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# Toward new camptothecins. Part 5: On the synthesis of precursors for the crucial Friedländer reaction

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ABSTRACT

The synthesis of potential precursors of ketones, which could be used to obtain camptothecin analogs, is described. Noteworthy is the difference of reactivity between indolizinone and pyrrolidinoquinazolinone heterocycle.



## 1. Introduction

The isolation and the structure of camptothecin were reported in 1966 by Wall et al.[1a] and many reviews, devoted to this compound, revealed its paramount importance.[1b–k] Interest in this cytotoxic drug and semisynthetic analogs was stimulated when its mode of action was discovered. Camptothecin is able to stabilize the cleavable complex between topoisomerase I and DNA; collision of this reversible complex with the replication fork[2] leads to cell death because of preventing DNA religation.[3] Derivatives of camptothecin such as irinotecan and topotecan have emerged from bioavailability and tolerance studies, and are used in cancer treatment.[4] Recently, the crystal structure of the DNA–topoisomerase I–camptothecin complex was solved and two models of camptothecin–DNA–topoisomerase I interaction were formulated.[5] In the camptothecin series, structure–activity relationships were well established in regard to modifications in A–D rings (Fig. 1). They also indicated the ability of substituents in positions 7, 9, 10, and 11 to maintain or improve the biological activity. The need for a hydroxy lactone ring E had been established as a golden rule.[6,7] However, this dogma fell with the discovery of other compounds stabilizing the complex between DNA and topoisomerase I in the same way as camptothecin: homocamptothecins such as diflomotecan or cyclopentanones such as S39625 are now in preclinical phase (Fig. 1).[8]

The indolizino[1,2-*b*]quinoline scaffold of camptothecin, represented by the A–D rings (Fig. 1), provides the required framework for DNA interaction.[9] This is also the case for mappicine ketone,[10] identified as an antiviral agent acting at the DNA level.[11] On the other hand, the quinazoline ring has often been found in the structure of anticancer agents such as batracylin;[12] as for luotonin A, it was recently reported to inhibit Topo I as well as Topo II (Fig. 2).[13]

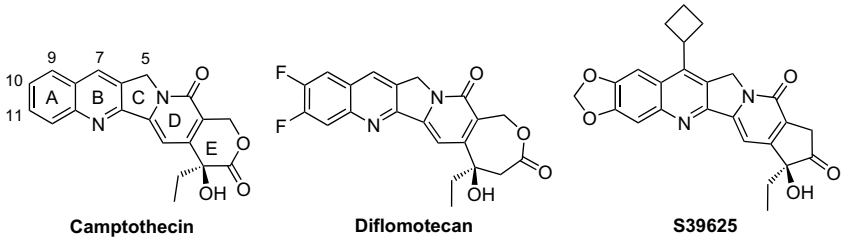


**Figure 1.** Structure of camptothecin derivatives.

As part of a program directed on potential anticancer agents,[14] we wished to elucidate the influence of carbonyl (acid, ester, amide) substituents on position 5 of cycle C along with modified E-rings.[15–17] Thus, we have projected the synthesis of compounds with the general scaffolds **1** and **2** (Fig. 3).

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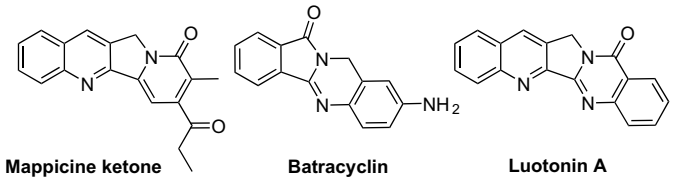



**Figure 2.**

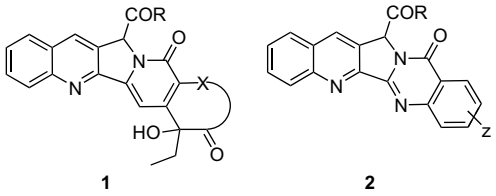
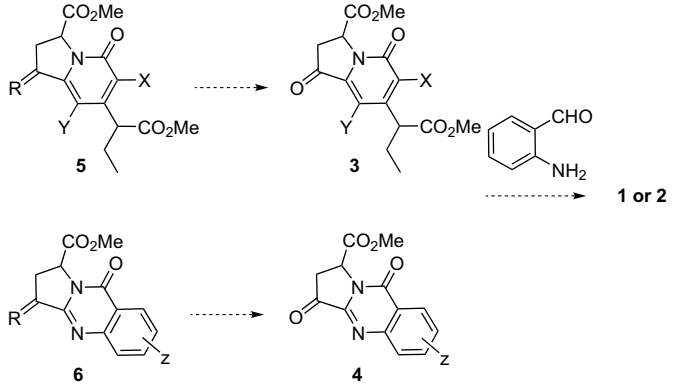



**Figure 3.** Final targets of the work.

In our retrosynthetic scheme, a key step was a Friedländer condensation[18] between 2-aminobenzaldehyde and keto indolizine **3** or keto pyrroloquinazolinone **4** (Scheme 1). In this paper, we are focusing on the synthesis of precursors **5** and **6** of ketones **3** and **4**. Because the reactivity of the new series proved often to be rather different compared to the previous compounds, results from literature are provided in the schemes.



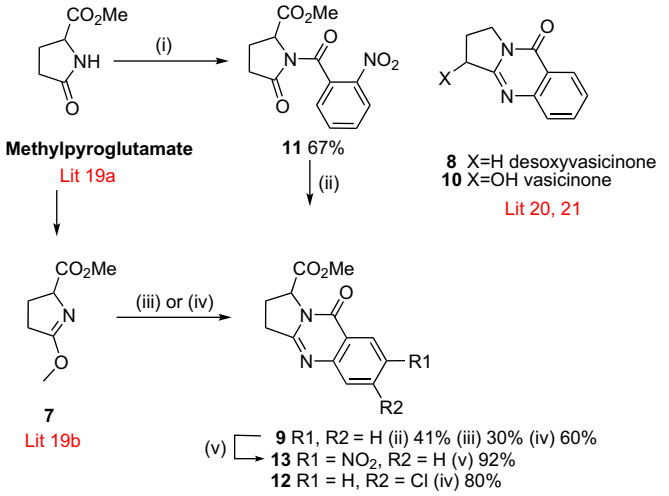

**Scheme 1.** Precursors of modified camptothecins.

## 2. Results and discussion

In order to prepare analogs **1** and **2** of camptothecin with an ester function in position 5, we used DL-methyl pyroglutamate[19a] as initial starting synthon, from which iminoether **7** was easily obtained in two steps and 60% overall yield according to a reported procedure (Scheme 2).[19b]

### 2.1. Starting quinazolinones

Desoxyvasicinone **8** is the natural analog of ester **9**. Syntheses of vasicinone derivatives **8** and **10** have been described. One of the reaction schemes used four steps from succinic anhydride,[20] but it seems difficult to introduce our methoxycarbonyl group at this stage. Other ways used Pd catalysis, or started from 3-hydroxy or 3-bromopyrrolidinone.[21] Some of these methods have been extended to pyroglutamic esters,[22] but they utilized rather expensive chemicals such as 2-azidobenzoyl chloride or supported reagents. We first reacted the sodium salt of methyl pyroglutamate with 2-nitrobenzoyl chloride; 67% of imide **11** was thus obtained, but the yield of reduction to **9** was 41% (27% for two steps) (Scheme 2). Thus,




**Scheme 2.** Reaction conditions: (i) NaH, THF then 2-nitrobenzoyl chloride, 20 °C, 24 h; (ii) $SnCl_2$, EtOH, reflux, 4 h; (iii) isatoic anhydride, toluene, reflux, 24 h; (iv) anthranilic acid, toluene, 55 °C, 3 h, then reflux, 8 h; (v) $HNO_3$, $H_2SO_4$, 0 °C, 2 h.

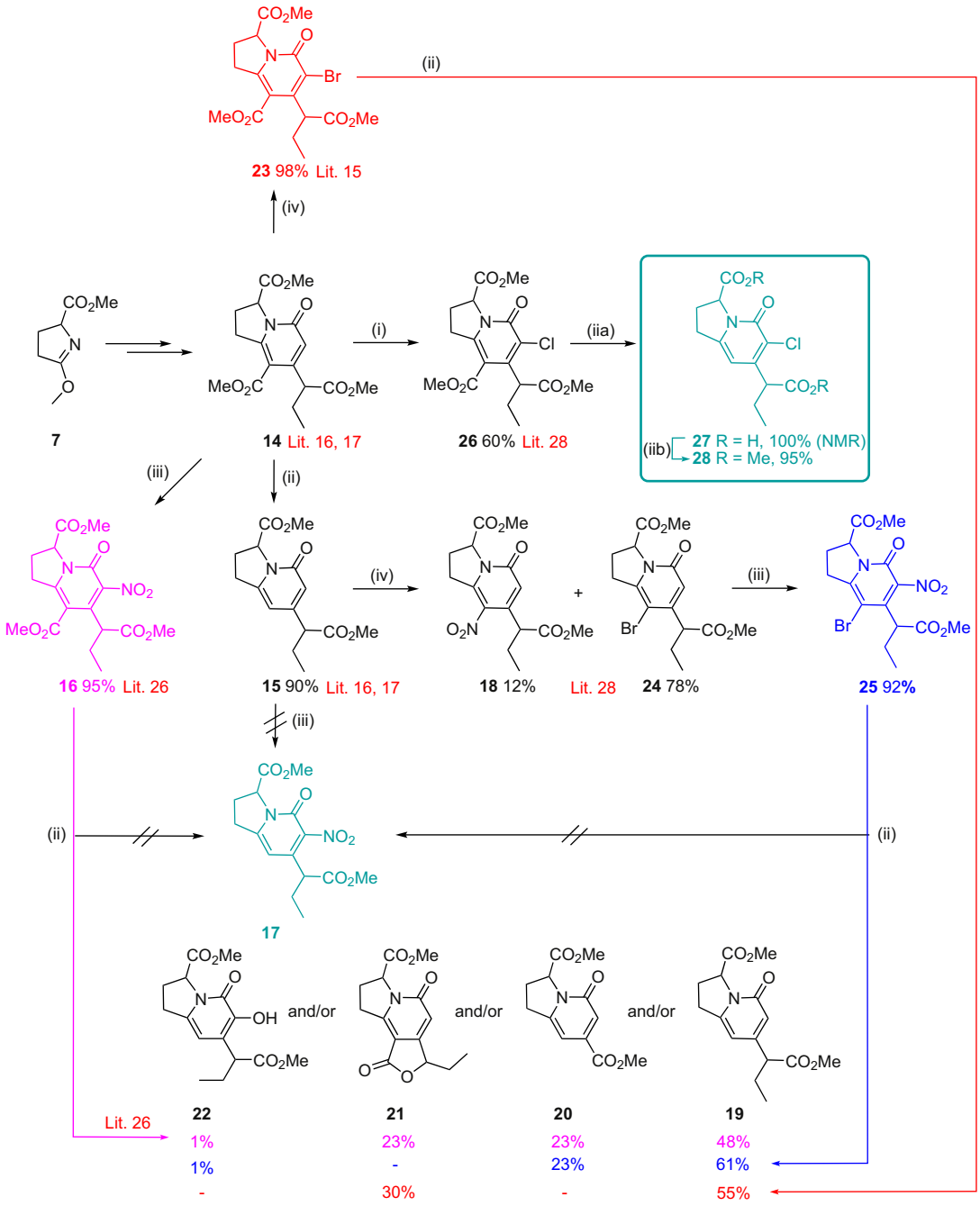
we chose to condense iminoether **7** with isatoic anhydride[23] or anthranilic acid.[24] 5-Methoxycarbonyldesoxyvasicinone **9** was then obtained in 30% and 60% yields, respectively. This last yield was comparable to the one described in literature[24] and this method was utilized to obtain chloroquinazolinone **12** in 80% yield (Scheme 2). The nitration of **9** gave nitroquinazolinone **13** with 92% yield.

