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Reductive-cyclization-mediated syntheses of fused polycyclic quinolines from the Baylis-Hillman adducts of acrylonitrile: Scope and limitations[§]

Virender Singh, Samiran Hutait and Sanjay Batra*

Dedicated to Prof. Raymond C. F. Jones on 60th Birthday

Keywords: Baylis-Hillman / acrylonitrile / reductive-cyclization / intramolecular cyclization / quinoline / annulation

Syntheses of a variety of polycyclic quinolines are described. The target molecules were obtained in two steps through initial reductive cyclization succeeded by another intramolecular cyclization in the allyl amines afforded either from the acetates or the allyl bromides of Baylis-Hillman adducts of 2-nitrobenzaldehydes and acrylonitrile. The two steps proceeded in one-pot for the substrates wherein formyl or hydroxyl group reacted with the amino group of 2-aminoquinoline for second intramolecular cyclization. On the contrary, basic medium was necessary for second intramolecular cyclization in the substrates where alkoxycarbonyl group and the amino-group group participated.

[a] Medicinal and Process Chemistry Division, Central Drug Research Institute, PO Box 173, Lucknow 226001, India
Fax+91-522-2623405, 2623938
E-mail: batra_san@yahoo.co.uk, s_batra@cdri.res.in
§ CDRI Communication no. **7610**

Introduction

Heterocyclic chemistry has been the frontier area of chemical research owing to the importance of a variety of heterocycles in the pharmaceutical, agrochemical and electronic industry. Amongst heterocyclic systems, syntheses of new polycyclic systems, especially the ones, incorporating privileged scaffolds is of great interest owing to their resemblance with natural products. In this context several elegant synthetic protocols involving multicomponent reactions, transition-metal catalyzed cyclizations, ring-closing metathesis and so on have been developed. Nevertheless, new alternative strategies to access them in cheap simplified fashion 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 disclosure of many new quinoline derivatives.[3] Notably, however, majority of routes to accomplish these syntheses take advantage of participation of the aromatic amino group and the carbonyl group originating from Baylis-Hillman derivatives of 2-nitrobenzaldehyde and acrylate or (cyclo)alkenone. On the other hand participation of the aromatic amino group and the nitrile group in the derivatives of 2-nitrobenzaldehyde and acrylonitrile for similar results remains unexplored. But literature incorporates a precedence wherein Yang et al. accomplished the synthesis of 2-aminoquinoline via Fe-AcOH-mediated intramolecular reductive cyclization in a derivative of 2-nitrobenzaldehyde with participation of the nitrile functionality.[4] In our continuing interest to develop general strategies for furnishing aza-heterocycles via Baylis-Hillman chemistry, we considered it worthwhile to investigate the potential of the Baylis-Hillman derivatives of 2-nitrobenzaldehydes and acrylonitrile for affording the polycyclic quinoline systems via reductive cyclization as the key step.

Retrosynthetic approach showed that quinoline-annulated architecture containing at least 3-different ring systems could be easily built up from appropriate allyl amines afforded from the Baylis-Hillman adduct of 2-nitrobenzaldehyde and acrylonitrile (fig. 1). More importantly the *Z*-stereochemistry of allyl amines generated from these reactants would assist the envisaged cyclizations. In principle, a S_N2'-reaction of a nucleophilic species such as imidazole-2-carbaldehyde with the acetyl derivative **(I)** or S_N2-reaction of the nucleophile with the allyl bromide **(II)** of the aforementioned adduct would lead to a substrate **(III)** which upon reduction of the aromatic nitro-group may trigger a domino process involving two successive intramolecular cyclizations to furnish the polycyclic system **(V)**. Alternatively, using proline ester as the nucleophilic partner in place of imidazole-2-carbaldehyde would give a system **VIII** via similar series of reaction. Consequently we have now carried out a detailed study with respect to understanding the scope and limitation of this strategy for the synthesis of diverse polycyclic quinoline systems from differently substituted allyl amines. Herein, we report results of this endeavour which can now be treated as a general and practical approach to such new 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] Notably, these reactions were carried

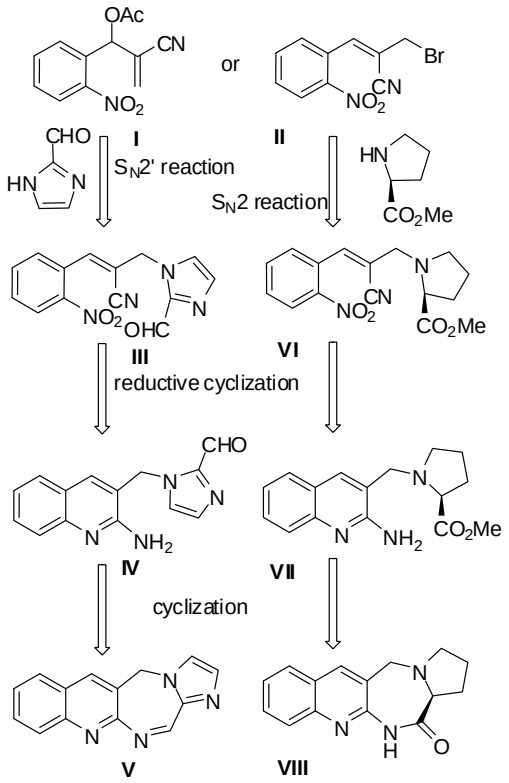
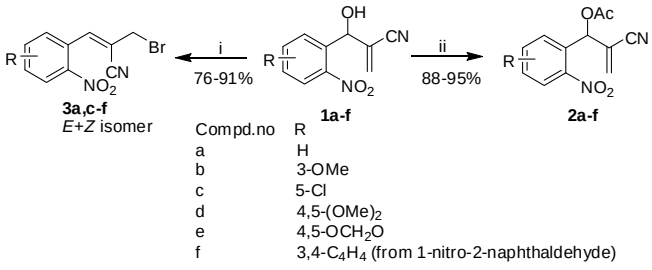


Figure 1. Retrosynthetic strategy for generating polycyclic quinolines

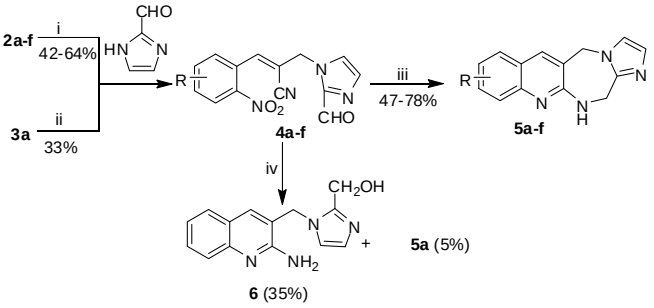
out in neat and were extremely fast to be over in less than 2 h. Acetylation of **1a-f** with acetyl chloride in the presence of pyridine provided the acetate **2a-f** in 88-95% yield (Scheme 1). On the other hand, allyl bromides **3a,c-f** were prepared from the reaction of **1a,c-f** with PBr_3 in CH_2Cl_2 in 76-91% yield.[6] Products **3a,c-f** were obtained as mixture of *E* and *Z* isomer which were not separated due to their close proximity on the tlc plate.



Compd.no	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-rt, 3 h. ii) AcCl, pyridine, CH_2Cl_2, 0°C-rt, 30 min

Compound **2a** and **3a** were simultaneously evaluated as the starting substrates to explore the optimal condition 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. Stereochemistry of **4a** was observed to be *Z* with no trace of *E*-isomer. Alternatively, substitution reaction 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 allyl amine **4a** in 33% yield. Herein relative stereochemistry of the product was assigned as *Z* with minor amount of *E*-isomer. In the attempt to enhance the yield of **4a** it was decided to initially perform the S_N2'-S_N2' displacement reaction with the imidazole-2-carbaldehyde in the presence of DABCO in aqueous medium and then subject the resulting product to 1,3-migration under a suitable condition 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% yields. To our delight, the spectroscopic data of the product was identical to that of **4a** as *Z*-isomer only (Scheme 2). Next we screened several metal-based reducing agents under different conditions to carry out reduction of the aromatic nitro group which would eventually trigger the intended domino process leading to the polycyclic quinoline system (see SI). It was satisfying to discover that heating the substrate **4a** in the presence of Fe-AcOH led to a clean reaction. Usual workup followed by triturating the afforded residue furnished a solid product (57%), the structure of which was



