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Reductive-Cyclization-Mediated Synthesis of Fused Polycyclic Quinolines from Baylis–Hillman Adducts of Acrylonitrile: Scope and Limitations[‡]

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Dedicated to Professor Raymond C. F. Jones on his 60th birthday

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The synthesis of a variety of polycyclic quinolines is described. The target molecules were obtained in two steps by an initial reductive cyclization followed by another intramolecular cyclization in the allylamines afforded from either the acetates or allyl bromides of Baylis–Hillman adducts of 2-nitrobenzaldehydes and acrylonitrile. The two steps proceeded in one-pot for those substrates in which a formyl or hydroxy group reacted with the amino group of the 2-aminoquinoline in the second intramolecular cyclization. In contrast, a basic medium was necessary for the second intramolecular cyclization reaction in substrates in which an alkoxycarbonyl group and the amino group participated.

Introduction

Heterocyclic chemistry plays an important rôle in chemical research owing to the importance of a variety of heterocycles in the pharmaceutical, agrochemical and electronic industries. Amongst heterocyclic systems, the synthesis of new polycyclic systems, especially those incorporating privileged scaffolds, is of great interest owing to their resemblance to natural products. In this context, several elegant synthetic protocols involving, for example, multicomponent reactions, transition-metal-catalyzed cyclizations and ring-closing metathesis have been developed. Nevertheless, new alternative strategies to their access through cheap simplified routes are always desired and this has been reaffirmed by Laird recently.[1]

Owing to their great biological properties, compounds containing the quinoline system have been the subject of several synthetic studies.[2] Reductive cyclization is an effective protocol for efficiently producing novel quinoline derivatives.[2d] Recently, the application of this methodology to the substrates afforded by Baylis–Hillman chemistry has resulted in the disclosure of many new quinoline derivatives.[3] Notably, however, the majority of these syntheses take advantage of the participation of the aromatic amino group and the carbonyl group originating from Baylis–Hillman derivatives of 2-nitrobenzaldehyde and acrylates or (cyclo)-alkenones. On the other hand, the participation of the aromatic amino group and the nitrile group in the Baylis–Hillman derivatives of 2-nitrobenzaldehyde and acrylonitrile, respectively, remains unexplored. However, the literature provides a precedence: Wang et al. accomplished the synthesis of 2-aminoquinoline by Fe/AcOH-mediated intramolecular reductive cyclization of a derivative of 2-nitrobenzaldehyde with participation of the nitrile functionality.[4] Owing to our continuing interest in developing general strategies for furnishing aza-heterocycles by Baylis–Hillman chemistry, we considered it worthwhile to investigate the potential of the Baylis–Hillman derivatives of 2-nitrobenzaldehydes and acrylonitrile to afford polycyclic quinoline systems by reductive cyclization as the key step.

A retrosynthetic analysis showed that quinoline-annulated architecture containing at least three different ring systems could easily be constructed from appropriate allylamines afforded from the Baylis–Hillman adduct of 2-nitrobenzaldehyde and acrylonitrile (Figure 1). More importantly the *Z* stereochemistry of the allylamines generated from these reactants would assist the envisaged cyclization reactions. In principle, the S_N2' reaction of a nucleophilic species such as imidazole-2-carbaldehyde with the acetyl derivative **I** or the S_N2 reaction of the nucleophile with the allyl bromide **II** of the aforementioned adduct would lead to substrate **III**, which upon reduction of the aromatic nitro group may trigger a domino process involving two successive intramolecular cyclizations to furnish the polycyclic sys-

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tem **V**. Alternatively, using a proline ester as the nucleophilic partner in place of imidazole-2-carbaldehyde would give **VIII** by a similar series of reactions. Consequently, we have now carried out a detailed study with a view to understanding the scope and limitations of this strategy for the synthesis of diverse polycyclic quinoline systems from differently substituted allylamines. Herein, we report the results of this endeavour, which can now be treated as a general and practical approach to such new polycyclic quinolines.

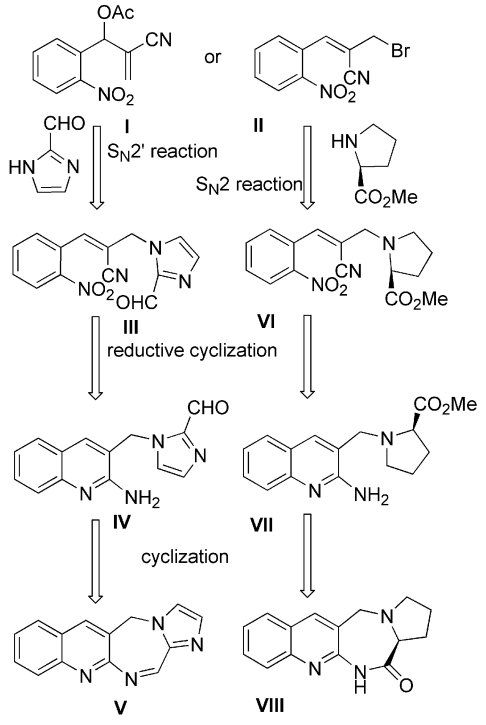
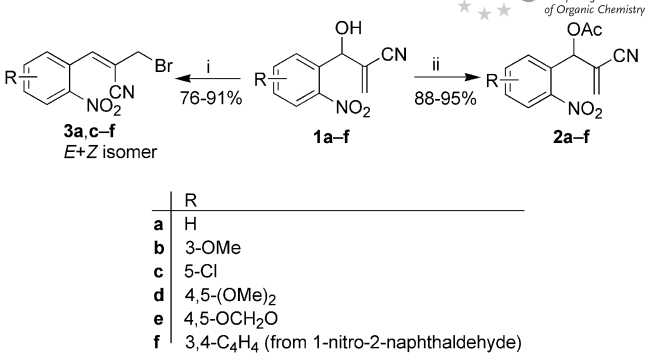


Figure 1. Retrosynthetic strategy for the generation of polycyclic quinolines.

Results and Discussion

In the first instance the Baylis–Hillman reaction between differently substituted 2-nitrobenzaldehydes and acrylonitrile was performed to obtain **1a**–**f**.[5] These reactions were carried out neat and were extremely fast, being complete in less than 2 h. Acetylation of **1a**–**f** with acetyl chloride in the presence of pyridine provided the acetates **2a**–**f** in 88–95% yields (Scheme 1). On the other hand, allyl bromides **3a**,**c**–**f** were prepared from the reaction of **1a**,**c**–**f** with PBr_3 in CH_2Cl_2 in 76–91% yields.[6] Products **3a**,**c**–**f** were obtained as mixtures of the *E* and *Z* isomers, which were not separated due to their close proximity on the TLC plate.

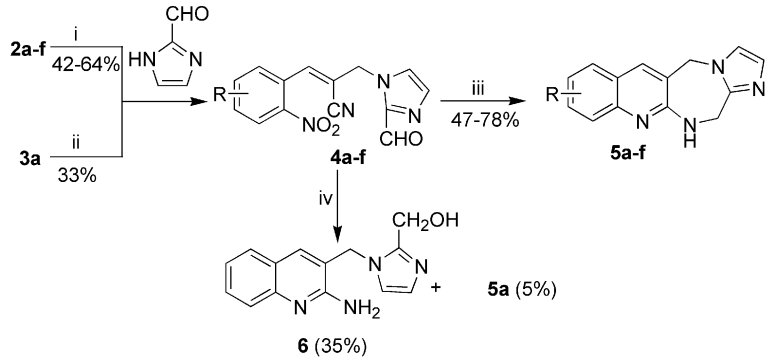
Compounds **2a** and **3a** were simultaneously evaluated as the starting substrates for exploring the optimal conditions for the substitution of imidazole-2-carbaldehyde. The S_N2' reaction of imidazole-2-carbaldehyde in the presence of K_2CO_3 in DMF for 3 h resulted in a mixture of products from which 30% of **4a** was isolated. The stereochemistry of



	R
a	H
b	3-OMe
c	5-Cl
d	4,5-$(OMe)_2$
e	4,5-OCH_2O
f	3,4-C_4H_4 (from 1-nitro-2-naphthaldehyde)

Scheme 1. Reagents and conditions: i) PBr_3, CH_2Cl_2, 0 °C–room temp., 3 h; ii) AcCl, pyridine, CH_2Cl_2, 0 °C–room temp., 30 min.

4a was observed to be *Z* with no trace of the *E* isomer. Alternatively, substitution of imidazole-2-carbaldehyde with allyl bromide **3a** in the presence of K_2CO_3 in DMF for 4 h resulted in isolation of the desired allylamine **4a** in 33% yield. The relative stereochemistry of this product was assigned as *Z* with minor amounts of the *E* isomer. In an attempt to enhance the yield of **4a** it was decided to initially perform the S_N2'–S_N2' displacement reaction with imidazole-2-carbaldehyde in the presence of DABCO in an aqueous medium and then subject the resulting product to 1,3-migration under suitable conditions to generate **4a**. Accordingly, compound **2a** was treated with imidazole-2-carbaldehyde in the presence of DABCO in a mixture of THF/H_2O (1:1, v/v) at room temperature. The reaction was complete in 4 h and normal work-up followed by purification resulted in the product in 54% yield (Scheme 2). The spectroscopic data of the product was identical to that of **4a** formed only as the *Z* isomer. Next we screened several metal-based reducing agents under different conditions to carry out reduction of the aromatic nitro group that would eventually trigger the intended domino process leading to the polycyclic quinoline system (see the Supporting Information). Heating the substrate **4a** in the presence of Fe and AcOH led to a clean reaction. The usual work-up followed by triturating the afforded residue furnished a solid product (57%), the structure of which was delineated as **5a**. On the basis of this result, the proposed mechanism for the formation of **5a** is presented in Figure 2. The isolation of **5a** implies that initially the reductive cyclization takes place as expected followed by another intramolecular cyclization by Schiff base formation between the generated 2-amino group of the resulting quinoline unit and the formyl functionality of the imidazole group. Subsequently, the reaction conditions induce reduction of the double bond of the intermediate imine leading to the final product. Even the reaction in the presence of Zn and AcOH was clean, but the isolated yield (49%) of **5a** was observed to be slightly lower. Interestingly, the reaction of **4a** with In and HCl yielded a mixture of two products, which were readily separated by column chromatography. One of the products isolated in 5% yield was identified as **5a** whereas the major product afforded in 35% yield was identified as **6**. With standardized conditions in hand, we investigated the reaction of sub-



Scheme 2. Reagents and conditions: i) DABCO, THF/H_2O (1:1, v/v), room temp., 4 h; ii) K_2CO_3, DMF, room temp., 1.5 h; iii) Fe, AcOH, N_2, 120 °C, 1.5 h; iv) In, HCl, THF/H_2O (1:1, v/v), room temp., 45 min.

strates **4b**–**f** with Fe and AcOH at 120 °C for 1.5 h to obtain the quinoline derivatives. We noted that all the compounds **4b**–**f** furnished the corresponding products **5b**–**f** in moderate-to-good yields.

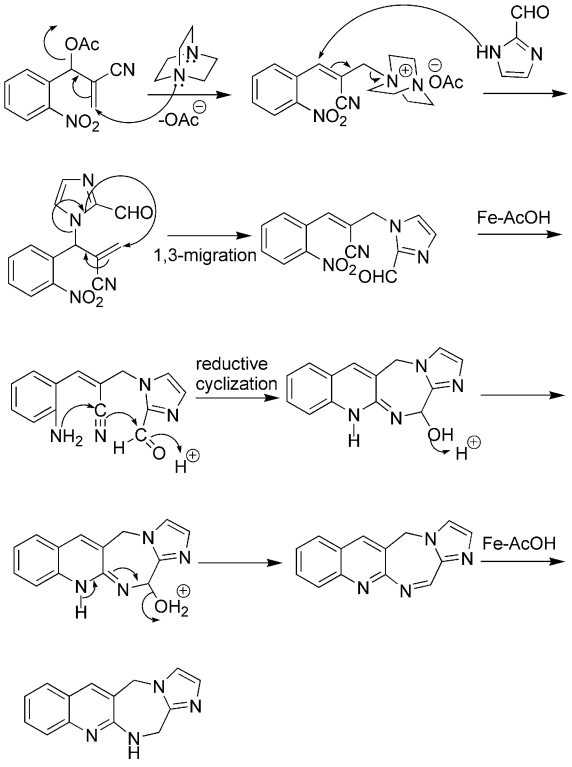
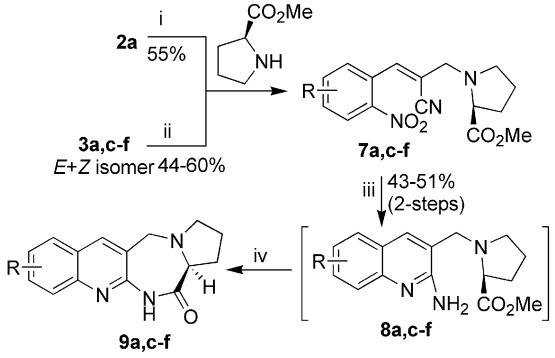


Figure 2. Mechanism for the formation of **5**.

