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4-Substituted 5-nitroisoquinolin-1-ones from intramolecular Pd-catalysed reaction of *N*-(2-alkenyl)-2-halo-3-nitrobenzamides

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ABSTRACT

4-Methyl- and 4-benzyl-5-aminoisoquinolin-1-ones are close analogues of the water-soluble PARP-1 inhibitor 5-AIQ. Their synthesis was approached through Pd-catalysed cyclisations of *N*-(2-alkenyl)-2-iodo-3-nitrobenzamides. Reaction of *N*,*N*-diallyl-2-iodo-3-nitrobenzamide with $Pd(PPh_3)_4$ gave a mixture of 2-allyl-4-methyl-5-nitroisoquinolin-1-one and 2-allyl-4-methylene-5-nitro-3,4-dihydroisoquinolin-1-one. *N*-Benzhydryl-*N*-cinnamyl-2-iodo-3-nitrobenzamide similarly gave 2-benzhydryl-4-benzyl-5-nitroisoquinolin-1-one and 2-benzhydryl-4-benzylidene-5-nitro-3,4-dihydroisoquinolin-1-one. The isomeric products are not interconvertible. A deuterium-labelling study indicated that the isomers were formed by different pathways: a π-allyl-Pd route and the classical Heck route. The corresponding secondary amides *N*-allyl-2-iodo-3-nitrobenzamide and *N*-((substituted)-cinnamyl)-2-iodo-3-nitrobenzamide gave good yields of the required 4-methyl- and 4-((substituted)-benzyl)-5-nitroisoquinolin-1-ones, respectively, under optimised conditions ($Pd(PPh_3)_4$, Et_3N, Bu_4NCl, 150 °C, rapid heating). Hydrogenation of the nitro groups gave 4-methyl- and 4-benzyl-5-aminoisoquinolin-1-ones, which were potent inhibitors of PARP-1 activity.

1. Introduction

Poly(ADP-ribose)polymerase-1 (PARP-1; EC 2.4.2.30) is a constitutively expressed enzyme that is located in the nuclei of most cell types. It is an essential component of the system, which detects damaged sites on DNA and initiates repair of single-strand breaks.[1–3] Inhibition of PARP-1 activity (and, indeed, of other PARP isoforms) has a large number of potential therapeutic applications.[4] Inhibitors of PARP-1 activity act as radiosensitising[5,6] and chemosensitising[7–9] agents in cancer therapy and there are recent indications that PARP-1 inhibitors may have activity against cancer as single agents in BRCA-2-deficient tumours[10,11] and as antimetastatic agents.[12,13]

The consensus pharmacophore for inhibition of PARP-1,[4] developed by classical structure–activity relationship (SAR) studies and by modelling using the X-ray crystal structure of the catalytic (NAD^+-binding) domain, is a primary or secondary benzamide, with the amide N–H and carbonyl conformationally constrained relative to the benzene ring (**1**, Fig. 1). Examples of potent inhibitors include the isoquinolin-1-ones **2** (and their 3,4-dihydro analogues),[5] the 4-benzylphthalazin-1-ones **4**,[14,15] the tricyclic lactams **5**[7,8] and the benzimidazole-4-carboxamides **6**.[16] In **6**, the carboxamide is held in

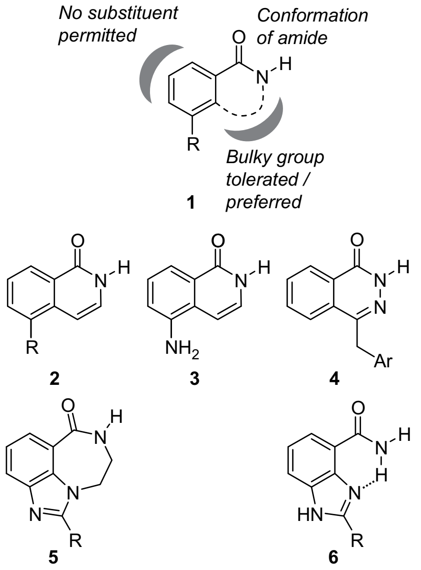

Figure 1. Structures of the consensus pharmacophore for PARP-1 inhibition **1** and of types of potent inhibitor **2**–**6**. Compound **3** is the potent water-soluble inhibitor 5-AIQ.

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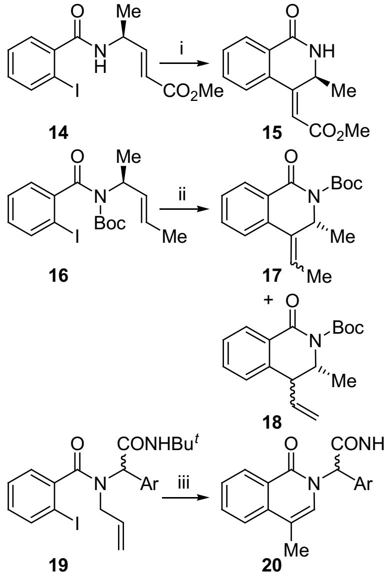
an intramolecularly hydrogen-bonded ring, rather than in a heterocyclic covalently bonded ring. Many inhibitors conforming to that pharmacophore have very limited solubility in water but we have shown 5-aminoisoquinolin-1(2*H*)-one (5-AIQ, **3**) to be highly soluble,[17] as its hydrochloride salt, and to have potent activity in a wide range of disease models in ischaemia–reperfusion injury,[18–20] inflammation[21,22] and metastasis.[12] We therefore wished to explore the SAR around the 4-position of this lead compound through synthesis and preliminary biochemical evaluation of the 4-methyl and 4-benzyl analogues of 5-AIQ.

Three synthetic routes have been reported for the preparation of 5-AIQ **3**. All proceed via reduction of the 5-nitro analogue **9** as the final step (Scheme 1). Wenkert et al.[23] and Suto et al.[5] used a rather unreliable Polonowski rearrangement of 5-nitroisoquinoline-1-oxide **8** (formed by oxidation of **7**) to generate **9** in modest overall yield. Radical bromination of the Ar–Me of **10** followed by displacement of the bromine of **11** with cyanide and selective low-temperature reduction of the nitrile of **12** led to **9** in 15% overall yield.[24] The most efficient synthesis of **9**, and thence **3**, reported to date comprises condensation of **10** with dimethylformamide dimethylacetal, with hydrolysis of the intermediate enamine and cyclisation during chromatography on wet silica, to form the isocoumarin **13**, which can be readily converted into **9** with ammonia; the overall yield is 39%.[18] However, none of these routes is adaptable for synthesis of analogues carrying substituents on the heterocyclic ring[24,25] and it was necessary to devise a novel route to such compounds. Our studies on development of such a route to 5-amino-4-methylisoquinolin-1-one and 5-amino-4-benzylisoquinolin-1-one are reported below.

The intramolecular version of the Heck reaction has been used to assemble a variety of carbocycles and oxygen- and nitrogen-heterocycles.[26] In the formation of isoquinolin-1-ones, cyclisation of *N*-allyl-2-iodobenzamides with Pd catalysts has been reported to give the direct Heck products (4-alkylidine-3,4-dihydroisoquinolin-1-ones) or products of Heck coupling preceded or succeeded by migration of the C=C double bond either away from the heterocycle (4-ethenyl-3,4-dihydroisoquinolin-1-ones) or into the heterocycle (3-alkylisoquinolin-1-ones). Examples are shown in Scheme 2; the secondary amide **14** gives the dihydroisoquinolin-1-one **15** with the exocyclic double bond, without double bond migration;[27] the *N*-allyl imide **16** gives a mixture of **17**, where the C=C remains in situ, and **18**, where the C=C has migrated away from the ring;[28] the tertiary amide **19** gives a very high yield of the 3-methylisoquinolin-1-one **20** with C=C migration into the ring.[29] Interestingly, in the latter case, the authors suggest that the 'unmigrated' direct Heck product is formed first and that migration of the C=C into the ring occurs from an intermediate 3-methylene-3,4-dihydroisoquinolin-1-one.



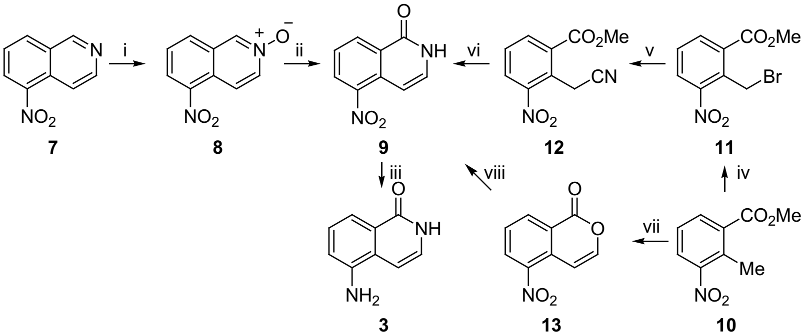
Scheme 2. Literature examples of formation of the isoquinolin-1-one ring by intramolecular Pd-catalysed cyclisation of *N*-allyl-2-iodobenzamides. *Reagents and conditions*: (i) Pd(OAc)$_2$, PPh$_3$, Et$_3$N, MeCN, 70 °C; (ii) Pd(OAc)$_2$, PPh$_3$, TPAB, DMF, 80 °C; (iii) Pd(OAc)$_2$, PCy$_3$, DMA, 100 °C.

None of the reported studies use *N*-allyl-3-substituted-2-iodobenzamides; the presence of an electron-withdrawing and bulky nitro group (required for synthesis of the 5-AIQ derivatives) flanking the iodine was thought to be likely to influence the outcome of the Pd-catalysed reactions. Moreover, the literature precedents were not consistent as to the ability of the C=C double bond to migrate into the ring (as required for the 5-AIQ derivatives). Thus we undertook a study on the Pd-catalysed reactions of *N*-allyl-2-iodo-3-nitrobenzamides with a view to develop a synthesis of 4-alkyl-5-nitroisoquinolin-1-ones and hence 4-alkyl-5-amino-isoquinolin-1-ones.

2. Chemistry

2.1. Pd-catalysed cyclisation of tertiary *N*-allyl-2-iodo-3-nitrobenzamides

Initially, we predicted that the ring-closure reaction would proceed more efficiently from an *N*-allyl tertiary amide than from a secondary amide, since the conformational preference would be for a *Z* (trans) amide in the latter, which places the alkene remote from the iodoarene. 2-Iodo-3-nitrobenzoic acid **21a** (prepared from



Scheme 1. Reported syntheses of 5-AIQ **3**. *Reagents and conditions*: (i) H_2O_2, AcOH; (ii) Ac_2O, Δ; (iii) H_2, Pd/C, EtOH, HCl; (iv) Br_2, $(PhCO_2)_2$, h*ν*, Δ; (v) Et_4NCN; (vi), $^i Bu_2AlH$, CH_2Cl_2, −78 °C; (vii) DMFDMA, DMF, Δ; (viii) NH_3, $MeOCH_2CH_2OH$, Δ.

3-nitrobenzene-1,2-dioic acid)[30] was converted to its acid chloride **22a**, from which the *N*,*N*-diallyl amide **23** was formed by treatment with diallylamine (Scheme 3). This tertiary amide is an ideal test substrate, since it carries two allyl groups; thus one will always be in an apposite conformation for Pd-catalysed cyclisation. However, a preliminary MM2 energy minimisation on the structure of **23** indicated a conformation in which the amide carbonyl should be approximately orthogonal to the benzene ring (Fig. 2), owing to steric interactions with the large adjacent iodine. This would make the molecule chiral, with the asymmetric centre located in the centre of the Ar–C bond. This chirality means that not only are the two allyl groups inequivalent (owing to restricted amide C–N bond rotation) but also the two aliphatic methylenes are each diastereotopic. This was evident in the ^{1}H NMR spectrum, which showed different chemical shifts for each of the four $N(CH_2CH{=}CH_2)_2$ protons with appropriate geminal couplings. Treatment of **23** with tetrakis(triphenylphosphine)palladium(0) (5 mol %) and triethylamine in boiling acetonitrile (80 °C) for 2 days gave a high yield (79%) of an inseparable mixture of the isomers **24** and **25** in the molar ratio 1:2. The latter is derived from direct Heck cyclisation of **23**, without prior C=C bond migration, and it was proposed that the former, required, isomer may be formed by Pd-catalysed migration of the double bond into conjugation with the amide nitrogen before or after cyclisation. None of the alternative product (2-allyl-5-nitro-2,3-dihydrobenzo[*c*]azepin-1-one) of Heck cyclisation of **23** at the terminal alkene carbon (which is less sterically hindered) was observed. To test whether **24** may have been formed from **25** by migration of the double bond into a doubly conjugated system after cyclisation, the mixture of isomers **24** and **25** was exposed to the cyclisation reaction conditions for a prolonged period. Examination of the products by ^{1}H NMR revealed that there was no change in the ratio of isomers, suggesting either that the isomers were not interconvertible (i.e., **24** was not formed from **25**) or that the 1:2 ratio of isomers with endocyclic or exocyclic C=C was the ratio at equilibrium. Furthermore, several other sets of catalyst/ligand conditions were investigated but all failed to effect a change in the ratio. Even treatment of the isomeric mixture with $Pd(PPh_3)_4$ in tetraglyme at increasing temperatures also failed to change the ratio of isomers, up to ca. 250 °C when decomposition set in. This contrasts with the very recent proposal of Ardizzoia et al.[31] that 2-allyl-4-methylene-3,4-dihydroisoquinolin-1-one may isomerise to 2-allyl-4-methylisoquinolin-1-one under similar Pd-catalysed conditions. These workers reported that the major product when *N*,*N*-diallyl-2-iodobenzamide was treated with methanol and $PdCl_2(PPh_3)_2$ in acetonitrile under 100 bar pressure of carbon monoxide was ±-2-allyl-4-(methoxycarbonylmethyl)-3,4-dihydroisoquin-1-one.

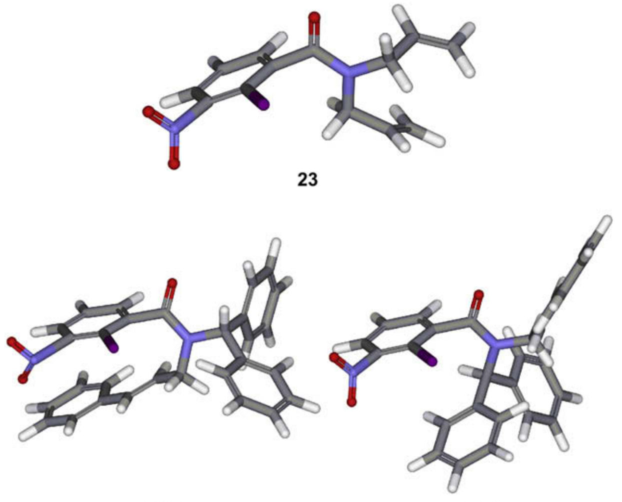
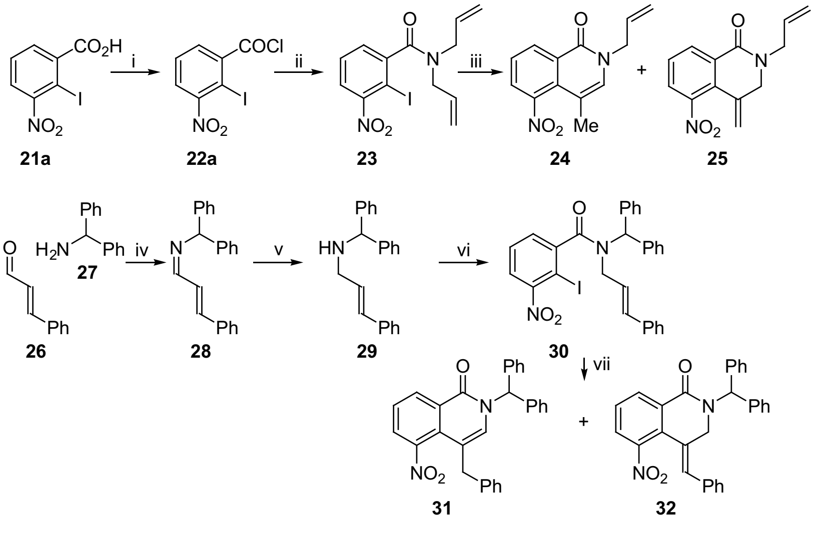


Figure 2. MM2-minimised structures of tertiary amides **23** and **30**, showing predicted orthogonality of the amide and the aromatic ring caused by the bulky *ortho*-iodo substituent.

To approach the 4-benzylisoquinolin-1-one series, an alternative *N*-protecting group, benzhydryl, was selected to provide major steric bulk. As shown in Scheme 3, the required secondary amine **28** was prepared by condensation of cinnamaldehyde **26** with diphenylmethylamine **27**. Subsequent reaction with the acid chloride **22a** provided the *N*-cinnamyl-*N*-diphenylmethyl tertiary amide **30**. MM2 minimisation studies of the structure of **30** suggested two low-energy rotamers arising from rotation about the amide C–N bond (Fig. 2). Both rotamers are also chiral, as the amide is again orthogonal to the iodobenzene ring. The ^{1}H NMR spectrum of **30** also showed the presence of these rotamers in the ratio 3:4, with appropriate magnetic inequivalence of the cinnamyl diastereotopic CH_2 protons in each rotamer. Reaction of **30** with $Pd(PPh_3)_4$



Scheme 3. Pd-catalysed cyclisation of *N*-allyl and *N*-cinnamyl tertiary amides **23** and **30**. *Reagents and conditions*: (i) $SOCl_2$, DMF, CH_2Cl_2, 94%; (ii) diallylamine, Et_3N, CH_2Cl_2, 75%; (iii) $(Ph_3P)_4Pd$, Et_3N, MeCN, 80 °C, 48 h, 26% (**24**), 63% (**25**); (iv) PhMe, Dean–Stark, 110 °C, 24 h, 97%; (v) $NaBH_4$, MeOH, 95%; (vi) **22a**, Et_3N, CH_2Cl_2, 54%; (vii) $(Ph_3P)_4Pd$, Et_3N, EtCN, 100 °C, 48 h, 10% ( ), 31% (**32**).