### 2.2. Starting pyridones

In the pyridone series, we chose to introduce in position 6 of the indolizine core a precursor of an amino group. The starting materials were esters **14** and **15**, which were obtained[16,17] by using the general synthesis of Shen and Danishefsky (Scheme 3).[25] We have already reported that nitration of diester **15** did not lead to 6-nitro compound **17** but only to the 8-nitro isomer **18**.[26] In the synthesis of camptothecin, position 8 was protected by using a methoxycarbonyl group.[25] In our case, nitration of triester **14** led to a very good yield of 6-nitroindolizine **16**. However, all attempts to remove the 8-protecting group by heating **16** in 48% HBr yield only the by-products **19**–**22** (we have previously discussed the possible reaction mechanisms leading to these compounds[26]). In the same way, heating pyridone **23**,[15] which is a bromo analog of nitrotriester **16**, in 48% HBr yielded also decomposition to products **19** and **21**.

It has recently been described that heating Ar–Br in concd HBr led to the unsubstituted arene.[27] Thus we thought to use a bromine atom as a protecting group. Bromination of **15** was accomplished with a procedure recently reported by our group, using HBr/*iso*-amyl nitrite.[28] This yielded 8-bromoindolizinone **24** contaminated by a low amount of nitrated product **18**. The mixture was easily separated by chromatography to afford **24** in 78% yield.[28] The nitration of this heterocycle in $HNO_3/Ac_2O$ then furnished the key bromonitro intermediate **25** in quantitative yield. Unfortunately, all attempts to remove the aromatic bromo group of **25** led, after the hydrogen substitution for bromine, to some of the same rearranged heterocycles **19**–**22** that were isolated after decarboxylation of **16**.

It is interesting to note that this particular reactivity of bromonitroindolizinones **16**, **23**, and **25** was not the same as for chloro analog **26**. This chloropyridone was obtained from **14** as already reported.[28] Indeed, reflux of diester **26** in 48% HBr led to hydrolysis of the ester function followed by a decarboxylation of the aromatic acid group. Reesterification of intermediate diacid **27** was realized with MeOH under ternary azeotropic conditions ($H_2O$/MeOH/$CHCl_3$).[15,16,19a] 6-Chloroindolizinone **28** was thus obtained in 95% yield.




**Scheme 3.** Reaction conditions: (i) *iso*-amyl nitrite (3 equiv), 37% HCl (1.5 equiv), THF, 20 °C, 7 days; (ii) (a) 48% HBr, reflux, 5 h; (b) MeOH, $MeSO_3H$, $CHCl_3$, molecular sieves 3 Å, reflux, 48 h; (iii) $Ac_2O$/63% $HNO_3$, 60 °C, 1 h; (iv) *iso*-amyl nitrite (2 equiv), 48% HBr (1 equiv), $CH_2Cl_2$, 20 °C, 4 h.

### 2.3. Direct oxidation

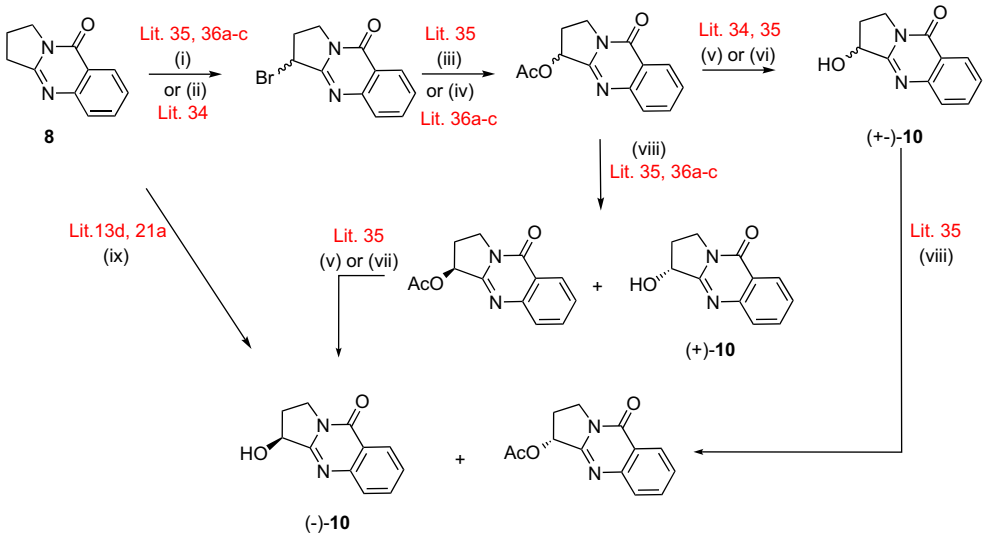
In the camptothecin series, an oxygen atom was introduced in position 1 of the intermediate indolizine via selenium oxidation[29] (Scheme 3). This approach was inefficient on the indolizines substituted by a methoxycarbonyl group such as **14**[16] and **16**[26] in the same way, direct oxidation of quinazolinones **9**, **12**, and **13** (Scheme 2) or pyridones **14** and **25** (Scheme 3) by reagents such as selenium oxide,[29] $KMnO_4$,[30] *meta*-chloroperbenzoic acid[31] or magnesium monoperoxyphtalate[32] did not allow the isolation of a major oxidized product.

Since desoxyvasicinone **8** was also not easily oxidized to ketones,[13d,21a,33] alternative methods based on the corresponding alcohols **10** have been reported.[34–36] The main reaction pathways leading to vasicinone **10** are depicted in Scheme 4. The hydroxyl function could be obtained by hydrolysis of an acetoxy group, introduced either directly or by displacement of a bromine atom brought in by using NBS (Scheme 4); in other conditions the dibromo analog was obtained in 75% yield.[36d]

Because of the results previously described in the syntheses of vasicinone, we decided to investigate the same reactions in our quinazolinone and indolizinone chemical families.

### 2.4. The bromination pathway

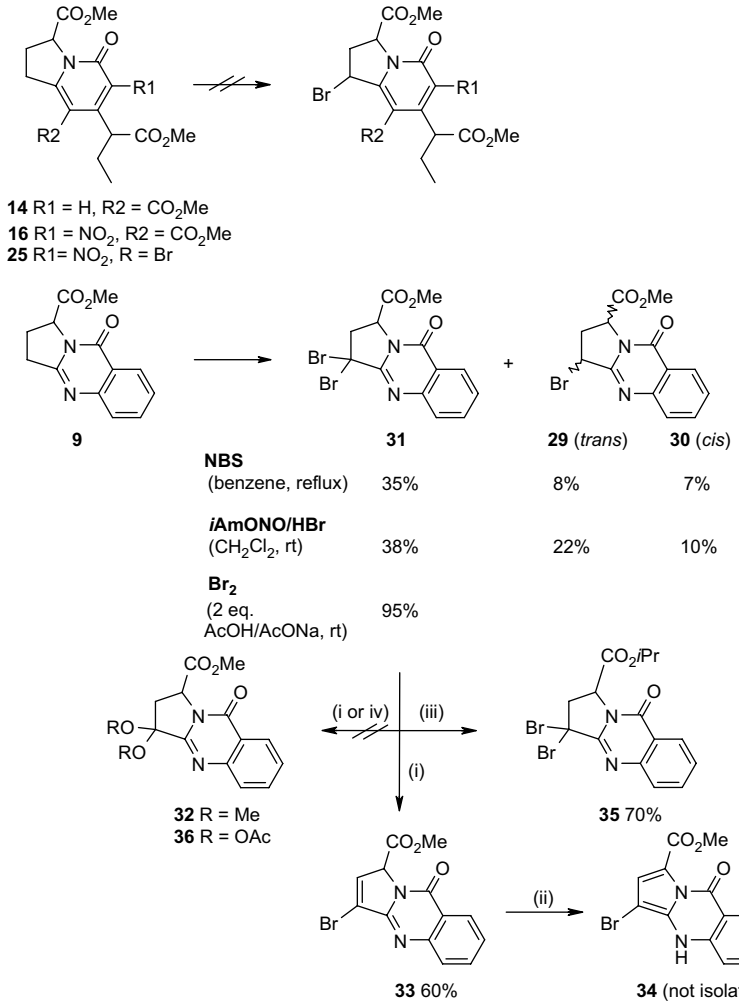
Thus a good precursor for the ketone target could be a bromine or an acetoxy group. However, all attempts to introduce a bromine atom in position 1 in the indolizinone series,




**Scheme 4.** Reaction conditions: (i) NBS, $(PhCO_2)_2$, $CCl_4$, reflux, 5 h, 52% yield; (ii) NaH, $Br_2$, THF, reflux, 75% yield; (iii) AcOK, 18-crown-6, MeCN, 20 °C, 1 h, 90% yield; (iv) AcONa, $AgNO_3$, THF/$H_2O$, reflux, 8 h, 90% yield; (v) KOH, EtOH/$H_2O$, reflux, 2 h, 95% yield; (vi) NaOH, MeOH/$H_2O$/EtOAc, 20 °C, 15 min, 97% yield; (vii) lipase PS, MeCN, rt, 7 h; (viii) vinyl acetate, lipase PS, $Et_3N$, THF; (ix) Davies reagent, LDA, THF, −78 °C, 1 h, 57% yield.

whatever the reagent ($Br_2$, NBS, *iso*-AmONO/HBr), either gave no halogenated products or resulted in reaction on the aromatic ring. Some compounds obtained in that way are reported in Scheme 3.

However, treatment of pyrimidone **9** in various conditions with 1 equiv of bromination reagent led to reaction in position 1. But unfortunately, all attempts to perform a selective mono-bromination failed, leading to mixtures of products **29**, **30**, and **31**.




**Scheme 5.** (i) MeONa, MeOH, rt, 2 h; (ii) MeOH, rt, several hours; (iii) $Ti(OPr)_4$, MeOH, rt, 12 h; (iv) AcONa.

This mixture was separated by chromatography on $SiO_2$, and the cis and trans isomers were identified by NMR. On the other hand, *gem*-dibromoquinazolinone **31** was obtained in quantitative yield using 2 equiv of bromine in acetic acid (Scheme 5).

The poor yields obtained for mono-bromo quinazolones **29** and **30** did not allow further functionalization as described in the vasicinone series. Recently the reaction of *gem*-dibromo compounds with DMSO[36,37] or dimethylamine[38] has been reported, leading to ketones in good yields. We used these conditions with dibromo heterocycle **31**, but only strong degradations were observed.

Thus, we attempted to transform quinazolinone **31** to dimethyl acetal **32**. However, reaction of sodium methoxide with **31** led to hydrobromine elimination, yielding 60% of heterocycle **33**. This product proved to be rather unstable during recrystallization in MeOH, leading to a mixture with the corresponding bromopyrrole **34**, which could not be purified. Less basic reagents were also utilized: $Ti(O^iPr)_4$ led only to trans esterification, and ester **35** was isolated in 70% yield, and sodium acetate does not react with **32** to give diacetate **36** (Scheme 5). In the desoxyvasicinone series, a ketone was easily obtained from hydrolysis of a dibromo precursor, and its reaction with phenyl hydrazine led to 89% of hydrazone.[36]

Bromination was thus abandoned and we became interested in a result published in 1935 by Morris et al.,[39] describing the α-oxidation of vasicine with lead tetracetate. In our case, this would afford the targeted hydroxy function as an acetate precursor. No reaction occurred in indolizinone series, however, quinazolinone **9** was oxidized by lead tetracetate in acetic acid to afford acetoxy compounds **36** and **37** with 90% yield along with minor product **38** (Scheme 6). They were separated by chromatography on $SiO_2$ followed by differential crystallization, allowing unambiguous NMR identification.