Because the formyl group of the imidazole readily participated in the intramolecular cyclization with the amino group, in the next stage of the study it was reasoned that an analogous system bearing an alkoxycarbonyl functionality instead of a formyl group could also undergo concomitant intramolecular cyclizations upon reduction of the nitro group. To investigate this approach, it was decided to employ L-proline ester as the nucleophilic partner in the substitution reaction to obtain the required starting substrate.

Thus, **2a** was treated with the proline methyl ester in the presence of K_2CO_3 in DMF, whereas **3a** was treated with the same nucleophile in the presence of Et_3N in methanol simultaneously. The usual processing and purification of the reaction mixture from **2a** resulted in the product **7a** in 55% yield as the *Z* isomer, whereas the reaction of **3a** resulted in the isolation of **7a** in 60% yield as a mixture of the *Z* (97%) and *E* (3%) isomers (Scheme 3). No attempt to separate the isomeric mixture was made at this stage. Compound **7a** obtained by both routes was reduced with Fe and AcOH at 100 °C for 1.5 h. However, purification of the crude product by column chromatography was tedious and furnished the pure product in around 30% yield in both cases. The structure of the isolated product was established as **8a**, which implies that the anticipated second intramolecular cyclization reaction did not occur during the reaction. To assess the possibility of an intramolecular cyclization in **8a**, it was treated with NaH in THF at room temperature; this reaction was complete in 1 h.

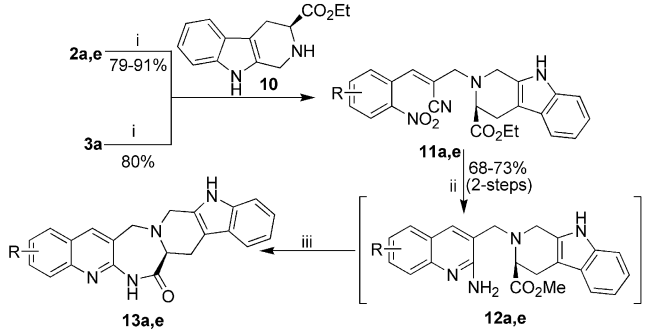


Scheme 3. Reagents and conditions: i) K_2CO_3, DMF, room temp., 1.5 h; ii) Et_3N, DIEA, MeOH, 70 °C, 3 h; iii) Fe, AcOH, N_2, 100 °C, 1.5 h; iv) NaH, THF, 0 °C–room temp., 1 h.

Because the purification of **8a** was found to be cumbersome it was decided to subject the crude material containing **8a**, afforded after work-up, directly to the NaH-promoted cyclization. This strategy was found to successfully furnish compound **9a** in 43% yield. Significantly, no racemization was observed during the formation of **9a**. Owing to the better yield of **7a** achieved from **3a** than from **2a**, different allyl bromides **3c**–**f** were subjected to a similar set

of reactions to investigate the generality of the protocol. In all cases the polycyclic quinolines **9c**–**f** were isolated, although in yields of only 47–51%.

Buoyed by this success, next we decided to investigate the scope of this approach with an analogous allylamine synthesized from the reaction between the ethyl ester derivative of the β-carboline **10** obtained from L-tryptophan following the reported procedure.[7] Here, too, **2a** and **3a** were simultaneously treated with **10** in the presence of K_2CO_3 in THF and yielded the desired allylamine **11a** in 91 and 80% yields, respectively. Fortunately, both reactions were found to stereoselectively yield only the *Z* isomer. Treatment of **11a** with Fe in AcOH at 120 °C resulted in the product **12a**, which was immediately subjected to NaH-promoted ring-closure to furnish the desired product **13a** (68%) stereoselectively without racemization (Scheme 4). This clearly indicates that the presence of the alkoxycarbonyl group does not facilitate the second intramolecular cyclization until the base has been added. The suitability of this strategy for the generation of polycyclic quinoline was further exemplified by using **2e**. The S_N2' reaction of **2e** with **10** resulted in the allylamine **11e** (79%). Fe/AcOH-mediated reductive cyclization followed by base-promoted intramolecular cyclization produced **13e** (73%).

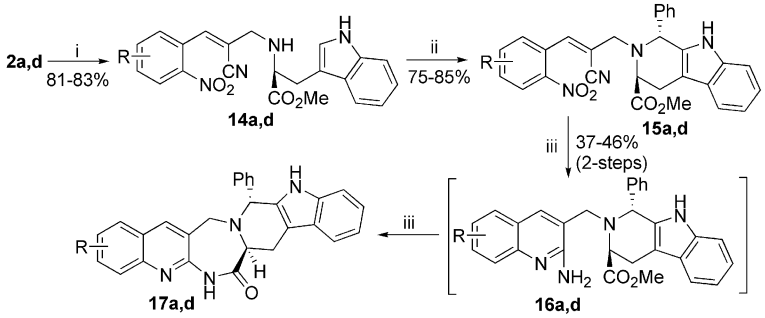


Scheme 4. Reagents and conditions: i) K_2CO_3, DMF, room temp., 4 h; ii) Fe, AcOH, N_2, 120 °C, 1.5 h; iii) NaH, THF, 0 °C–reflux, 1 h.

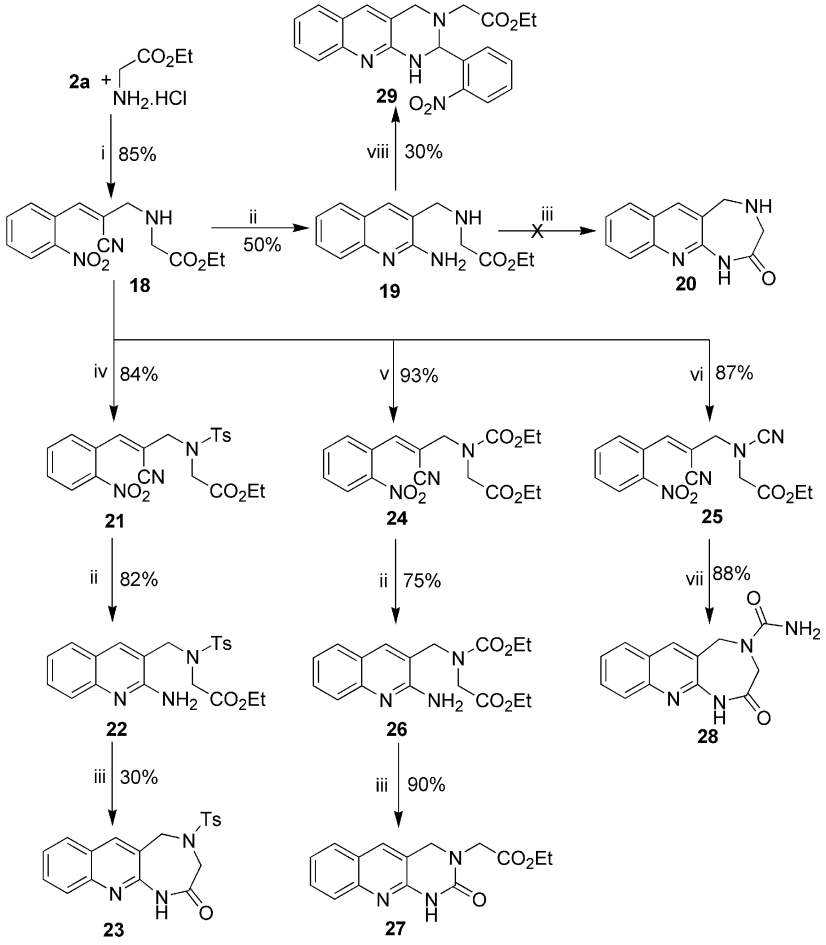
Encouraged by the successful formation of **13**, we decided to evaluate the feasibility of similar products by initiating the reaction with tetrahydro-β-carboline substituted at the 1-position. It is widely reported that tetrahydro-β-carbolines substituted at the 1-position synthesized by the Pictet–Spengler reaction are obtained as a mixture of *cis* and *trans* products.[8] It is also reported that if the tryptophan ester is first *N*-alkylated and then subjected to the Pictet–Spengler reaction it leads to the formation of the *trans* isomer exclusively.[8b] On the basis of these reports, we first treated **2a** with the tryptophan methyl ester in MeOH, which stereoselectively gave the *Z* isomer of **14a** (77%) in 1 h (Scheme 5). Pictet–Spengler reaction of **14a** with benzaldehyde in 2% TFA in DCM smoothly afforded the *trans* isomer of **15a**. The stereochemistry of **15a** was ascertained by NOESY spectroscopy. Heating **15a** in the presence of Fe and AcOH at 120 °C resulted in the formation of 2-aminoquinoline **16a**, which upon treatment with NaH in THF furnished the product **17a** (37% in two steps). The stereochemistry of the product was established to be *trans* on the basis of a NOESY experiment, which indicates that the ring-closure reaction was also stereoselective. During this reaction sequence too we did not observe racemization in any of the products. This was substantiated by subjecting substrate **14d** to similar reactions, which afforded **17d** (46%) stereoselectively.

Until now our attempts to synthesize polycyclic quinolines was restricted to the use of tertiary allylamines generated by nucleophilic substitution of a secondary amine and the Baylis–Hillman derivative. It was therefore considered important to examine the reactions of secondary allylamines generated by the S_N2' reaction between a primary allylamine and the Baylis–Hillman derivative. To this end, acetate **2a** was allowed to react with the glycine ethyl ester in the presence of Et_3N in MeOH to yield **18** (85%) in 1 h (Scheme 6). Reductive cyclization of **18** with Fe and AcOH at 100 °C for 30 min resulted in the formation of the product **19** (50%). Treatment of **19** with NaH in THF as solvent, however, resulted in the formation of an inseparable mixture of products. Unfortunately, several repetitions of this reaction failed to provide any isolable product. The failure to produce **20** indicates that our protocol is probably limited to allylamines with a tertiary nitrogen atom. On this basis we decided to install a tosyl group onto the NH group in compound **18** and investigate this strategy.

Thus, compound **21** was prepared by the reaction of **18** with TsCl in the presence of Et_3N in CH_2Cl_2 in 84% yield. Heating **21** with Fe and AcOH at 100 °C for 30 min yielded a product that was characterized as **22** (82%). Compound **22** underwent the desired cyclization in the presence of NaH within 1 h to afford **23** albeit in a low yield (30%). Encouraged by this outcome it was proposed to introduce functional groups onto the NH of **18** that could participate in intramolecular cyclization reactions with the generated amino group. Hence, it was decided to substitute the amino hydrogen atom with ethoxycarbonyl and nitrile groups using ethyl chloroformate and cyanogen bromide, respectively. The reaction of compound **18** with ethyl chloroformate furnished **24** (93%), whereas with cyanogen bromide it produced **25** (87%). The reductive cyclization of **24** in the presence of Fe and AcOH at 100 °C gave the product **26** (75%). Further treatment of **26** with NaH in THF at room temperature for 1 h, followed by work-up and purification resulted in the isolation of the product in 90% yield, identified as **27** on of the basis of its spectroscopic data. This indicates that the second intramolecular cyclization in **26** was regioselective, with the alkoxycarbonyl group directly attached to the nitrogen participating in the cyclization. However, unlike other substrates in which alkoxycarbonyls participate in the second cyclization, the reduction of **25** with Fe and AcOH by heating at reflux for 1.5 h afforded a product that was delineated to be **28** (88%). This implies that the reduction of the aromatic nitro group in **25** initiated a domino process. The transformation of the nitrile group into an amide functionality in **28** was attributed to the acidic medium of the reaction mixture. Thus, it seems



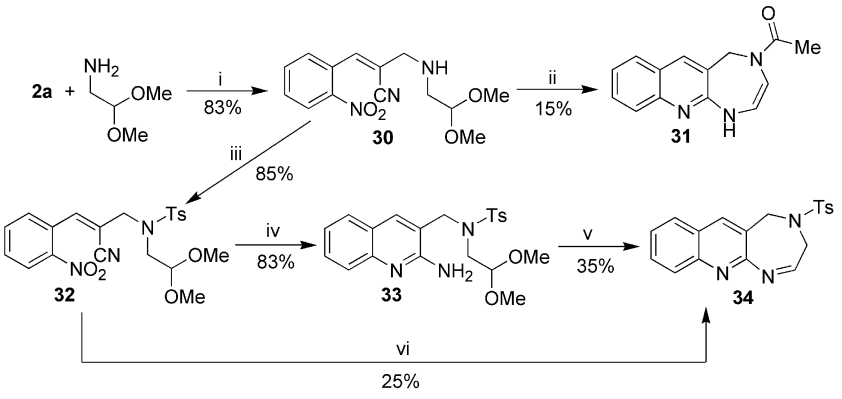
Scheme 5. Reagents and conditions: i) L-tryptophan methyl ester, MeOH, room temp., 1 h; ii) PhCHO, 2% TFA in CH_2Cl_2, room temp., 8 h; iii) NaH, THF, 0 °C–reflux, 1.0 h.



