One-pot tandem Hurtley – retro-Claisen – cyclisation reactions in the synthesis of 3-substituted analogues of 5-aminoisoquinolin-1-one (5-AIQ), a water-soluble inhibitor of PARPs

Esther C. Y. Woon,[†] Peter T. Sunderland, Helen A. Paine, Matthew D. Lloyd, Andrew S. Thompson and Michael D. Threadgill*

Medicinal Chemistry, Department of Pharmacy & Pharmacology, University of Bath, Claverton Down, Bath BA2 7AY, UK

e-mail: m.d.threadgill@bath.ac.uk

Abstract

Poly(ADP-ribose)polymerase-1 (PARP-1) is an important target for drug design for several therapeutic applications. 5-Aminoisoquinolin-1-one (5-AIQ) is a highly water-soluble lead compound; synthetic routes to 3-substituted analogues were explored. Tandem Hurtley coupling of β-diketones with 2-bromo-3-nitrobenzoic acid, retro-Claisen acyl cleavage and cyclisation gave the corresponding 3-substituted 5-nitroisocoumarins. Treatment with ammonia at high temperature and reduction with tin(II) chloride gave eleven target 3-substituted 5-AIQs, which were all soluble in water (>1% *w*/*v*) as their HCl salts. Most were more potent than 5-AIQ as inhibitors of PARP-1 and of PARP-2 *in vitro*, the most active being 5-amino-3-methylisoquinolin-1-one (PARP-1: IC_{50} = 0.23 μM *vs*. IC_{50} = 1.6 μM for 5-AIQ). Some rationalisation of the SAR was achieved through molecular modelling.

1. Introduction

The poly(ADP-ribose)polymerases (PARPs) comprise a superfamily of enzymes which use NAD^+ to generate electrophilic ADP-ribose units to attach to substrate proteins to build poly-anionic poly(ADP-ribose) polymers.[1] Two of the isoform members of this superfamily, the archetypal PARP-1 and PARP-2, detect sites of damage in DNA and use this poly(ADP-ribosyl)ation to open the chromatin structure and initiate and regulate repair of DNA.[1-3] Other members of the superfamily (*e.g.* PARP-3, PARP-4 (vault mPARP) and PARPs-5a,b (the tankyrases) have other regulatory functions within the cell.[1-6] Inhibitors of PARP-1 are in clinical trial for the treatment of cancer[7-9] and have demonstrated beneficial activity in experimental models in a range of other therapeutic applications, including inflammation,[10,11] organ damage following ischaemia-reperfusion,[12,13] neurological damage,[14,15] organ trans-plant[16] and multiple sclerosis.[17]

The known pharmacophore for optimum inhibition of PARP-1 comprises a lactam fused to an aromatic ring (*e.g.* quinazolin-4-one, isoquinolin-1-one or phthalazin-1-one) or a similar primary benzamide where the conformation of the C=O—NH is held in the plane of the benzene ring by an intramolecular hydrogen bond. This benzamide amide motif is required for hydrogen bonding to the conserved Gly^{863} and Ser^{904} and π-stacking with Tyr^{907} in the (NAD^+)-nicotinamide-binding site. The clinical candidates olaparib **1**, veliparib **2** and rucaparib **3** (Figure 1) fit this model. 5-Aminoisoquinolin-1-one (5-AIQ, **4**, Figure 1) is an inhibitor of PARP-1 and PARP-2, which is highly water-soluble as its hydrochloride salt. Interestingly, **4** shows potent therapeutic activity in models *in vivo* of a range of diseases and

[†] Present address: Department of Pharmacy, National University of Singapore, Block S4, Science Drive 4, Singapore 117543, Republic of Singapore

disorders, including haemorrhagic shock,[18] myocardial infarction,[12] colitis[19] and cerebral ischaemia.[15] In the context of cancer, it inhibits angiogenesis[20] (PARP-1 regulates NF-κB) and is potently antimetastatic,[21] *inter alia*. Exploring the structure-activity relationships around this core, we have reported that 4-aryl-5-AIQs and 5-benzamidoisoquinolin-1-ones are isoform-selective inhibitors of PARP-2.[22,23] 6-Arylthieno[3,4-*c*]pyridin-4(5*H*)ones inhibit PARP-1,[24] so we proposed that the analogous 3-substituted-5-AIQs should be explored.

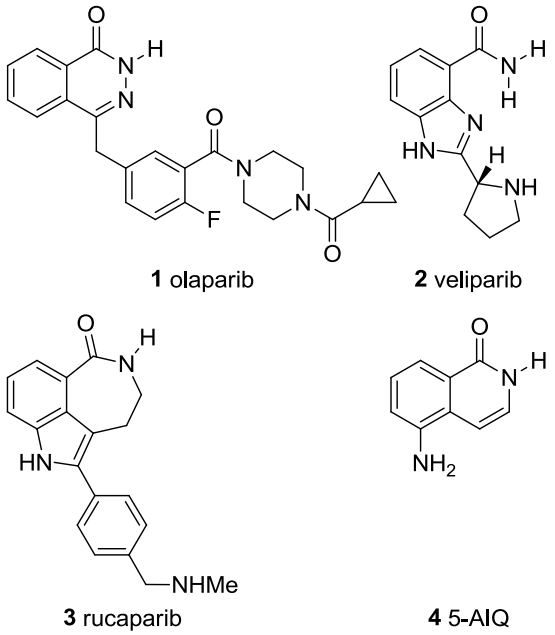
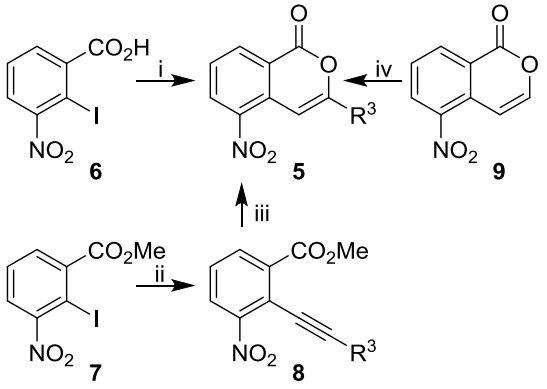


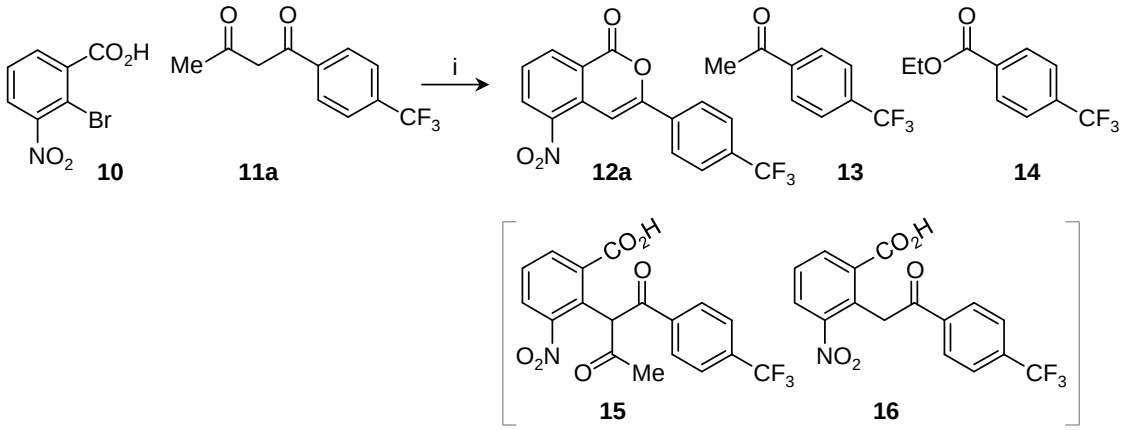
Figure 1. Structures of three inhibitors of PARP-1 in advanced clinical trial and of 5-AIQ.

We have previously reported the synthesis of **4** by condensation of methyl 2-methyl-3-nitrobenzoate with dimethylformamide dimethyl acetal (DMFDMA) to give 5-nitroisocoumarin, followed by conversion to 5-nitroisoquinolin-1-one with ammonia and reduction of the nitro group.[18] However, this method could not be extended to the 3-methyl analogue[25] and extension to the 3-aryl analogues was precluded by difficulty in accessing the required benzamide acetals. 3-Aryl-5-nitroisocoumarins **5** have been accessed by Castro-Stevens coupling of 2-iodo-3-nitrobenzoic acid **6** with arylethynes, followed by cyclisation *in situ* (Scheme 1) but this process was limited to three examples.[26] Sonogashira coupling of methyl 2-iodo-3-methylbenzoate **7** with phenylethynes was investigated, followed by cyclisation with Hg^{2+} as catalyst but this was only effective for one example (R^3 = Ph).[26] A more general but low-yielding method involved Friedel-Crafts acylation of 5-nitroisocoumarin **9** with aroyl chlorides under forcing conditions in nitrobenzene, followed by *in situ* rearrangement and decarboxylation; this was limited to benzoyl chloride and aroyl chlorides carrying electron-withdrawing *para*-substituents.[27] There is therefore a need for a more general route to 3-substituted-5-nitroisocoumarins and, hence, to 3-substituted analogues of **4**.



Scheme 1. Earlier syntheses of 3-substituted-5-nitroisocoumarins **5**. *Reagents*: i, $CuC{\equiv}CR^3$, pyridine, reflux (R^3 = Ph, 4-MePh, 4-MeOPh); ii, $HC{\equiv}CPh$, CuI, $(Ph_3P)_2PdCl_2$, Pr^i_2NH, THF; iii, $HgSO_4$, H_2SO_4, acetone, reflux; iv, R^3COCl, $SnCl_4$, $PhNO_2$. 130°C (R^3 = Ph, Ph-(EWG)).

