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Toward new camptothecins. Part 6: Synthesis of crucial ketones and their use in Friedländer reaction

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ABSTRACT

In the context of the preparation of camptothecin and luotonin A analogs, the synthesis of some key keto-precursors and their use in Friedländer condensation are described. This paper also focuses on the stability of these keto intermediates and emphasizes the major differences between indolizinones and pyrroloquinazolinones series. Noteworthy is also the report of some original structures isolated as by-products of some experiments.

1. Introduction

The concept of 'privileged structures' was first introduced by Evans in the late 80s.[1] In the anticancer area, the quinazolin-4-one ring system and the quinoline skeleton can be considered as privileged scaffolds. In particular, they can be found in a large number of natural and unnatural cytotoxic agents such as camptothecin (**1**),[2] luotonin A (**2**),[3] benzopyrrolizinoquinoline **3**,[4] and mackinazolinone **4**[5] derivatives (Fig. 1).

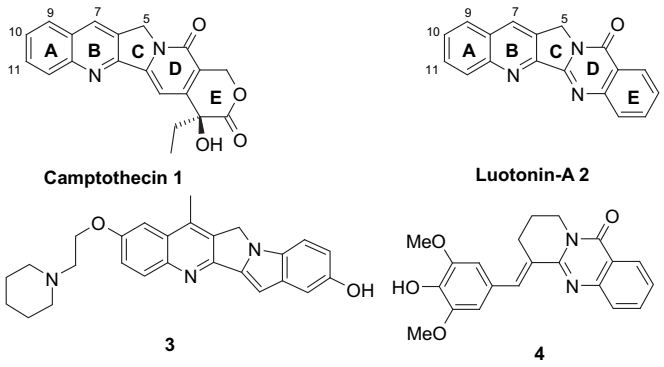

Figure 1. Representative cytotoxic agents owning a quinazolin-4-one or quinoline ring system.

As part of a program directed toward the synthesis of potential anticancer agents,[6] we wished to elucidate the influence of a carbonyl (acid, ester, amide) substituent on position-5 of cycle C of condensed quinolines **5** and **6**, along with modification of the E-rings of these camptothecin and luotonin analogs.[7–10] In our retrosynthetic scheme (Fig. 2), a strategic point consisted in the condensation of aminobenzaldehydes with ketoindolizines **7** or ketopyrroloquinazolinones **8**. In this paper, we report some details about the synthesis and their use in Friedländer reaction[11] of ketones **7** and **8**, starting from precursors **9** and **10** (already described by us[10]).

2. Results and discussion

2.1. Synthesis of protected *o*-aminobenzaldehydes

Some of the aminobenzaldehydes needed for the Friedländer reaction[11] were not commercial and had to be synthesized. Since many aminobenzaldehydes are unstable compounds, prone to dimerization and polymerization, they were protected as imines by reaction with *p*-toluidine.[12] We have already reported[13] that reduction of nitrobenzaldimines was more reproducible, easier and giving better yields of the expected amines, when performed with anhydrous sodium sulfide than with its nonahydrate form.[14]

Nitration of piperonal (**11**) in nitric acid at 0 °C was reported in literature to yield a mixture of nitroaldehyde **12** and 4-nitromethylenedioxybenzene.[15] It is also possible to perform this reaction by using nitric acid in the presence of acetic anhydride.[16] Under these conditions, only diacetoxy compound **13** was

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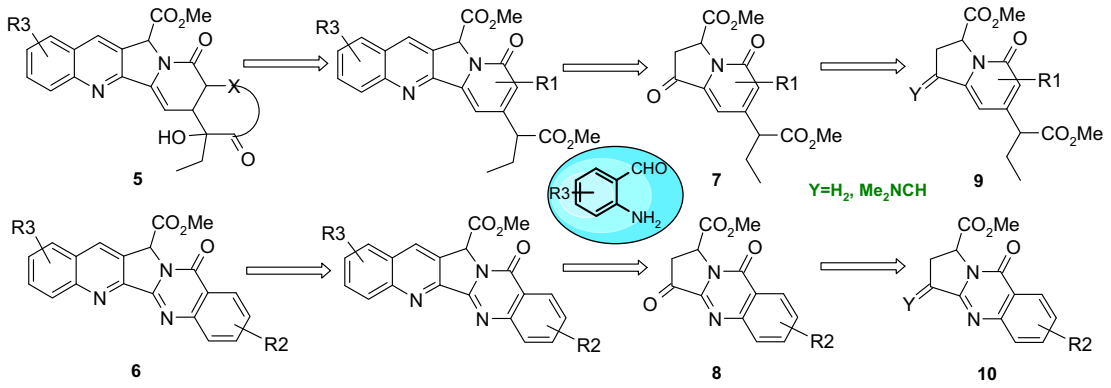
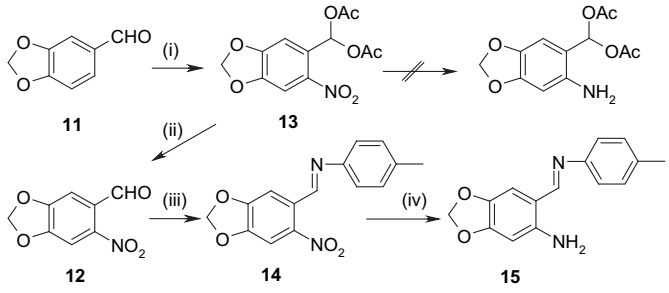


Figure 2. Retrosynthetic scheme leading to camptothecin and luotonin A analogs **5** and **6**.

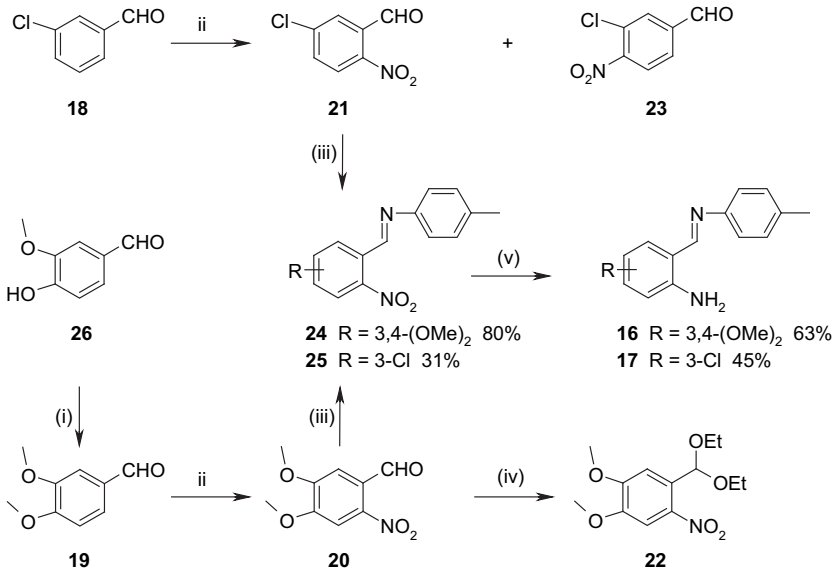
isolated in 55% yield. However, reduction of this protected nitroaldehyde with anhydrous Na_2S[13] as well as with Fe[17] or Zn[18] and ammonium chloride failed. Hydrolysis of **13** was then realized by sulfuric acid in ethanol and the nitroaldehyde product **12** (66%) thus obtained was reacted with *p*-toluidine, then reduced with anhydrous Na_2S. According to this sequence, the overall yield in the protected dimethoxyaminobenzaldehyde **15** was 20% (Scheme 1).



Scheme 1. Reagents and conditions: (i) HNO_3/Ac_2O, 0 °C, 2 h, 55%; (ii) H_2SO_4, EtOH, reflux, 10 h, 66%; (iii) *p*-toluidine, EtOH, reflux, 30 min, 85%; (iv) Na_2S anhyd, EtOH, reflux, 5 min, 65%.

The protected dimethoxyaminobenzaldehyde **16** and the 3-chloro analog **17** were obtained in a similar fashion (Scheme 2). In order to avoid the formation of a diacetoxylated compound, nitration of known aldehydes **18** and **19** (quantitatively formed by methylation of vanillin (**26**) by using dimethylsulfate in acetone[19]) was performed with HNO_3 in H_2SO_4[18] providing nitroaldehydes **20** and **21** in 84% and 80% yields, respectively. Noteworthy, recrystallization of product **20** in EtOH yielded a small amount of acetal **22**, and 6-nitroaldehyde **21** was accompanied by 9% of the 4-nitro isomer **23**, which was easily removed upon recrystallization. Protection of **20** and **21** followed by their reduction was performed as for the nitroaldehyde **12**, leading to **16** and **17** in a total yield of 42% and 11%, respectively.

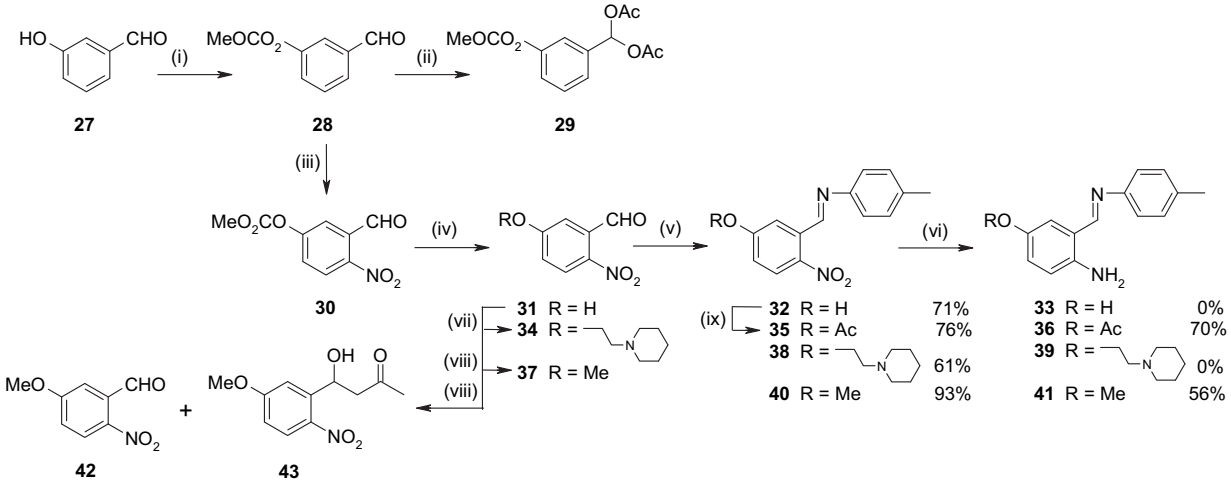
In the camptothecin series, a hydroxy substituent placed at C-10 position was reported to lead to significant increase in activity due to formation of new interactions in the DNA/topoisomerase I complex.[20] In order to introduce this group in some final compounds, *m*-hydroxybenzaldehyde (**27**) was used as starting material. The phenol function of this substrate was protected as a methyl carbamate by using methyl chloroformate in pyridine. The resulting aldehyde **28** was formed in 75% yield, and unreacted compound **27** could rapidly be recovered. The use of acetic anhydride as co-reagent for nitration of **28** led only to 1,1-diacetate **29** (83%), but the desired nitroaldehyde **30** was obtained in 75% yield when the reaction was carried out in sulfuric acid. Regeneration of the phenol group of **30** led to nitroaldehyde **31** (NaOH, 70%), and then imine **32** was easily obtained



Scheme 2. Reagents and conditions: (i) Me_2SO_4, Me_2CO, K_2CO_3, reflux, 90 min, 99%; (ii) HNO_3/H_2SO_4, 15 °C, 1 h, 84% for **20** and 80% for **21**; (iii) *p*-toluidine, EtOH, reflux, 30 min; (iv) EtOH, reflux, 15%; (v) Na_2S anhyd, EtOH, reflux, 5 min.

in 71% yield according to the previous standard protocol. However, due to the free OH function of this compound combined with the sensitivity of the imine group toward hydrolysis, it was not possible to isolate the amine **33** formed by reduction of the nitroimine **32** under the usual conditions (Scheme 3). Thus, acetylation of compound **32** was performed, leading to nitroimine **35** (76%), whose reduction gave 70% of the expected aminoimine **36**. This product could not be easily purified because of its decomposition upon exposure to silica gel during the chromatographic purification, and was used 'crude' in the following Friedländer reaction.

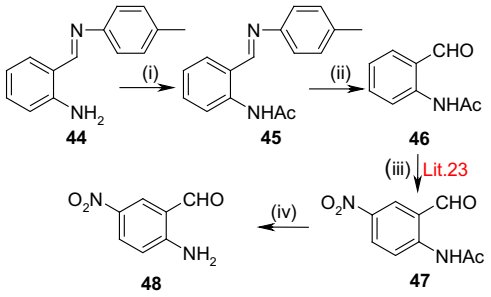
*2.2.1. Reactivity of tricyclic diester **49**.* Acetate **49** was a by-product isolated in 40% yield during the oxidation of desoxyvasicinone analog **57** by lead tetracetate (Scheme 5).[10] It was considered that alcohol **58a**, easily generated from the acetate-ester **49**, could react as a precursor of the *N*-acyliminium salt **A** in equilibrium with its vinylogous form **B**. Thus, treatment of **58a** with aminobenzaldehyde could give quinoline **6a** as depicted in Scheme 5. However, compound **58a**, obtained in a 65% crude yield by treatment of diester **49** with MeONa, then HCl, was not stable and rapidly ring opened to functionalized quinazoline **60a** (Scheme 5). Compound **58a** was mainly identified from similarities of its ^{1}H



Scheme 3. Reagents and conditions: (i) CH_3OCOCl, pyridine, rt, 4 h, 75%; (ii) HNO_3/Ac_2O, 0 °C, 1 h, 83%; (iii) HNO_3/H_2SO_4, 0 °C, 1 h, 75%; (iv) NaOH (10%), rt, 1 h, 70%; (v) *p*-toluidine, EtOH, reflux, 30 min, 71%; (vi) Na_2S anhyd, EtOH, reflux, 5 min; (vii) $Cl(CH_2)_2NC_5H_{10}\cdot HCl$, K_2CO_3, DMF, 80 °C, 4 h, 94%; (viii) MeI, K_2CO_3, DMF or acetone, 80 °C, 4 h, 66%; (ix) Ac_2O, pyridine, rt, 2 h, 76%.

Introduction of the same amino chain as found in the quinoline **3** (Fig. 1) was also attempted. Thus, alkylation of nitrophenol **31** to give **34**, then protection leading to **38** were realized without difficulty. However, reduction of **38** proved to be problematic and synthesis of **39** was not pursued. Starting from the same hydroxynitrobenzaldehyde **31**, the same reaction sequence led, after methylation of the phenol group, to the imine **40** then to the protected amine **41**. Methylation of **31** to give **42** needed to be performed in DMF instead of acetone because in the latter solvent, an aldolization reaction occurred, and only hydroxyketone **43** was isolated in 80% yield (Scheme 3).[22]

Synthesis of 2-amino-5-nitrobenzaldehyde (**48**) from 2-aminobenzaldehyde was already described (60%).[23] Because of the instability of this product, we chose to start from the imine **44**.[13] Acetylation of the amino group of **44** (Ac_2O/Pyridine) then hydrolysis of the protecting group (HCl/EtOH) of **45** led in two steps to 78% of acetamidobenzaldehyde **46**. Nitration of this compound was performed as described,[23] yielding 74% in **47**, whose hydrolysis in HCl gave 90% of aminoaldehyde **48**. Noteworthy, these two steps were poorly reproducible and the reported yields were the best obtained (Scheme 4).



Scheme 4. Reagents and conditions: (i) Ac_2O, pyridine, rt, 12 h; (ii) EtOH, HCl (5%), rt, 2 h, 78% in two steps; (iii) HNO_3/H_2SO_4, AcOH, 0 °C, 30 min then rt, 4 h, 74%; (iv) HCl (5%), reflux, 8 h, 90%.

2.2. Reactivity of precursors of quinolines

Various precursors are possible in order to get a quinoline nucleus. Those that we used in Friedländer reaction are shown in Figure 3, and their syntheses were described in a preceding paper.[10] Except for the tricyclic system **49**, which was utilized directly, we focused on the transformation of compounds **50**–**56** to the corresponding ketones.

NMR spectrum with that of **49**,[10] and structure of **60a** was deduced from the newly created carbonyl group (δ=179.7 ppm) and the coupling constant value of the double bound compatible with the trans isomer (J=16.2 Hz). A similar rearrangement pattern was also observed in another part of this work.

