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Abdulkareem Hamid, Abdelaziz Souizi, Ata Martin Lawson, Mohamed Othman, Alina Ghinet, et al.. Benzo[7,8]indolizinoquinoline scaffolds based on Mg(ClO₄)₂-promoted regiospecific imide reduction and π -cyclization of N-acyliminium species. Analogues of the topo-1 poison rosettacin and 22-hydroxyacuminatine alkaloids. *Arabian Journal of Chemistry*, 2019, 12 (5), pp.680-693. <10.1016/j.arabjc.2018.03.009>. <hal-02413296>

HAL Id: hal-02413296

<https://normandie-univ.hal.science/hal-02413296v1>

Submitted on 23 Dec 2019

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ORIGINAL ARTICLE

Benzo[7,8]indolizinoquinoline scaffolds based on $Mg(ClO_4)_2$ -promoted regiospecific imide reduction and π -cyclization of *N*-acyliminium species. Analogues of the topo-1 poison rosettacin and 22-hydroxyacuminatine alkaloids

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Received 12 August 2017; accepted 7 March 2018

Available online 14 March 2018

KEYWORDS

Regiospecific imide reduction;
Lewis and Brønsted acids catalysis;
N-Acyliminium species;

Abstract A general five-step synthesis of a short library of benzo[7,8]indolizinoquinolinine analogues of the topoisomerase-1 (topo-1) poison rosettacin and 22-hydroxyacuminatine alkaloids from DMAD and *ortho*-ketoanilines is reported. This consists on successively, the tandem aza-Michael addition/cyclodehydration, the hydrolysis of the resulting diesters into corresponding *o*-dicarboxylic acids, and the tandem intermolecular amidation/cyclodehydration into *N*-substituted imides. The regioselective reduction of one imide carbonyl into corresponding α -hydroxy lactams

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π -Cationic cyclization;
Alkaloids analogues

promoted by a Lewis acid Mg(ClO₄)₂ was followed ultimately with TFA-promoted π -cationic cyclization via stable *N*-acyliminiums species as an important key step.

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1. Introduction

The coupling process of *N*-acyliminium species, formed generally in situ by acidic treatment of amide or lactam bearing a leaving group at their α -position, constitute one of the power tools used in C–C bond forming reactions explored largely in contemporaneous synthetic organic chemistry (Hiemstra and Speckamp, 1991; DeKoning and Speckamp, 1996; Pili and Russowsky, 1997; Speckamp and Moolenaar, 2000; Maryanoff et al., 2004; Yazici and Pyne, 2009a,b). The high stability of these cationic species due to the presence of a carbonyl function at the nitrogen atom, gives them unlimited reactivity and hence deliver a wide range of natural and unnatural polycyclic systems including alkaloids with, among others, broad biological interests (Hiemstra and Speckamp, 1998; Marson, 2001). While the formation of C–heteroatom bonds seems to be scarce but constitutes a novel and powerful strategy to access new complex compounds containing cyclic mixed *N,O*-, *N,N*-, *N,S*-, and *N,Se*-acetals as compiled recently (Daich et al., 2014), the C–C bond formation, which has extensively been investigated, is still of interest and general uses for the exploration of new space of heterocyclic synthesis.

Among various nitrogen containing heterocyclic nuclei, pyrroloisoquinoline scaffolds have drawn tremendous interests in synthetic and medicinal chemistry due to their occurrence in many naturally occurring alkaloids and unnatural products with large spectrum of pharmacological activities. These systems can be exemplified by the antimicrobial, antioxidant and anti-inflammatory agents of general structure **1** including (-)-trolline (R=H, R₃=R₄=OH) (Moreno et al., 2012; Suyavaran et al., 2015), the corresponding amine such as (\pm)-crispine-A (**2**) which exhibits marked anticancer properties (Dhanasekaran et al., 2014; Mons et al., 2014), the first isoindoloisoquinoline alkaloid reported nuevamine (**3**) (Selvakumar and Ramanathan, 2011; Min and Kim, 2014; Maity and Roy, 2014) and the corresponding aza-analogues **4** (Hitchings and Vernon, 1988, 1990; Zamudio-Medina et al., 2010; Islas-Jácome et al., 2014) which curiously have not showed at this time any biological activity (Fig. 1).

