An Unusual Polyheterocyclic Diversity by the π-Cyclisation of *N*-Carbamoyliminium Ion, with or without Tandem *N*,*N*-Acetal Cleavage, from Spiro(imidazolidinoquinazolinones)

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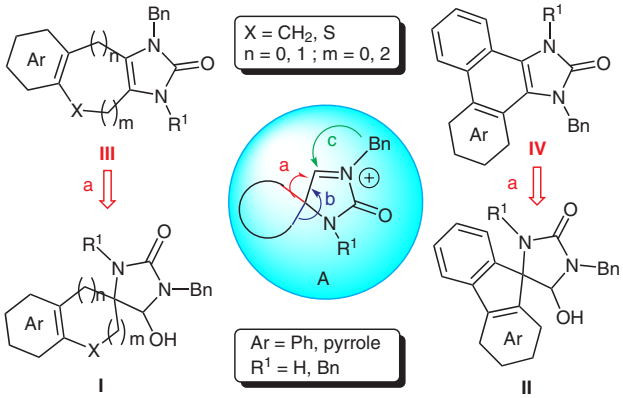
Abstract: Spiro(imidazolidinoquinazolinones), obtained easily in one step from 1-carbamoylisatins, are readily converted in three steps by successive N-alkylations and sodium borohydride regioselective reduction into the corresponding hydroxyspirolactams. The latter are valuable platforms for further transformations via the intermediacy of *N*-acyliminium species and have been applied to the synthesis of original isoquinoloquinazoline, indoloquinazoline and imidazoindole derivatives.

Key words: π-cyclisation, cleavage, *N*-acyliminium ion, hydroxy lactam, reduction, imidazolidine, quinazolinone

The quinazolinone skeleton is a frequently encountered heterocycle in many alkaloids[2] and synthetic structures showing many types of pharmaceutical activities as demonstrated in recent exhaustive reviews.[2,3] Aromatic quinazolines have been shown to possess tyrosine kinase inhibiting effects,[4] are useful to inhibit tumour growth, and exhibit other biological profiles including antiepileptic and anticonvulsant activity.[5] Others have also been used, for example, in the treatment of tuberculosis[6] as well as benign prostatic hyperplasia.[7] More importantly, substituted 3,4-dihydro-2(1*H*)-quinolinones have induced direct inhibition of the Na^+-dependant Ca^{2+} influx via the Na^+/Ca^{2+} exchanger in cardiomyocytes with high potency and exerted a protective effect against myocardial ischemic reperfusion injury.[8] As a consequence, these scaffolds are considered to be privileged structures for drug development, and have accelerated the quest for new ring synthesis methods.

In a recent contribution,[9] we have reported a novel approach to the synthesis of 4,5-fused imidazolidin-2-ones **III** and **IV** (Scheme 1) based on the action of TFAA–TFA combination on properly substituted α-hydroxylactams **I** and **II** derived from spirohydantoins. The key step of this sequential reaction is based on the formation of the cyclic *N*-acyliminium intermediate **A**, from which a transposition of the electronically rich group resulted in ring expansion leading to a stable cyclic cation. The latter ultimately loses one proton spontaneously to give the expected 4,5-fused tricyclic and tetracyclic imidazolidin-2-ones. During these investigations, we have demonstrated also that the tandem process seems to be easy, general, regiospecific and resulted in the formation of polyheterocyclic systems containing an imidazolidin-2-one nucleus in good to excellent yields (67–99%).



Scheme 1 Retrosynthetic scheme leading to 4,5-fused imidazolidin-2-ones **III** and **IV** via *N*-acyliminium chemistry

While spirohydroxylactams of types **I** and **II** substituted at the angular carbon C(5) with alkyl, arylalkyl, and aryl, derived from spirohydantoin systems have been widely synthesised and their behaviour in acid medium towards intermolecular and intramolecular α-amidoalkylation studied,[9,10] heteroaryl spirohydroxylactams have not so far been explored.

In this context and with our interest in the development of synthetic methodologies toward original aza-heterocyclic systems containing a quinazolinone ring fused to polycyclic skeletons with promising pharmaceutical properties, we have chosen to explore hydroxylactams of type **1**, derived from spiro(imidazoloquinazolinones) (Scheme 2). In particular, certain spiro(imidazoloquinazolinones) belonging to the quinazolinone family have been found to be highly potent as aldose reductase inhibitors,[11] but for obscure reasons no additional intensive work has been done on these spiro-systems since their discovery.

These substrates were chosen for the following reasons: 1) no investigations using *N*-acyliminium ion chemistry have been performed on this class of compounds; 2) the results obtained in this study, could answer questions

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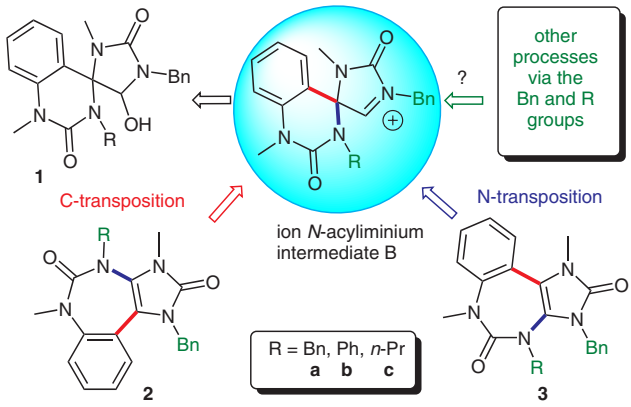


Scheme 2 *N*-Acyliminium intermediate **B** used as a novel platform from which to access new and original scaffolds

raised during the synthesis of 4,5-fused imidazolidin-2-ones reported earlier by us;[9] and 3) as highlighted in Scheme 2, the selection of different substituents (R = Bn, Ph and *n*-Pr) at one nitrogen atom of the quinazoline ring allows consideration of the stable *N*-acyliminium species **B**. This would act as an aryl group or nitrogen atom scavenger after their transposition to provide interestingly substituted imidazobenzo[1,3]diazepines **2** or **3**. In addition, if the R group or the benzyl (Bn) acts as an internal nucleophile, the process would produce original polyheterocyclic systems such as fused quinazolinones that are difficult to obtain through traditional approaches.