*2.2.2. Reactivity of tricyclic alcohol **50**.* In the desoxyvasicinone series, oxidation of the alcohol function was generally realized with Jones reagent.[24,25] By using either this oxidant or pyridinium chlorochromate or under Swern[26] or Oppenauer[27] oxidation conditions, it was not possible to obtain even a little amount of ketone **8a** starting from tricyclic alcohol **50**. However, when this compound was treated with chromic acid, 7% in diketoester **61** was isolated. Hydroxylactam **C** could be considered as a key intermediate for this cleavage, which pointed out the sensitivity of

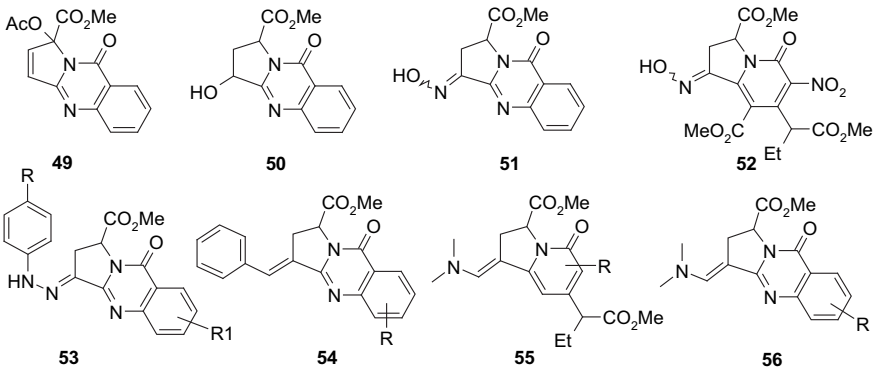
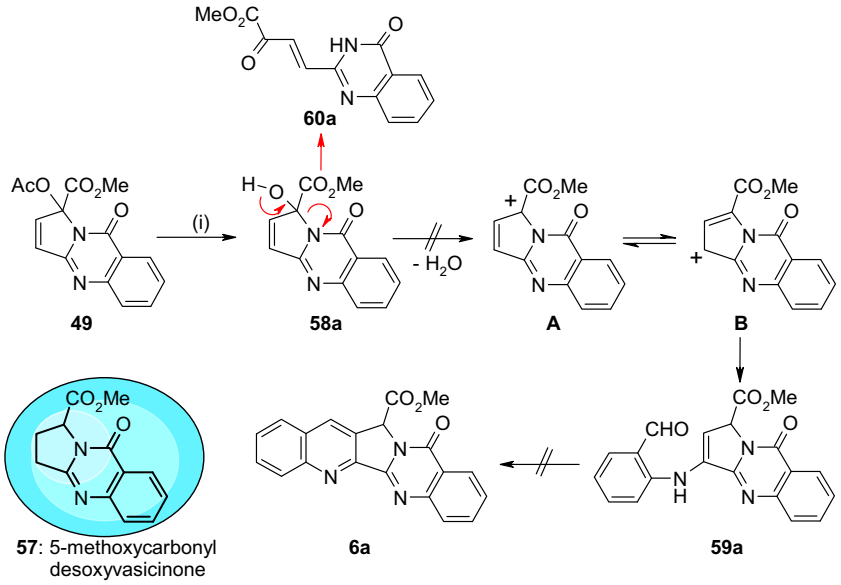
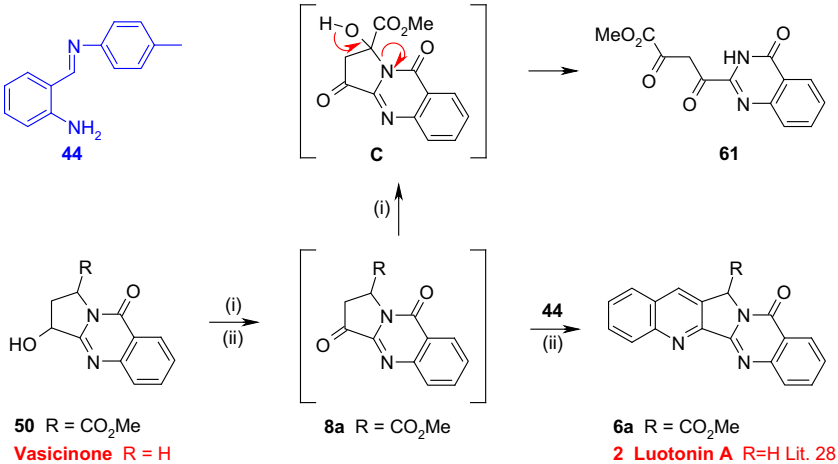


Figure 3. Precursors used for Friedländer reaction.



Scheme 5. Reagents and conditions: (i) MeONa/MeOH, rt, 4 h, 65% (crude product).

the α-position of the nitrogen and of the methoxycarbonyl group to over-oxidation reactions (Scheme 6). It was also described by Ma et al.[3d] that treatment of vasicinone (**50**, R=H; Scheme 6) with protected aminobenzaldehyde **44** (toluene/PTSA/4 Å MS, possibly in presence of *p*-benzoquinone) led to 30–46% in luotonin A (**2**) (Scheme 6). Under the same conditions, 5-methoxycarbonyl luotonin A (**6a**) was formed in the low yield of 15% (Scheme 6). Because better results were obtained starting from pure ketone **8a** (see

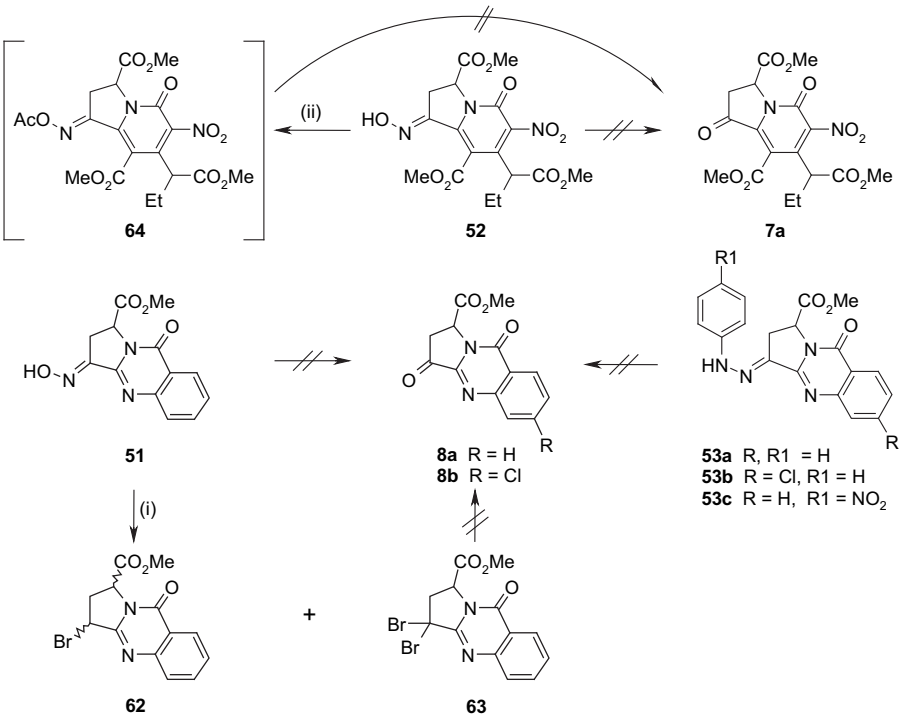


Scheme 6. Reagents and conditions: (i) $K_2Cr_2O_7$, H_2SO_4, H_2O, EtOH, 0 °C then rt, 2 h, 7%; (ii) **44**, pTSA, MS 3 Å, xylene, reflux, 20 h, 15% crude.

later), the product **6a** was not purified but only identified with NMR spectrum of the crude reaction mixture.

*2.2.3. Reactivity of tricyclic oximes **51**, **52**, and corresponding hydrazones **53**.* Many methods have been described for the regeneration of a carbonyl function from oximes or hydrazones.[28] The main reactions that were tested on **51**, **52**, and **53** without success were hydrolysis under acidic conditions (HCl,[29] HBr[30]), oxidation (MnO_2[31]), nitrosation (*iso*-AmONO/HCl,[32] $NaNO_2/Me_3SiCl$[33]), reduction ($NaHSO_3$,[34] Zn/HCl or AcOH[35]) or exchange reaction with cyclohexanone or acetone.[36] Generally speaking, no formation of the expected ketones was observed starting from the hydrazones **53**. However, a pink color often appeared from the oximes **51** and **52**, later accompanied by a total degradation of the reaction media. The same color, assigned to over-oxidation, was observed during storage of some unstable ketones such as **7a** and **8a** (see below). It was also reported that oxidation of oximes with bromine could lead to ketones.[37] Accordingly, only few amounts of halogenated products **62** and **63** were isolated in 7% and 12% yields, respectively, when oxime **51** was reacted under these conditions (Scheme 7). Elsewhere, we have already described that ketone **8a** could not be obtained from dibromo compound **63**,[10] although it was possible to isolate 79% of an oxidized desoxyvasicinone from its dibromo analog.[38]

*2.2.4. Reactivity of benzylidene compounds **54**.* In the desoxyvasicinone series, it was recently described by Molina et al.[44] that the crucial enolizable ketone required for the Friedländer reactions could be obtained by ozone cleavage of benzylidene precursors. Because we did not wish to use ozonolysis technique, we studied the oxidation of the benzylidene compound **54a** by $NaIO_4$ and catalyzed by RuO_2 in the solvent conditions already reported in the literature: a mixture of $MeCN/H_2O$ with, possibly, CCl_4 or EtOAc.[45] In our hands, by using $MeCN/H_2O$ as solvent and 10% of RuO_2 as catalyst, only a 55/45 mixture of diastereoisomers of diol **65** was obtained after 72 h of reaction at room temperature in the very low 4% yield upon silica gel purification; even if the whole starting material was consumed in these conditions, no expected ketone **8a** was isolated. In order to accelerate the reaction, 20% of catalyst was used. This experimental condition led instantaneously to the degradation of the medium; nevertheless, by using also EtOAc as cosolvent, the expected ketone was formed, escaping to a further oxidization reaction, in quantitative yield in 2 h at room temperature (it can be observed by ^{1}H NMR spectroscopy that a mixture of ketone **8a** and its enol form **8′a** in 9/1 ratio was obtained). However, medium (Ac_2O/DMAPcat./THF). However, product **64** proved to be unstable; even adding triphenylphosphine at the end of the acylating reaction, decomposition also occurred (Scheme 7).

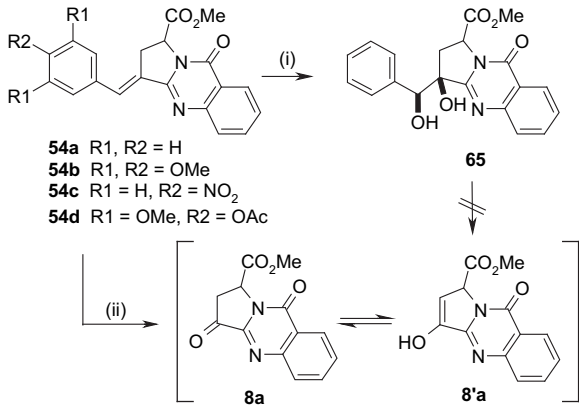


Scheme 7. Reagents and conditions: (i) Br_2, CH_2Cl_2, $NaHCO_3$, H_2O, rt, 15 h, 19%; (ii) Ac_2O, DMAP, THF, rt, 48 h, 100% by NMR.

Friedländer reactions are mainly carried out from ketones, but it is also possible to start from the corresponding enamines.[13] Literature reports that oximes can be converted to acetylenamides by reduction/acylation with iron in acetyl chloride[39] or with triethylphosphine in acetic anhydride.[40] However, when compound **52** was reacted with triphenylphosphine, only degradation was observed. Thus, we attempted to perform this transformation, in a two-step protocol, via the intermediate acetate **64**. Under standard conditions (Ac_2O/DMAP/Et_3N,[41] Ac_2O/Py[42] or AcCl/Et_3N[43]), only degradation of the starting material was observed, even at low temperature. Eventually, it was possible to obtain the acetate **64** quantitatively (according to ^{1}H NMR spectrum) by using a diluted these compounds entirely decomposed during the work-up, and the same pink color developed rapidly as observed previously (Section 2.2.3). The same reactions were tested with benzylidene compounds **54c** and **54d**, whose electronic density on the double bond was different. Unfortunately, their low solubility in the necessary solvent mixture (EtOAc/$MeCN/H_2O$) limited the study, and no interesting results were obtained (Scheme 8).

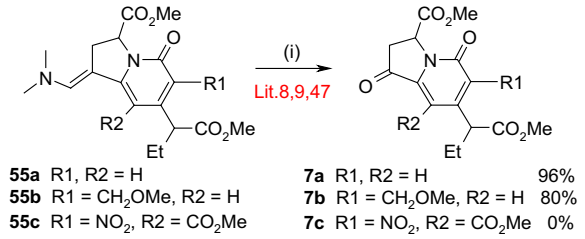
*2.2.5. Oxidation followed by Friedländer reaction of enamines **55** and **56**.*

2.2.5.1. Previous results. N,N-Dimethylenamines have been reported as carbonyl precursors, and we have already described



Scheme 8. Reagents and conditions: (i) **54a**, $NaIO_4$, RuO_2 (10%), MeCN/H_2O 3/1, rt, 3d, 4%; (ii) **54a**, $NaIO_4$, RuO_2 (20%), EtOAc/MeCN/H_2O 3/3/1, rt, 2 h, 100% (not isolated).

their oxidation in the synthesis of camptothecin analogs.[8,9] After a large screening, the best oxidizing agent found was $NaIO_4$, and the use of THF/H_2O combination as solvent allowed us, starting on enamines **55**, to isolate ketones **7a** and **7b** in the good 96% and 80% yields, respectively. However, products from these series exhibited a low stability, which probably explains our inability to obtain the ketoindolizine **7c**[46] (Scheme 9).



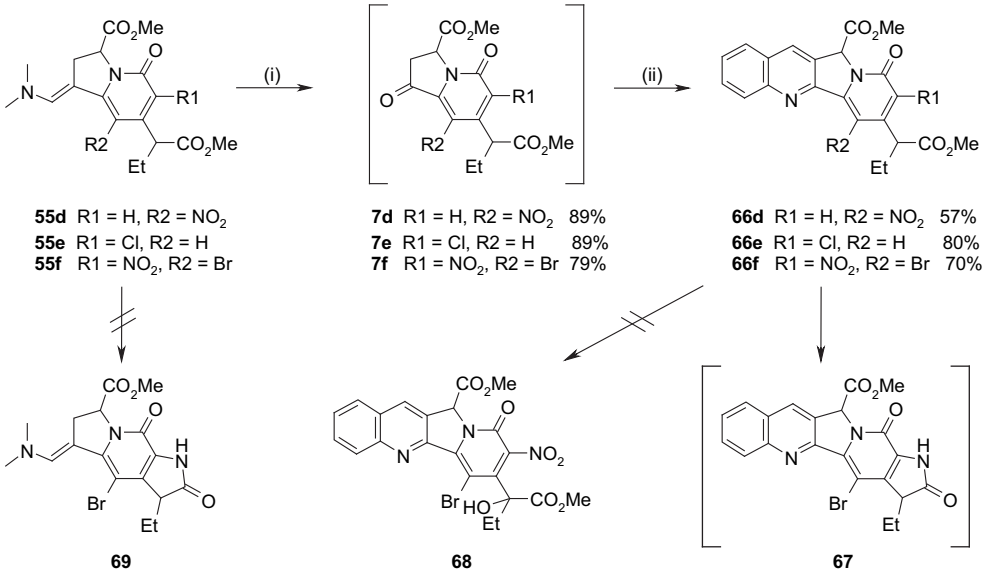
Scheme 9. Reagents and conditions: (i) $NaIO_4$, THF/H_2O, rt.

*2.2.5.2. Reactions of indolizines **55**.* Ketones **7d**–**f** decomposed during their formation when the previous combination THF/H_2O as solvent was used. However, by using the mixture EtOAc/MeCN/H_2O described earlier in this paper (see Section 2.2.4), *N*,*N*-dimethylaminomethylidene-indolizines **55d**–**f** led to the expected indolizinones **7d**–**f** in yields ranging from 80% to 90%. Due to their low stability, these compounds were not purified but directly engaged in Friedländer condensation. After extraction of the reaction mixture with CH_2Cl_2, protected aminobenzaldehyde **44** and acetic acid were added, dichloromethane was evaporated, and the mixture was then heated until disappearance of the starting ketone **7** according to TLC control. Under these conditions, the new quinolines **66d**–**f** were obtained in two steps (Scheme 10) in 52%, 71%, and 55% yields, respectively.

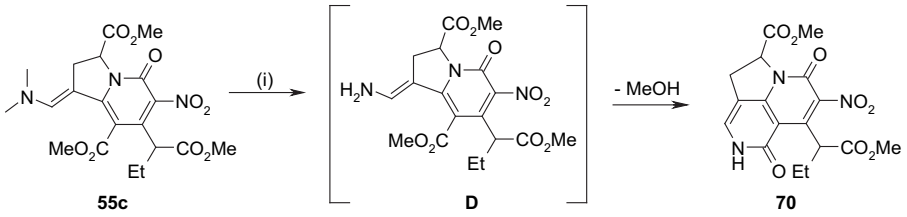
Many attempts to remove the bromine atom of reactant **66f** were performed while reducing its nitro group in order to obtain the pentacyclic lactam **67**. Indeed, this compound is a direct precursor of camptothecin analog **5** (Fig. 2). Whatever the conditions used (e.g., Pd/C, Mg/MeOH, Na_2S, $NaBH_4$, Et_3SiH, $SnCl_2$, Zn/HBr or Zn/NH_4Cl), only decomposition of initial compound was obtained. However, by using Zn/AcOH, it was possible to observe by NMR that lactam **66** was rapidly degraded upon attempt of isolation. In the same way, introduction of the needed alcohol function before the reduction process (see product **68**) was unsuccessful, as well as controlled reduction of compound **55f** to give the expected tricyclic lactam **69** (Scheme 10).

Because of these failures, we thought that it was better to first reduce the nitro function of the bicyclic enamine **55c**.[46] Complex mixtures were obtained, but ammonium formate/Pd/C/MeOH led to formation of the tricyclic pyridone **70** (Scheme 11); this compound is produced by an exchange reaction of the dimethylamino group of **55c** with ammonia. Heating compound **55c** only with ammonium formate in methanol led quantitatively to the expected product **70** (Scheme 11).