In 1929, Hurtley reported the displacement of the halogen from 2-bromobenzoic acid with the enolates of β-diketones and of β-ketoesters in the presence of copper catalysts to form the corresponding arylated β-dicarbonyl compound.[28] He noted "The presence of copper-bronze or copper acetate is necessary; the latter appears to be the more vigorous catalyst, but the former gives purer products and was used where possible." Later mechanistic studies have not proved fully conclusive.[29] Most have determined that the carboxylate of the aryl component is essential and that bromine is the optimum halogen.[29,30] Ames and Ribeiro extended this process by forcing a retro-Claisen condensation and ring closure on the Hurtley products with sodium chloride at 170°C to give isocoumarins in moderate yields, making the 3-substituted



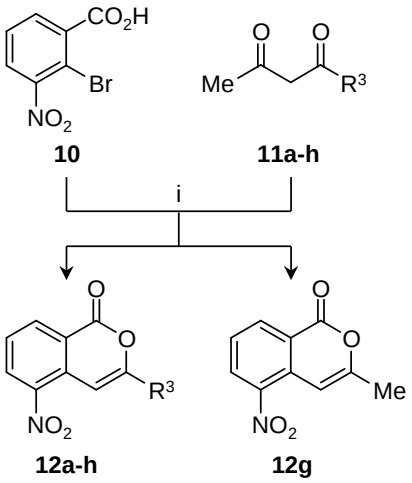
Scheme 2. Initial investigation of tandem Hurtley – retro-Claisen – cyclisation reaction of **10** with **11** under Hurtley's conditions. R*eagents & conditions*: i, Cu powder, NaOEt, EtOH, reflux.

isocoumarins available in two steps from 2-bromobenzoic acid and pentane-2,4-dione or 1,3-diphenylpropane-1,3-dione.[31] Very recently, Cai *et al.* developed a one-pot synthesis of 3-substituted isocoumarins by reaction of 2-iodo- or 2-bromobenzoic acid with β-diketones, catalysed by copper(I) iodide and potassium phosphate in dimethylformamide under forcing conditions in a sealed tube.[32] No 5-substituted analogues were reported. This tandem process has been extended to use of 2-iodobenzanilides, in place of 2-bromobenzoic acid, but Kavala *et al.* note that isocoumarins carrying nitro groups are unstable to the reaction conditions.[33] We therefore sought to expand the tandem Hurtley – retro-Claisen – cyclisation reaction to the one-pot synthesis of 5-nitro-3-substituted isocoumarins without recourse to sealed tubes.

2. Results & Discussion

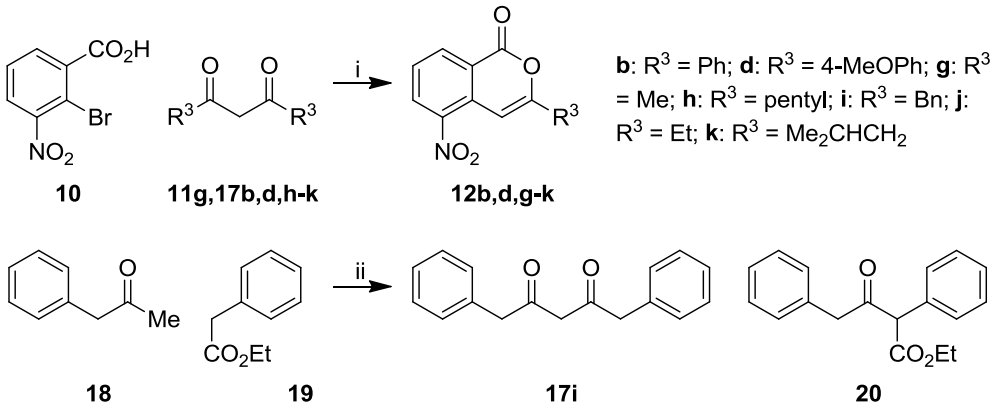
2-Bromo-3-nitrobenzoic acid **10** (Scheme 2) was prepared by mercury-catalysed decarboxylation of 3-nitrobenzene-1,2-dioic acid (3-nitrophthalic acid), followed by treatment of the intermediate aryl-mercury with bromine,[34] by analogy with our previous method for 2-iodo-3-nitrobenzoic acid.[26] Many of the β-dicarbonyl components were commercially available but Claisen condensations, either base-catalysed (sodamide) or Lewis-acid catalysed (boron trifluoride.acetic acid complex), were used to supply others.

As a preliminary study to establish suitable reaction conditions for the reaction, **10** was treated with the trifluoromethylphenyl β-diketone **11a**, using Hurtley's original reaction conditions (copper powder, with sodium ethoxide as base in boiling ethanol)[28] (Scheme 2). The isocoumarin **12a** was isolated in modest yield, through a tandem Hurtley – retro-Claisen – cyclisation sequence. The mono-ketone **13** and the ester **14** were also obtained as by-products. Interestingly, there was no evidence for formation of 3-methyl-5-nitroisocoumarin, arising from an alternative retro-Claisen reaction in the sequence, nor were the intermediate arylated diketone **15** and the



a: R^3 = 4-F_3CPh; **b**: R^3 = Ph; **c**: R^3 = 4-MePh; **d**: R^3 = 4-MeOPh; **e**: R^3 = 4-ClPh; **f**: R^3 = thiophen-2-yl; **g**: R^3 = Me; **h**: R^3 = pentyl

Scheme 3. Tandem Hurtley – retro-Claisen – cyclisation reactions of **10** with methyl β-diketones **11a-h** to form 3-substituted 5-nitroisocoumarins **12a-h**. *Reagents & conditions*: i, Cu powder, $KOBu^t$, Bu^tOH, reflux.



Scheme 4. Tandem Hurtley – retro-Claisen – cyclisation reactions of **10** with symmetrical β-diketones **11g, 17b,d,h-k** to form 3-substituted 5-nitroisocoumarins **12b,d,g-k** and syn thesis of symmetrical β-diketone **17i**. *Reagents & conditions*: i, Cu powder, $KOBu^t$, Bu^tOH, reflux; ii, $NaNH_2$, Et_2O, reflux.

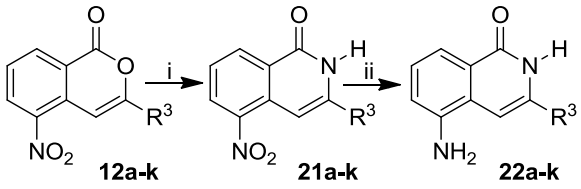
Table 1. Yields of 5-nitroisocoumarins **12** formed in the tandem Hurtley coupling → retro-Claisen → cyclisation reactions from **10** and unsymmetrical (**11**) and symmetrical (**17**) β-diketones. ND = not determined.

Isocoumarin 3-substituent	**Reaction of 10 with unsymmetrical diketones 11 ($KOBu^t$ / Bu^tOH)**		**Reaction of 10 with symmetrical diketones 17 ($KOBu^t$ / Bu^tOH)**
	Yield of target isocoumarin (%)	**Yield of 12g (%)**	**Yield of target isocoumarin (%)**
4-F_3CPh	16 (**12a**)	6	ND
Ph	4 (**12b**)	8	78 (**12b**)
4-MePh	21 (**12c**)	3	ND
4-MeOPh	15 (**12d**)	6	60 (**12d**)
4-ClPh	33 (**12e**)	4	ND
Thiophen-2-yl	21 (**12f**)	0	ND
Me	-	-	23 (**12g**)
pentyl	4 (**12h**)	0	26 (**12h**)
Bn	ND	ND	32 (**12i**)
Et	ND	ND	24 (**12j**)
CH_2CHMe_2	ND	ND	26 (**12k**)

intermediate retro-Claisen product **16** observed in the product mixture. Compounds **13** and **14** are products of retro-Claisen cleavage of the starting β-diketone **11a**. This suggests that the base, ethoxide, may be too nucleophilic, in that it attacks the carbonyls of **11a** before the Hurtley coupling can take place, consuming **11a** and thereby lowering the yield of **12a**.

Replacement of the base with the less nucleophilic potassium *t*-butoxide and the solvent with *t*-butanol obviated the premature retro-Claisen cleavage (Scheme 3), providing mixtures of the required 3-substituted 5-nitroisocoumarin **12a-h** and the 3-methyl analogue **12g**, arising from an alternative retro-Claisen cleavage as the second step. These were readily separated by column chromatography. As shown in Table 1, the yields of **12a-h** were poor-to-modest. Rationalising that material was being lost through the alternative retro-Claisen cleavage of the R^3CO group, we examined the tandem Hurtley – retro-Claisen – cyclisation reaction sequence with symmetrical β-diketones **17b,d,h-k** (Scheme 4). As for the unsymmetrical analogues **11**,

these were either commercially available (**17b**) or prepared by Claisen condensations. Interestingly, during the assembly of the dibenzyl symmetrical β-diketone **17i** from ketone **18** and ester **19**, a quantity of the homo-Claisen product **20** was also formed, reflecting the acidity of the α-protons in the intended electrophilic component **19** (Scheme 4). The yields of the required 3-alkyl and 3-aryl 5-nitroisocoumarins **12** were markedly higher when the symmetrical diketones were employed (Table 1), using the same reaction conditions (potassium *t*-butoxide in *t*-butanol). In cases where both methods were examined for the same target **12a,d,h**, the yield for the tandem reaction with the symmetrical diketones **17** was much higher. Indeed, the yields exceeded the sums of the yields of (desired isocoumarins + **12g**), suggesting that not only was the problem of the wrong acyl group being lost in the retro-Claisen step being resolved but also that the initial Hurtley reaction was proceeding better with the enolates of **17**. The dialkyl symmetrical β-diketones **17g-k** gave lower yields than the diaryl analogues **17b,d**.



a: R^3 = 4-F_3CPh; **b**: R^3 = Ph; **c**: R^3 = 4-MePh; **d**: R^3 = 4-MeOPh; **e**: R^3 = 4-ClPh; **f**: R^3 = thiophen-2-yl; **g**: R^3 = Me; **h**: R^3 = pentyl; **i**: R^3 = Bn; **j**: R^3 = Et; **k**: R^3 = Me_2CHCH_2

Scheme 5. Conversion of the 5-nitroisocoumarins **12a-k** into 5-aminoisoquinolin-1-ones **22a-k**. *Reagents*: i, NH_3, $MeO(CH_2)_2OH$, reflux; ii, $SnCl_2$, EtOH *or* H_2, Pc/C, EtOH, aq. HCl.

Thus the tandem reaction provided sufficient quantities of the isocoumarins **17a-k** for the remainder of the reaction sequence. Notably, the sequence proceeds with alkyl β-diketones and with aryl groups carrying electron-neutral, +M and –I *para*-substituents but it fails completely with –M substituents on the aryl group, such as nitro and cyano.