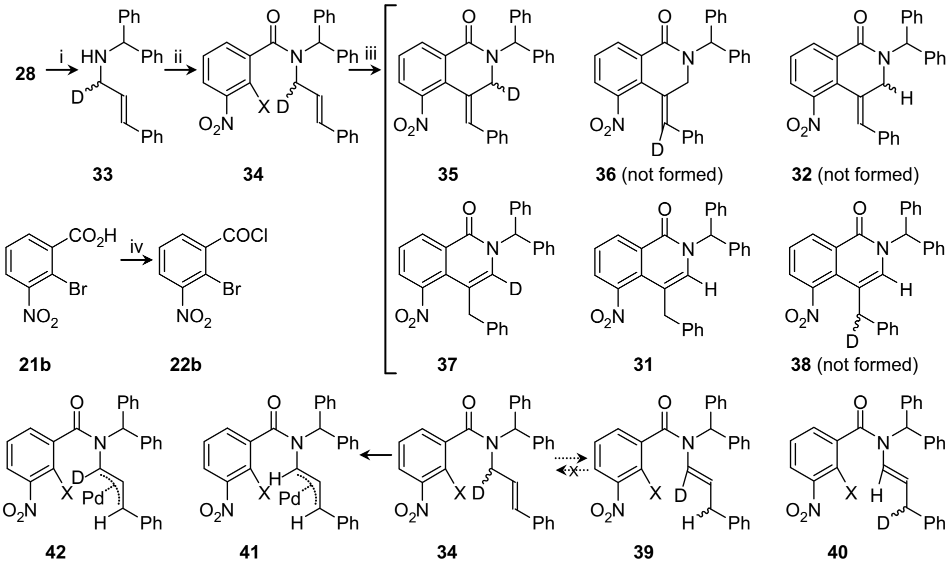
(5 mol %) and triethylamine in boiling propanenitrile (100 °C) for 2 days gave a moderate yield of an inseparable mixture of the isomers **31** and **32** in the molar ratio 1:3, an outcome similar to that of the cyclisation of **23**. As for the diallyl case, the required 4-benzyl-5-nitroisoquinolin-1-one **31** isomer was the minor product. Minor changes to the reaction conditions gave similar results, with small modifications to the ratios of isomers.

2.2. Deuterium-labelling studies

To test the hypotheses that the 4-alkylidine-3,4-dihydroisoquinolin-1-ones **25** and **32**, the major products, had been formed by Heck cyclisation before C═C bond migration could take place and that the required 4-alkylisoquinolin-1-ones **24** and **31** were formed by Pd-catalysed migration of the C═C before Pd-catalysed coupling/cyclisation, a series of deuterium-labelling experiments were carried out (Scheme 4). Firstly, one deuterium was introduced into the methylene of the *N*-benzhydryl cinnamylamine **33** by reduction of the unlabelled imine **28** with sodium borodeuteride. Reaction with 2-iodo-3-nitrobenzoyl chloride **22a** gave the tertiary amide **34a** carrying one deuterium. Recalling that the methylenes of the two rotamers of the unlabelled analogue **30** are each diastereotopic and inequivalent in the ^{1}H NMR spectrum, the racemic nature of **34a** with respect to the CHD centre was demonstrated in that each of the methylene ^{1}H signals was diminished by 50% in intensity in the spectrum of **34a**, with respect to that of **30**.

Reaction of **34a** with Pd(PPh$_3$)$_4$ and Et$_3$N in refluxing MeCN for 2 h gave an equimolar mixture of isotopomers **31** and **37** of the 4-benzylisoquinolin-1-ones (minor products) and a single isotopomer **35** of the 4-benzylidene-3,4-dihydroisoquinolin-1-ones (major product). The lower temperature and shorter reaction time were chosen such that unreacted tertiary amide starting material could be recovered and its isotopic composition determined; all the recovered tertiary amide was shown by ^{1}H NMR to be **34a**, i.e., it contained one deuterium at the original position. This demonstrates that molecules are committed to cyclisation once they had reacted initially with Pd, as no exchange or migration of the deuterium had occurred in molecules where the cyclisation was aborted. All the 4-benzylidene-3,4-dihydroisoquinolin-1-one product contained one deuterium which was shown by ^{1}H NMR to be located at the 3-position and was thus identified as **35**. The isomer **36**, where the deuterium has migrated prior to cyclisation, and the isotopomer **32**, where the deuterium has been lost, were not formed. These observations are consistent with Heck cyclisation by the classical mechanism directly from the amide **34a** to form **35**. Interestingly, the 4-benzylisoquinolin-1-ones observed by ^{1}H NMR were the monodeutero compound **37** with the deuterium located at the 3-position (i.e., unmigrated with respect to its initial location in the cinnamyl group in **34**) and the undeuterated isotopomer **31**; the isomer **38**, which would be one product of Pd-catalysed C═C migration (and thus H/D migration in the opposite direction) was not formed. Thus the 4-benzylisoquinolin-1-ones are not formed by initial double bond migration to intermediates **39** and **40**, prior to cyclisation. The remaining plausible mechanism is loss of D or H from the allylic position in the *N*-cinnamyl amide to generate π-allyl-Pd species such as **41** and **42**, respectively, as intermediates. Once formed, these intermediates are committed to cyclise to **31** and **37**, respectively, capturing an H from a source other than the starting material. Isotopomers **31** and **37** are formed in equimolar amounts, showing that there is no kinetic deuterium isotope effect in the breaking of the C–H/D bond in going to intermediates **41** and **42**. These experiments point to two independent Pd-catalysed reaction pathways leading from the *N*-allyl-2-iodobenzamides to the 4-alkylidene-3,4-dihydroisoquinolin-1-ones and to the 4-alkylisoquinolin-1-ones. These two pathways may have different rates and activation energies, indicating that modification of the reaction conditions may modulate the ratio of the products formed and allow production of a single (required) isomer.

To investigate this further, iodine was replaced by bromine in the starting 2-halo-3-nitro tertiary benzamides (Scheme 4). 2-Bromo-3-nitrobenzoic acid **21b**[32] was converted to its acid chloride **22b**, which was then coupled with the monodeutero secondary amine **33** to form the tertiary amide **34b**. Bromoarenes often undergo classical Heck couplings more slowly than do iodoarenes[33] and it was proposed that this effect may slow the direct Heck cyclisation sufficiently to allow formation of the π-allyl intermediates and thus lead to greater yields of the 4-benzylisoquinolin-1-one. However, reaction of **34b** with Pd(PPh$_3$)$_4$ and triethylamine in boiling acetonitrile (80 °C) again gave **35** as the major product, with equimolar amounts of the isotopomers **31** and **37** as very minor products. The similarity of the outcomes of the reactions of **34a** and **34b** suggests that the reaction of the Ar–Hal bond may not be rate-limiting or that breaking of this bond (with insertion of Pd) may be the common first step in both reaction pathways.



Scheme 4. Deuterium-labelling experiments to study the mechanism of the Pd-catalysed cyclisations: (a) X=I; (b) X=Br. *Reagents and conditions*: (i) NaBD$_4$, MeOH, 99%; (ii) **22a** or **22b**, Et$_3$N, CH$_2$Cl$_2$, 61% (**34a**), 54% (**34b**); (iii) (Ph$_3$P)$_4$Pd, Et$_3$N, EtCN, various conditions; (iv) SOCl$_2$, DMF, CH$_2$Cl$_2$, 86%.

2.3. Pd-catalysed cyclisation of secondary *N*-allyl-2-iodo-3-nitrobenzamides

In the light of the unfavourable distribution of isomeric products from the Pd-catalysed cyclisations of the tertiary *N*-allyl-2-iodo-3-nitrobenzamides and the later difficulty in removing the *N*-allyl and *N*-benzhydryl protecting groups from **24**/**25** and **31**, respectively, Pd-catalysed cyclisation of the corresponding secondary amides was explored. Treatment of the acid chloride **22a** with allylamine under mild conditions gave the expected *N*-allyl secondary amide **43**, along with a minor yield of **44**, in which the highly activated iodine has been lost in an S_NAr displacement by another molecule of allylamine. The structure of **44** was confirmed by an X-ray crystal structure determination (Fig. 3). Examination of the supramolecular array revealed that molecules link together via intermolecular hydrogen bonding, involving the hydrogen atom attached to N3 in one molecule and O3 of a lattice neighbour.

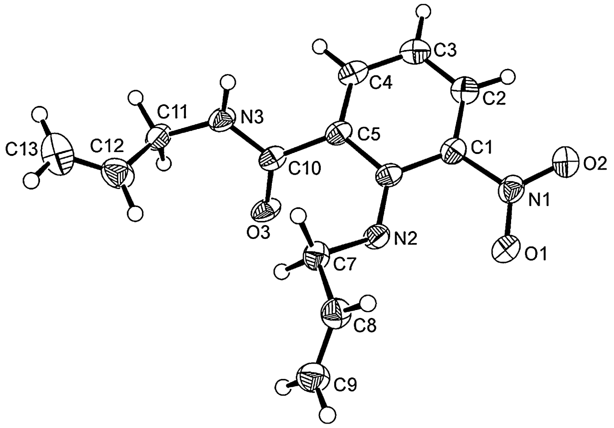


Figure 3. Crystal structure of **44**, with crystallographic numbering. Ellipsoids are represented at the 30% probability level.

Reaction of **43** with $Pd(PPh_3)_4$ under the conditions used for cyclisation of the tertiary amides (Et_3N, EtCN, 100 °C) gave the two cyclised products **45** (4-methyl-5-nitroisoquinolin-1-one) and **46** (4-methylene-5-nitro-3,4-dihydroisoquinolin-1-one) in a 1:1 ratio, along with the dehalogenated amide **47** (Table 1, entry 1). We have previously observed reductive dehalogenation as a major side reaction of attempted Pd-catalysed couplings to the closely related ester methyl 2-iodo-3-nitrobenzoate, arising from aborted couplings to the severely hindered aryl carbon.[34] Moreover, Majumder et al. very recently found that dehalogenation was the sole outcome of treatment of the secondary amide *N*-allyl-2-iodobenzamide under similar conditions.[35] Tetrabutylammonium chloride was added to modify the reaction conditions for later experiments and the solvent was changed to DMF to allow a greater range of temperatures to be explored. Running the reaction at 50 °C for 2 days (entry 2) gave a similar 1:1 ratio of the cyclised products **45** and **46**. Raising the reaction temperature to 100 °C for 2 days led to a mixture of **45** and **46** in which the required 4-methyl-5-nitroisoquinolin-1-one **46** predominated (7.3:1 ratio of products) (entry 3). The trend to increase the proportion of **45** in the product mixture was continued to 150 °C, at which temperature the sole isolable product was **45** (entry 4). This effect was only evident when the reaction mixture was heated rapidly to 150 °C during <1 min; slower heating to 150 °C led to the formation of significant amounts of the isomer **46**.

As a further investigation of the mechanistic pathways to the isomeric products, the migration of the C=C double bond in **43** into conjugation with the amide was achieved by treatment with $RuClH(CO)(PPh_3)_3$ in boiling benzene (Scheme 5); this provides a potential intermediate in a pathway from **43** whence conventional Heck coupling would furnish **45**. However, subjection of this putative intermediate to the optimised Pd-catalysed cyclisation conditions gave the reductively deiodinated material **49** as the sole isolable product, along with a trace of 3-nitrobenzamide **50** arising from decomposition of **49**. Since **49** arises from aborted coupling reactions, this observation demonstrates that **48** cannot cyclise under these conditions and is, therefore, not an intermediate in the reaction pathway from **43** to **45**. As with the Pd-catalysed cyclisation of the *N*-allyl tertiary amides, a π-allyl-Pd species is therefore likely to be involved in the formation of the required isomer **45**.

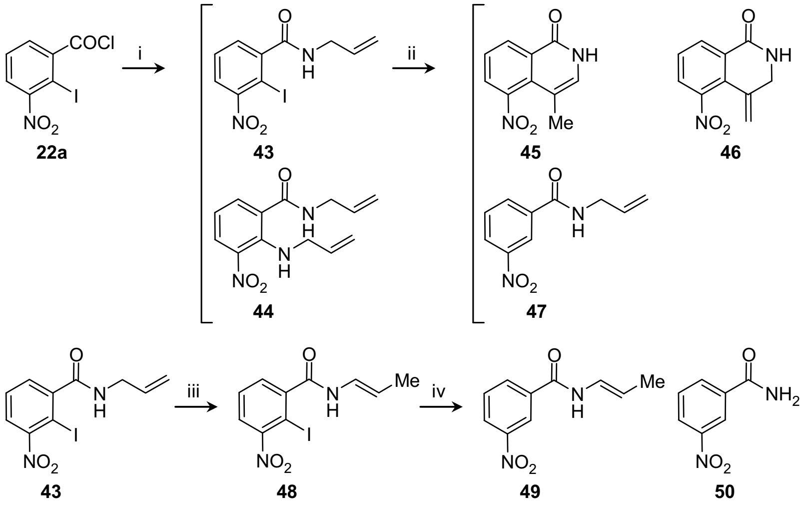
Schemes 6 and 7 show the extension of this optimisation of the conditions to the Pd-catalysed cyclisation of secondary *N*-cinnamyl 2-iodo-3-nitrobenzamides **63a**–**d**. The four cinnamylamines **53a**–**d** required for this study are not commercially available. The 4-unsubstituted cinnamylamine **53a** was prepared by displacement of the bromine of cinnamyl bromide **51** with the anion derived from trifluoroacetamide, followed by cleavage of the amide in **52** by hydrolysis or reductively with sodium borohydride (Scheme 6). The substituted analogues **53b**–**d** were assembled in a different manner by Heck coupling of a protected allylamine to an appropriate iodoarene. Thus *N*-allylphthalimide **54** was coupled in high yields with 4-iodotoluene and with 4-iodomethoxybenzene to afford the *N*-cinnamylphthalimides **55b**,**c**. Hydrazinolysis of the phthalimide then formed the 4-methyl- and 4-methoxy-cinnamylamines **53b**,**c**. Reaction of **53a**–**c** with the acid chloride **22a** then provided the *N*-cinnamyl secondary amides **63a**–**c**. The route to the 3-succinimido compounds started with condensation of 3-iodoaniline **56** with succinic anhydride at 190 °C in the absence of solvent to give the imide **57**. The phthalimide protection was not appropriate in this series, as the hydrazinolysis would also cleave the succinimide. Thus *N*-Boc allylamine **59** (prepared from allylamine **58** and di-*tert*-butyl dicarbonate) was then Heck coupled with **57**, using palladium(II) acetate. Interestingly, this process did not proceed regiospecifically, affording a chromatographically inseparable mixture (4:1) of the required *N*-Boc cinnamylamine **60** and the isomer **61** where the coupling has taken place at the more sterically hindered end of the alkene. This mixture was taken forward into acidolytic deprotection (giving amines **53d** and **62**) and reaction with the acid chloride **22a** to give an inseparable 4:1 mixture of the required benzamide **63d** and the isomer **64**.

Application of the modified cyclisation conditions ($Pd(PPh_3)_4$, Et_3N, Bu_4NCl, DMF, with rapid heating to 150 °C) to the cyclisation

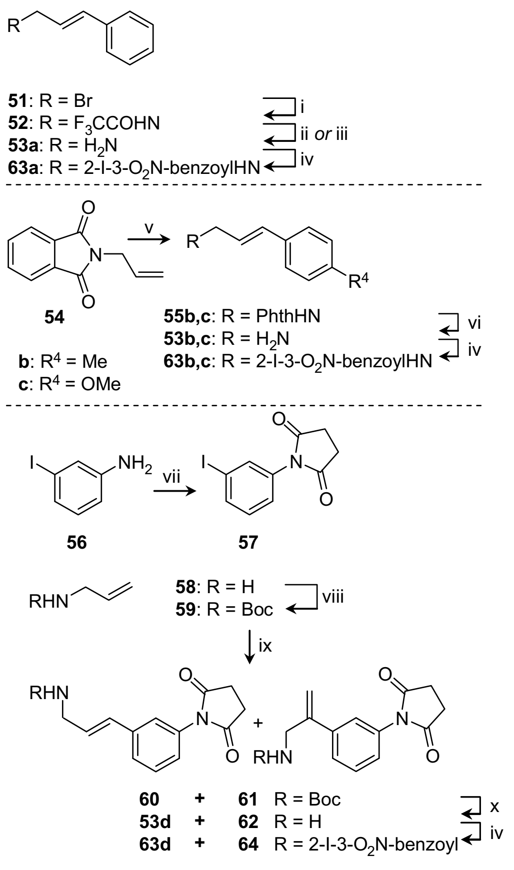
Table 1
Pd-catalysed cyclisations of **43** under different conditions

Entry	Reagents	Reaction temp	Reaction time	Yield of **45**	Yield of **46**	Yield of **47**
1	$Pd(PPh_3)_4$ (5 mol %), Et_3N (2 equiv), EtCN	100 °C	24 h	29%	29%	23%
2	$Pd(PPh_3)_4$ (5 mol %), Et_3N (2 equiv), Bu_4NCl, DMF	50 °C	48 h	27%	27%	27%
3	$Pd(PPh_3)_4$ (5 mol %), Et_3N (2 equiv), Bu_4NCl, DMF	100 °C	48 h	51%	7%	13%
4	$Pd(PPh_3)_4$ (5 mol %), Et_3N (2 equiv), Bu_4NCl, DMF	150 °C[a]	16 h	65%	0%	0%

[a] Rapid heating.