*2.2.5.3. Reactions of quinazolines **56**.* As hypothesized previously, the tricyclic ketones **8** are also instable, and oxidation of enamines **56** needs to be performed in the same way as for compounds **7** shown in Scheme 9. Thus, $NaIO_4$ in EtOAc/MeCN/H_2O mixture was used, and then the Friedländer condensation was performed with crude heterocycles **8** and protected aminobenzaldehyde derivatives **15**, **16**, **41**, **44** or aminobenzophenone **71**. Luotonin derivatives **6a**–**f** were thus obtained in yields ranging from 39% to 75% for two steps. On the other hand, reacting



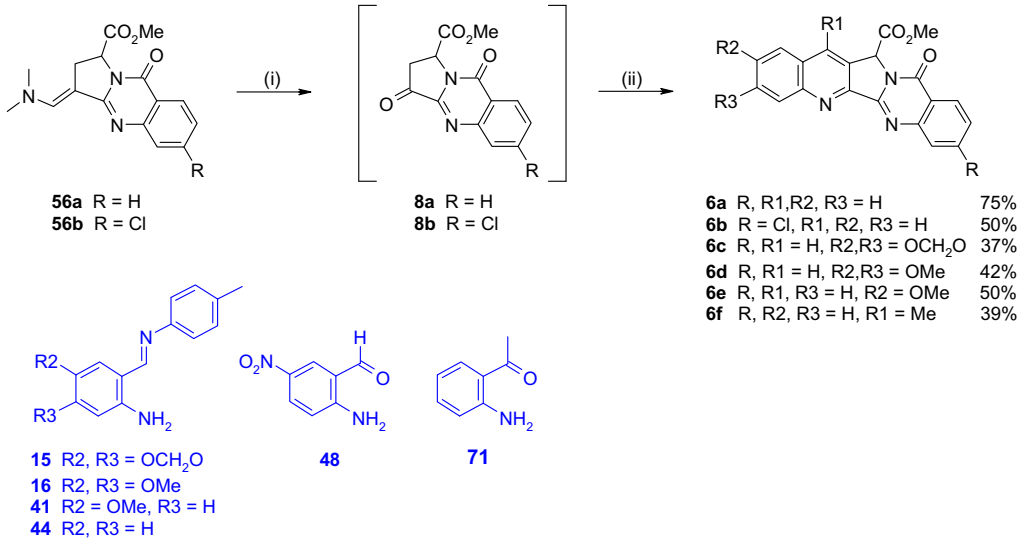
Scheme 10. Reagents and conditions: (i) $NaIO_4$, MeCN, EtOAc, H_2O, 45 s, 20 °C; (ii) **44**, AcOH, 2 h, 80 °C.



Scheme 11. Reagents and conditions: (i) HCO_2NH_4, MeOH, 24 h, reflux, 93%.

nitroaminobenzaldehyde **48** with ketone intermediate **8a** led only to decomposition, either in reflux of acetic acid or in more acidic[47] or basic[11b] conditions (Scheme 12).

luotonin derivative **6i** in the low 25% yield and in a very impure form (Scheme 14). From these results, it was decided to further check other oxidizing reagents. However, all other oxidizing agents tested



Scheme 12. Reagents and conditions: (i) $NaIO_4$, MeCN/EtOAc/H_2O (1/1/2), rt, 25 min; (ii) AcOH, reflux, 2 h.

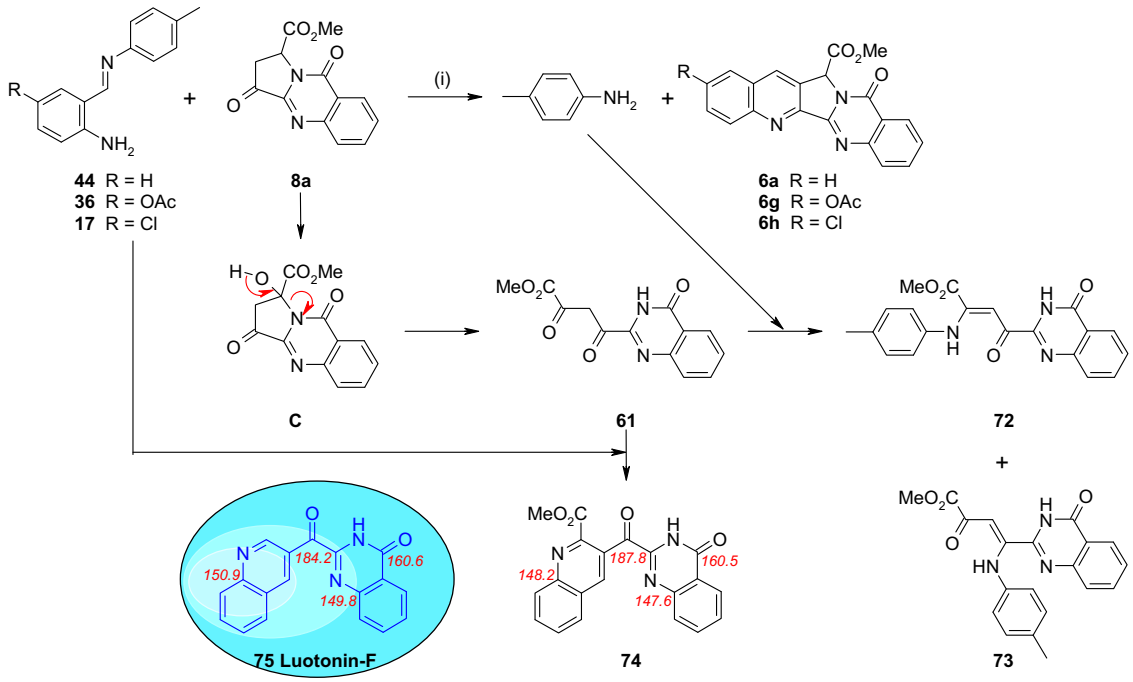
2.2.5.4. Side reactions observed during the Friedländer synthesis of quinazolines. When cleavage of the methoxy group of luotonine derivative **6e** was attempted by using BF_3 or Me_3SiI, only a decomposition of the starting material was observed. Because of this failure, acetoxybenzaldimine **36** was reacted with ketone **8a** according to Friedländer reaction, but compound **6g** was not formed and only 31% of the compound **72** was isolated. In a similar manner with chlorobenzaldimine **17**, a mixture of enaminoketones **72** (20%) and **73** (20%) was obtained along with 10% of luotonin analog **6h** (Scheme 13). These products were separated by chromatography on SiO_2, and characterized by NMR spectroscopy.

In the beginning of the work, RuO_2 was used as a catalyst for oxidation of ketone **8a**. After a Friedländer condensation between imine **44** and crude ketone **8a**, presumed to contain traces of the catalyst, an unexpected heterocyclic system **74** was obtained in 23% yield. Identification of the structure of this ketone was comforted by analogies of ^{13}C NMR spectrum with that of natural Luotonin-F (**75**)[3f] (Scheme 13). These reactions point out the sensitivity of the pyrroloquinazolindione scaffold **8** toward over-oxidation, and are reminiscent of the rearrangement of alcohol intermediate **58a** (Scheme 5) and of the formation of opened compounds **60a** and **61** (Schemes 5 and 6, respectively). A plausible mechanism leading to these systems is described in Scheme 13.

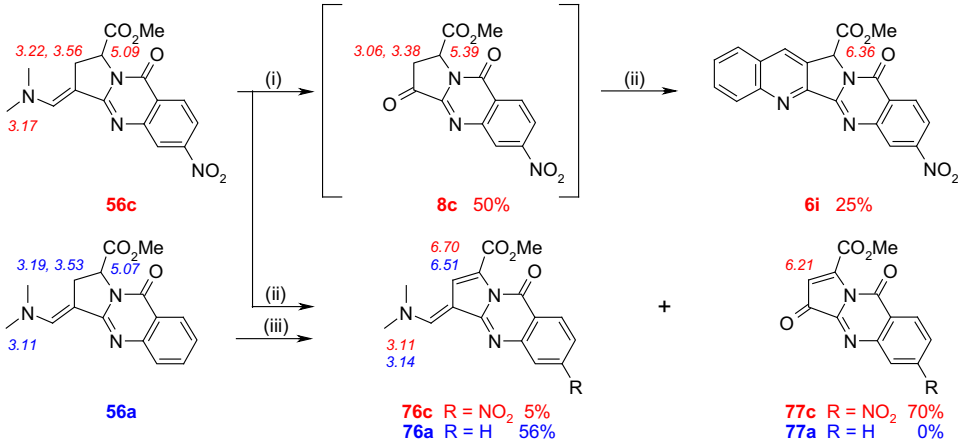
In some cases, other interesting products were obtained from the oxidation of fused quinazolines. Indeed, the tricyclic enamine **56c**[10] led only to 50% of the expected ketone **8c**. The subsequent Friedländer reaction of this unstable product **8c** gave the expected

gave bad results, but stirring enamine **56c** with oxone (acetone/$KHCO_3/H_2O$)resulted in a mixture, which could not be completely purified, and from which compounds **76c** (~5%) and **77c** (~70%) were identified from the ^1H NMR spectra of the crude products. Characteristic values of chemical shifts (ppm) in these series are provided in Scheme 14. Interestingly, scaffold of enamine **76c** is the same as the one of product **76a** that was formed in 56% yield when reagent **56a** was oxidized with $NaIO_4$ in THF/H_2O instead of the solvent mixture EtOAc/MeCN/H_2O previously used.

The structure of luotonin derivative **6i** shown in Scheme 14 was interesting, since the reduction of its nitro group could provide an amino compound. This group could lead advantageously to new hydrogen bonds in the active site of the target enzyme. On the other hand, it could easily be substituted to increase the solubility of such scaffold. Considering that compound **6i** was obtained in very low yield and poor analytical purity, and since reduction of a nitro group in the presence of *N*,*N*-dimethylaminomethylidene function did not succeed (Scheme 11), synthesis of precursor **78** was undertaken (Scheme 15). Treatment of nitrovasicinone derivative **79** by using the couple Zn/HBr led to a mixture of aminoester **78** and the corresponding aminoacid derivative. The mixture was reesterified under our standard conditions by drying the ternary azeotrope MeOH/$CHCl_3/H_2O$ with 3 Å molecular sieves.[48] The purification of the resulting mixture provided 55% of aminoester **78** accompanied by 20% of reduced derivative **80** (aminoester derivative of linaric acid)[49] and 10% of acetal **81**. The latter compound contained the same scaffold as ketoester **60a** described above



Scheme 13. Reagents and conditions: (i) AcOH, reflux. Some characteristic values of ^{13}C NMR chemical shifts are indicated in italic (and red) (ppm).



Scheme 14. Reagents and conditions: (i) $NaIO_4$, $CHCl_3$/MeCN/H_2O (1/1/1), rt, 30 min; (ii) **44**, AcOH, reflux, 2 h; (iii) Oxone, $KHCO_3$, Me_2CO, H_2O, rt, 1 h. Some characteristic values of ^1H NMR chemical shifts are indicated in italic (and red or blue) (ppm).

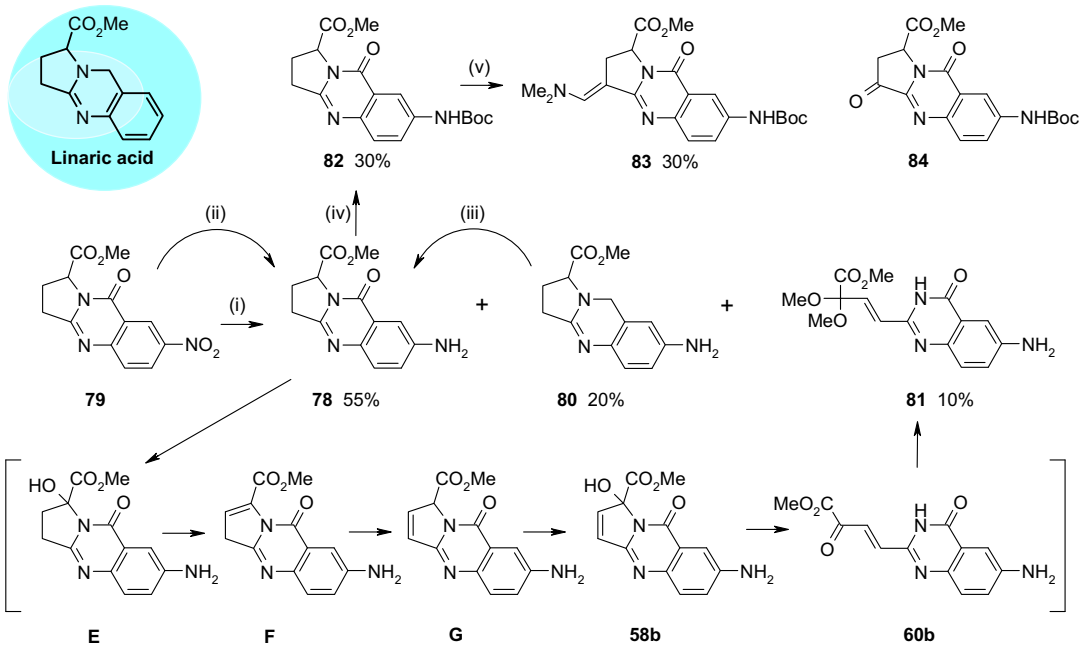
(Scheme 5). However, it was not possible to entirely characterize quinazoline **80**, which aromatized spontaneously to **78** during attempts of recrystallization. In this sense, Shakhidoyatov et al. observed analogous reduction of quinazolinone during the reduction of nitrodesoxyvasicinone.[50] As for acetal **81**, we thought that it was formed from oxidation of **78** during the esterification process; we have already described elsewhere some oxidations of compounds containing CONCHCO functionality, occurring by oxygen dissolved in MeOH.[51] On the other hand, reacting **79** with $SnCl_2$ in ethanol[52] gave 70% of amine **78** accompanied by 30% of the corresponding ethyl ester. Ultimately, by performing the reduction in methanol, methyl ester **78** was quantitatively obtained (Scheme 15).

In additional investigation, aminoester derivative **78** was protected with a Boc group to obtain the carbamate **82** in low 30–71% yield. The reaction of the latter with Bredereck's reagent afforded *N*,*N*-dimethylaminomethylidene compound **83** also in low 30–45% yield (Scheme 15). However, optimization of reaction conditions was not performed, and because the reaction occurred with low yields and purities, no further attempts to obtain a ketone **84** from the substrate **83** were performed.

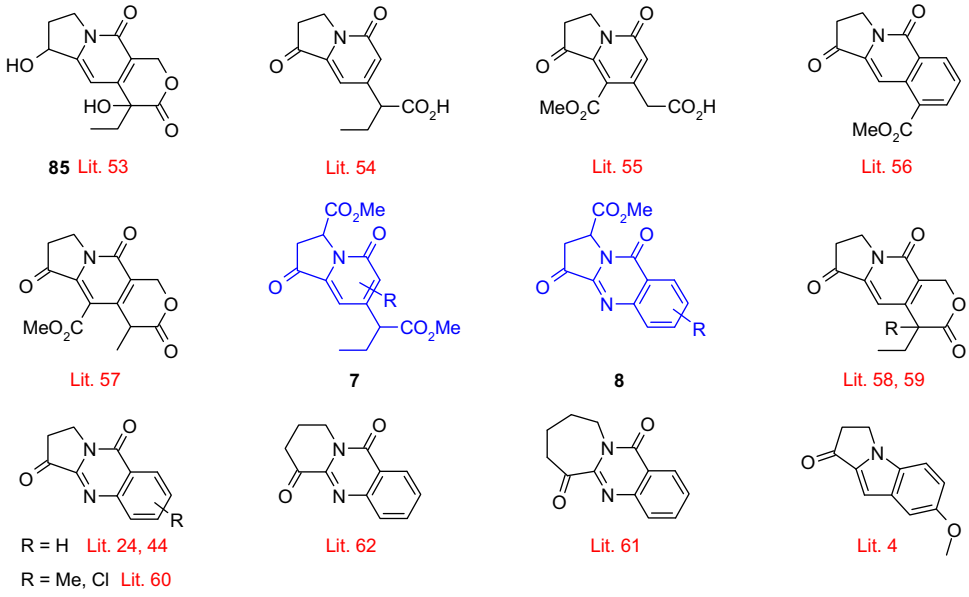
2.2.6. On the stability of ketones. The difference between the stability of close structures described in literature and summarized in Scheme 16, and the one of ketones **7** and **8** studied in this paper, is very scheming. Compounds depicted in this scheme were often purified by chromatography and/or by recrystallization and were not claimed as unstable, except for product **85** for which it was already reported that its "tricyclic α-hydroxy lactone substructure […] is rather unstable to oxidation conditions".[53] To learn more about this question, a HUMO/LUMO study has been performed on some of these ketones, and no significant difference was detected in order to explain the degradation observed.

3. Conclusion

In this paper, we have reported the first synthesis of some 5-substituted luotonin A derivatives, as well as some new 5-substituted E-ring modified camptothecin analogs. This prompted us to attempt various strategies in order to obtain unstable key ketones for the Friedländer condensation with aminobenzaldehydes. The study of the reactivity of some intermediates,



Scheme 15. Reagents and conditions: (i) (a) Zn, HBr, rt, 5 min; (b) MeOH, $MeSO_3H$, $CHCl_3$, MS 3 Å, reflux, **78** (55%), **80** (20%); (ii) $SnCl_2 \cdot 2H_2O$, MeOH, reflux, 2.5 h, 98%; (iii) air; (iv) Boc_2O, Et_3N, MeOH, reflux, 12 h; (v) Bredereck's reagent, 110 °C, 2 h.



Scheme 16

and particularly the benzilidene derivatives, led to optimized conditions for the oxidation of enamines derivatives. Straightforward conditions for the synthesis of the versatile carbonyl compounds could thus be achieved. No satisfactory conditions for the isolation of these compounds could be met due to their high unstability. However, an efficient two-step sequence has been demonstrated without purification of the intermediate. In order to introduce diversity on the target pattern, synthesis of aminobenzaldehyde derivatives was reproduced and compared with litterature results.

Interestingly, isolation and characterization of the main side-products pointed out some key properties of both intermediates and final products. In particular, opened pyrrolidino adducts demonstrated the sensitivity of this scaffold to over-oxidation, either as a tricyclic or pentacyclic ring system. This was especially observed while attempting unfavored Friedländer condensation with aminobenzaldehydes substituted with electroattractive groups. A key point exposed in this paper is the unstability of keto adducts, whose behavior is not fully rationalized, despite HOMO/LUMO calculations. Biological testing of representative compounds of each series are being performed and will be reported soon.