This study also constitutes a continuation of our efforts towards the exploration of the synthetic opportunities arrising from our previous studies on *N*-acyliminium cyclisation in tandem with Grignard reaction,[12] Pummerer cyclisation,[13] *N*-acyliminium ion isomerisation,[14] and *N*-acyliminium ion isomerisation/double alkyl transposition.[15]

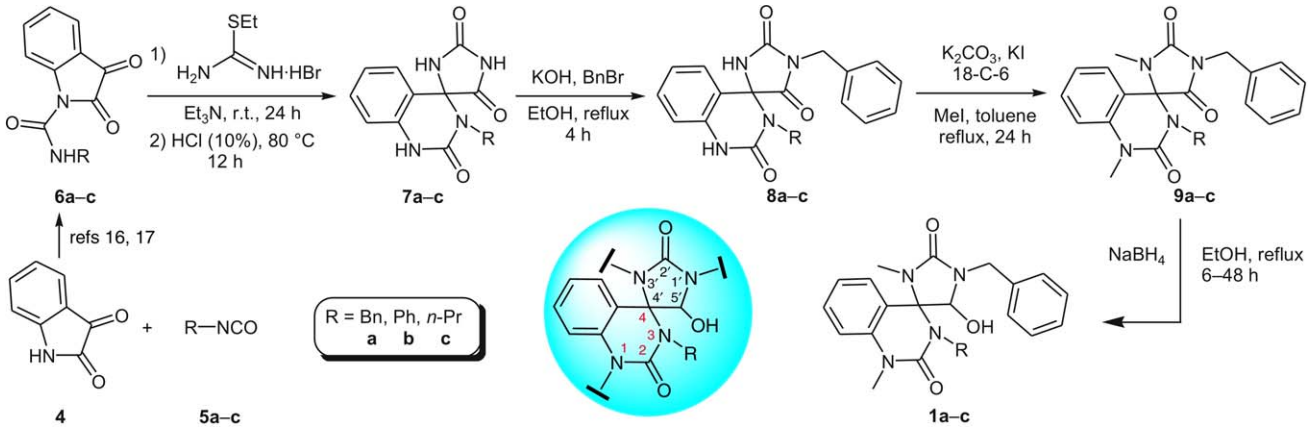
Our study started with the synthesis of hydroxyspirolactams **1a–c** substituted at the N(3)-position of the quinazoline skeleton (Table 1). These substrates were prepared in order to measure the impact of the substituent group on both the reduction reaction as well as the cyclisation step of these *N*-acyliminium precursors. The synthesis was easily accomplished in five steps from the commercially available isatin (**4**) and isocyanate derivatives **5a–c** using standard procedures.

Thus, the treatment of isatin (**4**) with isocyanates **5a–c** according to the protocol reported by Yamagishi et al.,[16] resulted in the installation of different substituents at the N(3)-position. Products **6a** (R = Bn) and **6b** (R = Ph) were described earlier,[16,17] **6c** (R = *n*-Pr), as a new compound, was isolated in 68% yield after purification by recrystallisation from ethanol. The 3-alkylated spiro[imidazolidine-4′,4(1*H*)-quinazoline]-2′,2,5′-triones **7a–c** were then obtained by reaction of **6a–c** with 2-ethyl-2-isothiourea hydrobromide and triethylamine followed by heating at 80 °C with 10% hydrochloric acid. The products **7a** and **7b** were identical to those reported in the literature[16,17] (Table 1), and were isolated in moderate yields of 49% and 47%, respectively, while **7c** was isolated in acceptable yield (66%). Using the published conditions, we never isolated either **7a** or **7b** in yields indicated by the authors or the relevant papers, which were of 69% and 72%, respectively. The installation of the benzyl group at the hydantoin N(1′)-position of **7a–c** was accomplished regiospecifically. Interestingly, since these kind of substrates have three possible points of diversity, a thorough study of the effects of solvent and base on regioselective N-alkylation of spiro(imidazoloquinazolinones) has been discussed in different papers.[15,17,18] After certain optimisation work taking into account these considerations, we have found that the best combination with which to accomplish this reaction seems to be the use of ethanolic potassium hydroxide at reflux for four hours. Under these conditions, the N(1′)-benzyl spirohydantoins **8a** and **8c**, being poorly soluble, crystallised out from the solution while **8b**, as an oily material, could not be isolated in pure form and decomposed slowly after a few days. The pure crystalline products **8a** and **8c** were isolated with moderate yields of 46% and 47%, however, the yield could be increased to 87% and 91%, respectively, by adding the solids obtained from the precipitation observed during the process as well as those obtained after the usual work-up of the filtrate liquor containing also these products. Next, methylation at both the N(1)- and N(3′)-positions of *N*-benzyl spirohydantoins **8a–c** was achieved successfully in moderate to excellent yields under PTC conditions (anhydrous K_2CO_3 as a base and a mixture of KI and 18-crown-6 as catalysts in anhydrous toluene at reflux for 24 h). Because of the difficulty encountered during the isolation of the starting *N*-benzyl derivative **8b**, the alkylated product **9b** was isolated as a crystalline solid after chromatographic separation in 51% yield calculated in two steps from spirohydantoin **7b**.

The polyalkylated spirohydantoins **9a–c** were then submitted to the reduction reaction to obtain the corresponding 5′-hydroxylactams **1a–c** as the *N*-acyliminium cation precursors (Scheme in Table 1). According to our reports in this field,[9,15] the reduction of spirohydantoins **9a–c** was carried out with a large excess of sodium borohydride (6 equiv) in anhydrous ethanol at reflux for 6–48 hours (the reaction was monitored by TLC) to easily provide the expected hydroxyspirolactams **1a–c** in 82–98% yields after recrystallisation from ethanol.

All hydroxyspirolactams **1a–c** were obtained as solids and their structure assignments were made on the basis on their IR, NMR (^{1}H and ^{13}C experiments including NOE difference and DEPT Programs, respectively) as well as elemental analysis. For instance, in the ^{1}H NMR spectra of hydroxyspirolactams **1a–c**, the methylene protons of the lateral functionality [N(1′)CH_2Ph; see Table 1 for the structure numbering] appeared as an AB system with chemical shifts at δ = 4.02, 4.25, 4.13 ppm for pseudo equatorial and δ = 4.82, 4.62, 4.79 ppm for pseudo axial protons, respectively. They also appeared as an AB system in spirohydantoin **9a** at δ = 4.58 and 4.70 ppm (*J* = 14 Hz) but appeared as singlets in N(1′)-benzyl spirohydan-

Table 1 Five-Step Sequence Leading to Spirohydroxylactam Precursors of *N*-Acyliminium Species **1a–c**



Product index	R	**7**, Yield (%)	**8**, Yield (%)	**9**, Yield (%)	Hydroxylactams **1**	
					Time (h)	Yield (%)
a	Bn	49[a]	46 (up to 87%)[b]	61	7	82
b	Ph	47[a]	–[a,c]	51[d]	48	98
c	*n*-Pr	66	47 (up to 91%)[b]	>99	6	82