In other conditions ($Pb(OAc)_4$/benzene), 3-acetoxy compound **39** was isolated in 40% yield. This product could also be obtained by acetoxy elimination of **36** or **37**, followed by a classical allylic reaction. It has also been described that acetoxylation can be accompanied by aromatic ring methylation.[40] Thus we thought that radical methylation of **39** led to an acetoxy precursor of **38**, which was hydrolyzed during purification.

The mixture of acetates **36** and **37** was reacted with sodium methoxide at room temperature, and alcohols **40** and **41** were obtained in 80% yield. However, as it will be described in another publication, all attempts to oxidize **40** or **41** were unsuccessful.

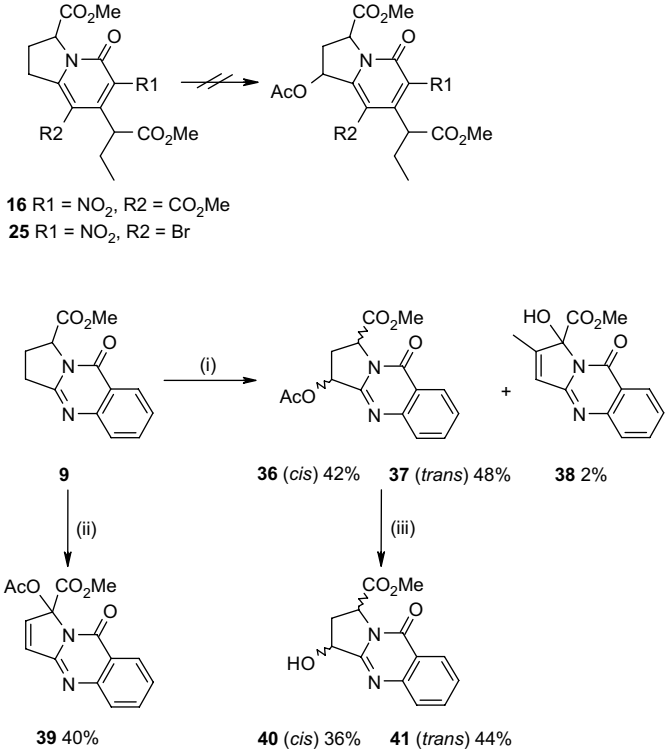
Consequently to the failure of these oxidations, some other strategies have been attempted to obtain other precursors of the ketone group. They included the synthesis of intermediates such as enamines, oximes, hydrazones or ethylenic compounds.

## 2.5. The enamine pathway

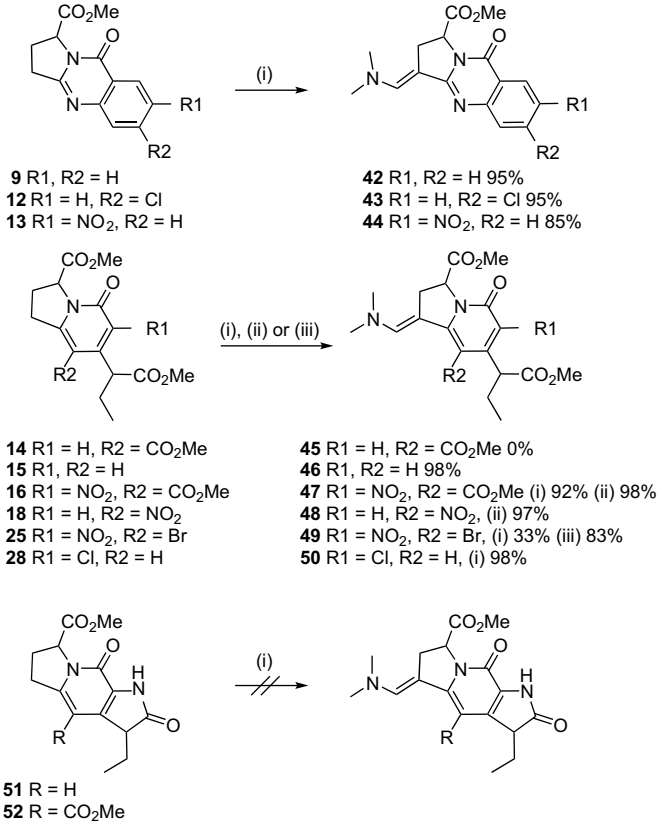
### *2.5.1. Synthesis of enamines*

Enamines have been reported as carbonyl precursors, and we have described their oxidation in the synthesis of analogs of camptothecin.[16,17] Various compounds for enamine synthesis have been described. Reaction of Vilsmeier reagent was generally not specific and generated many side products. DMF acetals such as DMFDMA or Bredereck's reagents are often more efficient and selective.

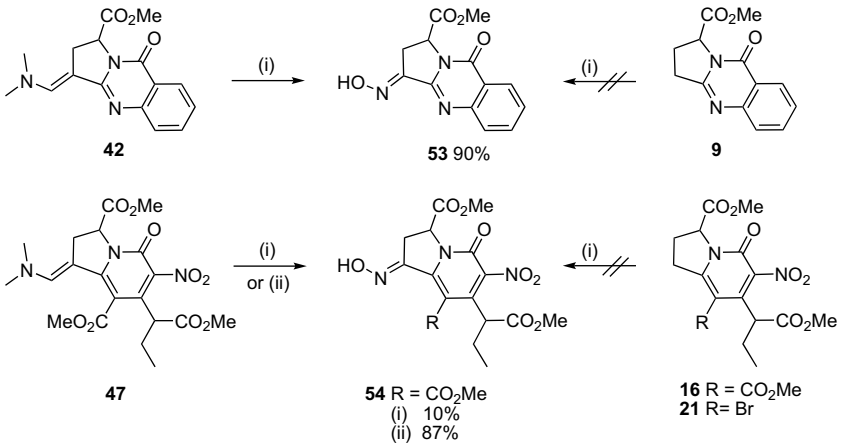
In the case of pyrroloquinazolinones **9**, **12**, and **13**, the condensation of Bredereck's reagent under solvent-free conditions gave the corresponding enamines **42**–**44** with excellent yields (85–95%) in a clean way (Scheme 7). The cases of pyridones are more complex, probably because of distant electronic effects. Indeed, as already reported, ester **14** did not react while pyridone **15** yielded quantitatively enamine **46**.[16] As for **47**–**50**, they can also be obtained with this reagent under the same conditions. Nonetheless, for compounds **47**, **48**, and **49**, DMFDMA gave higher yields and




**Scheme 6.** (i) $Pb(OAc)_4$, AcOH, reflux, 12 h; (ii) $Pb(OAc)_4$, benzene, reflux, 4 h; (iii) MeONa, MeOH, rt, 4 h.




**Scheme 7.** (i) Brederek's reagent (1.4 equiv), 110 °C, 2 h; (ii) DMFDMA (3 equiv), 110 °C, 3 h; (iii) DMFDMA (4 equiv), toluene, 110 °C, 4 h.



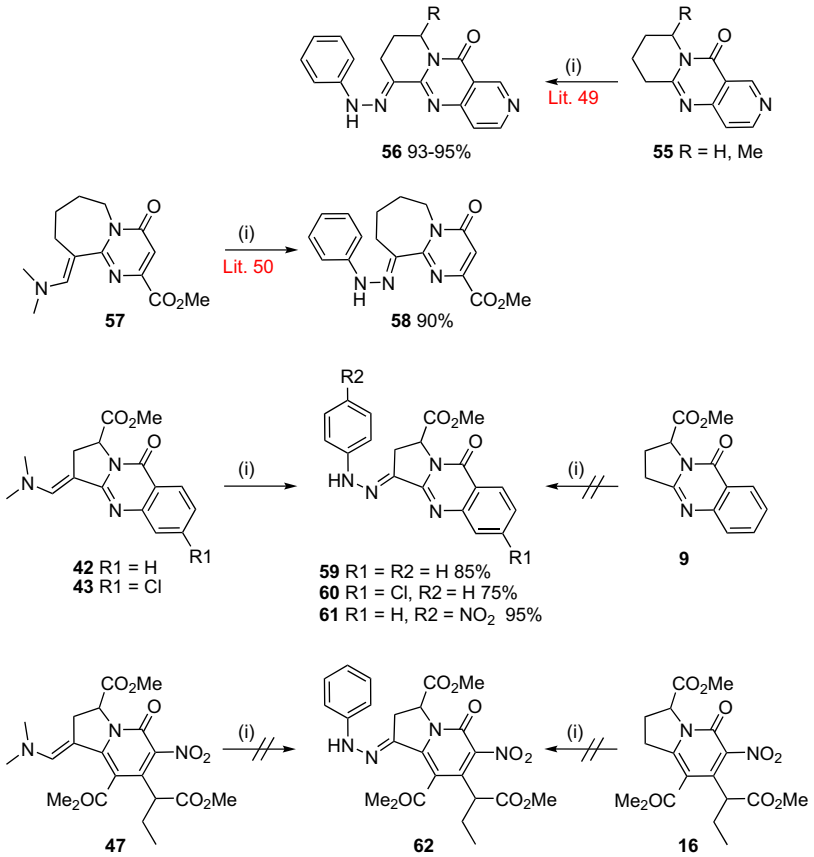

**Scheme 8.** (i) $NaNO_2$, HCl, $H_2O$, 0 °C, 2 h; (ii) $NaNO_2$, AcOH, 0 °C, 3 h.

cleaner reactions. This could be explained by the strong withdrawing nitropyridone part of **16**, **18**, and **25** responsible for a more activated α-methylene group. As a result, the less reactive DMFDMA reagent led to cleaner reactions, whereas Bredereck's reagent led to degraded reaction media. This was demonstrated for the bromonitroenamine **49**, which required to be formed in toluene. That also corroborated a result reported by our group on the non-reactivity of the aminopyridone analogs **51** and **52** whose α-methylene group was far more deactivated (Scheme 7).[26]

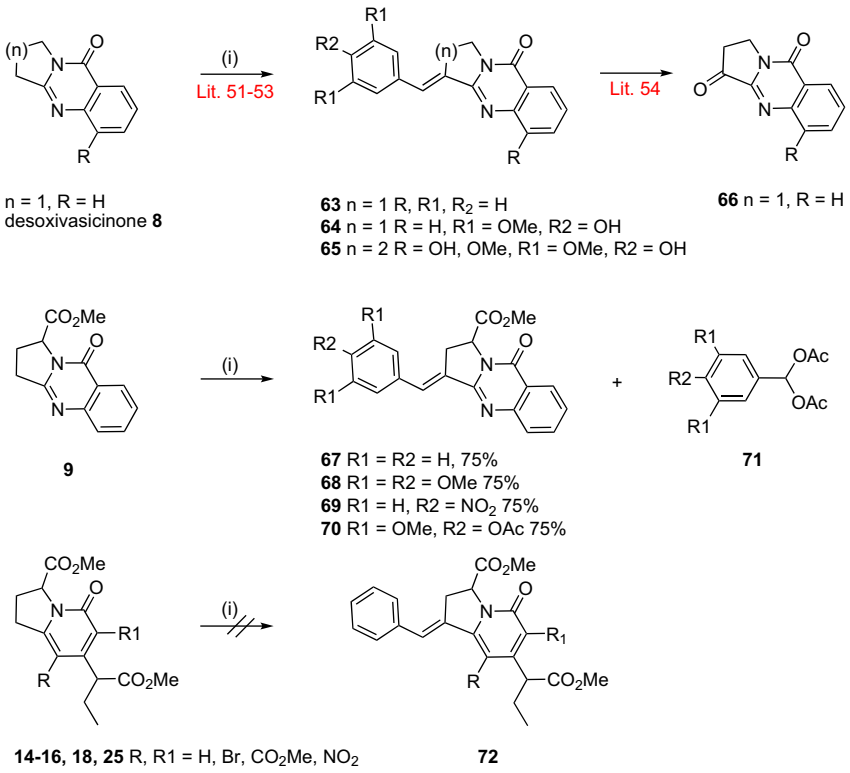
### 2.5.2. Synthesis of oximes

Oximes are commonly employed for introduction or purification of carbonyl groups.[41,42] Their syntheses are often performed by nitrosation of an active methylene group.[43] We have checked without results the direct nitrosation in our indolizinone and quinazolinone series by using the sodium nitrite/hydrochloric acid mixture; however, even with activated nitro pyridones **16** and **21**, no reaction was observed under these conditions (Scheme 8).