The 5-nitroisocoumarins **12** were readily converted into the corresponding 5-nitroisoquinolin-1-ones **21** by reaction with ammonia in boiling 2-methoxyethanol (Scheme 5), obviating the use of sealed tubes for the more usual transformation in ethanol. The yields were mostly good-to-high. Reduction of the nitro group to furnish the target 3-substituted 5-aminoisoquinolin-1-ones **22** was effected with tin(II) chloride. For one example, **21a**, catalytic hydrogenation was also explored but gave practical problems of separating the product **22a** efficiently from the catalyst.

3. Biochemical evaluation

All the hydrochloride salts of 5-aminoisoquinolin-1-ones **22a-k** showed good water-solubility (>1% *w/v*; > 30 mM). Each was evaluated *in vitro* for activity against human PARP-1 isolated from HeLa nuclear extract, using the KuDOS FlashPlate scintillation proximity assay method.[35] This isotopic assay measures PARP-1 activity through synthesis of [^{3}H]-ADP-ribose polymers from [^{3}H]-NAD^+. Tritium bound to the FlashPlate was counted using a scintillation plate reader. In this study, five different concentrations of the inhibitor, in a range surrounding the predicted IC_{50} value, were used. Three independent determinations were performed for each candidate inhibitor **22a-k**; the mean IC_{50} values are reported in Table 2.

In this assay, the mean IC_{50} value for PARP-1 inhibition by the lead compound, 5-AIQ **4**, was found to be 1.6 μM, which is higher than that reported previously by us[36] for an assay in a broken nuclear preparation (300 nM) and that reported by Suto *et al.*[37] (250 nM) from a calf-thymus preparation assay. Differences in absolute values of IC_{50} between assay types are well known for PARP-1 inhibition. All the 3-substituted 5-aminoisoquinolinones inhibited PARP-

1 activity, with many having IC_{50} values in the 0.2-1.0 μM range. Indeed, all except **22f,i** were more potent than the lead compound **4**. Generally, the simpler 3-alkyl compounds **22g,h,j** were slightly more potent than the 3-phenyl compound **22b**; this is in line with similar effects noted by White *et al*.[38] that 8-methoxy-2-methylquinazolin-4-one is *ca.* 5-fold more potent than is 8-methoxy-2-phenylquinazolin-4-one. Introduction of branching in the 3-alkyl chain, in the *iso*butyl analogue **22k** and the benzyl analogue **12i**, however, caused some loss of activity. A phenyl substituent is accepted at the 3-position (in **22b**), showing that steric bulk is unlikely to be the simple explanation of the weaker activity of **22i,k**. Curiously, the introduction of a thiophene ring at the 3-position resulted in a loss of potency in **22f**, despite the usually accepted pharmacoequivalence of benzene and thiophene.

Table 2. IC_{50} values for inhibition of human PARP-1 and murine PARP-2 by 3-substituted 5-aminoisoquinolin-1-ones. ND = not determined.

Cpd. No.	3-Substituent	PARP-1 IC_{50} (μM)	PARP-2 IC_{50} (μM)
4	H	1.6 ± 0.25	1.05 ± 0.15
22a	4-F_3CPh	0.33 ± 0.07	0.17 ± 0.02
22b	Ph	1.07 ± 0.07	0.48 ± 0.15
22c	4-MePh	0.88 ± 0.14	0.12 ± 0.03
22d	4-MeOPh	0.90 ± 0.45	0.73 ± 0.25
22e	4-ClPh	0.57 ± 0.03	0.16 ± 0.05
22f	thiophen-2-yl	5.61 ± 2.20	ND
22g	Me	0.23 ± 0.02	0.26 ± 0.05
22h	pentyl	0.32 ± 0.17	ND
22i	Bn	5.14 ± 1.60	ND
22j	Et	0.49 ± 0.04	0.83 ± 0.10
22k	CH_2CHMe_2	1.17 ± 0.56	ND

Selected compounds were also assayed for their inhibition of PARP-2 activity (Table 2), using the assay previously reported by us.[23] Most of the analogues tested showed slightly greater potency against PARP-2 but the selectivity was not large enough to allow use in biochemical studies as selective inhibitors.

4. Molecular modelling studies

The structures of the 3-substituted 5-AIQs **22a-k** were overlaid with the structure of the known inhibitor 8-hydroxy-2-methylquinazolin-4-one bound into the NAD^+-binding site of the catalytic domain of chicken PARP-1 derived from co-crystal X-ray data retrieved from the Brookhaven Protein Data Bank (PDB code: 4PAX), using Tripos Associates SYBYL software on a SGI Octane II workstation. The 3-substituted 5-AIQ derivatives were initially positioned such that the central rings were overlaid with the 8-hydroxy-2-methylquinazolin-4-one rings; the side chains were then subjected to molecular mechanics and molecular dynamics calculations while restraining the binding pocket and the heterocyclic core; the temperature was ramped to 300 K over 10 ps, then held at 300 K for a further 20 ps. Once an optimal orientation had been established for the side-chains, the restraints were removed and the whole binding pocket (10 Å) was subjected to further molecular dynamics (20 ps at 300K) and then refined with mechanics calculations, allowing free movement of both the ligands and the binding pocket. Examples of illustrations generated by these calculations are shown in Figure 2. As expected, each isoquinolin-1-one could make hydrogen bonds from the carbonyl oxygen to the side-chain O—H of Ser^{904} and to the backbone N—H of Gly^{863}. For example, in the minimised position for the most potent compound, **22g**, this oxygen was located 2.25 Å from the latter and 1.59 Å from the former (Figure 2A). The isoquinolin-1-one N—H was also located appropriately for a strong hydrogen bond to the backbone carbonyl of Gly^{863}, as exemplified for **22g** in Figure 2A with a distance of 2.08 Å. These hydrogen-bonding

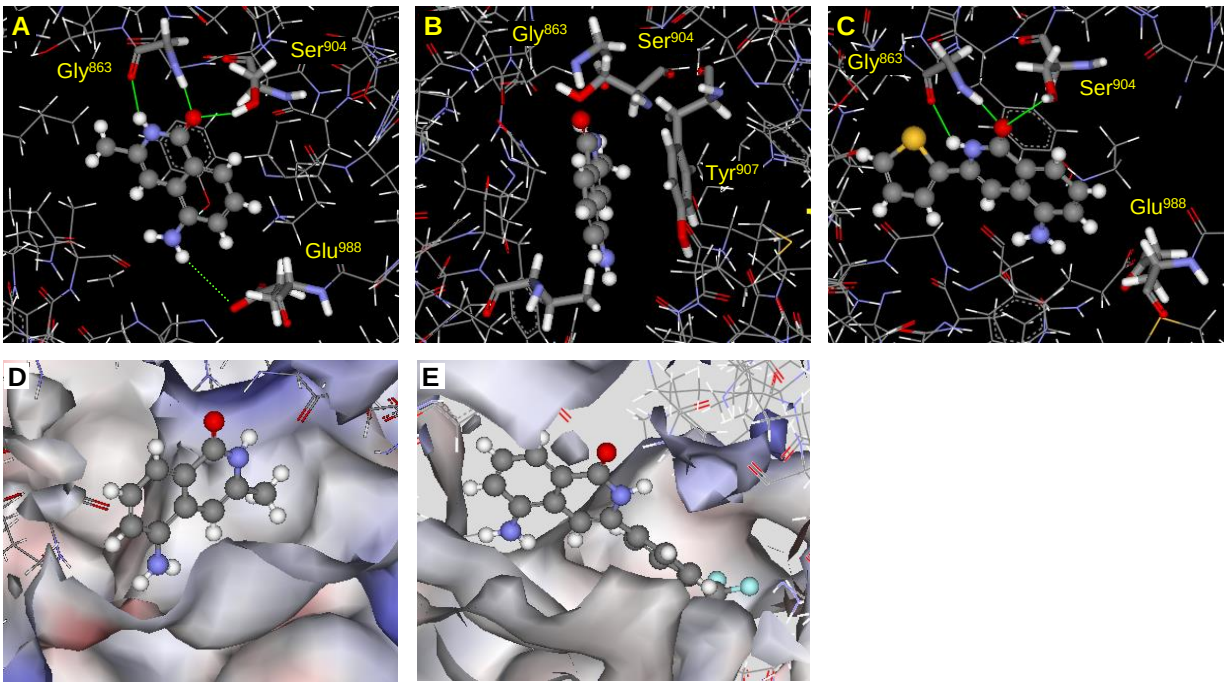


Figure 2. Illustrations of modes of binding of selected examples in the NAD^+-binding site of chicken PARP-1, as predicted by molecular modelling. **A**: Binding of **22g**, showing hydrogen bonds to Gly^{863} and Ser^{904} (green solid lines) and the proximity of the 5-amine to the carboxylate of Glu^{988}(green dotted line). **B**: Binding of **22g**, showing π-stacking to Tyr^{907}. **C**: Binding of **22f**, showing hydrogen bonds to Gly^{863} and Ser^{904} and potential steric obstruction by the sulfur. **D**: View of binding of **22g**, showing insertion of the 3-Me into a pocket. **E**: View of binding of **22a**, showing insertion of the 3-(4-trifluoromethylphenyl) into a pocket.

interactions are common in the modelled and co-crystal structures of inhibitors. It was also observed that the 5-NH_2 in these inhibitors was well accommodated within a small binding pocket and was orientated and located appropriately for a water-mediated hydrogen bond to the carboxylate of the important catalytic Glu^{988} in the active site; an ordered water molecule is located in this position in several crystal structures. The core aromatic isoquinolin-1-one rings of **22a-k** also formed a π-stack with the electron-rich aromatic side-chain of Tyr^{907}, as is common for PARP-1 inhibitors (illustrated for **22g** in Figure 2B). Notably, the bulk of the sulfur in **22f** (Figure 2C) may possibly interfere with the critical hydrogen bond from the inhibitor N—H to Gly^{863} of the enzyme, diminishing its potency.

These modelling studies indicated that the 3-substituents of **22a-k** should occupy a hydrophobic pocket. Figure 2D shows the 3-methyl of **22g** entering shallowly into this space, whereas the 3-(4-trifluoromethylphenyl) of **22a** appears to fill the pocket (Figure 2E), reflecting the increased inhibitory potency of these and closely related compounds when compared with **4**.