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

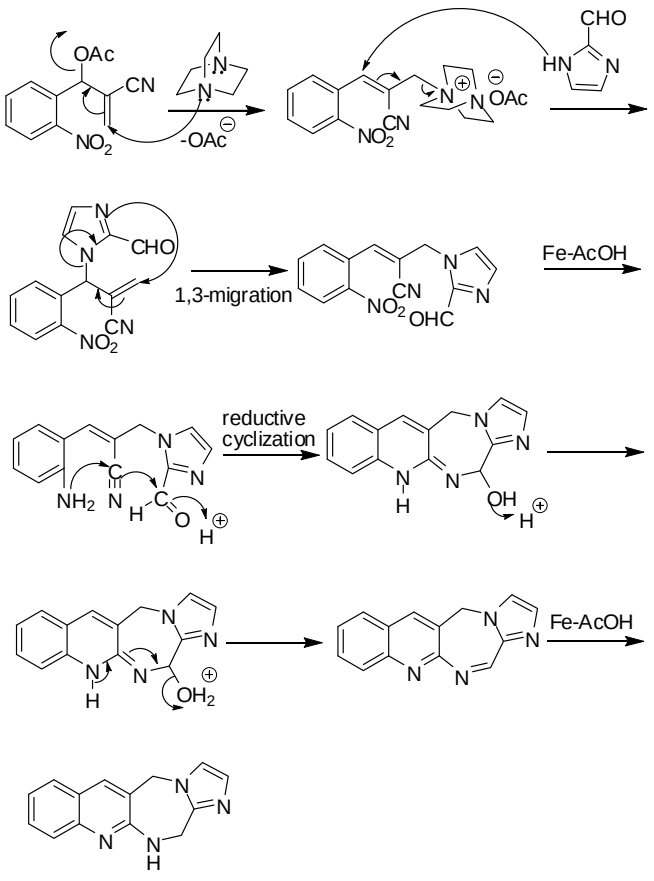
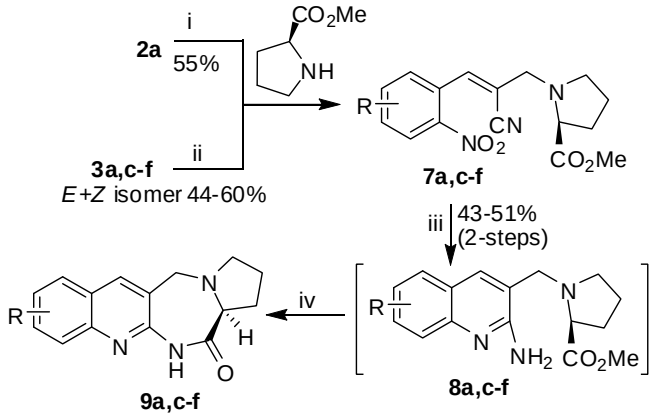


Figure 2. Mechanism for the formation of **5**

delineated as **5a**. On the basis of this result, the proposed mechanism for the formation of **5a** is presented in figure 2. Isolation of **5a** implied that initially the reductive cyclization take place as expected followed by another intramolecular cyclization via a Schiff's base formation between the generated 2-amino group of the resulting quinoline unit and the formyl functionality of the imidazole group. Subsequently the reaction condition induces reduction of double bond of the intermediate imine leading to the final product. Even the reaction in the presence of Zn-AcOH was clean but the isolated yield (49%) of **5a** was observed to be slightly lower. Interestingly, the reaction of **4a** with In-HCl yielded a mixture of two products which were readily separated via column chromatography. One of the products isolated in 5% yield was identified as **5a** whereas the major product afforded in 35% yield was identified to be **6**. With standardized conditions in hand, we investigated the reaction of several substrates **(4b-f)** with Fe-AcOH at 120 ^{o}C for 1.5 h for obtaining the quinoline derivatives. We were happy to note that all compounds **(4b-f)** furnished the corresponding products **(5b-f)** in moderate to good yields.

Since the formyl group of the imidazole participated nicely for the intramolecular cyclization with the amino group, in the next stage of the study it was reasoned that analogous system bearing alkoxycarbonyl functionality instead of formyl can 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 for obtaining the required starting substrate.

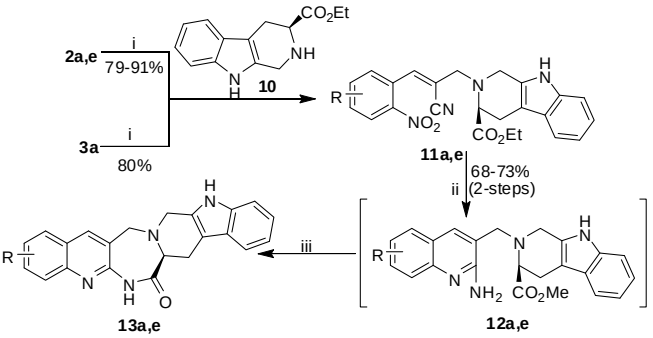
Therefore, **2a** was treated with proline methyl ester in the presence of K_2CO_3 in DMF whereas **3a** was reacted with same nucleophile in the presence of Et_3N in methanol simultaneously. Usual processing and purification of the reaction mixture from **2a** resulted in the product **7a** in 55% yield as *Z*-isomer whereas the reaction of **3a** resulted in isolation of **7a** in 60% yield as mixture of *Z* (97%) and *E* (3%) isomer (Scheme 3). No attempt to separate the isomeric mixture was made at this stage. Compound **7a** obtained from both routes was reduced with Fe-AcOH at 100 ^{o}C for 1.5 h. But purification of the crude product via column chromatography was tedious and furnished the pure product in around 30% yield for both cases. Structure of the isolated product was established as **8a** implying that anticipated second intramolecular cyclization did not occur during the reaction. In order to assess the possibility of intramolecular cyclization in **8a**, it was treated with NaH in THF at room temperature. Gratifyingly this reaction was complete in 1 h.



Scheme 3. Reagents and conditions. i) K_2CO_3, DMF, rt, 1.5 h. ii) Et_3N, DIEA, MeOH, 70^{o}C, 3 h. iii) Fe, AcOH, N_2, 100^{o}C, 1.5 h. iv) NaH, THF, 0^{o}C-rt, 1 h

Since the purification of **8a** was found to be cumbersome it was decided to subject the crude material containing **8a**, afforded after the work up, directly to the NaH-promoted cyclization. This strategy was found to be successful to furnish compound **9a** in 43% yields. Significantly, no racemisation was observed during the formation of **9a**. Owing to the better yield of **7a** achieved from **3a** as compared to **2a**, different allyl bromides **(6c-f)** were subjected to similar set of reactions to investigate the generality of the protocol. It was satisfying to observe that in all cases the polycyclic quinolines **(9c-f)** were isolated though in 47-51% yields only.

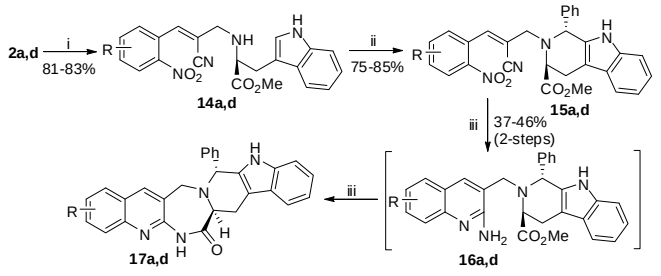
Buoyed by the success, next we decided to investigate the scope of this approach with analogous allyl amine synthesized from the reaction between the ethyl ester derivative of the β-carboline **(10)** obtained from *l*-tryptophan following the reported procedure.[7] Here too **2a** and **3a** were simultaneously treated with **10** in the presence of K_2CO_3 in THF to yield the desired allyl amine **11a** in 91% and 80% yield, respectively. Fortunately, both reactions were found to stereoselectively yield only the *Z*-isomer. Treating **11a** with Fe in AcOH under heating at 120 ^{o}C resulted in a product **12a** which was immediately subjected to NaH-promoted ring closure reaction to furnish the desired product **13a** (68%) in stereoselective fashion without racemisation (Scheme 4). This clearly indicated that the presence of alkoxycarbonyl group does not facilitate the second intramolecular cyclization until the base was added. Suitability of this strategy for the generation of polycyclic quinoline was further exemplified using **2e**. The S_N2'-reaction of **2e** with **10** resulted in the allyl amine **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, rt, 4 h. ii) Fe, AcOH, N_2, 120^{o}C, 1.5 h. iv) NaH, THF, 0^{o}C-reflux, 1 h

Encouraged by the successful formation of **13**, we decided to evaluate the feasibility of similar products by initiating the scheme with tetrahydro β-carboline carrying the substitution at 1-position. It is widely reported that tetrahydro-β-carbolines substituted a 1-position synthesized via Pictet-Spengler reaction are obtained as a mixture of cis and trans products. [8] It is further reported that if tryptophan ester is first N-alkylated and then subjected to Pictet-Spengler reaction it leads to the formation of trans isomer exclusively. [8b] Taking clue from these reports, first **2a** was reacted with tryptophan methyl ester in MeOH stereoselectively leading to the formation of *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 via NOESY spectrum. Heating **15a** in the presence of Fe-AcOH at 120 ^{o}C resulted in the formation of 2-aminoquinoline **16a** which upon treatment with NaH in THF furnished the product **17a** (37% in 2 steps). The stereochemistry of

the product was established to be trans on the basis of NOESY experiment, thereby reflecting that the ring-closure reaction was also stereoselective in nature. During this reaction sequence too we did not observe racemisation in any of the products. This was substantiated by subjecting another substrate **14d** to similar reactions to afford **17d** (46%) stereoselectively.



Scheme 5. Reagents and conditions. i) *l*-Tryptophan methyl ester, MeOH, rt, 1 h. ii) PhCHO, 2% TFA in CH_2Cl_2, rt, 8 h. iii) NaH, THF, 0°C-reflux, 1.0 h.

Until now our focus for obtaining polycyclic quinolines was restricted to substrates wherein allyl amines were tertiary since they were generated via nucleophillic-substitution reaction of secondary amine and the Baylis-Hillman derivative. It was, therefore, considered essential to examine substrates represented by secondary allyl amines generated via S_N2'-reaction between a primary allyl amine and the Baylis-Hillman derivative. To this end, acetate **2a** was allowed to react with 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-AcOH under heating at 100 °C for 30 min resulted in the formation of a product **19** (50%). Treatment of **19** with NaH in THF as solvent, however, resulted in the formation of inseparable mixture of products. Unfortunately, several repetition of this reaction failed to provide any isolable product. The failure to produce **20** reflected that probably our protocol was limited to substrates wherein the nitrogen of allyl amine was tertiary. Considering this fact we decided to install a tosyl-group on the NH-group in compound **18** and investigate the strategy.

