=C=O, 100), 173 ($M^{+\cdot}$ − CH_2=CvO–H, 38), 157 ($M^{+\cdot}$ − CH_2=C=O–OH, 40).

53: ν_{max}(nujol)/cm^{-1} 3458 and 3311 (NH), 1681, 1633, 1626, 1610, 1568 and 1491; δ_H(300 MHz, d_6-DMSO) 4.55 [2 H, s, C(6)CH_2], 5.21 [1 H, br s, OH], 6.63 [2 H, br s, NH_2], 6.77 [1 H, d, $J_{3,4}$ 8.9, C(3)H], 7.41–7.48 [2 H, m, C(7, 8)H], 7.56 [1 H, s†, C(5)H], 7.92 [1 H, d, $J_{3,4}$ 8.9, C(4)H]; δ_C(75 MHz, d_6-DMSO) 62.8 [C(6)CH_2], 122.1 [C(4a)], 124.0 [C(5)], 124.9 [C(8)], 128.7 [C(7)], 135.8 [C(6)], 137.5 [C(4)], 145.6 [C(8a)], 158.2 [C(2)]; *m*/*z* (EI) 174.0792 ($C_{10}H_{10}N_2O$ requires 174.0793), 158 ($M^{+\cdot}$ − OH + H, 42), 157 ($M^{+\cdot}$ − OH, 32), 147 ($M^{+\cdot}$ − HCN, 25), 146 ($M^{+\cdot}$ − HCN–H, 42).

2-Amino-5-(hydroxymethyl)quinoline 60. *N*-{[5-(Acetyloxy)-methyl]quinolin-2-yl}acetamide **58** prepared above (0.080 g, 0.31 mmol) was treated with potassium carbonate (0.043 g, 0.31 mmol) in methanol (4 mL) with stirring at *ca.* 50 °C for 2 h. After cooling, the solvent was removed and the residue was chromatographed on silica gel using 4 : 1 dichloromethane–methanol as eluant to afford the title compound **60** (0.050 g, 93%) (R_f 0.21), mp 155–157 °C. ν_{max}(nujol)/cm^{-1} 3467 and 3319 and 3203 (OH and/or NH), 1686, 1618, 1564 and 1512; δ_H(200 MHz, $CDCl_3$) 1.25 [1 H, br s, OH], 4.91 [2 H, br s, NH_2], 5.03 [2 H, s, C(5)CH_2], 6.77 [1 H, d, $J_{3,4}$ 9.2, C(3)H], 7.26 [1 H,

d, $J_{6,7}$ 7.0, C(6)H], 7.51 [1 H, dd, $J_{6,7}$ 7.0 $J_{7,8}$ 8.4, C(7)H], 7.63 [1 H, d, $J_{7,8}$ 8.4, C(8)H], 8.27 [1 H, d, $J_{3,4}$ 9.0, C(4)H]; δ_C(150 MHz, d_6-DMSO) 62.74 [C(5)CH_2], 111.12 [br, C(3)], 120.29 [C(4a)], 120.58 [C(6)], 123.57 [br, C(8)], 128.96 [C(7)], 134.28 [C(5)], 138.49 [C(4)], 146.35 [C(8a)], 157.12 [C(2)]; *m/z* (EI) 174.0792 ($C_{10}H_{10}N_2O$ requires 174.0793), 157 (31), 145 (64), 128 (52).

2-Amino-7-(hydroxymethyl)quinoline 61. The *ca.* 19 : 1 mixture of **59–58** prepared above (0.120 g, 0.46 mmol) was treated with potassium carbonate (0.0640 g, 0.46 mmol) in methanol (5 mL) with stirring at *ca.* 50 °C for 2 h. After cooling, the solvent was removed and the residue was chromatographed on silica gel using 4 : 1 dichloromethane–methanol as eluant to afford the title compound **61** (0.035 g, 44%) (R_f 0.18) mp 153–159 °C. An additional 0.035 g (44%) of **60–61** as a mixture was also isolated.

61: ν_{max}(nujol)/cm^{-1} 3467 and 3317 and 3201 (OH and/or NH), 1686, 1624, 1563 and 1514; δ_H(600 MHz, d_6-DMSO) 1.93 [1 H, br s, OH], 3.83 [1 H, br s, NH], 4.56 [2 H, s, C(7)CH_2], 6.41 [1 H, br s, NH], 6.75 [1 H, br s, C(3)H], 7.12 [1 H, d, $J_{5,6}$ 8.1 Hz, C(6)H], 7.41 [1 H, br s, C(8)H], 7.58 [1H, d, $J_{5,6}$ 8.1 Hz, C(5)H], 7.88 [1 H, d, $J_{3,4}$ 9.0 Hz C(4)H].; δ_C(150 MHz, d_6-DMSO) 63.48 [C(7)CH_2], 112.67 [br, C(3)], 121.29 [br, C(6, 8)], 121.80 [C(4a)], 128.00 [C(5)], 138.11 [C4)], 144.38 [C(7)], 147.03 [C(8a)], 158.29 [C(2)]; *m/z* (EI) 174.0790 ($C_{10}H_{10}N_2O$ requires 174.0793), 157 (23), 145 (70), 128 (52).