4. Experimental section

4.1. General

Melting points were determined using an Electrothermal apparatus and are uncorrected. ^1H and ^{13}C NMR spectra were obtained on a Varian Gemini 2000 at 200 and 50 MHz, respectively.

IR spectra were obtained in ATR mode on a FTIR Bruker Tensor 27. Thin layer chromatographies were performed on precoated Kieselgel 60F_{254} plates. HRMS were determined by the 'Centre Régional de Mesure Physique', Université Blaise Pascal, Aubière, France. Microanalyses were performed by the 'Service de Microanalyses' of LSEO, Université de Bourgogne, Dijon, France. All products are obtained as mixtures of diastereoisomers. In the text, atom numbering of compounds was the same as in camptothecin series (Fig. 1).[2i]

4.2. General procedure for Friedländer condensation

To a freshly obtained solution of the corresponding ketone (13.4 mmol) in a dichloromethane/acetonitrile/ethyl acetate mixture (450 mL) (cf. see Section 4.3) were added acetic acid (20 mL) and the related imine (13.4 mmol, 1 equiv). Volume of the resulting solution was partially reduced in order to remove most volatile organic solvents prior to additional acetic acid loading (30 mL). The reaction mixture was then refluxed for 2 h. The reaction medium was then stripped down to an oil and the residue dissolved in dichloromethane (75 mL). The resulting solution was then washed with HCl 1 N (20 mL), saturated $NaHCO_3$ (20 mL), and twice with water (2×20 mL). The organic phase was dried over magnesium sulfate and evaporated to dryness. The dark residue was recrystallized from the appropriate solvent (generally acetone) to give the pentacyclic derivative as a powder. Rework of the mother liquors could be carried out to obtain some additional material. In particular, residue obtained upon evaporation of the filtrate was refluxed in ether. Non-soluble solid was isolated by filtration and recrystallized to give 10–30% of additional product with identical properties as first crop. When utilizing impure ketone **8a** in Friedländer condensations, up to 31% of enaminoketone **72** can be isolated.

*4.2.1. Methyl 11-oxo-11,13-dihydroquino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-13-carboxylate (**6a**).* White powder; 75% yield; mp (acetone) 237–239 °C; TLC R_f (EtOAc/Hept 75/25)=0.57; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.85 (s, 3H, CO_2CH_3), 6.18 (d, J=1.3 Hz, 1H, $CHCO_2Me$), 7.61 (ddd, J=7.9, 7.1, 1.3 Hz, 1H, Ar*H*), 7.73 (ddd, J=8.3, 7.0, 1.3 Hz, 1H, Ar*H*), 7.88 (ddd, J=8.5, 7.0, 1.5 Hz, 1H, Ar*H*), 7.89 (ddd, J=8.3, 7.1, 1.5 Hz, 1H, Ar*H*), 8.00 (d, J=8.3 Hz, 1H, Ar*H*), 8.15 (d, J=8.3 Hz, 1H, Ar*H*), 8.44 (dd, J=7.9, 1.5 Hz, 1H, Ar*H*), 8.50 (d, J=8.5 Hz, 1H, Ar*H*), 8.57 (br s, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 53.6 (CH_3), 60.0 (CH), 121.5 (C), 126.7 (CH), 127.7 (CH), 128.1 (C), 128.2 (CH), 128.7 (C), 128.8 (CH), 128.9 (CH), 130.7 (CH), 131.2 (CH), 131.7 (CH), 134.8 (CH), 149.1 (C), 149.9 (C), 150.4 (C), 151.2 (C), 159.9 (C), 166.3 (C); IR ν cm^{-1}: 1277, 1606, 1628, 1676, 1736. Anal. Calcd for $C_{20}H_{13}N_3O_3$: C, 69.97; H, 3.82; N, 12.24. Found: C, 69.68; H, 3.94; N, 12.23.

*4.2.2. Methyl 8-chloro-11-oxo-11,13-dihydroquino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-13-carboxylate (**6b**).* Yellow powder; 50% yield; mp (ether/methanol) 262–264 °C; TLC R_f (EtOAc/Hept 75/25)=0.46; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.86 (s, 3H, CO_2CH_3), 6.17 (d, J=1.3 Hz, 1H, $CHCO_2Me$), 7.56 (dd, J=8.7, 1.8 Hz, 1H, Ar*H*), 7.75 (ddd, J=8.0, 7.0, 1.4 Hz, 1H, Ar*H*), 7.91 (ddd, J=8.6, 7.0, 1.7 Hz, 1H, Ar*H*), 8.01 (dd, J=8.0, 1.7 Hz, 1H, Ar*H*), 8.12 (d, J=1.8 Hz, 1H, Ar*H*), 8.36 (d, J=8.7 Hz, 1H, Ar*H*), 8.50 (d, J=8.6 Hz, 1H, Ar*H*), 8.58 (br s, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 53.7 (CH_3), 60.0 (CH), 120.0 (C), 128.1 (CH), 128.1 (C), 128.2 (CH), 128.3 (2×CH), 128.8 (C), 129.0 (CH), 130.8 (CH), 131.4 (CH), 131.7 (CH), 141.1 (C), 149.9 (C), 150.0 (C), 150.2 (C), 153.0 (C), 159.3 (C), 166.1 (C); IR ν cm^{-1}: 1014, 1247, 1598, 1624, 1674, 1744. HRMS (ESITOF) m/z calcd for $C_{20}H_{13}ClN_3O_3$ $(M+H)^+$ 378.0645; found 378.0647.

*4.2.3. Methyl 11-oxo-11,13-dihydro[1,3]dioxolo[6′,7′]quino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-13-carboxylate (**6c**).* Off-white powder; 37% yield; mp ($CHCl_3$) 254–256 °C; TLC R_f (EtOAc)=0.76; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.85 (s, 3H, CO_2CH_3), 6.09 (d, J=1.2 Hz, 1H, $CHCO_2Me$), 6.21 (s, 2H, OCH_2O), 7.20 (s, 1H, Ar*H*), 7.58 (ddd, J=8.1, 7.1, 1.2 Hz, 1H, Ar*H*), 7.74 (s, 1H, Ar*H*), 7.86 (ddd, J=8.6, 7.1, 1.5 Hz, 1H, Ar*H*), 8.12 (dd, J=8.6, 1.2 Hz, 1H, Ar*H*), 8.33 (br s, 1H, Ar*H*), 8.42 (dd, J=8.1, 1.5 Hz, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 53.5 (CH_3), 60.0 (CH), 102.4 (CH_2), 102.9 (CH), 106.6 (CH), 121.4 (C), 126.5 (C), 126.7 (CH), 126.8 (CH), 127.1 (C), 127.4 (CH), 129.6 (CH), 134.5 (CH), 148.1 (C), 148.9 (C), 149.3 (C), 149.9 (C), 152.2 (C), 152.3 (C), 159.9 (C), 166.5 (C); IR ν cm^{-1}: 1208, 1240, 1602, 1631, 1672, 1754. HRMS (ESITOF) m/z calcd for $C_{21}H_{14}N_3O_5$ $(M+H)^+$ 388.0933; found 388.0944.

*4.2.4. Methyl 2,3-dimethoxy-11-oxo-11,13-dihydroquino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-13-carboxylate (**6d**).* Off-white powder; 42% yield; mp (CH_2Cl_2) 234–236 °C; TLC R_f (EtOAc/Hept 75/25)=0.2; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.84 (s, 3H, CO_2CH_3), 4.07 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 6.11 (d, J=1.1 Hz, 1H, $CHCO_2Me$), 7.17 (s, 1H, Ar*H*), 7.58 (ddd, J=7.9, 7.2, 1.3 Hz, 1H, Ar*H*), 7.78 (s, 1H, Ar*H*), 7.86 (ddd, J=8.1, 7.2, 1.6 Hz, 1H, Ar*H*), 8.10 (ddd, J=8.1, 1.3, 0.6 Hz, 1H, Ar*H*), 8.36 (t, J=1.1 Hz, 1H, Ar*H*), 8.41 (ddd, J=7.9, 1.6, 0.6 Hz, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 53.6 (CH_3), 56.3 (CH_3), 56.4 (CH_3), 60.1 (CH), 105.1 (CH), 108.8 (CH), 121.4 (C), 125.3 (C), 126.7 (CH), 127.1 (C), 127.4 (CH), 128.7 (CH), 129.1 (CH), 134.8 (CH), 147.4 (C), 147.9 (C), 149.4 (C), 151.8 (C), 152.3 (C), 153.9 (C), 160.1 (C), 166.7 (C); IR ν cm^{-1}: 1179, 1213, 1257, 1602, 1633, 1678, 1751. Anal. Calcd for $C_{22}H_{17}N_3O_5 \cdot 5/4H_2O$: C, 62.04; H, 4.61; N, 9.87. Found: C, 61.89; H, 4.22; N, 9.62.

*4.2.5. Methyl 2-methoxy-11-oxo-11,13-dihydroquino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-13-carboxylate (**6e**).* Yellow powder; 50% yield; mp (acetone) 253–251 °C; TLC R_f (EtOAc/Hept 75/25)=0.35; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.84 (s, 3H, CO_2CH_3), 3.99 (s, 3H, OCH_3), 6.13 (d, J=1.1 Hz, 1H, $CHCO_2Me$), 7.20 (dd, J=2.8, 0.7 Hz; 1H, Ar*H*), 7.52 (dd, J=9.5, 2.8 Hz, 1H, Ar*H*), 7.58 (ddd, J=8.1, 7.2, 1.2 Hz, 1H, Ar*H*), 7.86 (ddd, J=8.2, 7.2, 1.7 Hz, 1H, Ar*H*), 8.11 (dd, J=8.2, 1.2 Hz, 1H, Ar*H*), 8.36 (d, J=9.5 Hz, 1H, Ar*H*), 8.41 (dd, J=8.1, 1.7 Hz, 1H, Ar*H*), 8.41 (br s, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 53.6 (CH_3), 57.8 (CH_3), 60.0 (CH), 105.3 (CH), 121.4 (C), 124.6 (CH), 126.7 (CH), 127.5 (CH), 128.4 (C), 128.8 (CH), 129.9 (CH), 130.4 (C), 132.1 (CH), 134.9 (CH), 146.2 (C), 147.9 (C), 149.3 (C), 152.1 (C), 159.6 (C), 160.0 (C), 166.5 (C); IR ν cm^{-1}: 1234, 1261, 1603, 1624, 1672, 1743. Anal. Calcd for $C_{21}H_{15}N_3O_4 \cdot 4/5H_2O$: C, 65.96; H, 4.22; N, 10.99. Found: C, 66.16; H, 4.27; N, 10.59.

*4.2.6. Methyl 14-methyl-11-oxo-11,13-dihydroquino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-13-carboxylate (**6f**).* Product purified by silica gel chromatography prior to recrystallization. Off-white powder; 39% yield; mp (acetone/ether) 250 °C (dec); TLC R_f (EtOAc/Hept 75/25)=0.43; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.96 (s, 3H, CH_3), 3.78 (s, 3H, CO_2CH_3), 6.21 (s, 1H, $CHCO_2Me$), 7.60 (ddd, J=8.2, 7.2, 1.2 Hz, 1H, Ar*H*), 7.74 (ddd, J=8.1, 6.6, 1.3 Hz, 1H, Ar*H*), 7.88 (ddd, J=8.4, 6.6, 1.1 Hz, 1H, Ar*H*), 7.89 (ddd, J=8.3, 7.2, 1.6 Hz, 1H, Ar*H*), 8.15 (ddd, J=8.1, 1.1, 0.6 Hz, 1H, Ar*H*), 8.17 (dd, J=8.3, 1.2 Hz, 1H, Ar*H*), 8.42 (ddd, J=8.2, 1.6, 0.7 Hz, 1H, Ar*H*), 8.49 (ddd, J=8.4, 1.3, 0.6 Hz, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 14.8 (CH_3), 53.2 (CH_3), 60.2 (CH), 121.3 (C), 123.7 (CH), 126.5 (CH), 126.9 (C), 127.5 (CH), 128.3 (CH), 128.6 (C), 128.7 (CH), 130.6 (CH), 131.2 (CH), 134.7 (CH), 141.8 (C), 149.2 (C), 150.0 (C), 152.1 (C), 159.8 (C), 166.7 (C). Anal. Calcd for $C_{21}H_{15}N_3O_3 \cdot 4/5H_2O$: C, 67.84; H, 4.50; N, 11.30. Found: C, 67.96; H, 4.37; N, 11.42.

*4.2.7. Methyl 2-chloro-11-oxo-11,13-dihydroquino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-13-carboxylate (**6h**), methyl 2-[(4-methylphenyl)amino]-4-oxo-4-(4-oxo-3,4-dihydroquinazolin-2-yl)but-2-enoate (**72**), and methyl 4-[(4-methylphenyl)amino]-2-oxo-4-(4-oxo-1,4-dihydro-2-quinazolinyl)-3-butenoate (**73**).* Starting from 200 mg of crude ketone, the reaction mixture was purified by silica gel column

chromatography using a gradient of ethyl acetate in heptane. The compounds isolated were only characterized by NMR.

4.2.7.1. Ester ***6h***. Oil, 10% yield; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.85 (s, 3H, CH_3), 6.16 (d, J=1 Hz 1H, CHCO$_2$Me), 7.60 (ddd, J=8.1, 7.0, 1.4 Hz, 1H, ArH), 7.79 (dd, J=9.1, 6.6, 2.4 Hz, 1H, ArH), 7.87 (ddd, J=8.6, 7.1, 1.5 Hz, 1H, ArH), 7.94 (d, J=2.4 Hz, 1H, ArH), 8.11 (dd, J=8.4, 1.3 Hz, 1H, ArH), 8.35–8.43 (m, 2H, ArH), 8.46 (t, J=1 Hz, 1H, ArH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 53.7 (CH_3), 59.9 (CH), 119.8 (C), 121.4 (C), 126.7 (CH), 126.8 (CH), 127.9 (CH), 128.9 (CH), 130.7 (CH), 131.9 (C), 132.1 (CH), 132.3 (CH), 133.2 (C), 134.9 (CH), 137.6 (C), 148.2 (C), 149.0 (C), 150.7 (C), 159.8 (C), 166.0 (C).

4.2.7.2. Ketone ***72***. Oil, 20% yield: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.36 (s, 3H, CH_3), 3.79 (s, 3H, CO$_2$CH_3), 7.00 (d, J=6.0 Hz, 2H, ArH), 7.03 (s, 1H, ArH), 7.18 (d, J=6.0 Hz, 2H, ArH), 7.59 (ddd, J=8.0, 6.3, 2.0 Hz, 1H, ArH), 7.78–7.91 (m, 2H, ArH), 8.36 (ddd, J=8.0, 1.4, 0.8 Hz, 1H, ArH), 10.22 (br s, 1H, NH), 11.93 (br s, 1H, NH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.9 (CH_3), 53.0 (CH_3), 93.1 (CH), 122.1 (2CH), 123.0 (C), 126.7 (CH), 128.5 (CH), 128.8 (CH), 129.9 (2CH), 134.6 (CH), 135.8 (C), 136.4 (C), 147.1 (C), 148.1 (C), 152.7 (C), 161.0 (C), 163.8 (C), 181.3 (C).

4.2.7.3. Ketone ***73***. Oil, 20% yield: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.34 (s, 3H, CH_3), 3.81 (s, 3H, CO$_2$CH_3), 5.53 (d, J=2.8 Hz, 1H, NHC=CCH), 6.00 (d, J=2.8 Hz, 1H, NHC=CCH), 6.84 (br s, 1H, NHC=O), 7.08 (d, J=8.6 Hz, 2H, ArH), 7.18 (d, J=8.6 Hz, 2H, ArH), 7.52 (ddd, J=8.1, 5.2, 2.9 Hz, 1H, ArH), 7.76–7.86 (m, 2H, ArH), 8.36 (ddd, J=8.1, 1.3, 0.9 Hz, 1H, ArH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.1 (CH_3), 52.7 (CH_3), 98.2 (CH), 117.4 (2CH), 120.4 (C), 125.3 (C), 126.2 (CH), 126.4 (CH), 126.7 (CH), 129.4 (2CH), 131.5 (C), 133.9 (CH), 135.1 (C), 137.4 (C), 148.3 (C), 153.1 (C), 158.6 (C), 166.9 (C).

*4.2.8. Methyl 9-nitro-11-oxo-11,13-dihydroquino[2′,3′:3,4]pyrrolo[2,1-b]quinazoline-13-carboxylate (****6i****).* Yellow powder; 25% yield; mp (DMSO) >220 °C; TLC R_f (EtOAc/Hept 75/25)=0.4; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.90 (s, 3H, CO$_2$CH_3), 6.36 (d, J=1.2 Hz, 1H, CHCO$_2$Me), 7.81 (ddd, J=8.2, 6.9, 1.4 Hz, 1H, ArH), 7.96 (ddd, J=8.5, 6.9, 1.6 Hz, 1H, ArH), 8.11 (ddd, J=8.5, 1.4, 0.7 Hz, 1H, ArH), 8.26 (d, J=9.1 Hz, 1H, ArH), 8.48 (ddd, J=8.2, 1.6, 0.7 Hz, 1H, ArH), 8.68 (dd, J=9.1, 2.6 Hz, 1H, ArH), 8.70 (br s, 1H, ArH), 9.23 (d, J=2.6 Hz, 1H, ArH); IR ν cm^{-1}: 1265, 1345, 1572, 1606, 1628, 1679, 1747. HRMS (ESITOF) m/z calcd for $C_{20}H_{13}N_4O_5$ $(M+H)^+$ 389.0886; found 389.0898.

