N- and *O*-Alkylation of isoquinolin-1-ones in the Mitsunobu reaction: development of potential drug delivery systems

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Regioselective methods were investigated to prepare *N*- and *O*-alkylated isoquinolin-1-ones efficiently. The predicted regioselective alkylation of the nitrogen with (hetero)benzyl halides was complemented using (hetero)benzylic Mitsunobu electrophiles to alkylate predominantly at the oxygen. A series of drug-delivery conjugates was prepared demonstrating control over the site of alkylation. The Mitsunobu reaction provides a new approach to 1-alkoxy-isoquinolines that were unavailable *via* previous harsher synthetic methods.

Introduction

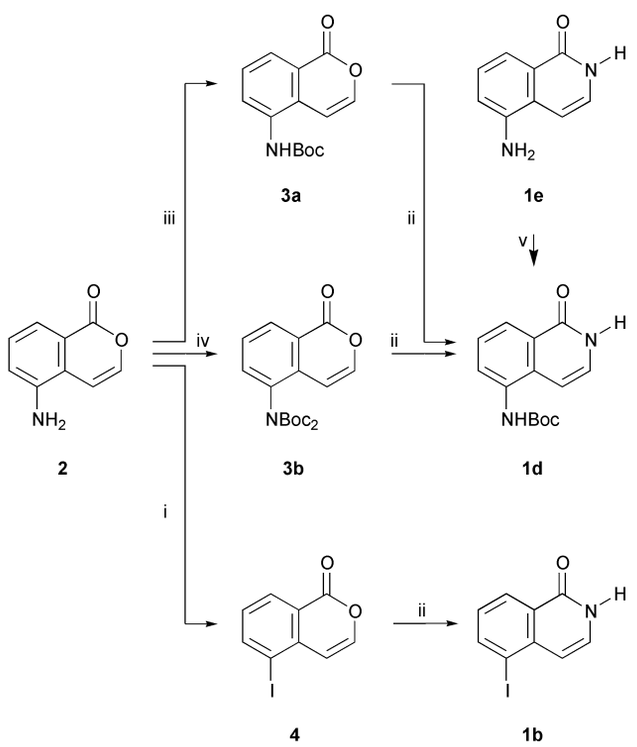
Repair and maintenance of chromosomes are, in part, controlled by the addition and removal of polymers of ADP-ribose to the DNA-binding proteins involved.[1] ADP-ribose units are added by poly(ADP-ribose)polymerase (PARP) and removed by poly(ADP-ribose)glycohydrolase (PARG). The involvement of poly(ADP-ribosyl)ation in a wide range of physiological and pathophysiological processes renders it a useful target to study biological systems and for therapeutic intervention strategies. Pathophysiological effects are mediated through overactivity of the isoform PARP-1, which depletes stores of nicotinamide adenine dinucleotide (NAD^+), the PARP substrate, leading to cell death.

5-Substituted isoquinoline-1-ones are potent inhibitors[2,3] of PARP with potential therapeutic applications in several diseases, including cancer,[4] myocardial infarction,[5] diabetes,[6] stroke,[7] rheumatoid arthritis,[8] haemorrhagic shock[3] and retroviral infections.[9] As a regulatory enzyme, PARP has beneficial roles in health and detrimental roles in disease and, therefore, inhibitors need to be targeted selectively to diseased tissues. We are developing analogues with greater aqueous solubility and prodrugs for their site-specific release. Our aim is to develop strategies to control attachment of masking prodrug units *via* either the 2-nitrogen or the exocyclic oxygen to compare the pharmacokinetic and drug release properties of these series of prodrugs.

Results and discussion

Deprotonation of isoquinolin-1-ones with base and reaction of the resulting anions with alkyl halides or tosylates are reported[10–12] to result in alkylation exclusively at nitrogen, giving 2-alkylisoquinolin-1-ones, although Kaneko *et al.*[13] note that traces (<2%) of the corresponding *O*-alkylated products (1-alkoxyisoquinolines) are also obtained in reactions with 4-bromobut-1-ene and its homologues. Interestingly, harder electrophiles, such as triflic anhydride[14] and silylating agents,[15] react at exocyclic oxygen, although the nucleophile may be the neutral molecule in these cases. 1-Alkoxyisoquinolines have generally been prepared by displacement of halides or other leaving groups from the 1-position of isoquinolines with nucleophilic alkoxides,[14,16] although the range of groups that can be introduced is limited to simple examples by the harsh conditions necessary.

Several routes were employed for the synthesis of the starting isoquinoline-1-ones used in this study (Scheme 1). Isoquinolin-1-one **1a** ("isocarbostyril") is commercially available. Our previously reported synthesis[11] of 5-iodoisoquinolin-1-one **1b**, by Curtius rearrangement of 2′-iodocinnamoyl azide and cyclisation of the intermediate 2-(2-iodophenyl)ethenyl isocyanate at



Scheme 1 Synthetic approaches to 5-iodoisoquinolin-1(2*H*)-one **1b** and 5-(Boc-amino)isoquinolin-1(2*H*)-one **1d**. *Reagents and conditions*: i, $NaNO_2$–aq. HCl–KI, 0 °C; ii, NH_3–$MeOCH_2CH_2OH$, reflux; iii, Boc_2O (1.5 equiv.)–Et_3N–CH_2Cl_2–DMF; iv, Boc_2O (3.0 equiv.)–Et_3N–CH_2Cl_2–DMF; v, Boc_2O (3.0 equiv.)–Et_3N–DMF.