The nitrosation of enamines is a less used synthesis of oximes,[44] and indeed, oximes **53** and **54** were obtained by reaction of the corresponding dimethylenamines **42** and **47** with a sodium nitrite/hydrochloric acid mixture. The yield of oxime **53** was good (90%), but it was necessary to exchange hydrochloric acid to acetic acid in order to obtain the best result for indolizinone **54** (87%) (Scheme 8).




**Scheme 9.** (i) $ArN{=}N^{+}Cl^{-}$, AcOH, $H_2O$, AcONa, 0 °C, 4 h.




**Scheme 10.** (i) ArCHO, $Ac_2O$, reflux, 72 h, 75% yield.

*2.5.3. Synthesis of hydrazones*

It was also interesting to synthesize hydrazones in these series because many methods were reported to regenerate a ketone from these compounds.[45–48] In a publication about azarutaecarpine,[49] Hermecz described the coupling of phenyl diazonium salt on condensed pyridones **55** in a very good yield; in another work,[50] he reported that the Japp–Klingemann condensation of enamine **57** led to 90% of hydrazone **58** (Scheme 9).

In our series, quinazolinone **9** does not react with phenyl diazonium chloride, while hydrazones **59**–**61** were easily obtained from **42** and **43**; on the other hand, none of these ways allowed the formation of indolizinone **62** (Scheme 9).

*2.5.4. The ethylenic pathway*

Another common way to introduce keto functionalities is the oxidative cleavage of double bonds. In the vasicinone analog series, reaction of aromatic aldehydes led to ethylenic compounds **63**–**65**,[24,51,52] and ozonolysis of the double bond of **62** yielded a targeted ketone **66**.[33a] Thus isaindigotone **64** was synthesized, but noteworthy, only analogs **65** with an enlarged ring were cytotoxic,[53] possibly acting by inhibition of tubulin polymerization.

In our case, this path was possible for quinazolinone **9**, which gave ethylenic compounds **67**–**70** with 75% yields when they are heated with aromatic aldehydes in acetic anhydride (a few amount of acylals **71** were also formed[54]), but compounds of the pyridone series did not react in that way, and products **72** could not be obtained (Scheme 10).

## 3. Conclusion

In this paper, we have described many compounds synthesized as potential precursors of camptothecin analogs. Noteworthy is the difference of reactivity between indolizinones and pyrrolidinoquinazolinones. The oxidation of these compounds will be described in further publication, which could be utilized for future Friedländer condensation leading to new alkaloid analogs.

## 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, or a Brüker Avance 300 at 300 and 75 MHz, respectively. IR spectra were obtained in ATR mode on an FTIR Bruker Tensor 27. Thin layer chromatographies were performed on precoated Kieselgel $60F_{254}$ plates. $APCI^+$ (atmospheric pressure chemical ionization) mass spectra were obtained on an LC–MS system Thermo Electron Surveyor MSQ. Microanalyses were performed by the 'Service de Microanalyses' of LSEO, Université de Bourgogne, Dijon, France. All products are obtained as mixtures of diastereoisomers.

### 4.2. Methyl 9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]-quinazoline-1-carboxylate (9)

$SnCl_2$ (0.872 g, 4.6 mmol) was added to a solution of ester **11** (268 mg, 0.92 mmol) in 50 mL of ethanol. The mixture was refluxed for 4 h, cooled to room temperature, and then neutralized with saturated sodium hydrogen carbonate solution (30 mL). The mixture was concentrated, diluted with water, and extracted with dichloromethane (2×15 mL). The organic phases were dried ($MgSO_4$), and then the residue obtained upon evaporation was purified by flash chromatography ($SiO_2$, 4/1 cyclohexane/EtOAc). Pink solid; 41% yield; mp (toluene) 101–103 °C; TLC $R_f$ (EtOAc/MeOH 50/50)=0.65; $^1H$ NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.29–2.73 (m, 2H, $CH_2$), 3.07–3.46 (m, 2H, $CH_2$), 3.82 (s, 3H, $OCH_3$), 5.18 (dd, $J$=9.4, 3.1 Hz, 1H, $CHCO$), 7.46 (ddd, $J$=8.0, 6.8, 1.5 Hz, 1H, Ar$H$), 7.67

(ddd, $J$=8.2, 1.5, 0.6 Hz, 1H, Ar*H*), 7.76 (ddd, $J$=8.2, 6.8, 1.5 Hz, 1H, Ar*H*), 8.27 (ddd, $J$=8.0, 1.5, 0.6 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ ppm: 24.4 ($CH_2$), 31.3 ($CH_2$), 53.1 ($OCH_3$), 59.2 (CH), 120.5 (C), 126.6 (CH), 126.7 (CH), 127.1 (CH), 134.6 (CH), 149.2 (C), 158.9 (C), 160.6 (C), 170.4 (C); IR $\nu$ cm$^{-1}$: 3019, 2986, 1734, 1687. Anal. Calcd for $C_{13}H_{12}N_2O_3$: C, 63.93; H, 4.95; N, 11.47. Found: C, 63.83; H, 4.82; N, 11.29.

Starting from iminoether **7** as described in literature,[24] compound **9** was obtained in 60% yield, with the same physical properties.

### 4.3. Methyl 1-(2-nitrobenzoyl)-5-oxopyrrolidine-2-carboxylate (11)

Sodium hydride in 60% mineral oil (600 mg, 9 mmol) was added in one portion at 0 °C to a stirred solution of methyl pyroglutamate (715 mg, 5 mmol) in THF (30 mL). The mixture was allowed to react at room temperature for 1 h and then at reflux until all the hydrogen gas disappeared (approximately 30 min). 2-Nitrobenzoyl chloride (0.67 mL, 5 mmol) in THF (6 mL) was added dropwise to the cooled solution (ice bath). The solution was stirred for 24 h at room temperature and then water (15 mL) was added. The organic layers obtained upon addition of $CH_2Cl_2$ (3×15 mL) were dried over $MgSO_4$, filtered, and then concentrated in vacuo to give ester **11** as yellow powder; 67% yield; mp=120–122 °C (toluene); $^1$H NMR ($CDCl_3$, 300 MHz) $\delta$ ppm: 2.45–2.58 (m, 4H, C$H_2$C$H_2$), 3.86 (s, 3H, OC$H_3$), 5.01–5.10 (m, 1H, C*H*), 7.41 (d, 1H, $J$=7.82 Hz, Ar*H*), 7.57 (t, 1H, $J$=7.82 Hz, Ar*H*), 7.65 (t, 1H, $J$=7.83 Hz, Ar*H*), 8.37 (d, 1H, $J$=7.83 Hz, Ar*H*); $^{13}$C NMR ($CDCl_3$, 75 MHz) $\delta$ ppm: 21.5 ($CH_2$), 31.3 ($CH_2$), 53.0 ($OCH_3$), 65.9 (CH), 124.1 (CH), 128.1 (CH), 130.4 (CH), 132.5 (C), 134.5 (CH), 145.2 (C), 166.4 (C), 171.3 (C), 173.6 (C); IR $\nu$ cm$^{-1}$: 3018, 2973, 1700, 1668. Anal. Calcd for $C_{13}H_{12}N_2O_6$: C, 53.43; H, 4.14; N, 9.59. Found: C, 53.31; H, 4.01; N, 9.29.

### 4.4. Methyl 7-chloro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]-quinazoline-1-carboxylate (12)

*m*-Chloro anthranilic acid (6.95 g, 40.5 mmol) was added to a stirred solution of iminoether **7** (7 g, 44.5 mmol) in toluene (100 mL). The mixture was stirred for 3 h at 55 °C and then for 8 h at 110 °C. The residue obtained after evaporation was diluted in dichloromethane (50 mL) and washed with aqueous $NaHCO_3$ (2×10 mL) and water (10 mL). The combined aqueous layers were extracted by $CH_2Cl_2$ (3×10 mL) and the combined organic layers were dried ($MgSO_4$). The residue obtained upon evaporation was crystallized from toluene. Gray powder; 80% yield; mp (toluene) 184–186 °C; TLC $R_f$ (EtOAc)=0.7; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.28–2.74 (m, 2H, CHC$H_2$C$H_2$), 3.04–3.46 (m, 2H, CHC$H_2$C$H_2$), 3.83 (s, 3H, $CO_2CH_3$), 5.16 (dd, $J$=9.3, 2.9 Hz, 1H, C*H*C$H_2$C$H_2$), 7.41 (dd, $J$=8.6, 2.0 Hz, 1H, Ar*H*), 7.66 (d, $J$=2.0 Hz, 1H, Ar*H*), 8.19 (d, $J$=8.6 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 24.2 ($CH_2$), 31.1 ($CH_2$), 53.0 ($CH_3$), 59.2 (CH), 118.9 (C), 126.6 (CH), 127.1 (CH), 128.0 (CH), 133.3 (C), 140.7 (C), 159.8 (C), 160.2 (C), 170.0 (C); IR $\nu$ cm$^{-1}$: 907, 1203, 1604, 1672, 1741. Anal. Calcd for $C_{13}H_{11}ClN_2O_3 \cdot 1/2\ H_2O$: C, 52.82; H, 4.42; N, 9.44. Found: C, 52.79; H, 4.14; N, 9.39.

### 4.5. Methyl 7-nitro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]-quinazoline-1-carboxylate (13)

Nitric acid (63%, 10 mL) was slowly added to a solution of quinazolinone **9** (11.5 g, 47.1 mmol) in sulfuric acid (50 mL) at 0 °C. The mixture was stirred at 0 °C for 2 h and then for 3 h at room temperature. The mixture was crystallized in iced water (750 mL) and then the precipitate was filtrated and recrystallized from toluene. Yellow powder; 92% yield; mp (toluene) 229–231 °C; TLC $R_f$ (EtOAc)=0.4; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.34–2.51 (m, 1H, CHC$H_2$C$H_2$), 2.54–2.79 (m, 1H, CHC$H_2$C$H_2$), 3.09–3.50 (m, 2H, CHC$H_2$C$H_2$), 3.84 (s, 3H, $CO_2CH_3$), 5.22 (dd, $J$=9.2, 3.1 Hz, 1H, C*H*C$H_2$C$H_2$), 7.79 (d, $J$=8.9 Hz, 1H, Ar*H*), 8.54 (dd, $J$=8.9, 2.6 Hz, 1H, Ar*H*), 9.13 (d, $J$=2.6 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 23.9 ($CH_2$), 31.3 ($CH_2$), 52.9 ($CH_3$), 59.3 (CH), 120.5 (C), 123.0 (CH), 128.2 (CH), 128.4 (CH), 145.2 (C), 153.0 (C), 160.2 (C), 162.7 (C), 169.6 (C); IR $\nu$ cm$^{-1}$: 1176, 1345, 1516, 1618, 1663, 1753. Anal. Calcd for $C_{13}H_{11}ClN_3O_5 \cdot 1/2\ H_2O$: C, 52.35; H, 4.06; N, 14.09. Found: C, 51.95; H, 3.73; N, 14.12.