Scheme 6. Reagents and conditions: i) Et_3N, MeOH, room temp., 1 h; ii) Fe, AcOH, N_2, 100 °C, 30 min; iii) NaH, THF, 0 °C–reflux, 1 h; iv) TsCl, Et_3N, DMAP, CH_2Cl_2, room temp., 15 h; v) $ClCO_2Et$, Et_3N, CH_2Cl_2, 0 °C–room temp., 1 h; vi) CNBr, K_2CO_3, dry THF, room temp., 3 h; vii) Fe, AcOH, 120 °C, 1.5 h; viii) 2-nitrobenzaldehyde, H_2O_2, CAN, 50 °C, 15 h.

that the tertiary nature of allylamines is necessary to effect the second intramolecular cyclization to obtain the annulated derivatives. In our attempt to demonstrate the use of diamine **19** for providing a quinoline-annulated system, we performed the reaction between **19** and 2-nitrobenzaldehyde in the presence of CAN and H_2O_2, which led to **29** (30%).[9]

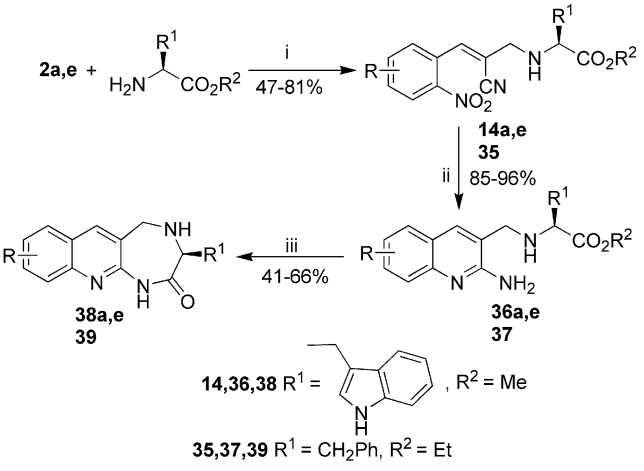
Continuing with our studies, we tested the protocol with **30**, which could be easily synthesized by a S_N2' reaction between amino acetaldehyde dimethyl acetal and **2a**, as reported previously.[10] It was expected that the amino group of 2-aminoquinoline would react with the protected aldehyde in the presence of acetic acid to afford another quinoline-annulated system. Hence **30** was prepared and sub-



Scheme 7. Reagents and conditions: i) MeOH, room temp., 1.0 h; ii) Fe, AcOH, N_2, 100 °C, 1.5 h; iii) TsCl, Et_3N, CH_2Cl_2, room temp., 15 h; iv) Fe, AcOH, N_2, 100 °C, 30 min; v) $CHCl_3$, TFA/H_2O (1:1), room temp., 5 d; vi) Fe, AcOH, N_2, 100 °C, 30 min, then H_2O, 100 °C, 15 h.

jected to the reduction in the presence of Fe and AcOH at 100 °C for 1.5 h. This reaction led to the formation of a mixture of products from which compound **31** was isolated in only 15% yield (Scheme 7). Isomerization to yield the double bond between the C-2 and C-3 atoms was evident from the ^1H and ^{13}C NMR spectra. Acetylation of the NH group would have occurred owing to the presence of AcOH. Considering our preceding experience with secondary allylamines, compound **30** was readily tosylated to generate **32** (85%). Further reaction of **32** with Fe and AcOH under heating resulted in a product that was established as **33**. Thus it is apparent that the acidity of the medium was not suited to unmasking the protected formyl group for further reaction. Nevertheless treatment of **33** with a mixture of $CHCl_3$, TFA and water for 5 d showed the complete disappearance of the starting material. Purification of the mixture furnished a product that was established as **34** (35%). Unlike **31**, no isomerization of the double bond was observed in this case. During the optimization of the reaction we discovered another set of conditions for obtaining **34** directly from **32** in a shorter period of time. In this method, after the treatment of **32** with Fe and AcOH for 30 min, water was added to the reaction mixture and heating was continued for 15 h to give **34** in an isolable yield of 25%.

A critical analysis of the reactions studied up to this point revealed that we had failed to achieve the quinoline-annulated product whenever the amine group of the allylamine was secondary because the expected second intramolecular cyclization did not take place. Interestingly, it was observed that for both substrates **18** and **30**, the carbon adjacent to the nitrogen of the introduced nucleophile did not carry any substitution. Therefore we decided to probe the scope of the protocol by installing a substituent on this carbon atom. This could be readily accomplished by generating allylamines from the esters of amino acids other than glycine. For this endeavour compound **14a** synthesized earlier was selected as the substrate. As expected, reductive cyclization with Fe and AcOH at 100 °C for 1 h resulted in the formation of **36a** (85%; Scheme 8). The subsequent reaction of **36a** under optimized conditions was completed with 10.0 equiv. of NaH under heating. Purification of the reaction mixture led to isolation of the product in 49% yield. Spectroscopic evidence led to its assignment as **38a** without any racemization. The successful isolation of **38a** prompted us to repeat the sequence with substrate **2e**. Under identical reaction conditions, **2e** afforded the annulated quinoline **38e** (41%).

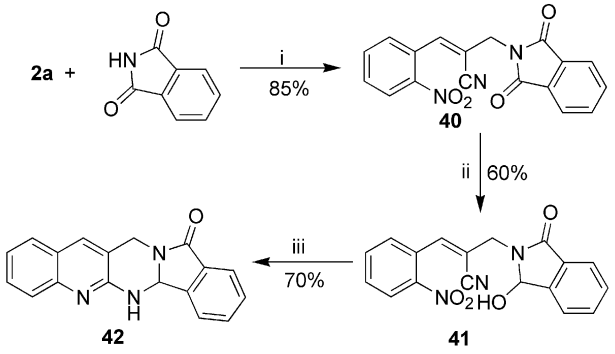


Scheme 8. Reagents and conditions: i) MeOH, room temp., 1 h (for tryptophan ester); K_2CO_3, DMF, room temp., 2 h (for phenylalanine ester); ii) Fe, AcOH, N_2, 100 °C, 1 h; iii) NaH, THF, 0 °C–reflux, 1 h.

To achieve greater variety, the tryptophan methyl ester was replaced by the phenylalanine ethyl ester as the nucleophile for generating the allylamine. Hence **2a** was treated with phenylalanine ethyl ester in the presence of K_2CO_3 in DMF to afford **35** (47%; Scheme 8). Fe/AcOH-mediated reductive cyclization at 100 °C was complete in 30 min to furnish 96% of **37**. Treatment of **37** with NaH in THF at reflux gave **39** (66%). These results make it apparent that the second step of the protocol for the synthesis of annulated quinolines developed by us works better for secondary allylamines in which the carbon adjacent to the nitrogen of the introduced nucleophile carry a substitution.

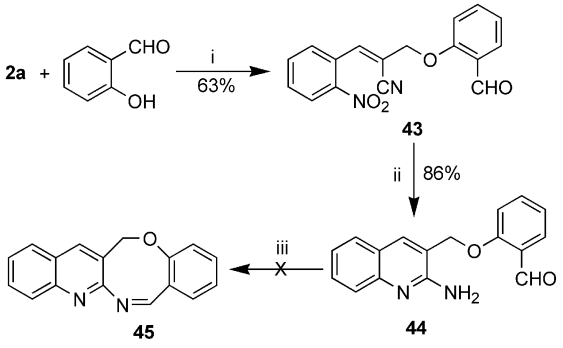
To further enhance the scope of our protocol, we investigated the participation of the hydroxy group in the second intramolecular cyclization. In principle, treatment of the

Baylis–Hillman acetate with phthalimide would yield an allylamine in which one of the amide carbonyl groups can be reduced to a secondary hydroxy group that may participate in the second intramolecular cyclization.[11] It can be speculated that in the presence of AcOH the partially reduced phthalimide can dehydrate to produce the *N*-acylinium ion, which can be attacked by the amino group to produce the desired polycyclic scaffold. Thus, **2a** was treated with phthalimide in the presence of K_2CO_3 in DMF to obtain **40** (85%) as a mixture of *Z* and *E* isomers (10:1; Scheme 9). Reduction of **40** in the presence of $NaBH_4$ resulted in the formation of product **41** (60%) within 10 min. Treatment of **41** with Fe and AcOH at 120 °C resulted in the completion of the reaction in 2 h and yielded a product that was delineated to be **42** (70%). The formation of **42** established that here too reduction of the aromatic nitro group triggered the domino process.



Scheme 9. Reagents and conditions: i) K_2CO_3, DMF, room temp., 2 h; ii) $NaBH_4$, MeOH, room temp., 10 min; iii) Fe, AcOH, N_2, 120 °C, 2 h.

Finally, we examined the suitability of this approach for a substrate originating from the S_N2' reaction of an oxygen nucleophile bearing a suitable group for intramolecular cyclization. For example, the reaction of salicylaldehyde with **2a** would yield a substrate that has the potential to participate in the intramolecular cyclization through the formyl group. Accordingly, compound **43** (63%) was readily generated by the reaction between **2a** and salicylaldehyde in the presence of K_2CO_3 in DMF (Scheme 10). Reductive cyclization with Fe and AcOH at 120 °C yielded a product that



Scheme 10. Reagents and conditions: i) K_2CO_3, DMF, room temp., 2 h; ii) Fe, AcOH, N_2, 120 °C, 1 h; iii) *p*TSA, PhMe, reflux, 3 d.

was established to be **44** (86%). Unfortunately, attempts to perform the intramolecular cyclization in the presence of *p*-toluenesulfonic acid (pTSA) to afford **45** failed and the starting was recovered.

Conclusions

We have disclosed the potential of allylamines originating from the Baylis–Hillman adducts of 2-nitrobenzaldehydes and acrylonitrile for the preparation of polycyclic quinoline frameworks employing reductive cyclization as the key step. The two-step synthetic protocol was found to be a domino process involving two successive intramolecular cyclizations triggered by the reduction of the aromatic nitro group in the case of substrates bearing a formyl or hydroxy group. In contrast, a similar two-step sequence for substrates bearing an alkoxycarbonyl group was found to proceed through an initial reductive cyclization followed by a base-promoted second intramolecular cyclization. A study of the scope of the approach indicates that tertiary allylic amines readily follow the protocol to furnish the desired annulated quinolines. On the other hand, secondary allylamines bearing an unsubstituted carbon adjacent to the nitrogen atom are unlikely to undergo the second intramolecular cyclization in contrast to secondary amines with a substituted carbon atom adjacent to the nitrogen atom. Rapid access to the starting substrates, simple reaction conditions and the diverse nature of nucleophiles that could be installed onto the Baylis–Hillman derivatives makes this an attractive approach that could be exploited further to generate more diverse polycyclic quinolines.

Experimental Section

General: Melting points were determined in capillary tubes with a Precision melting point apparatus containing silicon oil and are uncorrected. IR spectra were recorded using a Perkin–Elmer Spectrum RX I FTIR spectrometer. ^1H and ^{13}C NMR spectra were recorded with either a Bruker DPX-200 FT or an Avance DRX-300 spectrometer using TMS as an internal standard (chemical shifts are given as δ values). The ESMS were recorded with the MICROMASS Quadro-II LCMS system. The HRMS spectra were recorded as EI-HRMS spectra with a JEOL system or as DART-HRMS spectra (recorded as ES^+) with a JEOL-AccuTOF JMS-T100LC mass spectrometer with a DART (Direct Analysis in Real Time) source. The optical rotations were measured with an Autopol III instrument, serial no 30166 from Rudolph. Elemental analyses were performed with a Carlo–Erba 108 or an Elementar Vario EL III microanalyzer.

General Procedure for the Synthesis of Compounds 4a–f as Exemplified for Compound 4a: DABCO (1.02 g, 9.14 mmol) was added to a stirred solution of acetate **2a** (1.5 g, 6.09 mmol) in a mixture of THF/water (12 mL, 1:1, v/v) and stirring was continued for 15 min at room temperature. Thereafter, imidazole-2-carbaldehyde (0.64 g, 6.7 mmol) was added and the reaction was allowed to proceed for 4 h. After completion of the reaction, as monitored by TLC, THF was evaporated in vacuo and the residue was extracted with EtOAc (8×30 mL) and water (70 mL). The organic layers were combined and washed with brine (50 mL), dried with Na_2SO_4

and concentrated to yield the crude product. Purification by short column chromatography using hexane/EtOAc (1:1, v/v) afforded 0.93 g (54%) of pure **4a** as a yellowish brown solid.