4.3. General procedure for the preparation of ketones in indolizine and pyroloquinazolinone series

To a solution of enamine (1 equiv) in an ethyl acetate/acetonitrile 1/1 mixture (200 mL) was added an aqueous solution of sodium periodate (70 g/L, 200 mL, >4 equiv) at room temperature. The resulting biphasic mixture was allowed to stir at room temperature until disappearance of starting material (15–45 min). Reaction medium was then extracted with dichloromethane (3×100 mL). Organic phases were combined and rapidly washed with water (100 mL). The resulting organic phase was used directly in the following step without further work-up, except otherwise specified.

*4.3.1. Methyl 7-[1-(methoxycarbonyl)propyl]-8-nitro-1,5-dioxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (****7d****).* ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 0.92 and 0.97 (2t, J=7.4 Hz, 3H, CHCH$_2$CH_3), 1.73–1.94 (m, 1H, CHCH_2CH$_3$), 2.02–2.24 (m, 1H, CHCH_2CH$_3$), 2.79–3.01 (m, 1H, CH_2CH), 3.17–3.34 (m, 1H, CH_2CH), 3.57 and 3.58 (2t, J=7.5 Hz, 1H, CHCH$_2$CH$_3$), 3.71 and 3.75 (2s, 3H, CO$_2$CH_3), 3.86 (s, 3H, CO$_2$CH_3), 5.28 (dd, J=9.2, 3.5 Hz, 1H, CH$_2$CH$_2$CH), 7.04 and 7.08 (2s, 1H, ArH). This compound was not analyzed but used directly in the following step.

*4.3.2. Methyl 6-chloro-7-[1-(methoxycarbonyl)propyl]-1,5-dioxo-1,2,3,5-tetrahydro-3-indolizinecarboxylate (****7e****).* The organic phase was evaporated and the resulting oil purified by silica gel column chromatography using a gradient of ethyl acetate in heptane. Red oil; 89% yield; TLC R_f (EtOAc)=0.65; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 0.94 and 0.97 (2t, J=7.3 Hz, 3H, CHCH$_2$CH_3), 1.64–2.3 (m, 2H, CHCH_2CH$_3$), 2.8–3.29 (m, 2H, CH_2CH), 3.71 and 3.73 (2s, 3H, CO$_2$CH_3), 3.85 (s, 3H, CO$_2$CH_3), 4.16 (t, J=8 Hz, 1H, CHCH$_2$CH$_3$), 5.23 (dd, J=9.3, 3.9 Hz, 1H, CH$_2$CH), 7.01 and 7.03 (2s, 1H, CH); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 11.8, 11.9 (2s, CH_3), 25.1, 25.4 (2s, CH_2), 38.3 (CH_2), 49.7 (CH), 52.5 (CH), 53.5 (CH_3), 55.4 (CH_3), 103.2 (CH), 136.4 (C), 148.2 (C), 156.6 (C), 166.9 (C), 169.0 (C), 171.8 (C), 193.0 (C); IR ν cm^{-1}: 1739, 1656, 1193, 1174. Anal. Calcd for $C_{15}H_{16}ClNO_6\cdot 2/3H_20$: C, 50.93; H, 4.94; N, 3.96. Found: C, 50.60; H, 4.53; N, 3.82.

*4.3.3. Methyl 8-bromo-7-[1-(methoxycarbonyl)propyl]-6-nitro-1,5-dioxo-1,2,3,5-tetrahydro-3-indolizinecarboxylate (****7f****).* The organic phase was evaporated and the resulting oil purified by silica gel column chromatography using a gradient of ethyl acetate in heptane. Red oil; 79% yield; TLC R_f (EtOAc)=0.4; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 0.88 and 0.91 (2t, J=7.4 Hz, 3H, CHCH$_2$CH_3), 1.73–1.99 (m, 1H, CHCH_2CH$_3$), 2.21–2.41 (m, 1H, CHCH_2CH$_3$), 2.79–2.99 (m, 1H, CH_2CH), 3.16–3.33 (m, 1H, CH_2CH), 3.65 and 3.67 (2s, 3H, CO$_2$CH_3), 3.70–3.78 (m, 1H, CHCH$_2$CH$_3$), 3.79 and 3.80 (2s, 3H, CO$_2$CH_3), 5.15 and 5.16 (2dd, J=9.4, 5.8 and 9.4, 5.6 Hz, 1H, CH$_2$CH$_2$CH); IR ν cm^{-1}: 1742, 1673, 1545, 1259, 1211. Anal. Calcd for $C_{15}H_{15}BrN_2O_8\cdot 1/2$EtOAc: C, 42.96; H, 4.03; N, 5.89. Found: C, 42.83; H, 4.13; N, 5.14.

*4.3.4. Methyl 3,9-dioxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (****8a****).* ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.00 (dd, J=19.9, 3.5 Hz, 1H, CHCH_2C=O), 3.33 (dd, J=19.9, 9.4 Hz, 1H, CHCH_2C=O), 3.86 (s, 3H, CO$_2$CH_3), 5.35 (dd, J=9.4, 3.5 Hz, 1H, CHCH$_2$C=O), 7.68 (ddd, J=8.1, 7.2, 1.2 Hz, 1H, ArH), 7.90 (ddd, J=8.2, 7.2, 1.6 Hz, 1H, ArH), 8.04 (dd, J=8.2, 1.2 Hz, 1H, ArH), 8.39 (dd, J=8.1, 1.6 Hz, 1H, ArH).

Unambiguous signals corresponding to the enol form **8′a** (10%) are listed as follows: ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.82 (s, 3H, CO$_2$CH_3), 5.44 (d, J=3.0 Hz, 1H, CHCO$_2$CH$_3$), 6.03 (d, J=3.0 Hz, 1H, CH=COH). This compound was not analyzed but used directly in the following step.

*4.3.5. Methyl 6-chloro-3,9-dioxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (****8b****).* ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.99 (dd, J=19.9, 3.4 Hz, 1H, CHCH_2C=O), 3.33 (dd, J=19.9, 9.4 Hz, 1H, CHCH_2C=O), 3.86 (s, 3H, CO$_2$CH_3), 5.33 (dd, J=9.4, 3.4 Hz, 1H, CHCH$_2$C=O), 7.61 (dd, J=8.6, 2.0 Hz, 1H, ArH), 8.00 (dd, J=2.0, 0.5 Hz, 1H, ArH), 8.30 (dd, J=8.6, 0.5 Hz, 1H, ArH). This compound was not analyzed but used directly in the following step.

*4.3.6. Methyl 7-nitro-3,9-dioxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (****8c****).* ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.06 (dd, J=20.0, 3.4 Hz, 1H, CHCH_2C=O), 3.38 (dd, J=20.0, 9.4 Hz, 1H, CHCH_2C=O), 3.89 (s, 3H, CO$_2$CH_3), 5.39 (dd, J=9.4, 3.4 Hz, 1H, CHCH$_2$C=O), 8.17 (d, J=9.0 Hz, 1H, ArH), 9.23 (d, J=2.6 Hz, 1H, ArH), 8.67 (dd, J=9.0, 2.6 Hz, 1H, ArH). This compound was not analyzed but used directly in the following step.

4.4. Synthesis of benzaldehyde derivatives

*4.4.1. 6-Nitro-1,3-benzodioxole-5-carbaldehyde (****12****).* 1,1-Diacetyl compound **13** (28.0 g, 94.2 mmol) was dissolved in hot aqueous ethanol (70/30). Concentrated sulfuric acid (10 mL) was then slowly added and the reaction medium was refluxed for 10 h. The product

crystallized upon cooling and was isolated by filtration to give yellow crystals of 6-nitropiperonal (2.5 g, 14%). Filtrate was concentrated to an oil, which crystallized upon standing. Yellow crystals were filtered off to give an additional 52% (10.0 g) of 6-nitropiperonal. Yellow crystals; 66% yield; mp (EtOH) 91–93 °C (lit. 93–94 °C[63]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 6.23 (s, 2H, OCH_2O), 7.36 (s, 1H, Ar*H*), 7.55 (s, 1H, Ar*H*), 10.31 (s, 1H, C*H*O); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 103.9 (CH_2), 105.1 (CH), 107.6 (CH), 128.1 (C), 147.6 (C), 151.6 (C), 152.3 (C), 186.8 (CH); IR ν cm^{-1}: 1368, 1598, 1681. HRMS (ESITOF) *m*/*z* calcd for $C_8H_5NO_5Na$ (M+Na)$^+$ 218.0065; found 3218.0075.

*4.4.2. 5-(Diacetyloxy)-6-nitro-1,3-benzodioxole (**13**).* To a cold solution of piperonal (5.0 g, 33.3 mmol) in acetic anhydride (50 mL) was added dropwise nitric acid (7.5 mL, 170 mmol, 5 equiv). The reaction medium was stirred at 0 °C for 2 h and then allowed to warm to room temperature. The solution was then evaporated and the residue was taken in dichloromethane (50 mL). The organic phase was neutralized with a saturated aqueous $NaHCO_3$ solution, washed with water (2×20 mL), dried over magnesium sulfate, and evaporated. The resulting solid was recrystallized from ethanol to give acylal **13**. Yellowish crystals; 55% yield; mp (EtOH) 141–143 °C (lit. 142 °C[64]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.14 (s, 6H, $(OCOCH_3)_2$), 6.17 (s, 2H, OCH_2O), 7.13 (s, 1H, Ar*H*), 7.58 (s, 1H, C*H*($OCOCH_3)_2$), 8.16 (s, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.3 (2×CH_3), 85.7 (CH), 103.2 (CH), 105.6 (CH_2), 106.5 (CH), 127.3 (C), 142.0 (C), 148.4 (C), 151.9 (C), 167.9 (2×C); IR ν cm^{-1}: 1197, 1347, 1733, 1770. HRMS (ESITOF) *m*/*z* calcd for $C_{12}H_{11}NO_8Na$ (M+Na)$^+$ 320.0382; found 320.0385.

*4.4.3. 3,4-Dimethoxybenzaldehyde (**19**).* To a solution of vanillin (3.0 g, 19.7 mmol) in acetone (75 mL) were added potassium carbonate (5.5 g, 19.7 mmol, 1 equiv) and methyl sulfate (3.7 mL, 39.4 mmol, 2 equiv) at room temperature. The resulting suspension was refluxed for 90 min and allowed to cool to room temperature. Excess of methyl sulfate was neutralized by dropwise addition of triethylamine and the reaction mixture was concentrated. The residue was dissolved in dichloromethane (40 mL), washed with a 10% w/w sodium hydroxide solution (20 mL), and then with water (2×15 mL). The organic phase was dried over magnesium sulfate, filtered, and evaporated to give aldehyde **19** (3.26 g, 99%). White solid; mp (EtOH) 41–43 °C (lit. 43–45 °C[65]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.96 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 6.99 (d, *J*=8.2 Hz, 1H, Ar*H*), 7.42 (d, *J*=1.9 Hz, 1H, Ar*H*), 7.47 (dd, *J*=8.2, 1.9 Hz, 1H, Ar*H*), 9.85 (s, 1H, C*H*O); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 55.9 (CH_3), 56.1 (CH_3), 109.3 (CH), 110.6 (CH), 126.6 (CH), 130.3 (C), 149.7 (C), 154.6 (C), 190.7 (CH); IR ν cm^{-1}: 1269, 1587, 1683.

*4.4.4. 4,5-Dimethoxy-2-nitrobenzaldehyde (**20**).* Grinded veratraldehyde (5.65 g, 34 mmol) was added portionwise to nitric acid (35 mL) over 1 h while keeping internal temperature below 20 °C. Upon complete addition, reaction medium was allowed to stir for 10 min and was then poured into a water/ice mixture (350 mL) with vigorous stirring and keeping the resulting suspension in dark. Precipitated crystals were filtered, washed with cold water, and dried in dark to give nitroveratraldehyde (6.04 g, 84%). Yellowish crystals; mp (EtOH) 128–130 °C (lit. 132–133 °C[66]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 4.04 (s, 3H, OCH_3), 4.05 (s, 3H, OCH_3), 7.42 (s, 1H, Ar*H*), 7.65 (s, 1H, Ar*H*), 10.45 (s, 1H, C*H*O); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 55.9 (CH_3), 56.1 (CH_3), 106.9 (CH), 109.5 (CH), 125.2 (C), 143.5 (C), 152.0 (C), 152.8 (C), 187.2 (CH); IR ν cm^{-1}: 1336, 1522, 1574, 1687. HRMS (ESITOF) *m*/*z* calcd for $C_9H_9NO_5Na$ (M+Na)$^+$ 234.0378; found 234.0390.

*4.4.5. 5-Chloro-2-nitrobenzaldehyde (**21**).* To a solution of 3-chlorobenzaldehyde (20 g, 0.14 mol) in sulfuric acid (200 mL) was dropwise added nitric acid (15 mL) at 0 °C. The reaction medium was stirred at room temperature for 1 h, and then poured into ice. The resulting white precipitate was filtered, then washed with cold water, and dried under vacuum (20.8 g, 80%). White crystals; mp (EtOH) 73–75 °C (lit. 74 °C[67]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 7.71 (dd, *J*=8.6, 2.3 Hz, Ar*H*), 7.91 (d, *J*=2.3 Hz, 1H, Ar*H*), 8.12 (d, *J*=8.3 Hz, 1H, Ar*H*), 10.44 (s, 1H, C*H*O); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 125.6 (CH and C), 129.0 (CH), 132.1 (C), 132.8 (CH), 140.7 (C), 186.2 (CH). Traces of 3-chloro-4-nitrobenzaldehyde **23** were observed in the ^{1}H NMR spectra of the crude mixture, leading to formation of a peak at 9.96 ppm.

*4.4.6. 1-(Diethoxymethyl)-4,5-dimethoxy-2-nitrobenzene (**22**).* Nitroveratraldehyde was dissolved in hot ethanol and refluxed for 30 min. The solution was allowed to cool to room temperature and kept at −30 °C overnight. The resulting solid was filtered off to give acetal **22** (0.76 g, 56%). Yellow crystals; mp (EtOH) 57–59 °C; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 1.26 (t, *J*=7.0 Hz, 6H, $(OCH_2CH_3)_2$), 3.53–3.86 (m, 4H, $(OCH_2CH_3)_2$), 3.95 (s, 3H, OCH_3), 3.99 (s, 3H, OCH_3), 6.10 (s, 1H, C*H*), 7.34 (s, 1H, Ar*H*), 7. 56 (s, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 15.1 (2×CH_3), 56.3 ($2CH_3$), 63.9 ($2CH_2$), 98.6 (CH), 107.9 (CH), 109.2 (CH), 129.2 (2C), 148.4 (C), 152.9 (C); IR ν cm^{-1}: 1222, 1274, 1524, 1574, 1687. HRMS (ESITOF) *m*/*z* calcd for $C_{13}H_{19}NO_6Na$ (M+Na)$^+$ 308.1110; found 308.1106.

*4.4.7. 3-Formyl methyl carbonate (**28**).* Hydroxybenzaldehyde (60 g, 0.49 mol) was dissolved in pyridine (200 mL) and the resulting solution was cooled in an ice bath. Methyl chloroformate (65 mL, 0.84 mol) was then added dropwise over 30 min. The reaction medium was allowed to warm to room temperature and was stirred for 4 h. Pyridine was evaporated and residue was taken into water (200 mL). This aqueous layer was extracted with diethyl ether (3×75 mL). The organic layers were combined, washed once with water, once with diluted hydrochloric acid (5%), once with a cold aqueous solution of sodium hydroxide (5%), and again with water. The resulting ether layer was dried over magnesium sulfate and evaporated to dryness to give crude carbonate (147.8 g, 48%). Aqueous layers could be combined, acidified, and extracted with ether to recover unreacted hydroxybenzaldehyde (77.3 g, 37%). White crystals; 76% yield; mp (EtOH) 51–53 °C (lit. 47–49 °C[21]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.94 (s, 3H, C*H*$_3$OCO), 7.46 (ddd, *J*=7.8, 2.4, 1.3 Hz, 1H, Ar*H*), 7.58 (td, *J*=7.8, 0.5 Hz, 1H, Ar*H*), 7.72 (ddd, *J*=2.4, 1.3, 0.5 Hz, 1H, Ar*H*), 7.79 (dt, *J*=7.8, 1.3 Hz, 1H, Ar*H*), 10.01 (s, 1H, C*H*O); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 55.6 (CH_3), 121.7 (CH), 127.1 (CH), 127.4 (CH), 130.2 (CH), 137.8 (C), 151.6 (C), 153.8 (C), 190.9 (CH); IR ν cm^{-1}: 1249, 1691, 1753. HRMS (ESITOF) *m*/*z* calcd for $C_9H_8NO_4Na$ (M+Na)$^+$ 203.0320; found 203.0324.

*4.4.8. 3-(Diacetoxymethyl)phenyl methyl carbonate (**29**).* 1,1-Diacetyl compound **29** was obtained according to the same procedure as acylal **13**. Colorless crystals; 83% yield; mp (EtOH) 62–64 °C; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.13 (s, 6H, $COCH_3$), 3.92 (s, 3H, CO_2CH_3), 7.20–728 (m, 1H, Ar*H*), 7.34–7.48 (m, 2H, Ar*H*), 7.41 (d, *J*=1.0 Hz, Ar*H*), 7.68 (s, 1H, C*H*($OCOCH_3)_2$); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.7 ($2CH_3$), 55.3 (CH_3), 88.7 (CH), 119.3 (CH), 122.3 (CH), 124.3 (CH), 129.6 (CH), 137.0 (C), 151.0 (C), 153.9 (C), 168.5 (2C); IR ν cm^{-1}: 1218, 1743, 1762. HRMS (ESITOF) *m*/*z* calcd for $C_{13}H_{14}NO_7Na$ (M+Na)$^+$ 305.0637; found 305.0623.