### 4.6. Methyl 8-bromo-7-[1-(methoxycarbonyl)propyl]-6-nitro-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (25)

Nitric acid (63%, 19.5 mL) was slowly added to a solution of pyridone **24** (24.5 g, 66 mmol) in acetic anhydride (300 mL) at 0 °C. The mixture was stirred at room temperature for 2 h and the solvent was evaporated. The residue was diluted with EtOAc (500 mL) and washed with saturated sodium hydrogen carbonate solution (500 mL). The aqueous phase was extracted with EtOAc (3×300 mL) and the combined organic layers were dried over $MgSO_4$ and then evaporated. The residue was purified by chromatography on $SiO_2$ (heptane/EtOAc, 100/0% to 0/100%), to give compound **25**. Yellow powder; 92% yield; mp (EtOAc/ether) 72–74 °C; TLC $R_f$ (EtOAc)=0.5; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 0.95 and 0.98 (2t, $J$=7.4 Hz, 3H, $CH_2CH_3$), 1.81–2.05 (m, 1H, C$H_2$CH$_3$), 2.25–2.48 (m, 2H, C$H_2$CH$_3$, CH$_2$C$H_2$CH), 2.51–2.74 (m, 1H, CH$_2$C$H_2$CH), 3.22–3.34 (m, 2H, C$H_2$CH$_2$CH), 3.72 and 3.74 (2s, 3H, $COCH_3$), 3.83 and 3.84 (2s, 3H, $COCH_3$), 3.84–3.89 (m, 1H, C*H*CH$_2$CH$_3$), 5.27 and 5.29 (dd, $J$=9.4, 3.9 Hz and $J$=9.9, 3.8 Hz, 1H, CH$_2$CH$_2$C*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 12.3 ($CH_3$), 22.6 ($CH_2$), 25.3 ($CH_2$), 33.7 ($CH_2$), 49.3 ($CH_3$), 52.8 ($CH_3$), 53.3 (CH), 63.8 (CH), 94.8 (C), 144.8 (C), 152.0 (C), 152.3 (C), 169.1 (C), 169.4 (C), 169.9 (C); IR $\nu$ cm$^{-1}$: 1216, 1356, 1441, 1482, 1535, 1593, 1672, 1743. Anal. Calcd for $C_{15}H_{17}BrN_2O_7$: C, 43.18; H, 4.11; N, 6.71. Found: C, 42.80; H, 4.05; N, 6.99.

### 4.7. 7-(1-Carboxypropyl)-6-chloro-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylic acid (27)

A stirred solution of pyridone **26** (900 mg, 2.37 mmol) in 48% hydrobromic acid (20 mL) was heated at 130 °C for 6 h and then evaporated. The obtained product **27** was not purified and was directly engaged in the next step. Black oil; 100% yield; $^1$H NMR ($D_2O$, DSS, 200 MHz) $\delta$ ppm: 0.90 and 0.92 (2t, $J$=7.7 Hz and $J$=7.3 Hz, 3H, CHCH$_2$C$H_3$), 1.75–1.94 (m, 1H, CHC$H_2$CH$_3$), 1.99–2.18 (m, 1H, CHC$H_2$CH$_3$), 2.34–2.50 (m, 1H, CH$_2$C$H_2$CH), 2.58–2.80 (m, 1H, CH$_2$C$H_2$CH), 3.17–3.30 (m, 2H, C$H_2$CH$_2$CH), 4.09–4.18 (m, 1H, C*H*CH$_2$CH$_3$), 5.22 (dd, $J$=9.6, 3.5 Hz, 1H, CH$_2$CH$_2$C*H*), 6.61 (s, 1H, Ar*H*); $^{13}$C NMR ($D_2O$, DSS, 50 MHz) $\delta$ ppm: 10.7 ($CH_3$), 23.8 ($CH_2$), 25.8 ($CH_2$), 29.8 ($CH_2$), 49.9 (CH), 63.2 (CH), 103.4 (CH), 120.9 (CH), 149.9 (CH), 150.7 (CH), 158.6 (CH), 173.3 (CH), 175.9 (CH).

### 4.8. Methyl 6-chloro-7-[1-(methoxycarbonyl)propyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (28)

A stirred mixture of acid **27** (710 mg, 2.37 mmol) and methanesulfonic acid (0.10 mg) in methanol (200 mL) and chloroform (200 mL) was refluxed for 48 h. The solvent was dried by condensing it in a Soxhlet-type apparatus containing 3 Å molecular sieves (50 g). Dichloromethane (100 mL) was added to the residue obtained upon evaporation, and the solution was washed with aqueous $NaHCO_3$ (50 mL). The organic phase was dried ($MgSO_4$) and then evaporated. The residue was crystallized from ether. White powder; 95% yield; mp (ether) 138–140 °C; TLC $R_f$ (EtOAc)=0.5; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 0.93 and 0.96 (2t, $J$=7.5 Hz and $J$=7.4 Hz, 3H, CHCH$_2$C$H_3$), 1.66–2.19 (m, 2H, CHC$H_2$CH$_3$), 2.23–2.64 (m, 2H, CH$_2$C$H_2$CH), 2.96–3.33 (m, 2H,

$CH_2CH_2CH$), 3.7 and 3.72 (2s, 3H, $CO_2CH_3$), 3.81 (s, 3H, $CO_2CH_3$), 4.08 and 4.09 (2t, $J$=7.5 Hz and $J$=7.7 Hz, 1H, $CHCH_2CH_3$), 5.12 and 5.13 (2dd, 1H, $J$=9.4, 1.1 Hz, $CH_2CH_2CH$), 6.21 and 6.23 (2s, 1H, C*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 11.8 ($CH_3$), 25.0 ($CH_2$), 26.4 ($CH_2$), 30.2 ($CH_2$), 49.3 (CH), 52.2 ($CH_3$), 52.8 ($CH_3$), 62.0 (CH), 99.9 (CH), 112.4 (C), 147.6 (C), 148.2 (C), 157.32 (C), 170.1 (C), 172.3 (C). Anal. Calcd for $C_{15}H_{18}ClNO_5$: C, 54.97; H, 5.54; N, 4.27. Found: C, 55.18; H, 5.61; N, 4.19.

### 4.9. Isopropyl 3,3-dibromo-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline-1-carboxylate (35)

A solution of dibromo compound **31** (0.1 g, 0.25 mmol) in methanol (10 mL) with titanium *iso*-propoxide (0.1 mL) was stirred for 12 h at room temperature and then evaporated. The mixture was solubilized in dichloromethane (30 mL) and washed with water (2×20 mL). The organic layer was dried ($MgSO_4$) and evaporated to give **35**. Yellow oil; 70% yield; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 1.32 (t, $J$=6.4 Hz, 6H, $CH(CH_3)_2$), 3.53 (dd, $J$=14.7, 4.9 Hz, 1H, $CHCH_2CBr_2$), 3.69 (dd, $J$=14.7, 7.9 Hz, 1H, $CHCH_2CBr_2$), 5.10 (dd, $J$=7.9, 4.9 Hz, 1H, $CHCH_2CBr_2$), 5.18 (m, 1H, $CH(CH_3)_2$), 7.57 (ddd, $J$=7.9, 6.9, 1.7 Hz, 1H, Ar*H*), 7.84 (ddd, $J$=8.1, 6.9, 1.6 Hz, 1H, Ar*H*), 7.92 (ddd, $J$=8.1, 1.7, 0.6 Hz, 1H, Ar*H*), 8.32 (ddd, $J$=7.9, 1.6, 0.6 Hz, 1H, Ar*H*).

### 4.10. Acetoxylation of quinazolinone 9

A stirred solution of quinazolinone **9** (2 g, 8.2 mmol) in glacial acetic acid (25 mL) with lead acetate (9.1 g, 20.5 mmol) was heated at 110 °C for 12 h and then cooled in ice water (100 mL). The filtrate obtained upon filtration on Celite was extracted by EtOAc (3×50 mL) and was dried ($MgSO_4$). The residue obtained upon evaporation was purified by chromatography on $SiO_2$ (heptane/$CH_2Cl_2$/EtOAc 50/20/30) to give quinazolinones **36**–**38**. The pure cis isomer has been obtained by four successive recrystallizations in diethyl ether and the trans isomer has been only studied by $^1$H NMR.

#### *4.10.1. Methyl 3-(acetyloxy)-9-oxo-1,2,3,9-tetrahydropyrrolo-[2,1-b]quinazoline-1-carboxylate (**36**–**37**)*

*4.10.1.1. Cis isomer (**36**).* White foam; 35% yield; mp (ether) 146–148 °C; TLC $R_f$ (EtOAc/heptane 70/30)=0.5; $^1$H NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 2.16 (s, 3H, $OCOCH_3$), 2.41 (dt, $J$=14.8, 3.6 Hz, 1H, $CHCH_2CHOAc$), 3.02 (ddd, $J$=14.8, 9.2, 7.2 Hz, 1H, $CHCH_2CHOAc$), 3.83 (s, 3H, $CO_2CH_3$), 5.12 (dd, $J$=9.2, 3.6 Hz, 1H, $CHCH_2CHOAc$), 6.02 (dd, $J$=7.2, 3.6 Hz, 1H, $CHCH_2CHOAc$), 7.54 (ddd, $J$=8.2, 5.0, 3.5 Hz, 1H, Ar*H*), 7.79 (ddd, $J$=8.3, 1.5, 0.7 Hz, 1H, Ar*H*), 7.83 (ddd, $J$=8.3, 5.0, 1.3 Hz, 1H, Ar*H*), 8.32 (ddd, $J$=8.2, 1.3, 0.7 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 20.6 ($CH_3$), 32 ($CH_2$), 53.9 ($CH_3$), 57.2 (CH), 72.4 (CH), 121 (C), 126.5 (CH), 127.4 (CH), 127.8 (CH), 134.6 (CH), 148.8 (C), 154.8 (C), 159.9 (C), 169.3 (C), 169.6 (C); IR $\nu$ cm$^{-1}$: 1179, 1209, 1608, 1629, 1683, 1743. Anal. Calcd for $C_{15}H_{14}N_2O_5$: C, 59.60; H, 4.67; N, 9.27. Found: C, 59.32; H, 4.54; N, 9.24.

*4.10.1.2. Trans isomer (**37**).* Yellow oil; 40% yield; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.23 (s, 3H, $OCOCH_3$), 2.50 (ddd, $J$=14.0, 9.6, 7.7 Hz, 1H, $CHCH_2CHOAc$), 2.90 (ddd, $J$=14.0, 7.9, 3.0 Hz, 1H, $CHCH_2CHOAc$), 3.83 (s, 3H, $CO_2CH_3$), 5.20 (dd, $J$=9.6, 3 Hz, 1H, $CHCH_2CHOAc$), 6.13 (t, $J$=7.9 Hz, 1H, $CHCH_2CHOAc$), 7.46–7.56 (m, 1H, Ar*H*), 7.83–7.83 (m, 2H, Ar*H*), 8.30 (dt, $J$=7.9, 1.1 Hz, 1H, Ar*H*).

#### *4.10.2. Methyl 1-hydroxy-2-methyl-9-oxo-1,9-dihydropyrrolo[2,1-b]quinazoline-1-carboxylate (**38**)*

Yellow powder; 2% yield; mp (acetone) 176–178 °C; TLC $R_f$ (EtOAc/heptane 75/25)=0.4; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.23 (d, $J$=1.6 Hz, 3H, $CHCCH_3$), 3.82 (s, 3H, $CO_2CH_3$), 5.01 (s, 1H, O*H*), 6.48 (q, $J$=1.6 Hz, 1H, $CHCCH_3$), 7.50 (ddd, $J$=8.2, 5.2, 3.6 Hz, 1H, Ar*H*), 7.72–7.84 (m, 2H, Ar*H*), 8.27 (dt, $J$=7.8, 1.2, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 11.1 ($CH_3$), 54.1 ($CH_3$), 89.6 (C), 120.9 (C), 126.5 (CH), 127.2 (CH), 128.0 (CH), 134.6 (CH), 135.0 (CH), 138.9 (C), 149.1 (C), 156.1 (C), 159.3 (C), 168.4 (C); IR $\nu$ cm$^{-1}$: 1153, 1605, 1647, 1672, 1758, 3296.