2. Results and discussion

In our group, we have long been interested in the synthesis of analogues of such tetracyclic alkaloids containing in particular a pyrrolidone or isoindolone moiety. For that objective, we explored synthetic methodologies using π -cationic cyclization of thionium ions under Pummerer conditions (Bousquet et al., 2006), catalytic Lewis acid or Brønsted acid-promoted chiral π -cyclization versus aza-cyclization of *N*-acyliminium species (Fleury et al., 2011), aza-MIRC sequence in combination with diastereoselective arylation through cationic species (Saber et al., 2010, 2011; Hamid and Daich, 2011) and an intramolecular catalytic cyclization using in particular Bi(OTf)₃ in very low catalyst loadings (1 mol%) (Pin et al., 2007). In

parallel investigations some other heteroanalogues were provided by the tandem heterocyclisation/isomerisation/ π -cationic cyclization (Daich et al., 2014).

In this context allied to our another ongoing pharmacological project directed to the development of short and effective synthetic approaches leading to the natural topoisomerase-1 (topo-1) poisons (Fox et al., 2003) such as rosettacin (**5a**, R=H), acuminatine (**5b**, R=Me) and 22-hydroxyacuminatine (**5c**, R=CH₂OH) as well as synthetic derivatives (Pin et al., 2008, 2009), we envisioned in this report the synthesis of a short library of the pentacyclic structures of type **6**. These unknown compounds equipped with both quinoline fused via 2,3-positions to pyrrolo[2,1-*a*]isoquinolinone skeleton instead of pyrrolo[1,2-*b*]isoquinoline nuclei in the case of natural aromathecines **5**, can be considered reasonably in point of view of structure-activity relationship studies (QSAR) as aromathecines analogues. Concisely, our investigations will be focused on the synthesis of compounds bearing isoquinoline skeleton with an alkoxy substituent or not, able to involve a hydrogen linkage often positive for the biological activity, and also quinoline substituted at its C₄- and C₆-positions. In addition, the position of R₁ and R₂ substituents will be favorable for further biological activities if any as inspired by the QSAR studies conducted on camptothecines as the most potent topo-1 inhibitors (Wu, 2003; Pommier, 2009; Pourquier and Lansiaux, 2011; Moukharskaya and Verschraegen, 2012).

Most of the hitherto reported syntheses leading to these types of compounds rely on an appreciable number of strategies. They can be divided into two main categories of reactions using radical or ionic process in the ultimate stage. Although the arylation through cationic species is largely documented in the literature in pyrrolidinone and isoindolinone series, the

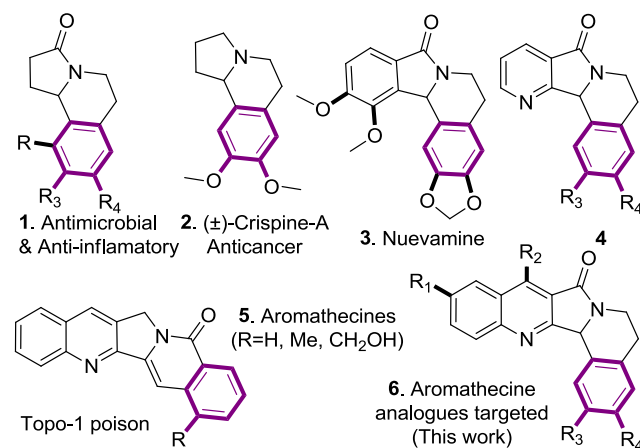
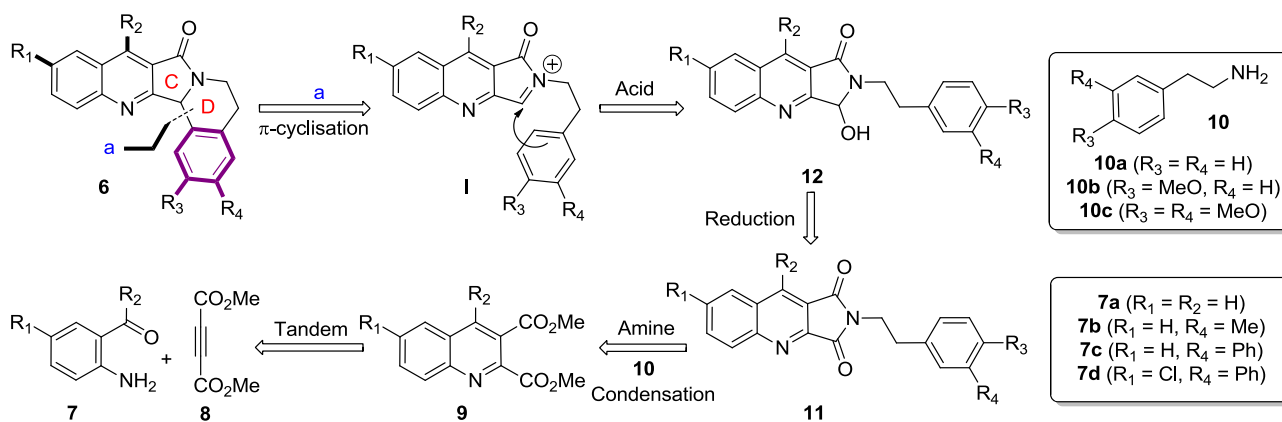