*4.4.9. 3-Formyl-4-nitrophenyl methyl carbonate (**30**).* To a solution of carbonate **28** (50 g, 0.28 mol) in concentrated sulfuric acid (600 mL) was dropwise added a cold solution of nitric acid (17 mL, 0.31 mol, 1.1 equiv) in sulfuric acid (100 mL) in an ice bath over 1 h. The resulting solution was stirred at 0 °C for 1 h and was then carefully poured onto ice (2 kg). The precipitate was filtered off,

vacuum dried, and recrystallized from ethanol to give nitrocarbonate **30** (47.3 g, 75%). White crystals; mp (EtOH) 80–82 °C (lit. 76–78 °C[21]); TLC R_f (EtOAc/Hept 75/25)=0.67; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.97 (s, 3H, CO_2CH_3), 7.60 (dd, J=8.8, 2.7 Hz, 1H, Ar*H*), 7.77 (d, 1H, J=2.7 Hz, Ar*H*), 8.21 (d, J=8.8 Hz, Ar*H*), 10.44 (s, 1H, C*H*O); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 56.1 (CH_3), 122.0 (CH), 125.7 (CH and C), 126.6 (CH), 152.8 (C), 154.8 (C), 186.9 (C); IR ν cm^{-1}: 1226, 1347, 1525, 1585, 1695, 1763.

*4.4.10. 5-Hydroxy-2-nitrobenzaldehyde (**31**).* Carbonate **30** (4.25 g, 20 mmol) was dissolved in concentrated sodium hydroxide (30% w/w, 30 mL) and the resulting solution was stirred at room temperature for 1 h. Reaction medium was then cooled in an ice bath and carefully neutralized with acetic acid. Precipitating hydroxynitrobenzaldehyde was filtered, dried, and recrystallized from ethanol (2.35 g, 70%). Yellow crystals; mp (EtOH) 158–160 °C (lit. 167–169 °C[68]); TLC R_f (EtOAc/Hept 75/25)=0.47; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 6.16 (br s, 1H, O*H*), 7.13 (dd, J=8.8, 2.9 Hz, 1H, Ar*H*), 7.29 (d, J=2.9 Hz, 1H, Ar*H*), 8.16 (d, J=8.8 Hz, 1H, Ar*H*), 10.48 (s, 1H, C*H*O); ^{13}C NMR: (DMSO d_6, 50 MHz) δ ppm: 117.1 (CH), 120.8 (CH), 128.3 (CH), 131.2 (C), 137.9 (C), 174.9 (C), 191.6 (CH); IR ν cm^{-1}: 1310, 1332, 1521, 1577, 1668, 3119. HRMS (ESITOF) m/z calcd for $C_7H_5NO_4Na$ $(M+Na)^+$ 190.0116; found 190.0118.

*4.4.11. 2-Nitro-5-[2-(1-piperidinyl)ethoxy]benzaldehyde (**34**).* To a solution of hydroxynitrobenzaldehyde **31** (3.0 g, 18.0 mmol) in DMF (30 mL) was added potassium carbonate (9.92 g, 71.8 mmol, 4 equiv) followed by addition of 1-(2-chloroethyl)piperidine hydrochloride (3.30 g, 18 mmol, 1 equiv). The solution was heated at 80 °C for 4 h. Solvent was evaporated, and then the residue partitioned between dichloromethane (50 mL) and water (15 mL). The organic layer was separated, washed with water (3×15 mL), dried over magnesium sulfate, and evaporated to give compound **34** (4.75 g, 95%). Dark oil; TLC R_f (EtOAc/Hept 70/30)=0.23; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 1.39–1.52 (m, 2H, $N(CH_2CH_2)_2CH_2$), 1.52–1.74 (m, 4H, $N(CH_2CH_2)_2CH_2$), 2.44–2.58 (m, 4H, $N(CH_2CH_2)_2CH_2$), 2.81 (t, J=5.9 Hz, 2H, OCH_2CH_2N), 4.24 (t, J=5.9 Hz, 2H, OCH_2CH_2N), 7.16 (dd, J=9.1, 2.8 Hz, 1H, Ar*H*), 7.34 (d, J=2.8 Hz, 1H, Ar*H*), 8.15 (d, J=9.1 Hz, 1H, Ar*H*), 10.48 (s, 1H, C*H*O). This compound was not analyzed but used directly in the following step.

*4.4.12. 3-{(E)-[(4-Methylphenyl)imino]methyl}-4-nitrophenyl acetate (**35**).* To a solution of phenol **32** (2.0 g, 3.9 mmol) in pyridine (10 mL) was dropwise added acetic anhydride (1.3 mL, 6.8 mmol, 1.7 equiv) at room temperature, and then the solution was stirred for 2 h. Solvents were evaporated and the residue was dissolved in dichloromethane (20 mL). The solution was washed once with 5% hydrochloric acid, twice with water, and dried over magnesium sulfate. Solid obtained upon evaporation was recrystallized from ethanol (1.77 g, 76%). Yellow powder; mp (EtOH) 98–100 °C; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.34 (s, 3H, CH_3), 2.36 (s, 3H, $COCH_3$), 7.19 (s, 4H, Ar*H*), 7.33 (dd, J=8.9, 2.6 Hz, 1H, Ar*H*), 8.04 (d, J=2.6 Hz, 1H, Ar*H*), 8.11 (d, J=8.9 Hz, 1H, Ar*H*), 8.95 (s, 1H, CH=N); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.9 ($2CH_3$), 121.1 ($2CH_2$), 122.3 (CH), 124.0 (CH), 126.3 (CH), 129.8 ($2CH_2$), 133.2 (C), 137.2 (C), 146.1 (C), 148.0 (C), 153.7 (CH), 154.1 (C), 168.2 (C); IR ν cm^{-1}: 1192, 1339, 1516, 1574, 1750. HRMS (ESITOF) m/z calcd for $C_{16}H_{15}N_2O4$ $(M+H)^+$ 299.1032; found 299.1047.

*4.4.13. 5-Methoxy-2-nitrobenzaldehyde (**37**).* To a solution of hydroxynitrobenzaldehyde **31** (10 g, 59.8 mmol) in DMF (20 mL) was added potassium carbonate (8.4 g, 59.8 mmol, 1 equiv) followed by addition of iodomethane (3.8 mL, 59.8 mmol, 1 equiv). The solution was heated at 80 °C for 4 h. Solvent was then evaporated and the residue partitioned between dichloromethane (50 mL) and 5% aqueous hydrochloric acid (15 mL). The organic layer was separated, washed with water (3×15 mL), dried over magnesium sulfate, and evaporated. The resulting solid was recrystallized from ethanol to give methoxynitrobenzaldehyde (7.1 g, 66%). Brown crystals; mp (EtOH) 81–83 °C (lit. 82 °C[68]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.96 (s, 3H, OCH_3), 7.16 (dd, J=9.1, 2.9 Hz, 1H, Ar*H*), 7.34 (d, J=2.9 Hz, 1H, Ar*H*), 8.17 (d, J=9.1 Hz, 1H, Ar*H*), 10.49 (s, 1H, C*H*O); ^{13}C NMR: ($CDCl_3$+DMSO-d_6, 50 MHz) δ ppm: 56.1 (CH_3), 113.0 (CH), 118.3 (CH), 126.9 (CH), 134.0 (C), 142.0 (C), 163.7 (C), 188.2 (CH); IR ν cm^{-1}: 1234, 1288, 1328, 1501, 1581, 1690. HRMS (ESITOF) m/z calcd for $C_8H_8NO_4$ $(M+H)^+$ 182.0453; found 182.0453.

*4.4.14. 4-Hydroxy-4-(5-methoxy-2-nitrophenyl)butan-2-one (**43**).* To a solution of hydroxynitrobenzaldehyde **31** (1 g, 6.0 mmol) in acetone (20 mL) was added potassium carbonate (820 mg, 6.0 mmol, 1 equiv) followed by addition of iodomethane (0.3 mL, 6.0 mmol, 1 equiv). The solution was heated to reflux overnight. Solvent was then evaporated and the residue partitioned between dichloromethane (50 mL) and 5% aqueous hydrochloric acid (15 mL). The organic layer was separated, washed with water (3×15 mL), dried over magnesium sulfate, and evaporated. The resulting solid was recrystallized from acetone to give compound **43** (1.15 g, 80%). Yellow powder; mp (acetone) 92–94 °C; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.24 (s, 3H, $COCH_3$), 2.64 (dd, J=17.7, 9.2 Hz, 1H, $COCH_2CHOH$), 3.16 (dd, J=17.7, 1.9 Hz, 1H, $COCH_2CHOH$), 3.71 (br s, 1H, O*H*), 3.92 (s, 3H, OCH_3), 5.82 (dd, J=9.2, 1.9 Hz, 1H, $COCH_2$-C*H*OH), 6.88 (dd, J=9.2, 2.8 Hz, 1H, Ar*H*), 7.40 (d, J=2.8 Hz, 1H, Ar*H*), 8.10 (d, J=9.2 Hz, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 30.3 (CH_3), 50.8 (CH_2), 55.8 (CH_3), 65.8 (CH), 112.2 (CH), 113.4 (CH), 127.5 (CH), 142.0 (2C), 164.0 (C), 208.1 (C); IR ν cm^{-1}: 1226, 1283, 1321, 1500, 1572, 1696, 3406. HRMS (ESITOF) m/z calcd for $C_{11}H_{13}NO_5Na$ $(M+Na)^+$ 262.0691; found 262.0702.

*4.4.15. N-(2-Formylphenyl)acetamide (**46**).* Acetylation of compound **44** was carried out under the same conditions as for compound **45**. Resulting organic layer was washed three times with a 5% aqueous hydrochloric acid. The organic layer is then evaporated. The residue was taken in a 50/50 mixture of ethanol/HCl (5%) and stirred for 4 h. Ethanol was then partially evaporated and the solution neutralized with a diluted aqueous solution of sodium hydroxide. The resulting reaction medium was extracted with dichloromethane (3×20 mL). The organic layers were combined, washed with water (3×15 mL), dried over magnesium sulfate, and evaporated to give acetylated aminobenzaldehyde **46** (3.80 g, 97%). Yellow powder; mp (EtOH) 72–74 °C (lit. 66–69 °C[69]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.25 (s, 3H, $COCH_3$), 7.20 (t, J=7.6 Hz, 1H, Ar*H*), 7.56–7.71 (m, 2H, Ar*H*), 8.74 (d, J=8.5 Hz, 1H, Ar*H*), 9.92 (s, 1H, C*H*O), 11.20 (br s, 1H, N*H*).

*4.4.16. N-(2-Formyl-4-nitrophenyl)acetamide (**47**).* To a solution of compound **46** (3.5 g, 23.3 mmol) in a 17/3 sulfuric acid/acetic acid mixture (20 mL) was dropwise added a nitric acid/sulfuric acid mixture (50/50, 10 mL) at 0 °C. The solution was kept at this temperature for 30 min with stirring, warmed to room temperature, aged for 4 h, and poured into iced water. Precipitated crystals were filtered, washed with cold water, dried under reduced pressure, and recrystallized from ethanol (3.29 g, 74%). Yellow powder; mp (EtOH) 161–163 °C (lit. 160 °C[70]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.33 (s, 3H, $COCH_3$), 8.45 (dd, J=9.3, 2.7 Hz, 1H, Ar*H*), 8.62 (d, J=2.7 Hz, 1H, Ar*H*), 8.96 (d, J=9.3 Hz, 1H, Ar*H*), 10.02 (d, J=0.7 Hz, 1H, C*H*O), 11.40 (br s, 1H, N*H*).

*4.4.17. 2-Amino-5-nitrobenzaldehyde (**48**).* A suspension of compound **47** (3.0 g, 14.4 mmol) in 5% aqueous hydrochloric acid (20 mL) was heated to reflux overnight. The solution was neutralized with aqueous sodium hydroxide and precipitated crystals

were filtered off, washed with cold water, and vacuum dried (2.16 g, 90%). Orange powder; mp (EtOH) 150 °C (dec) (lit. 201 °C[70]); ^{1}H NMR: ($CDCl_3$+DMSO-d_6, 200 MHz) δ ppm: 6.80 (d, J=9.3 Hz, 1H, Ar*H*), 7.62 (br s, 2H, NH_2), 8.12 (dd, J=9.3, 2.6 Hz, 1H, Ar*H*), 8.47 (d, J=2.6 Hz, 1H, Ar*H*), 9.90 (d, J=0.6 Hz, 1H, C*H*O); ^{13}C NMR: ($CDCl_3$+DMSO-d_6, 50 MHz) δ ppm: 116.2 (CH), 129.6 (CH), 132.7 (CH), 136.7 (C), 154.6 (C), 167.8 (C), 192.4 (CH); IR ν cm^{-1}: 1321, 1560, 1667, 3413.

4.5. General procedure for the synthesis of aldimines

To a solution of substituted nitrobenzaldehyde (1 equiv) in ethanol (3 vol%) was added *p*-toluidine (1 equiv) and the resulting solution was heated to reflux for 30 min. The reaction medium was then cooled to 0 °C and allowed to crystallize overnight. Precipitated imine was filtered, washed once with cold ethanol, and dried under reduced pressure.

*4.5.1. N-(4-Methylphenyl)-N-[(1E)-(6-nitro-1,3-benzodioxol-5-yl) methylene]amine (**14**).* Yellow powder; 85% yield; mp (EtOH) 120–122 °C (lit. 121 °C[71]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.39 (s, 3H, CH_3), 6.19 (s, 2H, OCH_2O), 7.21 (s, 4H, Ar*H*), 7.55 (s, 1H, Ar*H*), 7.74 (s, 1H, Ar*H*), 8.94 (s, 1H, C*H*=N). HRMS (ESITOF) m/z calcd for $C_{15}H_{13}N_2O_4$ $(M+H)^+$ 285.0875; found 285.0883.

*4.5.2. N-[(1E)-(4,5-Dimethoxy-2-nitrophenyl)methylene]-4-methylaniline (**24**).* Yellow foam; 80% yield; mp (EtOH) 130–132 °C (lit. 147 °C[72]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.39 (s, 3H, CH_3), 4.02 (s, 3H, OCH_3), 4.08 (s, 3H, OCH_3), 7.22 (s, 4H, Ar*H*), 7.63 (s, 1H, Ar*H*), 7.79 (s, 1H, Ar*H*), 9.05 (s, 1H, C*H*=N); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 21.0 (CH_3), 56.5 (CH_3), 56.6 (CH_3), 107.2 (CH), 109.8 (CH), 121.1 (2CH), 125.9 (C), 129.8 (2CH), 136.7 (C), 142.4 (C), 148.4 (C), 150.4 (C), 153.0 (C), 155.1 (CH); IR ν cm^{-1}: 1219, 1328, 1513, 1574, 1615. HRMS (ESITOF) m/z calcd for $C_{16}H_{17}N_2O_4$ $(M+H)^+$ 301.1188; found 301.1193.

*4.5.3. N-[(5-Chloro-2-nitrophenyl)methylene]-4-methylaniline (**25**).* Yellow foam; 31% yield; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.40 (s, 3H, CH_3), 7.23 (s, 4H, Ar*H*), 7.56 (dd, J=8.9, 2.3 Hz, 1H, Ar*H*), 8.05 (d, J=8.9 Hz, 1H, Ar*H*), 8.32 (d, J=2.3 Hz, 1H, Ar*H*), 8.96 (s,1H, C*H*=N); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.9 (CH_3), 121.3 (2CH), 126.1 (CH), 129.5 (CH), 130.0 (2CH), 130.8 (CH), 132.9 (C), 137.5 (2C), 140.3 (C), 147.9 (C), 153.3 (CH). HRMS (ESITOF) m/z calcd for $C_{14}H_{12}ClN_2O_2$ $(M+H)^+$ 275.0587; found 275.0587.

*4.5.4. 3-{(E)-[(4-Methylphenyl)imino]methyl}-4-nitrophenol (**32**).* Yellow foam; 71% yield; mp (EtOH) 185 °C (dec); TLC R_f (EtOAc/Hept 75/25)=0.63; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.40 (s, 3H, CH_3), 7.00 (dd, J=9.0, 2.8 Hz, 1H, Ar*H*), 7.25 (s, 4H, Ar*H*), 7.66 (d, J=2.8 Hz, 1H, Ar*H*), 8.14 (d, J=9.0 Hz, 1H, Ar*H*), 9.09 (s, 1H, C*H*=N); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.7 (CH_3), 114.8 (CH), 117.8 (CH), 121.2 (2CH), 127.8 (CH), 129.9 (2CH), 133.9 (C), 136.3 (C), 140.8 (C), 148.3 (C), 156.6 (CH), 162.5 (C); IR ν cm^{-1}: 1252, 1321, 1506, 1586, 1598, 3119. HRMS (ESITOF) m/z calcd for $C_{14}H_{13}N_2O_3$ $(M+H)^+$ 257.0926; found 3257.0931.

*4.5.5. 4-Methyl-N-{[2-nitro-5-(2-piperidin-1-ylethoxy)phenyl]methylene}aniline (**38**).* Purple powder; 61% yield; mp (EtOH) 70–72 °C; TLC R_f (EtOAc/Hept 75/25)=0.16; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 1.40–1.55 (m, 2H, N(CH_2CH_2)$_2$CH_2), 1.55–1.72 (m, 4H, N(CH_2CH_2)$_2$$CH_2$), 2.39 (s, 3H, C$H_3$), 2.50–2.63 (m, 4H, N(C$H_2$$CH_2$)$_2$$CH_2$), 2.85 (t, J=5.8 Hz, 2H, OCH_2CH_2N), 4.29 (t, J=5.8 Hz, 2H, OC$H_2$$CH_2$N), 7.05 (dd, J=9.1, 2.9 Hz, 1H, Ar*H*), 7.22 (s, 4H, Ar*H*), 7.73 (d, J=2.9 Hz, 1H, Ar*H*), 8.12 (d, J=9.1 Hz, 1H, Ar*H*), 9.04 (s, 1H, C*H*=N); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 21.0 (CH_3), 23.9 (CH_2), 25.7 (2CH_2), 55.0 (2CH_2), 57.5 (CH_2), 66.8 (CH_2), 113.7 (CH), 117.1 (CH), 121.2 (2×CH), 127.3 (CH), 129.8 (2CH), 134.1 (C), 136.9 (C), 142.1 (C), 148.4 (C), 155.5 (CH), 162.8 (C); IR ν cm^{-1}: 1085, 1205, 1288, 1328, 1502, 1572, 1612. HRMS (ESITOF) m/z calcd for $C_{21}H_{26}N_3O_3$ $(M+H)^+$ 368.1974; found 368.1987.