(*Z*)-2-[(2-Formyl-1*H*-imidazol-1-yl)methyl]-3-(2-nitrophenyl)prop-2-enenitrile (4a): M.p. 153–155 °C; R_f = 0.68 (hexane/EtOAc, 30:70). IR (KBr): $\tilde{\nu}_{max}$ = 1678 (CHO), 2227 (CN) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 5.42 (s, 2 H, CH_2), 7.40 (d, J = 7.9 Hz, 2 H, $ArH_{imid.}$), 7.61–7.78 (m, 4 H, ArH), 8.24 (d, J = 8.0 Hz, 1 H, ArH), 9.87 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 48.4, 111.3, 115.9, 125.0, 127.5, 128.9, 130.7, 131.2, 131.6, 134.5, 142.8, 144.3, 147.0, 181.8 ppm. MS (ES^+): m/z (%) = 283.1 (%) $[M + 1]^+$, 315.0 (100) $[M + 32]^+$. $C_{14}H_{10}N_4O_3$ (282.0753): calcd. C 59.57, H 3.57, N 19.85; found C 59.73, H 3.46, N 19.97.

General Procedure for the Synthesis of Compounds 5b–f, 8a, 12a, 16a, 19, 22, 26, 28, 31, 33, 36a,e, 37, 42 and 44 as Exemplified for the Compound 5a: Iron powder (0.54 g, 9.57 mmol) was added to a solution of **4a** (0.45 g, 1.60 mmol) in glacial acetic acid (10 mL) and the reaction was heated at reflux at 120 °C whilst stirring under nitrogen for 1.5 h. On completion, excess acetic acid was evaporated in vacuo and the reaction mixture was poured into a 10% aq. $NaHCO_3$ solution whilst stirring with a glass rod. Then EtOAc (50 mL) was added and the contents were passed through a bed of Celite. The organic layer was separated and the aqueous layer was extracted with EtOAc (5 × 15 mL).The combined organic layers were evaporated in vacuo and the residue was recrystallized from EtOAc to furnish 0.21 g (57%) of **5a** as a yellow solid.

12,13-Dihydro-5*H*-imidazo[1′,2′:1,2][1,4]diazepino[5,6-*b*]quinoline (5a): M.p. >240 °C; R_f = 0.27 (MeOH/$CHCl_3$, 05:95). IR (KBr): $\tilde{\nu}_{max}$ = 3187 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 4.75 (s, 2 H, CH_2NH), 5.27 (s, 2H, CH_2N), 5.81 (br. s, 1 H, NH), 6.95 (d, J = 1.0 Hz, 1 H, $ArH_{imid.}$), 6.99 (d, J = 1.0 Hz, 1 H, $ArH_{imid.}$), 7.20–7.26 (m, 1 H, ArH), 7.57 (t, J = 8.5 Hz, 3 H, ArH), 7.76 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 38.7, 47.4, 117.4, 119.8, 121.7, 122.5, 124.7, 125.9, 127.3, 129.6, 136.7, 145.6, 147.5, 156.4 ppm. MS (ES+): m/z (%) = 237.2 (100) $[M + 1]^+$; DART-HRMS (ES+): calcd. for $C_{14}H_{13}N_4$ 237.1140; found 237.1141.

10-Methoxy-12,13-dihydro-5*H*-imidazo[1′,2′:1,2][1,4]diazepino[5,6-*b*]-quinoline (5b): The title compound was prepared following the above-described general procedure and after purification by crystallization using EtOAc [R_f = 0.23 (MeOH/$CHCl_3$, 05:95)] was obtained as a yellowish brown solid (0.21 g from 0.50 g); yield 48%; m.p. >240 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3425 (NH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 3.84 (s, 3 H, OCH_3), 4.56 (d, J = 4.2 Hz, 2 H, CH_2NH), 5.43 (s, 2 H, CH_2N), 6.77 (s, 1 H, $ArH_{imid.}$), 6.96 (t, J = 7.6 Hz, 1 H, ArH), 7.07 (t, J = 7.6 Hz, 1 H, ArH), 7.19 (d, J = 7.6 Hz, 1 H, ArH), 7.24 (s, 1 H, $ArH_{imid.}$), 7.59 (br. s, 1 H, NH), 7.88 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 38.7, 47.4, 55.3, 108.9, 117.5, 119.1, 119.8, 121.6, 123.3, 125.8, 136.8, 139.0, 145.7, 152.7, 155.7 ppm. MS (ES+): m/z (%) = 267.2 (100) $[M + 1]^+$. EI-HRMS: calcd. for $C_{15}H_{14}N_4O$ 266.1168; found 266.1158.

8-Chloro-12,13-dihydro-5*H*-imidazo[1′,2′:1,2][1,4]diazepino[5,6-*b*]-quinoline (5c): The title compound was prepared following the above-described general procedure and after purification by column chromatography [hexane/EtOAc, 45:55; R_f = 0.25 (MeOH/$CHCl_3$, 05:95)] was obtained as a yellowish brown solid (0.19 g from 0.24 g); yield 78%; m.p. >240 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3184 (NH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 4.58 (d, J = 4.3 Hz, 2 H, CH_2NH), 5.45 (s, 2 H, CH_2N), 6.78 (s, 1 H, $ArH_{imid.}$), 7.26 (s, 1 H, $ArH_{imid.}$), 7.39–7.47 (m, 2 H, ArH), 7.62 (br. s, 1 H, NH), 7.74 (s, 1 H, ArH), 7.90 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 38.7, 47.3, 118.5, 120.0, 123.2, 125.5, 125.9, 126.0, 126.7, 130.0, 136.0, 145.5, 146.1, 156.8 ppm. MS (ES): m/z (%) = 271.2 (100) $[M + 1]^+$, 273.2 (33) $[M + 3]^+$. DART-HRMS (ES+): calcd. for $C_{14}H_{11}ClN_4$ 271.0751; found 271.0744.

8,9-Dimethoxy-12,13-dihydro-5*H*-imidazo[1′,2′:1,2][1,4]diazepino-[5,6-*b*]quinoline (5d): The title compound was prepared following the above-described general procedure and after purification by column chromatography [hexane/EtOAc, 1:1; R_f = 0.25 (MeOH/$CHCl_3$, 05:95)] was obtained as a yellowish brown solid (0.13 g from 0.30 g); yield 49%; m.p. >240 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3393 (NH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 3.80 (s, 3 H, OCH_3), 3.82 (s, 3 H, OCH_3), 4.55 (d, J = 4.8 Hz, 2 H, CH_2NH), 5.38 (s, 2 H, CH_2N), 6.76 (s, 1 H, $ArH_{imid.}$), 6.84 (s, 1 H, $ArH_{imid.}$), 7.05 (s, 1 H, ArH), 7.24 (s, 1 H, ArH), 7.75 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 38.9, 47.5, 55.4, 55.5, 104.8, 106.2, 114.5, 116.8, 119.7, 125.7, 135.4, 144.0, 145.7, 146.1, 152.3, 155.2 ppm. MS (ES): m/z (%) = 297.2 (100) $[M + 1]^+$. DART-HRMS (ES+): calcd. for $C_{16}H_{16}N_4O_2$ 297.1352; found 297.1330.

6,12-Dihydro-7*H*-[1,3]dioxolo[4,5-*g*]imidazo[1′,2′:1,2][1,4]diazepino-[5,6-*b*]quinoline (5e): The title compound was prepared following the above-described general procedure and after purification by column chromatography [hexane/EtOAc, 1:1; R_f = 0.27 (MeOH/$CHCl_3$, 05:95)] was obtained as a yellowish brown solid (0.12 g from 0.30 g); yield 47%; m.p. >240 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3411 (NH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 4.53 (d, J = 4.7 Hz, 2 H, CH_2NH), 5.37 (s, 2 H, CH_2N), 6.06 (s, 2 H, OCH_2O), 6.76 (s, 1 H, $ArH_{imid.}$), 6.82 (s, 1 H, $ArH_{imid.}$), 7.08 (s, 1 H, ArH), 7.16 (t, J = 4.4 Hz, 1 H, NH), 7.23 (s, 1 H, ArH), 7.73 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 40.4, 47.3, 79.2, 101.2, 102.1, 103.0, 114.5, 117.8, 119.7, 125.7, 135.9, 143.9, 145.2, 145.6, 150.3, 155.3 ppm. MS (ES): m/z (%) = 281.2 (100) $[M + 1]^+$. DART-HRMS (ES+): calcd. for $C_{15}H_{12}N_4O_2$ 281.1039; found 281.1022.

13,14-Dihydro-8*H*-benzo[*h*]imidazo[1′,2′:1,2][1,4]diazepino[5,6-*b*]-quinoline (5f): The title compound was prepared following the above-described general procedure and after purification by crystallization using EtOAc [R_f = 0.41 (MeOH/$CHCl_3$, 05:95)] was obtained as a yellowish brown solid (0.10 g from 0.15 g); yield 74%; m.p. 240–242 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3244 (NH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 4.66 (d, J = 4.8 Hz, 2 H, CH_2NH), 5.50 (s, 2 H, CH_2N), 6.79 (s, 1 H, $ArH_{imid.}$), 7.27 (s, 1 H, $ArH_{imid.}$), 7.52–7.62 (m, 5 H, ArH), 7.88 (t, J = 4.5 Hz, 1 H, ArH), 7.99 (s, 1 H, ArH), 8.87 (t, J = 4.5 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 38.7, 47.3, 116.1, 118.8, 119.9, 122.1, 123.7, 125.2, 125.8, 127.6, 129.2, 133.8, 137.1, 144.9, 145.6, 156.2 ppm. MS (ES): m/z (%) = 287.3 (100) $[M + 1]^+$. EI-HRMS: calcd. for $C_{18}H_{14}N_4$ 286.1218; found 286.1218.

2-Oxo-1,2,3,5-tetrahydro-4*H*-[1,4]diazepino[5,6-*b*]quinoline-4-carboxamide (28): The title compound was prepared following the above-described general procedure and after purification by crystallization with EtOAc [R_f = 0.35 (MeOH/$CHCl_3$, 05:95)] was obtained as a white solid (0.32 g from 0.45 g); yield 88%; m.p. 180–182 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1696 (CONH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 3.97 (s, 2 H, CH_2), 4.42 (s, 2 H, CH_2), 6.35 (br. s, 2 H, NH_2), 7.16–7.20 (m, 1 H, ArH), 7.47 (d, J = 3.8 Hz, 2 H, ArH), 7.68 (d, J = 8.1 Hz, 1 H, ArH), 7.85 (s, 1 H, ArH), 10.99 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 42.3, 51.1, 118.4, 121.6, 123.1, 124.8, 127.6, 129.1, 135.3, 147.3, 156.3, 157.8, 171.8, 172.2 ppm. MS (ES): m/z (%) = 257.2 (100) $[M + 1]^+$. $C_{13}H_{12}N_4O_2$ (256.0960): calcd. for C 60.93, H 4.72, N 21.86; found C 60.78, H 4.89, N 21.73.

1-(1,5-Dihydro-4*H*-[1,4]diazepino[5,6-*b*]quinolin-4-yl)ethan-1-one (31): The title compound was prepared following the above-described general procedure and after purification by column chromatography [MeOH/$CHCl_3$, 03:97; R_f = 0.60 (MeOH/$CHCl_3$, 10:90)] was obtained as a yellow solid (0.04 g from 0.30 g); yield 15%; m.p. >250 °C °C. IR (KBr): $\tilde{\nu}_{max}$ = 1718 (COMe) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 2.16 (s, 3 H, $COCH_3$), 4.82 (s, 2 H, CH_2N), 5.66 (d, J = 7.0 Hz, 1 H, =CH), 5.85 (d, J = 7.0 Hz, 1 H, =CH), 7.26–7.34 (m, 2 H, ArH and NH), 7.55–7.60 (m, J = 7.8 Hz, 1 H, ArH), 7.66 (d, J = 8.2 Hz, 2 H, ArH), 7.96 (s, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 22.5, 47.5, 109.7, 116.8, 121.9, 123.9, 124.5, 125.7, 127.7, 130.3, 138.0, 146.8, 156.6, 168.8 ppm. MS (ES): m/z (%) = 240.2 (100) $[M + 1]^+$. $C_{14}H_{13}N_3O$ (239.1059): calcd. C 70.28, H 5.48, N 17.56; found C 70.17, H 5.39, N 17.67.