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280 °C, proved not to be amenable to the routine preparation of large quantities and a new route was required. Following the newer route to **1b**, 5-aminoisocoumarin **2** was diazotised and the diazonium group was replaced with iodine using potassium iodide; 5-iodoisocoumarin **4** was obtained in good yield (Scheme 1). Conversion to the isoquinolin-1-one **1b** was achieved in the usual manner, in a reliable 48% yield from **2**. 5-Bromoisoquinolin-1-one **1c** was prepared by diazotisation and Sandmeyer reaction of 5-aminoisocoumarin **2**, followed by replacement of the ring oxygen with nitrogen by treatment with ammonia at high temperature, as described previously.[17]

5-Aminoisoquinolin-1(2*H*)-one **1e** is a particularly effective inhibitor of PARP *in vivo*[3] but, to be able to study the nucleophilic reactivity of the 2-nitrogen and the exocyclic oxygen, the potentially more nucleophilic 5-amine required protection. In the first route to **1e**, the Boc-amino unit was assembled on the isocoumarin prior to conversion to the isoquinolinone (Scheme 1). Reaction of 5-aminoisocoumarin **2** with a small excess of di-*tert*-butyl dicarbonate led to the mono-Boc compound **3a**, whereas treatment with three equivalents gave the *N*,*N*-diBoc analogue **3b** in good yield. As expected, **3a** was converted to the mono-Boc isoquinolinone **1d** with ammonia in refluxing 2-methoxyethanol. When **3b** was subjected to the same conditions, not only was the isocoumarin converted to the isoquinolinone but also one of the Boc groups was ammonolysed from the 5-amino function, also giving the mono-Boc isoquinolinone **1d** efficiently. Direct introduction of Boc protection to 5-aminoisoquinolin-1(2*H*)-one **1e** also gave **1d** but in lower yield.

In model studies, (Scheme 2), the reactions of the isoquinolin-1(2*H*)-ones **1** with simple benzyl electrophiles were investigated. The 5-unsubstituted isoquinolinone **1a** was deprotonated with sodium hydride and the anion reacted with benzyl bromide to give the *N*-benzylated compound **6a** as the only isolable product.[11] Generation of the anions from the 5-haloisoquinolinones **1b**,**c** with the soluble non-nucleophilic base lithium bis(trimethylsilyl)amide was technically more facile. Again, alkylation with the benzyl chlorides **5b**,**c** gave only the products of *N*-alkylation, **6b**,**c**, respectively.[11] In contrast, reaction of **1a** with benzyl alcohol under Mitsunobu conditions gave only the *O*-benzylated product **7**.

Extension of the study to *pseudo*benzylic 5-membered ring heterocycles produced a similar outcome. The anion derived from isoquinolinone **1a** reacted only at nitrogen[11] with 2-chloromethylfuran **8a** and 5-nitrofuran-2-yl tosylates **8b**, affording the isoquinolinones **9a**,**b**. The yield of the nitrofuranylmethylisoquinolinone was low, probably owing to side-reactions involving the relatively acidic methylene protons in **8b**. Similarly, the anion of **1a** reacted with 2-chloromethylthiophene **8c** only at nitrogen, giving **9c**. However, this anion only served to degrade the corresponding nitrothiophene electrophile 2-chloromethyl-5-nitrothiophene;[18] the methylene protons are presumably even more acidic in these molecules than are those in **8b**. In this series, the Mitsunobu alkylations were carried out using (5-nitro-2-thienyl)methanol **8d** as the electrophile; this represents a sterner test of the applicability of the process, owing to the possibility of reduction of the nitro group by the triphenylphosphine. Reaction of the isoquinolinones **1a**–**c** with **8d** under the standard Mitsunobu conditions, however, led to the *O*-alkylated products **10a**–**c**, respectively, in moderate yields but without any trace of formation of *N*-alkylated materials.