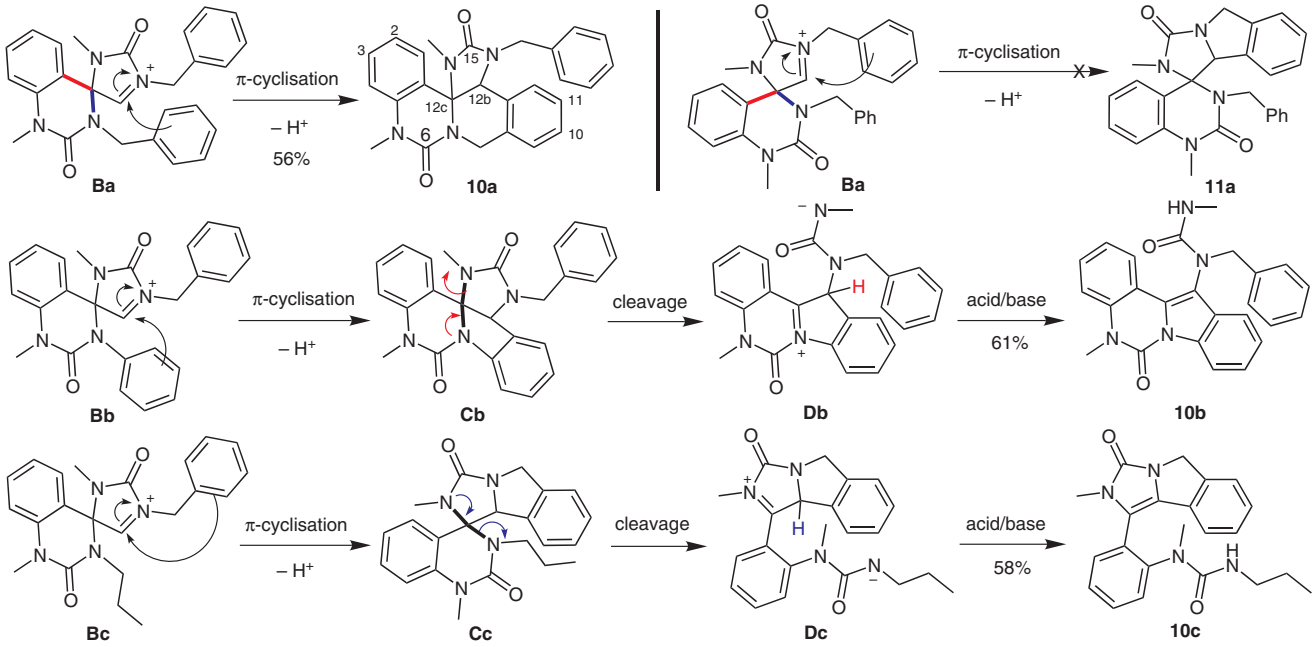
[a] These products are reported in the literature.[16,17]
[b] Yields of products formed by precipitation. Yields in brackets correspond to products obtained after complete isolation.
[c] Spirohydantoin **8b**, as an oily material, was not isolated in pure form.
[d] The yield over two steps starting from spirohydantoin **7b**.

toin derivatives **9b** and **9c** (δ = 4.49 and 4.76 ppm) used as starting materials. This is due to the presence of a diastereotopic effect with a coupling constant of about J = 15 Hz in all cases. The spectra also showed two doublets corresponding to the coupling of the angular proton at C(5′) (δ = 4.61, 4.75 and 4.49 ppm) and OH [CH(OH) geminal coupling] with classical constants ranging from J = 6 to 7.8 Hz, which disappeared after D_2O exchange. This phenomenon was absent in the spectra of their congener spirohydantoins **9a–c**. A confirmation of these structures also came with their ^{13}C NMR. In the latter, one additional ternary carbon C(5′) appeared to the detriment of a quaternary carbon in the aromatic region corresponding to the carbonyl function in the starting hydantoins **9a–c**. From these results, it is clear that the reduction reaction occurred regioselectively and cleanly without any traces of by-products in very good yields.

Because no body of literature on hydroxy quinazoline-spiroimidazolidines regarding the reactivity of these functionalities in acidic medium exists, the behaviour of α-hydroxyspirolactams of types **1a**, **1b** and **1c** bearing one (**1c**) or two (**1a** and **1b**) nucleophiles was examined under the influence of acid. For a better comparison of the results, only the nature of the R group on the N(5)-position of the quinazoline nuclei in hydoxyspirohydantoin substrates **1a–c** was changed.

At the outset of our investigations, the hydroxyspirolactam **1a** (R = Bn) was chosen as a test compound for the amidoalkylation transformation (Scheme 3). Thus, treatment of this *N*-acyliminium precursor **1a** with a mixture of TFAA–TFA in precise equimolar amounts as mentioned by us[9] and in a few cases by others[18a,b] [i.e., TFAA–TFA (1:1) with a slight excess (1.3 equiv) of each reactant relative to substrate, CH_2Cl_2, reflux, 24 h], gave the cyclised product **10a**, identified as 13(8*H*)-benzyl-5,15-dimethylimidazo[4′,5′:3,4]isoquinolo[3,4-*c*]quinazoline-6,14-dione, as a crystalline material in 56% yield after chromatographic purification. From this result, its seems that the reaction occurred by direct attack on the *N*-acyliminium intermediate **Ba** (Scheme 3) by the π-aromatic system linked to the N(3) of the quinazolinone system, to provide the imidazole-fused isoquinoloquinazoline product **10a**. This product formed via a 6-*endo-trig* process, which was favored over the 5-*endo-trig*, which could led to the spiropentacyclic product **11a**. Also, in contrast to our first hypothesis highlighted in Scheme 2, neither C- nor N-transposition, providing imidazobenzo[1,3]diazepine **2a** or **3a**, respectively, occurred. Ultimately, confirmation of the structure of the product **10a** was made by an array of mono- and bidimensional NMR studies. The ^1H NMR spectra showed two AB systems characteristic of the methylene groups with usual coupling constants of J = 15 and J = 16 Hz and one singlet at δ = 4.69 ppm attributed to the angular proton H(12b). Furthermore, the ^{13}C NMR and DEPT spectra of **10a** were in accordance with the above considerations since one additional quaternary carbon appeared as a consequence of the π-cyclisation process.

Using the cyclisation protocol delineated in Scheme 3 on hydroxyspirolactams **1b** and **1c** proved successful in both



Scheme 3 Mechanistic considerations of hydroxyspirolactams **1a–c** conversion to isoquinoloquinazoline, indoloquinazoline and imidazoindole derivatives **10a–c**

cases; in each case only one product was obtained with yields of 61% and 58%, respectively. The products were identified as *N*-(*N*′-methylcarboxamido)benzylamino-5-methylindolo[1,2-*c*]quinazolin-6-one (**10b**) and 8-methyl-9-*o*-[*N*-methyl-*N*-(*N*′-propylcarboxamido)amino]phenylimidazo[4,3-*a*]isoindol-7-one (**10c**). Because neither spectroscopic analyses (^{1}H and ^{13}C NMR and DEPT programs), nor other analytical approaches, proved to be sufficient to determine the structure of the formed polyheterocyclic system exactly, a complementary single-crystal X-ray crystallographic analysis was carried out (Figure 1). This unambiguously secured the identity of the product **10b**.[19]

Because no traces of products **2** or **3** were found in the reaction mixture (examined by TLC at the end of the reaction process before any purification), the suggested reaction mechanism illustrates two pathways that appear possible, depending on the substituent R group (Scheme 3). The initially formed *N*-acyliminium cation **Ba** led to the π-cyclisation product **10a**, the cationic species **Bb** and **Bc** generated in acidic medium afforded the indoloquinazoline and imidazoindole derivatives **10b** and **10c** as the sole reaction products. In both cases, the *N*-acyliminium ions **Bb** and **Bc** undergo π-cationic cyclisation via the 5-*endo-trig* process into the intermediates **Cb** and **Cc** followed by cleavage of the polycyclic *N*,*N*-acetal function into the mesoionic tertiary *N*-acyliminium species **Db** and **Dc**. The observed products **10b** and **10c** are finally formed by tandem acid–base/elimination. During these transformations, the different ways taken upon *N*,*N*-aminal cleavage to form **10b** and **10c** could be due to the constraint of the five-membered ring system being formed. This result unambiguously confirms the important role exerted by the neighbouring R group during the cyclisation step.