6,13-Dihydroisoindolo[2′,1′:1,2]pyrimido[4,5-*b*]quinolin-11(6a*H*)-one (42): The title compound was prepared following the above-described general procedure and after purification with EtOAc [R_f = 0.50 (MeOH/$CHCl_3$, 05:95)] was obtained as a white solid (0.36 g from 0.60 g); yield 70%; m.p. >250 °C; $[\alpha]_D^{29}$ = 216 (c = 0.600, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1689 (CO) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 4.65 (d, J = 17.1 Hz, 1 H, C*H*H), 5.26 (d, J = 17.1 Hz, 1 H, CH*H*), 5.97 (s, 1 H, CH), 7.22–7.27 (m, 1 H, ArH), 7.49–7.58 (m, 2 H, ArH), 7.62 (d, J = 7.4 Hz, 1 H, ArH), 7.69–7.72 (m, 2 H, ArH), 7.76 (d, J = 7.8 Hz, 1 H, ArH), 7.97 (d, J = 7.4 Hz, 1 H, ArH), 8.03 (s, 1 H, ArH), 8.29 (br. s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 65.3, 115.5, 122.4, 123.1, 123.4, 124.0, 125.2, 127.4, 129.3, 129.6, 131.3, 132.2, 133.8, 143.1, 146.6, 153.5, 165.6 ppm. MS (ES): m/z (%) = 288.0 (100) $[M + 1]^+$. $C_{18}H_{13}N_3O$ (287.1059): calcd. C 75.25, H 4.56, N 14.63; found C 75.40, H 4.67, N 14.45.

2-[(2-Aminoquinolin-3-yl)methoxy]benzaldehyde (44): The title compound was prepared following the above-described general procedure and after purification by column chromatography [MeOH/$CHCl_3$, 02:98; R_f = 0.43 (MeOH/$CHCl_3$, 05:95)] was obtained as a white solid (0.39 g from 0.50 g); yield 86%; m.p. 169–171 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1659 (CHO), 3167 (NH_2) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 5.27 (s, 2 H, OCH_2), 6.51 (s, 2 H, NH_2), 7.09–7.21 (m, 2 H, ArH), 7.43 (d, J = 8.3 Hz, 1 H, ArH), 7.50 (d, J = 8.3 Hz, 2 H, ArH), 7.67–7.76 (m, 3 H, ArH), 8.17 (s, 1 H, ArH), 10.50 (s, 1 H, CHO) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 67.0, 114.3, 118.3, 121.1, 121.6, 122.8, 124.8, 124.9, 127.8, 128.1, 129.4, 135.9, 136.3, 147.6, 156.2, 160.4, 189.7 ppm. MS (ES): m/z (%) = 279.1 (100) $[M + 1]^+$. $C_{17}H_{14}N_2O_2$ (278.1055): calcd. C 73.37, H 5.07, N 10.07; found C 73.53, H 5.10, N 9.95.

Typical Procedure for the Synthesis of Compound 6: Water was added (3 mL) to a solution of **2a** (0.21 g, 0.85 mmol) in THF (3 mL) followed by indium powder (0.39 g, 3.41 mmol) and the mixture was stirred for 10 min at room temperature. Thereafter HCl (0.56 mL, 5.12 mmol) was added dropwise and stirring was continued for another 45 min. On completion, the reaction mixture was poured into a 10% aq. $NaHCO_3$ solution whilst stirring with a glass rod. EtOAc (50 mL) was added and the contents were passed through a bed of Celite. The organic layer was separated and the aqueous layer was further extracted with EtOAc (5 × 15 mL).The combined organic layers were evaporated in vacuo to obtain the crude material, which was purified by column chromatography. Elution with MeOH/$CHCl_3$ [3:97; R_f = 0.48 (MeOH/$CHCl_3$, 10:90)] first furnished 0.01 g (5%) of **5a** as a yellow solid followed by 0.07 g (35%) of **6** as a yellowish brown solid.

{1-[(2-Aminoquinolin-3-yl)methyl]-1*H*-imidazol-2-yl}methanol (6): M.p. >240 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3239 (NH_2 and OH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 4.51 (d, J = 4.2 Hz, 2 H, CH_2OH), 5.22 (s, 2 H, CH_2), 5.58 (br. s, 1 H, OH), 6.49 (br. s, 2 H, NH_2), 6.88 (s, 1 H, $ArH_{imid.}$ and ArH), 7.11–7.17 (m, 2 H, $ArH_{imid.}$), 7.31 (s, 1 H, ArH), 7.49–7.56 (m, 3 H, ArH) ppm. ^{13}C NMR (75 MHz, [D_6]DMSO): δ = 45.5, 55.9, 119.7, 121.1, 121.6, 122.8, 124.9, 127.0, 127.5, 129.2, 134.6, 147.2, 147.3, 155.8 ppm. MS (ES): m/z (%) = 255.1 (100) $[M + 1]^+$. $C_{14}H_{14}N_4O$ (254.1168): calcd. C 66.13, H 5.55, N 22.03; found C 66.34, H 5.77, N 21.86.

General Procedure for the Synthesis of Compounds 7a,c,e–g as Exemplified for Compound 7a: Et_3N (0.53 mL, 3.77 mmol) was added to a stirred solution of the proline methyl ester hydrochloride (0.25 g, 1.51 mmol) in dry MeOH (6 mL) and the mixture was stirred for 15 min at room temperature. Thereafter, DIEA (0.13 mL, 0.83 mmol) was added followed by **3a** (0.25 g, 1.51 mmol) and the reaction was heated at 70 °C whilst stirring for 3 h. After completion of the reaction, MeOH was evaporated in vacuo and the residue was dissolved in CH_2Cl_2 and the slurry prepared with silica-gel. Purification on a short column of silica gel using hexane/ EtOAc (85:15, v/v) afforded 0.14 g (60%) of pure **7a** as a yellow oil.

Methyl 1-[(*Z*)-2-Vyano-3-(2-nitrophenyl)prop-2-enyl]pyrrolidine-2-carboxylate (7a): Yield: 60% (0.14 g from 0.20 g) as a yellow oil; R_f = 0.62 (hexane/EtOAc, 70:30); $[\alpha]_D^{29}$ = –49 (c = 0.274, $CHCl_3$). IR (neat): $\tilde{\nu}_{max}$ = 1737 (CO_2Me), 2221 (CN) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86–2.07 (m, 3 H, CH_2 and C*H*H), 2.16–2.22 (m, 1 H, CH*H*), 2.71 (q, J = 7.3 Hz, 1 H, C*H*H), 3.21–3.28 (m, 1 H, CH*H*), 3.50–3.57 (m, 2 H, CH_2), 3.74 (s, 3 H, CO_2CH_3), 3.76–3.81 (m, 1 H, CH), 7.56–7.62 (m, 1 H, ArH), 7.66 (s, 1 H, ArCH), 7.70–7.81 (m, 2 H, ArH), 8.18 (dd, J_1 = 1.0, J_2 = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.6, 29.5, 52.0, 53.0, 57.0, 64.5, 114.5, 117.5, 125.2, 130.0, 130.5, 131.1, 134.3, 142.0, 147.3, 174.2 ppm. MS (ES): m/z (%) = 316.1 (100) $[M + 1]^+$. $C_{16}H_{17}N_3O_4$ (315.1219): calcd. C 60.94, H 5.43, N 13.33; found C 60.83, H 5.59, N 13.50.

General Procedure for the Synthesis of Compounds 9a,c–f from 7a,c–f as Exemplified for Compound 9c: Iron powder (0.116 g, 2.06 mmol) was added to a solution of **7c** (0.12 g, 0.34 mmol) in glacial acetic acid (5 mL) and the reaction was heated at reflux at 120 °C whilst stirring under nitrogen for 1.5 h. On completion, excess acetic acid was evaporated in vacuo and the reaction mixture was poured into a 10% $NaHCO_3$ aq. solution whilst stirring with a glass rod. EtOAc (15 mL) was added and the contents were passed through a bed of Celite. The organic layer was partitioned and separated and the aqueous layer was further extracted with EtOAc (5 × 15 mL). The combined organic layers were washed with brine, dried with Na_2SO_4 and the solvents evaporated in vacuo to furnish 0.072 g of a yellow solid residue (**8c**). This residue was dissolved in dry THF (3 mL) and NaH (0.016 g, 0.677 mmol) was added at 0 °C and the reaction was stirred at room temp. for 1 h. On completion of the reaction, as monitored by TLC, excess THF was evaporated in vacuo and EtOAc (20 mL) was added. The reaction mixture was poured into water (20 mL) and extracted further (5 × 10 mL) with EtOAc. The organic layers were combined and washed with brine (20 mL), dried with Na_2SO_4 and concentrated in vacuo. The product was further recrystallized from EtOAc to furnish 0.05 g (47%) of **9c** as a yellowish brown solid.

8-Chloro-1,2,3,5,12,13a-hexahydro-13*H*-pyrrolo[1′,2′:1,2][1,4]diazepino[5,6-*b*]quinolin-13-one (9c): R_f = 0.72 (MeOH/$CHCl_3$, 05:95); m.p. 171–173 °C; $[\alpha]_D^{27}$ = 264 (c = 0.100, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1673 (CONH) cm^{-1}. ^1H NMR (300 MHz, [D_6]DMSO): δ = 1.70–1.91 (m, 3 H, CH_2 and C*H*H), 2.21–2.30 (m, 1 H, CH*H*), 2.50 (br. s, 1 H, C*H*H), 2.99–3.01 (m, 1 H, CH*H*), 3.51–3.58 (m, 2 H, CH_2),

4.12 (d, J = 12.2 Hz, 1 H, CH), 7.69–7.73 (m, 1 H, ArH), 7.83 (d, J = 8.9 Hz, 1 H, ArH), 8.04 (d, J = 2.0 Hz, 1 H, ArH), 8.30 (s, 1 H, ArH), 10.62 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.2, 24.7, 53.3, 62.0, 126.0, 126.2, 126.5, 129.2, 129.5, 130.3, 136.9, 144.6, 152.5, 171.5 ppm. MS (ES): m/z (%) = 288.1 (100) [M + 1]$^+$. EI-HRMS: calcd. for $C_{15}H_{14}ClN_3O$ 287.0825; found 287.0368.

1,2,3,5,12,13a-Hexahydro-13*H*-pyrrolo[1′,2′:1,2][1,4]diazepino[5,6-*b*]-quinolin-13-one (9a): The title compound was prepared following the above-described general procedure and after purification by crystallization using EtOAc [R_f = 0.75 (MeOH/CHCl$_3$, 05:95)] was obtained as a yellowish brown solid (0.034 g from 0.10 g); yield 43%; m.p. 121–123 °C; $[a]_D^{27}$ = 312 (c = 0.064, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1671 (CONH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.72–1.86 (m, 3 H, CH$_2$ and C*H*H), 2.21–2.30 (m, 1 H, C*H*H), 2.47–2.50 (m, 1 H, CH*H*), 2.99–3.01 (m, 1 H, C*H*H), 3.49–3.58 (m, 2 H, CH$_2$), 4.13 (d, J = 12.1 Hz, 1 H, CH), 7.51 (t, J = 7.0 Hz, 1 H, ArH), 7.69–7.74 (m, 1 H, ArH), 7.83 (d, J = 8.3 Hz, 1 H, ArH), 7.92 (d, J = 7.9 Hz, 1 H, ArH), 8.32 (s, 1 H, ArH), 10.58 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.2, 24.6, 53.2, 53.3, 61.9, 125.0, 125.4, 125.8, 127.2, 127.6, 129.9, 137.6, 146.2, 152.0, 171.5 ppm. MS (ES): m/z (%) = 254.1 (100) [M + 1]$^+$. EI-HRMS: calcd. for $C_{15}H_{15}N_3O$ 253.1215; found 253.1204.

8,9-Dimethoxy-1,2,3,5,12,13a-hexahydro-13*H*-pyrrolo[1′,2′:1,2][1,4]-diazepino[5,6-*b*]quinolin-13-one (9d): The title compound was prepared following the above-described general procedure and after purification by column chromatography [MeOH/CHCl$_3$, 02:98; R_f = 0.52 (MeOH/CHCl$_3$, 05:95)] was obtained as a yellowish brown solid (0.046 g from 0.12 g); yield 46%; m.p. 158–160 °C; $[a]_D^{27}$ = 308 (c = 0.112, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1677 (CONH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.72–1.94 (m, 3 H, CH$_2$ and C*H*H), 2.28 (t, J = 9.8 Hz, 1 H, CH*H*), 2.44–2.50 (m, 1 H, C*H*H), 3.00 (s, 1 H, CH*H*), 3.79–3.82 (m, 2 H, CH$_2$), 3.88 (s, 3 H, OCH$_3$), 3.90 (s, 3 H, OCH$_3$), 4.05 (d, J = 12.0 Hz, 1 H, CH), 7.17 (s, 1 H, ArH), 7.29 (s, 1 H, ArH), 8.12 (s, 1 H, ArH), 10.37 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.3, 24.4, 53.3, 55.7, 61.6, 105.6, 106.4, 121.0, 122.6, 136.0, 143.0, 150.0, 152.5, 171.4 ppm. MS (ES): m/z (%) = 314.11 (100) [M + 1]$^+$. EI-HRMS: calcd. for $C_{17}H_{19}N_3O_3$, 313.1426; found 313.1434.