***N*-{6-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-quinolin-2-yl}acetamide 54.** A mixture of *N*-[6-(bromomethyl)-quinolin-2-yl]acetamide **46** (0.342 g, 1.22 mmol) and potassium phthalimide (0.238 g, 1.29 mmol) was stirred in DMF (8 mL) at *ca.* 80 °C for 14 h. After cooling the mixture was diluted with ethyl acetate (60 mL) and washed with water (4 × 60 mL) and brine (2 × 60 mL). During the last three washes a precipitate formed in the organic layer, and this 'sticky' material was collected by filtration. The filtrate was then dried (Na_2SO_4) and the solvent was removed to afford the title compound **54** (0.224 g, 51%) as a pale yellow powder. The glassware used during workup was rinsed thoroughly with dichloromethane and the resulting extract was evaporated under a reduced pressure to afford additional 'sticky' material. The additional products isolated were combined and filtered through silica gel using 17 : 3 dichloromethane–ethyl acetate as eluant to afford an additional sample of analytically pure **54** (0.123 g, 29%) (R_f 0.13) as a white powder, mp 231–235 °C. (Total yield of **54**, 0.347 g, 80%). (Found: C, 69.65; H, 4.4; N, 12.15%. $C_{20}H_{15}N_3O_3$ requires C, 69.55; H, 4.4; N, 12.15%); ν_{max}(nujol)/cm^{-1} 3395 and 3334 (NH), 1768 (CO, asym), 1717 (CO, sym), 1706, 1603, 1581 and 1493; δ_H(300 MHz, $CDCl_3$) 2.20 [3 H, s, CH_3], 4.98 [2 H, s, C(6)CH_2], 7.69–7.72 [4 H, m, C(5′, 6′, 5*, 7*)H], 7.82–7.86 [3 H, m, C(4′, 7′, 8*)H], 8.12 [1 H, d, $J_{3,4}$ 8.9, C(4)], 8.38 [1 H, br d, $J_{3,4}$ 8.9, C(3)H], 8.73 [1 H, br s, NH]; δ_C(75 MHz, $CDCl_3$) 25.5 [CH_3], 42.0 [C(6)CH_2], 115.2 [C(3)], 124.1 [C(4′, 7′)], 126.7 [C(4a)], 128.0 [C(5)], 128.3 [C(8)], 131.4 [C(7)], 132.7 [C(3′a, 7′a)], 133.9 [C(6)], 134.8 [C(5′, 6′)], 139.5 [C(4)], 146.4 [C(8a)], 151.9 [C(2)], 168.7 [C(1′, 3′)], 169.9 [N*C*OCH$_3$]; *m/z* (EI) 345 ($M^{+\cdot}$, 85), 303 ($M^{+\cdot}$ − CH_2=C=O, 100), 157 ($M^{+\cdot}$ − CH_2=C=O–$C_8H_4NO_2$, 15).

*These assignments may be reversed.

2-Amino-6-(aminomethyl)quinoline 55. *N*-{6-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]quinolin-2-yl}acetamide **54** (0.216 g, 0.625 mmol) was heated at reflux in 20% aq. sodium hydroxide (10 mL) for 4 h. After cooling, this solution was extracted with 3 : 1 chloroform–isopropanol (5 × 15 mL), the combined organic extracts were dried (Na_2SO_4), then the solvent was removed to afford 0.056 g of a pale yellow solid. ^{1}H NMR analysis of this material indicated it consisted of the title compound **55** accompanied by a small amount (<5%) of **53**. This material was used in SH3 ligand binding studies without further purification. The presence of **53** was confirmed by mass spectrometry.

55: ν_{max}(nujol)/cm^{-1} 3306 and 3134 (NH), 1646, 1625, 1610, 1590, 1566 and 1494; δ_H(300 MHz, d_6-acetone) 1.29 [2 H, br s, CH_2NH_2 or $ArNH_2$], 4.50 [2 H, s, C(6)CH_2], 5.81 [2 H, br s, CH_2NH_2 or $ArNH_2$], 6.82 [1 H, d, $J_{3,4}$ 8.7, C(3H], 7.48 [2 H, m, C(7, 8)], 7.57 [1 H, s†, C(5)H], 7.85 [1 H, d, *J* 8.7, C(4)H]; δ_C(75 MHz, d_6-acetone) 55.5 [C(6)CH_2], 112.8 [C(3)], 124.1 [C(4a)], 126.5 [C(5, 8)], 130.5 [C(7)], 135.4 [C(6)], 137.9 [C(4)], 148.2 [C(8a)], 158.8 [C(2)]; *m/z* (EI) 173.0949 ($C_{10}H_{11}N_3$ requires 173.0953), 157 ($M^{+\cdot}$ − NH_2, 32), 145 ($M^{+\cdot}$ − H–HCN, 35), 43 (100).

53: *m/z* (EI) 174.0791 ($C_{10}H_{10}N_2O$ requires 174.0793) [a more thorough characterisation of **53** is provided above for its explicit synthesis from **51**].

Acknowledgements

We would like to thank Dr Jonathan Morris for directing us towards suitable methods for the deprotection of 4-methoxybenzylamines.

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