*4.5.6. N-[(5-Methoxy-2-nitrophenyl)methylene]-4-methylaniline (**40**).* Yellow powder; 93% yield; mp (EtOH) 110–112 °C; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.39 (s, 3H, CH_3), 3.99 (s, 3H, OCH_3), 7.05 (dd, J=9.1, 2.9 Hz, 1H, Ar*H*), 7.73 (d, J=2.9 Hz, 1H, Ar*H*), 8.14 (d, J=9.1 Hz, 1H, Ar*H*), 9.06 (s, 1H, C*H*=N), 7.23 (s, 4H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.9 (CH_3), 56.1 (CH_3), 112.9 (CH), 116.9 (CH), 121.2 (2CH), 127.2 (CH), 129.8 (2CH), 134.2 (C), 136.9 (C), 142.2 (C), 148.4 (C), 155.5 (CH), 163.5 (C); IR ν cm^{-1}: 1293, 1325, 1497, 1575, 1612. HRMS (ESITOF) m/z calcd for $C_{15}H_{15}N_2O_3$ $(M+H)^+$ 271.1083; found 271.1096.

4.6. General procedure for the reduction of nitrobenzaldimines

To a solution of protected aminobenzaldehyde derivative (1 equiv) in ethanol (10 vol%) was added anhydrous sodium sulfide[13] (1.66 equiv), and the resulting solution was heated to reflux for 5 min in a preheated oil bath. The hot solution was then poured into iced water (40 vol%). The precipitating reduced imine was filtered, washed once with cold ethanol, and dried under reduced pressure.

*4.6.1. N-[(1E)-(6-Amino-1,3-benzodioxol-5-yl)methylene]-N-(4-methylphenyl)amine (**15**).* Yellow powder; 65% yield; mp (EtOH) 124–126 °C (lit. 134 °C[71]); ^{1}H NMR: ($CDCl_3$+Et_3N,[13] 200 MHz) δ ppm: 2.36 (s, 3H, CH_3), 5.90 (s, 2H, OCH_2O), 6.25 (s, 1H, Ar*H*), 6.64 (br s, 2H, NH_2), 6.74 (s, 1H, Ar*H*), 7.07 (d, J=8.3 Hz, 2H, Ar*H*), 7.18 (d, J=8.3 Hz, 2H, Ar*H*), 8.37 (s, 1H, C*H*=N); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.7 (CH_3), 96.2 (CH), 100.8 (CH_2), 110.1 (C), 111.3 (CH), 120.5 (2CH), 129.5 (2CH), 134.6 (C), 138.9 (C), 146.4 (C), 149.3 (C), 150.6 (C), 160.9 (CH); IR ν cm^{-1}: 1211, 1581, 1631, 3444. HRMS (ESITOF) m/z calcd for $C_{15}H_{15}N_2O_2$ $(M+H)^+$ 255.1134; found 255.1129.

*4.6.2. 4,5-Dimethoxy-2-{[(4-methylphenyl)imino]methyl}aniline (**16**).* Yellow powder; 63% yield; mp (EtOH) 182–184 °C (dec) (lit. 123 °C[72]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.37 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 3.91 (s, 3H, OCH_3), 7.22 (s, 4H, Ar*H*), 7.63 (s, 1H, Ar*H*), 7.79 (s, 1H, Ar*H*), 8.44 (s, 1H, C*H*=N); ^{13}C NMR: ($CDCl_3$+Et_3N,[13] 50 MHz) δ ppm: 20.3 (CH_3), 55.4 (CH_3), 54.7 (CH_3), 101.8 (CH), 110.8 (CH), 119.1 (2CH), 129.4 (2CH), 130.9 (C), 134.3 (C), 143.4 (C), 144.1 (C), 144.3 (C), 146.1 (C), 149.4 (CH); IR ν cm^{-1}: 1204, 1222, 1619, 3442. HRMS (ESITOF) m/z calcd for $C_{16}H_{19}N_2O_2$ $(M+H)^+$ 271.1447; found 271.1444.

*4.6.3. 4-Chloro-2-{[(4-methylphenyl)imino]methyl}aniline (**17**).* Yellow powder; 45% yield; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.38 (s, 3H, CH_3), 6.58 (br s, 2H, NH_2), 6.65 (dd, J=8.6, 2.2 Hz, 1H, Ar*H*), 7.05–7.34 (m, 6H, Ar*H*), 8.46 (s,1H, C*H*=N). HRMS (ESITOF) m/z calcd for $C_{14}H_{14}ClN_2$ $(M+H)^+$ 245.0846; found 245.0845.

*4.6.4. 4-Amino-3-{(E)-[(4-methylphenyl)imino]methyl}phenyl acetate (**36**).* Brown powder; 70% yield; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.24 (s, 3H, COCH_3), 2.39 (s, 3H, CH_3), 6.64 (d, J=8.0 Hz, 2H, Ar*H*), 7.22 (dd, J=9.1, 2.9 Hz, 1H, Ar*H*), 6.97 (d, J=8.0 Hz, 2H, Ar*H*), 7.43 (d, J=2.9 Hz, 1H, Ar*H*), 8.03 (d, J=9.1 Hz, 1H, Ar*H*), 9.00 (s, 1H, C*H*=N). This compound was not analyzed but used directly in the following step.

*4.6.5. 4-Methoxy-2-{(E)-[(4-methylphenyl)imino]methyl}aniline (**41**).* Yellow powder; 56% yield; mp (EtOH) 190–192 °C; TLC R_f (EtOAc/Hept 75/25)=0.5; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.37

(s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 6.21 (br s, 2H, NH_2), 6.65–6.72 (m, 1H, Ar*H*), 6.84–6.92 (m, 2H, Ar*H*), 7,11 (dd, *J*=8.3, 2.4 Hz, 2H, Ar*H*), 7,20 (dd, *J*=8.3, 2.4 Hz, 2H, Ar*H*), 8.50 (s, 1H, C*H*=N); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.4 (CH_3), 55.5 (CH_3), 66.0 (CH_3), 112.3 (CH), 115.2 (CH), 118.9 (CH), 119.2 (2CH), 125.7 (C), 129.6 (2CH), 131.0 (C), 134.3 (C), 144.4 (C), 153.4 (CH); IR: ν cm^{-1} 1229, 1572, 3243. This compound was not analyzed but used directly in the following step.

4.7. *N*-(2-{(E)-[(4-Methylphenyl)imino]methyl}phenyl)-acetamide (45)

To a solution of reduced imine **44**[13] (0.23 g, 1.1 mmol) in pyridine (5 mL) was dropwise added acetic anhydride (0.2 mL, 2.2 mmol, 2 equiv) at room temperature. The solution was allowed to stand with stirring overnight. Solvent was then evaporated and the residual oil partitioned between dichloromethane (50 mL) and cold water (10 mL). The organic layer was separated, washed with cold water (2×10 mL), dried over magnesium sulfate, and evaporated. The resulting solid was recrystallized from ethanol to give compound **45** (150 mg, 57%). Yellow powder; mp (EtOH) 117–119 °C (lit. 146–147 °C[73]); ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.21 (s, 3H, COCH_3), 2.37 (s, 3H, CH_3), 7.10 (dd, *J*=7.5, 1.1 Hz, 1H, Ar*H*), 7.14 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.22 (d, *J*=8.1 Hz, 2H, Ar*H*), 7.40 (t, *J*=7.5 Hz, 2H, Ar*H*), 8.51 (s, 1H, C*H*=N), 8.74 (d, *J*=7.5 Hz, 1H, Ar*H*), 12.80 (br s, 1H, N*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 20.9 (CH_3), 25.2 (CH_3), 119.8 (CH), 120.7 (2CH), 122.4 (CH), 129.2 (C), 129.9 (2CH), 132.0 (CH), 133.9 (CH), 136.7 (C), 140.1 (C), 146.9 (C), 161.6 (CH), 169.2 (C); IR ν cm^{-1}: 1299, 1617, 1678, 2921. HRMS (ESITOF) *m*/*z* calcd for $C_{16}H_{17}N_2O$ $(M+H)^+$ 253.1341; found 253.1339.

4.8. Methyl 1-hydroxy-9-oxo-1,9-dihydropyrrolo[2,1-*b*] quinazoline-1-carboxylate (58a) and methyl (3*Z*)-2-oxo-4-(4-oxo-1,4-dihydro-2-quinazolinyl)-3-butenoate (60a)

A stirred mixture of acetate **49** (0.47 g, 1.5 mmol) was solubilized in dry methanol (4 mL) and 30% sodium methylate (0.07 mL, 0.27 mmol) was added. After 4 h, the solution was neutralized by 37% hydrochloric acid and partitioned between dichloromethane (4 mL) and water (2 mL). The organic layer was washed with water, and then dried ($MgSO_4$) to give alcohol **58a** as a crude oil. ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 3.81 (s, 3H, CO_2CH_3), 6.80 (d, *J*=5.9 Hz, 1H, C*H*=CHCOH), 6.85 (d, *J*=5.9 Hz, 1H, CH=C*H*COH), 7.50 (ddd, *J*=8.0, 5.6, 2.5 Hz, 1H, Ar*H*), 7.62–7.80 (m, 2H, Ar*H*), 8.27 (ddd, *J*=8.0, 1.4, 0.9 Hz, 1H, Ar*H*), 11.49 (br s, 1H, O*H*).

Alcohol **58a** rapidly evolved to give ketone **60a**; white crystals; 65% crude yield. This product was characterized only by NMR. White powder; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.90 (s, 3H, CO_2CH_3), 7.21 (d, *J*=16.2 Hz, 1H, CH=C*H*CO), 7.48 (d, *J*=16.2 Hz, 1H, CH=C*H*CO), 7.57 (ddd, *J*=7.9, 6.0, 2.4 Hz, Ar*H*), 7.77–7.90 (m, 2H, Ar*H*), 8.35 (ddd, *J*=7.9, 1.5, 0.7 Hz, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 52.5 (CH_3), 121.4 (C), 126.4 (CH), 127.5 (CH), 128.1 (CH), 128.4 (CH), 135.2 (CH), 136.9 (CH), 148.3 (C), 149.0 (C), 163.1 (C), 165.8 (C), 179.7 (C).

4.9. Methyl 2,4-dioxo-4-(4-oxo-3,4-dihydroquinazolin-2-yl) butanoate (61)

To a solution of compound **50** (0.2 g, 0.8 mmol) in dichloromethane (5 mL) at 0 °C was dropwise added a cold solution of chromic acid (8 mL). The reaction mixture was allowed to stir at this temperature for 2 h, then at room temperature for 30 min. The reaction medium was partitioned between dichloromethane (5 mL) and water (5 mL). The organic layer was separated, washed once with a saturated aqueous solution of $NaHCO_3$, twice with water, dried over magnesium sulfate, and evaporated. The residue was then purified by silica gel column chromatography using a gradient of ethyl acetate in heptane (17 mg, 80%). Yellow oil; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.82 (s, 3H, CO_2CH_3), 4.73 (s, 2H, $COCH_2CO$), 7.53 (ddd, *J*=8.1, 6.5, 2.0 Hz, Ar*H*), 7.70–7.85 (m, 2H, Ar*H*), 8.00 (br s, 1H, N*H*), 8.32 (ddd, *J*=8.1, 1.4, 0.7 Hz, 1H, Ar*H*). This compound was not furthermore analyzed.

4.10. Methyl 3-bromo-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*] quinazoline-1-carboxylate (62) and methyl 3,3-dibromo-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline-1-carboxylate (63)

To a solution of compound **51** (0.2 g, 0.7 mmol) in dichloromethane (10 mL) was added a solution of sodium hydrogencarbonate (12 mg, 0.14 mmol, 2 equiv) in water (5 mL) then a solution of bromine in dichloromethane (0.05 M, 1.5 mL, 1.05 equiv). The resulting biphasic reaction mixture was stirred at room temperature for 15 h. Water (5 mL) was then added and the organic layer was separated, washed three times with water, dried over magnesium sulfate, and evaporated. Yields given in text were determined by NMR analysis of the residue. Products were isolated with the same properties as already described.[10]

4.11. Methyl 3-hydroxy-3-[hydroxy(phenyl)methyl]-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline-1-carboxylate (65)

Dialcohol **65** was isolated (but not purified) as a by-product of the oxidation of ethylenic compound **54a**, by using the same procedure as for oxidation of enamines **56**, with a catalytic amount of ruthenium tetroxide (10 mol %). 4% yield; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 2.05 (dd, *J*=14.7, 2.4 Hz, 1H, CH_2CH), 2.80 (dd, *J*=14.7, 10.1 Hz, 1H, CH_2CH), 3.66 (s, 3H, CO_2CH_3), 4.72 (s, 1H, C*H*OH), 5.19 (dd, *J*=10.1, 2.4 Hz, 1H, CH_2CH), 7.28–7.59 (m, 3H, Ar*H*), 7.75–7.85 (m, 4H, Ar*H*), 8.31 (ddd, *J*=8.0, 1.3, 0.8 Hz, 2H, Ar*H*).

4.12. General procedure for the synthesis of indolizinoquinolines 66

To a solution of crude compound **7** (100–400 mg, 1 equiv) in acetic acid (2–5 mL) was added protected aminobenzaldehyde **44** (1.3–1.5 equiv). The solution was heated at 80 °C for 2 h, and then solvents were evaporated under reduced pressure. The residue was partitioned between dichloromethane (20 mL) and a 5% aqueous HCl solution (5 mL). The organic layer was then neutralized with a saturated $NaHCO_3$ solution (30 mL). The aqueous layers were back extracted twice with dichloromethane (30 mL). The organic layers were combined, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with a gradient of ethyl acetate in heptane (0/100 to 100/0).

*4.12.1. Methyl 7-[1-(methoxycarbonyl)propyl]-6-nitro-9-oxo-9,11-dihydroindolizino[1,2-b]quinoline-11-carboxylate (**66d**).* This compound was obtained starting from 100 mg of precursor, and was not subjected to elemental analysis. Yellow oil; 57% yield; TLC R_f (EtOAc)=0.7; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 0.99 and 1.04 (2 t, *J*=7.4 Hz, 3H, $CHCH_2CH_3$), 1.88–2.09 (m, 1H, $CHCH_2CH_3$), 2.15–2.37 (m, 1H, $CHCH_2CH_3$), 3.72 (t, *J*=7.5 Hz, 1H, $CHCH_2CH_3$), 3.74 and 3.79 (2s, 3H, CO_2CH_3), 3.87 (s, 3H, CO_2CH_3), 6.14 (s, 1H, $CHCO_2CH_3$), 7.43 (d, *J*=6.8 Hz, 1H, Ar*H*), 7.67–7.77 (m, 1H, Ar*H*), 7.84–7.94 (m, 1H, Ar*H*), 7.94–8.01 (m, 1H, Ar*H*), 8.22–8.29 (m, 1H, Ar*H*), 8.49 (br s, 1H, Ar*H*); IR ν cm^{-1}: 1209, 1435, 1662, 1718, 1740.

*4.12.2. Methyl 8-chloro-7-[1-(methoxycarbonyl)propyl]-9-oxo-9,11-dihydroindolizino[1,2-b]quinoline-11-carboxylate (**66e**).* This compound was obtained starting from 100 mg of precursor, and was not subjected to elemental analysis. Yellow powder; 80% yield; mp

(ether) 181–183 °C; TLC R_f (EtOAc)=0.65; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 0.99 and 1.04 (2t, J=7.3 and 7.2 Hz, 3H, $CHCH_2CH_3$), 1.84–2.35 (m, 2H, $CHCH_2CH_3$), 3.74 and 3.75 (2s, 3H, CO_2CH_3), 3.85 (s, 3H, CO_2CH_3), 4.25 (t, J=7.7 Hz, 1H, $CHCH_2CH_3$), 6.10 and 6.11 (2d, J=1.3 Hz, 1H, NC*H*), 7.36 and 7.39 (2s, 1H, Ar*H*), 7.67 (t, J=7.4 Hz, 1H, Ar*H*), 7.85 (t, J=8 Hz, 1H, Ar*H*), 7.93 (d, J=7.8 Hz, 1H, Ar*H*), 8.21 (d, J=7.4 Hz, 1H, Ar*H*), 8.44 (s, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 11.8 and 11.9 (2s, CH_3), 24.9 and 25.2 (2s, CH_2), 49.8 (CH), 52.3 (CH_3), 53.5 (CH_3), 62.9 (CH), 100.0 (CH), 127.0 (CH), 127.8, 128.0 (CH), 128.3 (CH), 129.6 (CH), 131.0 (CH), 142.6 (CH), 142.7 (CH), 148.7 (CH), 149.3 (CH), 151.5 (CH), 156.7 (CH), 166.0 (CH), 172.0 (CH); IR ν cm^{-1}: 1628, 1661–1495, 1725, 1736.