6,7a,8,9,10,12-Hexahydro-7*H*-[1,3]dioxolo[4,5-*g*]pyrrolo[1′,2′:1,2]-[1,4]diazepino[5,6-*b*]quinolin-7-one (9e): The title compound was prepared following the above-described general procedure and after purification by crystallization using EtOAc [R_f = 0.65 (MeOH/CHCl$_3$, 05:95)] was obtained as a yellowish brown solid (0.045 g from 0.11 g); yield 49%; m.p. 151–153 °C; $[a]_D^{28}$ = 363 (c = 0.114, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1678 (CONH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.72–1.98 (m, 4 H, 2 CH$_2$), 2.27 (br. s, 1 H, C*H*H), 2.44–2.50 (m, 2 H, CH*H* and C*H*H), 2.98 (br. s, 1 H, CH*H*), 4.03 (d, J = 11.3 Hz, 1 H, CH), 6.18 (s, 2 H, OCH$_2$O), 7.17 (s, 1 H, ArH), 7.28 (s, 1 H, ArH), 8.09 (s, 1 H, ArH), 10.34 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.4, 24.3, 53.4, 61.6, 102.1, 102.8, 103.9, 122.4, 122.7, 136.8, 144.3, 146.9, 150.4, 150.9, 171.4 ppm. MS (ES): m/z (%) = 298.1 (100) [M + 1]$^+$. EI-HRMS: calcd. for $C_{16}H_{15}N_3O_3$ 297.1113; found 297.1119.

8,10,11,12,12a,14-Hexahydro-13*H*-benzo[*h*]pyrrolo[1′,2′:1,2][1,4]di-azepino[5,6-*b*]quinolin-13-one (9f): The title compound was prepared following the above-described general procedure and after purification by crystallization using EtOAc [R_f = 0.73 (MeOH/CHCl$_3$, 05:95)] was obtained as a yellowish brown solid (0.051 g from 0.12 g); yield 51%; m.p. 171–173 °C; $[a]_D^{29}$ = 123 (c = 0.100, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1672 (CONH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 1.78–1.87 (m, 3 H, CH$_2$ and C*H*H), 2.31 (br. s, 1 H, CH*H*), 2.50–2.59 (m, 1 H, C*H*H), 3.00 (br. s, 1 H, CH*H*), 3.62–3.66 (m, 2 H, CH$_2$), 4.17 (d, J = 12.3 Hz, 1 H, CH), 7.73 (t, J = 3.2 Hz, 2 H, ArH), 7.85 (dd, J_1 = 4.7, J_2 = 8.3 Hz, 2 H, ArH), 8.01, (s, 1 H, ArH), 8.37 (s, 1 H, ArH), 9.04 (d, J = 3.6 Hz, 1 H, ArH), 10.59 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.3, 24.8, 53.5, 62.3, 123.3, 123.8, 124.8, 125.0, 126.2, 126.7, 128.0, 128.2, 129.9, 133.5, 137.9, 143.9, 151.0, 171.8 ppm. MS (ES): m/z (%) = 304.1 (100) [M + 1]$^+$. $C_{19}H_{17}N_3O$ (303.1372): calcd. C 75.23, H 5.65, N 13.85; found C 75.11, H 5.73, N 13.78.

General Procedure for the Synthesis of Compounds 13a, 13f, 17a, 17d, 23, 27, 38a, 38e and 40 as Exemplified by Compound 13a: NaH (0.10 g, 4.00 mmol) was added to a stirred solution of compound **12** (0.20 g, 0.50 mmol) in dry THF (5 mL) at 0 °C and then the mixture was heated at reflux for 1 h. On completion of the reaction, excess THF was evaporated in vacuo and EtOAc was added to the residue. Then the contents were poured into water (20 mL) and extracted with EtOAc (5 × 15 mL). The combined organic layers were washed with brine (30 mL), dried with Na_2SO_4 and concentrated to yield a brown solid. The product was further purified on a short silica gel column using MeOH/CHCl$_3$ [3:97; R_f = 0.40 (MeOH/CHCl$_3$, 05:95)] as eluent to furnish 0.12 g (68%) of **13a** as a yellow solid.

6,7a,8,13,14,16-Hexahydro-7*H*-indolo[3′′,2′′:4′,5′]pyrido[1′,2′:1,2]-[1,4]diazepino[5,6-*b*]quinolin-7-one (13a): M.p. 210–212 °C; $[a]_D^{33}$ = 6.0 (c = 0.600, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1673 (CONH), 3385 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 2.65 (d, J = 14.2 Hz, 1 H, C*H*H), 3.09–3.19 (m, 2 H, CH$_2$), 3.79 (d, J = 14.7 Hz, 1 H, CH*H*), 3.92 (d, J = 14.6 Hz, 1 H, C*H*H), 4.06 (d, J = 14.7 Hz, 1 H, CH*H*), 4.23 (d, J = 14.6 Hz, 1 H, CH), 6.90–7.02 (m, 2 H, ArH), 7.25 (d, J = 7.8 Hz, 1 H, ArH), 7.37 (d, J = 7.5 Hz, 1 H, ArH), 7.55 (t, J = 7.5 Hz, 1 H, ArH), 7.71–7.76 (m, 1 H, ArH), 7.86 (d, J = 8.4 Hz, 1 H, ArH), 7.98 (d, J = 8.0 Hz, 1 H, ArH), 8.40 (s, 1 H, ArH), 10.72 (s, 1 H, NH), 10.75 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.9, 48.8, 55.3, 60.8, 105.8, 111.0, 117.5, 118.4, 120.5, 122.1, 125.6, 125.7, 126.7, 127.4, 127.8, 130.2, 131.8, 136.1, 138.8, 146.5, 152.0, 171.4 ppm. MS (ES): m/z (%) = 355.1.0 (100) [M + 1]$^+$. $C_{22}H_{18}N_4O$ (354.1481): calcd. C 74.56, H 5.12, N 15.81; found C 74.62, H 5.17, N 15.61.

6,7a,8,13,14,16-Hexahydro-7*H*-[1,3]dioxolo[4,5-*g*]indolo[3′′,2′′:4′,5′]pyrido[1′,2′:1,2][1,4]diazepino[5,6-*b*]quinolin-7-one (13e): The title compound was prepared following the above-described general procedure and after purification by column chromatography [MeOH/CHCl$_3$, 03:97; R_f = 0.38 (MeOH/CHCl$_3$, 05:95)] was obtained as a yellow solid (0.17 g from 0.25 g); yield 73%; m.p. 195–197 °C; $[a]_D^{33}$ = 15 (c = 0.600, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1669 (CONH), 3413 (NH) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 3.08 (d, J = 7.3 Hz, 2 H, CH$_2$), 3.73 (d, J = 14.5 Hz, 2 H, CH$_2$), 3.89 (d, J = 14.6 Hz, 1 H, C*H*H), 3.95 (d, J = 14.7 Hz, 1 H, CH*H*), 4.16 (d, J = 14.6 Hz, 1 H, CH), 6.18 (s, 2 H, OCH$_2$O), 6.88–7.02 (m, 2 H, ArH), 7.24 (t, J = 8.7 Hz, 2 H, ArH), 7.35 (s, 1 H, ArH), 7.37 (s, 1 H, ArH), 8.18 (s, 1 H, ArH), 10.56 (s, 1 H, NH), 10.72 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 23.9, 48.8, 55.3, 60.8, 102.2, 103.0, 104.0, 105.9, 111.1, 117.6, 118.5, 119.7, 120.7, 122.4, 126.7, 131.9, 136.2, 137.8, 144.7, 147.1, 150.2, 151.1, 171.4 ppm. MS (ES): m/z (%) = 399.0 (100) [M + 1]$^+$. $C_{23}H_{18}N_4O_3$ (398.1379): calcd. C 69.34, H 4.55, N 14.06; found C 69.55, H 4.29, N 13.88.

14-Phenyl-6,7a,8,13,14,16-hexahydro-7*H*-indolo[3′′,2′′:4′,5′]pyrido-[1′,2′:1,2][1,4]diazepino[5,6-*b*]quinolin-7-one (17a): The title compound was prepared following the above-described general pro-

cedure (**13a**) and after purification by using short silica gel column [EtOAc/hexane, 25:75; R_f = 0.50 (hexane/EtOAc, 20:80)] was obtained as a yellow solid (0.09 g from 0.25 g); yield 37%; m.p. 194–196 °C; $[a]_D^{32}$ = 118 (*c* = 0.126, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1665 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.30, 3.32 (dd, J_1 = 4.1, J_2 = 15.3 Hz, 1 H, C*H*H), 3.79 (d, *J* = 15.0 Hz, 1 H, CH*H*), 4.10 (d, *J* = 16.2 Hz, 1 H, C*H*H), 4.32 (d, *J* = 16.2 Hz, 1 H, CH*H*), 4.48 (d, *J* = 3.6 Hz, 1 H, CH), 4.93 (s, 1 H, ArCH), 7.07–7.18 (m, 6 H, ArH), 7.33 (d, *J* = 7.6 Hz, 3 H, ArH), 7.45 (t, *J* = 7.6 Hz, 1 H, ArH), 7.60 (t, *J* = 4.1 Hz, 1 H, ArH), 7.68 (d, *J* = 9.3 Hz, 3 H, ArH and NH), 7.86 (d, *J* = 8.7 Hz, 1 H, ArH), 8.51 (br. s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 23.9, 55.8, 59.8, 62.8, 107.6, 110.9, 118.8, 119.6, 122.0, 122.4, 125.6, 127.0, 127.1, 127.6, 128.7, 128.9, 129.0, 130.4, 133.3, 136.8, 138.6, 139.9, 146.8, 149.6, 173.8 ppm. MS (ES): *m*/*z* (%) = 431.0 (100) $[M + 1]^+$. EI-HRMS: calcd. for $C_{28}H_{22}N_4O$ 430.1794; found 430.1764.

2,3-Dimethoxy-14-phenyl-6,7a,8,13,14,16-hexahydro-7*H*-indolo-[3′′,2′′:4′,5′]pyrido[1′,2′:1,2][1,4]diazepino[5,6-*b*]quinolin-7-one (17d): The title compound was prepared following the above-described general procedure as for **13a** and after purification by crystallization using EtOAc [R_f = 0.50 (MeOH/$CHCl_3$, 05:95)] was obtained as a yellow solid (0.21 g from 0.25 g); yield 46%; m.p. 151–153 °C; $[a]_D^{29}$ = 831 (*c* = 0.232, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1666 (CONH), 3021 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.30 (d, *J* = 12.9 Hz, 1 H, C*H*H), 3.78 (d, *J* = 15.8 Hz, 1 H, CH*H*), 3.95 (d, *J* = 16.2 Hz, 1 H, C*H*H), 4.02 (s, 3 H, OCH_3), 4.05 (s, 3 H, OCH_3), 4.29 (d, *J* = 16.2 Hz, 1 H, CH*H*), 4.46 (s, 1 H, CH), 4.93 (s, 1 H, ArCH), 6.92 (s, 1 H, ArH), 7.10 (s, 3 H, ArH), 7.18 (d, *J* = 6.0 Hz, 3 H, ArH), 7.25 (s, 2 H, ArH), 7.33 (s, 2 H, ArH), 7.49 (s, 1 H, NH), 7.58 (d, *J* = 7.0 Hz, 1 H, ArH), 8.35 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 23.4, 54.5, 55.3, 55.6, 59.9, 60.3, 105.4, 105.9, 106.1, 111.1, 117.9, 118.3, 120.3, 120.5, 120.7, 126.4, 127.9, 128.4, 128.7, 134.1, 136.3, 136.7, 140.9, 142.7, 148.5, 148.8, 152.5, 173.0 ppm. MS (ES): *m*/*z* (%) = 491.1 (100) $[M + 1]^+$. $C_{30}H_{26}N_4O_3$ (490.2005): calcd. C 73.45, H 5.34, N 11.42; found C 73.53, H 5.44, N 11.34.