Scheme 5. Formation and Pd-catalysed cyclisation of secondary *N*-allyl amide **43** and effect of migration of C=C before reaction with Pd catalyst. *Reagents and conditions*: (i) $H_2C{=}CHCH_2NH_2$, Et_3N, CH_2Cl_2, 71% (**43**), 10% (44); (ii) various Pd catalysts, various conditions (see Table 1); (iii) $RuClH(CO)(PPh_3)_3$, benzene, 80 °C, 96%; (iv) $Pd(PPh_3)_4$, Et_3N, Bu_4NCl, DMF, reflux, 52% (**49**), trace (**50**).

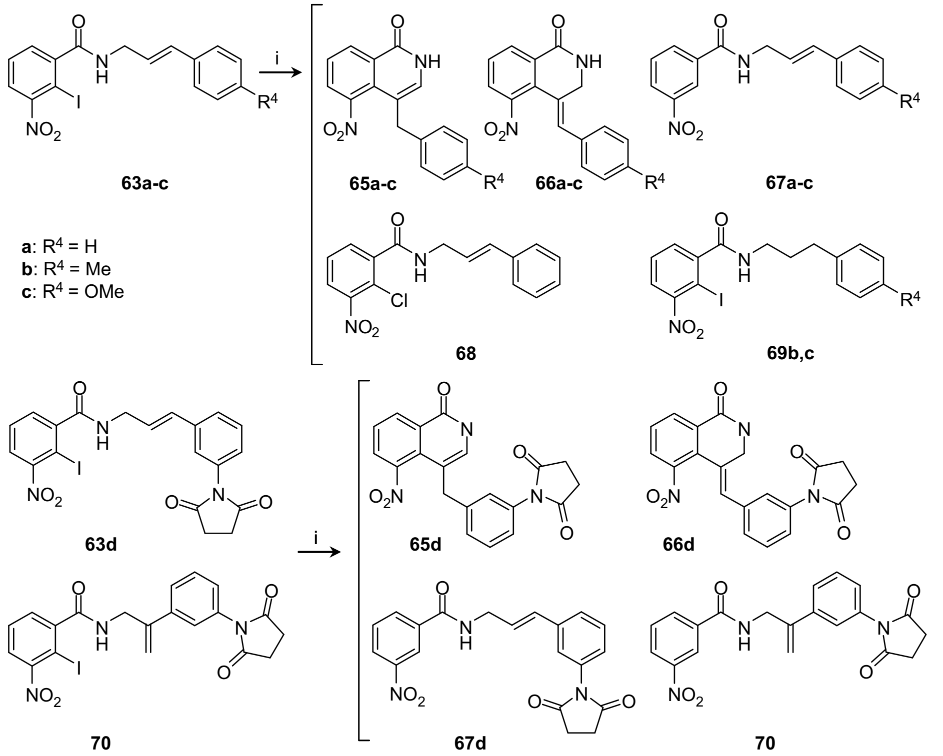


Scheme 6. The three synthetic routes to *N*-cinnamyl secondary 2-iodo-3-nitrobenzamides **63a–c**: (a) $R^4{=}H$; (b) $R^4{=}Me$; (c) $R^4{=}OMe$. *Reagents and conditions*: (i) H_2NCOCF_3, KO^tBu, THF, 33%; (ii) NH_3, aq EtOH, 4 days, 88%; (iii) $NaBH_4$, EtOH, 16 h, 90%; (iv) **22a**, Et_3N, CH_2Cl_2, 74% (**63a**), 82% (**63b**), 75% (**63b**), 25.6% (**63d**), 6.4% (**64**); (v) 4-iodotoluene or 4-iodomethoxybenzene, $Pd(OAc)_2$, Et_3N, Δ, 82% (**55b**), 94% (**55c**); (vi) $N_2H_4{\cdot}H_2O$, EtOH, 65% (**53b**), 89% (**53c**); (vii) succinic anhydride, 190 °C, 74%; (viii) Boc_2O, CH_2Cl_2, 83%; (ix) $Pd(OAc)_2$, Et_3N, 29% (**60**), 7% (**61**); (x) HCl, CH_2Cl_2.

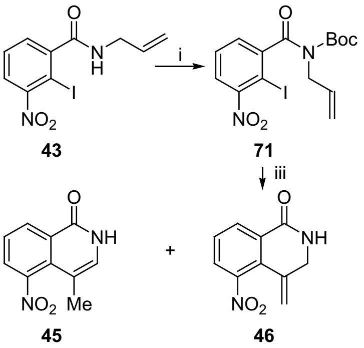
of **63a** afforded a chromatographically separable mixture of the 4-benzylisoquinolin-1-one **65a** and the isomer **66a** in approximately 1:1 ratio in moderate overall yield. Interestingly, two side-products were also formed, **67a** (the expected product of reductive dehalogenation) and 3-amino-2-chloro-*N*-cinnamylbenzamide **68**. The latter appears to have been formed by S_NAr displacement of iodine by chloride from the Bu_4NCl additive, with subsequent reduction of the nitro group to an amine. Of course, the Ar–Cl intermediate is much less likely to undergo Pd-catalysed coupling than the Ar–I starting material but it is unclear why this intermediate (putatively 2-chloro-*N*-cinnamyl-3-nitrobenzamide) should be selectively reduced at the nitro group. In view of this unwanted S_NAr side reaction, tetrabutylammonium chloride was replaced by the corresponding iodide for the Pd-catalysed cyclisations of the *N*-(4-substituted cinnamyl)benzamides **63b–d**, making the displacement a futile reaction. The 4-(substituted benzyl)isoquinolin-1-ones **65b–d** and the 4-(substituted benzylidene)-3,4-dihydroisoquinolin-1-ones **66b–d** were again formed in moderate overall yield, with the ratios of these products ca. 1:1. Significant amounts of reduced side-products were isolated. *N*-Cinnamylamides **67b–d** were formed by the usual reductive dehalogenation; unexpected hydrogenation of the C=C double bond then led to the 3-nitro *N*-(3-phenylpropyl)benzamides **69b,c** in two of the examples. Interestingly, the contaminating starting material **64** in the succinimido reaction, which formally carries an *N*-allyl-2-iodobenzamide, failed to cyclise and formed only the reductively dehalogenated product **70**. The conventional Heck route is, of course, blocked owing to the presence of the Ar group at the 2-position of the *N*-allyl unit; presumably the presence of this Ar group also inhibits the formation of π-allyl-Pd intermediates. These studies are illustrated in Scheme 7.

2.4. Pd-catalysed cyclisation of an *N*-allylimide

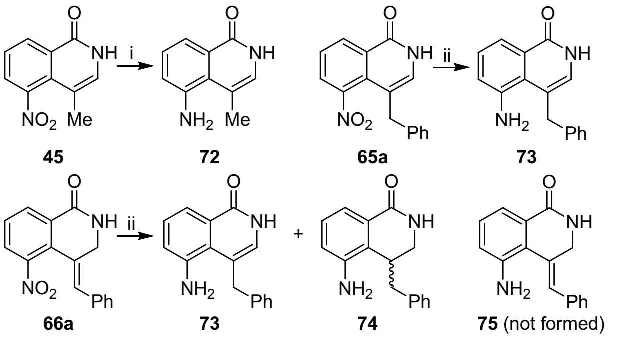
Scheme 8 shows the outcome of a short study on an alternative approach to favour a conformation suitable for Pd-catalysed cyclisation, use of an *N*-allyl imide. The Boc group was introduced in high yield at the amide nitrogen of substrate **43** by treatment with di-*tert*-butyl dicarbonate and DMAP. Subjection of the imide **71** to the cyclisation conditions optimised for the formation of **45** from **43** ($Pd(PPh_3)_4$, Et_3N, Bu_4NCl, DMF, 150 °C, rapid heating) gave a 1:1 mixture of the isomeric cyclised products **45** and **46**, which lack the Boc group. Since direct cyclisation of **43** under these conditions gives **45** as the sole cyclised product, i.e., a different outcome, it is proposed that cyclisation of the *N*-allylimide occurs prior to thermal loss of the Boc group.



Scheme 7. Pd-catalysed cyclisations of *N*-cinnamyl secondary 2-iodo-3-nitrobenzamides **63a–d**: (a) R^4=H; (b) R^4=Me; (c) R^4=OMe. *Reagents and conditions*: (i) e.g. $Pd(PPh_3)_4$, Et_3N, Bu_4NCl, DMF, reflux, rapid heating (see text and Experimental).



Scheme 8. Effect of *N*-Boc substitution on outcome of Pd-catalysed cyclisation. *Reagents and conditions:* i, Boc_2O, Et_3N, DMAP, CH_2Cl_2, 92%; ii, $Pd(PPh_3)_4$, Et_3N, Bu_4NCl, DMF, 150 °C.



Scheme 9. Hydrogenation of **45**, **65a** and **66a**. *Reagents*: (i) H_2, Pd/C, EtOH, aq, HCl, 70%; (ii) H_2, Pd/C, EtOH, aq, HCl, 51% (**73** from **65a**).

2.5. Reduction of the 5-nitro group

Catalytic hydrogenation was used to convert the 5-nitro groups of the 4-substituted isoquinolin-1-ones **45** and **65a** to provide the target 5-aminoisoquinolin-1-ones **72** and **73**, respectively (Scheme 9). Reduction of the 4-methyl-5-nitro compound **45** to 5-amino-4-methylisoquinolin-1-one **72** was uneventful and high yielding. Application of the same procedure to the 4-benzyl analogue **65a** furnished the 5-amino-4-benzylisoquinolin-1-one **73**. However, application of this apparently straightforward process to the 4-benzylidene-3,4-dihydroisoquinolin-1-one **66a** gave only two unexpected products, **73** and **74**. Compound **74** results from reduction of both the C=C double bond and the nitro group. Interestingly, **73** is a product of reduction of the nitro group and C=C bond migration. It is not clear whether the bond migration occurs before or after the reduction but it is catalysed by the Pd metal surface. Unfortunately, it was not possible to reduce the nitro groups of **65b–d** cleanly, as the products always comprise inseparable mixtures of the 5-aminoisoquinolin-1-ones and over-reduced materials.

3. Biochemistry

The 4-substituted 5-AIQ analogues **72** and **73** were evaluated for inhibition of the enzymatic activity of recombinant human PARP-1 using the Trevigen kit with a protocol modified slightly from the manufacturer's instructions.[36] 5-AIQ **3** was also tested as a positive control for comparison. The IC_{50} values are presented in Table 2. Both 4-substituted 5-AIQs were more potent in this assay than was the parent 5-AIQ, the 4-methyl compound **73** being 7-fold more active and the 4-benzyl analogue **74** being 3.5 times more potent.

Table 2
Inhibition of PARP-1 activity by 4-substituted 5-AIQs

Compound	IC_{50} (μM)	log IC_{50} [a]
3	1.8	0.26±0.14
72	0.25	−0.60±0.28
73	0.50	−0.34±0.11

[a] Data are the mean of three experiments and are reported as mean±SEM.

These data suggest that substitution in the 4-position with lipophilic groups enables the compounds to bind more tightly to the active site of the enzyme, consistent with the pharmacophore and with modelling studies.

4. Conclusion

In this paper, we have reported the Pd-catalysed cyclisations of tertiary and secondary *N*-allyl and *N*-cinnamyl 2-iodo-3-nitrobenzamides to two isomeric products, the 4-alkyl-5-nitroisoquinolin-1-ones **24**, **31**, **45** and **65a–c** and the 4-alkyl-5-nitro-3,4-dihydroisoquinolin-1-ones **25**, **32**, **46** and **66a–c**. A deuterium-labelling study indicated that the two products may arise from different types of Pd-containing intermediates, π-allyl-Pd and conventional σ-aryl-Pd species, respectively. Secondary *N*-allyl-2-iodobenzamides cyclised as efficiently as did the tertiary amides. The ratios of the isomeric products from the secondary amides **43** and **63a–d** varied with the reaction conditions. In particular, optimum yields of the 4-alkyl-5-nitroisoquinolin-1-ones were obtained in the presence of tetrabutylammonium chloride and with rapid heating to the reaction temperature of 150 °C, suggesting that the required reaction through the π-allyl-Pd intermediate may need high temperatures and that the conventional Heck coupling (giving the C═C unmigrated isomers) was favoured at lower temperatures. A 2-iodo-*N*-(prop-1-enyl)benzamide did not cyclise, confirming that it is not an intermediate. Interestingly, the proportion of the 4-alkylidene-3,4-dihydroisoquinolin-1-one products was higher when the starting material was an *N*-cinnamyl amide than when *N*-allyl amides were used; this may reflect more difficult formation of the π-allyl-Pd species in the presence of the terminal aryl group.

This Pd-catalysed cyclisation is now available, with careful control of the reaction conditions, for the future preparation of a range of 4-substituted-5-nitroisoquinolin-1-ones and thence to analogues of the potent water-soluble PARP-1 inhibitor, 5-AIQ. Two 4-substituted 5-AIQs do show significantly increased potency for inhibition of human PARP-1.

5. Experimental

5.1. General

^{1}H NMR spectra were recorded on Varian GX270 or EX400 spectrometer of samples in $CDCl_3$, unless otherwise stated. HMQC and HMBC were used in each case to assign the ^{13}C NMR spectra. IR spectra were recorded on a Perkin–Elmer 782 spectrometer as KBr discs, unless otherwise stated. Mass spectra were obtained using fast atom bombardment (FAB) ionisation in the positive ion mode, unless otherwise stated. The chromatographic stationary phase was silica gel. DMF refers to dimethylformamide. THF (tetrahydrofuran) was dried over Na. Solutions in organic solvents were dried over $MgSO_4$. Solvents were evaporated under reduced pressure. The aq $NaHCO_3$ was saturated. Experiments were conducted at ambient temperature, unless otherwise stated. Melting points were measured with a Thermo Galen Kofler block and are uncorrected.

5.2. 2-Iodo-3-nitrobenzoyl chloride (22a)

2-Iodo-3-nitrobenzoic acid **21a**[25] (3.0 g, 10 mmol) was boiled under reflux with DMF (0.2 mL) and $SOCl_2$ (30 mL) for 24 h. Evaporation and recrystallisation (hexane) yielded **22a** (3.0 g, 94%) as yellow crystals: mp 71–73 °C (lit.[37] mp 70–71 °C); IR ν_{max} (KBr) 1348 and 1530 (NO_2), 1758 (C═O) cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 7.64 (1H, t, *J*=7.8 Hz, 5-H), 7.79 (1H, dd, *J*=7.8, 1.6 Hz, 4-H), 7.95 (1H, dd, *J*=7.8, 1.6 Hz, 6-H).

5.3. 2-Bromo-3-nitrobenzoyl chloride (22b)

2-Bromo-3-nitrobenzoic acid **21b**[32] (1.0 g, 4.5 mmol) and DMF (100 μL) were boiled under reflux in $SOCl_2$ (10 mL) for 24 h. Evaporation and recrystallisation (Et_2O) yielded **22b** (1.02 g, 86%) as white solid: mp 65–67 °C (lit.[38] mp 66–66.5 °C); IR ν_{max} 1756, 1534, 1345 cm^{-1}; ^{1}H NMR $(CD_3)_2SO$ δ 7.62 (1H, t, *J*=7.9 Hz, 5-H), 7.87 (1H, dd, *J*=8.1, 1.7 Hz, 4-H), 8.03 (1H, dd, *J*=8.0, 1.5 Hz, 6-H).

5.4. *N*,*N*-Di(prop-2-enyl)-2-iodo-3-nitrobenzamide (23)

Di(prop-2-enyl)amine (310 mg, 3.2 mmol) was stirred with 2-iodo-3-nitrobenzoyl chloride **22a** (1.0 g, 3.2 mmol) and Et_3N (646 mg, 6.4 mmol) in CH_2Cl_2 (5 mL) for 30 min. Washing (5% aq HCl, 5% aq $NaHCO_3$), drying, evaporation and chromatography (CH_2Cl_2/EtOAc 20:1) gave **23** (890 mg, 75%) as a pale buff wax: IR (film) ν_{max} 1733, 1532, 1360 cm^{-1}; ^{1}H NMR δ 3.63 (1H, dd, *J*=16.3, 3.9 Hz, propenyl 1-H), 3.75–3.77 (2H, m, 2×propenyl 1-H), 4.60 (1H, dd, *J*=14.9, 4.3 Hz, propenyl 1-H), 5.12 (1H, dq, *J*=17.2, 1.6 Hz, propenyl 3-H), 5.20 (1H, dq, *J*=10.2, 1.2 Hz, propenyl 3-H), 5.30 (1H, dq, *J*=10.6, 1.2 Hz, propenyl 3-H), 5.35 (1H, dq, *J*=17.2, 1.2 Hz, propenyl 3-H), 5.64–5.66 (1H, m, propenyl 2-H), 5.94–5.96 (1H, m, propenyl 2-H), 7.34 (1H, dd, *J*=7.6, 1.5 Hz, 6-H), 7.49 (1H, t, *J*=7.8 Hz, 5-H), 7.68 (1H, dd, *J*=7.9, 1.5 Hz, 4-H); ^{13}C NMR δ 46.76 (propenyl 1-C), 50.16 (propenyl 1-C), 85.22 (2-C), 118.46 (propenyl 3-C), 119.06 (propenyl 3-C), 124.63 (4-C), 129.47 (5-C), 129.75 (6-C), 131.78 (propenyl 2-C), 131.95 (propenyl 3-C), 145.88 (1-C), 154.34 (3-C), 169.13 (C═O); MS (EI) *m*/*z* 371.9958 (M) ($C_{13}H_{13}IN_2O_3$ requires 371.9970).