5. Conclusion

This paper reports a one-pot tandem Hurtley – retro-Claisen – cyclisation reaction sequence, which is useful in preparing 3-aryl and 3-alkyl 5-nitroisocoumarins **12**. These are important intermediates in accessing the corresponding 3-aryl and 3-alkyl 5-aminoisoquinolin-1-ones **22**. The tandem sequence can be carried out with either unsymmetrical or symmetrical β-diketones. The whole preparation of the targets **22** is achieved without recourse to sealed tubes, particularly for the Hurtley step and for the isocoumarin-to-isoquinolinone step, which have previously required such specialised equipment.[32,39] This new sequence tolerates most

groups, except –M substituents on the aryl units in diaryl-β-diketones. It is therefore complementary to our one-pot formation of 3-aryl-5-nitroisocoumarins by Friedel-Crafts acylation of 5-nitroisocoumarin, rearrangement and decarboxylation, for which –M substituents are optimal.[27]

Many of the 3-substituted 5-AIQ derivatives **22a-k** showed moderately more potent inhibition of the enzymatic activities of PARP-1 and PARP-2 than the parent **4**, although there was no selectivity evident for either isoform. As demonstrated by molecular modelling, the 3-substituents entered a modestly-sized hydrophobic pocket in both enzymes. The ready access to these structures through the tandem Hurtley – retro-Claisen – cyclisation reaction sequence now enables further structure-activity studies for design and discovery of new inhibitors of these clinically important enzymes.

6. Experimental

6.1. Chemistry

Mps were determined using a Reichert-Jung Thermo Galen Kofler block and are uncorrected. IR spectra were recorded on a Perkin-Elmer RXI FT-IR spectrometer as KBr discs. NMR spectra were recorded on either a JEOL GX 270 (270.05 MHz ^{1}H; 67.8 MHz ^{13}C) or a JEOL EX 400 (399.65 MHz ^{1}H; 100.4 MHz ^{13}C; 376.05 MHz ^{19}F) spectrometer. Mass spectra were obtained using a VG 7070 mass spectrometer. Column chromatography was performed using silica gel 60 (0.040-0.063 mm, Merck). Experiments were conducted at ambient temperature, unless otherwise stated. Solutions in organic solvents were dried using anhydrous $MgSO_4$ and solvents were evaporated under reduced pressure.

6.1.1. 5-Nitro-3-(4-trifluoromethylphenyl)isocoumarin (12a). Method A.

Compound **10**[34] (2.5 g, 10 mmol) and Cu powder (220 mg, 3.5 mmol) were added to **11a**[40] (3.5 g, 15 mol) and NaOEt (1.6 g, 23 mmol) in EtOH (35 mL). The mixture was boiled under reflux for 16 h, then poured into H_2O and acidified with aq. HCl (2 M). Extraction (Et_2O), evaporation and chromatography (hexane / EtOAc 4:1) gave **12a** (160 mg, 5%) as yellow crystals, with data as below. Further elution gave **13** (210 mg, 11%) as a colourless oil (lit.[41] oil): ^{1}H NMR ($CDCl_3$) δ 2.56 (3 H, s, Me), 7.55 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H_2), 8.14 (2 H, d, *J* = 8.2 Hz, Ph 2,6-H_2). Further elution gave **14** (130 mg, 6%) as a colourless oil (lit.[42] oil): ^{1}H NMR ($CDCl_3$) δ 1.41 (3 H, t, *J* = 7.2 Hz, Me), 4.41 (2 H, q, *J* = 7.2 Hz, CH_2), 7.75 (2 H, d, *J* = 8.2 Hz, 3,5-H_2), 8.16 (2 H, d, *J* = 8.2 Hz, 2,6-H_2).

6.1.2. 5-Nitro-3-(4-trifluoromethylphenyl)isocoumarin (12a) and 3-methyl-5-nitro-isocoumarin (12g). Method B.

Compound **10**[34] (3.6 g, 16 mmol) was boiled under reflux with **11a** (760 mg, 3.1 mmol), KOBu^{t} (700 mg, 6.3 mmol) and Cu powder (20 mg, 0.3 mmol) in Bu^{t}OH (50 mL) for 16 h. The mixture was poured into H_2O (350 mL) and was acidified with aq. HCl (2 M). Extraction (Et_2O), evaporation and chromatography (hexane / EtOAc 9:1) gave **12a** (160 mg, 16%) as yellow crystals: mp 163-164°C (lit.[27] mp 163-164°C); IR ν_{max} 1724, 1626, 1537, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.67 (1 H, t, *J* = 8.2 Hz, 6-H), 7.75 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H_2), 7.93 (1 H, d, *J* = 0.8 Hz, 4-H), 8.03 (2 H, d, *J* = 8.2 Hz, Ph 2,6-H_2), 8.51 (1 H, dd, *J* = 8.2, 1.6 Hz), 8.57 (1 H, ddd, *J* = 8.2, 1.6, 0.8 Hz, 8-H); ^{19}F NMR ($CDCl_3$) δ -63.54 (s, CF_3). Further elution yielded **12g** (40 mg, 6%) as yellow crystals, with data as below.

6.1.3. 5-Nitro-3-phenylisocoumarin (12b) and 3-methyl-5-nitroisocoumarin (12g). Method A.

Compound **10**[34] was treated with **11b**, Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12a** (Method B) (chromatographic eluent: hexane / EtOAc 10:1) to give **12b** (4%) as yellow crystals: mp 142-143°C (lit.[26] mp 142-143°C); IR ν_{max} 1739, 1525, 1341 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.50-7.53 (3 H, m, Ph 3,4,5-H_3), 7.62 (1 H, t, *J* = 7.8 Hz, 7-H), 7.89 (1 H, d, *J* = 0.8 Hz, 4-H), 7.93-7.97 (2 H, m, Ph 2,6-H_2), 8.51 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.65 (1 H, dt, *J* = 8.2, 1.2, 0.8 Hz, 8-H); MS (EI) *m/z* 267.0532 (M) ($C_{15}H_9NO_4$ requires 267.0532). Further elution yielded **12g** (170 mg, 8%) as yellow crystals, with data as below.

6.1.4. 5-Nitro-3-phenylisocoumarin (12b). Method B.

Compound **10**[34] (5.0 g, 20 mmol) and Cu powder (150 mg, 2.4 mmol) were added to **17b** (22.9 g, 102 mmol) and KOBu^t (4.6 g, 41 mmol) in Bu^{t}OH (100 mL). The mixture was boiled under reflux for 16 h, then poured into water and acidified with aq. HCl (2 M). This suspension was extracted (Et_2O). Evaporation and chromatography (hexane / EtOAc 10:1) gave **12b** (4.2 g, 78%) as yellow crystals, with data as above.

6.1.5. 3-(4-Methylphenyl)-5-nitroisocoumarin (12c).

Compound **10**[34] (22.7 g, 100 mmol) was treated with **11c**, Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12a** (Method B) (chromatographic eluent: hexane / EtOAc 10:1) to give **12c** (21%) as pale yellow crystals: mp 180-181°C (lit.[27] mp 181-182°C); ^{1}H NMR ($CDCl_3$) δ 2.42 (3 H, s, Me), 7.29 (2 H, d, *J* = 8.6 Hz, Ph 3,5-H_2), 7.57 (1 H, t, *J* = 8.2 Hz, 7-H), 7.82 (1 H, s, 4-H), 7.83 (2 H, d, *J* = 8.4 Hz, Ph 2,6-H_2), 8.48 (1 H, brd, *J* = 8.2 Hz, 6-H), 8.61 (1 H, brd, *J* = 8.5 Hz, 8-H). Further elution yielded **12g** (3%), with data as below.

6.1.6. 3-(4-Methoxyphenyl)-5-nitroisocoumarin (12d). Method A.

Compound **10**[34] was treated with **11d**[40], Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12a** (Method B) (chromatographic eluent: hexane / EtOAc 10:1) to give **12d** (15%) as yellow crystals: mp 241-242°C (lit.[26] mp 241-242°C); ^{1}H NMR ($CDCl_3$) δ 3.88 (3 H, s, Me), 6.99 (2 H, d, *J* = 9.0 Hz, Ph 3,5-H_2), 7.54 (1 H, t, *J* = 8.2 Hz, 7-H), 7.76 (1 H, s, 4-H), 7.88 (2 H, d, *J* = 9.0 Hz, Ph 2,6-H_2), 8.46 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.59 (1 H, dd, *J* = 8.2, 1.2 Hz, 8-H); ^{13}C NMR ($CDCl_3$) (C_q omitted) δ 55.56 (Me), 94.74 (4-C), 114.52 (Ph 3,5-C_2), 126.56 (7-C), 127.73 (Ph 2,6-C_2), 131.71 (6-C), 135.92 (8-C); MS (EI) *m/z* 297.0639 (M) ($C_{16}H_{11}NO_5$ requires 297.0637), 266 (M - OMe). Further elution yielded **12g** (6%) as yellow crystals, with data as below.

6.1.7. 3-(4-Methoxyphenyl)-5-nitroisocoumarin (12d). Method B.

Compound **10**[34] was treated with **17d**,[43] Cu and KOBu^t in Bu^{t}OH, as for the synthesis of 12b (Method B) (chromatographic eluent: hexane / EtOAc 4:1) to give **12d** (61%) as yellow crystals, with data as above.

6.1.8. 3-(4-Chlorophenyl)-5-nitroisocoumarin (12e). Method A.

Compound **10**[34] was treated with **11e**, Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12a** (Method B) (chromatographic eluent: hexane / EtOAc 8:1) to give **12e** (33%) as pale yellow crystals: mp 204-205°C; (lit.[27] mp 204-205°C); ^{1}H NMR ($CDCl_3$) δ 7.47 (2 H, d, *J* = 6.6 Hz,

Ph 3,5-H_2), 7.62 (1 H, t, *J* = 8.0 Hz, 7-H), 7.87 (2 H, d, *J* = 6.9 Hz, Ph 2,6-H_2), 7.88 (1 H, brs, 4-H), 8.50 (1 H, dd, *J* = 8.3, 1.9 Hz, 6-H), 8.63 (1 H, brd, *J* = 8.0 Hz, 8-H); ^{13}C NMR δ (C_q not observed) 96.62, 127.23, 127.50, 129.44, 131.74, 135.92; MS (EI) *m/z* 303.0111 (M) ($C_{15}H_8{}^{37}ClNO_4$ requires 303.0112), 301.0137 (M) ($C_{15}H_8{}^{35}ClNO_4$ requires 301.0142). Further elution yielded **12g** (4%) as yellow crystals, with data as below.