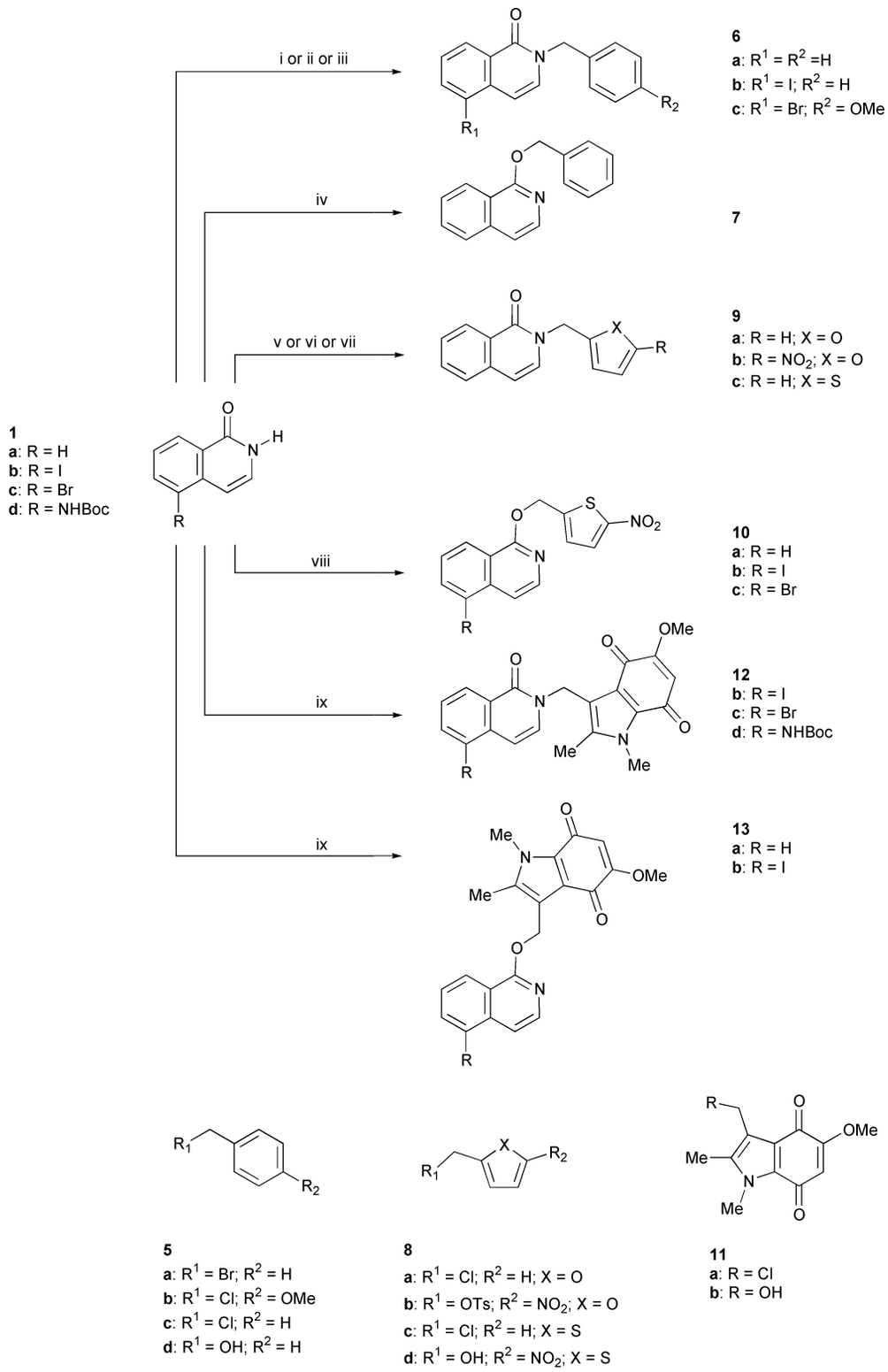
Thus, in the cases of the monocyclic benzylic electrophiles **5** and **8**, the outcomes of the reactions are clearly defined: conventional alkylation with benzylic halides and tosylates gives only reaction at nitrogen, whereas the Mitsunobu conditions give exclusively the *O*-alkylated products. With the bicyclic electrophiles **11** based on the 4,7-dioxoindole-3-methylene unit, however, the outcomes are more subtle. All attempts to alkylate the anions derived from the isoquinolinones **1a**–**c** with the chloromethyl-1*H*-indole-4,7-dione **11a**[19] failed. The indoledione unit was destroyed under the basic reaction conditions; the isoquinolinone anions are clearly much more basic than are the phenolate anions which are reported[19] to react smoothly with this reagent. Naylor *et al.*[19] observed solvent-dependent regioselectivity in alkylation of 2-fluorophenolate and 4-fluorophenolate, ethyl acetate favouring *C*-alkylation and DMF favouring *O*-alkylation. When the isoquinolinones **1a**–**d** were treated with the corresponding alcohol **11b** under Mitsunobu conditions, both the *N*-alkylated isoquinolinones **12** and the 1-alkoxyisoquinolines **13** were obtained, although never as mixtures. In repeated experiments, the 5-unsubstituted isoquinolinone **1a** only reacted at oxygen, giving **13a**. In contrast, the 5-bromo- and 5-Boc-amino analogues **1c**,**d** gave only the *N*-linked compounds **12c**,**d**. Most surprisingly, the 5-iodoisoquinolin-1(2*H*)-one **1b** gave the *N*-linked product **12b** and the *O*-linked product **13b** not as a mixture but as the sole isolable products from different experiments under apparently the same conditions.

Table 1 Selected NMR chemical shifts[a] for the *N*-alkylisoquinolinones and 1-alkoxyisoquinolines

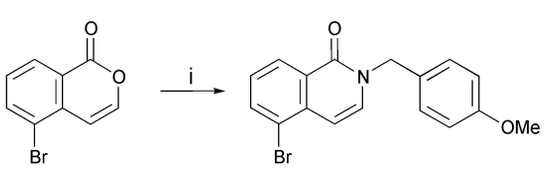
Compound	δ_H (CH_2)	δ_C (CH_2)	δ_H (3-H)	δ_H (4-H)
6a	5.20[b]	51.6[b]	7.06[b]	6.46[b]
6b	5.22[b]	51.9[b]	7.19[b]	6.72[b]
6c	5.15	[c]	7.18	6.82
7	5.58	[c]	8.00	7.25
9a	5.17[b]	44.2[b]	7.14[b]	6.45[b]
9b	5.23[b]	[c]	7.24[b]	6.58[b]
9c	5.34	[c]	7.5	6.49
10a	5.74	62.3	8.00	7.30
10b	5.74	62.8	8.10	7.49
10c	5.75	62.9	8.12	7.65
12b	5.29	32.6	7.80	6.66
12c	5.30	32.6	7.82	6.77
12d	5.25	[c]	7.47	6.57
13a	5.72	53.4	8.00	7.20
13b	5.71	56.4	8.08	7.40

[a] Spectra recorded of solutions in $CDCl_3$. [b] Data taken from [ref. 10]. [c] Not determined.