Fig. 1 Selected examples of bioactive natural **1–3** and unnatural **1,4** pyrroloisoquinolines fused or not, natural aromathecines **5** and our targets **6**.



use of π -cationic cyclization of *N*-acyliminium ions seems to be particularly adapted in our case. In addition, problematic which can be raised during the feasibility of this strategy in pyrrolo[3,4-*b*]quinoline-1,3-dione ring, which is both unsymmetrical and possesses an additional alkaline quinoline nitrogen atom, are of high interests.

As highlighted in the retrosynthetic plan (Scheme 1), our strategy was based first on the exploration of Friedländer reaction (Boisse et al., 2009) starting from simple aromatic amines **7** and unconventional Friedländer substrate **8** to provide quinoline-2,3-diester **9** already substituted at the expected C₄- and C₆-positions. The treatment of these derivatives or corresponding dicarboxylic acids by an appropriate amine **10** supplies the imides **11** which it is advisable to reduce regioselectively into the expected hydroxy lactams **12**. The targeted products **6** bearing different substituents would then be reached in an ultimate stage of π -cationic cyclization (disconnection a in Scheme 1) in an acidic medium of the stable *N*-acyliminium ions intermediate **I** stemming from **12**. The viability of this strategy is based fundamentally on our capacity to control two sequence keys; the access to a wide variety of disubstituted diesters **9** and the imides **11** as well as the regio-control of the reduction of the latter **11** into the expected *N*-acyliminium precursors **12** (see Table 1).

Our study started with the synthesis of quinoline diesters **9** with different substituents R₁ and R₂ in adequate positions as outlined above for the QSAR study reasons (Scheme 2). This can serve also to measure the impact of these substituents first on both the reaction yields for the production of diesters **9** themselves and *N*-arylalkyl-imides **11**. Thus, the Michael adduct **14** obtained by addition of aniline (**13**) to the activated acetylene DMAD **8** (80%) is obtained in ethanol instead of methanol as reported (Heindel et al., 1968; Jaen et al., 1995). The latter under Vilsmeier-Haak formulation (e.g., POCl₃, DMF, 0 °C for 1 h then 2 h at reflux) furnished the expected diester **9a** in 76% yield. During this reaction, the formyl derivative **J** obtained regioselectively under the orientation effect of the amine function was never isolated but cyclizes directly into **9a** after departure of one molecule of H₂O. The reaction is applicable to other anilines but show serious problems with anilines *o*- and *m*-substituted. Because of this approach is not generalizable for the synthesis of quinoline diesters **9** bearing in particular at their C₄-position substituent R₂ different to H, the reaction of the instable 2-amino-

benzaldehyde (**7a**) was reacted with DMAD **8** according to the report of Heindel's group (Eq. (2)) (Taylor and Heindel, 1967; Bryce et al., 1983; Rao et al., 1994). This provided in one-pot (two steps) procedure the expected product **9a** in 75% yield. We were interested by an easy approach in one-pot protocol, without using benzene as solvent, and applicable in large scale.