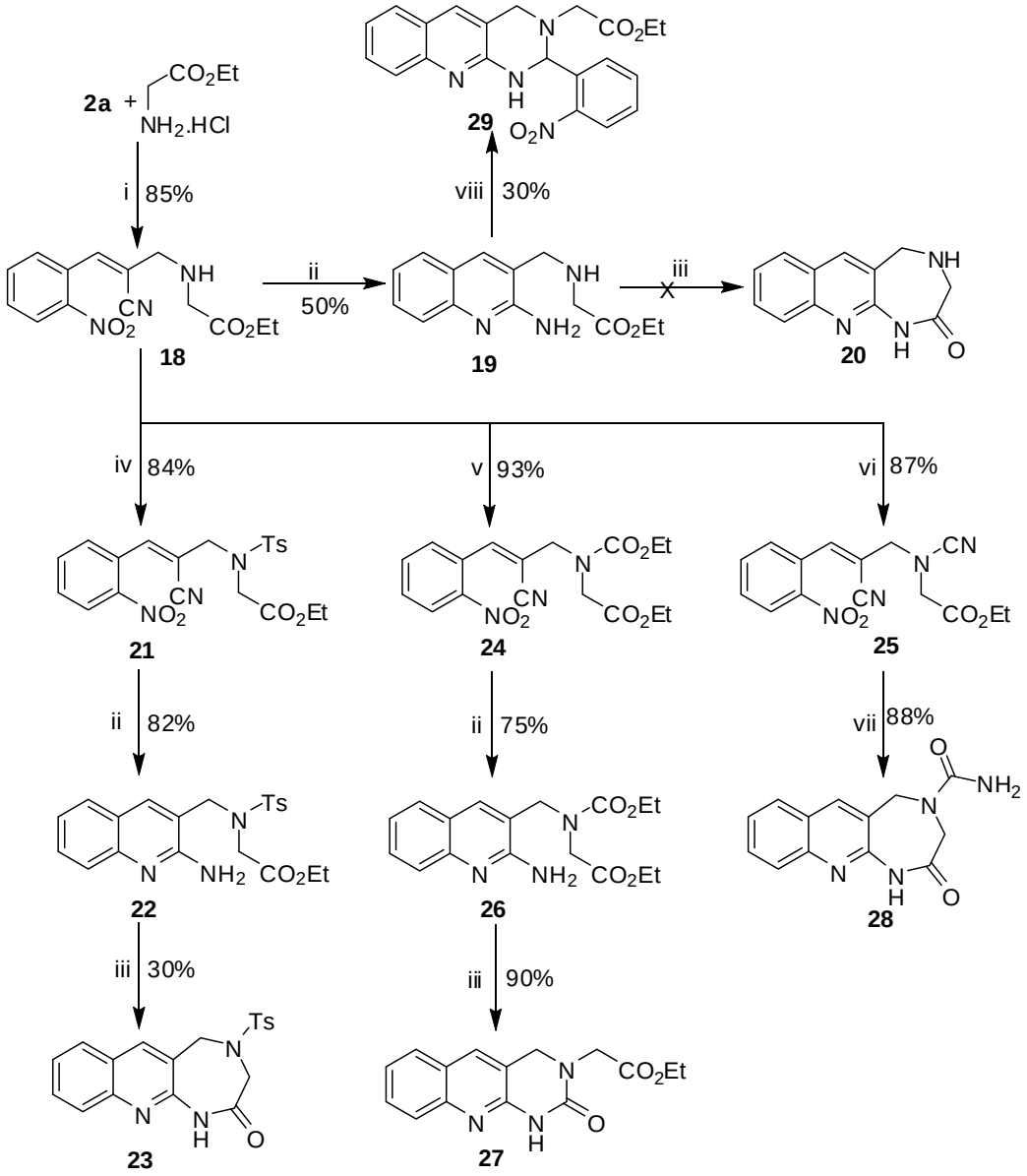
Therefore, compound **21** was prepared by the reaction of **18** with TsCl in the presence of Et_3N in CH_2Cl_2 in 84% yield. Heating **21** with Fe-AcOH at 100 °C for 30 min yielded a product which was characterized to be **22** (82%). To our satisfaction, **22** underwent the desired cyclization in the presence of NaH within 1 h to afford **23** but in low yield (30%). Encouraged by this outcome it was proposed to introduce such functional groups on the NH of **18** which could participate in the intramolecular cyclizations with the generated amino group. Hence it was decided to substitute the NH with ethoxycarbonyl and nitrile groups using ethyl chloroformate and cyanogen bromide, respectively. Consequently, reacting 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-AcOH under heating 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 isolation of product in 90% yield which was identified as **27** on account of the spectral data. This inferred that the second intramolecular cyclization in **26** was regioselective for the alkoxycarbonyl group directly attached to the nitrogen. Surprisingly, however, unlike other substrates wherein alkoxycarbonyl was participating for second cyclization, the reduction of **25** with Fe-AcOH by heating under reflux for 1.5 h afforded a product which was delineated to be **28** (85%). This implied that reduction of the aromatic nitro-group in **25** initiated a domino process. Transformation of the nitrile group to the amide functionality in **28** was attributed to acidic medium of the reaction mixture. It seems that the tertiary nature of allyl amines was necessary to effect the second intramolecular cyclization reactions for obtaining the annulated derivatives. In our attempt to demonstrate the use of diamine **19** for providing quinoline annulated system, we performed the reaction between **19** and 2-nitrobenzaldehyde in the presence of CAN and H_2O_2 leading to **29** (30%).[9]

Continuing with our studies further, we desired to test the protocol with **30** which could be smoothly synthesized via a S_N2'-reaction between amino acetaldehyde dimethylacetal and **2a** as reported earlier.[10] It can be 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 subjected to the reduction in the presence of Fe-AcOH at 100 °C for 1.5 h. This reaction led to formation of a mixture of products from which compound **31** was isolated in 15% yield only (Scheme 7). The isomerisation of the double bond to be placed between C-2 and C-3 was evident from the ^1H and ^{13}C-NMR spectra. Acetylation of the NH group would have occurred due to the presence of AcOH. Considering the preceding experience with secondary allyl amines, compound **30** was readily tosylated to generate **32** (85%). Further reaction of **32** with Fe-AcOH under heating resulted in a product which was established to be **33** making it apparent that the acidity of the medium was not suited to unmask the protected formyl group for further reaction. Nevertheless treatment of **33** with a mixture of $CHCl_3$, TFA and water for 5 days showed complete disappearance of the starting material. Purification of the mixture furnished a product which was established to be **34** (35%). Unlike **31**, no isomerization of the double bond was observed in this case. During optimization of the reaction we discovered another condition to obtain **34** directly from **32** in shorter period. In this method, after the treatment of **32** with Fe-AcOH for 30 min, water was added to the reaction mixture and the heating was continued for 15 h resulting in 25% of isolable yield of **34**.

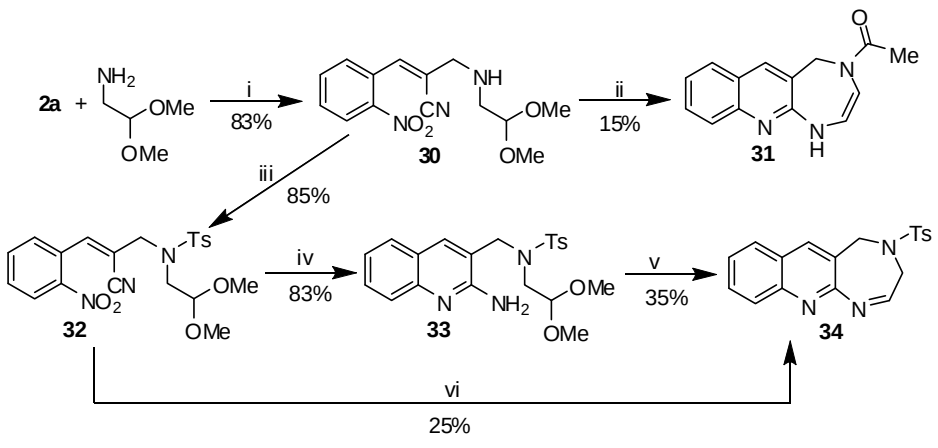
A critical analysis of reactions studied till this point revealed that we failed to achieve the quinoline annulated product whenever the nature of the allyl amine was secondary because the expected second intramolecular cyclization did not take place. Interestingly, however, it was observed that in both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

To bring about more variation, the tryptophan methyl ester was replaced by phenyl alanine ethyl ester as nucleophile for generating

the allyl amine. Hence **2a** was reacted with phenyl alanine ethyl ester in the presence of K_2CO_3 in DMF to afford **35** (47%)