#### *4.10.3. Methyl 1-(acetyloxy)-9-oxo-1,9-dihydropyrrolo[2,1-b]-quinazoline-1-carboxylate (**39**)*

A stirred solution of quinazolinone **9** (1 g, 4.1 mmol) in benzene (50 mL) with lead acetate (7.26 g, 16.4 mmol) was heated at 110 °C for 4 h and then cooled in ice water (100 mL). The filtrate obtained upon filtration on Celite was extracted by EtOAc (3×50 mL) and was dried ($MgSO_4$). The residue upon evaporation was purified by chromatography on $SiO_2$ (EtOAc/$CH_2Cl_2$/heptane 30/20/50) to give **39**. White powder; 40% yield; mp (ether) 137–139 °C; TLC $R_f$ (EtOAc/heptane 50/50)=0.7; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.21 (s, 3H, $OCOCH_3$), 3.83 (s, 3H, $CO_2CH_3$), 6.81 (d, $J$=5.8 Hz, 1H, Ar*H*), 7.43 (d, $J$=5.8 Hz, 1H, Ar*H*), 7.52 (ddd, $J$=7.9, 6.5, 1.9 Hz, 1H, Ar*H*), 7.73 (ddd, $J$=8.1, 1.9, 0.6 Hz, 1H, Ar*H*), 7.79 (ddd, $J$=7.9, 6.5, 1.9 Hz, 1H, Ar*H*), 8.29 (ddd, $J$=7.9, 1.5, 0.6 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 21.0 ($CH_3$), 54.0 ($CH_3$), 93.1 (C), 121.0 (C), 127.0 (CH), 127.6 (CH), 128.0 (CH), 130.0 (CH), 134.8 (CH), 139.5 (CH), 148.4 (C), 155.5 (C), 158.4 (C), 163.4 (C), 168.8 (C); IR $\nu$ cm$^{-1}$: 1182, 1210, 1604, 1639, 1693, 1753, 1783.

### 4.11. Methyl 3-hydroxy-9-oxo-1,2,3,9-tetrahydropyrrolo-[2,1-*b*]quinazoline-1-carboxylates (40 and 41)

A stirred mixture of quinazolines **36** and **37** (4.7 g, 15.5 mmol) was solubilized in dry methanol (40 mL) and 30% sodium methylate (0.7 mL, 2.7 mmol) was added. After 4 h, the solution was neutralized by 37% hydrochloric acid and partitioned between dichloromethane (20 mL) and water (10 mL). The organic layer was washed with water and then dried ($MgSO_4$). The mixture of isomers obtained upon evaporation was purified by chromatography on $SiO_2$ (heptane/$CH_2Cl_2$/EtOAc 50/20/30).

#### *4.11.1. Cis isomer (**40**)*

Yellow oil; 36% yield; $R_f$ (EtOAc)=0.5; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.44 (dt, $J$=14.1, 3.3 Hz, 1H, $CHCH_2CHOH$), 2.87 (ddd, $J$=14.1, 8.5, 7.1 Hz, 1H, $CHCH_2CHOH$), 3.77 (br s, 1H, O*H*), 3.86 (s, 3H, $CO_2CH_3$), 5.10 (dd, $J$=8.5, 3.3 Hz, 1H, $CHCH_2CHOH$), 5.16 (dd, $J$=7.1, 3.3 Hz, 1H, $CHCH_2CHOH$), 7.52 (ddd, $J$=8.0, 6.0, 2.3 Hz, 1H, Ar*H*), 7.75 (ddd, $J$=8.2, 2.3, 0.7 Hz, 1H, Ar*H*), 7.80 (ddd, $J$=8.2, 6.0, 1.5 Hz, 1H, Ar*H*), 8.31 (ddd, $J$=8.0, 1.5, 0.7 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 33.8 ($CH_2$), 53.2 ($CH_3$), 57.5 (CH), 71.5 (CH), 121.2 (C), 126.8 (CH), 127.2 (CH), 127.3 (CH), 134.7 (CH), 148.7 (C), 159.2 (C), 160.1 (C), 170.3 (C).

#### *4.11.2. Trans isomer (**41**)*

White powder; 44% yield; mp (acetone) 189–190 °C; $R_f$ (EtOAc)=0.6; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.58 (ddd, $J$=13.5, 9.5, 8.8 Hz, 1H, $CHCH_2CHOH$), 2.79 (ddd, $J$=13.5, 8.0, 2.4 Hz, 1H, $CHCH_2CHOH$), 3.83 (s, 3H, $CO_2CH_3$), 5.22 (dd, $J$=9.5, 2.4 Hz, 1H, $CHCH_2CHOH$), 5.35 (dd, $J$=8.8, 8.0 Hz, 1H, $CHCH_2CHOH$), 6.41 (br s, 1H, O*H*), 7.52 (ddd, $J$=8.0, 5.8, 2.3 Hz, 1H, Ar*H*), 7.76 (ddd, $J$=8.2, 2.3, 0.7 Hz, 1H, Ar*H*), 7.81 (ddd, $J$=8.2, 5.8, 1.4 Hz, 1H, Ar*H*), 8.30 (ddd, $J$=8.0, 1.4, 0.7 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 34 ($CH_2$), 53.2 ($CH_3$), 56.4 (CH), 70.4 (CH), 121 (C), 126.8 (CH), 126.9 (CH), 127.2 (CH), 134.8 (CH), 148.6 (C), 159.9 (C), 160 (C), 170.1 (C); IR $\nu$ cm$^{-1}$: 1212, 1620, 1682, 1749, 3168. Anal. Calcd for $C_{13}H_{12}N_2O_4$: C, 60.00; H, 4.65; N, 10.76. Found: C, 60.10; H, 4.67; N, 10.72.

### 4.12. Bredereck reaction with quinazolinones 9, 12, 13 or pyridone 28

A stirred mixture of heterocycles **9**, **12**, **13** or **28** (68 mmol) and Bredereck's reagent (16.35 g, 94 mmol) was heated at 110 °C for 2 h ($N_2$). The residue obtained upon evaporation was diluted in dichloromethane (50 mL) and washed with water (3×30 mL), and then the organic layer was dried ($MgSO_4$). The residue obtained upon evaporation was crystallized from methanol.

#### *4.12.1. Methyl 3-[(dimethylamino)methylene]-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**42**)*

Yellow powder; 95% yield; mp (methanol) 178–180 °C; TLC $R_f$ (MeOH/EtOAc 50/50)=0.75; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.11 (s, 6H, N($CH_3$)$_2$), 3.19 (ddd, $J$=15.0, 4.2, 1.5 Hz, 1H, CHC$H_2$C=CH), 3.53 (ddd, $J$=15.0, 10.8, 1.5 Hz, 1H, CHC$H_2$C=CH), 3.79 (s, 3H, $CO_2CH_3$), 5.07 (dd, $J$=10.8, 4.2 Hz, 1H, C$H$CH$_2$CH$_2$), 7.23 (ddd, $J$=7.9, 6.9, 1.3 Hz, 1H, Ar$H$), 7.48 (ddd, $J$=8.3, 1.3, 0.6 Hz, 1H, Ar$H$), 7.50 (br s, 1H, CH$_2$C=C$H$N), 7.62 (ddd, $J$=8.3, 6.9, 1.6 Hz, 1H, Ar$H$), 8.27 (ddd, $J$=7.9, 1.6, 0.6 Hz, 1H, Ar$H$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 26.6 ($CH_2$), 42.1 (2×$CH_3$), 52.2 ($CH_3$), 56.7 (CH), 92.7 (C), 119.4 (C), 123.4 (CH), 125.6 (CH), 126.4 (CH), 134.0 (CH), 142.5 (C), 150.9 (CH), 158.4 (C), 161.0 (C), 170.6 (C); IR $\nu$ cm$^{-1}$: 1117, 1207, 1360, 1548, 1650, 1661, 1741. Anal. Calcd for $C_{16}H_{17}N_3O_3\cdot 1/2\ H_2O$: C, 62.33; H, 5.88; N, 13.63. Found: C, 62.72; H, 5.61; N, 13.53.

#### *4.12.2. Methyl 7-chloro-3-[(dimethylamino)methylene]-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**43**)*

Yellow powder; 95% yield; mp (methanol) 228–230 °C; TLC $R_f$ (EtOAc)=0.6; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.12 (s, 6H, N($CH_3$)$_2$), 3.18 (ddd, $J$=14.9, 4.0, 1.4 Hz, 1H, CHC$H_2$C=CH), 3.52 (ddd, $J$=14.9, 10.9, 1.4 Hz, 1H, CHC$H_2$C=CH), 3.79 (s, 3H, $CO_2CH_3$), 5.05 (dd, $J$=10.9, 4.0 Hz, 1H, C$H$CH$_2$CH$_2$), 7.16 (dd, $J$=8.5, 0.4 Hz, 1H, Ar$H$), 7.45 (dd, $J$=8.5, 2 Hz, 1H, Ar$H$), 7.47 (br s, 1H, CH$_2$C=C$H$N), 8.05 (dd, $J$=2, 0.4 Hz, 1H, Ar$H$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 28.5 ($CH_2$), 42.0 (2×$CH_3$), 52.6 ($CH_3$), 56.6 (CH), 92.3 (C), 117.7 (C), 123.6 (CH), 124.9 (CH), 127.7 (CH), 140.0 (C), 143.1 (CH), 151.9 (C), 159.4 (C), 160.3 (C), 170.4 (C); IR $\nu$ cm$^{-1}$: 914, 1113, 1205, 1367, 1551, 1655, 1665, 1751. Anal. Calcd for $C_{16}H_{16}ClN_3O_3$: C, 57.58; H, 4.83; N, 12.59. Found: C, 57.20; H, 4.90; N, 12.98.

#### *4.12.3. Methyl 3-[(dimethylamino)methylene]-7-nitro-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**44**)*

Orange foam; 85% yield; mp (methanol) 247–249 °C; TLC $R_f$ (EtOAc)=0.3; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.17 (s, 6H, N($CH_3$)$_2$), 3.22 (ddd, $J$=14.9, 11.0, 1.8 Hz, 1H, CHC$H_2$C=CH), 3.56 (ddd, $J$=14.9, 4.2, 1.5 Hz, 1H, CHC$H_2$C=CH), 3.81 (s, 3H, $CO_2CH_3$), 5.09 (dd, $J$=11.0, 4.2 Hz, 1H, C$H$CH$_2$CH$_2$), 7.44 (d, $J$=9.2 Hz, 1H, Ar$H$), 7.58 (br s, 1H, CH$_2$C=C$H$N), 8.37 (dd, $J$=9.2, 2.8 Hz, 1H, Ar$H$), 9.00 (d, $J$=2.8 Hz, 1H, Ar$H$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 28.7 ($CH_2$), 42.4 (2×$CH_3$), 52.9 ($CH_3$), 56.8 (CH), 92.4 (C), 118.7 (C), 123.6 (CH), 126.3 (CH), 128.4 (CH), 142.6 (C), 145.2 (CH), 155.6 (C), 159.9 (C), 161.5 (C), 170.1 (C); IR $\nu$ cm$^{-1}$: 1119, 1168, 1317, 1506, 1541, 1650, 1676, 1743. Anal. Calcd for $C_{16}H_{16}N_4O_5\cdot 1/2\ H_2O$: C, 54.39; H, 4.85; N, 15.86. Found: C, 54.25; H, 4.56; N, 15.95.