5.5. Pd-catalysed cyclisation of 23 in MeCN: 4-methyl-5-nitro-2-(prop-2-enyl)isoquinolin-1(2*H*)-one (24) and 4-methylene-5-nitro-2-(prop-2-enyl)-3,4-dihydroisoquinolin-1(2*H*)-one (25)

Compound **23** (310 mg, 0.81 mmol) was boiled under reflux in dry MeCN (10 mL) with $(Ph_3P)_4Pd$ (40.3 mg, 35 μmol) and Et_3N (175 mg, 1.7 mmol) for 48 h. The evaporation residue, in EtOAc, was washed (5% aq HCl, 5% aq $NaHCO_3$) and dried. Evaporation and chromatography (hexane/EtOAc 4:1) yielded an inseparable mixture of **24** and **25** (1:2) (150 mg, 79%) as a buff oil. IR (film) ν_{max} 1658, 1531, 1365 cm^{-1}; ^{1}H NMR (**24**) δ 2.10 (3H, d, *J*=1.2 Hz, Me), 4.60 (2H, dt, *J*=5.7, 1.5 Hz, propenyl 1-H_2), 5.18–5.20 (2H, m, propenyl 3-H_2), 5.95–5.96 (1H, m, propenyl 2-H), 6.93 (1H, q, *J*=1.2 Hz, 3-H), 7.53 (1H, t, *J*=7.9 Hz, 7-H), 7.74 (1H, dd, *J*=7.8, 1.5 Hz, 6-H), 8.66 (1H, dd, *J*=7.8, 1.5 Hz, 8-H); ^{1}H NMR (**25**) δ 4.12 (2H, s, 3-H_2), 4.20 (2H, dt, *J*=5.9, 1.5 Hz, propenyl 1-H_2), 5.25–5.26 (2H, m, propenyl 3-H_2), 5.29 (1H, br s, 4-═CH), 5.45 (1H, s, 4-═CH), 5.81–5.82 (1H, m, propenyl 2-H), 7.47 (1H, t, *J*=7.9 Hz, 7-H), 7.70 (1H, dd, *J*=8.1, 1.5 Hz, 6-H), 8.31 (1H, dd, *J*=7.8, 1.3 Hz, 8-H); ^{13}C NMR (**24**) δ 15.81 (Me), 50.67 (propenyl 1-C), 108.36 (4-C), 118.74 (propenyl 3-C), 125.95 (7-C), 127.18 (6-C), 131.86 (8-C), 131.99 (propenyl 2-C), 132.60 (10-C), 133.18 (3-C), 133.87 (9-C), 147.33 (5-C), 159.87 (1-C); ^{13}C NMR (**25**) δ 49.33 (propenyl 1-C), 52.18 (3-C), 118.12 (propenyl 3-C), 119.39 (4-═CH_2), 126.60 (6-C), 128.69 (7-C), 129.13 (10-C), 130.68 (9-C), 131.55 (4-C), 131.78 (8-C), 131.89 (propenyl 2-C), 147.51 (5-C), 161.05 (1-C).

5.6. *E*-*N*-(Diphenylmethyl)-3-phenylpropenaldimine (28)

Diphenylmethylamine **27** (6.9 g, 38 mmol) and *E*-3-phenylpropenal **26** (5.0 g, 38 mmol) were boiled in toluene (50 mL) in a Dean–Stark apparatus for 24 h. Evaporation and recrystallisation (Et_2O) gave **28** (11.0 g, 97%) as yellow crystals: Mp 115–117 °C (lit.[39] mp 116–118 °C); IR ν_{max} 1598, 1489, 1444 cm^{-1}; ^{1}H NMR δ 5.48 (1H, s, Ph_2CH), 6.96 (1H, br d, *J*=16.1 Hz, 3-H), 7.06 (1H, dd, *J*=16.0, 8.1 Hz, 2-H), 7.20–7.40 (13H, m, 2×Ph′–H_5+Ph 3,4,5-H_3), 7.47 (2H, d, J=9.4 Hz, Ph 2,6-H_2), 8.18 (1H, dd, J=8.2, 0.8 Hz, 1-H).

5.7. *E*-*N*-Diphenylmethyl-3-phenylprop-2-en-1-amine (29)

$NaBH_4$ (770 mg, 20 mmol) was added to **28** (6.0 g, 20 mmol) in MeOH (250 mL) at 45 °C for 20 min. The evaporation residue, in Et_2O, was washed (5% aq $NaHCO_3$) and dried. Evaporation gave **29**[40] (5.8 g, 95%) as a pale yellow semi-solid: IR (film) ν_{max} 3332, 1598, 1492, 1451 cm^{-1}; ^{1}H NMR δ 1.94 (1H, br, N–H), 3.52 (2H, dd, J=6.2, 1.0 Hz, CH_2), 5.07 (1H, s, Ph_2CH), 6.47 (1H, dt, J=15.8, 6.0 Hz, 2-H), 6.65 (1H, d, J=15.8 Hz, 3-H), 7.34–7.61 (15H, m, 3×Ph–H_5).

5.8. *N*-Diphenylmethyl-2-iodo-3-nitro-*N*-(3-phenylprop-2-enyl)benzamide (30)

Compound **22** (1.5 g, 4.8 mmol) was stirred with **29** (1.43 g, 4.8 mmol) and Et_3N (0.97 g, 9.6 mmol) in CH_2Cl_2 (10 mL) for 30 min. Washing (5% aq HCl, 5% aq $NaHCO_3$), drying, evaporation and chromatography (hexane/EtOAc 4:1) gave **30** (1.49 g, 54%) as a pale buff solid: mp 134–136 °C; IR ν_{max} 1636, 1530, 1360 cm^{-1}; ^{1}H NMR showed the presence of two rotamers, α and β, about the amide bond, in the ratio 3:4. ^{1}H NMR (α rotamer) δ 3.91–4.06 (2H, m, propenyl 1-H_2), 5.20 (1H, dt, J=15.5, 6.5 Hz, propenyl 2-H), 5.42 (1H, d, J=16.0 Hz, propenyl 3-H), 7.31 (1H, s, Ph_2CH), 6.9–7.65 (18H, m, 3×Ph–H_5+Ar 4,5,6-H_3); ^{1}H NMR (β rotamer) δ 3.99–4.00 (1H, m, propenyl 1-H), 4.81 (1H, dd, J=14.5, 5.5 Hz, propenyl 1-H), 5.83 (1H, s, Ph_2CH), 5.88 (1H, d, J=16.0 Hz, propenyl 3-H), 6.0 (1H, dt, J=16.0, 6.0 Hz, propenyl 2-H), 6.90–7.65 (18H, m, 3×Ph–H_5+Ar 4,5,6-H_3); ^{13}C NMR (α rotamer) δ 49.33 (propenyl 1-C), 61.21 (Ph_2CH), 85.89 (2-C), 123.91 (propenyl 2-C), 124.34 (4-C), 126.03, 127.16, 127.32, 127.66, 127.76, 128.26, 128.38, 128.54, 128.84, 129.25, 130.66, 132.73 (propenyl 3-C), 135.45, 138.16, 138.60, 145.95 (1-C), 154.19 (3-C), 168.80 (C=O); ^{13}C NMR (β rotamer) δ 46.72 (propenyl 1-C), 66.63 (Ph_2CH), 85.18 (2-C), 123.42 (propenyl 2-C), 124.49 (4-C), 126.15, 127.08, 127.58, 127.68, 127.72, 128.16, 128.24, 128.35, 128.63, 128.79, 129.22, 132.36 (propenyl 3-C), 136.63, 137.51, 139.25, 145.17, 154.26, 169.42; MS (EI) *m*/*z* 575.0821 (M+H) ($C_{29}H_{24}IN_2O_3$ requires 575.0826).

5.9. Pd-catalysed cyclisation of 30 in EtCN: 2-diphenylmethyl-5-nitro-4-phenylmethylisoquinolin-1(2*H*)-one (31) and *Z*-4-benzylidene-2-diphenylmethyl-5-nitro-3,4-dihydroisoquinolin-1(2*H*)-one (32)

Compound **30** (500 mg, 0.87 mmol) was boiled under reflux with $(Ph_3P)_4Pd$ (50 mg, 44 μmol) and dry Et_3N (170 mg, 1.7 mmol) in dry EtCN (15 mL) for 48 h. The evaporation residue, in EtOAc, was washed (5% aq HCl, 5% aq $NaHCO_3$) and dried. Evaporation and chromatography (hexane/EtOAc 4:1) yielded a chromatographically inseparable mixture of **31** and **32** (160 mg, 41%) (^{1}H NMR showed the ratio **31**/**32** to be 1:3) as yellow crystals. Careful examination of the melting behaviour revealed that the isomers formed different crystals, one with mp 75–77 °C and one with mp 121–123 °C; IR ν_{max} 1654, 1524, 1347 cm^{-1}; ^{1}H NMR (**31**) δ 3.75 (2H, s, CH_2), 6.54 (1H, s, 3-H), 6.86–7.30 (15H, m, 3×Ph-H_5), 7.44 (1H, s, Ph_2CH), 7.52 (1H, t, J=7.8 Hz, 7-H), 7.79 (1H, dd, J=7.5, 1.4 Hz, 6-H), 8.75 (1H, dd, J=8.2, 1.7 Hz, 8-H); ^{1}H NMR (**32**) δ 4.24 (2H, d, J=1.1 Hz, 3-CH_2), 6.82 (1H, s, =CH), 7.24 (1H, s, Ph_2CH), 6.86–7.30 (15H, m, 3×Ph–H_5), 7.51 (1H, t, J=8.2 Hz, 7-H), 7.78 (1H, dd, J=7.8, 1.3 Hz, 6-H), 8.41 (1H, dd, J=7.8, 1.3 Hz, 8-H); ^{13}C NMR (**31**) δ 35.45 (CH_2), 60.72 (Ph_2C), 112.07 (4-C), 125.96 (7-C), 126.59 (6-C), 128.16, 128.39, 128.62, 128.69, 129.05, 131.27, 132.76 (8-C), 133.47 (3-C), 133.38, 137.54, 147.88 (5-C), 159.95 (1-C); ^{13}C NMR (**32**) δ 43.66 (CH_2), 60.77 (Ph_2C), 124.93 (4-C), 127.14 (6-C), 127.48, 127.56, 128.30 (7-C), 128.38, 128.42, 128.44, 128.74, 131.15, 131.33, 134.63, 134.75 (=CH), 137.95, 147.94 (5-C), 161.52 (1-C). MS (EI) *m*/*z* 447.1703 (M+H) ($C_{29}H_{23}N_2O_3$ requires 447.1707).

5.10. ±-*E*-1-Deuterio-*N*-diphenylmethyl-3-phenylprop-2-en-1-amine (33)

Compound **28** was treated with $NaBD_4$, as for the synthesis of **29**, to give **33** (99%) as a pale yellow semi-solid: IR (film) ν_{max} 3325, 2248, 1599, 1493, 1451 cm^{-1}; ^{1}H NMR δ 2.09 (1H, br s, N–H), 3.61 (1H, d, J=6.0 Hz, 1-H), 5.19 (1H, s, Ph_2CH), 6.57 (1H, dd, J=15.8, 6.0 Hz, 2-H), 6.81 (1H, d, J=15.8 Hz, 3-H), 7.41–7.81 (15H, m, 3×Ph–H_5); ^{13}C NMR δ 49.41 (1:1:1t, J=20 Hz, 1-C), 126.18, 126.96, 127.25, 128.27, 128.36, 128.44, 128.46, 131.26, 137.05, 143.82.

5.11. ±-*N*-(1-Deuterio-3-phenylprop-2-enyl)-*N*-diphenylmethyl-2-iodo-3-nitrobenzamide (34a)

Compound **22a** was treated with **33**, as for the synthesis of **30** except that the chromatographic eluant was hexane/EtOAc 6:1, to give **34a** (61%) as pale yellow crystals: mp 135–137 °C; IR ν_{max} 1634, 1529, 1339 cm^{-1}; ^{1}H NMR (α rotamer) δ 3.93–3.94 (1H, m, propenyl 1-H), 5.16 (1H, dd, J=16.0, 7.0 Hz, propenyl 2-H), 5.40 (1H, d, J=16.0 Hz, propenyl 3-H), 7.29 (1H, s, Ph_2CH), 6.90–7.65 (18H, m, 3×Ph–H_5+Ar 4,5,6-H_3); ^{13}C NMR (α rotamer) δ 49.25 (t, J=20.7 Hz, propenyl 1-C), 61.34 (Ph_2CH), 86.08 (2-C), 124.06 (propenyl 2-C), 124.56 (4-C), 126.21, 127.24, 127.26, 127.87, 128.35, 128.46, 128.62, 128.82, 128.84, 129.47, 132.64, 132.69 (propenyl 3-C), 135.61, 138.28, 138.84, 146.27 (1-C), 154.30 (3-C), 168.66 (C=O); ^{1}H NMR (β rotamer) δ 3.89–3.90 (0.5H, m, propenyl 1-H), 4.8 (0.5H, d, J=5.4 Hz, propenyl 1-H), 5.78 (1H, s, Ph_2CH), 5.84 (1H, dd, J=16.0, 5.0 Hz, propenyl 3-H), 5.96 (1H, dd, J=16.0, 7.5 Hz, propenyl 2-H), 6.9–7.65 (18H, m, 3×Ph–H_5+Ar 4,5,6-H_3); ^{13}C NMR (β rotamer) 46.68 (t, J=20.7 Hz, propenyl 1-C), 66.84 (Ph_2CH), 85.43 (2-C), 123.44 (propenyl 2-C), 124.69 (4-C), 126.21, 126.36, 127.37, 127.89, 128.48, 128.54, 128.74, 128.89, 129.38, 130.91, 132.95 (propenyl 3-C), 136.83, 137.68, 139.53, 145.45 (1-C), 154.48 (3-C), 170.03 (C=O).

5.12. Pd-catalysed reaction of 34 in boiling EtCN: 2-diphenylmethyl-5-nitro-4-phenylmethylisoquinolin-1(2*H*)-one (31), 3-deutero-2-diphenylmethyl-5-nitro-4-phenylmethylisoquinolin-1(2*H*)-one (37) and ±-*Z*-4-benzylidene-3-deutero-2-diphenylmethyl-5-nitro-3,4-dihydroisoquinolin-1(2*H*)-one (35)

Compound **34** was treated with $(Ph_3P)_4Pd$ and Et_3N in EtCN, as for the reaction of **30** except that the reaction time was 2 h, to give a mixture of **31**, **37** and **35** (^{1}H NMR ratio 1:1:40) (85%) as a pale yellow solid: IR ν_{max} 1654, 1523, 1347 cm^{-1}; ^{1}H NMR (**31**) data as above; ^{1}H NMR (**37**) δ 3.73 (2H, s, CH_2), 6.86–7.30 (15H, m, 3×Ph–H_5), 7.42 (1H, s, Ph_2CH), 7.53 (1H, t, J=7.9 Hz, 7-H), 7.81(1H, dd, J=7.7, 1.5 Hz, 6-H), 8.74 (1H, dd, J=7.9, 1.4 Hz, 8-H); ^{1}H NMR (**35**) δ 4.19 (1H, br s, 3-H), 6.80 (1H, s, =CH), 7.23 (1H, s, Ph_2CH), 6.86–7.30 (15H, m, 3×Ph–H_5), 7.52 (1H, t, J=8.0 Hz, 7-H), 7.77 (1H, dd, J=8.0, 1.2 Hz, 6-H), 8.39 (1H, dd, J=7.9, 1.2 Hz, 8-H); ^{13}C NMR (**35**) δ 43.43 (t, J=20.7 Hz, 3-C), 60.73 (Ph_2CH), 124.87 (4-C), 127.11 (6-C), 127.52, 127.56, 128.28, 128.34, 128.36, 128.41, 128.43, 128.64, 128.81, 129.07, 132.01 (8-C), 134.61, 134.74 (=CH), 137.92, 137.95, 147.91 (5-C), 161.48 (1-C). MS (ESI +ve) (**35**/**37**) *m*/*z* 470.1527 (M+Na) ($C^1_{29}H^2_{21}H_1N_2NaO_3$ requires 470.1591).