4-(*p*-Tosyl)-4,5-dihydro-1*H*-[1,4]diazepino[5,6-*b*]quinolin-2(3*H*)-one (23): The title compound was prepared following the above-described general procedure as for **13a** and after purification by column chromatography [MeOH/$CHCl_3$, 02:98; R_f = 0.50 (MeOH/$CHCl_3$, 05:95)] was obtained as a white solid (0.05 g from 0.20 g); yield 30%; m.p. 200–201 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1663 (CONH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 2.26 (s, 3 H, $ArCH_3$), 4.20 (s, 2 H, CH_2), 4.63 (s, 2 H, CH_2), 7.18 (d, *J* = 7.9 Hz, 2 H, ArH), 7.50–7.57 (m, 3 H, ArH), 7.72 (d, *J* = 7.5 Hz, 2 H, ArH), 7.87 (t, *J* = 7.9 Hz, 1 H, ArH), 8.26 (s, 1 H, ArH), 10.56 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 21.0, 49.3, 52.3, 121.2, 125.1, 125.7, 127.0, 127.2, 127.6, 129.7, 130.5, 134.7, 138.5, 143.8, 146.0, 149.7, 167.9 ppm. MS (ES): *m*/*z* (%) = 368.1 (100) $[M + 1]^+$. $C_{19}H_{17}N_3O_3S$ (367.0991): calcd. C 62.11, H 4.66, N 11.44; found C 62.23, H 4.54, N 11.25.

Ethyl 2-[2-Oxo-1,4-dihydro-2*H*-pyrimido[4,5-*b*]quinolin-3-yl]acetate (27): The title compound was prepared following the above-described general procedure as for **13a** and after purification by crystallization with EtOAc [R_f = 0.50 (MeOH/$CHCl_3$, 05:95)] was obtained as a white solid (0.27 g from 0.33 g); yield 90%; m.p. 195–196 °C. IR (KBr): $\tilde{\nu}_{max}$ = 1718 (CO_2Et), 1676 (CONH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.24 (t, *J* = 7.1 Hz, 3 H, OCH_2CH_3), 4.10 (q, *J* = 7.1 Hz, 2 H, OCH_2CH_3), 4.63 (s, 2 H, CH_2), 4.66 (s, 2 H, CH_2), 7.47 (s, 1 H, ArH), 7.68 (s, 1 H, ArH), 7.76 (t, *J* = 7.4 Hz, 1 H, ArH), 7.83 (s, 1 H, ArH), 8.08 (s, 1 H, ArH), 8.44 (s, 1 H, NH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.6, 49.4, 52.8, 62.5, 122.3, 122.6, 125.6, 126.0, 127.5, 127.6, 127.8, 130.6, 138.2, 146.5, 170.3, 170.5 ppm. MS (ES): *m*/*z* (%) = 286.1 (100) $[M + 1]^+$. $C_{15}H_{15}N_3O_3$ (285.1113): calcd. C 63.15, H 5.30, N 14.73; found C 63.27, H 5.42, N 14.54.

3-[(1*H*-Indol-3-yl)methyl]-1,3,4,5-tetrahydro-2*H*-[1,4]diazepino[5,6-*b*]-quinolin-2-one (38a): The title compound was prepared following the above-described general procedure as for **13a** and after purification by crystallization with EtOAc [R_f = 0.50 (MeOH/$CHCl_3$, 5:95)] was obtained as a yellow solid (0.09 g from 0.18 g); yield 49%; m.p. 205–207 °C; $[a]_D^{34}$ = 130 (*c* = 0.600, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1670 (CONH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 2.84–2.91 (m, 1 H, C*H*H), 3.18–3.25 (m, 2 H, CH_2), 3.62 (br. s, 1 H, CH*H*), 3.95 (s, 2 H, CH_2), 6.88 (t, *J* = 7.6 Hz, 1 H, ArH), 7.00 (t, *J* = 7.6 Hz, 1 H, ArH), 7.07 (s, 1 H, ArH), 7.28 (d, *J* = 7.5 Hz, 1 H, ArH), 7.46 (d, *J* = 7.2 Hz, 1 H, ArH), 7.67 (t, *J* = 7.2 Hz, 1 H, ArH), 7.77 (d, *J* = 8.0 Hz, 1 H, ArH), 7.85 (d, *J* = 7.5 Hz, 1 H, ArH), 8.15 (s, 1 H, ArH), 10.41 (s, 1 H, NH), 10.77 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 27.3, 47.9, 60.4, 110.9, 111.3, 118.2, 120.8, 123.8, 125.3, 125.7, 126.6, 127.1, 127.4, 129.8, 136.0, 136.9, 146.0, 152.1, 173.7 ppm. MS (ES): *m*/*z* (%) = 343.1 (100) $[M + 1]^+$. EI-HRMS: calcd. for $C_{22}H_{18}N_4O$ 342.1481; found 342.0749.

3-[(1*H*-Indol-3-yl)methyl]-1,3,4,5-tetrahydro-2*H*-[1,4]diazepino[5,6-*b*]-[1,3]dioxolo[4,5-*g*]quinolin-2-one (38e): The title compound was prepared following the above-described general procedure as for **13a** and after purification by column chromatography [MeOH/$CHCl_3$, 02:98; R_f = 0.48 (MeOH/$CHCl_3$, 05:95)] was obtained as a yellow solid (0.16 g from 0.45 g); yield 41%; m.p. 124–126 °C; $[a]_D^{24}$ = 271 (*c* = 0.118, DMSO). IR (KBr): $\tilde{\nu}_{max}$ = 1663 (CONH) cm^{-1}. ^1H NMR (300 MHz, $[D_6]$DMSO): δ = 2.81–2.86 (m, 1 H, C*H*H), 3.15–3.22 (m, 2 H, CH_2), 3.34–3.54 (m, 1 H, CH*H*), 3.87 (br. s, 2 H, CH and NH), 6.16 (s, 2 H, OCH_2O), 6.88 (t, *J* = 7.1 Hz, 1 H, ArH), 6.97–7.05 (m, 2 H, ArH), 7.12 (s, 1 H, ArH), 7.26 (t, *J* = 8.1 Hz, 2 H, ArH), 7.44 (d, *J* = 7.8 Hz, 1 H, ArH), 8.00 (s, 1 H, ArH), 10.23 (s, 1 H, NH), 10.77 (s, 1 H, CONH) ppm. ^{13}C NMR (75 MHz, $[D_6]$DMSO): δ = 27.1, 47.7, 59.9, 101.9, 102.7, 103.8, 111.0, 111.3, 118.2, 118.3, 120.8, 122.2, 123.7, 124.1, 127.4, 136.0, 136.1, 143.9, 146.6, 150.3, 150.6, 173.4 ppm. MS (ES): *m*/*z* (%) = 387.1 (100) $[M + 1]^+$. $C_{22}H_{18}N_4O_3$ (386.1379): calcd. C 68.38, H 4.70, N 14.50; found C 68.44, H 4.82, N 14.34.

3-Benzyl-1,3,4,5-tetrahydro-2*H*-[1,4]diazepino[5,6-*b*]quinolin-2-one (39): The title compound was prepared following the above-described general procedure as for **13a** and after purification by column chromatography [hexane/EtOAc, 30:70; R_f = 0.50 (hexane/EtOAc, 60:40)] was obtained as a yellow solid (0.20 g from 0.35 g); yield 66%; m.p. 164–166 °C; $[a]_D^{24}$ = –42 (*c* = 0.252, $CHCl_3$). IR (KBr): $\tilde{\nu}_{max}$ = 1667 (CONH), 3420 (NH) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 3.05 (dd, J_1 = 8.2, J_2 = 13.7 Hz, 1 H, C*H*H), 3.37 (dd, J_1 = 4.2, J_2 = 13.7 Hz, 1 H, CH*H*), 3.97 (t, *J* = 6.5 Hz, 2 H, CH_2), 4.20 (d, *J* = 14.9 Hz, 1 H, CH), 7.23 (t, *J* = 8.1 Hz, 5 H, ArH), 7.44 (t, *J* = 7.4 Hz, 1 H, ArH), 7.63–7.72 (m, 2 H, ArH), 7.88 (d, *J* = 9.5 Hz, 1 H, ArH), 8.50 (br. s, 1 H, CONH) ppm. ^{13}C NMR (50 MHz, $[D_6]$DMSO): δ = 38.6, 49.2, 63.0, 109.7, 125.7, 125.8, 126.9, 127.2, 127.7, 128.7, 129.5, 130.3, 137.0, 137.8, 146.5, 150.6, 174.6 ppm. MS (ES): *m*/*z* (%) = 304.1 (100) $[M + 1]^+$. DART-HRMS (ES+): calcd. for $C_{19}H_{17}N_3O$ 303.1372; found 303.1365.

Typical Procedure for the Synthesis of Compound 18: Et_3N (0.42 mL, 3.04 mmol) was added to a stirred solution of the glycine ethyl ester hydrochloride salt (0.42 g, 3.04 mmol) in dry MeOH (10 mL) and the mixture was stirred for 15 min at room temperature. Then a solution of **2a** (0.50 g, 2.03 mmol) in MeOH (80 mL)

was added dropwise to the reaction. After completion of the reaction, as monitored by TLC, MeOH was evaporated in vacuo and the residue was extracted with EtOAc (3 × 30 mL) and water (70 mL). The organic layers were combined and washed with brine (50 mL), dried with Na_2SO_4 and concentrated to yield the crude product. Purification by column chromatography through a short column using hexane/EtOAc (25:75, v/v) afforded 0.50 g (85%) of pure **18** as a yellow oil.

Ethyl 2-{[(*Z*)-2-Cyano-3-(2-nitrophenyl)prop-2-enyl]amino}acetate (18): R_f = 0.50 (hexane/EtOAc, 30:70). IR (KBr): $\tilde{\nu}_{max}$ = 1734 (CO_2Et), 2221 (CN) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.30 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 3.51 (s, 2 H, CH_2), 3.68 (s, 2 H, CH_2), 4.22 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.26 (s, 1 H, NH), 7.56–7.70 (m, 2 H, ArCH and ArH), 7.77 (t, J = 7.5 Hz, 2 H, ArH), 8.19 (d, J = 8.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.3, 49.5, 52.2, 61.2, 115.2, 117.1, 125.2, 129.9, 130.6, 131.0, 134.2, 141.4, 172.2 ppm. MS (ES): *m*/*z* (%) = 290.1 (100) $[M + 1]^+$. $C_{14}H_{15}N_3O_4$ (289.1063): calcd. C 58.13, H 5.23, N 14.53; found C 58.33, H 5.39, N 14.37.

Typical Procedure for the Synthesis of Compound 25: K_2CO_3 (0.29 g, 2.07 mmol) was added to a solution of **18** (0.50 g, 1.73 mmol) in dry THF (10 mL) and the mixture was stirred for 15 min at room temperature. Subsequently, cyanogen bromide (0.22 g, 2.07 mmol) was added and the reaction was allowed to proceed for 3 h at room temperature. After completion of the reaction, as monitored by TLC, THF was evaporated and the residue was extracted with EtOAc (3 × 30 mL) and water (70 mL). The organic layers were combined and washed with brine (50 mL), dried with Na_2SO_4 and concentrated to yield the crude product. Purification by column chromatography using hexane/EtOAc (30:70, v/v) afforded 0.47 g (87%) of pure **25** as a white solid.

Ethyl 2-{Cyano[(*Z*)-2-cyano-3-(2-nitrophenyl)prop-2-enyl]amino}-acetate (25): M.p. 125–127 °C; R_f = 0.48 (hexane/EtOAc, 30:70). IR (KBr): $\tilde{\nu}_{max}$ = 1747 (CO_2Et), 2222 (CN) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.34 (t, 3 H, OCH_2CH_3), 3.96 (s, 2 H, CH_2), 4.19 (s, 2 H, CH_2), 4.31 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 7.64–7.70 (m, 1 H, ArH), 7.75 (s, 1 H, ArH), 7.80 (d, J = 4.1 Hz, 2 H, ArH), 8.26 (d, J = 8.1 Hz, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, $CDCl_3$): δ = 14.2, 51.6, 55.2, 62.4, 109.6, 115.7, 115.8, 125.4, 128.9, 131.1, 131.4, 134.7, 146.1, 167.6 ppm. MS (ES): *m*/*z* (%) = 314.9 (50) $[M + 1]^+$. $C_{15}H_{14}N_4O_4$ (314.1015): calcd. C 57.32, H 4.49, N 17.83; found C 57.53, H 4.53, N 17.65.

General Procedure for the Synthesis of Compounds 21 and 32 as Exemplified for Compound 21: Et_3N (0.36 mL, 2.60 mmol) and DMAP (catalytic amount) were added to a solution of **18** (0.50 g, 1.73 mmol) in dry CH_2Cl_2 (10 mL) and the mixture was stirred for 15 min at 0 °C. Thereafter *p*-tosyl chloride (0.41 g, 2.16 mmol) was added to the reaction and the mixture was allowed to proceed at room temperature for 15 h. After completion of the reaction, as monitored by TLC, the residue was extracted with CH_2Cl_2 (3 × 30 mL) and water (70 mL). The combined organic layers were washed with a 10% $NaHCO_3$ solution (30 mL) and brine (30 mL), dried with Na_2SO_4 and concentrated to yield the crude product. Purification by column chromatography using hexane/EtOAc (20:80, v/v) afforded 0.64 g (84%) of pure **21** as a colourless oil.