#### *4.12.4. Methyl 6-chloro-1-[(dimethylamino)methylene]-7-[1-(methoxycarbonyl)propyl]-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (**50**)*

Black oil; 98% yield; TLC $R_f$ (EtOAc)=0.5; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 0.93 and 0.95 (2t, $J$=7.4 Hz, 3H, CHCH$_2$C$H_3$), 1.57–2.19 (m, 2H, CHC$H_2$CH$_3$), 3.01 (s, 6H, N($CH_3$)$_2$), 3.06–3.46 (m, 2H, C$H_2$CH), 3.69 and 3.71 (2s, 3H, $CO_2CH_3$), 3.79 (s, 3H, $CO_2CH_3$), 4.04 and 4.05 (2t, $J$=7.7 Hz and $J$=7.5 Hz, 1H, C$H$CH$_2$CH$_3$), 5.04 (dd, $J$=11.4, 4.9 Hz, 1H, CH$_2$CH$_2$C$H$), 5.98 and 6.01 (2s, 1H, C$H$), 6.65 (s, 1H, C$H$).

### 4.13. Methyl 1-[(dimethylamino)methylene]-7-[1-(methoxycarbonyl)propyl]-8-nitro-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (48)

A stirred mixture of pyridone **18** (200 mg, 0.59 mmol) and DMFDMA (211 mg, 1.77 mmol) was heated at 110 °C for 3 h ($N_2$). The residue obtained upon evaporation was diluted in dichloromethane (100 mL) and washed with water (2×40 mL), and then the organic layer was dried ($MgSO_4$). Orange powder; 74% yield; mp (EtOAc)=117–119 °C; TLC $R_f$ (EtOAc)=0.4; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 0.94 and 0.98 (2t, $J$=7.4 Hz, 3H, CHCH$_2$C$H_3$), 1.72–1.91 (m, 1H, CHC$H_2$CH$_3$), 1.93–2.16 (m, 1H, CHC$H_2$CH$_3$), 3.11 (s, 6H, N($CH_3$)$_2$), 3.11–3.22 (m, 1H, C$H_2$CH), 3.38–3.57 (m, 3H, C$H_2$CH, C$H$CH$_2$CH$_3$), 3.68 and 3.72 (2s, 3H, $CO_2CH_3$), 3.80 (s, 3H, $CO_2CH_3$), 5.07 (dd, $J$=10.9, 4.65 Hz, 1H, CH$_2$C$H$), 5.96 and 5.99 (2s, 1H, Ar$H$), 6.87 (s, 1H, C$H$N($CH_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 12.0 ($CH_3$), 26.3 ($CH_2$), 30.1 ($CH_2$), 42.3 ($CH_3$), 42.5 ($CH_3$), 47.6, 47.7 ($CH_3$), 52.3 ($CH_3$), 52.8, 52.9 (CH), 59.8, 60.1 (CH), 89.9 (C), 95.9 (C), 133.0 (CH), 142.6 (C), 147.9 (C), 154.2 (CH), 155.7 (C), 170.0 (C), 172.6 (C); IR $\nu$ cm$^{-1}$: 1717, 1650, 1557, 1487, 1304, 1263, 1199. Anal. Calcd for $C_{18}H_{23}N_3O_7$: C, 54.96; H, 5.89; N, 10.68. Found: C, 55.24; H, 5.86; N, 10.51.

### 4.14. Methyl 8-bromo-1-[(dimethylamino)methylene]-7-[1-(methoxycarbonyl)propyl]-6-nitro-5-oxo-1,2,3,5-tetrahydroindolizine-3-carboxylate (49)

A stirred mixture of pyridone **25** (200 mg, 0.48 mmol) and DMFDMA (260 mg, 1.44 mmol) was heated at 110 °C for 3 h ($N_2$) in toluene (2.5 mL). The residue obtained upon evaporation was purified by chromatography on $SiO_2$ (heptane/EtOAc, 100/0% to 0/100%) to give compound **49**. Red powder; 83% yield; mp (ether)=88–89 °C; TLC $R_f$ (EtOAc)=0.3; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 0.98 and 0.99 (2t, $J$=7.4 Hz, 3H, CHCH$_2$C$H_3$), 1.76–1.98 (m, 1H, CHC$H_2$CH$_3$), 2.24–2.49 (m, 1H, CHC$H_2$CH$_3$), 3.11 (s, 6H, N($CH_3$)$_2$), 3.13–3.25 (m, 1H, C$H_2$CH), 3.40–3.58 (m, 1H, C$H_2$CH), 3.70 and 3.72 (2s, 3H, $CO_2CH_3$), 3.80 and 3.81 (2s, 3H, $CO_2CH_3$), 3.77–3.86 (m, 1H, C$H$CH$_2$CH$_3$), 5.06 and 5.08 (2dd, $J$=10.9, 5.7 Hz and $J$=11.0, 5.4 Hz, 1H, CH$_2$CH$_2$C$H$), 8.08 and 8.11 (2s, 1H, C$H$N($CH_3$)$_2$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 12.4 ($CH_3$), 22.8, 22.9 ($CH_2$), 30.9 ($CH_2$), 42.9 ($CH_3$), 43.0 ($CH_3$), 43.2 ($CH_3$), 43.3 ($CH_3$), 49.8 ($CH_3$), 52.4 ($CH_3$), 52.9, 53.0 (CH), 59.5, 59.8, 60.0 (CH), 96.9, 97.0 (C), 110.4 (C), 146.7 (C), 147.6 (C), 147.9 (C), 150.7 (C), 152.9 (CH), 169.7 (C), 170.9 (C); IR $\nu$ cm$^{-1}$: 1744, 1656, 1620, 1482, 1211, 1120. Anal. Calcd for $C_{18}H_{22}BrN_3O_7\cdot 1/2\ H_2O$: C, 44.92; H, 4.82; N, 8.73. Found: C, 44.92; H, 4.82; N, 8.42.

### 4.15. Methyl 3-(hydroxyimino)-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-*b*]quinazoline-1-carboxylate (53)

Hydrochloric acid (33 mL) was added to quinazolinone **42** (5 g, 16.7 mmol) in water (50 mL). A solution of sodium nitrite (1.5 g, 21.7 mmol) in cold water (50 mL) was slowly added and the mixture was stirred at 0 °C for 2 h. The product was purified by crystallization in ice water (100 mL). White powder; 90% yield; mp ($CHCl_3$) 185–187 °C; TLC $R_f$ (EtOAc)=0.6; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.20 (dd, $J$=19.5, 3.9 Hz, 1H, CHC$H_2$C=N), 3.47 (dd, $J$=19.5, 9.9 Hz, 1H, CHC$H_2$C=N), 3.84 (s, 3H, $CO_2CH_3$), 5.23 (dd, $J$=9.9, 3.9 Hz, 1H, C$H$CH$_2$C=N), 7.53 (ddd, $J$=7.8, 6.6, 1.4 Hz, 1H, Ar$H$), 7.79 (ddd, $J$=8.4, 1.4, 0.6 Hz, 1H, Ar$H$), 7.85 (td, $J$=8.4, 1.4 Hz, 1H, Ar$H$), 8.30 (dd, $J$=7.8, 1.4 Hz, 1H, Ar$H$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 27.3 ($CH_2$), 53 ($CH_3$), 55.4 (CH), 121.1 (C), 126.4 (CH), 127.2 (CH), 128.2 (CH), 134.7 (CH), 149.2 (C), 149.8 (C), 150 (C), 160.2 (C), 169.6 (C); IR $\nu$ cm$^{-1}$: 1206, 1464, 1607, 1691, 1750, 3602. Anal. Calcd for $C_{13}H_{11}N_3O_4\cdot 2/3\ H_2O$: C, 54.74; H, 4.36; N, 14.73. Found: C, 54.31; H, 4.62; N, 14.30.

### 4.16. Dimethyl 1-(hydroxyimino)-7-[1-(methoxycarbonyl)-propyl]-6-nitro-5-oxo-1,2,3,5-tetrahydro-indolizine-3,8-dicarboxylate (54)

A cold solution of sodium nitrite (183 mg, 26.25 mmol) in water (3 mL) was added to a stirred solution of enamine **47** (1.14 g, 25 mmol) in acetic acid for 3 h. The solution was neutralized by satd aqueous $NaHCO_3$ (50 mL) and was extracted by dichloromethane (2×100 mL). The combined organic layers were dried over $MgSO_4$ and then evaporated. The residue was purified by chromatography on $SiO_2$ (heptane/EtOAc, 100/0% to 0/100%). White powder; 87% yield; mp (MeOH) 92–95 °C; TLC $R_f$ (EtOAc)=0.6; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 0.94 and 0.96 (2t, $J$=7.7 Hz, 3H, $CHCH_2CH_3$), 1.59–1.80 (m, 1H, $CHCH_2CH_3$), 2.11–2.34 (m, 1H, $CHCH_2CH_3$), 3.07–3.24 (m, 1H, $CH_2CH$), 3.30–3.41 (m, 1H, $CH_2CH$), 3.49 (t, $J$=7.5 Hz, 1H, $CHCH_2CH_3$), 3.69, 3.72 (2s, 3H, $CO_2CH_3$), 3.80 (s, 3H, $CO_2CH_3$), 3.85 and 3.86 (2s, 3H, $CO_2CH_3$), 5.17 and 5.19 (2dd, $J$=9.8, 1.6 Hz and $J$=9.9, 1.6 Hz, 1H, $CH_2CH$), 8.90 (br s, 1H, NO*H*); IR $\nu$ cm$^{-1}$: 1738, 1673, 1537, 1433, 1262, 1218. Anal. Calcd for $C_{17}H_{19}N_3O_{10}$: C, 48.00; H, 4.50; N, 9.88. Found: C, 48.23; H, 4.99; N, 9.19.

### 4.17. General procedure of hydrazone synthesis

Substituted aniline (20 mmol) was dissolved in 37% hydrochloric acid (5 mL) and water (5 mL) cooled on an ice bath. A solution of sodium nitrite (1.4 g, 21 mmol) in cold water (5 mL) was slowly added to the mixture. Sodium acetate (12 g) was added, and then a solution of enamine **42** or **43** in 75% acetic acid (60 mL) was poured. During the addition of products and 4 h after, the stirred solution was kept at 0 °C. The product obtained upon filtration was filtrated, washed with water, dried ($MgSO_4$), and then crystallized from methanol.

#### *4.17.1. Methyl 9-oxo-3-(phenylhydrazono)-1,2,3,9-tetrahydro-pyrrolo[2,1-b]quinazoline-1-carboxylate (**59**)*

White powder; 85% yield; mp (MeOH) 181–183 °C; TLC $R_f$ (EtOAc/heptane 70/30)=0.7; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.01 (dd, $J$=17.9, 3.9 Hz, 1H, $CHCH_2C$=N), 3.32 (dd, $J$=17.9, 10.2 Hz, 1H, $CHCH_2C$=N), 3.78 (s, 3H, $CO_2CH_3$), 5.21 (dd, $J$=10.2, 3.9 Hz, 1H, $CHCH_2C$=N), 7.01 (m, 1H, Ar*H*), 7.29 (d, $J$=7.1 Hz, 4H, Ar*H*), 7.48 (ddd, $J$=7.9, 7.0, 1.4 Hz, 1H, Ar*H*), 7.79 (ddd, $J$=8.2, 7.0, 1.4 Hz, 1H, Ar*H*), 7.89 (dd, $J$=8.2, 1.4 Hz, 1H, Ar*H*), 8.07 (br s, 1H, =NN*H*), 8.28 (dd, $J$=7.9, 1.4 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$/DMSO-$d_6$, 50 MHz) $\delta$ ppm: 27.3 ($CH_2$), 53.1 ($CH_3$), 55.6 (CH), 113.2 (2×CH), 121 (CH), 125.8 (C), 126.8 (C), 127.3 (CH), 127.4 (CH), 127.9 (CH), 129.3 (2×CH), 134.6 (CH), 143.4 (C), 148.3 (C), 148.8 (C), 160 (C), 169.2 (C); IR $\nu$ cm$^{-1}$: 1208, 1465, 1575, 1671, 1751, 3601. Anal. Calcd for $C_{19}H_{16}N_4O_3\cdot 3/2\ H_2O$: C, 60.79; H, 5.10; N, 14.93. Found: C, 60.73; H, 4.96; N, 14.75.