5.13. ±-2-Bromo-*N*-(1-deuterio-3-phenylprop-2-enyl)-*N*-diphenylmethyl-3-nitrobenzamide (34b)

Compound **22b** was treated with **33**, as for the synthesis of **30**, to give **34b** (54%) as pale buff crystals: mp 114–116 °C; IR ν_{max} 1638, 1532, 1359 cm^{-1}; ^{1}H NMR showed the presence of two rotamers, α and β, about the amide bond, in the ratio 2:3; ^{1}H NMR (α rotamer) δ 3.93–3.94 (1H, m, propenyl 1-H), 5.10 (1H, dd, *J*=15.9, 6.8 Hz, propenyl 2-H), 5.41 (1H, d, *J*=15.9 Hz, propenyl 3-H), 7.29 (1H, s, Ph_2CH), 6.80–7.46 (17H, m, 3×Ph–H_5+Ar 5,6-H_2), 7.74 (1H, dd, *J*=7.35, 2.1 Hz, Ar 4-H); ^{1}H NMR (β rotamer) δ 3.90–3.92 (0.5H, m, propenyl 1-H), 4.75 (0.5H, d, *J*=5.0 Hz, propenyl 1-H), 5.81 (1H, s, Ph_2CH), 5.81–5.88 (2H, m, propenyl 2,3-H_2), 6.9–7.65 (16H, m, 3×Ph-H_5+Ar 5-H), 6.98 (1H, dd, *J*=8.2, 1.8 Hz, Ar 4-H), 7.71 (1H, dt, *J*=7.9, 1.8 Hz, Ar 6-H); ^{13}C NMR (α rotamer) δ 48.96 (t, *J*=22.2 Hz, propenyl 1-C), 111.79 (2-C), 124.00 (propenyl 2-C), 125.16 (4-C), 126.11, 128.04, 128.12, 128.17, 128.44, 128.74, 128.84, 130.14 (Ar 6-C), 131.62, 132.60 (propenyl 3-C), 135.59 (Ph 1-C), 138.79, 139.26, 141.67 (Ar 1-C), 152.53 (Ar 3-C), 168.22 (C=O); ^{13}C NMR (β rotamer) δ 46.33 (t, *J*=22.2 Hz, propenyl 1-C), 66.72 (Ph_2CH), 111.49 (Ar 2-C), 123.42 (propenyl 2-C), 125.29 (Ar 4-C), 126.35, 127.88, 128.30, 128.48, 128.57, 128.78, 129.16 (Ar 6-C), 130.57, 132.85 (propenyl 3-C), 136.75 (Ph 1-C), 137.59, 138.24, 141.01 (Ar 1-C), 150.61 (Ar 3-C), 167.77 (C=O); MS (EI) *m*/*z* 527.0945 (M) ($C_{29}H^{2}_{22}HN_2O_3Br$ requires 527.0949).

5.14. 2-Iodo-3-nitro-*N*-(prop-2-enyl)benzamide (43) and 2-iodo-*N*-(prop-2-enyl)-2-(prop-2-enylamino)benzamide (44)

Compound **22a** (1.65 g, 5.3 mmol) was stirred with prop-2-enylamine (300 mg, 5.3 mmol) and Et_3N (1.07 g, 10.6 mmol) in CH_2Cl_2 (20 mL) for 1 h. Washing (5% aq HCl, 5% aq $NaHCO_3$), drying, evaporation and chromatography (CH_2Cl_2/EtOAc 4:1) gave **43** (1.25 g, 71%) as pale yellow crystals: mp 108–110 °C; IR ν_{max} 3264, 3077, 1643, 1588, 1529, 1349 cm^{-1}; ^{1}H NMR δ 3.95 (2H, dt, *J*=5.9, 1.5 Hz, propenyl 1-H_2), 5.11 (1H, dq, *J*=10.4, 1.3 Hz, propenyl 3-H), 5.25 (1H, dq, *J*=17.1, 1.5 Hz, propenyl 3-H), 5.77–5.90–5.91 (1H, m, propenyl 2-H), 6.28 (1H, br, NH), 7.41 (1H, dd, *J*=7.7, 1.8 Hz, 4-H), 7.49 (1H, t, *J*=7.5 Hz, 5-H), 7.62 (1H, dd, *J*=7.7, 1.8 Hz, 6-H); ^{13}C NMR δ 42.48 (propenyl 1-C), 84.86 (2-C), 117.42 (propenyl 3-C), 125.00 (6-C), 129.40 (5-C), 130.30 (4-C), 132.99 (propenyl 2-C), 146.03 (1-C), 154.75 (3-C), 168.24 (C=O); MS (FAB$^+$) *m*/*z* 331.9677 (M) ($C_{10}H_9IN_2O_3$ requires 371.9657); Anal. Calcd for $C_{10}H_9IN_2O_3$: C, 36.17; H, 2.73; N, 8.44; Found: C, 36.6; H, 2.85; N, 8.36. Further elution gave **44** (140 mg, 10%) as bright yellow crystals: mp 54–57 °C; IR ν_{max} 3468, 3334, 1639, 1578, 1516, 1345 cm^{-1}; ^{1}H NMR δ 3.75 (2H, s, amide propenyl 1-H_2), 4.01 (2H, tt, *J*=6.0, 1.4 Hz, arylamino propenyl 1-H_2), 5.13–5.25 (4H, m, 2×propenyl 3-H_2), 5.78–5.92 (2H, m, 2×propenyl 2-H), 6.77 (1H, t, *J*=8.2 Hz, 5-H), 6.82 (1H, br, NH), 7.66 (1H, dd, *J*=7.4, 1.7 Hz, 4-H), 7.72 (1H, br, NH), 8.10 (1H, dd, *J*=8.2, 1.7 Hz, 6-H); ^{13}C NMR δ 42.41 (amide propenyl 1-C), 50.24 (arylamino propenyl 1-C), 117.21 (5-C), 117.31 (propenyl 3-C), 117.40 (propenyl 3-C), 126.31 (2-C), 128.63 (6-C), 133.30 (propenyl 2-C), 133.72 (propenyl 2-C), 136.30 (4-C), 137.23 (1-C), 143.58 (3-C), 167.37 (C=O).

5.15. Pd-catalysed cyclisation of 43 in DMF: 5-nitro-4-methylisoquinolin-1(2*H*)-one (45), 5-nitro-4-methylisoquinolin-1(2*H*)-one (46) and 3-nitro-*N*-(prop-2-enyl)benzamide (47)

Compound **43** (200 mg, 0.6 mmol) was heated to reflux in dry DMF (0.7 mL) with $(Ph_3P)_4Pd$ (14 mg, 12 μmol), dry Et_3N (152 mg, 0.75 mmol) and Bu_4NCl (170 mg, 0.6 mmol) for 48 h. The evaporation residue, in $CHCl_3$, was washed (5% aq HCl, 5% aq $NaHCO_3$) and dried. Evaporation and chromatography (hexane/EtOAc 2:1) yielded **43** (40 mg, 33%) as a pale buff powder: mp 209–211 °C; IR ν_{max} 3448, 3173, 1639, 1529, 1350 cm^{-1}; ^{1}H NMR δ 2.16 (3H, s, Me), 7.05 (1H, s, 3-H), 7.52 (1H, t, *J*=7.9 Hz, 7-H), 7.82 (1H, dd, *J*=7.8, 1.4 Hz, 6-H), 8.68 (1H, dd, *J*=7.8, 1.4 Hz, 8-H), 10.72 (1H, br s, NH); ^{13}C NMR δ 15.80 (Me), 109.03 (4-C), 126.08 (7-C), 127.79 (6-C), 127.87 (10-C), 129.47 (3-C), 129.74 (9-C), 131.37 (8-C), 147.50 (5-C), 161.83 (1-C); MS (ESI +ve) *m*/*z* 205.0608 (M+H) ($C_{10}H_9N_2O_3$ requires 205.0613). Further elution gave a mixture of **45** (21 mg, 18%) and **46** (9 mg, 8%) as a pale buff semi-solid: ^{1}H NMR (**46**) δ 4.22 (2H, d, *J*=1.2 Hz, CH_2), 5.34 (1H, s, =CH), 5.50 (1H, s, =CH), 7.06 (1H, br s, NH), 7.52 (1H, t, *J*=8.2 Hz, 7-H), 7.76 (1H, dd, *J*=8.2, 1.4 Hz, 6-H), 8.32 (1H, dd, *J*=8.2, 1.4 Hz, 8-H); ^{13}C NMR (**46**) δ 47.45 (NCH_2), 119.57 (=CH_2), 127.19 (6-C), 128.81 (7-C), 129.77 (10-C), 129.76 (9-C), 131.46 (8-C), 131.51 (4-C), 147.92 (5-C), 163.25 (1-C). Further elution gave 3-nitro-*N*-(prop-2-enyl)benzamide **47** (16 mg, 13%) as a yellow semi-solid: IR ν_{max} (film) 3468, 3349, 1639, 1528, 1350 cm^{-1}; ^{1}H NMR δ 4.09 (2H, t, *J*=5.9 Hz, propenyl 1-H_2), 5.20 (1H, dt, *J*=10.1, 1.6 Hz, propenyl 3-H), 5.27 (1H, dd, *J*=17.2, 1.9 Hz, propenyl 3-H), 5.86–5.96 (1H, m, propenyl 2-H), 6.73 (1H, br s, NH), 7.62 (1H, t, *J*=8.2 Hz, 5-H), 8.15 (1H, dd, *J*=7.8, 1.6 Hz, 6-H), 8.33 (1H, ddd, *J*=8.2, 2.4, 1.2 Hz, 4-H), 8.60 (1H, t, *J*=1.9 Hz, 2-H); ^{13}C NMR δ 42.70 (propenyl 1-C), 117.23 (propenyl 3-C), 121.77 (2-C), 126.04 (4-C), 129.82 (5-C), 130.29 (6-C), 133.44 (propenyl 2-C), 135.96 (1-C), 148.06 (3-C), 164.97 (C=O); MS (ESI +ve) *m*/*z* 207.077 (M+H) ($C_{10}H_{11}N_2O_3$ requires 207.0764).

5.16. *E*-2-Iodo-3-nitro-*N*-(prop-1-enyl)benzamide (48)

Compound **43** (100 mg, 0.3 mmol) was heated to 80 °C with $RuClH(CO)(PPh_3)_3$ (1.4 mg, 1.5 μmol) in benzene (200 μL) for 3 h under Ar. EtOAc (25 mL) was added. The mixture was cooled to 0 °C and filtered. Evaporation of the filtrate and chromatography (hexane/EtOAc 4:1) gave **46** (96 mg, 96%) as a pale yellow solid: mp 169–172 °C; IR ν_{max} 3245, 3067, 1644, 1586, 1528, 1349 cm^{-1}; ^{1}H NMR δ 1.76 (3H, dd, *J*=6.8, 1.8 Hz, propenyl 3-H_3), 5.37–5.38 (1H, m, propenyl 2-H), 6.83–6.92 (1H, tq, *J*=10.5, 1.8 Hz, propenyl 1-H), 7.20 (1H, br, NH), 7.51–7.56 (2H, m, 5,6-H_2), 7.69–7.70 (1H, m, 4-H); ^{13}C NMR δ 14.94 (propenyl 3-C), 84.89 (2-C), 110.99 (propenyl 2-C), 122.50 (propenyl 1-C), 125.44 (4-C), 129.55 (6-C), 130.65 (5-C), 130.83 (1-C), 154.99 (3-C), 164.91 (C=O); MS (EI) *m*/*z* 331.9672 (M) ($C_{10}H_9IN_2O_3$ requires 331.9658).

5.17. *E*-3-Nitro-*N*-(prop-1-enyl)benzamide (49)

Compound **48** (200 mg, 0.6 mmol) was boiled under reflux with $(Ph_3P)_4Pd$ (17.3 mg, 12 μmol), dry Et_3N (151 mg, 1.5 mmol) and Bu_4NCl (210 g, 0.75 mmol) in dry DMF (1.0 mL) for 7 days. The evaporation residue, in $CHCl_3$, was washed (5% aq HCl, 5% aq $NaHCO_3$) and dried. Evaporation and chromatography (hexane/EtOAc 2:1) yielded **49** (42 mg, 52%) as a buff semi-solid: IR ν_{max} 3306, 3078, 1654, 1638, 1528, 1350 cm^{-1}; ^{1}H NMR δ 1.76 (3H, dd, *J*=6.6, 1.6 Hz, Me), 5.36–5.45 (1H, m, propenyl 2-H), 6.94–6.95 (1H, m, propenyl 1-H), 7.66 (1H, t, *J*=8.2 Hz, 5-H), 7.70 (1H, br s, NH), 8.17 (1H, dt, *J*=7.8, 1.2 Hz, 6-H), 8.36 (1H, ddd, *J*=8.2, 2.4, 1.2 Hz, 4-H), 8.60 (1H, t, *J*=1.9 Hz, 2-H); ^{13}C NMR δ 14.99 (Me), 110.47 (propenyl 2-C), 121.65 (2-C), 123.04 (propenyl 1-C), 126.35 (4-C), 130.04 (5-C), 133.33 (6-C), 135.44 (1-C), 148.50 (3-C), 161.64 (C=O); MS (ESI +ve) *m*/*z* 229.0579 (M+Na) ($C_{10}H_{10}N_2O_3Na$ requires 229.0589). Further elution gave a trace of 3-nitrobenzamide **50**, identical with a commercial sample.

5.18. *E*-*N*-(3-Phenylprop-2-enyl)-2,2,2-trifluoroacetamide (52)

KO^{t}Bu (2.84 g, 25.4 mmol) was stirred with trifluoroacetamide (2.86 g, 25.4 mmol) in dry THF (25 mL) for 30 min. (3-Bromoprop-1-enyl)benzene **51** (5.03 g, 25.4 mmol) was added and the mixture was stirred for 2 h. The evaporation residue, in CH_2Cl_2, was washed (H_2O) and dried. Evaporation and chromatography (hexane/EtOAc 4:1) yielded **52** (1.89 g, 33%) as white powder: mp 101–103 °C (lit.[41] mp 100–102 °C); IR ν_{max} 3299, 3116, 1704, 1556, 1179 cm^{-1}; ^{1}H NMR δ 4.13 (2H, t, *J*=6.5 Hz, propenyl 1-H_2), 6.17 (1H, dt, *J*=15.4, 6.9 Hz, propenyl 2-H), 6.52 (1H, br, NH), 6.60 (1H, d, *J*=15.4 Hz, propenyl 2-

H), 7.25–7.37 (5H, m, Ph-H_5); ^{13}C NMR δ 41.91 (propenyl 1-C), 117.22 (q, J=288.3 Hz, CF_3), 122.62 (propenyl 2-C), 126.48 (Ph 2,6-C_2), 128.24 (Ph 4-C), 128.68 (Ph 3,5-C_2), 134.18 (propenyl 3-C), 135.78 (Ph 1-C), 157.23 (q, J=37.6 Hz, C=O); ^{19}F NMR ($CDCl_3$) δ −75.81 (s, CF_3).

5.19. *E*-3-Phenylprop-2-enamine (53a): method A

Compound **52** (1.2 g, 5.2 mmol) was stirred with aq NH_3 (35%, 1.0 mL) in EtOH (15 mL), for 4 days. The evaporation residue, in CH_2Cl_2, was washed (H_2O) and dried. Evaporation and chromatography (CH_2Cl_2/MeOH 10:1) gave **53a**[42] (616 mg, 88%) as a pale yellow oil: IR (film) ν_{max} 3390, 1598 cm^{-1}; ^{1}H NMR δ 3.47 (2H, d, J=6.7 Hz, CH_2), 6.10 (1H, dt, J=15.8, 6.9 Hz, propenyl 2-H), 6.39 (2H, br, NH_2), 6.54 (1H, d, J=15.8 Hz, HCPh), 7.20–7.31 (5H, m, Ph–H_5).

5.20. *E*-3-Phenylprop-2-enamine (53a): method B

Compound **52** (810 mg, 3.52 mmol) was stirred with $NaBH_4$ (1.06 g, 28.2 mmol) in EtOH (10 mL) for 16 h. The evaporation residue, in CH_2Cl_2, was washed (H_2O) and dried. Evaporation and chromatography (CH_2Cl_2/MeOH 10:1) gave **53a**[42] (422 mg, 90%) as a pale yellow oil with properties as above.

5.21. *E*-3-(4-Methylphenyl)prop-2-en-1-amine (53b)

Compound **55b** (270 mg, 1.0 mmol) was boiled under reflux with $N_2H_4\cdot H_2O$ (32 mg, 1.0 mmol) in EtOH (10 mL) for 3 h. The solid was filtered, washed with ethanol and then suspended in aq NaOH (5%, 10 mL). This mixture was extracted with Et_2O (2×10 mL) and with CH_2Cl_2 (1×10 mL). The combined extracts were washed (H_2O) and dried. Evaporation gave **53b**[43] (150 mg, 65%) as a pale yellow oil: IR (film) ν_{max} 3460 cm^{-1}; ^{1}H NMR δ 2.32 (3H, s, Me), 3.43 (2H, d, J=5.8 Hz, CH_2), 6.19–6.29 (1H, dt, J=16.0, 6.0 Hz, C*H*CH_2), 6.48 (1H, d, J=15.9 Hz, C*H*Ph), 7.08 (2H, d, J=8.0 Hz, Ph 2,6-H_2), 7.24 (2H, d, J=7.9 Hz, Ph 3,5-H_2).