*4.12.3. Methyl 6-bromo-7-[1-(methoxycarbonyl)propyl]-8-nitro-9-oxo-9,11-dihydroindolizino[1,2-b]quinoline-11-carboxylate (**66f**).* Yellow powder; 70% yield; mp (EtOAc)=195–196 °C; TLC R_f (EtOAc)=0.6; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 1.02 and 1.05 (2t, J=7.3 Hz, 3H, $CHCH_2CH_3$), 1.98–2.19 (m, 1H, $CHCH_2CH_3$), 2.35–2.61 (m, 1H, $CHCH_2CH_3$), 3.75 and 3.77 (2s, 3H, CO_2CH_3), 3.79–3.83 (m, 1H, $CHCH_2CH_3$), 3.79 and 3.83 (2s, 3H, CO_2CH_3), 6.11 (s, 1H, $CHCO_2CH_3$), 7.78–7.79 (m, 1H, Ar*H*), 7.85–7.94 (m, 1H, Ar*H*), 7.95–8.00 (m, 1H, Ar*H*), 8.29–8.36 (m, 1H, Ar*H*), 8.49 (br s, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 12.3 (CH_3), 22.7 (CH_2), 49.5 (CH_3), 52.7 (CH_3), 53.9 (CH), 62.6 (CH), 98.9 (C), 127.8 (C), 127.4 (CH), 127.9 (C), 128.0 (CH), 129.2 (CH), 130.7 (CH), 130.8 (CH), 131.2 (C), 142.6 (C), 145.8 (C), 149.0 (C), 150.9 (C), 151.9 (C), 165.1 (C), 170.0 (C); IR ν cm^{-1}: 1210, 1255, 1538, 1670, 1745. Anal. Calcd for $C_{22}H_{18}BrN_3O_7$: C, 51.18; H, 3.51; N, 8.14. Found: C, 51.04; H, 3.77; N, 8.34.

4.13. Methyl 4-bromo-3-ethyl-2,13-dioxo-2,3,11,13-tetrahydro-1*H*-pyrrolo[2′,3′:6,7]indolizino[1,2-b]quinoline-11-carboxylate (67)

To a solution of **66f** (500 mg, 0.97 mmol) in glacial acetic acid was added zinc powder (750 mg) and the resulting suspension was allowed to stir at room temperature for 2 h prior to filtration. NMR analysis of filtrate led to the identification of lactam **67**, which rapidly degraded upon attempt of isolation. ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 0.85 and 0.88 (2t, J=7.3 and 5.9 Hz, 3H, $CHCH_2CH_3$), 2.18–2.66 (m, 2H, $CHCH_2CH_3$), 3.74–3.86 (m, 1H, $CHCH_2CH_3$), 3.87 (s, 3H, CO_2CH_3), 6.13 and 6.16 (2s, 1H, $CHCO_2CH_3$), 7.61–7.71 (m, 1H, Ar*H*), 7.77–7.95 (m, 2H, Ar*H*), 8.20–8.31 (m, 1H, Ar*H*), 8.39 (m, 1H, Ar*H*), 8.90 and 9.04 (2br s, 1H, N*H*).

4.14. Methyl 9-[1-(methoxycarbonyl)propyl]-8-nitro-1,7-dioxo-2,4,5,7-tetrahydro-1*H*-pyrrolo[3,2,1-*ij*]-1,6-naphthyridine-5-carboxylate (70)

To a solution of compound **55c** (10 mg, 0.22 mmol) in methanol (2 mL) was added ammonium formate (100 mg, 2.2 mmol, 10 equiv) and the solution was heated to reflux for 24 h. The reaction mixture was then evaporated and the residue was partitioned between water and dichloromethane. The aqueous layer was separated and back extracted with dichloromethane. The organic layers were combined, dried over magnesium sulfate, and evaporated. The residue was purified by column chromatography on silica gel with a gradient of ethyl acetate in heptane (0/100 to 100/0). Yellow powder; 93% yield; mp (EtOAc) >150 °C (dec); TLC R_f (EtOAc)=0.2; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 0.98 and 0.99 (2t, J=7.6 and 7.4 Hz, 3H, $CHCH_2CH_3$), 1.76–1.98 (m, 1H, $CHCH_2CH_3$), 2.25–2.45 (m, 1H, $CHCH_2CH_3$), 2.76–2.85 (m, 2H, CH_2CH), 3.71 and 3.72 (2s, 3H, CO_2CH_3), 3.80 and 3.81 (2s, 3H, CO_2CH_3), 3.83 (m, 1H, $CHCH_2CH_3$), 4.46 and 4.51 (2br s, H, N*H*), 5.15 (dd, J=11.2, 4.3 Hz, 1H, CH_2CH), 8.27 (t, J=10.8 Hz, 1H, Ar*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 12.3 (CH_3), 22.7 (CH_2), 49.5 (CH_3), 52.7 (CH_3), 53.9 (CH), 62.6 (CH), 98.9 (C), 127.8 (C), 127.4 (CH), 127.9 (C), 128.0 (CH), 129.2 (CH), 130.7 (CH), 130.8 (CH), 131.2 (C), 142.6 (C), 145.8 (C), 149.0 (C), 150.9 (C), 151.9 (C), 165.1 (C), 170.0 (C); IR ν cm^{-1}: 1205, 1437, 1538, 1664, 1740. Anal. Calcd for $C_{19}H_{22}N_2O_{10}$: C, 58.96; H, 5.24; N, 8.09. Found: C, 58.55; H, 5.02; N, 8.16.

4.15. Methyl 3-(4-oxo-3,4-dihydroquinazoline-2-carbonyl) quinoline-2-carboxylate (74)

To a solution of enamine **56a** (90 mg, 0.3 mmol) in an ethyl acetate/acetonitrile/dichloromethane mixture (3/3/1, 23 mL) was added a solution of sodium periodate (0.65 g, 3 mmol, 10 equiv) in water (5 mL) and ruthenium oxide (8 mg, 0.06 mmol, 0.2 equiv). The reaction mixture was then stirred at room temperature for 30 min and separated. The organic layer containing ketone **8a** was washed twice with water. Aminobenzaldehyde **44** (65 mg, 0.3 mmol, 1 equiv) and acetic acid (5 mL) were then added to the organic layer. The resulting solution was partially evaporated and additional acetic acid (5 mL) was introduced. The reaction medium was then refluxed for 2 h and evaporated. The residue was partitioned between dichloromethane and a saturated aqueous $NaHCO_3$ solution. The organic layer was separated, washed twice with water, dried over magnesium sulfate, and evaporated. The residue was then purified by column chromatography on silica gel using a gradient of ethyl acetate in heptane to provide product **74** in a 23% yield as a brown powder. Recrystallization from acetone led to a degraded product. Brown powder; ^{1}H NMR: ($CDCl_3$, 200 MHz) δ ppm: 3.80 (s, 3H, CO_2CH_3), 7.56–7.66 (m, 2H, Ar*H*), 7.72–7.82 (m, 2H, Ar*H*), 7.91–8.01 (m, 2H, Ar*H*), 7.99–8.06 (m, 2H, Ar*H*), 8.58 (d, J=0.9 Hz, 1H, Ar*H*), 10.15 (br s, 1H, N*H*); ^{13}C NMR: ($CDCl_3$, 50 MHz) δ ppm: 53.4 (CH_3), 123.2 (C), 127.0 (CH), 127.9 (C), 128.5 (CH), 128.9 (CH), 129.4 (CH), 129.5 (CH), 129.7 (C), 130.5 (CH), 132.3 (CH), 134.9 (CH), 138.8 (CH), 146.6 (C), 147.3 (C), 147.6 (C), 148.2 (C), 160.5 (C), 166.5 (C), 187.8 (C).

4.16. Methyl 3-(*N*,*N*-dimethylaminomethylidene)-9-oxo-3,9-dihydropyrrolo[2,1-*b*]quinazoline-1-carboxylate (76a)

To a stirred solution of compound **56a** (200 mg, 0.66 mmol) in a mixture of H_2O (10 mL) and THF (10 mL) was added sodium metaperiodate (1.4 g, 2 mmol, 3 equiv). The solution was stirred at room temperature for 5 h and the solid formed was filtered off and washed with CH_2Cl_2 (2×5 mL). The filtrate was extracted with CH_2Cl_2 (2×10 mL), dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography using a mixture of cyclohexane/EtOAc (2/3) to provide product **76a**. Yellow solid; 56% yield; mp=153–155 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ ppm: 3.14 (s, 6H, $N(CH_3)_2$), 4.02 (s, 3H, OCH_3), 6.51 (s, 1H, $CH{=}CCO_2Me$), 7.54 (t, J=6.3 Hz, 1H, Ar*H*), 7.82 (dt, J=7.1, 6.3 Hz, 2H, Ar*H*), 8.31 (d, J=7.8 Hz, 1H, Ar*H*), 10.15 (s, 1H, C*H*=C); ^{13}C NMR ($CDCl_3$, 75 MHz) δ ppm: 41.1 ($2CH_3$), 53.6 (CH_3), 88.3 (CH), 123.2 (C), 126.9 (CH), 128.3 (CH), 128.7 (CH), 129.4 (C), 134.5 (CH), 142.9 (CH), 148.4 (C), 151.6 (C), 157.8 (C), 165.7 (C), 167.9 (C); IR ν cm^{-1}: 1700, 2994, 3009. Anal. Calcd for $C_{16}H_{15}N_3O_3$: C, 64.64; H, 5,09; N, 14,13. Found: C, 64.49; H, 4.86; N, 14.00.

4.17. Methyl 3-[(dimethylamino)methylene]-7-nitro-9-oxo-3,9-dihydropyrrolo[2,1-*b*]quinazoline-1-carboxylate (76c) and methyl 7-nitro-3,9-dioxo-3,9-dihydropyrrolo[2,1-*b*] quinazoline-1-carboxylate (77c)

Nitro esters **76c** and **77c** were formed whatever the exact conditions, by reacting enamine **56c** with oxone in acetone for 1 h at room temperature, in the presence of potassium hydrogencarbonate. It was not possible to isolate these products, which were identified by NMR of the crude reaction mixture. Partial ^{1}H NMR spectrum of **76c**: 3.11 (s, 6H, $N(CH_3)_2$), 6.70 (s, 1H, $CH{=}CCO_2Me$); partial ^{1}H NMR spectrum of **77c**: 6.21 (s, 1H, $CH{=}CCO_2Me$).

4.18. Methyl 7-amino-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*] quinazoline-1-carboxylate (78)

To a stirred solution of compound **79** (2 g, 6.9 mmol) in MeOH (100 mL) was added tin chloride dihydrate (14 g, 57.6 mmol, 8 equiv). The solution was refluxed for 2.5 h. After cooling, the mixture was poured on ice (250 g), neutralized with sodium hydrogencarbonate, and extracted with EtOAc (3×50 mL). Organic phases were washed with water, dried over $MgSO_4$, filtered, and evaporated under reduced pressure to provide product **78**. White crystals; 90% yield; mp=198–200 °C; TLC R_f (EtOAc/Hept 40/60)=0.35; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 2.26–2.43 (m, 1H, $CHCH_2CH_2$), 2.47–2.70 (m, 1H, $CHCH_2CH_2$), 3.01–3.36 (m, 2H, $CHCH_2CH_2$), 3.51 (br s, 2H, NH_2), 3.81 (s, 3H, OCH_3), 5.15 (dd, J=9.5, 3.2 Hz, 1H, CH_2CH), 7.10 (dd, J=8.7, 2.7 Hz, 1H, Ar*H*), 7.44 (d, J=2.7 Hz, 1H, Ar*H*), 7.50 (d, J=8.7 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 24.3 (CH_2), 30.5 (CH_2), 52.9 (CH_3), 58.9 (CH), 108.9 (CH), 121.3 (C), 123.1 (CH), 127.9 (CH), 141.8 (C), 145.3 (C), 155.3 (C), 170.3 (2C); IR ν cm^{-1}: 1322, 1612, 1667, 1731, 3357, 3441. HRMS (ESITOF) m/z calcd for $C_{13}H_{14}N_3O_3$ $(M+H)^+$ 260.1035; found 260.1035.

4.19. Methyl 7-amino-1,2,3,9-tetrahydropyrrolo[2,1-*b*] quinazoline-1-carboxylate (80) and methyl (3*E*)-4-(6-amino-1,4-dihydro-2-quinazolinyl)-2,2-dimethoxy-3-butenoate (81)

To a stirred solution of compound **79** (1 g, 3.4 mmol) in 48% HBr (10 mL) was added zinc powder (2 g, 30.6 mmol, 9 equiv). After 5 min, the solution was neutralized with sodium hydrogencarbonate, filtered on Celite, and then extracted with CH_2Cl_2 (3×50 mL), leading to organic phases A. Water phases were evaporated, and MeOH (100 mL), $CHCl_3$ (100 mL), and $MeSO_3H$ (0.1 mL) were added to the residue. The solution was refluxed for 48 h by using a Soxhlet filled with 3 Å MS. Upon evaporation, the residue was dissolved in CH_2Cl_2, and then washed with water. Organic phases A were added and the combined phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure. The residue was purified by flash chromatography using a gradient of heptane/EtOAc.

*4.19.1. Compound **80**.* Yellow powder; 20% yield; TLC R_f (EtOAc/MeOH 70/30)=0.52; ^{1}H NMR ($CDCl_3$, 200 MHz) δ ppm: 2.22–2.42 (m, 1H, $CHCH_2CH_2$), 2.54–2.80 (m, 1H, $CHCH_2CH_2$), 3.09–3.50 (m, 2H, $CHCH_2CH_2$), 3.85 (s, 3H, OCH_3), 4.55 (dd, J=9.5, 4.3 Hz, 1H, CH_2CH), 4.66 (d, J=14.6 Hz, 1H, CCH_2N), 4.77 (d, J=14.6 Hz, 1H, CCH_2N), 6.28 (d, J=2.5 Hz, 1H, Ar*H*), 6.53 (dd, J=8.4, 2.5 Hz, 1H, Ar*H*), 7.33 (d, J=8.4 Hz, 1H, Ar*H*). This compound was not analyzed, but utilized directly in the next syntheses.

*4.19.2. Compound **81**.* Yellow powder; 20% yield; TLC R_f (EtOAc/MeOH 70/30)=0.78; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 3.91 (s, 3H, OCH_3), 3.95 (s, 6H, $(OCH_3)_2$), 4.08 (br s, 1H, N*H*), 6.37 (d, J=12.9 Hz, 1H, $CHCH(OMe)_2$), 6.80 (d, J=8.5 Hz, 1H, Ar*H*), 6.98 (d, J=12.9 Hz, 1H, $CHCH(OMe)_2$), 7.06 (dd, J=8.5, 2.1 Hz, 1H, Ar*H*), 7.49 (d, J=2.1 Hz, 1H, Ar*H*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 55.0 ($2CH_3$), 55.8 (CH_3), 97.0 (C), 109.6 (CH), 116.5 (C), 123.1 (CH), 125.3 (CH), 129.1C,142.1 (CH), 142.3 (C), 144.5 (C), 147.0 (C), 172.4 (C), 174.7 (C). HRMS (ESITOF) m/z calcd for $C_{15}H_{18}N_3O_5$ $(M+H)^+$ 320.1246; found 320.1234.

4.20. Methyl 7-[(*tert*-butoxycarbonyl)amino]-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline-1-carboxylate (82)

To a stirred solution of compound **78** (0.5 g, 1.9 mmol) in MeOH (10 mL) was added di-*tert*-butyl dicarbonate (0.53 g, 1.5 mmol) and Et_3N (0.3 mL, 1.9 mmol). The solution was refluxed for 12 h. Dichloromethane 15 mL was added, and then the solution was washed with water. Organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to provide product **78**. Off-white powder; 30% yield; mp=198–200 °C; ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.54 (s, 9H, $C(CH_3)_3$), 2.27–2.44 (m, 1H, $CHCH_2CH_2$), 2.47–2.70 (m, 1H, $CHCH_2CH_2$), 3.13–3.36 (m, 2H, $CHCH_2CH_2$), 3.81 (s, 3H, OCH_3), 5.17 (dd, J=9.4, 2.8 Hz, 1H, CH_2CH), 6.72 (br s, 1H, Ar*H*), 7.62 (d, J=9.2 Hz, 1H, Ar*H*), 8.00 (s, 1H, Ar*H*), 8.04 (s, N*H*); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 24.0 (CH_2), 27.7 ($2CH_3$), 30.2 (CH_2), 52.5 (CH_3), 58.7 (CH), 80.5 (C), 113.7 (CH), 120.1 (C), 125.2 (CH), 127.5 (CH), 136.7 (C), 144.2 (C), 152.0 (C), 156.9 (C), 169.5 (C), 169.9 (C); IR ν cm^{-1}: 1152, 1212, 1620, 1667, 1721, 1747, 3315. This compound was not analyzed, but utilized directly in the next syntheses.

4.21. Methyl (3*E*)-7-[(*tert*-butoxycarbonyl)amino]-3-[(dimethylamino)methylene]-1,2,3,9-tetrahydropyrrolo[2,1-*b*] quinazoline-1-carboxylate (83)

A stirred mixture of compound **82** (0.2 g, 0.6 mmol) and Bredereck's reagent (0.1 g, 0.8 mmol) was heated at 110 °C for 2 h. After cooling at room temperature, CH_2Cl_2 was added, and then the solution was washed with water. Organic phases were dried over $MgSO_4$, filtered, and evaporated under reduced pressure to provide product **83** as black oil, which was only characterized by NMR and IR. ^{1}H NMR ($CDCl_3$, 200 MHz) δ: 1.53 (s, 9H, $C(CH_3)_3$), 3.08 (s, 6H, $N(CH_3)_2$), 3.10–3.25 (m, 1H, $CHCH_2$), 3.39–3.61 (m, 1H, $CHCH_2$), 3.78 (s, 3H, OCH_3), 5.05 (dd, J=10.7, 3.9 Hz, 1H, CH_2CH), 6.56 (br s, 1H, Ar*H*), 7.32–7.57 (m, 2H, Ar*H*), 7.75–8.06 (m, 2H, C=*CH*N, N*H*); IR ν cm^{-1}: 1092, 1155, 1367, 1563, 1649, 1723, 1750, 3255.

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Supplementary data

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.tet.2010.07.048.

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