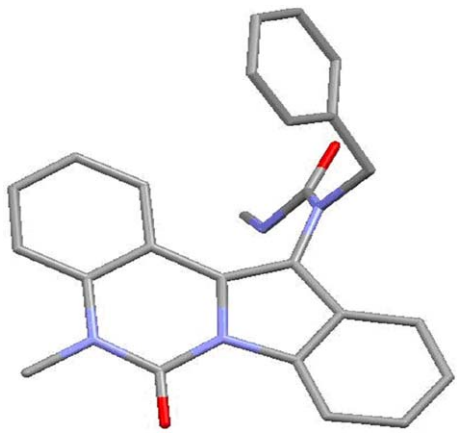


Figure 1 ORTEP view of the molecular structure of **10b** resulting from the cyclisation of hydroxy lactam **1b**

In summary, spirohydantoins **9a–c**, obtained through a three-step sequence by reaction of *N*-carbamoylisatins **6a–c** with 2-ethyl-2-isothiourea, followed by three N-alkylation processes including, at the outset, one regiospecific benzylation, have been shown to undergo sodium borohydride reduction to give hydroxyspirolactams **1a–c** in good to excellent yields. The cyclisation of the latter cyclic *N*-acyliminium precursors with a TFAA–TFA combination in precise equimolar proportions, provides a versatile, short synthesis of two categories of products **10a** and **10b**,**c**. The latter were obtained under mild conditions and via an interesting π-cationic cyclisation either with or without an associated cyclic transposition. The key step of this transformation is based on the formation of the cyclic *N*-acyliminium intermediates **B**, from which,

in the case of **Ba**, the π-attack of the benzyl group led to the imidazole-fused tetracyclic product **10a**. Importantly, the intermediates **Cb** and **Cc** obtained via the classical π-cyclisation reaction of the phenyl and benzyl groups attached to N(3) and N(1′), respectively, provides a new generation of *N*-amidoyliminium species **Db** and **Dc**, which undergo an acid/base exchange leading to new classes of products **10b** and **10c**.

Finally, we have developed a new approach and documented the effectiveness of the readily available spiro(imidazoloquinazolinones) to provide useful heterocycles. This approach capitalises on complementary regioselective transformations based on the *N*-acyliminium arylation allied (or not) with imidazolone or quinazolinone opening via an interesting and original *N*,*N*-aminal function. The syntheses of more complex polyhydroxylated targets using these methodologies are under investigation in our laboratory and the results will be reported soon.

Melting points were taken with a capillary melting point apparatus and are uncorrected. The infrared (IR) absorption spectra were determined as dispersions in KBr discs and are indicated in cm^{-1}. The ^1H and ^{13}C NMR spectra were recorded as solutions in $CDCl_3$ or DMSO-d_6 at 200 or 300 MHz (^1H) and 50.3 or 75 MHz (^{13}C), respectively, and chemical shifts (δ) are expressed in ppm relative to TMS as internal standard. Thin layer chromatography (TLC) was performed using silica gel analytical plates (F_{254}) of 0.25 mm thickness; detection was facilitated by UV light at 254 or 365 nm or using *p*-anisaldehyde. The analytical results of elemental analysis are within 0.4% of theoretical values and were obtained from INSA institution at Rouen, 76130 Mt-St-Aignan, France.

Synthesis of Spirohydantoins 7a–c; General Procedure

To a stirred solution of isatin (**4**; 10.3 g, 70 mmol) in anhydrous DMF (70 mL) was added Et_3N (9.8 mL, 70 mmol). After stirring for 15 min, the appropriate isocyanate **5** (70 mmol) was added dropwise at 0 °C and the reaction was stirred for an additional 1 h. The yellow solid formed (**6**) was collected by filtration and washed successively with H_2O and Et_2O. To a crude mixture of carbamoylisatin **6** (20 mmol) and Et_3N (3.1 mL, 22 mmol) in anhydrous THF (100 mL) was added in one portion *S*-ethylisothiouronium bromide (3.7 g, 20 mmol). After stirring at r.t. for 24 h, the solution was concentrated under reduced pressure. The crude solid was then diluted with HCl (10%, 50 mL) and heated at 80 °C for 24 h then cooled to r.t. The resulting solid **7** was filtered, triturated with Et_2O and recrystallised from EtOH.

3′-Benzylspiro(imidazolidine-4,4′-quinazoline)-2,2′(1′*H*),5-trione (7a)

Obtained from the benzyl isocyanate (**5a**).

Yield: 49% (Lit.[16,17] 69%); yellow solid; R_f = 0.28 (EtOAc); mp >300 °C (Lit.[16,17] >280 °C).

IR (KBr): 3242 (3 × NH), 1787 (C=O), 1723 (C=O), 1660 (C=O) cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 4.25 (d, J = 16 Hz, 1 H, CH_2), 4.60 (d, J = 16 Hz, 1 H, CH_2), 6.89–7.01 (m, 2 H, H_{Ar}), 7.26 (m, 7 H, H_{Ar}), 9.14 (br s, 1 H, NH), 10.02 (br s, 1 H, NH), 11.22 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 40.8 (CH_2), 78.2 (C_q), 114.2 (CH_{Ar}), 116.3 [$C_{q(Ar)}$], 121.9 (CH_{Ar}), 125.0 (CH_{Ar}), 126.7 (CH_{Ar}), 127.2 (2 × CH_{Ar}), 128.0 (2 × CH_{Ar}), 130.5 (CH_{Ar}), 136.5 [$C_{q(Ar)}$], 138.4 [$C_{q(Ar)}$], 151.5 (C=O), 155.5 [C(2)=O], 173.2 [C(4)=O].

Anal. Calcd for $C_{17}H_{14}N_4O_3$: C, 63.35; H, 4.38; N, 17.38. Found: C, 63.17; H, 4.22; N, 17.17.

3′-Phenylspiro(imidazolidine-4,4′-quinazoline)-2,2′(1′*H*),5-trione (7b)

Obtained from the phenyl isocyanate (**5b**).

Yield: 47% (Lit.[16,17] 72%); brown solid; R_f = 0.12 (EtOAc); mp >300 °C (Lit.[16,17] >280 °C).