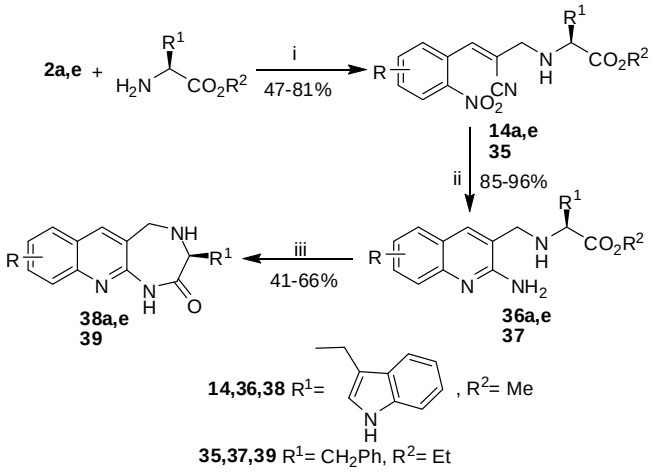


Scheme 6. i) Et_3N, MeOH, rt, 1 h. ii) Fe, AcOH, N_2, 100°C, 30 min. iii) NaH, THF, 0°C-reflux, 1 h. iv) TsCl, Et_3N, DMAP, CH_2Cl_2, rt, 15 h. v) $ClCO_2Et$, Et_3N, CH_2Cl_2, 0°C-rt, 1h. vi) CNBr, K_2CO_3, dry THF, rt, 3 h. vii) Fe-AcOH, 120°C, 1.5 h. viii) 2-Nitrobenzaldehyde, H_2O_2, CAN, 50°C, 15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



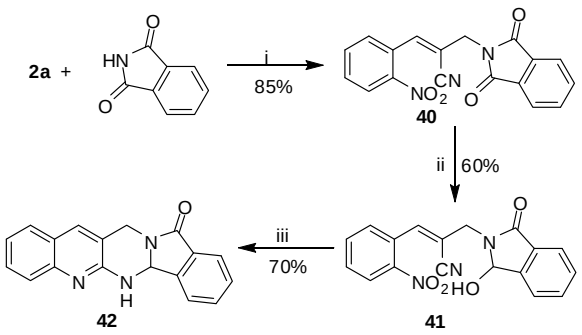
Scheme 7. Reagents and conditions. i) MeOH, rt, 1.0 h. ii) Fe, AcOH, N_2, 100°C, 1.5 h. iii) TsCl, Et_3N, CH_2Cl_2, rt, 15 h. iv) Fe, AcOH, N_2, 100°C, 30 min. v) $CHCl_3$, TFA:H_2O (1:1), rt, 5d. vi) Fe, AcOH, N_2, 100°C, 30 min then add H_2O, 100°C, 15 h.

(Scheme 8). Fe-AcOH-mediated reductive cyclization at 100 °C was complete in 30 min to furnish 96% of **37**. Treating **37** with NaH in THF under heating at reflux gave **39** (66%). These results made it apparent that the second step of the protocol for the synthesis of annulated quinolines developed by us works better for cases of secondary allyl amines where the carbon adjacent to the nitrogen of the introduced nucleophile carried a substitution.



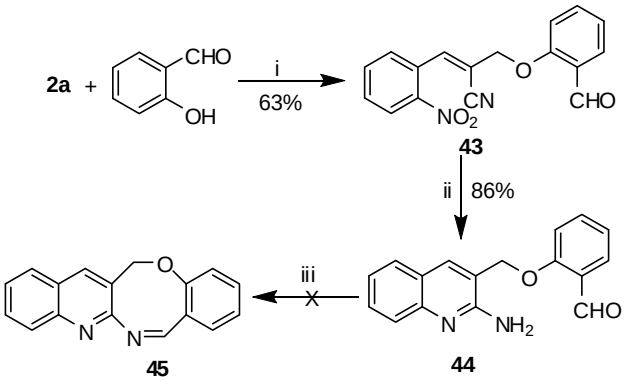
Scheme 8. Reagents and conditions. i) MeOH, rt, 1 h (for tryptophan ester) K_2CO_3, DMF, rt, 2 h (for phenylalanine ester). ii) Fe, AcOH, N_2, 100°C, 1 h. iii) NaH, THF, 0°C - reflux, 1 h

Focused to further enhance the scope of our protocol, we were motivated to investigate the participation of the hydroxyl group for the second intramolecular cyclization. In principle, treatment of the Baylis-Hillman acetate with phthalimide would yield an allyl amine wherein one of the amide carbonyl can be reduced to secondary hydroxyl group which 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. Therefore, **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* isomer (10:1) (Scheme 9). Reduction of **40** in the presence of $NaBH_4$ within 10 min resulted in the formation of product **41** (60%). To our satisfaction, treatment of **41** with Fe-AcOH under heating at 120 °C resulted in the completion of reaction in 2 h to produce a product which was delineated to be **42** (70%). Formation of **42** established that here too the reduction of the aromatic nitro group triggered the domino process.



Scheme 9. Reagents and conditions. i) K_2CO_3, DMF, rt, 2 h. ii) $NaBH_4$, MeOH, rt ,10 min. iii) Fe, AcOH, N_2, 100°C, 2 h.

Finally, it was considered worthwhile to examine the suitability of such approach in the substrate originating from the S_N2'-reaction of oxygen nucleophile bearing a suitable group for intramolecular cyclization. For example the reaction of salicaldehyde with **2a** would yield a substrate which 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 salicaldehyde in the presence of K_2CO_3 in DMF (Scheme 10). Reductive cyclization with Fe-AcOH under heating at 120 °C yielded the product which was established to be **44** (86%). Unfortunately, attempts to perform the intramolecular cyclization in the presence of *p*-TSA to achieve **45** failed and the starting was recovered unreacted.



Scheme 10. Reagents and Conditions: i) K_2CO_3, DMF, rt, 2 h. ii) Fe, AcOH, N_2, 120°C, 1 h. iii) pTSA, PhMe, reflux, 3 d.

Conclusions

In conclusion, we have disclosed the potential of the allyl amines 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 2-step synthetic protocol was found to be a domino process, involving two successive intramolecular cyclizations triggered by the reduction of the aromatic nitro group, for the substrates bearing a formyl or the hydroxyl group. In contrast, similar 2-step sequence for the substrates bearing an alkoxycarbonyl group was found to proceed through initial reductive-cyclization followed by base-promoted second intramolecular cyclization. The study toward understanding the scope of the approach indicated that the tertiary allylic amines smoothly follow the protocol to furnish the desired annulated quinolines. On the other hand the secondary allyl amines bearing an unsubstituted carbon adjacent to the nitrogen atom were unlikely to undergo the second intramolecular cyclization in contrast to the secondary amines with substituted carbon adjacent to the nitrogen atom. Rapid access to the starting substrates, simple reaction conditions and diverse nature of nucleophiles that could be installed on the Baylis-Hillman derivatives makes it an attractive approach that could be exploited further for generation of more diverse polycyclic quinolines.

Experimental Section

Melting points are uncorrected and were determined in capillary tubes on a Precision melting point apparatus containing silicon oil. IR spectra were recorded using a Perkin Elmer's Spectrum RX I FTIR spectrophotometer. ^{1}H NMR and ^{13}C NMR spectra were recorded either on a Bruker DPX-200

FT or Bruker Avance DRX-300 spectrometer, using TMS as an internal standard (chemical shifts in δ). The ESMS were recorded on MICROMASS Quadro-II LCMS system. The HRMS spectra were recorded as EI-HRMS on a JEOL system or as DART-HRMS (recorded as ES+) on a JEOL-AccuTOF JMS-T100LC Mass spectrometer having DART (Direct Analysis in Real Time) source. The optical rotations were measured on an Autopol III, serial no 30166 from Rudolph. Elemental analyses were performed on a Carlo Erba's 108 or an Elementar's Vario EL *III* microanalyzer.

General procedure for the synthesis of compounds 4a-f as exemplified for compound 4a

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), DABCO (1.02 g, 9.14 mmol) was added and continued for 15 min at room temperature. Thereafter, imidazole-2-carboxaldehyde (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 x 30 mL) and water (70 mL). The organic layers were combined and washed with brine (50 mL), dried over Na_2SO_4 and concentrated to yield the crude product. Purification via 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). Mp 153-155 °C, R_f = 0.68 (hexane/EtOAc, 30:70); ν_{max} (KBr) 1678 (CHO), 2227 (CN) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ= 5.42 (s, 2H, CH_2), 7.40 (d, 2H, *J*= 7.9 Hz, ArH_{imida}), 7.61-7.78 (m, 4H, ArH), 8.24 (d, 1H, *J* = 8.0 Hz, ArH), 9.87 (s, 1H, CHO); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 283.1 (M^++1, 50%), 315.0 (M^++32, 100%). Anal. Calcd. for $C_{14}H_{10}N_4O_3$ (282.0753), 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