Thus, we explored this reaction with same ingredients by screening other solvents and different reaction conditions. Gratifyingly, the best formulation seems to be the use of glacial acetic acid at reflux for 3 h (Eq. (3)). Under these conditions, diester **9a** was obtained in 88% yield better than the one obtained in last both cases (Scheme 2). Finally, the application of this new and simple protocol to an array of aromatic amino-ketones **7b-d** resulted in the formation of the expected quinoline-2,3-diester **9b-d** via the intermediacy of **K** similar to **J**. The products were isolated in yields superior to 88% in all cases rendering this 'one-pot' two-step procedure more practical and competitive than the ones published more recently (Madhav et al., 2010; Guerrini et al., 2011; Tamoy et al., 2012).

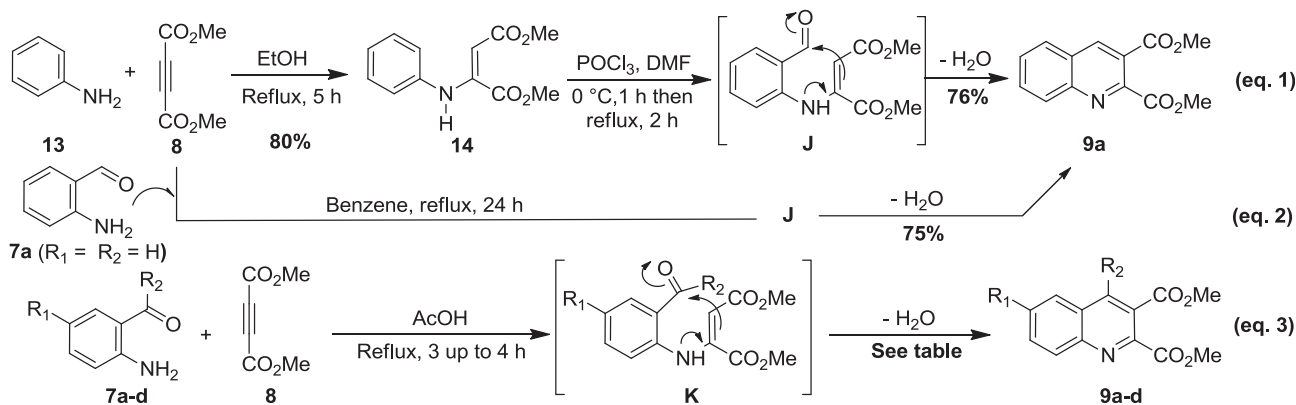
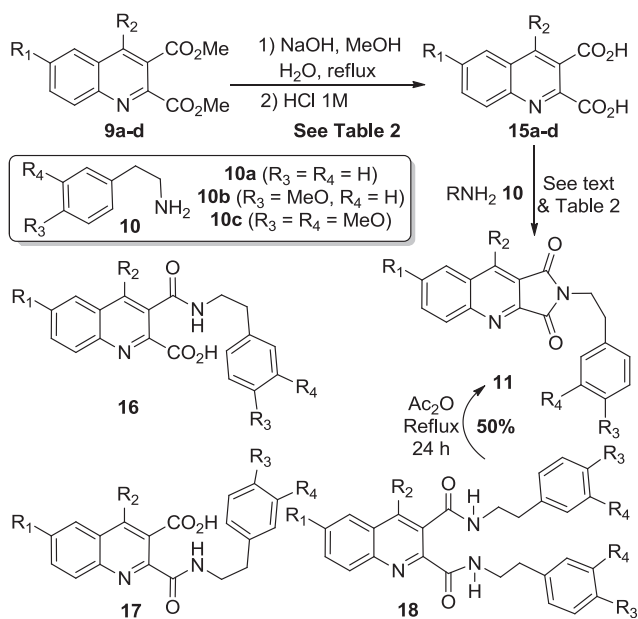
With high quantity of desirable quinoline-2,3-diester **9b-d** in hand (up to 10 g), we then targeted the *N*-substituted imides **11** precursors of the expected α -hydroxy lactams **12**. Thus, as shown in Scheme 3, saponification of the diesters **9b-d** (e.g., NaOH, MeOH/H₂O, reflux 12 h than AcOH) (Kim et al., 1993; Brown et al., 1994) resulted in the formation of the diacids **15b-d** after acid treatment. It is worth of mentioning that the use of HCl_{aq} in high concentration or other strong acids provide the expected diacids **15b-d** but with low up to marginal yields. This is due to the protonation of quinoline nuclei which has a pK_a value of 9.50 (pK_a of hydroquinolium is of 4.94). Interestingly acetic acid with pK_a value of 4.75 seems to be particularly adapted to resolve this problem since the diacids **15b-d** were isolated in high yields (82–91%; Table 2).