IR (KBr): 3345 (3 × NH), 1749 (C=O), 1722 (C=O), 1647 (C=O) cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 6.88–7.07 (m, 2 H, H_{Ar} and NH), 7.20–7.41 (m, 9 H, H_{Ar} and NH), 9.98 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 87.0 (C_q), 113.9 (CH_{Ar}), 121.4 (CH_{Ar}), 126.2 (CH_{Ar}), 127.1 (CH_{Ar}), 127.3 (2 × CH_{Ar}), 128.6 (2 × CH_{Ar}), 130.7 (CH_{Ar}), 136.2 [$C_{q(Ar)}$], 138.6 [$C_{q(Ar)}$], 141.8 [$C_{q(Ar)}$], 151.2 (C=O), 151.7 [C(2)=O], 170.9 [C(4)=O].

Anal. Calcd for $C_{16}H_{12}N_4O_3$: C, 62.33; H, 3.92; N, 18.17. Found: C, 62.12; H, 3.78; N, 18.02.

3′-Propylspiro(imidazoline-4,4′-quinazoline)-2,2′(1′*H*),5-trione (7c)

Obtained from the *n*-propyl isocyanate (**5c**), recrystallised from EtOH.

Yield: 66%; brown solid; R_f = 0.32 (cyclohexane–EtOAc, 1:1); mp 279 °C.

IR (KBr): 3232 (3 × NH), 1769 (C=O), 1722 (C=O), 1666 (C=O) cm^{-1}.

^1H NMR (300 MHz, DMSO-d_6): δ = 0.81 (t, J = 7 Hz, 3 H, CH_3), 1.50–1.61 (m, 2 H, CH_2), 2.76–2.90 (m, 1 H, CH_2), 3.23–3.38 (m, 1 H, CH_2), 6.86 (dd, J = 1.6, 8.6 Hz, 1 H, H_{Ar}), 6.94–7.04 (m, 2 H, H_{Ar}), 7.25–7.33 (m, 1 H, H_{Ar}), 9.19 (br s, 1 H, NH), 9.89 (br s, 1 H, NH), 11.3 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.5 (CH_3), 22.4 (CH_2), 44.8 (CH_2), 78.2 (C_q), 114.2 [$C_{q(Ar)}$], 116.2 (CH_{Ar}), 122.0 (CH_{Ar}), 125.1 (CH_{Ar}), 130.6 (CH_{Ar}), 136.6 [$C_{q(Ar)}$], 151.2 (C=O), 155.5 [C(2)=O], 173.7 [C(4)=O].

Anal. Calcd for $C_{13}H_{14}N_4O_3$: C, 56.93; H, 5.14; N, 20.43. Found: C, 56.80; H, 5.00; N, 20.29.

Synthesis of Benzylspirohydantoins 8a–c; General Procedure

To a stirred mixture of spirohydantoins (**7a–c**; 10 mmol) and KOH (0.56 g, 10 mmol) in anhydrous EtOH (70 mL) was added, dropwise, benzyl bromide (1.2 mL, 10 mmol) in anhydrous EtOH (30 mL). The mixture was then refluxed for 4 h under stirring then cooled to r.t. The solution was concentrated under reduced pressure to provide a residue which was purified by flash chromatography on silica gel (cyclohexane–EtOAc, 4:1).

1,3′-Dibenzylspiro(imidazolidine-4,4′-quinazoline)-2,2′(1′*H*),5-trione (8a)

Yield: 46%; pale-yellow solid; R_f = 0.66 (cyclohexane–EtOAc, 2:3); mp 203 °C.

IR (KBr): 3248 (2 × NH), 1793 (C=O), 1721 (C=O), 1664 (C=O) cm^{-1}.

^1H NMR (200 MHz, DMSO-d_6): δ = 4.26 (d, J = 16 Hz, 1 H, CH_2), 4.37 (d, J = 15 Hz, 1 H, CH_2), 4.52 (d, J = 16 Hz, 1 H, CH_2), 4.54 (d, J = 16 Hz, 1 H, CH_2), 6.87–6.99 (m, 3 H, H_{Ar}), 7.15–7.30 (m, 11 H, H_{Ar}), 9.56 (br s, 1 H, NH), 10.12 (br s, 1 H, NH).

^{13}C NMR (50.3 MHz, DMSO-d_6): δ = 40.8 (CH_2), 41.6 (CH_2), 77.0 (C_q), 114.4 (CH_{Ar}), 116.0 [$C_{q(Ar)}$], 122.0 (CH_{Ar}), 124.8 (CH_{Ar}), 126.9 (CH_{Ar}), 127.2 (2 × CH_{Ar}), 127.7 (2 × CH_{Ar}), 127.8 (CH_{Ar}), 128.1 (2 × CH_{Ar}), 128.7 (2 × CH_{Ar}), 130.7 (CH_{Ar}), 136.2 [$C_{q(Ar)}$],

136.6 [$C_{q(Ar)}$], 138.0 [$C_{q(Ar)}$], 151.6 (C=O), 154.7 [C(2)=O], 171.4 [C(4)=O].

Anal. Calcd for $C_{24}H_{20}N_4O_3$: C, 69.89; H, 4.89; N, 13.58. Found: C, 69.76; H, 4.69; N, 13.33.

1-Benzyl-3′-phenylspiro(imidazolidine-4,4′-quinazoline)-2,2′(1′*H*),5-trione (8b)
Because this product was not isolated in pure form, the crude oily mixture obtained at the end of the reaction was used in the next step.

1-Benzyl-3′-propylspiro(imidazolidine-4,4′-quinazoline)-2,2′(1′*H*),5-trione (8c)
Yield: 47%; colourless solid; R_f = 0.64 (cyclohexane–EtOAc, 1:1); mp 192 °C.

IR (KBr): 3228 (2 × NH), 1788 (C=O), 1722 (C=O), 1664 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, DMSO-d_6): δ = 0.61 (t, J = 7 Hz, 3 H, CH_3), 1.40–1.53 (m, 2 H, CH_2), 2.69–2.83 (m, 1 H, CH_2), 2.94–3.09 (m, 1 H, CH_2), 4.66 (s, 2 H, CH_2), 6.84–7.00 (m, 3 H, H_{Ar}), 7.25–7.37 (m, 6 H, H_{Ar}), 9.56 (br s, 1 H, NH), 9.97 (br s, 1 H, NH).

^{13}C NMR (75 MHz, DMSO-d_6): δ = 11.1 (CH_3), 22.0 (CH_2), 41.8 (CH_2), 44.6 (CH_2), 77.0 (C_q), 114.2 (CH_{Ar}), 115.8 [$C_{q(Ar)}$], 121.8 (CH_{Ar}), 125.1 (CH_{Ar}), 127.9 (CH_{Ar}), 128.0 (2 × CH_{Ar}), 128.7 (2 × CH_{Ar}), 130.6 (CH_{Ar}), 136.3 [$C_{q(Ar)}$], 136.6 [$C_{q(Ar)}$], 150.9 (C=O), 154.6 [C(2)=O], 171.7 [C(4)=O].