To a solution of **4a** (0.45 g, 1.60 mmol) in glacial acetic acid (10 mL), iron powder (0.54 g, 9.57 mmol) was added and the reaction was refluxed at 120 °C under stirring in nitrogen atmosphere for 1.5 h. On completion, excess acetic acid was evaporated in vacuo and the reaction mixture was poured into 10% aq. $NaHCO_3$ solution under stirring with glass rod. Then EtOAc (50 mL) was added to it and contents were passed through a bed of Celite. The organic layer was separated whereas the aqueous layer was extracted with EtOAc (5 x 15 mL).The organic layers were combined 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). Mp >240 °C, R_f = 0.27 (MeOH/$CHCl_3$, 05:95); ν_{max} (KBr) 3187 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ= 4.75 (s, 2H, C*H*$_2$NH), 5.27 (s, 2H CH_2N), 5.81 (brs, 1H, NH), 6.95 (d, 1H, *J* = 1.0 Hz, ArH_{imida}), 6.99 (d, 1H, *J* = 1.0 Hz, ArH_{imida}), 7.20-7.26 (m, 1H, ArH), 7.57 (t, 3H, *J* = 8.5 Hz, ArH), 7.76 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 237.2 (M^++1, 100%); 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%, mp >240 °C; ν_{max} (KBr) 3425 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ= 3.84 (s, 3H, OCH_3), 4.56 (d, 2H, *J* = 4.2 Hz, C*H*$_2$NH), 5.43 (s, 2H CH_2N), 6.77 (s, 1H, ArH_{imida}), 6.96 (t, 1H, *J* = 7.6 Hz, ArH), 7.07 (t, 1H, *J* = 7.6 Hz, ArH), 7.19 (d, 1H, *J* = 7.6 Hz, ArH), 7.24 (s, 1H, ArH_{imida}), 7.59 (brs, 1H, NH), 7.88 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 267.2 (M^++1, 100%); HR-EIMS 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%, mp >240 °C; ν_{max} (KBr) 3184 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ= 4.58 (d, 2H, *J* = 4.3 Hz, C*H*$_2$NH), 5.45 (s, 2H, CH_2N), 6.78 (s, 1H, ArH_{imida}), 7.26 (s, 1H, ArH_{imida}), 7.39-7.47 (m, 2H, ArH), 7.62 (brs, 1H, NH), 7.74 (s, 1H, ArH), 7.90 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 271.2 (M^++1, 100%), 273.2 (M^++3, 33%); 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%, mp >240 °C; ν_{max} (KBr) 3393 (NH); ^1H NMR (300 MHz, DMSO-d_6) δ= 3.80 (s, 3H, OCH_3), 3.82 (s, 3H, OCH_3), 4.55 (d, 2H, *J* = 4.8 Hz, C*H*$_2$NH), 5.38 (s, 2H, CH_2N), 6.76 (s, 1H, ArH_{imida}), 6.84 (s, 1H, ArH_{imida}), 7.05 (s, 1H, ArH), 7.24 (s, 1H, ArH), 7.75 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 297.2 (M^++1, 100%), 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%, mp >240 °C; ν_{max} (KBr) 3411 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ= 4.53 (d, 2H, *J* = 4.7 Hz, C*H*$_2$NH), 5.37 (s, 2H, CH_2N), 6.06 (s, 2H, OCH_2O), 6.76 (s, 1H, ArH_{imida}), 6.82 (s, 1H, ArH_{imida}), 7.08 (s, 1H, ArH), 7.16 (t, 1H, *J* = 4.4 Hz, NH), 7.23 (s, 1H, ArH), 7.73 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 281.2 (M^++1, 100%); 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%, mp 240-242 °C; ν_{max} (KBr) 3244 (NH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ= 4.66 (d, 2H, *J*= 4.8 Hz, C*H*$_2$NH), 5.50 (s, 2H, CH_2N), 6.79 (s, 1H, ArH_{imida}), 7.27 (s, 1H, ArH_{imida}), 7.52-7.62 (m, 5H, ArH), 7.88 (t, 1H, *J* = 4.5 Hz, ArH), 7.99 (s, 1H, ArH), 8.87 (t, 1H, *J* = 4.5 Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 287.3 (M^++1, 100%); HR-EIMS 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%, mp 180-182 ºC, ν_{max} (KBr) 1696 (CONH) cm^{-1};^{1}H NMR (300 MHz, DMSO-d_6) δ= 3.97 (s, 2H, CH_2), 4.42 (s, 2H, CH_2), 6.35 (brs, 2H, NH_2), 7.16-7.20 (m, 1H, ArH), 7.47 (d, 2H, *J* = 3.8 Hz, ArH), 7.68 (d, 1H, *J* = 8.1 Hz, ArH), 7.85 (s, 1H, ArH), 10.99 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 257.2 (M^++1, 100%). Anal. Calcd. for $C_{13}H_{12}N_4O_2$ (256.0960), 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%, mp >250ºC ºC; ν_{max} (KBr) 1718 (COMe); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 2.16 (s, 3H, $COCH_3$), 4.82 (s, 2H, CH_2N), 5.66 (d, 1H, *J* = 7.0 Hz, =CH), 5.85 (d, 1H, *J* = 7.0 Hz, =CH), 7.26-7.34 (m, 2H, ArH and NH), 7.55-7.60 (m, 1H, *J* = 7.8 Hz, ArH), 7.66 (d, 2H, *J* = 8.2 Hz, ArH), 7.96 (s, 1H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 240.2 (M^++1, 100%). Anal. Calcd. for $C_{14}H_{13}N_3O$ (239.1059), 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 (432 The title compound was prepared following the above described general procedure and after purification by crystallization 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%, mp >250 ºC, **[α]**^{29} D 216º (c 0.600, DMSO); ν_{max} (KBr) 1689 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 4.65 (d, 1H, *J* = 17.1 Hz, C*H*H), 5.26 (d, 1H, *J* = 17.1 Hz, CH*H*), 5.97 (s, 1H, CH), 7.22-7.27 (m, 1H, ArH), 7.49-7.58 (m, 2H, ArH), 7.62 (d, 1H, *J* = 7.4 Hz, ArH), 7.69-7.72 (m, 2H, ArH), 7.76 (d, 1H, *J* = 7.8 Hz, ArH), 7.97 (d, 1H, *J* = 7.4 Hz, ArH), 8.03 (s, 1H, ArH), 8.29 (brs, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 288.0 (M^++1, 100%). Anal. Calcd. for $C_{18}H_{13}N_3O$ (287.1059), 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%, mp 169-171 ºC, ν_{max} (KBr) 1659 (CHO), 3167 (NH_2) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 5.27 (s, 2H, OCH_2), 6.51 (s, 2H, NH_2), 7.09-7.21 (m, 2H, ArH), 7.43 (d, 1H, *J* = 8.3 Hz, ArH), 7.50 (d, 2H, *J* = 8.3 Hz, ArH), 7.67-7.76 (m, 3H, ArH), 8.17 (s, 1H, ArH), 10.50 (s, 1H, CHO); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 279.1 (M^++1, 100%). Anal. Calcd. for $C_{17}H_{14}N_2O_2$ (278.1055), 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

To a solution of **2a** (0.21 g, 0.85 mmol) in THF (3 mL), water was added (3 mL) followed by Indium powder (0.39 g, 3.41 mmol) and 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, reaction mixture was poured into 10% aq. $NaHCO_3$ solution under stirring with glass rod. EtOAc (50 mL) was added to it and contents were passed through a bed of Celite. The organic layer was separated whereas the aqueous layer was further extracted with EtOAc (5 x 15 mL).The organic layers were combined, evaporated in vaccuo to obtain the crude material which was purified via column chromatography. Elution with MeOH/$CHCl_3$, 03:97 (R_f = 0.48 (MeOH/$CHCl_3$, 10:90) initially 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). Mp >240ºC; ν_{max} (KBr) 3239 (NH_2 and OH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 4.51 (d, 2H, *J*= 4.2 Hz, C*H*$_2$OH), 5.22 (s, 2H, CH_2), 5.58 (brs, 1H, OH), 6.49 (brs, 2H, NH_2), 6.88 (s, 1H, ArH_{imida} and ArH), 7.11-7.17 (m, 2H, ArH_{imida}), 7.31 (s, 1H, ArH), 7.49-7.56 (m, 3H, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 255.1 (M^++1, 100%). Anal. Calcd. for $C_{14}H_{14}N_4O$ (254.1168) 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 the compound 7a

To a stirred solution of proline methyl ester hydrochloride (0.25 g, 1.51 mmol) in dry MeOH (6 mL), Et_3N (0.53 mL, 3.77 mmol) was added and 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 ºC under stirring for 3 h. After completion of the reaction, MeOH was evaporated in vacuo and the residue was taken in CH_2Cl_2 and slurry was 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 yellow oil.

Methyl 1-[(*Z*)-2-cyano-3-(2-nitrophenyl)prop-2-enyl]pyrrolidine-2-carboxylate (7a). Yield: 60% (0.14 g from 0.20 g) as yellow oil, R_f = 0.62 (hexane/EtOAc, 70:30) [α]^{29} D -49º (c 0.274, $CHCl_3$); ν_{max} (Neat) 1737 (CO_2Me), 2221 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 1.86-2.07 (m, 3H, CH_2 and C*H*H), 2.16-2.22 (m, 1H, CH*H*), 2.71 (q, 1H, *J* = 7.3 Hz, C*H*H), 3.21-3.28 (m, 1H, CH*H*), 3.50-3.57 (m, 2H, CH_2), 3.74 (s, 3H, CO_2CH_3), 3.76-3.81 (m, 1H, CH), 7.56-7.62 (m, 1H, ArH), 7.66 (s, 1H, ArCH), 7.70-7.81 (m, 2H, ArH), 8.18 (dd, 1H, J_1 = 1.0 Hz, J_2 = 8.1 Hz, ArH); ^{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; mass (ES+) *m/z*= 316.1 (M^++1, 100%). Anal. Calcd. for $C_{16}H_{17}N_3O_4$ (315.1219), 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