5.22. *E*-3-(4-Methoxyphenyl)prop-2-en-1-amine (53c)

Compound **55c** was treated with hydrazine, as for the synthesis of **53b**, to give **53c**[44] (89%) as a pale yellow oil: IR (film) ν_{max} 3460, 1518 cm^{-1}; ^{1}H NMR δ 1.35 (2H, br, NH_2), 3.44 (2H, dd, J=5.8, 1.4 Hz, propenyl 1-H_2), 3.79 (3H, s, Me), 6.16 (1H, dt, J=16.0, 5.8 Hz, propenyl 2-H), 6.45 (1H, d, J=15.7 Hz, propenyl 3-H), 6.86 (2H, d, J=8.8 Hz, Ph 3,5-H_2), 7.31 (2H, d, J=8.8 Hz, Ph 2,6-H_2).

5.23. *E*-2-(3-(4-Methylphenyl)prop-2-enyl)isoindoline-1,3-dione (55b)

4-Iodotoluene (220 mg, 1.1 mmol) was heated with *E*-2-(prop-2-enyl)isoindoline-1,3-dione **54**[45] (200 mg, 1.1 mmol), Et_3N (222 mg, 2.2 mmol) and $Pd(OAc)_2$ (2.5 mg, 0.1 mmol) in DMF (5 mL) under N_2 at 90 °C for 24 h. The evaporation residue, in EtOAc, was washed (5% aq HCl, 5% aq $NaHCO_3$) and dried. Evaporation and chromatography (hexane/EtOAc 2:1) gave **55b** (240 mg, 82%) as a pale buff solid: mp 164–166 °C (lit.[43] mp 165–166 °C); IR ν_{max} 1704 cm^{-1}; ^{1}H NMR δ 2.29 (3H, s, Me), 4.42 (2H, dd, J=6.6, 1.1 Hz, CH_2), 6.19 (1H, dt, J=16.0, 6.3 Hz, C*H*CH_2), 6.64 (1H, d, J=16.0 Hz, C*H*Ph), 7.08 (2H, d, J=8.0 Hz, Ph 2,6-H_2), 7.24 (2H, d, J=8.0 Hz, Ph 3,5-H_2), 7.68–7.72 (2H, m, Phth 3,6-H_2), 7.83–7.86 (2H, m, Phth 4,5-H_2).

5.24. *E*-2-(3-(4-Methoxyphenyl)prop-2-enyl)isoindoline-1,3-dione (55c)

Compound **54**[45] was treated with 1-iodo-4-methoxybenzene, Et_3N and $Pd(OAc)_2$, as for the synthesis of **55b**, to give **55c** (94%) as a pale yellow solid: mp 137–139 °C (lit.[46] mp 139.7–140 °C); IR ν_{max} 1704 cm^{-1}; ^{1}H NMR δ 3.77 (3H, s, Me), 4.39 (2H, dd, J=6.6, 1.1 Hz, CH_2), 6.13 (1H, dt, J=15.9, 6.6 Hz, propenyl 2-H), 6.56 (1H, d, J=16.0 Hz, propenyl 3-H), 6.80 (2H, d, J=8.0 Hz, Ph 3,5-H_2), 7.28 (2H, d, J=8.0 Hz, Ph 2,6-H_2), 7.68–7.72 (2H, m, Phth 3,6-H_2), 7.84–7.87 (2H, m, Phth 4,5-H_2).

5.25. 1-(3-Iodophenyl)pyrrolidine-2,5-dione (57)

Succinic anhydride (1.0 g, 10 mmol) and 3-iodoaniline **56** (2.19 g, 10 mmol) were heated at 190 °C for 6 h. Recrystallisation (EtOAc) afforded **57** (2.23 g, 74%) as pale buff crystals: mp 167–169 °C; IR ν_{max} 1714 cm^{-1}; ^{1}H NMR δ 2.82 (4H, s, succinimide 3,4-H_4), 7.19 (1H, t, J=8.2 Hz, Ph 5-H), 7.28 (1H, dt, J=7.8, 1.2 Hz, Ph 6-H), 7.71 (1H, t, J=1.9 Hz, Ph 2-H), 7.73 (1H, dt, J=7.8, 1.6 Hz, Ph 4-H); ^{13}C NMR δ 28.35 (succinimide 3,4-C_2), 93.69 (Ph 3-C), 125.79 (Ph 6-C), 130.52 (Ph 5-C), 132.84 (Ph 1-C), 135.23 (Ph 2-C), 137.65 (Ph 4-C), 175.70 (2×C=O); MS (ESI +ve) m/z 301.9658 (M+H) ($C_{10}H_8NO_2$ requires 301.9678).

5.26. 1,1-Dimethylethyl *N*-(prop-2-enyl)carbamate (59)

Prop-2-en-1-amine **58** (570 mg, 10 mmol) was added slowly to Boc_2O (2.18 g, 10.0 mmol) in CH_2Cl_2 (5 mL) at 0 °C and the mixture was stirred at this temperature for 3 h. Evaporation gave **59** (1.3 g, 83%) as colourless prisms: mp 33–35 °C (lit.[47] mp 35–36 °C); IR ν_{max} 3354, 1684, 1531 cm^{-1}; ^{1}H NMR δ 1.42 (9H, s, Me_3), 3.72 (2H, t, J=5.2 Hz, propenyl 1-H_2), 4.60 (1H, br, NH), 5.05 (1H, dq, J=10.2, 1.6 Hz, propenyl 3-H), 5.19 (1H, dq, J=17.1, 1.7 Hz, propenyl 3-H), 5.80–5.81 (1H, m, propenyl 2-H).

5.27. *E*-1,1-Dimethylethyl *N*-(3-(3-(2,5-dioxopyrrolidin-1-yl)phenyl)prop-2-enyl)carbamate (60) and 1,1-dimethylethyl *N*-(2-(3-(2,5-dioxopyrrolidin-1-yl)phenyl)prop-2-enyl)carbamate (61)

Compound **59** (1.57 g, 10 mmol) was boiled under reflux with **57** (3.0 g, 10 mmol), Et_3N (2.02 g, 20 mmol) and $Pd(OAc)_2$ (22.5 mg, 10 μmol) under N_2 for 48 h. The evaporation residue, $CHCl_3$, was washed (5% aq HCl, aq $NaHCO_3$) and dried. Evaporation gave a chromatographically inseparable mixture of **60** (960 mg, 29%) and **61** (240 mg, 7%) as a pale buff semi-solid: IR (film) ν_{max} 3370, 1709 cm^{-1}; ^{1}H NMR (**60**) δ 1.44 (9H, s, Me_3), 2.87 (4H, s, succinimide 3,4-H_4), 3.87–3.89 (2H, m, propenyl 1-H_2), 4.71 (1H, br, NH), 6.22 (1H, dt, J=16.0, 5.9 Hz, propenyl 2-H), 6.5 (1H, d, J=16.0 Hz, propenyl 3-H), 7.13 (1H, dt, J=7.4, 1.6 Hz, Ar 6-H), 7.24 (1H, s, Ar 2-H), 7.36 (1H, dd, J=7.8, 1.6 Hz, Ar 4-H), 7.41 (1H, t, J=7.8 Hz, Ar 5-H); ^{1}H NMR (**61**) δ 1.43 (9H, s, Me_3), 2.87 (4H, s, succinimide 3,4-H_4), 4.15 (2H, d, J=5.4 Hz, propenyl 1-H_2), 4.5 (1H, br, NH), 5.26 (1H, s, propenyl 3-H), 5.43 (1H, s, propenyl 3-H), 7.13–7.41 (4H, m, Ar 2,4,5,6-H_4); ^{13}C NMR (**60**) δ 28.34 (succinimide 3,4-C_2), 28.37 (Me_3), 42.47 (propenyl 1-C), 79.48 (CMe_3), 124.29 (Ar 2-C), 125.37 (Ar 4-C), 126.55 (Ar 6-C), 127.89 (propenyl 2-C), 129.32 (Ar 5-C), 130.14 (propenyl 3-C), 132.13 (Ar 3-C), 138.01 (Ar 1-C), 155.68 (carbamate C=O), 176.15 (2×succinimide C=O); ^{13}C NMR (**61**) δ 28.16 (succinimide 3,4-C_2), 28.22 (Me_3), 44.14 (propenyl 1-C), 79.48 (C–*C*Me_3), 114.39 (propenyl 3-C), 124.38 (Ar 2-C), 125.88 (Ar 4-C), 126.36 (Ar 6-C), 129.40 (Ar 5-C), 129.46 (propenyl 2-C), 129.87 (Ar 3-C), 132.03 (Ar 1-C), 155.68 (carbamate C=O), 176.04 (2×succinimide C=O); MS (ESI +ve) m/z 331.1652 (M+H) ($C_{18}H_{23}N_2O_4$ requires 331.1658).

5.28. *E*-2-Iodo-3-nitro-*N*-(3-phenylprop-2-enyl)benzamide (63a)

Compound **22a** (1.55 g, 5.0 mmol) was stirred with **53a** (660 mg, 5.0 mmol) and Et_3N (1.01 g mL, 10 mmol) in CH_2Cl_2 (20 mL) for 2 h. Washing (5% aq HCl, aq $NaHCO_3$), drying, evaporation and chromatography (hexane/EtOAc 4:1) gave **63a** (1.51 g, 74%) as yellow crystals: mp 146–148 °C; IR ν_{max} 3263, 3066, 1645, 1537, 1377 cm^{-1}; ^{1}H NMR δ 4.22 (2H, t, J=6.3 Hz, propenyl 1-H$_2$), 6.08 (1H, br, NH), 6.26 (1H, dt, J=15.9, 6.3 Hz, propenyl 2-H), 6.64 (1H, d, J=15.6 Hz, propenyl 3-H), 7.22–7.36 (5H, m, Ph–H$_5$), 7.42–7.50 (2H, m, Ar 5,6-H$_2$), 7.63–7.74 (1H, m, Ar 4-H); ^{13}C NMR δ 42.24 (propenyl 2-C), 84.91 (Ar 2-C), 124.05 (propenyl 2-C), 125.14 (Ar 4-C), 126.40 (Ph 2,6-C$_2$), 127.97 (Ph 4-C), 128.65 (Ph 3,5-C$_2$), 129.46 (Ar 6-C), 130.35 (Ar 5-C), 133.23 (propenyl 1-C), 136.15 (Ph 1-C), 146.06 (Ar 1-C), 154.85 (Ar 3-C), 168.24 (C=O); MS (ESI +ve) m/z 409.0035 (M+H) ($C_{16}H_{14}IN_2O_3$ requires 409.0049). Anal. Calcd for $C_{16}H_{13}IN_2O_3$: C, 47.08; H, 3.21; N, 6.86. Found: C, 47.58; H, 3.19; N, 6.93%.

5.29. *E*-2-Iodo-3-nitro-*N*-(3-(4-methylphenyl)prop-2-enyl)benzamide (63b)

Compound **53b** was treated with **22a** and Et$_3$N, as for the synthesis of **63a**, to give **63b** (82%) as yellow crystals: mp 159–162 °C; IR ν_{max} 3468, 3268, 1644, 1589, 1530, 1361 cm^{-1}; ^{1}H NMR δ 2.34 (3H, s, Me), 4.23 (2H, t, J=5.9 Hz, CH$_2$), 5.99 (1H, br, NH), 6.23 (1H, dt, J=16.0, 6.6 Hz, C*H*CH$_2$), 6.63 (1H, d, J=16.0 Hz, C*H*Ph), 7.14 (2H, d, J=7.8 Hz, Ph 3,5-H$_2$), 7.27 (2H, d, J=7.8 Hz, Ph 2,6-H$_2$), 7.51–7.53 (2H, m, Ar 5,6-H$_2$), 7.68–7.69 (1H, m, 4-H); ^{13}C NMR δ 21.21 (Me), 42.34 (CH$_2$), 84.94 (Ar 2-C), 124.94 (propenyl 2-C), 125.15 (Ar 4-C), 126.32 (Ph 2,6-C$_2$), 129.35 (Ph 3,5-C$_2$), 129.47 (Ar 5-C), 130.37 (Ar 6-C), 133.27 (propenyl 3-C), 133.36 (Ph 1-C), 137.93 (Ph 4-C), 146.13 (Ar 1-C), 154.89 (Ar 3-C), 168.19 (C=O); Anal. Calcd for $C_{17}H_{15}IN_2O_3$: C, 48.36; H, 3.58; N, 6.63. Found: C, 47.84; H, 3.37; N, 6.54%.

5.30. *E*-2-iodo-*N*-(3-(4-methoxyphenyl)prop-2-enyl)-3-nitrobenzamide (63c)

Compound **53c** was treated with **22a** and Et$_3$N, as for the synthesis of **63a**, to give **63c** (75%) as yellow crystals: mp 124–127 °C; IR ν_{max} 3468, 3259, 1640, 1588, 1529, 1348 cm^{-1}; ^{1}H NMR δ 3.79 (3H, s, Me), 4.21 (2H, t, J=6.7 Hz, propenyl 1-H$_2$), 6.01 (1H, br, NH), 6.11 (1H, dt, J=16.0, 6.6 Hz, propenyl 2-H), 6.59 (1H, d, J=16.0 Hz, propenyl 3-H), 6.83 (2H, d, J=8.6 Hz, Ph 3,5-H$_2$), 7.28 (2H, d, J=8.9 Hz, Ph 2,6-H$_2$), 7.48–7.51 (2H, m, Ar 5,6-H$_5$), 7.65–7.66 (1H, m, Ar 4-H); ^{13}C NMR δ 42.40 (propenyl 2-C), 55.28 (Me), 84.94 (Ar 2-C), 114.02 (Ph 3,5-C$_2$), 121.68 (propenyl 2-C), 125.13 (Ar 4-C), 127.62 (Ph 2,6-C$_2$), 128.88 (Ph 1-C), 129.45 (5-C), 130.36 (6-C), 132.91 (propenyl 3-C), 146.12 (Ar 1-C), 154.86 (Ar 3-C), 159.44 (Ph 4-C), 168.19 (C=O). Anal. Calcd for $C_{17}H_{15}IN_2O_4$: C, 46.59; H, 3.45; N, 6.39. Found: C, 46.48; H, 3.33; N, 6.31%.

5.31. *E*-*N*-(3-(3-(2,5-Dioxopyrrolidin-1-yl)phenyl)prop-2-enyl)-2-iodo-3-nitrobenzamide (63d) and *N*-(2-(3-(2,5-dioxopyrrolidin-1-yl)phenyl)prop-2-enyl)-2-iodo-3-nitrobenzamide (64)

A mixture of **60** and **61** (4:1, 1.2 g, 3.6 mmol) in CH$_2$Cl$_2$ (15 mL) was treated with excess HCl for 30 min. Evaporation gave a mixture of **53d** and **62** (4:1), which was used without further purification or characterisation. This mixture (1.65 g, 5.0 mmol) was stirred with **22a** (1.5 g, 5.0 mmol) and Et$_3$N (1.01 g, 10 mmol) in CH$_2$Cl$_2$ (15 mL) for 6 h. Washing (5% aq HCl, aq NaHCO$_3$), drying, evaporation and chromatography (hexane/EtOAc 4:1) gave a mixture of **63d** (640 mg, 25.6%) and **64** (160 mg, 6.4%). Further careful chromatography allowed the isolation of a very small sample of pure **63d** for characterisation: yellow crystals, mp 147–149 °C; IR ν_{max} 3467, 3313, 1702, 1631, 1534, 1391 cm^{-1}; ^{1}H NMR ((CD$_3$)$_2$SO) δ 2.78 (4H, s, succinimide 3,4-H$_4$), 4.06 (2H, t, J=5.5 Hz, propenyl 1-H$_2$), 6.38 (1H, dt, J=15.7, 5.9 Hz, propenyl 2-H), 6.69 (1H, d, J=16.0 Hz, propenyl 3-H), 7.12 (1H, dt, J=7.4, 1.6 Hz, Ar′ 6-H), 7.33 (1H, d, J=1.6 Hz, Ar′ 2-H), 7.45 (1H, t, J=7.4 Hz, Ar′ 5-H), 7.49 (1H, dt, J=7.8, 1.6 Hz, Ar′ 4-H), 7.59 (1H, dd, J=7.8, 1.6 Hz, Ar 4-H), 7.64 (1H, t, J=7.8 Hz, Ar 5-H), 7.85 (1H, dd, J=7.8, 1.6 Hz, Ar 6-H), 8.88 (1H, t, J=5.5 Hz, NH); ^{13}C NMR ((CD$_3$)$_2$SO) δ 28.55 (succinimide 3,4-C$_2$), 40.89 (propenyl 1-C), 86.77 (Ar 2-C), 124.03 (Ar 4-C), 124.83 (Ar′ 2-C), 126.09 (Ar′ 6-C), 126.21 (Ar′ 4-C), 127.42 (propenyl 2-C), 129.19 (Ar′ 5-C), 129.57 (propenyl 3-C), 129.77 (Ar 6-C), 130.34 (Ar 5-C), 133.19 (Ar′ 1-C), 137.44 (Ar′ 3-C), 146.39 (Ar 1-C), 155.26 (Ar 3-C), 168.13 (amide C=O), 177.60 (2×succinimide C=O); MS (ESI +ve) m/z 506.0207 (M+H) ($C_{20}H_{17}IN_3O_5$ requires 506.0213). NMR data for **64**: ^{1}H NMR ((CD$_3$)$_2$SO) δ 2.82 (4H, s, succinimide 3,4-H$_4$), 4.48 (2H, d, J=5.0 Hz, CH$_2$), 5.38 (1H, br s, =CH), 5.40 (1H, br s, =CH), 7.01–7.73 (5H, m, 5-H+Ph–H$_4$), 8.19–8.20 (1H, m, 4-H), 8.28–8.29 (1H, m, 6-H); ^{13}C NMR ((CD$_3$)$_2$SO) δ 27.38, 51.63, 121.02, 127.47, 129.54, 129.81, 131.99, 132.14, 132.52, 133.37, 142.66, 149.00, 162.00, 171.16.