6.1.9. 5-Nitro-3-(thiophen-2-yl)isocoumarin (12f).

Compound **10**[34] was treated with **11f**,[44] Cu and and KOBu^t in Bu^{t}OH, as for the synthesis of **12a** (Method B) (chromatographic eluent: hexane / EtOAc 8:1) to give **12f** (21%) as pale yellow crystals: mp 189-190°C; IR ν_{max} 1744, 1619, 1530, 1338 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.15 (1 H, dd, *J* = 5.1, 3.9 Hz, thiophene 4-H), 7.50 (1 H, dd, *J* = 5.1, 1.2 Hz, thiophene 5-H), 7.55 (1 H, t, *J* = 8.2 Hz, 7-H), 7.71 (1 H, dd, *J* = 3.9, 1.2 Hz, thiophene 3-H), 7.71 (1 H, d, *J* = 0.8 Hz, 4-H), 8.47 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.59 (1 H, ddd, *J* = 8.2, 1.2, 0.8 Hz, 8-H); MS (EI) *m/z* 273.0088 (M) ($C_{13}H_7NO_4S$ requires 273.0096).

6.1.10. 3-Methyl-5-nitroisocoumarin (12g).

Compound **10**[34] was treated with **11g**, Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12a** (Method B) (chromatographic eluent: hexane / EtOAc 3:2) to give **12g** (23%) as yellow crystals: mp 199-200°C (lit.[23] mp 199-200°C); IR ν_{max} 1746, 1648, 1520, 1331 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 2.37 (3 H, s, Me), 7.13 (1 H, d, *J* = 0.8 Hz, 4-H), 7.55 (1 H, t, *J* = 8.2 Hz, 7-H), 8.41 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.56 (1 H, ddd, *J* = 8.2, 1.2, 0.8 Hz, 8-H); ^{13}C NMR δ 20.46, 98.36, 121.92, 126.88, 131.36, 131.84, 135.74, 143.85, 158.63, 160.83; MS (EI) *m/z* 205.0384 (M) ($C_{10}H_7NO_4$ requires 205.0375); Anal. Calcd. for $C_{10}H_7NO_4$: C, 58.54; H, 3.44; N, 6.83. Found: C, 58.3; H, 3.47; N, 6.78.

6.1.11. 5-Nitro-3-pentylisocoumarin (12h). Method A.

Compound **10**[34] was treated with **11h**, Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12a** (Method B) (chromatographic eluent: hexane / EtOAc 10:1) to give **12h** (4%) as a pale yellow oil: IR ν_{max} (film) 1736, 1646, 1530, 1344 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.90-0.94 (3 H, m, pentyl 5-H_3), 1.35-1.40 (4 H, m, pentyl 3,4-H_4), 1.70-1.78 (2 H, m, pentyl 2-H_2), 2.59 (2 H, t, *J* = 7.8 Hz, pentyl 1-H_2), 7.12 (1 H, d, *J* = 0.8 Hz, 4-H), 7.55 (1 H, t, *J* = 7.8 Hz, 7-H), 8.41 (1 H, dd, *J* = 7.8, 1.6 Hz, 6-H), 8.56 (1 H, ddd, *J* = 7.8, 1.6, 0.8 Hz, 8-H); ^{13}C NMR δ 13.96, 22.37, 26.61, 31.18, 34.20, 97.69, 122.08, 126.83, 131.34, 131.85, 135.71, 143.82, 160.99, 162.36; MS (EI) *m/z* 261.1002 (M) ($C_{14}H_{15}NO_4$ requires 261.1001).

6.1.12. 5-Nitro-3-pentylisocoumarin (12h). Method B.

Compound **10**[34] was treated with **17h**,[45] Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12b** (Method B) to give **12h** (36%) as a pale yellow oil, with data as above.

6.1.13. 5-Nitro-3-phenylmethylisocoumarin (12i).

Compound **10**[34] was treated with **17i**, as for the synthesis of **12b** (Method B) (chromatographic eluent: hexane / EtOAc 9:1) to give **12i** (32%) as yellow crystals: mp 137-138°C; IR ν_{max} 1740, 1647, 1564, 1346 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.88 (2 H, s CH_2), 7.13 (1 H, d, *J* = 0.5 Hz, 4-H), 7.24–7.36 (5 H, m, Ph-H_5), 7.54 (1 H, t, *J* = 8.0 Hz, 7-H), 8.39 (1 H, dd, *J* = 8.0, 1.4 Hz, 6-H), 8.53 (1 H, ddd, *J* = 8.0, 1.4, 0.5 Hz, 8-H); MS (EI) *m/z* 281.0690 (M) ($C_{16}H_{11}NO_4$ requires 281.0688), 190 (M – Bn).

6.1.14. 3-Ethyl-5-nitroisocoumarin (12j).

Compound **10**[34] was treated with **17j**, Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12b** (Method B) (chromatographic eluent: hexane / EtOAc 9:1) to give **12j** (24%) as yellow crystals: mp 77-78°C; IR ν_{max} 1747, 1645, 1524, 1347 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.17 (3 H, t, *J* = 7.6 Hz, Me), 2.55 (2 H, q, *J* = 7.6 Hz, CH_2), 7.01 (1 H, d, *J* = 0.9 Hz, 4-H), 7.48 (1 H, t, *J* = 8.1 Hz, 7-H), 8.32 (1 H, dd, *J* = 8.1, 2.6 Hz, 6-H), 8.44 (1 H, ddd, *J* = 8.1, 2.6, 0.9 Hz, 8-H); ^{13}C NMR δ 11.73, 27.99, 97.41, 122.65, 127.41, 131.89, 132.38, 136.22, 144.43, 161.43, 163.92; MS (EI) *m/z* 219.0533 (M) ($C_{11}H_9NO_4$ requires 219.0532).

6.1.15. 3-(2-Methylpropyl)-5-nitroisocoumarin (12k).

Compound **10**[34] treated with **17k**, Cu and KOBu^t in Bu^{t}OH, as for the synthesis of **12b** (Method B) (chromatographic eluent: hexane / EtOAc 9:1) to give **12k** (26%) as yellow crystals: mp 71-72°C; IR ν_{max} 1737, 1645, 1531, 1346 cm^{-1}; ^{1}H NMR δ ($CDCl_3$) 0.99 (6 H, d, *J* = 6.6 Hz, 2 × Me), 2.16 (1 H, m, CH_2CH), 2.45 (2 H, d, *J* = 7.4 Hz, CH_2), 7.09 (1 H, s, 4-H), 7.55 (1 H, t, *J* = 8.2 Hz, 7-H), 8.40 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.54 (1 H, dd, *J* = 8.2, 1.2 Hz, 8-H); MS (EI) *m/z* 247.0848 (M) ($C_{13}H_{13}NO_4$ requires 247.0845).

6.1.16. 1,5-Diphenyl-2,4-pentanedione (17i) and ethyl 2,4-diphenyl-3-oxobutanoate (20).

1-Phenylpropan-2-one **18** (26.8 g, 0.20 mol) in dry Et_2O (50 mL) was added during 10 min to $NaNH_2$ (50% in toluene, 31.2 ml, 0.40 mol) and dry Et_2O (100 mL) and the mixture was stirred for 30 min. Ethyl phenylacetate **19** (65.6 g, 0.40 mol) in dry Et_2O (50 mL) was added dropwise. The mixture was boiled under reflux for 2 h, poured into H_2O (300 mL) and neutralised with aq HCl (2 M). The solution was extracted with Et_2O. The solvent was evaporated. The residue was dissolved in an equal volume of MeOH. To this methanolic solution was added a hot solution of $Cu(OAc)_2$ (40.0 g) in H_2O (350 mL) and the mixture was allowed to stand until it cooled to 20°C. The precipitated copper salt was filtered, washed with cold petroleum ether and shaken with a mixture of aq. H_2SO_4 (10%, 300 mL) and Et_2O (100 mL) until the Et_2O layer was colourless. Evaporation and recrystallisation (hexane / EtOAc) yielded **17i** (26%) as orange crystals: mp 68-69°C (lit.[46] mp 65.5-66.5°C); ^{1}H NMR ($CDCl_3$) δ 3.56 (4 H, s, 1,5-H_4), 5.43 (1 H, s, 3-H), 7.18-7.32 (10 H, m, 2 × Ph-H_5), 15.27 (1 H, br s, OH); MS (EI) *m/z* 252.1144 (M) ($C_{17}H_{16}O_2$ requires 252.1150), 161 (M – CH_2Ph), 133 (M – $COCH_2Ph$). Isolated from the methanolic mother liquor was **20** (41%) as colourless crystals: mp 76-78°C (lit.[47] mp 75°C); IR ν_{max} 1734, 1715 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 1.22 (3 H, t, *J* = 7.1 Hz, Me), 3.74 (2 H, s, 4-H_2), 4.17 (2 H, q, *J* = 7.1 Hz, CH_2Me), 4.81 (1 H, s, 2-H), 7.05-7.39 (10 H, m, 2 × Ph-H_5); MS (EI) *m/z* 282.1255 (M) ($C_{18}H_{18}O_3$ requires 282.1256).

6.1.17. 5-Nitro-3-(4-trifluoromethylphenyl)isoquinolin-1-one (21a).

Compound **12a** (560 mg, 1.7 mmol) in $MeO(CH_2)_2OH$ (50 mL) was saturated with NH_3 and boiled under reflux for 4 h. The solvent and excess reagent were evaporated until 10 mL remained. The concentrate was stored at 4°C for 16 h. The crystals were collected by filtration, washed (H_2O, then EtOH) and recrystallised (MeOH) to give **21a** (150 mg, 27%) as yellow crystals: mp 230-231°C; ^{1}H NMR ($(CD_3)_2SO$) δ 7.28 (1 H, s, 4-H), 7.68 (1 H, t, *J* = 7.8 Hz, 7-H), 7.88 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H_2), 7.97 (2 H, d, *J* = 8.2 Hz, Ph 2,6-H_2), 8.47 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 8.58 (1 H, d, *J* = 7.8, 1.2 Hz, 8-H), 12.21 (1 H, brs, NH); ^{19}F NMR ($(CD_3)_2SO$) δ -61.84 (s, CF_3); MS (EI) *m/z* 334.0560 (M) ($C_{16}H_9F_3N_2O_3$ requires 334.0565).