Distinction between the structures of the *N*-alkylisoquinolinones **6**, **9**, **12** and 1-alkoxyisoquinolines **7**, **10**, **13** was made primarily on the basis of their ^1H and ^{13}C NMR spectra (Table 1). Taking the isomeric pair **6a** and **7**, the NCH_2 protons of **6a** resonate at δ 5.20, whereas the OCH_2 proton signal of **7** appears downfield at δ 5.58, due to the greater electronegativity of oxygen. Significant changes in chemical shift are also seen for two of the isoquinoline protons. In **6a**, the 3-H resonates at δ 7.06 and the 4-H at δ 6.46; in **7**, the corresponding signals are at δ 8.00 and δ 7.25, respectively, reflecting the enamide character of the isoquinolin-1(2*H*)-one and the greater aromaticity of the 1-alkoxyisoquinoline. The signals of the protons of the carbocyclic rings are relatively similar for the two compounds and are not diagnostic. Using this guide, **6b**,**c** can be identified as *N*-benzylisoquinolinones in showing chemical shifts for the CH_2 protons and for 3-H and 4-H as does **6a**. Further confirmation of the structure of **6b** was given by an unequivocal synthesis, as shown in Scheme 3. 5-Bromoisocoumarin **14** (prepared as described previously by us[17]) was condensed with 4-methoxybenzylamine to give **6b** in modest yield. Since the methoxybenzyl unit was attached to nitrogen in the reagent, the product of this reaction must be 5-bromo-*N*-(4-methoxybenzyl)isoquinolin-1(2*H*)-one **6b**, rather than any *O*-linked isomer. The general pattern of proton chemical shifts was similar for the furans **9a**,**b** and the thiophenes **9c**, **10a**–**c**. In the *N*-linked compounds **9**, the CH_2 protons resonated in the range δ 5.1–5.4 and in the *O*-linked **10**, the corresponding signals appeared at δ *ca.* 5.7. In **9**, the isoquinoline 3-H and 4-H signals were at δ 7.1–7.5 and δ 6.4–6.6, whereas in **10**, the signals



Scheme 2 Studies on the *N*- and *O*-alkylation of isoquinolin-1(2*H*)-ones **1a**–**d**. *Reagents*: i, NaH–DMF–**5a**; ii, $LiN(SiMe_3)_2$–THF–**5b**–NaI; iii, $LiN(SiMe_3)_2$–THF–**5c**–NaI; iv, Ph_3P–diethyl azodicarboxylate (DEAD)–**5d**–THF; v, $LiN(SiMe_3)_2$–THF–**8a**–NaI; vi, NaH–DMF–**8b**; vii, $LiN(SiMe_3)_2$–THF–**8c**; viii, Ph_3P–DEAD–**8d**–THF; ix, Ph_3P–DEAD–**11b**–THF.



14 **6c**

Scheme 3 Unequivocal synthesis of 5-bromo-2-(4-methoxybenzyl)isoquinolin-1(2*H*)-one **6c**. *Reagents and conditions*: i, 4-$MeOBnNH_2$, $MeOCH_2CH_2OH$, reflux.

were at δ 8.0–8.1 and δ 7.3–7.7, respectively. Clearly, the range of chemical shifts for 4-H in **10** is greater than that for 3-H, as the former is expected to be more influenced by the nature of the 5-substituent than is the latter. Similarly, in the indole-4,7-dione series **12** and **13**, highly diagnostic trends in chemical shift were observed. In these series, the nature of the *O*- or *N*-substituent is constant, so the chemical shifts should be more directly comparable. Hence, the resonances for the CH_2 protons of **12b**–**d** fall in the very narrow range δ 5.25–5.30 and the corresponding signals for **13a**,**b** are at δ 5.72 and δ 5.71,

respectively. As expected, the chemical shifts of 3-H and 4-H are sensitive to the nature of the 5-substituent. The chemical shifts in the ^{13}C NMR spectra show analogous trends, although the ranges are wider and sometimes overlapping. In the *N*-linked isoquinolinones **6**, **9**, **12**, the $^{13}CH_2$ peaks are in the range δ 32–52; whereas, in the *O*-linked isoquinolines **10**, **13**, the corresponding range is δ 53–63.

In this paper, we have reaffirmed the regioselectivity of alkylation of isoquinolin-1-one anions with (hetero)benzyl halides as taking place essentially exclusively at nitrogen. In contrast, reaction with benzylic and heterobenzylic Mitsunobu electrophiles takes place at oxygen in most cases. In some cases, the outcome of the reaction is extremely sensitive to the reaction conditions and to the nature of the 5-substituent of the isoquinolin-1-one; mixtures of products were never observed. Although Mitsunobu reactions with isoquinolin-1-ones as the nucleophilic component are previously unreported, Manhas *et al.*[20] achieved reaction of quinazolin-4-ones with steroid alcohols through the exocyclic oxygen of the heterocycles. These observations are consistent with regioselectivity being controlled by the hardness/softness of the nucleophiles and electrophiles involved. Such control is also evident in the *O*-selective alkylation of amides and the *S*-selective alkylation of thioamides with alcohols under Mitsunobu conditions;[21] phthalimide, of course, is alkylated at nitrogen in a synthetically useful approach to primary amines.[22] The Mitsunobu electrophile derived from the 4,7-dioxoindol-3-ylmethanol **11b** must be very close to matching hardness with the O and N nucleophilic centres of the isoquinolinone anions.

The Mitsunobu reaction is shown here to offer a potential approach to 1-alkoxyisoquinolines carrying useful functionality in the 1-substituent; such compounds are not available through previous harsh synthetic methods. The 2-(4,7-dioxo-1*H*-indol-3-ylmethyl)isoquinolin-1(2*H*)-ones and 1-[(4,7-dioxo-1*H*-indol-3-yl)methoxy]isoquinolines may represent a new class of prodrugs to target PARP inhibitors to hypoxic regions of solid tumours[17] and other diseased tissues.

Experimental

NMR spectra were recorded on samples in $CDCl_3$, unless otherwise stated. Mass spectra were obtained by fast atom bombardment (FAB) in the positive ion mode, unless otherwise stated. The stationary phase for chromatography was silica gel. Melting points are uncorrected. Solutions in organic solvents were dried with $MgSO_4$. Solvents were evaporated under reduced pressure. Experiments were conducted at ambient temperature, unless otherwise stated. The brine was saturated. DEAD refers to diethyl azodicarboxylate. DMF refers to dimethylformamide.