5.32. Pd-catalysed cyclisation of 63a: 4-benzyl-5-nitroisoquinolin-1(2*H*)-one (65a), *Z*-4-benzylidene-5-nitro-3,4-dihydroisoquinolin-1(2*H*)-one (66a), *E*-3-nitro-*N*-(3-phenylprop-2-enyl)benzamide (67a) and *E*-3-amino-2-chloro-*N*-(3-phenylprop-2-enyl)benzamide (68)

Compound **63a** (100 mg, 0.24 mmol) was heated rapidly (<1 min) to 150 °C with Pd(PPh$_3$)$_4$ (6.0 mg, 5 μmol), Et$_3$N (63 mg, 0.62 mmol) and Bu$_4$NCl (70 mg, 0.25 mmol) in dry DMF (0.5 mL) and stirred at reflux for 48 h. The evaporation residue, in CHCl$_3$, was washed (5% aq HCl, 5% aq NaHCO$_3$) and dried. Evaporation and chromatography (hexane/EtOAc 2:1) gave **67a** (8 mg, 11%) as a yellow solid: mp 108–110 °C; IR ν_{max} 3468, 3283, 1638, 1530, 1345 cm^{-1}; ^{1}H NMR δ 4.24 (2H, t, J=6.7 Hz, propenyl 1-H$_2$), 6.25 (1H, dt, J=15.6, 6.3 Hz, propenyl 2-H), 6.57 (1H, d, J=16.0 Hz, propenyl 3-H), 7.06 (1H, t, J=5.5 Hz, NH), 7.20–7.33 (5H, m, Ph-H$_5$), 7.57 (1H, t, J=7.8 Hz, Ar 5-H), 8.20 (1H, dd, J=7.8, 1.6 Hz, Ar 6-H), 8.29 (1H, ddd, J=8.2, 2.4, 1.2 Hz, Ar 4-H), 8.63 (1H, t, J=1.6 Hz, Ar 2-H); ^{13}C NMR δ 42.38 (propenyl 1-C), 121.81 (Ar 2-C), 124.56 (propenyl 2-C), 125.98 (Ar 4-C), 126.29 (Ph 2,6-C$_2$), 127.84 (Ph 4-C), 128.54 (Ph 3,5-C$_2$), 129.73 (Ar 5-C), 132.78 (propenyl 3-C), 133.33 (Ar 6-C), 135.84 (Ar 1-C), 136.14 (P 1-C), 147.98 (Ar 3-C), 165.00 (C=O); MS (ESI +ve) m/z 283.1077 (M+H) ($C_{16}H_{15}N_2O_3$ requires 283.1083). Further elution gave **68** (10 mg, 14%) as a yellow semi-solid: IR (film) ν_{max} 3340, 3061, 1644 cm^{-1}; ^{1}H NMR δ 4.20 (2H, s, NH$_2$), 4.22–4.24 (2H, m, propenyl 1-H$_2$), 6.11 (1H, br, NH), 6.26 (1H, dt, J=15.7, 6.3 Hz, propenyl 2-H), 6.58 (1H, d, J=16.0 Hz, propenyl 3-H), 6.80 (1H, dd, J=8.2, 1.6 Hz, Ar 4-H), 6.88 (1H, dd, J=7.8, 1.6 Hz, Ar 6-H), 7.07 (1H, t, J=7.8 Hz, Ar 5-H), 7.23–7.37 (5H, m, Ph–H$_5$); ^{13}C NMR δ 41.97 (propenyl 1-C), 115.36 (Ar 2-C), 116.99 (Ar 4-C), 118.28 (Ar 6-C), 124.95 (propenyl 2-C), 126.38 (Ph 2,6-C$_2$), 127.52 (Ph 4-C), 127.76 (Ar 5-C), 128.58 (Ph 3,5-C$_2$), 132.44 (propenyl 3-C), 136.37 (Ar 1-C), 136.42 (Ph 1-C), 143.64 (Ar 3-C), 167.29 (C=O); MS (ESI +ve) m/z 287.0946 (M+H) ($C_{16}H_{16}ClN_2O$ requires 287.0951). Further elution gave **65a** (12 mg, 17%) as an orange solid: mp 210–212 °C; ^{1}H NMR δ 3.88 (2H, s, CH$_2$), 6.75 (1H, s, 3-H), 7.11 (2H, d, J=7.0 Hz, Ph 2,6-H$_2$), 7.23–7.31 (3H, m, Ph 3,4,5-H$_3$), 7.56 (1H, t, J=7.8 Hz, 7-H), 7.82 (1H, dd, J=7.8, 1.2 Hz, 6-H), 8.68 (1H, dd, J=7.8, 1.2 Hz, 8-H), 11.07 (1H, br, NH); ^{13}C NMR δ 35.45 (CH$_2$), 113.27 (4-C), 126.11 (7-C), 126.94 (Ph 4-C), 127.94 (8-C), 128.71 (5-C), 128.81 (Ph 3,5-C$_2$), 129.39 (Ph 2,6-C$_2$), 129.59 (8a-C), 130.93 (3-C), 131.85 (7-C), 137.71 (Ph 1-C), 147.65 (4a-C), 161.89 (1-C); MS (ESI +ve) m/z 281.0921 (M+H) ($C_{16}H_{13}N_2O_3$ requires 281.0926). Further elution gave **66a** (10 mg, 14%) as a yellow solid: mp 183–185 °C; ^{1}H NMR δ 4.50 (2H, d, J=1.4 Hz, 3-CH$_2$), 6.74 (1H, br, NH), 6.79 (1H, s, =CH), 7.18 (2H, d, J=7.2 Hz, Ph 2,6-H$_2$), 7.30–7.41 (3H, m, Ph 3,4,5-H$_3$), 7.50 (1H, t, J=7.9 Hz, 7-H), 7.82 (1H, dd, J=8.2, 1.4 Hz, 6-H), 8.30 (1H, dd, J=7.9, 1.4 Hz, 8-H); ^{13}C NMR δ 41.99 (3-C), 124.34 (4-C), 127.65 (5-C), 128.34 (6-C), 128.58 (Ph 3,4,5-C$_3$), 129.14 (Ph 2,6-C$_2$), 130.31 (8-C), 131.21 (7-C), 131.66 (8a-C), 134.72 (=CH), 134.80 (Ph 1-C), 148.39 (4a-C), 162.89 (1-C). Anal. Calcd for $C_{16}H_{12}N_2O_3$: C, 68.56; H, 4.32; N, 9.99. Found: C, 68.43; H, 4.07; N, 9.99.

5.33. Pd-catalysed cyclisation of 63b: 4-(4-methylbenzyl)-5-nitroisoquinolin-1(2*H*)-one (65b), *Z*-4-(4-methylbenzylidene)-5-nitro-3,4-dihydroisoquinolin-1(2*H*)-one (66b), *E*-*N*-(3-(4-methylphenyl)prop-2-enyl)-3-nitrobenzamide (67b) and *N*-(3-(4-methylphenyl)propyl)-3-nitrobenzamide (69b)

Compound **63b** (150 mg, 0.35 mmol) was boiled under reflux with $\mathrm{Pd(PPh_3)_4}$ (8.2 mg, 7 μmol), $\mathrm{Et_3N}$ (90 mg, 0.89 mmol) and $\mathrm{Bu_4NI}$ (129 mg, 0.35 mmol) in dry DMF (0.7 mL) for 48 h. The evaporation residue, in $\mathrm{CHCl_3}$, was washed (5% aq HCl, 5% aq $\mathrm{NaHCO_3}$) and dried. Evaporation and chromatography (hexane/EtOAc 2:1) yielded an inseparable mixture of **67b** (12 mg, 12%) and **69b** (5 mg, 5%) as pale yellow semi-solid: IR (film) ν_{max} 3467, 3312, 1641, 1524, 1350 cm^{-1}; ^{1}H NMR (**67b**) δ 2.33 (3H, s, Me), 4.23 (2H, t, J=6.3 Hz, propenyl 1-$\mathrm{H_2}$), 6.24 (1H, dt, J=15.6, 6.6 Hz, propenyl 2-H), 6.55 (1H, d, J=16.0 Hz, propenyl 3-H), 6.61 (1H, br, NH), 7.10–7.11 (2H, m, Ph 3,5-$\mathrm{H_2}$), 7.26 (2H, d, J=7.8 Hz, Ph 2,6-$\mathrm{H_2}$), 7.64 (1H, t, J=8.2 Hz, Ar 5-H), 8.18 (1H, d, J=8.2, 1.6 Hz, Ar 6-H), 8.34 (1H, ddd, J=8.2, 2.4, 1.2 Hz, Ar 4-H), 8.63 (1H, t, J=1.9 Hz, Ar 2-H); ^{1}H NMR (**69b**) δ 1.96 (2H, quintet, J=7.0 Hz, propyl 2-$\mathrm{H_2}$), 2.29 (3H, s, Me), 2.71 (2H, t, J=7.4 Hz, propyl 3-$\mathrm{H_2}$), 3.54 (2H, q, J=6.6 Hz, propyl 1-$\mathrm{H_2}$), 7.10–7.11 (2H, m, Ph 3,5-$\mathrm{H_2}$), 7.26 (2H, d, J=8.2 Hz, Ph 2,6-$\mathrm{H_2}$), 7.60 (1H, t, J=7.8 Hz, Ar 5-H), 7.98 (1H, dt, J=7.4, 1.9 Hz, Ar 6-H), 8.30 (1H, ddd, J=8.2, 2.4, 1.2 Hz, Ar 4-H), 8.44 (1H, t, J=1.9 Hz, Ar 2-H), 8.54 (1H, br, NH); ^{13}C NMR (**67b**) δ 21.18 (Me), 42.50 (propenyl 1-C), 121.75 (Ar 2-C), 123.38, 126.06 (Ar 4-C), 126.28 (Ph 2,6-$\mathrm{C_2}$), 129.31 (Ph 3,5-$\mathrm{C_2}$), 129.85 (Ar 5-C), 133.11 (propenyl 3-C), 133.29 (Ar 6-C), 135.73 (Ph 1-C), 135.97 (Ar 1-C), 137.85 (Ph 4-C), 148.10 (Ar 3-C), 164.86 (C=O); ^{13}C NMR (**69b**) δ 20.94 (Me), 30.81 (propyl 2-C), 33.19 (propyl 3-C), 40.26 (propyl 1-C), 121.54 (Ar 2-C), 125.88 (Ar 4-C), 126.28 (Ph 2,6-$\mathrm{C_2}$), 129.31 (Ph 3,5-$\mathrm{C_2}$), 129.68 (Ar 5-C), 133.36 (Ar 6-C), 135.02 (Ph 1-C), 136.11 (Ar 1-C), 138.14 (Ph 4-C), 148.10 (Ar 3-C), 164.86 (C=O); MS (ESI +ve) *m*/*z* 321.1207 (M+Na) ((**69b**) $\mathrm{C_{17}H_{18}N_2NaO_3}$ requires 321.1215), 297.1240 (M+H) ((**67b**) $\mathrm{C_{17}H_{17}N_2O_3}$ requires 297.1239). Further elution gave **65b** (16 mg, 15%) as a pale orange powder: mp 186–188 °C; IR ν_{max} 3392, 3118, 1660, 1526, 1367 cm^{-1}; ^{1}H NMR δ 2.33 (3H, s, Me), 3.82 (2H, s, $\mathrm{CH_2}$), 6.75 (1H, s, 3-H), 6.98 (2H, d, J=7.9 Hz, Ph 3,5-$\mathrm{H_2}$), 7.10 (2H, d, J=7.9 Hz, Ph 2,6-$\mathrm{H_2}$), 7.54 (1H, t, J=7.9 Hz, 7-H), 7.83 (1H, dd, J=7.9, 1.1 Hz, 6-H), 8.67 (1H, d, J=7.9, 1.1 Hz, 8-H), 11.32 (1H, br s, NH); ^{13}C NMR δ 21.07 (Me), 34.98 ($\mathrm{CH_2}$), 113.56 (4-C), 126.01 (6-C), 127.85 (8-C), 128.67 (5-C), 129.26 (Ph 3,5-$\mathrm{C_2}$), 129.49 (Ph 2,6-$\mathrm{C_2}$), 126.62 (8a-C), 130.91 (3-C), 131.77 (7-C), 134.54 (Ph 1-C), 136.51 (Ph 4-C), 147.63 (4a-C), 162.03 (1-C); MS (ESI +ve) *m*/*z* 295.1077 (M+H) ($\mathrm{C_{17}H_{15}N_2O_3}$ requires 295.1083). Further elution gave **66b** (14 mg, 13%) as a yellow solid: mp 152–154 °C; IR ν_{max} 3042, 1662, 1529, 1352 cm^{-1}; ^{1}H NMR δ 2.30 (3H, s, Me), 4.50 (2H, d, J=1.6 Hz, $\mathrm{CH_2}$), 6.75 (1H, s, =CH), 6.84 (1H, br, NH), 7.09 (2H, d, J=7.8 Hz, Ph 2,6-$\mathrm{H_2}$), 7.19–7.21 (2H, m, Ph 3,5-$\mathrm{H_2}$), 7.50 (1H, t, J=8.2 Hz, 7-H), 7.80 (1H, dd, J=8.12, 1.2 Hz, 6-H), 8.30 (1H, dd, J=7.8, 1.2 Hz, 8-H); ^{13}C NMR δ 21.32 (Me), 42.04 (3-C), 123.51 (4-C), 127.64 (5-C), 128.15 (6-C), 129.15 (Ph 2,6-$\mathrm{C_2}$), 129.25 (Ph 3,5-$\mathrm{C_2}$), 130.24 (8-C), 131.14 (7-C), 131.85 (8a-C), 132.01 (Ph 4-C), 134.83 (=CH), 138.74 (Ph 1-C), 148.41 (4a-C), 162.96 (1-C); MS (ESI +ve) *m*/*z* 295.1066 (M+H) ($\mathrm{C_{17}H_{15}N_2O_3}$ requires 295.1083).

5.34. Pd-catalysed cyclisation of 63c: *E*-*N*-(3-(4-methoxyphenyl)prop-2-enyl)-3-nitrobenzamide (67c), *N*-(3-(4-methoxyphenyl)propyl)-3-nitrobenzamide (69c), 4-(4-methoxybenzyl)-5-nitroisoquinolin-1(2*H*)-one (65c) and *Z*-4-(4-methoxybenzylidene)-5-nitro-3,4-dihydroisoquinolin-1(2*H*)-one (66c)