To a solution of **7c** (0.12 g, 0.34 mmol) in glacial acetic acid (5 mL), iron powder (0.116 g, 2.06 mmol) was added and the reaction was refluxed at 120 ºC under stirring in nitrogen atmosphere for 1.5 h. On completion, excess acetic acid was evaporated in vacuo and the reaction mixture was poured into 10% $NaHCO_3$ aq. solution under stirring with glass rod. EtOAc (15 mL) was added to it and the contents were passed through a bed of Celite. The organic layer was partitioned and separated. The aqueous layer was further extracted with EtOAc (5 x 15 mL). The organic layers were combined, washed with brine, dried over Na_2SO_4 and evaporated in vacuo to furnish 0.072 g of 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 ºC and the reaction was stirred at rt for 1 h. On completion of reaction as monitored by TLC, excess THF was evaporated in vacuo and EtOAc (20 mL) was added to it and the reaction mixture was poured into 20 mL of water and extracted further (5 x 10 mL) with EtOAc. The organic layers were combined and washed with brine (20 mL), dried over 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)), mp 171-173 °C, $[\alpha]^{27}$ D 264° (c 0.100, DMSO); ν_{max} (KBr) 1673 (CONH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 1.70-1.91 (m, 3H, CH_2 and C*H*H), 2.21-2.30 (m, 1H, CH*H*), 2.50 (brs, 1H, C*H*H), 2.99-3.01 (m, 1H, CH*H*), 3.51-3.58 (m, 2H, CH_2), 4.12 (d, 1H, *J* = 12.2 Hz, CH), 7.69-7.73 (m, 1H, ArH), 7.83 (d, 1H, *J* = 8.9 Hz, ArH), 8.04 (d, 1H, *J*= 2.0 Hz, ArH), 8.30 (s, 1H, ArH), 10.62 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 288.1 (M^++1, 100%); HR-EIMS 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%, mp 121-123 °C, $[\alpha]^{27}$ D 312° (c 0.064, DMSO); ν_{max} (KBr) 1671 (CONH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 1.72-1.86 (m, 3H, CH_2 and C*H*H), 2.21-2.30 (m, 1H, C*H*H), 2.47-2.50 (m, 1H, CH*H*), 2.99-3.01 (m, 1H, C*H*H), 3.49-3.58 (m, 2H, CH_2), 4.13 (d, 1H, *J* = 12.1 Hz, CH), 7.51 (t, 1H, *J* = 7.0 Hz, ArH), 7.69-7.74 (m, 1H, ArH), 7.83 (d, 1H, *J* = 8.3 Hz, ArH), 7.92 (d, 1H**,** *J* = 7.9 Hz, ArH), 8.32 (s, 1H, ArH), 10.58 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 254.1 (M^++1, 100%); HR-EIMS 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%, mp 158-160 °C, $[\alpha]^{27}$ D 308° (c 0.112, DMSO); ν_{max} (KBr) 1677 (CONH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 1.72-1.94 (m, 3H, CH_2 and C*H*H), 2.28 (t, 1H, *J* = 9.8 Hz, CH*H*), 2.44-2.50 (m, 1H, C*H*H), 3.00 (s, 1H, CH*H*), 3.79-3.82 (m, 2H, CH_2), 3.88 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 4.05 (d, 1H, *J* = 12.0 Hz, CH), 7.17 (s, 1H, ArH), 7.29 (s, 1H, ArH), 8.12 (s, 1H, ArH), 10.37 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 314.11 (M^++1, 100%); HR-EIMS 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]diaz epino[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%, mp 151-153 °C, $[\alpha]^{28}$ D 363° (c 0.114, DMSO); ν_{max} (KBr) 1678 (CONH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 1.72-1.98 (m, 4H, 2 x CH_2), 2.27 (brs, 1H, C*H*H), 2.44-2.50 (m, 2H, CH*H* and C*H*H), 2.98 (brs, 1H, CH*H*), 4.03 (d, 1H, *J* = 11.3 Hz, CH), 6.18 (s, 2H, OCH_2O), 7.17 (s, 1H, ArH), 7.28 (s, 1H, ArH), 8.09 (s, 1H, ArH), 10.34 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 298.1 (M^++1, 100%); HR-EIMS 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]diazepino[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%, mp 171-173 °C, $[\alpha]^{29}$ D 123° (c 0.100, DMSO); ν_{max} (KBr) 1672 (CONH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 1.78-1.87 (m, 3H, CH_2 and C*H*H), 2.31 (brs, 1H, CH*H*), 2.50-2.59 (m, 1H, C*H*H), 3.00 (brs, 1H, CH*H*), 3.62-3.66 (m, 2H, CH_2), 4.17 (d, 1H, *J* = 12.3 Hz, CH), 7.73 (t, 2H, *J* = 3.2 Hz, ArH), 7.85 (dd, 2H, J_1 = 4.7 Hz, J_2 = 8.3 Hz, ArH), 8.01, (s, 1H, ArH), 8.37 (s, 1H, ArH), 9.04 (d, 1H, *J* = 3.6 Hz, ArH), 10.59 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 304.1 (M^++1, 100%). Anal. Calcd. for $C_{19}H_{17}N_3O$ (303.1372), 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, 40 as exemplied by compound 13a

To the stirred solution of compound **12** (0.20 g, 0.50 mmol) in dry THF (5 mL), NaH (0.10 g, 4.00 mmol) was added at 0 °C and then refluxed for 1 h. On completion of reaction, excess THF was evaporated in vacuo and EtOAc was added to the residue. Then the contents were poured into 20 mL of water and extracted with EtOAc (5 x 15 mL). The organic layers were combined, washed with brine (30 mL), dried over Na_2SO_4 and concentrated to yield a brown solid. The product was further purified by column chromatography over a short silica gel column using MeOH/$CHCl_3$, 03:97 (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). Mp 210-212 °C, **[**α**]**^{33} D 6.0° (c 0.600, DMSO); ν_{max} (KBr) 1673 (CONH), 3385 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 2.65 (d, 1H, *J* = 14.2 Hz, C*H*H), 3.09-3.19 (m, 2H, CH_2), 3.79 (d, 1H, *J* = 14.7 Hz, CH*H*), 3.92 (d, 1H, *J* = 14.6 Hz, C*H*H), 4.06 (d, 1H, *J* = 14.7 Hz, CH*H*), 4.23 (d, 1H, *J* = 14.6 Hz, CH), 6.90-7.02 (m, 2H, ArH), 7.25 (d, 1H, *J* = 7.8 Hz, ArH), 7.37 (d, 1H, *J* = 7.5 Hz, ArH), 7.55 (t, 1H, *J* = 7.5 Hz, ArH), 7.71-7.76 (m, 1H, ArH), 7.86 (d, 1H, *J* = 8.4 Hz, ArH), 7.98 (d, 1H, *J* = 8.0 Hz, ArH), 8.40 (s, 1H, ArH), 10.72 (s, 1H, NH), 10.75 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 355.1.0 (M^++1, 100%). Anal. Calcd. for $C_{22}H_{18}N_4O$ (354.1481), 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%, mp 195-197 °C, **[**α**]**^{33} D 15° (c 0.600, DMSO); ν_{max} (KBr) 1669 (CONH), 3413 (NH) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 3.08 (d, 2H, *J* = 7.3 Hz, CH_2), 3.73 (d, 2H, *J* = 14.5 Hz, CH_2), 3.89 (d, 1H, *J* = 14.6 Hz, C*H*H), 3.95 (d, 1H, *J*= 14.7 Hz, CH*H*), 4.16 (d, 1H, *J* = 14.6 Hz, CH), 6.18 (s, 2H, OCH_2O), 6.88-7.02 (m, 2H, ArH), 7.24 (t, 2H, *J* = 8.7 Hz, ArH), 7.35 (s, 1H, ArH), 7.37 (s, 1H, ArH), 8.18 (s, 1H, ArH), 10.56 (s, 1H, NH), 10.72 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 399.0 (M^++1, 100%). Anal. Calcd. for $C_{23}H_{18}N_4O_3$ (398.1379), 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 procedure (**13a**) and after purification by using short silica gel column (25:75 EtOAc: hexane, R_f = 0.50 (EtOAc: hexane 20:80)) was

obtained as a yellow solid (0.09 g from 0.25 g). Yield: 37%, mp 194-196 °C, R_f = 0.50 (hexane/EtOAc, 20:80), $[\alpha]^{32}$ D 118° (c 0.126, DMSO); ν_{max} (KBr) 1665 (CONH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ= 3.30, 3.32 (dd, 1H, J_1 = 4.1 Hz, J_2 = 15.3 Hz, C*H*H), 3.79 (d, 1H, *J* = 15.0 Hz, CH*H*), 4.10 (d, 1H, *J*= 16.2 Hz, C*H*H), 4.32 (d, 1H, *J* = 16.2 Hz, CH*H*), 4.48 (d, 1H, *J* = 3.6 Hz, CH), 4.93 (s, 1H, ArCH), 7.07-7.18 (m, 6H, ArH), 7.33 (d, 3H, *J* = 7.6 Hz, ArH), 7.45 (t, 1H, *J* = 7.6 Hz, ArH), 7.60 (t, 1H, *J*= 4.1 Hz, ArH), 7.68 (d, 3H, *J* = 9.3 Hz, ArH and NH), 7.86 (d, 1H, *J* = 8.7 Hz, ArH), 8.51 (brs, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 431.0 (M^++1, 100%); HR-EIMS 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%, mp 151-153 °C, $[\alpha]^{29}$ D 831° (c 0.232, DMSO); ν_{max} (KBr) 1666 (CONH), 3021 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ= 3.30 (d, 1H, *J* = 12.9 Hz, C*H*H), 3.78 (d, 1H, *J* = 15.8 Hz, CH*H*), 3.95 (d, 1H, *J* = 16.2 Hz, C*H*H), 4.02 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 4.29 (d, 1H, *J* = 16.2 Hz, CH*H*), 4.46 (s, 1H, CH), 4.93 (s, 1H, ArCH), 6.92 (s, 1H, ArH), 7.10 (s, 3H, ArH), 7.18 (d, 3H, *J* = 6.0 Hz, ArH), 7.25 (s, 2H, ArH), 7.33 (s, 2H, ArH), 7.49 (s, 1H, NH), 7.58 (d, 1H, *J* = 7.0 Hz, ArH), 8.35 (s, 1H, CONH), ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 491.1 (M^++1, 100%). Anal. Calcd. for $C_{30}H_{26}N_4O_3$ (490.2005) C, 73.45; H, 5.34; N, 11.42. Found, C, 73.53; H, 5.44; N, 11.34.