Anal. Calcd for $C_{20}H_{20}N_4O_3$: C, 65.92; H, 5.53; N, 15.38. Found: C, 65.81; H, 5.42; N, 15.41.

Synthesis of Polysubstituted Spirohydantoins 9a–c; General Procedure
To a stirred mixture of benzylspirohydantoins (**8a–c**; 50 mmol) and 18-crown-6 ether (1% w/w) in anhydrous toluene (50 mL) were added solid K_2CO_3 (1.72 g, 125 mmol) and anhydrous KI (0.1 equiv). After stirring for 15 min, MeI (150 mmol, 0.93 mL) in anhydrous toluene (15 mL) was added dropwise over a period of 30 min. The mixture was refluxed for 24 h under stirring and then cooled to r.t. After filtration over a short column of Celite, the organic layer was concentrated under reduced pressure to provide a colourless oil which was purified by flash column chromatography on silica gel (cyclohexane–EtOAc, 1:4).

1,3′-Dibenzyl-1′,3-dimethylspiro(imidazolidine-4,4′-quinazoline)-2,2′,5-trione (9a)
Obtained from benzylspirohydantoin **8a**.

Yield: 60%; pale-yellow solid; R_f = 0.89 (cyclohexane–EtOAc, 2:3); mp 92 °C.

IR (KBr): 1781 (C=O), 1725 (C=O), 1662 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.20 (s, 3 H, CH_3), 3.45 (s, 3 H, CH_3), 3.92 (d, J = 16 Hz, 1 H, CH_2), 4.58 (d, J = 14 Hz, 1 H, CH_2), 4.70 (d, J = 14 Hz, 1 H, CH_2), 4.91 (d, J = 16 Hz, 1 H, CH_2), 6.63 (d, J = 7.8 Hz, 1 H, H_{Ar}), 6.89–7.07 (m, 4 H, H_{Ar}), 7.18–7.22 (m, 3 H, H_{Ar}), 7.30–7.42 (m, 6 H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.9 (CH_3), 30.7 (CH_3), 42.9 (CH_2), 48.3 (CH_2), 80.2 (C_q), 114.0 (CH_{Ar}), 122.8 (CH_{Ar}), 124.8 (CH_{Ar}), 127.6 (CH_{Ar}), 128.1 (2 × CH_{Ar}), 128.4 (2 × CH_{Ar}), 128.5 (CH_{Ar}), 128.9 (2 × CH_{Ar}), 129.2 (2 × CH_{Ar}), 131.3 (CH_{Ar}), 135.8 [2 × $C_{q(Ar)}$], 137.4 [2 × $C_{q(Ar)}$], 152.8 (C=O), 154.2 [C(2)=O], 170.5 [C(4)=O].

Anal. Calcd for $C_{26}H_{24}N_4O_3$: C, 70.89; H, 5.49; N, 12.72. Found: C, 70.73; H, 5.28; N, 12.66.

1-Benzyl-1′,3-dimethyl-3′-phenylspiro(imidazolidine-4,4′-quinazoline)-2,2′,5-trione (9b)
Obtained from spirohydantoin **8b**.

Yield: 51% (2 steps from **7b**); colourless solid; R_f = 0.67 (cyclohexane–EtOAc, 2:3); mp 187 °C.

IR (KBr): 1783 (C=O), 1725 (C=O), 1664 (C=O) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.80 (s, 3 H, CH_3), 3.43 (s, 3 H, CH_3), 4.49 (s, 2 H, CH_2), 6.78 (dd, J = 1.6, 8.6 Hz, 1 H, H_{Ar}), 6.96–7.22 (m, 11 H, H_{Ar}), 7.35–7.40 (m, 2 H, H_{Ar}).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 25.4 (CH_3), 30.4 (CH_3), 42.6 (CH_2), 80.8 (C_q), 114.1 (CH_{Ar}), 114.2 (CH_{Ar}), 123.0 (CH_{Ar}), 125.4 (CH_{Ar}), 125.7 (CH_{Ar}), 127.9 (CH_{Ar}), 128.3 (2 × CH_{Ar}), 128.7 (2 × CH_{Ar}), 128.9 (CH_{Ar}), 129.1 (CH_{Ar}), 131.4 (CH_{Ar}), 131.5 (CH_{Ar}), 135.1 [2 × $C_{q(Ar)}$], 136.7 [$C_{q(Ar)}$], 139.2 [$C_{q(Ar)}$], 152.3 (C=O), 154.2 [C(2)=O], 170.1 [C(4)=O].

Anal. Calcd for $C_{25}H_{22}N_4O_3$: C, 70.41; H, 5.20; N, 13.14. Found: C, 70.29; H, 5.05; N, 13.02.

1-Benzyl-1′,3-dimethyl-3′-propylspiro(imidazolidine-4,4′-quinazoline)-2,2′,5-trione (9c)
Obtained from N_3-benzylspirohydantoin **8c**.

Yield: 100%; colourless solid; R_f = 0.56 (cyclohexane–EtOAc, 1:1); mp 163 °C.

IR (KBr): 1781 (C=O), 1724 (C=O), 1666 (C=O) cm^{-1}.

^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.58 (t, J = 7 Hz, 3 H, CH_3), 1.18–1.59 (m, 2 H, CH_2), 2.60 (s, 3 H, CH_3), 2.70–2.85 (m, 1 H, CH_2), 2.96–3.09 (m, 1 H, CH_2), 3.36 (s, 3 H, CH_3), 4.76 (s, 2 H, CH_2), 6.70 (dd, J = 1.6, 8.6 Hz, 1 H, H_{Ar}), 6.92 (dd, J = 1.6, 8.6 Hz, 2 H, H_{Ar}), 7.29–7.44 (m, 6 H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.2 (CH_3), 21.5 (CH_2), 24.8 (CH_3), 30.1 (CH_3), 42.9 (CH_2), 46.6 (CH_2), 79.8 (C_q), 113.7 (CH_{Ar}), 114.3 [$C_{q(Ar)}$], 122.6 (CH_{Ar}), 125.0 (CH_{Ar}), 128.3 (CH_{Ar}), 128.8 (2 × CH_{Ar}), 128.9 (2 × CH_{Ar}), 131.2 (CH_{Ar}), 135.5 [$C_{q(Ar)}$], 138.9 [$C_{q(Ar)}$], 151.9 (C=O), 154.2 [C(2)=O], 170.6 [C(4)=O].

Anal. Calcd for $C_{22}H_{24}N_4O_3$: C, 67.33; H, 6.16; N, 14.28. Found: C, 67.20; H, 6.04; N, 14.15.