5-Iodoisoquinolin-1(2*H*)-one 1b

Compound **4** (300 mg, 1.1 mmol), in 2-methoxyethanol (50 cm^3), was saturated with ammonia for 1 h after which the mixture was boiled under reflux for 24 h. Evaporation yielded the isoquinolinone **1b** as pale buff crystals (200 mg, 68%): mp 239–242 °C (lit.[11] mp 238–244 °C); δ_H 6.67 (1 H, d, J = 7.4 Hz, 4-H), 7.13 (1 H, d, J = 7.4 Hz, 3-H), 7.17 (1 H, t, J = 7.5 Hz, 7-H), 8.15 (1 H, dd, J = 7.5, 1.1 Hz, 6-H), 8.35 (1 H, dd, J = 7.5, 1.1 Hz, 8-H) and 11.20 (1 H, s, NH).

5-(1,1-Dimethylethoxycarbonylamino)isoquinolin-1(2*H*)-one 1d

Method A. Compound **3a** was treated with ammonia, as in Method B, to give **1d** (76%) with properties as below.

Method B. Compound **3b** (68 mg, 0.19 mmol), in 2-methoxyethanol (10 cm^3), was saturated with NH_3 for 1 h after which the mixture was boiled under reflux for 24 h. Evaporation and chromatography (ethyl acetate–hexane 1 : 1) gave **1d** (35 mg, 71%) as pale yellow crystals: mp >230 °C (Found: C, 63.5; H, 6.28; N, 10.58. $C_{14}H_{16}N_2O_3 \cdot 0.25\ H_2O$ requires C, 63.60; H, 6.22, N, 10.20%); ν_{max} (KBr)/cm^{-1} 3320, 1690 and 1670; δ_H ($CDCl_3$) 1.54 (9 H, s, Bu^t), 6.58 (1 H, d, J 7.3, 4-H), 6.61 (1 H, brs, N*H*Boc), 7.22 (1 H, d, J 7.3, 3-H), 7.49 (1 H, t, J = 8.1 Hz, 7-H), 8.04 (1 H, d, J = 8.1 Hz, 6-H), 8.22 (1 H, d, J = 8.1 Hz, 8-H) and 10.60 (1 H, brs, NH); *m*/*z* 261.1235 (M + H) ($C_{14}H_{17}N_2O_3$ requires 261.1239) and 260.1169 (M) ($C_{14}H_{16}N_2O_3$ requires 260.1161).

Method C. Triethylamine (1.8 g, 18 mmol) was added to 5-aminoisoquinolin-1(2*H*)-one **1e**[3] (600 mg, 3.7 mmol) in DMF (40 cm^3) and the solution was cooled to 0 °C. Di-*tert*-butyl dicarbonate (2.45 g, 11.2 mmol) was added in portions during 2 d. The evaporation residue, in ethyl acetate, was washed with water and brine and was dried. Evaporation and chromatography (ethyl acetate–hexane 1 : 4) gave **1d** (0.57 g, 60%) as a pale yellow powder with properties as above.

5-(1,1-Dimethylethoxycarbonylamino)isocoumarin 3a

To 5-aminoisocoumarin[17] **2** (700 mg, 4.4 mmol) in dichloromethane (3.0 cm^3) was added DMF (3.5 cm^3) and triethylamine (0.070 cm^3). The solution was cooled to 0 °C, di-*tert*-butyl dicarbonate (1.4 g, 6.4 mmol) in CH_2Cl_2 (3.0 cm^3) was added and the mixture was stirred for 4 d. The evaporation residue, in ethyl acetate, was washed with water and brine. Evaporation and chromatography (ethyl acetate–hexane 1 : 4) gave **3a** (895 mg, 79%) as very pale yellow crystals: mp 188–190 °C (Found: C, 64.20; H, 5.83; N, 5.35. $C_{14}H_{15}N_1O_4$ requires C, 64.36; H, 5.75; N, 5.36%); ν_{max} (KBr)/cm^{-1} 3320, 1720 and 1682; δ_H 1.45 (9 H, s, Bu^t), 6.49 (1 H, d, J = 5.9 Hz, 4-H), 6.50 (1 H, br s, NH), 7.22 (1 H, d, J = 5.9 Hz, 3-H), 7.42 (1 H, t, J = 7.9 Hz, 7-H), 7.97 (1 H, d, J = 7.9 Hz, 6-H) and 8.02 (1 H, d, J = 7.9 Hz, 8-H); *m*/*z* 262.1085 (M + H) ($C_{14}H_{16}N_1O_4$ requires 262.1079), 261.1008 (M) ($C_{14}H_{15}N_1O_4$ requires 261.1001) and 206 (M − Bu^t).

5-[*N*,*N*-Bis(1,1-dimethylethoxycarbonyl)amino]isocoumarin 3b

To 5-aminoisocoumarin[17] **2** (100 mg, 0.62 mmol) in dichloromethane (1.0 cm^3) was added DMF (0.5 cm^3) and triethylamine (0.010 cm^3). The solution was cooled to 0 °C and di-*tert*-butyl dicarbonate (403 mg, 1.84 mmol) in dichloromethane (1.0 cm^3) was added during 10 min. The mixture was stirred for 4 d. The evaporation residue, in ethyl acetate, was washed with water and brine. Evaporation and chromatography (ethyl acetate–hexane 1 : 4) gave **3b** (130 mg, 58%) as white crystals: mp 165–167 °C; ν_{max} (KBr)/cm^{-1} 1720; δ_H 1.38 (18 H, s, 2 × Bu^t), 6.47 (1 H, dd, J = 5.9, 0.6 Hz, 4-H), 7.32 (1 H, d, J = 5.9 Hz, 3-H), 7.53 (1 H, t, J = 7.9 Hz, 7-H), 7.54 (1 H, dd, J = 7.9, 1.3 Hz, 6-H) and 8.29 (1 H, ddd, J = 7.9, 1.3, 0.6 Hz, 8-H); *m*/*z* 362.1617 (M + H) ($C_{19}H_{24}N_1O_6$ requires 362.1604), 361.1544 (M) ($C_{19}H_{23}N_1O_6$ requires 361.1525), 262 (M + H − Boc) and 206 (M + H − Boc − Bu^t).