6.1.18. 5-Nitro-3-phenylisoquinolin-1-one (21b).

Compound **12b** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21b** (73%) as bright yellow crystals: mp 127-128°C; IR ν_{max} 3482, 1665, 1536, 1348 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 7.25 (1 H, s, 4-H), 7.53-7.55 (3 H, m, Ph 3,4,5-H_3), 7.66 (1 H, t, *J* = 7.8 Hz, 7-H), 7.78-7.80 (2 H, m, Ph 2,6-H_2), 8.49 (1 H, d, *J* = 7.8 Hz, 6-H), 8.60 (1 H, d, *J* = 7.8 Hz, 8-H), 12.11 (1 H, br s, NH); MS (EI) *m/z* 266.0694 (M) ($C_{15}H_{10}N_2O_3$ requires 266.0691).

6.1.19. 3-(4-Methylphenyl)-5-nitroisoquinolin-1-one (21c).

Compound **12c** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21c** (86%) as bright yellow crystals: mp 175-176°C; ^1H NMR ($(CD_3)_2SO$) δ 2.37 (3 H, s, Me), 7.20 (1 H, d, *J* = 0.8 Hz, 4-H), 7.32 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H_2), 7.62 (1 H, t, *J* = 8.2 Hz, 7-H), 7.66 (2 H, d, *J* = 8.2 Hz, Ph 2,6-H_2), 8.45 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.56 (1 H, ddd, *J* = 8.2, 1.2, 0.8 Hz, 8-H), 12.03 (1 H, brs, NH); MS (EI) *m/z* 280.0856 (M) ($C_{16}H_{12}N_2O_3$ requires 280.0848); Anal. Calcd. for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.2; H, 4.28; N, 10.0.

6.1.20. 3-(4-Methoxyphenyl)-5-nitroisoquinolin-1-one (21d).

Compound **12d** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21d** (65%) as bright yellow crystals: mp 236-237°C; IR ν_{max} 3468, 1677, 1515, 1323 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.82 (3 H, s, Me), 7.07 (2 H, d, *J* = 9.0 Hz, Ph 3,5-H_2), 7.18 (1 H, d, *J* = 0.8 Hz, 4-H), 7.60 (1 H, t, *J* = 8.2 Hz, 7-H), 7.73 (2 H, d, *J* = 9.0 Hz, Ph 2,6-H_2), 8.45 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.55 (1 H, ddd, *J* = 8.2, 1.2, 0.8 Hz, 8-H), 12.00 (1 H, br s, NH); MS (EI) *m/z* 296.0802 (M) ($C_{16}H_{12}N_2O_4$ requires 296.0797); Anal. Calcd. for $C_{16}H_{12}N_2O_4 \cdot 0.5H_2O$: C, 62.95; H, 4.26; N, 9.18. Found: C, 63.2; H, 4.12; N, 9.49.

6.1.21. 3-(4-Chlorophenyl)-5-nitroisoquinolin-1-one (21e).

Compound **12e** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21e** (64%) as bright yellow crystals: mp 231-233°C (decomp.); ^1H NMR ($(CD_3)_2SO$) δ 7.22 (1 H, d, *J* = 0.8 Hz, 4-H), 7.59 (2 H, d, *J* = 8.6 Hz, Me 3,5-H_2), 7.65 (1 H, t, *J* = 8.2 Hz, 7-H), 7.79 (2 H, d, *J* = 8.6 Hz, Ph 2,6-H_2), 8.47 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.58 (1 H, ddd, *J* = 8.2, 1.2, 0.8 Hz, 8-H), 12.13 (1 H, br s, NH); (FAB) *m/z* 303.0360 (M + H) ($C_{15}H_{10}{}^{37}ClN_2O_3$ requires 303.0350), 301.0377 (M + H) ($C_{15}H_{10}{}^{35}ClN_2O_3$ requires 301.0380); Anal. Calcd. for $C_{15}H_9ClN_2O_3 \cdot 0.25H_2O$: C, 59.02; H, 3.11; N, 9.18. Found: C, 58.8; H, 3.11; N, 9.11.

6.1.22. 5-Nitro-3-(thiophen-2-yl)isoquinolin-1-one (21f).

Compound **12f** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21f** (63%) as orange crystals: mp 225°C (decomp.); IR ν_{max} 3458, 1670, 1616, 1514, 1319 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 7.21 (1 H, dd, *J* = 5.1, 3.9 Hz, thiophene 4-H), 7.33 (1 H, d, *J* = 0.8 Hz, 4-H), 7.60 (1 H, t, *J* = 8.2 Hz, 7-H), 7.77 (1 H, dd, *J* = 5.1, 1.2 Hz, thiophene 5-H), 7.93 (1 H, dd, *J* = 3.9, 1.2 Hz, thiophene 3-H), 8.47 (1 H, dd, *J* = 8.2, 1.2 Hz, 6-H), 8.54 (1 H, ddd, *J* = 8.2, 1.2, 0.8 Hz, 8-H), 12.13 (1 H, br s, NH); ^{13}C NMR δ (some C_q omitted) 95.84, 125.24, 126.48, 127.88, 128.63, 129.12, 130.12, 130.88, 133.29; MS (EI) *m/z* 272.0257 (M) ($C_{13}H_8N_2O_3S$ requires 272.0256); Anal. Calcd. for $C_{13}H_8N_2O_3S \cdot 0.25H_2O$: C, 56.42; H, 3.07; N, 10.13. Found: C, 56.7; H, 3.15; N, 10.0.

6.1.23. 3-Methyl-5-nitroisoquinolin-1-one (21g).

Compound **12g** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21g** (68%) as bright yellow crystals: mp 231-232°C (lit.[23] mp 231-232°C); IR ν_{max} 3435, 1668, 1523, 1346 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 2.29 (3 H, s, Me), 6.78 (1 H, brs, 4-H), 7.55 (1 H, t, *J* = 7.8 Hz, 7-H), 8.38 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 8.49 (1 H, ddd, *J* = 7.8, 1.2 Hz, 8-H), 11.79 (1 H, brs, NH); MS (FAB) *m/z* 205.0617 (M + H) ($C_{10}H_9N_2O_3$ requires 205.0613), 189 (M – Me); Anal. Calcd. for $C_{10}H_8N_2O_3$: C, 58.82; H, 3.95; N, 13.72. Found: C, 58.4; H, 3.99; N, 13.5.

6.1.24. 5-Nitro-3-pentylisoquinolin-1-one (21h).

Compound **12h** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21h** (29%) as bright yellow crystals: mp 158-159°C; IR ν_{max} 3467, 1666, 1524, 1375 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 0.86-0.89 (3 H, m, pentyl 5-H_3), 1.28-1.34 (4 H, m, pentyl 3,4-H_4), 1.60-1.67 (2 H, m, pentyl 2-H_2), 2.55 (2 H, t, *J* = 7.6 Hz, pentyl 1-H_2), 6.79 (1 H, s, 4-H), 7.56 (1 H, t, *J* = 7.8 Hz, 7-H), 8.39 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 8.50 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 11.77 (1 H, brs, NH); MS (EI) *m/z* 260.1162 (M) ($C_{14}H_{16}N_2O_3$ requires 260.1161).

6.1.25. 5-Nitro-3-phenylmethylisoquinolin-1-one (21i).

Compound **12i** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21i** (83%) as bright yellow crystals: mp 203-204°C (decomp.); IR ν_{max} 3186, 1645, 1524, 1323 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 3.92 (2 H, s CH_2), 6.80 (1 H, s, 4-H), 7.24-7.34 (5 H, m, Ph-H_5), 7.57 (1 H, t, *J* = 7.8 Hz, 7-H), 8.39 (1 H, d, *J* = 7.8 Hz, 6-H), 8.49 (1 H, d, *J* = 7.8 Hz, 8-H), 11.93 (1 H, br s, NH); MS (EI) *m/z* 280.0848 (M) ($C_{16}H_{12}N_2O_3$ requires 280.0848).

6.1.26. 3-Ethyl-5-nitroisoquinolin-1-one (21j).

Compound **12j** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21j** (38%) as bright yellow crystals: mp 196-197°C; IR ν_{max} 3432, 1666, 1524, 1372 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 1.22 (3 H, t, *J* = 7.5 Hz, Me), 2.59 (2 H, q, *J* = 7.5 Hz, CH_2), 6.80 (1 H, s, 4-H), 7.56 (1 H, t, *J* = 8.1 Hz, 7-H), 8.40 (1 H, dd, *J* = 8.1, 1.5 Hz, 6-H), 8.51 (1 H, dd, *J* = 8.1, 1.5 Hz, 8-H), 11.79 (1 H, brs, NH); MS (FAB) *m/z* 219.0779 (M + H) ($C_{11}H_{11}N_2O_3$ requires 219.0770).

6.1.27. 5-Nitro-3-(2-methylpropyl)isoquinolin-1-one (21k).

Compound **12k** was treated with NH_3 in 2-methoxyethanol, as for the synthesis of **21a**, to give **21k** (89%) as bright yellow crystals: mp 184-185°C; IR ν_{max} 3436, 1655, 1523, 1376 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 0.91 (6 H, d, *J* = 6.6 Hz, 2 × Me), 1.97-2.04 (1 H, m, CH_2CH), 2.43 (2 H, d, *J* = 7.0 Hz, CH_2), 6.77 (1 H, s, 4-H), 7.56 (1 H, t, *J* = 7.8 Hz, 7-H), 8.40 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 8.50 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 11.76 (1 H, brs, NH); MS (EI) *m/z* 246.1003 (M) ($C_{13}H_{14}N_2O_3$ requires 246.1004).

6.1.28. 5-Amino-3-(4-trifluoromethylphenyl)isoquinolin-1-one (22a). Method A.