#### *4.17.2. Methyl 7-chloro-9-oxo-3-(phenylhydrazono)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**60**)*

Yellow powder; mp (MeOH) 136–138 °C; 75% yield; TLC $R_f$ (EtOAc/heptane 80/20)=0.4; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.01 (dd, $J$=17.9, 3.9 Hz, 1H, $CHCH_2C$=N), 3.32 (dd, $J$=17.9, 10.2 Hz, 1H, $CHCH_2C$=N), 3.78 (s, 3H, $CO_2CH_3$), 5.21 (dd, $J$=10.2, 3.9 Hz, 1H, $CHCH_2C$=N), 7.01 (m, 1H, Ar*H*), 7.29 (d, $J$=7.1 Hz, 4H, Ar*H*), 7.48 (ddd, $J$=7.9, 7.0, 1.4 Hz, 1H, Ar*H*), 7.79 (ddd, $J$=8.2, 7.0, 1.4 Hz, 1H, Ar*H*), 7.89 (dd, $J$=8.2, 1.4 Hz, 1H, Ar*H*), 8.07 (br s, 1H, =NN*H*), 8.28 (dd, $J$=7.9, 1.4 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$/DMSO-$d_6$, 50 MHz) $\delta$ ppm: 27.3 ($CH_2$), 53.1 ($CH_3$), 55.6 (CH), 113.2 (2×CH), 121 (CH), 125.8 (C), 126.8 (C), 127.3 (CH), 127.4 (CH), 127.9 (CH), 129.3 (2×CH), 134.6 (CH), 143.4 (C), 148.3 (C), 148.8 (C), 160 (C), 169.2 (C); IR $\nu$ cm$^{-1}$: 1208, 1465, 1575, 1671, 1751, 3601. Anal. Calcd for $C_{19}H_{16}N_4O_3\cdot 3/2\ H_2O$: C, 60.79; H, 5.10; N, 14.93. Found: C, 60.73; H, 4.96; N, 14.75.

#### *4.17.3. Methyl 3-[(4-nitrophenyl)hydrazono]-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**61**)*

Yellow powder; 95% yield; mp (MeOH) 239–241 °C; TLC $R_f$ (EtOAc/heptane 80/20)=0.4; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.08 (dd, $J$=17.7, 3.5 Hz, 1H, $CHCH_2C$=N), 3.39 (dd, $J$=17.7, 9.9 Hz, 1H, $CHCH_2C$=N), 3.83 (s, 3H, $CO_2CH_3$), 5.33 (dd, $J$=9.9, 3.5 Hz, 1H, $CHCH_2C$=N), 7.39 (d, $J$=9.2 Hz, 2H, Ar*H*), 7.54 (td, $J$=7.3, 1.4 Hz, 1H, Ar*H*), 7.83 (td, $J$=7.3, 1.4 Hz, 1H, Ar*H*), 7.92 (d, $J$=8.2 Hz, 1H, Ar*H*), 8.07 (br s, 1H, =NN*H*), 8.24 (d, $J$=9.2 Hz, 2H, Ar*H*), 8.31 (dd, $J$=8.2, 1.4 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 28.6 ($CH_2$), 53.1 ($CH_3$), 55.2 (CH), 113.6 (2×CH), 120.9 (C), 125.5 (C), 125.5 (2×CH), 126.4 (CH), 126.9 (CH), 128.2 (CH), 134.7 (CH), 138.5 (C), 141.4 (C), 149.5 (C), 150.8 (C), 160.2 (C), 169.6 (C); IR $\nu$ cm$^{-1}$: 1187, 1322, 1499, 1580, 1688, 1728, 3298. Anal. Calcd for $C_{19}H_{15}N_5O_5$, $H_2O$: C, 55.48; H, 4.17; N, 17.02. Found: C, 55.33; H, 3.94; N, 16.62.

### 4.18. General procedure of ethylenic synthesis

A stirred solution of quinazolinone **9** (8 g, 33 mmol) and substituted benzaldehyde (26.7 mL, 0.26 mmol) in acetic anhydride (300 mL) was heated at reflux for 72 h. The cooled solution was kept overnight in freezer. The product obtained upon filtration was washed with ether and then recrystallized from methanol.

#### *4.18.1. Methyl 3-benzylidene-9-oxo-1,2,3,9-tetrahydropyrrolo-[2,1-b]quinazoline-1-carboxylate (**67**)*

White powder; 75% yield; mp (MeOH) 200–202 °C; TLC $R_f$ (EtOAc/heptane 70/30)=0.8; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.30 (ddd, $J$=17.6, 3.4, 2.8 Hz, 1H, $CHCH_2C$=CH), 3.66 (ddd, $J$=17.6, 10.1, 2.8 Hz, 1H, $CHCH_2C$=CH), 3.80 (s, 3H, $CO_2CH_3$), 5.25 (dd, $J$=10.2, 3.4 Hz, 1H, $CHCH_2C$=CH), 7.37–7.58 (m, 6H, Ar*H*), 7.76–7.80 (m, 2H, Ar*H*), 7.88 (t, $J$=2.8 Hz, 1H, $CHCH_2C$=C*H*), 8.29 (dd, $J$=7.9, 1.0 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 30.7 ($CH_2$), 53.0 ($CH_3$), 56.9 (CH), 121.0 (C), 126.5 (CH), 126.7 (CH), 127.5 (CH), 129.0 (2×CH), 129.1 (C), 129.3 (CH), 129.9 (2×CH), 131.7 (CH), 134.6 (CH), 135.2 (C), 149.7 (C), 155.0 (C), 160.7 (C), 170.0 (C); IR $\nu$ cm$^{-1}$: 1227, 1591, 1666, 1750. Anal. Calcd for $C_{20}H_{16}N_2O_3\cdot 1/8\ H_2O$: C, 71.79; H, 4.90; N, 8.37. Found: C, 71.59; H, 5.25; N, 8.57.

#### *4.18.2. Methyl 9-oxo-3-(3,4,5-trimethoxybenzylidene)-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**68**)*

Yellow power; 45% yield; mp (toluene) 208–210 °C; TLC $R_f$ (EtOAc)=0.8; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.28 (ddd, $J$=17.5, 3.8, 2.6 Hz, 1H, $CHCH_2C$=CH), 3.66 (ddd, $J$=17.5, 10.1, 2.9 Hz, 1H, $CHCH_2C$=CH), 3.81 (s, 3H, $CO_2CH_3$), 3.91 (s, 3H, $OCH_3$), 3.93 (s, 6H, 2×$OCH_3$), 5.25 (dd, $J$=10.1, 3.8 Hz, 1H, $CHCH_2C$=CH), 6.76 (s, 2H, Ar*H*), 7.47 (ddd, $J$=8.1, 5.0, 3.3 Hz, 1H, Ar*H*), 7.75–7.80 (m, 2H, Ar*H*), 7.82 (d, $J$=2.6 Hz, 1H, $CHCH_2C$=C*H*), 8.30 (td, $J$=8.0, 1.0, 1.0 Hz, 1H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 30.5 ($CH_2$), 53.1 ($CH_3$), 56.3 (2×$CH_3$), 56.9 (CH), 60.9 ($CH_3$), 107.4 (2×CH), 120.8 (C), 126.4 (CH), 126.7 (CH), 127.4 (CH), 127.9 (C), 130.6 (C), 131.6 (CH), 134.6 (CH), 139.5 (C), 149.7 (C), 153.4 (2×C), 155.0 (C), 160.6 (C), 170.0 (C); IR $\nu$ cm$^{-1}$: 1245, 1459, 1577, 1673, 1744. Anal. Calcd for $C_{23}H_{22}N_2O_6\cdot 2/7\ H_2O$: C, 64.61; H, 5.32; N, 6.55. Found: C, 64.91; H, 5.64; N, 6.85.

#### *4.18.3. Methyl 3-(4-nitrobenzylidene)-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**69**)*

Yellow powder; 75% yield; TLC $R_f$ (EtOAc/heptane 75/25)=0.8; mp (MeOH) 260 °C (dec); $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 3.32 (ddd, $J$=18.0, 3.5, 2.7 Hz, 1H, $CHCH_2C$=CH), 3.69 (ddd, $J$=18.0, 9.9, 2.7 Hz, 1H, $CHCH_2C$=CH), 3.83 (s, 3H, $CO_2CH_3$), 5.29 (dd, $J$=9.9, 3.5 Hz, 1H, $CHCH_2C$=CH), 7.52 (ddd, $J$=8.3, 4.9, 3.5 Hz, 1H, Ar*H*), 7.76–7.64 (m, 2H, Ar*H*), 7.88–7.77 (m, 2H, Ar*H*), 7.94 (t, $J$=2.7 Hz, 1H, $CHCH_2C$=C*H*), 8.42–8.26 (m, 3H, Ar*H*); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 30.7 ($CH_2$), 53.1 ($CH_3$), 56.7 (CH), 121.0 (C), 124.1 (2×CH), 126.4 (CH), 127.0 (CH), 127.6 (CH), 128.7 (CH), 130.1 (2×CH), 133.4 (C), 134.7 (CH), 141.1 (C),

147.5 (C), 149.3 (C), 154.0 (C), 160.4 (C), 169.6 (C); IR $\nu$ $cm^{-1}$: 1278, 1340, 1518, 1578, 1668, 1749. Anal. Calcd for $C_{20}H_{15}N_3O_5$: C, 63.66; H, 4.01; N, 11.14. Found: C, 63.30; H, 4.32; N, 11.15.

#### *4.18.4. Methyl 3-{[4-(acetyloxy)-3,5-dimethoxyphenyl]hydrazono}-9-oxo-1,2,3,9-tetrahydropyrrolo[2,1-b]quinazoline-1-carboxylate (**70**)*

White powder; 87% yield; mp (acetonitrile) 257–259 °C; TLC $R_f$ (EtOAc/heptane 70/30)=0.6; $^1$H NMR ($CDCl_3$, 200 MHz) $\delta$ ppm: 2.37 (s, 3H, OCOC$H_3$), 3.29 (ddd, $J$=17.5, 3.7, 2.5 Hz, 1H, CHC$H_2$C=CH), 3.65 (ddd, $J$=17.5, 10.2, 2.5 Hz, 1H, CHC$H_2$C=CH), 3.82 (s, 3H, $CO_2CH_3$), 3.88 (s, 6H, 2×OC$H_3$), 5.26 (dd, $J$=10.2, 3.7 Hz, 1H, C$H$CH$_2$C=CH), 6.77 (s, 2H, Ar$H$), 7.47 (ddd, $J$=8.4, 5.1, 3.5 Hz, 1H, Ar$H$), 7.75–7.80 (m, 2H, Ar$H$), 7.83 (t, $J$=2.5 Hz, 1H, CHCH$_2$C=C$H$), 8.30 (d, $J$=7.7 Hz, 1H, Ar$H$); $^{13}$C NMR ($CDCl_3$, 50 MHz) $\delta$ ppm: 20.5 ($CH_3$), 30.6 ($CH_2$), 53.1 ($CH_3$), 56.3 (2×$CH_3$), 56.9 (CH), 106.7 (2×CH), 121.0 (C), 126.6 (CH), 126.8 (CH), 127.5 (CH), 129.2 (C), 131.5 (CH), 133.4 (C), 134.7 (CH), 149.7 (C), 152.5 (3×C), 154.8 (C), 160.7 (C), 168.6 (C), 169.9 (C); IR $\nu$ $cm^{-1}$: 1122, 1185, 1210, 1587, 1676, 1746, 1757. Anal. Calcd for $C_{24}H_{22}N_2O_7$: C, 64.00; H, 4.92; N, 6.22. Found: C, 64.34; H, 5.21; N, 6.44.

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