5-Iodoisocoumarin 4

Sodium nitrite (2.6 g, 37.3 mmol) in water (200 cm^3) was added to 5-aminoisocoumarin **2**[17] (7.0 g, 43.4 mmol) in aq. hydrochloric acid (4.5 M, 250 cm^3) at 0 °C. A chilled solution of potassium iodide (10.0 g, 60 mmol) in water (250 cm^3) was added during 10 min. The mixture was stirred for 2 h before extraction with ethyl acetate. Evaporation and chromatography (hexane–ethyl acetate 4 : 1) yielded **4** (8.3 g, 70%) as off-white crystals: mp 155–156 °C; δ_H ($(CD_3)_2SO$) 6.75 (1 H, d, J = 5.9 Hz, 3-H), 7.37 (1 H, d, J = 7.9 Hz, 7-H), 7.75 (1 H, d,J = 5.9 Hz, 4-H), 8.22 (1 H, d, J = 7.6 Hz, 6-H) and 8.31 (1 H, d, J = 7.9 Hz, 8-H). This material was used without further purification or characterisation.

5-Bromo-2-(4-methoxyphenylmethyl)isoquinoline-1(2*H*)-one 6c

5-Bromoisocoumarin **14**[17] (100 mg, 0.44 mmol) in 2-methoxyethanol (1.0 cm^3) was boiled under reflux with 4-methoxybenzylamine (61 mg, 0.44 mmol) for 24 h. Evaporation, chromatography (hexane–ethyl acetate 5 : 1) and trituration (diethyl ether) gave **6c** (40 mg, 27%) as white crystals: mp 97–100 °C (lit.[11] mp 98–100 °C); ν_{max} (KBr)/cm^{-1} 1640, 1610 and 690; δ_H 3.79 (3 H, s, Me), 5.15 (2 H, s, CH_2), 6.82 (1 H, dd, J = 7.6, 0.5 Hz, 4-H), 6.87 (2 H, d, J = 8.5 Hz, Ph 3,5-H_2), 7.18 (1 H, d, J = 7.6 Hz, 3-H), 7.27 (2 H, J = 8.5 Hz, Ph 2,6-H_2), 7.33 (1 H, t, J = 8.0 Hz, 7-H), 7.87 (1 H, dd, J = 8.0, 1.5 Hz, 6-H) and 8.43 (1 H, ddd, J = 8.0, 1.5, 0.5 Hz, 8-H).

1-Phenylmethoxyisoquinoline 7

Isoquinolin-1(2*H*)-one **1a** was treated with triphenylphosphine, DEAD and **5d**, as for the synthesis of **10a**, except that the chromatographic eluant was ethyl acetate, to give **7** (39%) as a colourless oil: δ_H 5.58 (2 H, s, CH_2), 7.25 (1 H, d, J = 6.2 Hz, 4-H), 7.36 (5 H, m, Ph-H_5), 7.55 (1 H, dd, J = 8.5, 8.2 Hz, 7-H), 7.66 (1 H, t, J = 8.2 Hz, 6-H), 7.70 (1 H, d, J = 8.2 Hz, 5-H), 8.00 (1 H, d, J = 6.2 Hz, 3-H) and 8.31 (1 H, d, J = 8.5 Hz, 8-H); MS (EI^+) m/z 235.0997 (M) ($C_{16}H_{13}ON$ requires 235.0989).

2-(2-Thienylmethyl)isoquinolin-1(2*H*)-one 9c

2-Chloromethylthiophene[23] **8c** (270 mg, 2.0 mmol) and sodium iodide (5 mg) were added to isoquinolin-1-one **1a** (200 mg, 1.4 mmol) and lithium bis(trimethylsilyl)amide (1.0 M in THF, 2.8 mL, 2.8 mmol) in dry DMF (10 cm^3) and the mixture was stirred for 2 d under Ar. The evaporation residue, in ethyl acetate, was washed with water (2×) and brine (2×) and was dried. Evaporation and chromatography (ethyl acetate–hexane 1 : 1) gave **9c** (150 mg, 45%) as a pale buff glass; ν_{max} (KBr)/cm^{-1} 1640; δ_H 5.34 (2 H, s, CH_2), 6.49 (1 H, d, J = 7.3 Hz, isoquinoline 4-H), 6.95 (1 H, dd, J = 5.1, 3.5 Hz, thiophene 4-H), 7.11 (1 H, br d, J = 3.5 Hz, thiophene 3-H), 7.14 (1 H, d, J = 7.3 Hz, isoquinoline 5-H), 7.24 (1 H, dd, J = 5.3, 1.4 Hz, thiophene 5-H), 7.5 (2 H, m, isoquinoline 3,7-H_2), 7.62 (1 H, t, J = 7.5 Hz, isoquinoline 6-H) and 8.45 (1 H, d, J = 7.5 Hz, isoquinoline 8-H); δ_C 46.5, 106.6, 125.9, 126.1, 126.8, 126.9, 127.3, 128.0 (2 × C), 130.6, 132.3, 136.9, 138.8 and 161.9; m/z 242.0635 (M + H) ($C_{14}H_{11}NOS$ requires 242.0639).