Compound **21a** (1.0 g, 3.0 mmol) was heated at 70°C with $SnCl_2$ (1.8 g, 9.5 mmol) in EtOH (50 mL) for 4 h, then poured into ice-H_2O (200 mL). The suspension was made alkaline with aq. NaOH and filtered. Extraction of the filtrate (EtOAc), evaporation and recrystallisation (hexane / EtOAc) gave **22a** (360 mg, 40%) as yellow crystals: mp 214-215°C; IR ν_{max} 3419,

3218, 1651 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 5.86 (2 H, br s, NH_2), 6.88 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.18 (1 H, t, *J* = 7.8 Hz, 7-H), 7.22 (1 H, s, 4-H), 7.40 (1 H, d, *J* = 7.8, 1.2 Hz, 8-H), 7.82 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H_2), 8.02 (2 H, d, *J* = 8.2 Hz, 2,6-H_2), 11.45 (1 H, brs, NH); ^{19}F NMR ($(CD_3)_2SO$) δ_F -61.60 (s, CF_3); MS (FAB) *m/z* 305.0898 (M + H) ($C_{16}H_{12}F_3N_2O$ requires 305.0902). A sample was converted into **22a**.HCl salt: pale buff solid; mp >350°C; ^1H NMR ($(CD_3)_2SO$) δ 7.14 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.18 (1 H, s, 4-H), 7.31 (1 H, t, *J* = 7.8 Hz, 7-H), 7.63 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 7.85 (2 H, d, *J* = 8.2 Hz, Ph 3,5-H_2), 8.01 (2 H, d, *J* = 8.2 Hz, 2,6-H_2), 11.60 (1 H, brs, NH); ^{19}F NMR ($(CD_3)_2SO$) δ -59.50 (s, CF_3). A small sample of **22a** was also converted into **22a**.HBr salt: buff solid; mp >360°C; IR ν_{max} 3414, 3165, 1647, 1327, 1170, 1116; ^1H NMR ($(CD_3)_2SO$) δ 7.17 (2 H, m, 4,6-H_2), 7.32 (1 H, t, *J* = 7.5 Hz, 7-H), 7.67 (1 H, d, *J* = 7.5 Hz, 8-H), 7.88 (2 H, d, *J* = 8.0 Hz, Ph 3,5-H_2), 8.04 (2 H, d, *J* = 8.0 Hz, Ph 2,6-H_2), 11.63 (1 H, br, NH); ^{13}C NMR ($(CD_3)_2SO$) (HSQC / HMBC) δ 99.53 (4-C), 117.08 (8-C), 118.87 (6-C), 123.51 (8a-C), 124.11 (q, *J* = 270.6 Hz, CF_3), 125.64 (q, *J* = 3.5 Hz, Ph 3,5-C_2), 126.28 (4a-C), 127.41 (7-C + Ph 2,6-C_2), 129.20 (q, *J* = 31.8 Hz, Ph 4-C), 136.82 (Ph 1-C), 137.83 (3-C), 139.92 (5-C), 162.46 (1-C); ^{19}F NMR ($(CD_3)_2SO$) d -61.02 (s, CF_3); MS *m/z* (ES) 303.0756 (M - H) ($C_{16}H_{10}F_3N_2O$ requires 303.0745).

6.1.29. 5-Amino-3-(4-trifluoromethylphenyl)isoquinolin-1-one hydrochloride (22a). Method B.

Compound **21a** (140 mg, 0.42 mmol) and Pd/C (10%, 70 mg) in EtOH (15 mL) and aq. HCl (34%, 0.4 mL) were stirred vigorously under H_2 for 2 h. The suspension was filtered through Celite. The Celite pad and residue were suspended in water (100 mL) and heated. The hot suspension was filtered through a second Celite pad. Evaporation of the solvent and drying gave **21a** (60 mg, 42%), with data as above.

6.1.30. 5-Amino-3-phenylisoquinolin-1-one (22b).

Compound **21b** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22b** (57%) as yellow crystals: mp 215-217°C; IR ν_{max} 3569, 3329, 3230, 1655 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.00 (2 H, br s, NH_2), 6.64 (1 H, s, 4-H), 6.93 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.22 (1 H, t, *J* = 7.8 Hz, 7-H), 7.36-7.45 (3 H, m, Ph 3,4,5-H_3), 7.64-7.66 (2 H, m, Ph 2,6-H_2), 7.80 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 10.08 (1 H, br s, NH); MS *m/z* (FAB) 237.1019 (M + H) ($C_{15}H_{13}N_2O$ requires 237.1028). Compound **22b** (50 mg, 0.2 mmol) was stirred with aq. HCl (2 M, 20 mL) for 30 min. Evaporation and recrystallisation (MeOH) yielded **22b**.HCl salt (53 mg, 91%) as a pale buff solid: mp 192-193°C; ^1H NMR (D_2O) δ 6.98 (1 H, s, 4-H), 7.52-7.59 (3 H, m, Ph 3,4,5-H_3), 7.59 (1 H, t, *J* = 8.1 Hz, 7-H), 7.68-7.75 (2 H, m, Ph 2,6-H_2), 7.84 (1 H, d, *J* = 8.1 Hz, 6-H), 8.31 (1 H, d, *J* = 8.1 Hz, 8-H). A small sample of **22b** was also converted into **22b**.HBr salt: pale buff solid; mp 274-275°C; IR ν_{max} 3425, 2923, 1629; ^1H NMR (CD_3OD) δ 7.10 (1 H, s, 4-H), 7.28 (1 H, d, *J* = 7.7 Hz, 6-H), 7.38 (1 H, t, *J* = 7.8 Hz, 7-H), 7.55 (3 H, m, Ph 3,4,5-H_3), 7.80 (1 H, d, *J* = 7.6 Hz, 8-H), 7.87 (2 H, m, Ph 2,6-H_2), 11.55 (1 H, s, N-H); ^{13}C NMR (CD_3OD) (HSQC / HMBC) δ 98.36 (4-C), 127.45 (4a-C), 127.67 (7-C), 128.13 (Ph 2,6-C_2), 128.96 (8-C), 129.46 (6-C), 130.32 (Ph 3,4,5-C_3), 131.34 (Ph 4-C), 134.00 (8a-C), 135.28 (Ph 1-C), 144.34 (5-C), 164.63 (1-C).

6.1.31. 5-Amino-3-(4-methylphenyl)isoquinolin-1-one (22c). Method A.

Compound **21c** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22c** (92%) as pale yellow crystals: mp 213-214°C; IR ν_{max} 3476, 3253, 1669 cm^{-1}; ^1H

NMR ($CDCl_3$) δ 2.41 (3 H, s, Me), 4.06 (2 H, br, NH_2), 6.68 (1 H, s, 4-H), 6.99 (1 H, d, *J* = 7.8 Hz, 6-H), 7.28 (1 H, t, *J* = 7.8 Hz, 7-H), 7.29 (2 H, d, *J* = 7.8 Hz, Ph 3,5-H_2), 7.59 (2 H, d, *J* = 7.8 Hz, Ph 2,6-H_2), 7.86 (1 H, d, *J* = 7.8 Hz, 8-H), 9.92 (1 H, br, NH); MS *m/z* (FAB) 251.1181 (M + H) ($C_{16}H_{15}N_2O$ requires 251.1184). A sample was converted into **22c**.HCl salt: pale buff solid; mp >350°C; ^{1}H NMR ($(CD_3)_2SO$) δ 2.23 (3 H, s, Me), 6.48 (1 H, s, 4-H), 7.31 (2 H, d, *J* = 7.8 Hz, Ph 3,5-H_2), 7.36 (1 H, t, *J* = 7.8 Hz, 7-H), 7.61 (1 H, d, *J* = 7.8 Hz, 6-H), 7.75 (1 H, d, *J* = 7.8 Hz, 8-H), 7.96 (2 H, d, *J* = 7.8 Hz, Ph 2,6-H_2), 11.47 (1 H, br, NH).

6.1.32. 5-Amino-3-(4-methylphenyl)isoquinolin-1-one hydrochloride (22c). Method B.

Compound **21c** was treated with H_2 and Pd/C in EtOH and aq. HCl, as for the synthesis of **22a** (Method B), to give **22c** (79%) as a pale buff solid, with data as above.

6.1.33. 5-Amino-3-(4-methoxyphenyl)isoquinolin-1-one (22d).

Compound **21d** (80 mg, 0.3 mmol) was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22d** (83%) as yellow crystals: mp 189-190°C; IR ν_{max} 3438, 3233, 1660 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 3.86 (3 H, s, Me), 4.11 (2 H, br, NH_2), 6.64 (1 H, s, 4-H), 6.97 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 6.99 (2 H, d, *J* = 8.8 Hz, Ph 3,5-H_2), 7.25 (1 H, t, *J* = 7.8 Hz, 7-H), 7.66 (2 H, d, *J* = 8.8 Hz, Ph 2,6-H_2), 7.85 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 10.45 (1 H, brs, NH); MS (FAB) *m/z* 267.1132 (M + H) ($C_{16}H_{15}N_2O_2$ requires 267.1134). A sample was converted into **22d**.HCl salt: buff solid; mp >350°C; ^{1}H NMR (D_2O) δ 3.86 (3 H, s, OMe), 6.84 (2 H, d, *J* = 8.1 Hz, Ph 3,5-H_2), 6.92 (1 H, s, 4-H), 7.11 (1 H, t, *J* = 8.1 Hz, 7-H), 7.55 (1 H, d, *J* = 8.1 Hz, 6-H), 7.70 (1 H, d, *J* = 8.1 Hz, 8-H), 7.94 (2 H, *J* = 8.1 Hz, Ph 2,6-H_2).

6.1.34. 5-Amino-3-(4-chlorophenyl)isoquinolin-1-one (22e).

Compound **21e** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22e** (41%) as yellow crystals: mp 231-232°C; IR ν_{max} 3548, 3338, 3236, 1654 cm^{-1}; ^{1}H NMR ($(CD_3)_2SO$) δ 5.81 (2 H, br, NH_2), 6.86 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.11 (1 H, s, 4-H), 7.15 (1 H, t, *J* = 7.8 Hz, 7-H), 7.38 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 7.53 (2 H, d, *J* = 6.6 Hz, Ph 3,5-H_2), 7.83 (2 H, d, *J* = 6.6 Hz, Ph 2,6-H_2), 11.34 (1 H, brs, NH); MS (FAB) *m/z* 273.0618 (M + H) ($C_{15}H_{12}{}^{37}ClN_2O$ requires 273.0609), 271.0629 (M + H) ($C_{15}H_{12}{}^{35}ClN_2O$ requires 271.0638). A sample was converted into **22e**.HCl salt: buff solid; mp >350°C; ^{1}H NMR ($(CD_3)_2SO$) δ 7.08 (1 H, s, 4-H), 7.14 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.28 (1 H, t, *J* = 7.8 Hz, 7-H), 7.56 (2 H, d, *J* = 9.0 Hz, Ph 3,5-H_2), 7.64 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 7.83 (2 H, d, *J* = 9.0 Hz, Ph 2,6-H_2), 11.50 (1 H, brs, NH); ^{13}C NMR ($(CD_3)_2SO$) (HSQC / HMBC) δ 98.36 (4-C), 119.82 (8-C), 120.94 (6-H), 125.98 (8a-C), 126.92 (7-C), 127.68 (4a-C), 128.36 (Ph 2,6-C_2), 128.75 (Ph 3,5-C_2), 132.77 (Ph 1-C), 133.93 (Ph 4-C), 136.71 (5-C), 138.30 (3-C), 160.61 (1-C).