Carboxylic acids have been reported to react with amines under heating solvent free (or in the presence of solvent) or under azeotropic removal of water in Dean-Stark apparatus (Kato et al., 1999; Dahr et al., 2003). In the latter case, aromatic hydrocarbons were used as solvent and the addition of catalytic amount of dry NEt₃ is needed in certain cases in racemic or chiral series (Polniaszek et al., 1990; Lee et al., 1995, 1997a,b). According to the above both procedures, all attempts of reaction of *o*-dicarboxylic acids **15** with primary

Table 1 Substituted quinoline-2,3-diester **9a-d** produced via [Scheme 2](#).^a

Entry	Starting amino-ketone	R ₁ group	R ₂ group	Time (h)	Diester Product	Yield (%)	Ref. (Yield%)
1	7a	H	H	3	9a	88	(Rao et al., 1994) (95); (Tanmoy et al., 2012) (82)
2	7b	H	Me	3	9b	90	(Madhav et al., 2010) (92)
3	7c	H	Ph	3	9c	91	(Taylor et al., 1967) (76); (Madhav et al., 2010) (85)
4	7d	Cl	Ph	4	9d	89	(Taylor et al., 1967) (78); (Madhav et al., 2010) (83)

^a The yield given in brackets were obtained by using other reaction conditions as indicated in the reference in the last table column.

**Scheme 2** Different schemes leading to substituted quinoline-2,3-diester **9a-d**.**Scheme 3** Production of imides **11** by imidation of the diacids **15b-d**.

amines **10** solvent free, in toluene or xylene in the absence or presence of catalytic amounts of NEt₃ failed to deliver the expected diacid products **11**.

During these attempts, in addition to the starting dicarboxylic acids **15**, we observe at a minimum three compounds

corresponding to **16**, **17** and **18** which resulted from the reaction of amine with carboxylic acid function. Frustratingly, only traces of the expected imides **11** were observed rendering this protocol inefficient in our cases.

From these results, attempts were then made on the basis of known peptide coupling procedures ([Karmali et al., 2004](#)) by using DCC as peptidic coupling agent, DMAP as base, phenethylamine (**10a**) and quinoline-2,3-dicarboxylic acid (**15a**). The purification of the crude reaction mixture provides in all cases the expected imide **11aa** which is contaminated with small amounts of DCC and the amide-acid **16aa**. Heating the reaction mixtures at different temperatures, in different solvents with different DCC/DMAP ratio, etc. did not bring significant improvement to deliver the expected imide **11aa** as the sole reaction product ([Scheme 3](#) and [Table 2](#)).

The latter protocol is better in regard to the precedent in terms of chemoselectivity but the reaction is incomplete since near **11** the amide-acid **16** was formed in variable proportions always in disfavor of **11** ([Table 2](#)). Elsewhere, treatment of the mixture under cyclodehydration conditions ([Mehta et al., 1960](#)) by using Ac₂O at reflux in the presence of AcONa resulted in the formation of imide **11** with however average yields not exceeding 50%.

Given the efficiency of glacial acetic acid in the previous transformation (**7a-d** + **8** → **9a-d**), as well as that shown in the literature including ours in a close domain ([Chihab-Eddine et al., 2001](#); [Cul et al., 2004](#)), we envisioned the evaluation of *o*-dicarboxylic acids **15a-d** under these conditions. Thus heating diacid **15** and amine **10** at reflux of glacial AcOH (Method B) provided pleasingly the expected imide **11** as the

Table 2 Quinoline-2,3-dicarboxylic acids (**15a-d**) and substituted quinoline-2,3-imides **11** produced in Scheme 3.