4-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%, mp 200-201 °C, ν_{max} (KBr) 1663 (CONH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ= 2.26 (s, 3H, $ArCH_3$), 4.20 (s, 2H, CH_2), 4.63 (s, 2H, CH_2), 7.18 (d, 2H, *J* = 7.9 Hz, ArH), 7.50-7.57 (m, 3H, ArH), 7.72 (d, 2H, *J* = 7.5 Hz, ArH), 7.87 (t, 1H, *J* = 7.9 Hz, ArH), 8.26 (s, 1H, ArH), 10.56 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 368.1 (M^++1, 100%). Anal. Calcd. for $C_{19}H_{17}N_3O_3S$ (367.0991), 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-dihydropyrimido[4,5-*b*]quinolin-3(2*H*)-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%, mp 195-196 °C, ν_{max} (KBr) 1718 (CO_2Et), 1676 (CONH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ= 1.24 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 4.10 (q, 2H, *J*= 7.1 Hz, OCH_2CH_3), 4.63 (s, 2H, CH_2), 4.66 (s, 2H CH_2), 7.47 (s, 1H, ArH), 7.68 (s, 1H, ArH), 7.76 (t, 1H, *J* = 7.4 Hz, ArH), 7.83 (s, 1H, ArH), 8.08 (s, 1H, ArH), 8.44 (s, 1H, NH); ^{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; mass (ES+) *m/z*= 286.1 (M^++1, 100%). Anal. Calcd. for $C_{15}H_{15}N_3O_3$ (285.1113), C, 63.15; H, 5.30; N, 14.73. Found, C, 63.27; H, 5.42; N, 14.54.

3-(1*H*-Indol-2-ylmethyl)-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/$CHCl_3$, 05:95)) was obtained as a yellow solid (0.09 g from 0.18 g). Yield: 49%, mp 205-207 °C, $[\alpha]^{34}$ D 130° (c 0.600, DMSO); ν_{max} (KBr) 1670 (CONH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ= 2.84-2.91 (m, 1H, C*H*H), 3.18-3.25 (m, 2H, CH_2), 3.62 (brs, 1H, CH*H*), 3.95 (s, 2H, CH2), 6.88 (t, 1H, *J* = 7.6 Hz, ArH), 7.00 (t, 1H, *J* = 7.6 Hz, ArH), 7.07 (s, 1H, ArH), 7.28 (d, 1H, *J* = 7.5 Hz, ArH), 7.46 (d, 1H, *J* = 7.2 Hz, ArH), 7.67 (t, 1H, *J* = 7.2 Hz, ArH), 7.77 (d, 1H, *J* = 8.0 Hz, ArH), 7.85 (d, 1H, *J* = 7.5 Hz, ArH), 8.15 (s, 1H, ArH), 10.41 (s, 1H, NH), 10.77 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 343.1 (M^++1, 100%); HR-EIMS Calcd. for $C_{22}H_{18}N_4O$, 342.1481, found, 342.0749.

3-(1*H*-Indol-2-ylmethyl)-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%, mp 124-126 °C, $[\alpha]^{24}$ D 271° (c 0.118, DMSO); ν_{max} (KBr) 1663 (CONH) cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ= 2.81-2.86 (m, 1H, C*H*H), 3.15-3.22 (m, 2H, CH_2), 3.34-3.54 (m, 1H, CH*H*), 3.87 (brs, 2H, CH and NH), 6.16 (s, 2H, OCH_2O), 6.88 (t, 1H, *J* = 7.1 Hz, ArH), 6.97-7.05 (m, 2H, ArH), 7.12 (s, 1H, ArH), 7.26 (t, 2H, *J* = 8.1 Hz, ArH), 7.44 (d, 1H, *J* = 7.8 Hz, ArH), 8.00 (s, 1H, ArH), 10.23 (s, 1H, NH), 10.77 (s, 1H, CONH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 387.1 (M^++1, 100%). Anal. Calcd. for $C_{22}H_{18}N_4O_3$ (386.1379), 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%, mp 164-166 °C, **[α]**^{24} D -42° (c 0.252, $CHCl_3$); ν_{max} (KBr) 1667 (CONH), 3420 (NH) cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ= 3.05 (dd, 1H, J_1 = 8.2 Hz, J_2 = 13.7 Hz, C*H*H), 3.37 (dd, 1H, J_1 = 4.2 Hz, J_2 = 13.7 Hz, CH*H*), 3.97 (t, 2H, *J* = 6.5 Hz, CH_2), 4.20 (d, 1H, *J* = 14.9 Hz, CH), 7.23 (t, 5H, *J* = 8.1 Hz, ArH), 7.44 (t, 1H, *J* = 7.4 Hz, ArH), 7.63-7.72 (m, 2H, ArH), 7.88 (d, 1H, *J* = 9.5 Hz, ArH), 8.50 (brs, 1H, CONH); ^{13}C NMR (50 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 304.1 (M^++1, 100%); DART-HRMS (ES+) Calcd. for $C_{19}H_{17}N_3O$ (303.1372), found, (303.1365).

Typical procedure for the synthesis of compound 18

To a stirred solution of glycine ethyl ester hydrochloride salt (0.42 g, 3.04 mmol) in dry MeOH (10 mL), Et_3N (0.42 mL, 3.04 mmol) was added and stirred for 15min at room temperature. After that, solution of **2a** (0.50 g, 2.03 mmol) in MeOH (80 mL) was added dropwise to the reaction. After completion of reaction as monitored by TLC, MeOH was evaporated in vacuo and the residue was extracted with EtOAc (3 x 30 mL) and water (70 mL). The organic layers were combined and washed with brine (50 mL), dried over Na_2SO_4 and concentrated to yield the crude product. Purification via chromatography in a short column using hexane: EtOAc (25:75, v/v) afforded 0.50 g (85%) of pure **18** as yellow oil.

Ethyl 2-{[(*Z*)-2-cyano-3-(2-nitrophenyl)prop-2-enyl]amino}acetate (18). R_f = 0.50 (hexane/EtOAc, 30:70); ν_{max} (KBr) 1734 (CO_2Et), 2221 (CN) cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ= 1.30 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 3.51 (s, 2H, CH_2), 3.68 (s, 2H, CH_2), 4.22 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 7.26 (s, 1H, NH), 7.56-7.70 (m, 2H, ArCH and ArH), 7.77 (t, 2H, *J* = 7.5 Hz, ArH),

8.19 (d, 1H, *J* = 8.0 Hz, ArH); ^{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; mass (ES+) *m/z*= 290.1 (M^++1, 100%). Anal. Calcd. for $C_{14}H_{15}N_3O_4$ (289.1063), 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

To the solution of **18** (0.50 g, 1.73 mmol) in dry THF (10 mL), K_2CO_3 (0.29 g, 2.07 mmol) was added and 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 reaction as monitored by TLC, THF was evaporated and the residue was extracted with EtOAc (3 x 30 mL) and water (70 mL). The organic layers were combined and washed with brine (50 mL), dried over Na_2SO_4 and concentrated to yield the crude product. Purification via 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). Mp 125-127 °C, R_f = 0.48 (hexane/EtOAc, 30:70); ν_{max} (KBr) 1747 (CO_2Et), 2222 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 1.34 (t, 3H, OCH_2CH_3), 3.96 (s, 2H, CH_2), 4.19 (s, 2H, CH_2), 4.31 (q, 2H, *J*= 7.1 Hz, OCH_2CH_3), 7.64-7.70 (m, 1H, ArH), 7.75 (s, 1H, ArH), 7.80 (d, 2H, *J* = 4.1 Hz, ArH), 8.26 (d, 1H, *J* = 8.1 Hz, ArH); ^{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; mass (ES+) *m/z*= 314.9 (M^++1, 50%). Anal. Calcd. for $C_{15}H_{14}N_4O_4$ (314.1015), 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

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

Ethyl 2-{[(*Z*)-2-cyano-3-(2-nitrophenyl)prop-2-enyl]amino methylphenylsulfonamido}acetate (21). R_f = 0.52 (hexane/EtOAc, 30:70); ν_{max} (Neat) 1738 (CO_2Et), 2223 (CN) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 1.22 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 2.43 (s, 3H, $ArCH_3$), 4.10 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 4.22 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 7.32 (d, 2H, *J* = 7.6 Hz, ArH), 7.63 (d, 2H, *J* = 7.6 Hz, ArH), 7.77 (t, 4H, *J* = 7.6 Hz, ArH), 8.21 (d, 2H, *J* = 8.1 Hz, ArH); ^{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; mass (ES+) *m/z*= 444.0 (M^++1, 100%). Anal. Calcd. for $C_{21}H_{21}N_3O_6S$ (443.1151), 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

To a stirred solution of **18** (0.50 g, 1.73 mmol) in dry CH_2Cl_2 (10 mL), Et_3N (0.48 mL, 3.46 mmol) was added and reaction was continued at room temperature for 15 min. Subsequently ethyl chloroacetate (0.28 mL, 2.60 mmol) in CH_2Cl_2 was added dropwise at 0°C and stirred further for 1 h at same temperature. On completion (as monitored by tlc) contents were poured in water (50 mL) and extracted with CH_2Cl_2 (3 x 40 mL). Usual workup followed by purification via column chromatography using hexane/EtOAc, 80:20 (R_f = 0.60, hexane/EtOAc, 30:70) furnished 0.53 g (93%) of **24** as colorless oil.