6.1.35. 5-Amino-3-(thiophen-2-yl)isoquinolin-1-one (22f).

Compound **21f** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22b** (66%) as yellow crystals: mp 229-230°C; IR ν_{max} 3470, 3365, 1659 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 4.03 (2 H, br s, NH_2), 6.70 (1 H, s, 4-H), 6.99 (1 H, dd, *J* = 7.8, 1.1 Hz, 6-H), 7.14 (1 H, dd, *J* = 4.9, 3.8 Hz, thiophene 4-H), 7.28 (1 H, t, *J* = 7.8 Hz, 7-H), 7.37 (1 H, dd, *J* = 4.9, 1.1 Hz, thiophene 5-H), 7.49 (1 H, dd, *J* = 3.8, 1.1 Hz, thiophene 3-H), 7.86 (1 H, dd, *J* = 7.8, 1.1 Hz, 8-H), 9.50 (1 H, br s, NH); MS (EI) *m/z* 242.0517 (M) ($C_{13}H_{10}N_2OS$ requires 242.0514). A sample was converted into **22f**.HCl salt: buff solid: mp >350°C; ^{1}H NMR (D_2O)

δ 6.87 (1 H, s, 4-H), 7.07 (1 H, dd, *J* = 4.9, 3.8 Hz, thiophene 4-H), 7.26 (1 H, d, *J* = 4.9 Hz, thiophene 5-H), 7.53 (1 H, d, *J* = 3.8 Hz, thiophene 3-H), 7.58 (1 H, t, *J* = 7.8 Hz, 7-H), 7.77 (1 H, d, *J* = 7.8 Hz, 6-H), 8.22 (1 H, d, *J* = 7.8 Hz, 8-H).

6.1.36. 5-Amino-3-methylisoquinolin-1-one (22g).

Compound **21g** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22g** (59%) as pale yellow crystals: mp 183-184°C (lit.[23] mp 183-184°C); IR ν_{max} 3467, 3375, 3298, 1655 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 2.18 (3 H, s, Me), 5.47 (2 H, br, NH_2), 6.44 (1 H, s, 4-H), 6.80 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.05 (1 H, t, *J* = 7.8 Hz, 7-H), 7.32 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 11.06 (1 H, brs, NH); MS *m/z* (FAB) 175.0874 (M + H) ($C_{10}H_{11}N_2O$ requires 175.0871), 159 (M – Me). A sample was converted into **22g**.HCl salt: pale buff solid: mp >350°C; IR ν_{max} 3414, 2851, 1685 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) (COSY / NOESY) δ 2.23 (3 H, s, Me), 6.48 (1 H, s, 4-H), 7.37 (1 H, t, *J* = 7.8 Hz, 7-H), 7.69 (1 H, d, *J* = 7.8 Hz, 6-H), 7.99 (1 H, d, *J* = 7.8 Hz, 8-H), 11.50 (1 H, brs, NH); ^{13}C NMR ($(CD_3)_2SO$) (HMQC, HMBC) 19.21 (Me), 97.20 (4-C), 125.25 (8-C), 125.51 (6-C), 125.7 (8a-C), 126.2 (7-C), 130.3 (4a-C), 138.79 (3-C), 140.0 (5-C), 161.99 (1-C); Anal. Calcd. for $C_{10}H_{11}ClN_2O$: C, 57.02; H, 5.26; N, 13.30. Found: C, 56.82; H, 5.01; N, 13.45.

6.1.37. 5-Amino-3-pentylisoquinolin-1-one (22h).

Compound **21h** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22h** (67%) as yellow crystals: mp 75-76°C; IR ν_{max} 3448, 3395, 3166, 1651 cm^{-1}; ^1H NMR δ 0.76-0.88 (3 H, m, pentyl 5-H_3), 1.21-1.34 (4 H, m, pentyl 3,4-H_4), 1.66-1.78 (2 H, m, pentyl 2-H_2), 2.57 (2 H, t, *J* = 7.6 Hz, pentyl 1-H_2), 3.94 (2 H, br s, NH_2), 6.21 (1 H, s, 4-H), 6.92 (1 H, dd, *J* = 7.7, 1.2 Hz, 6-H), 7.20 (1 H, t, *J* = 7.7 Hz, 7-H), 7.84 (1 H, dd, *J* = 7.7, 1.2 Hz, 8-H), 11.75 (1 H, brs, NH); MS (EI) *m/z* 230.1418 (M) ($C_{14}H_{18}N_2O$ requires 230.1419). A sample was converted into **22h**.HCl salt: buff solid; mp 129-130°C; ^1H NMR (D_2O) δ 0.74-0.82 (3 H, m, pentyl 5-H_3), 1.19-1.29 (4 H, m, pentyl 3,4-H_4), 1.55-1.66 (2 H, m, pentyl 2-H_2), 2.55 (2 H, t, *J* = 7.6 Hz, pentyl 1-H_2), 6.53 (1 H, s, 4-H), 7.49 (1 H, t, *J* = 7.8 Hz, 7-H), 7.74 (1 H, d, *J* = 7.8 Hz, 6-H), 8.20 (1 H, d, *J* = 7.8 Hz, 8-H).

6.1.38. 5-Amino-3-phenylmethylisoquinolin-1-one (22i).

Compound **21i** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22i** (64%) as yellow crystals: mp 85-86°C; IR ν_{max} 3469, 3394, 3162, 1661 cm^{-1}; ^1H NMR ($CDCl_3$) δ 3.91 (2 H, s CH_2), 4.00 (2 H, br s, NH_2), 6.72 (1 H, d, *J* = 8.1 Hz, 6-H), 6.86 (1 H, s, 4-H), 6.91 (1 H, t, *J* = 8.1 Hz, 7-H), 7.17–7.43 (5 H, m, Ph-H_5), 7.83 (1 H, d, *J* = 8.1 Hz, 8-H), 10.94 (1 H, br s, NH); MS (EI) *m/z* 250.1100 (M) ($C_{16}H_{14}N_2O$ requires 250.1106). A sample was converted into **22i**.HCl salt: buff solid; mp >350°C; ^1H NMR (D_2O) δ 3.94 (2 H, s CH_2), 6.49 (1 H, s, 4-H), 7.25–7.37 (5 H, m, Ph-H_5), 7.51 (1 H, t, *J* = 7.8 Hz, 7-H), 7.73 (1 H, d, *J* = 7.8 Hz, 6-H), 8.23 (1 H, d, *J* = 7.8 Hz, 8-H).

6.1.39. 5-Amino-3-ethylisoquinolin-1-one (22j).

Compound **21j** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22j** (24%) as pale yellow crystals: mp 162-163°C; IR ν_{max} 3447, 3395, 3164, 1646 cm^{-1}; ^1H NMR ($(CD_3)_2SO$) δ 1.21 (3 H, t, *J* = 7.5 Hz, Me), 2.47 (2 H, q, *J* = 7.4 Hz, CH_2), 5.51 (2 H, br s, NH_2), 6.44 (1 H, d, *J* = 0.8 Hz, 4-H), 6.80 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.05 (1 H, t, *J* = 7.8 Hz, 7-H), 7.33 (1 H, ddd, *J* = 7.8, 1.2, 0.8 Hz, 8-H), 11.04 (1 H, brs, NH); MS (FAB)

m/z 189.1026 (M + H) ($C_{11}H_{13}N_2O$ requires 189.1028). Anal. Calcd. for ($C_{11}H_{12}N_2O$.0.25 H_2O) C, 68.57; H, 6.49; N, 14.55; Found: C, 68.9; H, 6.45; N, 14.3. A sample was converted into **22j**.HCl salt: buff solid; mp 133-134°C; ^{1}H NMR ($(CD_3)_2SO$) δ 1.22 (3 H, t, *J* = 7.4 Hz, Me), 2.53 (2 H, q, *J* = 7.4 Hz, CH_2), 6.44 (1 H, s, 4-H), 7.34 (1 H, t, *J* = 7.8 Hz, 7-H), 7.47 (1 H, dd, *J* = 7.8, 1.2 Hz, 6-H), 7.91 (1 H, dd, *J* = 7.8, 1.2 Hz, 8-H), 11.41 (1 H, brs, NH).

6.1.40. 5-Amino-3-(2-methylpropyl)isoquinolin-1-one (22k).

Compound **21k** was treated with $SnCl_2$ in EtOH, as for the synthesis of **22a** (Method A), to give **22k** (83%) as yellow crystals: mp 113-114°C; IR ν_{max} 3468, 3396, 3165, 1645 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.82 (6 H, d, *J* = 6.4 Hz, 2 × Me), 1.90-2.02 (1 H, m, CH_2CH), 2.32 (2 H, d, *J* = 7.4 Hz, CH_2), 3.99 (2 H, br, NH_2), 6.14 (1 H, s, 4-H), 6.84 (1 H, dd, *J* = 7.9, 1.2 Hz, 6-H), 7.10 (1 H, t, *J* = 7.9 Hz, 7-H), 7.71 (1 H, dd, *J* = 7.9, 1.2 Hz, 8-H), 11.52 (1 H, br s, NH); MS (EI) *m/z* 216.1263 (M) ($C_{13}H_{16}N_2O$ requires 216.1263). A sample was converted into **22k**.HCl salt: buff crystals; mp 151-152°C; ^{1}H NMR (D_2O) δ 0.88 (6 H, d, *J* = 6.6 Hz, 2 × Me), 1.89-1.93 (1 H, m, CH_2CH), 2.47 (2 H, d, *J* = 7.4 Hz, CH_2), 6.52 (1 H, s, 4-H), 7.50 (1 H, t, *J* = 7.9 Hz, 7-H), 7.76 (1 H, d, *J* = 7.9 Hz, 6-H), 8.22 (1 H, d, *J* = 7.9 Hz, 8-H).

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