Synthesis of Spirohydroxylactams 1a–c; General Procedure
To a well-stirred solution of spirohydantoins (**9a–c**; 4 mmol) in anhydrous EtOH (40 mL) was added, in portions at r.t., $NaBH_4$ (0.91 g, 24 mmol) over a period of 10 min. The mixture was stirred under reflux for 6–48 h (the reaction was monitored by TLC using CH_2Cl_2 as eluent), cooled to r.t. and concentrated under reduced pressure. H_2O (40 mL) was added and the mixture was extracted into CH_2Cl_2 (2 × 30 mL). The organic layers were combined, dried over $MgSO_4$ and concentrated under reduced pressure to provide a colourless solid which was recrystallised from a suitable solvent to give 5-hydroxyspiroimidazolidin-2-ones **1a–c** in good to excellent yields.

1,3′-Dibenzyl-1′,5-dihydro-5-hydroxy-1′,3-dimethylspiro(imidazolidine-4,4′-quinazoline)-2,2′-dione (1a)
Obtained from spirohydantoin **9a**.

Yield: 82%; colourless crystals; R_f = 0.78 (cyclohexane–EtOAc, 2:3); mp 114 °C.

IR (KBr): 3343 (OH), 1704 (C=O), 1656 (C=O) cm^{-1}.

^{1}H NMR (200 MHz, $CDCl_3$): δ = 2.38 (s, 3 H, CH_3), 3.25 (d, J = 7.8 Hz, 1 H, OH), 3.37 (s, 3 H, CH_3), 4.02 (d, J = 15 Hz, 1 H, CH_2), 4.49 (d, J = 16 Hz, 1 H, CH_2), 4.61 (d, J = 7.8 Hz, 1 H, CH), 4.82 (d, J = 15 Hz, 1 H, CH_2), 5.02 (d, J = 16 Hz, 1 H, CH_2), 6.78–7.01 (m, 2 H, H_{Ar}), 7.19–7.30 (m, 12 H, H_{Ar}).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.1 (CH_3), 30.7 (CH_3), 44.3 (CH_2), 48.4 (CH_2), 80.8 (C_q), 87.4 (CH), 121.3 (CH_{Ar}), 122.7

[$C_{q(Ar)}$], 125.0 (CH_{Ar}), 127.1 (CH_{Ar}), 127.5 (2 × CH_{Ar}), 127.6 (CH_{Ar}), 128.4 (2 × CH_{Ar}), 128.5 (2 × CH_{Ar}), 128.7 (2 × CH_{Ar}), 128.9 (CH_{Ar}), 130.2 (CH_{Ar}), 136.6 [$C_{q(Ar)}$], 137.8 [$C_{q(Ar)}$], 138.9 [$C_{q(Ar)}$], 154.8 (C=O), 157.9 (C=O).

Anal. Calcd for $C_{26}H_{26}N_4O_3$: C, 70.57; H, 5.92; N, 12.66. Found: C, 70.41; H, 5.78; N, 12.57.

1-Benzyl-1′,5-dihydro-5-hydroxy-1′,3-dimethyl-3′-phenylspiro(imidazolidine-4,4′-quinazoline)-2,2′-dione (1b)
Obtained from spirohydantoin **9b**.

Yield: 98%; colourless crystals; R_f = 0.62 (cyclohexane–EtOAc, 2:3); mp 117 °C.

IR (KBr): 3323 (OH), 1702 (C=O), 1654 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.45 (s, 3 H, CH_3), 3.29 (s, 3 H, CH_3), 4.25 (d, *J* = 15 Hz, 1 H, CH_2), 4.61 (d, *J* = 15 Hz, 1 H, CH_2), 4.75 (s, 1 H, CH), 6.94–7.11 (m, 6 H, H_{Ar}), 7.20–7.45 (m, 8 H, H_{Ar}), 7.61 (br s, 1 H, OH).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.3 (CH_3), 30.7 (CH_3), 44.2 (CH_2), 81.0 (C_q), 87.0 (CH), 113.8 (CH_{Ar}), 122.8 (CH_{Ar}), 123.6 [$C_{q(Ar)}$], 124.2 (CH_{Ar}), 127.4 (CH_{Ar}), 127.6 (CH_{Ar}), 128.2 (CH_{Ar}), 128.4 (2 × CH_{Ar}), 128.5 (2 × CH_{Ar}), 128.7 (CH_{Ar}), 128.8 (CH_{Ar}), 129.9 (CH_{Ar}), 130.1 (CH_{Ar}), 137.12 [$C_{q(Ar)}$], 138.2 [$C_{q(Ar)}$], 138.3 [$C_{q(Ar)}$], 154.9 (C=O), 157.9 (C=O).

Anal. Calcd for $C_{25}H_{24}N_4O_3$: C, 70.08; H, 5.65; N, 13.08. Found: C, 69.85; H, 5.54; N, 13.12.

1-Benzyl-1′,5-dihydro-5-hydroxy-1′,3-dimethyl-3′-propylspiro(imidazolidine-4,4′-quinazoline)-2,2′-dione (1c)
Obtained from spirohydantoin **9c**.

Yield: 82%; colourless crystals; R_f = 0.52 (cyclohexane–EtOAc, 1:1); mp 164 °C.

IR (KBr): 3327 (OH), 1699 (C=O), 1649 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.75 (t, *J* = 7 Hz, 3 H, CH_3), 1.22–1.34 (m, 1 H, CH_2), 1.67–1.77 (m, 1 H, CH_2), 2.71 (s, 3 H, CH_3), 2.85–3.05 (m, 1 H, CH_2), 3.17 (s, 3 H, CH_3), 3.33–3.52 (m, 1 H, CH_2), 4.13 (d, *J* = 15 Hz, 1 H, CH_2), 4.49 (d, *J* = 6 Hz, 1 H, OH), 4.66 (d, *J* = 6 Hz, 1 H, CH), 4.79 (d, *J* = 15 Hz, 1 H, CH_2), 6.74–6.97 (m, 3 H, H_{Ar}), 7.18–7.29 (m, 6 H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 11.7 (CH_3), 22.6 (CH_2), 26.9 (CH_3), 30.2 (CH_3), 44.3 (CH_2), 47.7 (CH_2), 80.7 (C_q), 87.5 (CH), 113.2 (CH_{Ar}), 121.1 [$C_{q(Ar)}$], 122.4 (CH_{Ar}), 124.9 (CH_{Ar}), 127.6 (CH_{Ar}), 128.4 (2 × CH_{Ar}), 128.6 (2 × CH_{Ar}), 130.1 (CH_{Ar}), 136.8 [$C_{q(Ar)}$], 137.9 [$C_{q(Ar)}$], 154.1 (C=O), 158.1 (C=O).

Anal. Calcd for $C_{22}H_{26}N_4O_3$: C, 66.99; H, 6.64; N, 14.20. Found: C, 66.76; H, 6.49; N, 14.05.