Ethyl 2-[[(*Z*)-2-cyano-3-(2-nitrophenyl)prop-2-enyl](ethoxycarbonyl)amino]acetate (24). ν_{max} (Neat) 1708 (CO_2Et), 1745 (CO_2Et), 2222 (CN) cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ= 1.22-1.35 (m, 6H, 2 x OCH_2CH_3), 4.11 (s, 2H, CH_2), 4.16 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 4.32 (q, 2H, *J* = 7.1 Hz, OCH_2CH_3), 4.39 (s, 2H, CH_2), 7.61 (t, 2H, *J* = 6.7 Hz, ArH), 7.77 (d, 2H, *J* = 6.7 Hz, ArH), 8.22 (d, 1H, *J* = 8.0 Hz, ArH); ^{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; mass (ES+) *m/z*= 362.0 (M^++1, 80%). Anal. Calcd. for $C_{17}H_{19}N_3O_6$ (361.1274), 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 that the reaction mixture was poured in ice-water and extracted with EtOAc (3 x 30mL). Usual work up of the organic layer followed by purification via column chromatography using (hexane/EtOAc, 65:35, R_f = 0.35 (hexane/EtOAc, 60:40)) gave 0.09 g (30%) of **29** as a yellow solid.

Ethyl 2-[2-(2-nitrophenyl)-1,4-dihydropyrimido[4,5-*b*]quinolin-3(2*H*)-yl]acetate (29). Mp 153-155 °C, ν_{max} (KBr) 3192 (NH), 1718 (CO_2Et) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 1.25 (t, 3H, *J* = 7.1 Hz, OCH_2CH_3), 3.36 (d, 1H, *J* = 16.2 Hz, C*H*H), 3.53 (d, 1H, *J*= 16.2 Hz, CH*H*), 3.66 (d, 1H, *J* = 17.0 Hz, C*H*H), 3.86 (d, 1H, *J* = 17.0 Hz, CH*H*), 4.16 (q, 2H, J = 7.1, OCH_2CH_3), 6.21 (s, 1H, ArCH), 7.23-7.29 (m, 1H, ArH), 7.42-7.49 (m, 2H, ArH), 7.50-7.59 (m, 3H, ArH), 7.65-7.70 (m, 2H, ArH), 7.82-7.85 (m, 1H, ArH); ^{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; mass (ES+) *m/z*= 393.1 (M^++1, 100%). Anal. Calcd. for $C_{21}H_{20}N_4O_4$ (392.1485), 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 compounds 34

To a solution of **33** (0.10 g, 0.24 mmol) in $CHCl_3$ (5 mL), 50% TFA in water (2.00 mL) was added and stirred for 5 days at room temperature. After completion of reaction as monitored by TLC, the content was poured in 10% aq. $NaHCO_3$ with stirring. The aqueous layer was further extracted with $CHCl_3$ (4 x 20 mL). The organic layers were combined and washed with brine (50 mL), dried over Na_2SO_4 and concentrated to yield the crude product. Purification via column chromatography using MeOH:$CHCl_3$ (02:98, v/v) afforded 0.03 g (35%) of pure **34** as a yellow solid.

(*Z*)-4-Tosyl-4,5-dihydro-3*H*-[1,4]diazepino[5,6-b]quinoline (34). Mp 200-202 °C, R_f = 0.63 (MeOH/$CHCl_3$, 05:95); ^{1}H NMR (300 MHz, DMSO-d_6) δ= 2.05 (s, 3H, $ArCH_3$), 4.62 (s, 2H, CH_2), 5.70 (d, 1H, *J* = 3.8 Hz, CH_2), 7.01 (d, 1H, *J* = 8.1 Hz, ArH), 7.30 (t, 1H, *J* = 7.8 Hz, ArH), 7.46-7.54 (m, 4H, ArH), 7.71 (d, 1H, *J* = 7.7 Hz, ArH), 7.87 (s, 1H, ArH), 8.76 (s, 1H, =CH); ^{13}C NMR (50 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 352.1 (M^++1, 100%). Anal. Calcd. for $C_{19}H_{17}N_3O_2S$ (351.4222), 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

To the stirred solution of phthalimide (0.60 g, 4.07 mmol) in dry DMF (10 mL), K_2CO_3 (0.66 g, 4.88 mmol) was added and allowed to proceed for 15 min at room temperature. After that **2a** (1.00 g, 4.07 mmol) was added to the reaction and continued for 2 h. After completion of reaction as monitored by TLC, the content was poured in water (150 mL) with stirring. The solid separates out which was filtered off and redissolved in EtOAc (100 mL), washed with brine (40 mL), dried over Na_2SO_4 and concentrated

to yield crude solid product. The product was further purified via crystallization with EtOAc to afforded 1.15 g (85%) of pure **40** as a white solid.

(*Z*)-2-[(1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-3-(2-nitrophenyl)prop-2-enenitrile (*Z*:*E*, 10:1)(40). Mp 179-181 ºC, R_f = 0.48 (hexane/EtOAc, 20:80); ν_{max} (KBr) 1720 (CO) cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ= 4.43 (d, 2H, *J* = 1.3 Hz, CH_2), 4.69 (d, 2H, *J* = 1.2 Hz, CH_2), 7.58-7.64 (m, 1H, ArH), 7.70-7.81 (m, 6H, ArCH and ArH), 7.84-7.96 (m, 2H, ArH), 8.19-8.32 (m, 1H, ArH); ^{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; mass (ES+) *m/z*= 334.1 (M^++1, 100%). Anal. Calcd. for $C_{18}H_{11}N_3O_4$ (333.0750), 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

To a stirred solution of **40** (0.70 g, 2.10 mmol) in dry MeOH (15 mL), $NaBH_4$ (0.16 g, 4.20 mmol) was added in portions and stirred further for 10 min at room temperature. Thereafter MeOH was evaporated in vacuo and residue was extracted with EtOAc (3 x 30 mL) and water (70 mL). The organic layers were combined and washed with brine (30 mL), dried over Na_2SO_4 and concentrated to yield a white solid. The product was further purified via crystallization with EtOAc to afford 0.45 g (60%) of pure **41** as a white solid.

(*Z*)-2-[(1-Hydroxy-3-oxo-1,3-dihydro-2*H*-isoindol-2-yl)methyl]-3-(2-nitrophenyl)prop-2-enenitrile (*Z*:*E*, 10:1) (41). Mp 145-147 ºC, R_f = 0.35 (hexane/EtOAc, 50:50); ν_{max} (KBr) 3244 (OH), 2226 (CN), 1683 (CO), 1665 (CO) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ= 4.27 (d, 2H, *J* = 15.8 Hz, 2 x C*H*H), 4.65-4.72 (m, 2H, 2 x CH*H*), 5.95 (d, 1H, *J* = 8.9 Hz, CHO*H*), 6.03 (d, 1H, *J* = 9.1 Hz, CHO*H*), 6.71 (d, 1H, *J* = 9.1 Hz, C*H*OH), 6.82 (d, 1H, *J* = 8.9 Hz, C*H*OH), 7.55-7.61 (m, 3H, ArCH and ArH), 7.66-7.70 (m, 5H, ArH), 7.74 (d, 2H, *J* = 7.4 Hz, ArH), 7.82-7.91 (m, 6H, ArH), 8.08 (dd, 1H, J_1 = 1.7 Hz, J_2 = 8.1 Hz, ArH), 8.21 (dd, 1H, J_1 = 0.8 Hz, J_2 = 8.2 Hz, ArH); ^{13}C NMR (75 MHz, DMSO-d_6) 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; mass (ES+) *m/z*= 336.0 (M^++1, 100%), 358.1 (M^++Na, 100%). Anal. Calcd. for $C_{18}H_{13}N_3O_4$ (335.0906), C, 64.47; H, 3.91; N, 12.53. Found, C, C, 64.63; H, 3.98; N, 12.37.

Supporting Information: The spectral data for all remaining compounds and copies of ^{1}H- and ^{13}C-NMR spectra for all compounds have been provided.

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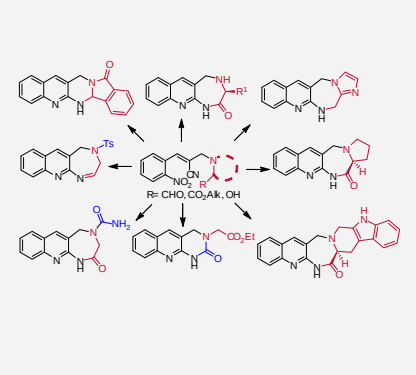
Entry for the Table of Contents (Please choose one layout)

Layout 1:

Polycyclic Quinolines

The Baylis-Hillman derivatives generated from adducts of 2-nitrobenzaldehydes and acrylonitrile serves as versatile precursors to the synthesis of a variety of polycyclic quinolines. The strategy involves two successive intramolecular cyclizations triggered by the catalytic reduction of the aromatic nitro group.



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Reductive-cyclization-mediated syntheses of fused polycyclic quinolines from the Baylis-Hillman adducts of acrylonitrile: Scope and limitations

Keywords: Baylis-Hillman / acrylonitrile / reductive-cyclization / intramolecular cyclization / quinoline