1-(5-Nitro-2-thienylmethoxy)isoquinoline 10a

Isoquinolin-1(2*H*)-one **1a** (90 mg, 0.62 mmol) was stirred with triphenylphosphine (330 mg, 1.3 mmol) in dry tetrahydrofuran (20 cm^3) under Ar for 5 min. DEAD (209 mg, 1.2 mmol) was added dropwise. After 15 min, (5-nitro-2-thienyl)methanol[18] **8d** (100 mg, 0.63 mmol) was added and the mixture was stirred for 16 h. Evaporation and chromatography (ethyl acetate–hexane 1 : 1) gave **10a** (67 mg, 38%) as a pale buff oil: ν_{max} (film)/cm^{-1} 1631; δ_H 5.74 (2 H, s, CH_2), 7.12 (1 H, d, J = 4.0 Hz, thiophene 3-H), 7.30 (1 H, d, J = 6.0 Hz, isoquinoline 4-H), 7.55 (1 H, dd, J = 8.2, 7.7 Hz, isoquinoline 7-H), 7.70 (1 H, t, J = 7.7 Hz, isoquinoline 6-H), 7.75 (1 H, d, J = 7.7 Hz, isoquinoline 5-H), 7.80 (1 H, d, J = 4.0 Hz, thiophene 4-H), 8.00 (1 H, d, J = 6.0 Hz, isoquinoline 3-H) and 8.25 (1 H, d, J = 8.2 Hz, isoquinoline 8-H); δ_C 62.3, 116.1, 126.1, 127.4, 128.1, 128.5, 130.0, 131.5, 131.8, 132.3, 148.2, 158.9 and 165.6; m/z 287.0486 (M + H) ($C_{14}H_{10}N_2O_3S$ requires 287.0490).

5-Iodo-1-(5-nitro-2-thienylmethoxy)isoquinoline 10b

5-Iodoisoquinolin-1(2*H*)-one **1b** was treated with triphenylphosphine, DEAD and **8d**, as for the synthesis of **10a**, to give **10b** (30%) as a yellow powder: mp 78–82 °C (Found: C, 40.7; H, 2.09; N, 6.4. $C_{14}H_9IN_2O_3S$ requires C, 40.87; H, 2.18; N, 6.80%); ν_{max} (KBr)/cm^{-1} 1618; δ_H 5.74 (2 H, s, CH_2), 7.12 (1 H, d, J = 3.9 Hz, thiophene 3-H), 7.27 (1 H, dd, J = 7.4, 8.5 Hz, isoquinoline 7-H), 7.49 (1 H, d, J = 6.3 Hz, isoquinoline 4-H), 7.83 (1 H, d, J = 3.9 Hz, thiophene 4-H), 8.10 (1 H, d, J = 6.3 Hz, isoquinoline 3-H), 8.22 (1 H, d, J = 7.4 Hz, isoquinoline 6-H) and 8.27 (1 H, d, J = 8.5 Hz, isoquinoline 8-H); δ_C 62.8, 96.9, 119.7, 120.0, 124.3, 125.9, 127.9, 139.6, 140.5, 141.7, 147.6 and 158.9; MS (EI^+) m/z 412 (M).

5-Bromo-1-(5-nitro-2-thienylmethoxy)isoquinoline 10c

5-Bromoisoquinolin-1(2*H*)-one[2] **1c** was treated with triphenylphosphine, DEAD and **8d**, as for the synthesis of **10a**, to give **10c** (41%) as a yellow powder: mp 128–130 °C; ν_{max} (KBr)/cm^{-1} 1616; δ_H 5.75 (2 H, s, CH_2), 7.13 (1 H, d, J = 4.2 Hz, thiophene 3-H), 7.42 (1 H, dd, J = 8.2, 7.8 Hz, isoquinoline 7-H), 7.65 (1 H, d, J = 6.0 Hz, isoquinoline 4-H), 7.84 (1 H, d, J = 4.2 Hz, thiophene 4-H), 7.97 (1 H, d, J = 7.8 Hz, isoquinoline 6-H), 8.12 (1 H, d, J = 6.0 Hz, isoquinoline 3-H) and 8.25 (1 H, d, J = 8.2 Hz, isoquinoline 8-H); δ_C 62.9, 115.2, 120.1, 121.5, 123.7, 126.1, 127.5, 128.2, 134.7, 139.0, 140.6, 147.8 and 158.9; m/z 366.9575 (M + H) ($C_{14}H_9{}^{81}BrN_2O_3S$ requires 366.9589).

1,2-Dimethyl-3-(5-iodo-1-oxo-2*H*-isoquinolin-2-ylmethyl)-5-methoxy-1*H*-indole-4,7-dione 12b

5-Iodoisoquinolin-1(2*H*)-one **1b** was treated with triphenylphosphine, DEAD and **11b**, as for the synthesis of **10a**, to give **12b** (36%) as a purple powder: mp >230 °C; ν_{max} (KBr)/cm^{-1} 1702; δ_H 2.47 (3 H, s, indole 2-Me), 3.81 (3 H, s, NMe), 3.88 (3 H, s, OMe), 5.29 (2 H, s, CH_2), 5.62 (1 H, s, indole 6-H), 6.66 (1 H, d, J = 7.9 Hz, isoquinoline 4-H), 7.12 (1 H, t, J = 7.8 Hz, isoquinoline 7-H), 7.80 (1 H, d, J = 7.9 Hz, isoquinoline 3-H), 8.11 (1 H, dd, J = 7.8, 1.1 Hz, isoquinoline 6-H) and 8.38 (1 H, brd, J = 8.2 Hz, isoquinoline 8-H); δ_C 10.2, 32.6, 42.2, 56.5, 106.5, 109.1, 121.1, 126.7, 127.2, 128.0, 128.7, 134.1, 138.7, 138.9, 142.5, 159.0, 161.1 and 178.1; m/z 489.0309 (M + H) ($C_{21}H_{18}IN_2O_4$ requires 489.0311).