Ethyl 2-{[(*Z*)-2-Cyano-3-(2-nitrophenyl)prop-2-enyl](methylphenylsulfonamido)amino}acetate (21): R_f = 0.52 (hexane/EtOAc, 30:70). IR (neat): ῡmax = 1738 (CO_2Et), 2223 (CN) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.22 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 2.43 (s, 3 H, $ArCH_3$), 4.10 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.22 (s, 2 H, CH_2), 4.37 (s, 2 H, CH_2), 7.32 (d, J = 7.6 Hz, 2 H, ArH), 7.63 (d, J = 7.6 Hz, 2 H, ArH), 7.77 (t, J = 7.6 Hz, 4 H, ArH), 8.21 (d, J = 8.1 Hz, 2 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.6, 44.2, 50.7, 106.1, 110.5, 110.7, 127.6, 128.9, 129.1, 129.9, 130.8, 133.0, 136.6, 143.1, 143.9, 146.0, 148.8 ppm. MS (ES): *m*/*z* (%) = 444.0 (100) $[M + 1]^+$. $C_{21}H_{21}N_3O_6S$ (443.1151): calcd. C 56.87, H 4.77, N 9.48; found C 56.92, H 4.83, N 9.33.

Typical Procedure for the Synthesis of Compound 24: Et_3N (0.48 mL, 3.46 mmol) was added to a stirred solution of **18** (0.50 g, 1.73 mmol) in dry CH_2Cl_2 (10 mL) and the reaction was stirred at room temperature for a further 15 min. Subsequently ethyl chloroacetate (0.28 mL, 2.60 mmol) in CH_2Cl_2 was added dropwise at 0 °C and the mixture was stirred for a further 1 h at the same temperature. On completion, as monitored by TLC, the contents were poured into water (50 mL) and extracted with CH_2Cl_2 (3 × 40 mL). The usual work-up followed by purification by column chromatography using hexane/EtOAc [80:20; R_f = 0.60 (hexane/EtOAc, 30:70)] furnished 0.53 g (93%) of **24** as a colourless oil.

Ethyl 2-{[(*Z*)-2-Cyano-3-(2-nitrophenyl)prop-2-enyl](ethoxycarbonyl)-amino}acetate (24): IR (neat): $\tilde{\nu}_{max}$ = 1708 (CO_2Et), 1745 (CO_2Et), 2222 (CN) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ = 1.22–1.35 (m, 6 H, 2 OCH_2CH_3), 4.11 (s, 2 H, CH_2), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.32 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 4.39 (s, 2 H, CH_2), 7.61 (t, J = 6.7 Hz, 2 H, ArH), 7.77 (d, J = 6.7 Hz, 2 H, ArH), 8.22 (d, J = 8.0 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.3, 14.6, 48.7, 51.1, 61.6, 62.8, 112.5, 116.5, 125.3, 131.0, 131.1, 134.4, 142.4, 142.7, 147.2, 156.1, 169.5 ppm. MS (ES): *m*/*z* (%) = 362.0 (80) $[M + 1]^+$. $C_{17}H_{19}N_3O_6$ (361.1274): calcd. C 56.51, H 5.30, N 11.63; found C 56.67, H 5.43, N 11.55.

Typical Procedure for the Synthesis of Compound 29: A mixture of **19** (0.20 g, 0.77 mmol), 2-nitrobenzaldehyde (0.14 g, 0.93 mmol), H_2O_2 (0.26 mL, 3.86 mmol) and $[NH_4Ce(NO_3)_6]$ (0.04 g, 0.08 mmol) was heated at 50 °C for 15 h, after which the reaction mixture was poured into ice/water and extracted with EtOAc (3 × 30 mL). The usual work-up of the organic layer followed by purification by column chromatography using hexane/EtOAc [65:35; R_f = 0.35 (hexane/EtOAc, 60:40)] as eluent gave 0.09 g (30%) of **29** as a yellow solid.

Ethyl 2-[2-(2-Nitrophenyl)-1,4-dihydro-2*H*-pyrimido[4,5-*b*]quinolin-3-yl]acetate (29): M.p. 153–155 °C. IR (KBr): $\tilde{\nu}_{max}$ = 3192 (NH), 1718 (CO_2Et) cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ = 1.25 (t, J = 7.1 Hz, 3 H, OCH_2CH_3), 3.36 (d, J = 16.2 Hz, 1 H, C*H*H), 3.53 (d, J = 16.2 Hz, 1 H, CH*H*), 3.66 (d, J = 17.0 Hz, 1 H, C*H*H), 3.86 (d, J = 17.0 Hz, 1 H, CH*H*), 4.16 (q, J = 7.1 Hz, 2 H, OCH_2CH_3), 6.21 (s, 1 H, ArCH), 7.23–7.29 (m, 1 H, ArH), 7.42–7.49 (m, 2 H, ArH), 7.50–7.59 (m, 3 H, ArH), 7.65–7.70 (m, 2 H, ArH), 7.82–7.85 (m, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, $CDCl_3$): δ = 14.2, 47.0, 55.1, 61.0, 70.4, 115.8, 122.8, 124.2, 125.3, 125.4, 127.4, 128.9, 129.3, 129.7, 132.2, 135.0, 135.6, 147.2, 149.0, 152.8, 169.8 ppm. MS (ES): *m*/*z* (%) = 393.1 (100) $[M + 1]^+$. $C_{21}H_{20}N_4O_4$ (392.1485): calcd. C 64.28, H 5.14, N 14.28; found C 64.17, H 5.23, N 14.35.

Typical Procedure for the Synthesis of Compound 34: A 50% aq. solution of TFA (2.00 mL) was added to a solution of **33** (0.10 g, 0.24 mmol) in $CHCl_3$ (5 mL) and the mixture was stirred for 5 d at room temperature. After completion of the reaction, as monitored by TLC, the mixture was poured into a 10% aq. $NaHCO_3$ solution whilst stirring. The aqueous layer was further extracted with $CHCl_3$ (4 × 20 mL). The organic layers were combined and washed with brine (50 mL), dried with Na_2SO_4 and concentrated to yield the crude product. Purification by column chromatography using MeOH/$CHCl_3$ (2:98, v/v) afforded 0.03 g (35%) of pure **34** as a yellow solid.

(*Z*)-4-(*p*-Tosyl)-4,5-dihydro-3*H*-[1,4]diazepino[5,6-*b*]quinoline (34): M.p. 200–202 °C; R_f = 0.63 (MeOH/$CHCl_3$, 05:95). ^1H NMR

(300 MHz, [D$_6$]DMSO): δ = 2.05 (s, 3 H, ArCH$_3$), 4.62 (s, 2 H, CH$_2$), 5.70 (d, J = 3.8 Hz, 1 H, CH$_2$), 7.01 (d, J = 8.1 Hz, 1 H, ArH), 7.30 (t, J = 7.8 Hz, 1 H, ArH), 7.46–7.54 (m, 4 H, ArH), 7.71 (d, J = 7.7 Hz, 1 H, ArH), 7.87 (s, 1 H, ArH), 8.76 (s, 1 H, =CH) ppm. ^{13}C NMR (50 MHz, [D$_6$]DMSO): δ = 20.7, 40.1, 51.2, 106.1, 119.1, 120.1, 123.3, 123.4, 125.6, 127.1, 127.5, 129.3, 129.9, 135.1, 137.7, 143.3, 146.4, 155.7 ppm. MS (ES): *m*/*z* (%) = 352.1 (100) [M + 1]$^+$. $C_{19}H_{17}N_3O_2S$ (351.4222): calcd. C 64.94, H 4.88, N 11.96; found C 65.03, H 4.79, N 11.89.

Typical Procedure for the Synthesis of Compound 40: K_2CO_3 (0.66 g, 4.88 mmol) was added to a stirred solution of phthalimide (0.60 g, 4.07 mmol) in dry DMF (10 mL) and the reaction was allowed to proceed for 15 min at room temperature. After that **2a** (1.00 g, 4.07 mmol) was added and the reaction as allowed to proceed for a further 2 h. After completion of the reaction, as monitored by TLC, the mixture was poured into water (150 mL) whilst stirring. A solid separated out, which was filtered and redissolved in EtOAc (100 mL), washed with brine (40 mL), dried with Na_2SO_4 and concentrated to yield a crude solid product. The product was further purified by crystallization with EtOAc to afford 1.15 g (85%) of pure **40** as a white solid in a 10:1 ratio of the *Z*/*E* isomers.

(*Z*)-2-[(1,3-Dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-3-(2-nitrophenyl)prop-2-enenitrile (40): M.p. 179–181 °C; R_f = 0.48 (hexane/EtOAc, 20:80). IR (KBr): $\tilde{\nu}_{max}$ = 1720 (CO) cm^{-1}. ^{1}H NMR (300 MHz, CDCl$_3$): δ = 4.43 (d, J = 1.3 Hz, 2 H, CH$_2$), 4.69 (d, J = 1.2 Hz, 2 H, CH$_2$), 7.58–7.64 (m, 1 H, ArH), 7.70–7.81 (m, 6 H, ArCH and ArH), 7.84–7.96 (m, 2 H, ArH), 8.19–8.32 (m, 1 H, ArH) ppm. ^{13}C NMR (50 MHz, CDCl$_3$): δ = 40.4, 111.0, 124.0, 125.3, 129.2, 131.0, 131.9, 134.4, 134.6, 143.9, 167.3 ppm. MS (ES): *m*/*z* (%) = 334.1 (100) [M + 1]$^+$. $C_{18}H_{11}N_3O_4$ (333.0750): calcd. C 64.86, H 3.33, N 12.61; found C 64.97, H 3.42, N 12.52.

Typical Procedure for the Synthesis of Compound 41: $NaBH_4$ (0.16 g, 4.20 mmol) was added in portions to a stirred solution of **40** (0.70 g, 2.10 mmol) in dry MeOH (15 mL) and the mixture was stirred for a further 10 min at room temperature. Then MeOH was evaporated in vacuo and the residue was extracted with EtOAc (3 × 30 mL) and water (70 mL). The organic layers were combined and washed with brine (30 mL), dried with Na_2SO_4 and concentrated to yield a white solid. The product was further purified by crystallization with EtOAc to afford 0.45 g (60%) of pure **41** as a white solid in a 10:1 ratio of the *Z*/*E* isomers.

(*Z*)-2-[(1-Hydroxy-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-3-(2-nitrophenyl)prop-2-enenitrile (41): M.p. 145–147 °C; R_f = 0.35 (hexane/EtOAc, 50:50). IR (KBr): $\tilde{\nu}_{max}$ = 3244 (OH), 2226 (CN), 1683 (CO), 1665 (CO) cm^{-1}. ^{1}H NMR (300 MHz, [D$_6$]DMSO): δ = 4.27 (d, J = 15.8 Hz, 2 H, 2 C*H*H), 4.65–4.72 (m, 2 H, 2 CH*H*), 5.95 (d, J = 8.9 Hz, 1 H, CHO*H*), 6.03 (d, J = 9.1 Hz, 1 H, CHO*H*), 6.71 (d, J = 9.1 Hz, 1 H, C*H*OH), 6.82 (d, J = 8.9 Hz, 1 H, C*H*OH), 7.55–7.61 (m, 3 H, ArCH and ArH), 7.66–7.70 (m, 5 H, ArH), 7.74 (d, J = 7.4 Hz, 2 H, ArH), 7.82–7.91 (m, 6 H, ArH), 8.08 (dd, J_1 = 1.7, J_2 = 8.1 Hz, 1 H, ArH), 8.21 (dd, J_1 = 0.8, J_2 = 8.2 Hz, 1 H, ArH) ppm. ^{13}C NMR (75 MHz, [D$_6$]DMSO): δ = 32.1, 41.3, 80.5, 81.4, 111.9, 116.8, 122.7, 123.7, 123.9, 124.9, 125.1, 128.9, 129.4, 129.5, 130.8, 130.9, 131.0, 132.1, 132.5, 133.1, 133.8, 134.4, 143.2, 145.0, 147.0, 166.2, 166.6 ppm. MS (ES): *m*/*z* (%) = 336.0 (100) [M + 1]$^+$, 358.1 (100) [M + Na]$^+$. $C_{18}H_{13}N_3O_4$ (335.0906): calcd. C 64.47, H 3.91, N 12.53; found C 64.63, H 3.98, N 12.37.

Supporting Information (see also the footnote on the first page of this article): The spectroscopic data for all the remaining compounds and copies of the ^{1}H and ^{13}C NMR spectra for all compounds.

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