Entry	Diester	R ₁ group	R ₂ group	Diacid	Yield (%)	R ₁ /R ₂ and R ₃ /R ₄ groups	Method A ^a		Method B ^c	
							Imide/Diamide	Yield (%) ^b	Imide	Yield (%) ^d
1	9a	H	H	15a	90	H/H and H/H	11/18aa	55 (30)	11aa	71
2	9a					H/H and MeO/H	11/18ab	46 (21)	11ab	34
3	9a					H/H and MeO/MeO	11/18ac	53 (29)	11ac	39
4	9b	H	Me	15b	88	H/Me and H/H	11/18ba	68 (31)	11ba	75
5	9b					H/Me and MeO/H	11/18bb	64 (25)	11bb	70
6	9b					H/Me and MeO/MeO	11/18bc	66 (34)	11bc	66
7	9c	H	Ph	15c	91	H/Ph and H/H	11/18ca	60 (32)	11ca	75
8	9c					H/Ph and MeO/H	11/18cb	61 (29)	11cb	68
9	9c					H/Ph and MeO/MeO	11/18cc	58 (30)	11cc	62
10	9d	Cl	Ph	15d	82	Cl/Ph and H/H	11/18da	60 (51)	11da	66
11	9d					Cl/Ph and MeO/H	11/18db	67 (35)	11db	68
12	9d					Cl/Ph and MeO/MeO	11/18dc	59 (39)	11dc	67

^a Method A. DCC (1.73 mmol) was added to an ice-cold and stirred solution of acid **15a** (1.73 mmol) in dry DCM and one drop of dry DMF. After half an hour of stirring at rt, phenethylamine (**10a**, 1.44 mmol) and DMAP (catalytic) dissolved in dry DCM were added to the reaction mixture.

^b The yields given without brackets correspond to the imides **11** extracted from the reaction mixture of imides **11** and diamides **18**.

^c Method B. Quinoline-2,3-dicarboxylic acid **15** (1 eq.) and amine **10** (1.1 eq.) in AcOH (3 mL for 1 mmol of the reactant **15**) was heated at reflux for 24 h.

^d Yields obtained for imides **11** after purification on chromatography on silica gel column.

sole reaction product generally in appreciable yields (Table 2). From these results, some remarks deserve to be underlined:

- (i) the reaction yields are appreciable and ranged from 62% up to 90% except for imides **11ab** (34%) and **11ac** (39%);
- (ii) the reaction is very easy to use, proceeds cleanly and occurs in one-pot 'two-steps' procedure via the tandem intermolecular amidation/cyclodehydration without isolation of the intermediate amide-acid **16** and/or **17**;
- (iii) the reaction is reproducible and even at large-scale (up to 15 g); and finally
- (iv) the reaction, in particular its yield, seems to be very sensitive to the analytical quality of AcOH which has a pivotal role as a solvent and probably as a catalyst.

Reactions of unsymmetrical imides with hydride agents (Hitchings and Vernon, 1988, 1990; Wijnberg et al., 1975; Kim et al., 1981; Goto et al., 1989; Mamouni et al., 1996; Chihab-Eddine et al., 2000; Ding et al., 2015) and organometallic reagents (Bahajaj et al., 1994, 2001; Saito et al., 2001) are very scarce and resulted often in the formation of two regioisomers depending strongly on the reaction conditions. In spite of the importance of quinoline and derivatives in medicinal chemistry notably, only one paper (Chiurato et al., 2010), in addition to our contribution (Pin et al., 2007), is dedicated to the reduction reaction of *N*-substituted pyrroloquinolinediones. These investigations were inspired also from the investigations given in pyrrolo[3,4-*b*]pyridinediones series as outlined previously (Hitchings and Vernon, 1988, 1990) and especially from the ones given by Goto's group in 1989 (Goto et al., 1989).

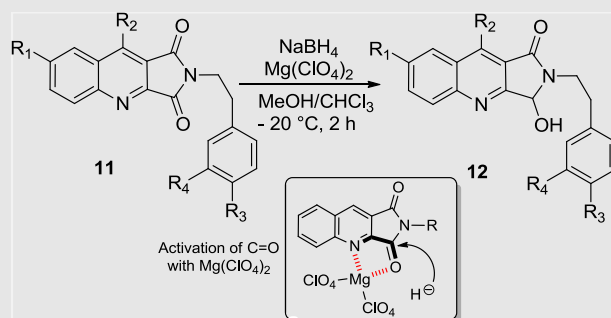
In this context, attempts to reduce regioselectively one carbonyl function of the model imide **11aa** was performed in a mixture of MeOH/CHCl₃ in a 1/1 ratio (V/V) by using 1.5 equivalents of NaBH₄ in the presence of Mg(ClO₄)₂ at

−20 °C (Goto et al., 1989; Chiurato et al., 2010). The optimal conditions were reached with the use of 2 equivalents of Mg(ClO₄)₂. Thus under these conditions, *N*-phenylethyl imide **11aa** deliver after 2 h of reaction the expected hydroxy lactam **12aa** in 85% yield after purification by chromatography on silica gel column using cyclohexane/EtOAc (1/2) as the eluent (Pin et al., 2007). Importantly, no traces of the hydroxy lactam regioisomer were detected in the crude reaction mixture.