Acid-Mediated Cyclisation of Spirohydroxylactams 1a–c; General Procedure
To a well-stirred, cold solution of spirolactams **1a–c** (1 mmol) in anhydrous CH_2Cl_2 (10 mL), was added, dropwise, a solution of TFAA (0.18 mL, 1.3 mmol) and TFA (0.096 mL, 1.3 mmol) in anhydrous CH_2Cl_2 (10 mL). After heating at reflux for 24 h under stirring, the reaction mixture was diluted carefully with H_2O (25 mL) and neutralised with cold 10% $NaHCO_3$. The solution was extracted with CH_2Cl_2 (2 × 10 mL) and the organic layer was washed with H_2O (2 × 10 mL), brine (2 × 10 mL), separated, dried over $MgSO_4$ and evaporated in vacuo. The resulting residue was purified by flash chromatography on silica gel column (cyclohexane–EtOAc, 1:3) to give the cyclic products **10a–c** as crystalline materials.

8*H*-13-Benzyl-5,15-dimethylimidazo[4′,5′:3,4]isoquinolo[3,4-*c*]quinazoline-6,14-dione (10a)
Obtained from spirohydroxylactam **1a**.

Yield: 56%; colourless solid; R_f = 0.61 (cyclohexane–EtOAc, 2:3); mp 215 °C.

IR (KBr): 1688 (C=O), 1655 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.62 (s, 3 H, CH_3), 3.29 (s, 3 H, CH_3), 3.48 (d, *J* = 16 Hz, 1 H, CH_2), 4.05 (d, *J* = 15 Hz, 1 H, CH_2), 4.69 (s, 1 H, CH), 5.03 (d, *J* = 16 Hz, 1 H, CH_2), 5.33 (d, *J* = 15 Hz, 1 H, CH_2), 6.82 (d, *J* = 7.8 Hz, 1 H, H_{Ar}), 6.96–7.11 (m, 4 H, H_{Ar}), 7.20–7.43 (m, 8 H, H_{Ar}).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 25.3 (CH_3), 30.2 (CH_3), 41.3 (CH_2), 44.6 (CH_2), 63.4 (CH), 76.9 (C_q), 112.9 (CH_{Ar}), 120.1 [$C_{q(Ar)}$], 122.7 (CH_{Ar}), 126.4 (CH_{Ar}), 127.2 (CH_{Ar}), 127.3 (CH_{Ar}), 127.8 (CH_{Ar}), 128.3 (2 × CH_{Ar}), 128.7 (CH_{Ar}), 128.9 (2 × CH_{Ar}), 130.1 (CH_{Ar}), 130.3 (CH_{Ar}), 131.0 [$C_{q(Ar)}$], 136.9 [$C_{q(Ar)}$], 137.8 [$C_{q(Ar)}$], 138.0 [$C_{q(Ar)}$], 151.6 (C=O), 157.6 (C=O).

Anal. Calcd for $C_{26}H_{24}N_4O_2$: C, 73.56; H, 5.70; N, 13.20. Found: C, 73.39; H, 5.56; N, 13.05.

***N*-(*N*′-Methylcarboxamido)benzylamino-5-methylindolo[1,2-*c*]quinazolin-6-one (10b)**
Obtained from spirohydroxylactam **1b**.

Yield: 61%; colourless solid; R_f = 0.71 (cyclohexane–EtOAc, 2:3); mp 236 °C.

IR (KBr): 3389 (NH), 1692 (C=O), 1649 (C=O) cm^{-1}.

^1H NMR (200 MHz, $CDCl_3$): δ = 2.73 (d, *J* = 5 Hz, 3 H, CH_3), 3.54 (s, 3 H, CH_3), 4.60 (d, *J* = 13 Hz, 1 H, CH_2), 4.85 (q, *J* = 5 Hz, 1 H, NH), 5.27 (d, *J* = 13 Hz, 1 H, CH_2), 7.02–7.23 (m, 10 H, H_{Ar}), 7.45 (td, *J* = 1.6, 8.6 Hz, 1 H, H_{Ar}), 7.98 (dd, *J* = 1.6, 7.8 Hz, 1 H, H_{Ar}), 8.44–8.52 (m, 1 H, H_{Ar}).

^{13}C NMR (50.3 MHz, $CDCl_3$): δ = 27.7 (CH_3), 30.1 (CH_3), 52.1 (CH_2), 114.2 (CH_{Ar}), 114.6 (C_q=), 115.9 (CH_{Ar}), 117.9 (CH_{Ar}), 123.8 (CH_{Ar}), 123.9 (CH_{Ar}), 124.4 (CH_{Ar}), 124.5 (CH_{Ar}), 127.4 (C_q), 127.5 (CH_{Ar}), 127.8 (C_q), 128.2 (2 × CH_{Ar}), 129.7 (2 × CH_{Ar}), 129.8 (CH_{Ar}), 132.0 (C_q), 135.4 (C_q), 138.3 (2 × C_q), 147.4 (C=O), 158.1 (C=O).

Anal. Calcd for $C_{25}H_{22}N_4O_2$: C, 73.15; H, 5.40; N, 13.65. Found: C, 73.02; H, 5.15; N, 13.49.

8-Methyl-9-*o*-[*N*-methyl-*N*-(*N*′-propylcarboxamido)amino]phenylimidazo[4,3-*a*]isoindol-7-one (10c)
Obtained from spirohydroxylactam **1c**.

Yield: 58%; yellow oil; R_f = 0.50 (cyclohexane–EtOAc, 1:1); mp 87 °C (product **10c** crystallizes in the refrigerator after several days).

IR (KBr): 3054 (NH), 1698 (C=O), 1655 (C=O) cm^{-1}.

^1H NMR (300 MHz, $CDCl_3$): δ = 0.37 (t, *J* = 7 Hz, 3 H, CH_3), 1.04–1.29 (m, 3 H, CH_2 and NH), 2.85–2.99 (m, 1 H, CH_2), 3.09 (s, 3 H, CH_3), 3.40 (s, 3 H, CH_3), 3.72–3.86 (m, 1 H, CH_2), 4.77 (d, *J* = 16 Hz, 1 H, CH_2), 4.97 (d, *J* = 16 Hz, 1 H, CH_2), 7.17–7.33 (m, 8 H, H_{Ar}).

^{13}C NMR (75 MHz, $CDCl_3$): δ = 10.3 (CH_3), 21.0 (CH_2), 28.7 (CH_3), 37.5 (CH_3), 45.5 (CH_2), 49.4 (CH_2), 121.6 (CH_{Ar}), 121.9 (C_q=), 122.3 (C_q=), 124.7 (CH_{Ar}), 125.5 (CH_{Ar}), 126.7 (2 × CH_{Ar}), 127.6 (CH_{Ar}), 128.6 [$C_{q(Ar)}$], 128.7 (2 × CH_{Ar}), 136.4 [2 × $C_{q(Ar)}$], 143.1 [$C_{q(Ar)}$], 153.4 (C=O), 165.5 (C=O).

Anal. Calcd for $C_{22}H_{24}N_4O_2$: C, 70.19; H, 6.43; N, 14.88. Found: C, 70.03; H, 6.23; N, 14.64.

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(19) Full crystallographic data have been deposited at the Cambridge Crystallographic Data Centre; CCDC reference number 637457 for product **10b**. Copies of the data can be obtained free of charge at the following address: http://www.ccdc.cam.ac.uk.