Compound **63c** was treated with $\mathrm{Pd(PPh_3)_4}$, $\mathrm{Et_3N}$ and $\mathrm{Bu_4NI}$ in DMF, as for the synthesis of **65b** and **66b**, to give an inseparable mixture of **67c** (8%) and **69c** (12%) as a pale yellow semi-solid: IR (film) ν_{max} 3300, 3095, 1637, 1539, 1357 cm^{-1}; ^{1}H NMR (**67c**) δ 3.76 (3H, s, Me), 4.17 (2H, t, J=6.7 Hz, propenyl 1-$\mathrm{H_2}$), 6.07 (1H, dt, J=16.0, 6.3 Hz, propenyl 2-H), 6.48 (1H, d, J=16.0 Hz, propenyl 3-H), 6.79 (2H, d, J=8.6 Hz, Ph 3,5-$\mathrm{H_2}$), 7.21 (2H, d, J=9.0 Hz, Ph 2,6-$\mathrm{H_2}$), 7.33 (1H, br, NH), 7.56 (1H, t, J=8.2 Hz, Ar 5-H), 8.18 (1H, dt, J=8.2, 1.6 Hz, Ar 6-H), 8.27 (1H, ddd, J=8.2, 2.4, 1.2 Hz, Ar 4-H), 8.64 (1H, t, J=1.9 Hz, Ar 2-H); ^{1}H NMR (**69c**) δ 1.90 (2H, qn, J=7.4 Hz, propyl 2-$\mathrm{H_2}$), 2.63 (2H, t, J=7.4 Hz, propyl 3-$\mathrm{H_2}$), 3.48–3.49 (2H, m, propyl 1-$\mathrm{H_2}$), 3.76 (3H, s, Me), 6.90 (1H, t, J=5.4 Hz, NH), 6.79 (2H, J=8.6 Hz, Ph 3,5-$\mathrm{H_2}$), 7.06 (2H, d, J=8.9 Hz, Ph 2,6-$\mathrm{H_2}$), 7.50 (1H, t, J=7.8 Hz, Ar 5-H), 8.02 (1H, dt, J=7.8, 1.2 Hz, Ar 6-H), 8.23 (1H, ddd, J=8.2, 2.4, 1.2 Hz, Ar 4-H), 8.48 (1H, t, J=1.9 Hz, Ar 2-H); ^{13}C NMR (**67c**) δ 42.44 (propenyl 1-C), 55.14 (Me), 113.88 (Ph 3,5-$\mathrm{C_2}$), 121.88 (Ar 2-C), 122.24 (propenyl 2-C), 125.84 (Ar 4-C), 127.42 (Ph 2,6-$\mathrm{C_2}$), 128.88 (Ph 1-C), 129.61 (Ar 5-C), 132.16 (propenyl 3-C), 133.29 (Ar 6-C), 135.88 (Ar 1-C), 147.91 (Ar 3-C), 159.20 (Ph 4-C), 164.99 (C=O); ^{13}C NMR (**69c**) δ 30.85 (propyl 2-C), 32.45 (propyl 3-C), 40.09 (propyl 1-C), 55.08 (Me), 113.78 (Ph 3,5-$\mathrm{C_2}$), 121.64 (Ar 2-C), 125.70 (Ar 4-C), 129.10 (Ph 2,6-$\mathrm{C_2}$), 129.52 (Ar 5-C), 133.19 (Ph 1-C), 133.11 (Ar 6-C), 136.03 (Ar 1-C), 147.83 (Ar 3-C), 157.76 (Ph 4-C), 165.05 (C=O); MS (ESI +ve) *m*/*z* 335.0996 (M+Na) ((**67c**) $\mathrm{C_{17}H_{16}N_2NaO_4}$ requires 335.1008), 315.1320 (M+H) ((**69c**) $\mathrm{C_{17}H_{19}N_2O_4}$ requires 315.1345). Further elution gave **65c** (17%) as a pale orange powder: mp 121–124 °C; IR ν_{max} 3119, 3042, 1661, 1604, 1527, 1367 cm^{-1}; ^{1}H NMR δ 3.79 (3H, s, Me), 3.81 (2H, s, $\mathrm{CH_2}$), 6.76 (1H, s, 3-H), 6.82 (2H, d, J=8.6 Hz, Ph 3,5-$\mathrm{H_2}$), 7.02 (2H, d, J=8.6 Hz, Ph 2,6-$\mathrm{H_2}$), 7.52 (1H, t, J=7.8 Hz, 7-H), 7.83 (1H, dd, J=7.8, 1.2 Hz, 6-H), 8.65 (1H, dd, J=7.8, 1.6 Hz, 8-H), 11.68 (1H, br, NH); ^{13}C NMR δ 34.52 (Me), 55.23 ($\mathrm{CH_2}$), 113.77 (4-C), 114.18 (Ph 3,5-$\mathrm{C_2}$), 125.98 (6-C), 127.81 (8-C), 128.66 (5-C), 129.52 (8a-C), 130.41 (Ph 2,6-$\mathrm{C_2}$), 130.93 (3-C), 131.75 (7-C), 147.61 (4a-C), 158.47 (Ph 4-C), 162.21 (1-C); MS (ESI +ve) *m*/*z* 311.1026 (M+H) ($\mathrm{C_{17}H_{15}N_2O_4}$ requires 311.1032). Further elution gave **66c** (15%) as a pale yellow solid: mp 203–204 °C; ^{1}H NMR δ 3.83 (3H, s, Me), 4.52 (2H, s, 3-$\mathrm{H_2}$), 6.24 (1H, br, NH), 6.72 (1H, s, =CH), 6.92 (2H, d, J=8.9 Hz, Ph 2,6-$\mathrm{H_2}$), 7.12 (2H, d, J=8.2 Hz, Ph 3,5-$\mathrm{H_2}$), 7.52 (1H, t, J=8.2 Hz, 7-H), 7.80 (1H, dd, J=8.2, 1.2 Hz, 6-H), 8.31 (1H, dd, J=7.8, 1.2 Hz, 8-H); ^{13}C NMR δ 42.14 (3-C), 55.37 (Me), 114.00 (Ph 3,5-$\mathrm{C_2}$), 122.58 (4-C), 127.48 (Ph 1-C), 127.67 (5-C), 128.02 (6-C), 130.15 (8-C), 130.73 (Ph 2,6-$\mathrm{C_2}$), 131.21 (7-C), 131.95 (8a-C), 134.56 (=CH), 148.43 (4a-C), 159.83 (Ph 4-C), 162.63 (1-C); MS (ESI +ve) *m*/*z* 311.1001 (M+H) ($\mathrm{C_{17}H_{15}N_2O_4}$ requires 311.1032).

5.35. Pd-catalysed cyclisation of 63d: *E*-*N*-(3-(3-(2,5-dioxopyrrolidin-1-yl)phenyl)prop-2-enyl)-3-nitrobenzamide (67d), *N*-(2-(3-(2,5-dioxopyrrolidin-1-yl)phenyl)prop-2-enyl)-3-nitrobenzamide (70), 1-(3-((5-nitro-1-oxo-1,2-dihydroisoquinolin-4-yl)methyl)phenyl)pyrrolidine-2,5-dione (65d) and *Z*-1-(3-((5-nitro-1-oxo-2,3-dihydroisoquinolin-4-ylidene)methyl)phenyl)pyrrolidine-2,5-dione (66d)

A mixture of **63d** and **64** (4:1) was treated with $\mathrm{Pd(PPh_3)_4}$, $\mathrm{Et_3N}$ and $\mathrm{Bu_4NI}$ in DMF, as for the synthesis of **65b** and **66b**, to give an inseparable mixture of **67d** (12 mg, 15%) and **70** (2 mg, 3%) as a yellow semi-solid: IR (film) ν_{max} 3351, 3078, 1709, 1658, 1528, 1350 cm^{-1}; ^{1}H NMR (**67d**) δ 2.87 (4H, s, succinimide 3,4-$\mathrm{H_4}$), 4.17 (2H, t, J=6.3 Hz, propenyl 1-$\mathrm{H_2}$), 6.20 (1H, dt, J=16.0, 6.3 Hz, propenyl 2-H), 6.69 (1H, d, J=16.0 Hz, propenyl 3-H), 7.10 (1H, dt, J=8.2, 1.6 Hz, Ar′ 6-H), 7.19 (1H, t, J=1.9 Hz, Ar′ 2-H), 7.27 (1H, d, J=8.2 Hz, Ar′ 4-H), 7.49 (1H, dt, J=7.8, 1.6 Hz, Ar′ 5-H), 7.59 (1H, t, J=7.8 Hz, Ar 5-H), 8.20 (1H, dt, J=7.8, 1.6 Hz, Ar 6-H), 8.29 (1H, ddd, J=8.2, 2.4, 1.2 Hz, Ar 4-H), 8.66 (1H, t, J=1.9 Hz, Ar 2-H); ^{1}H NMR (**70**) δ 2.88 (4H, s, succinimide 3,4-$\mathrm{H_4}$), 4.48 (2H, d, J=5.0 Hz, $\mathrm{NCH_2}$), 5.36 (1H, s, =CH), 5.49 (1H, s, =CH), 7.08–7.63 (5H, m, Ar 5-H+Ar′ 2,4,5,6-$\mathrm{H_4}$), 8.19–8.20 (1H, m, Ar 6-H), 8.28–8.29 (1H, m, Ar 4-H), 8.56 (1H, s, Ar 2-H); ^{13}C NMR (**67d**) δ 28.38 (succinimide 3,4-$\mathrm{C_2}$), 42.20 (propenyl 1-C), 121.92 (Ar′ 2-C), 124.22 (Ar 4-C), 125.62 (Ar 2-C), 125.98 (Ar′ 6-C), 126.36 (Ar′ 4-C), 126.56 (propenyl 2-C), 129.35 (Ar′ 5-C), 129.67 (propenyl 3-C), 131.37 (Ar 6-C), 131.89 (Ar 5-C), 133.51 (Ar′ 1-C), 135.70 (Ar′ 3-C), 137.60 (Ar 1-C), 147.99 (Ar 3-C), 164.96 (amide C=O), 176.36 (2×succinimide C=O); ^{13}C NMR (**70**) δ 28.38 (succinimide 3,4-C_2), 50.66 (NCH_2), 122.02, 128.45, 128.57, 129.41, 129.61, 131.99, 132.04, 132.14, 132.52, 133.37, 142.66, 149.00 (Ar 3-C), 165.00 (amide C=O), 171.26 (2×succinimide C=O); MS (ESI +ve) *m*/*z* 380.1246 (M+H) ($C_{20}H_{18}N_3O_5$ requires 380.1240).

Also isolated was an inseparable mixture of **65d** (8 mg, 10.5%) and **66d** (8 mg, 10.5%) as a pale yellow gum: IR (film) ν_{max} 3351, 3078, 1658, 1528, 1350 cm^{-1}; ^{1}H NMR (**65d**) δ 2.85 (4H, s, succinimide 3,4-H_4), 4.48 (2H, s, 4-CH_2), 7.04 (1H, s, 3-H), 7.15–7.43 (4H, m, Ph-H_4), 7.53 (1H, t, J=7.8 Hz, 7-H), 7.81 (1H, dd, J=8.2, 1.2 Hz, 6-H), 8.65 (1H, dd, J=7.8, 1.6 Hz, 8-H), 10.34 (1H, br, NH); ^{1}H NMR (**66d**) δ 2.91 (4H, s, succinimide 3,4-H_4), 4.49 (2H, s, 3-H_2), 6.14 (1H, br, NH), 6.78 (1H, s, =CH), 7.15–7.16 (1H, m, Ph 2-H), 7.22–7.23 (1H, m, Ph 4-H), 7.31–7.32 (1H, m, Ph 6-H), 7.51 (1H, t, J=7.8 Hz, Ph 5-H), 7.54 (1H, t, J=7.8 Hz, 7-H), 7.83 (1H, dd, J=8.2, 1.2 Hz, 6-H), 8.33 (1H, dd, J=7.8, 1.2 Hz, 8-H); ^{13}C NMR (**65d**) δ 28.38, 35.15, 60.39, 125.02, 126.19, 126.97, 128.64, 129.17, 129.60, 131.37, 132.04, 132.22, 139.11, 148.27, 161.20, 176.15; ^{13}C NMR (**66d**) δ 30.93, 41.82, 59.27, 125.91, 126.29, 127.65, 128.69, 129.45, 129.72, 131.04, 131.97, 133.14, 135.78, 147.51, 162.67, 176.02.

5.36. *N*-(1,1-Dimethylethoxycarbonyl)-2-iodo-3-nitro-*N*-(prop-2-enyl)benzamide (71)

Boc_2O (100 mg, 0.45 mmol) was added slowly to **43** (100 mg, 0.3 mmol) in CH_2Cl_2 (5.0 mL) at 0°C. Et_3N (45 mg, 0.45 mmol) and 4-(dimethylamino)pyridine (7.4 mg, 60 µmol) were added and the mixture was stirred for 3 h. Washing (5% aq citric acid, aq $NaHCO_3$, H_2O), drying and evaporation gave **71** (120 mg, 92%) as a yellow semi-solid: IR (film) ν_{max} 1739, 1672, 1535, 1347 cm^{-1}; ^{1}H NMR δ 1.19 (9H, s, ^{t}Bu), 4.46 (2H, d, J=5.5 Hz, propenyl 1-H_2), 5.11–5.23 (1H, dd, J=10.2, 1.4 Hz, propenyl 3-H), 5.27–5.35 (1H, dq, J=17.1, 1.4 Hz, propenyl 3-H), 5.87–6.02 (1H, m, propenyl 2-H), 7.27 (1H, dd, J=7.4, 1.4 Hz, 4-H), 7.49 (1H, t, J=7.7 Hz, 5-H), 7.66 (1H, dd, J=8.0, 1.3 Hz, 6-H); ^{13}C NMR δ 27.46 (Me_3), 46.66 (propenyl 1-C), 83.95 (2-C), 84.45 (CMe_3), 117.94 (propenyl 3-C), 124.05 (4-C), 128.86 (6-C), 129.10 (5-C), 132.05 (propenyl 2-C), 148.45 (1-C), 151.04 (carbamate C=O), 154.16 (3-C), 169.64 (amide C=O); MS (ESI +ve) *m*/*z* 455.0048 (M+Na) ($C_{15}H_{17}IN_2NaO_5$ requires 455.0080).

5.37. 5-Amino-4-methylisoquinolin-1-one hydrochloride (72)

A slurry of 10% Pd/C (100 mg) in EtOH (2 mL) was added to **45** (58 mg, 0.28 mmol) in EtOH (5 mL) and concd aq HCl (0.2 mL). The mixture was stirred under H_2 for 2 h. The suspension was then filtered (Celite®). The Celite® pad and residue were suspended in water (100 mL) and heated. The hot suspension was filtered through a second Celite® pad. Concentration of the filtrate and drying gave **72** (42 mg, 70%) as pale buff crystals: mp 227–229 °C; IR ν_{max} 3421, 1654 cm^{-1}; ^{1}H NMR (D_2O) δ 2.37 (3H, s, Me), 6.94 (1H, s, 3-H), 7.42 (1H, t, J=8.2 Hz, 7-H), 7.63 (1H, d, J=7.8 Hz, 6-H), 8.14 (1H, d, J=8.2 Hz, 8-H); ^{13}C NMR δ 18.41 (Me), 110.74 (4-C), 126.89 (5-C), 127.04 (8a-C), 127.24 (7-C), 128.48 (8-C), 128.64 (3-C), 129.55 (6-C), 132.52 (4a-C), 162.72 (1-C); MS (ESI +ve) *m*/*z* 175.0866 (M+H) ($C_{10}H_{11}N_2O_1$ requires 175.0871).

5.38. 5-Amino-4-phenylmethylisoquinolin-1-one (73)

A slurry of 10% Pd/C (50 mg) in EtOH (2 mL) was added to **65a** (20 mg, 70 µmol) in EtOH (5 mL). The mixture was stirred under H_2 for 1 h. The suspension was then filtered (Celite®). The Celite® pad and residue were suspended in water (100 mL) and heated. The hot suspension was filtered through a second Celite® pad. Concentration of the filtrate and drying gave **73** (9 mg, 51%) as a pale buff powder: 121–123 °C; IR ν_{max} 3407, 3337, 1623 cm^{-1}; ^{1}H NMR δ 4.32 (2H, s, CH_2), 6.87 (1H, d, J=7.4 Hz, 6-H), 6.9 (1H, s, 3-H), 7.22 (1H, t, J=7.4 Hz, 7-H), 7.25–7.35 (5H, m, Ph–H_5), 8.02 (1H, d, J=7.8 Hz, 8-H), 11.51 (1H, br s, NH); ^{13}C NMR δ 38.39 (CH_2), 113.34 (4-C), 119.11 (8-C), 120.92 (6-C), 126.64 (4a-C), 126.93 (Ph 4-C), 127.23 (3-C), 127.43 (7-C), 128.09 (Ph 2,6-C_2), 128.16 (8a-C), 129.16 (Ph 3,5-C_2), 140.05 (Ph 1-C), 143.50 (5-C), 163.99 (1-C); MS (ESI +ve) *m*/*z* 251.1179 (M+H) ($C_{16}H_{15}N_2O$ requires 251.1184).

5.39. 5-Amino-4-phenylmethylisoquinolin-1-one (73) and ±-5-amino-4-phenylmethyl-3,4-dihydroisoquinolin-1-one (74)

Compound **66a** was treated with H_2 and Pd/C, as for the synthesis of **73** from **65a**, to give an inseparable mixture of **73** (14%) and **74** (54%). Careful examination of the melting behaviour revealed that the compound formed different crystals, one (**73**) with mp 121–123 °C and one (**74**) with mp 169–170 °C; Data for **74**: ^{1}H NMR δ 2.92 (2H, d, J=3.5 Hz, $PhCH_2$), 2.99 (1H, dd, J=9.4, 3.5 Hz, 4-H), 3.35 (1H, ddd, J=12.5, 5.1, 1.2 Hz, 3-H), 3.61 (1H, dd, J=12.5, 3.9 Hz, 3-H), 6.64 (1H, br s, NH), 6.82 (1H, dd, J=7.8, 1.2 Hz, 6-H), 7.16 (2H, d, J=7.4 Hz, Ph 2,6-H_2), 7.18 (1H, t, J=7.8 Hz, 7-H), 7.20–7.35 (3H, m, Ph 3,4,5-H_3), 7.62 (1H, dd, J=7.8, 1.2 Hz, 8-H); ^{13}C NMR δ 35.08 (4-C), 37.55 (CH_2Ph), 42.82 (3-C). 119.25 (8-C), 119.94 (6-C), 126.66 (Ph 4-C), 127.71 (4a-C), 127.61 (7-C), 128.71 (8a-C), 128.75 (Ph 3,5-C_2), 129.03 (Ph 2,6-C_2), 139.29 (Ph 1-C), 142.81 (5-C), 166.67 (1-C); MS (ESI +ve) *m*/*z* 253.1328 (M+H) ($C_{16}H_{17}N_2O$ requires 253.1335).

5.40. Crystal data for 44

Crystal Data for **44**: $C_{13}H_{14}N_3O_3$, M=260.27, λ=0.71073 Å, monoclinic, space group $P2_1$, a=11.1000(5), b=5.0730(2), c=11.9100(6) Å, β=101.651(2)°, V=656.84(5) Å^3, Z=2, D_c 1.316 g cm^{-3}, μ=0.096 mm^{-1}, $F(000)$=274, crystal size 0.50×0.10×0.10 mm, unique reflections =2887 [R(int)=0.0555], observed $I>2\sigma(I)$=2417, data/restraints/parameters=2887/1/173, $R1$=0.0457 $wR2$=0.1019 (obsd data), $R1$=0.0603 $wR2$=0.1092 (all data), max peak/hole 0.534 and −0.169 e Å^{-3}, software used: SHELXS,[48] SHELXL[49] and ORTEX.[50] The Flack parameter had no credibility for assignment of the absolute configuration in this structure. The stereochemistry as presented was dictated by chemical information.

Crystallographic data for **44** have been deposited with the Cambridge Crystallographic Data Centre as Supplementary data (CCDC 702633). Requests for data should be addressed to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK.

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