3-(5-Bromo-1-oxo-2*H*-isoquinolin-2-ylmethyl)-1,2-dimethyl-5-methoxy-1*H*-indole-4,7-dione 12c

5-Bromoisoquinolin-1(2*H*)-one **1c** was treated with triphenylphosphine, DEAD and **11b**, as for the synthesis of **10a**, to give **12c** (36%) as a purple powder: mp 278–280 °C; ν_{max} (KBr)/cm^{-1} 1695; δ_H 2.47 (3 H, s, indole 2-Me), 3.81 (3 H, s, NMe), 3.88 (3 H, s, OMe), 5.30 (2 H, s, CH_2), 5.62 (1 H, s, indole 6-H), 6.77 (1 H, d, J = 8.0 Hz, isoquinoline 4-H), 7.27 (1 H, dd, J = 7.8, 7.3 Hz, isoquinoline 7-H), 7.82 (1 H, d, J = 8.0 Hz, isoquinoline 3-H), 7.84 (1 H, dd, J = 7.3, 0.9 Hz, isoquinoline 6-H) and 8.36 (1 H, br d, J = 7.8 Hz, isoquinoline 8-H); δ_C 10.2, 32.6, 42.2, 56.5, 104.3, 106.6, 116.1, 120.4, 121.2, 126.8, 127.4, 128.1, 128.5, 128.8, 134.1, 135.6, 136.3, 138.8, 159.3, 161.2 and 178.2; m/z 441.0443 (M + H) ($C_{21}H_{18}N_2O_4Br$ requires 441.0449).

1,2-Dimethyl-3-[5-(1,1-dimethylethoxycarbonylamino)-1-oxo-2*H*-isoquinolin-2-ylmethyl]-5-methoxy-1*H*-indole-4,7-dione 12d

Compound **1d** was treated with triphenylphosphine, DEAD and **11b**, as for the synthesis of **10a**, to give **12d** (12%) as an orange solid: mp >230 °C; δ_H 1.54 (9 H, s, Bu^t), 2.47 (3 H, s, indole 2-Me), 3.81 (3 H, s, NMe), 3.88 (3 H, s, OMe), 5.25 (2 H, s, CH_2), 5.62 (1 H, s, indole 6-H), 6.57 (1 H, d, J = 8.0 Hz, isoquinoline 4-H), 7.27 (1 H, t, J = 8.0 Hz, isoquinoline 7-H), 7.47 (2 H, m, isoquinoline 3,6-H_2) and 8.21 (1 H, d, J = 7.8 Hz, isoquinoline 8-H).

1,2-Dimethyl-3-(isoquinolin-1-yloxymethyl)-1*H*-indole-4,7-dione 13a

Isoquinolin-1(2*H*)-one **1a** was treated with triphenylphosphine, DEAD and **11b**, as for the synthesis of **10a**, to give **13a** (40%) as a red powder: mp >230 °C; ν_{max} (KBr)/cm^{-1} 1725, 1694; δ_H 2.38

(3 H, s, indole 2-Me), 3.80 (3 H, s, NMe), 3.89 (3 H, s, OMe), 5.62 (1 H, s, indole 6-H), 5.72 (2 H, s, CH_2), 7.20 (1 H, d, J = 5.8 Hz, isoquinoline 4-H), 7.45 (1 H, td, J = 8.2, 1.1 Hz, isoquinoline 7-H), 7.61 (1 H, td, J = 8.2, 1.1 Hz, isoquinoline 6-H), 7.70 (1 H, d, J = 8.2 Hz, isoquinoline 5-H), 8.00 (1 H, d, J = 5.8 Hz, isoquinoline 3-H) and 8.17 (1 H, d, J = 8.6 Hz, isoquinoline 8-H); δ_C 9.8, 50.8, 53.4, 56.4, 114.8, 117.3, 119.8, 122.0, 124.4, 125.9, 126.4, 129.0, 130.3, 137.9, 138.0, 139.6, 142.4, 159.7, 160.3, 177.6 and 178.9; MS (EI^+) *m*/*z* 363.1346 (M) ($C_{21}H_{18}N_2O_4$ requires 363.1344).

1,2-Dimethyl-3-(5-iodoisoquinolin-1-yloxymethyl)-5-methoxy-1*H*-indole-4,7-dione 13b

2-Iodoisoquinolin-1(2*H*)-one **1c** was treated with triphenylphosphine, DEAD and **11b**, as for the synthesis of **10a**, to give **13b** (39%) as a purple powder: mp >230 °C; ν_{max} (KBr)/cm^{-1} 1702; δ_H 2.37 (3 H, s, indole 2-Me), 3.81 (3 H, s, NMe), 3.88 (3 H, s, OMe), 5.62 (1 H, s, indole 6-H), 5.71 (2 H, s, CH_2), 7.16 (1 H, dd, J = 8.3, 7.4 Hz, isoquinoline 7-H), 7.40 (1 H, d, J = 6.1 Hz, isoquinoline 4-H), 8.08 (1 H, d, J = 6.1 Hz, isoquinoline 3-H), 8.15 (1 H, dd, J = 7.4, 1.0 Hz, isoquinoline 6-H) and 8.20 (1 H, br d, J = 8.3 Hz, isoquinoline 8-H); δ_C 9.9, 32.4, 56.4, 58.6, 106.6, 117.0, 118.5, 120.6, 125.1, 127.5, 128.9, 134.5, 138.0, 139.5, 141.1, 159.7, 160.5, 177.6 and 178.9; *m*/*z* 489.0309 (M + H) ($C_{21}H_{18}IN_2O_4$ requires 489.0311).

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