Having demonstrated the efficiency of the quinoline-imide complexation by Mg(ClO₄)₂, which resulted in the activation of one C=O function as shown in the scheme of Table 3, this reaction thus was extended successfully to other imides **11** and the results are summarized in Table 3. Interestingly, the reduction occurred regioselectively providing the expected corresponding hydroxyl lactams **12** in yields ranging from 69% up to 88% after purification. Advantageously, the nature and the position of the substituents, particularly on the pyrroloquinolinedione scaffold bearing the imide functionality, did not exert any influence on the reduction process.

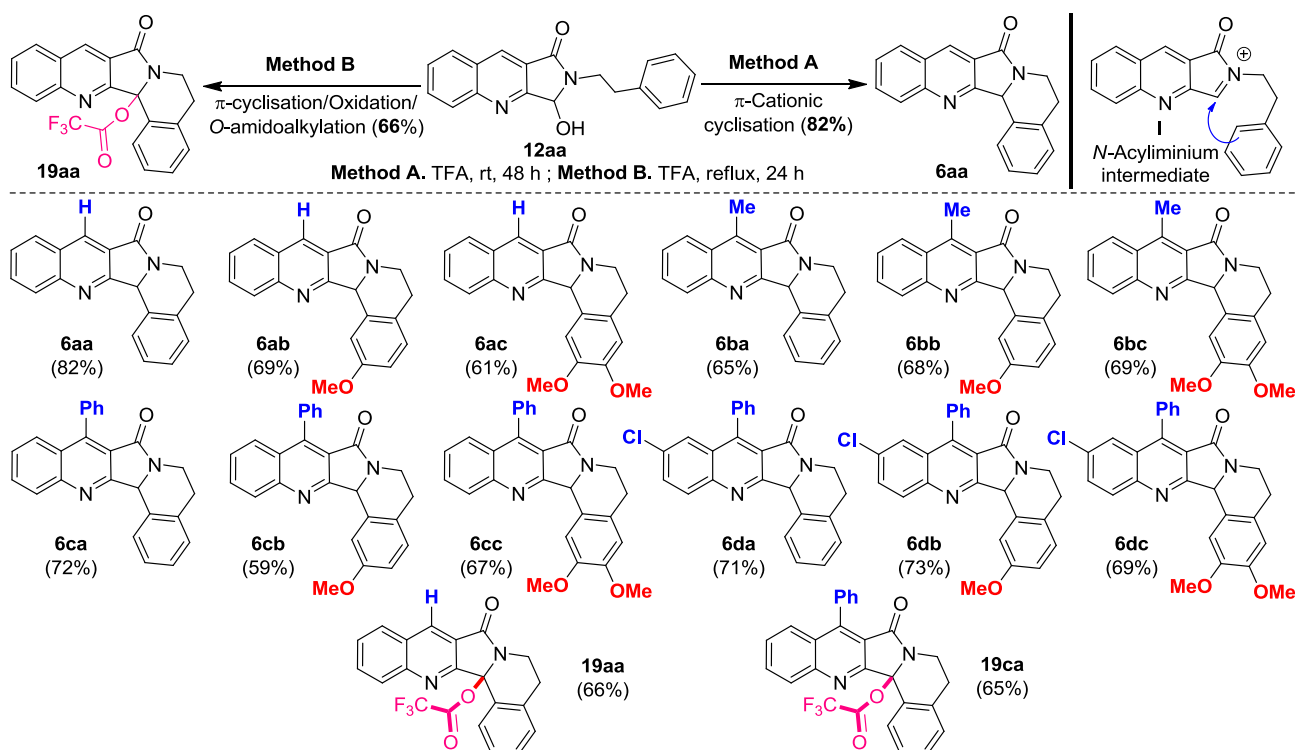
The hydroxyl lactams **12** being obtained could allow reasonably a facile approach via an intramolecular catalytic π -cationic cyclization to new pentacyclic compounds **6** analogues to the active natural aromathecines **5** as potent topo-1 inhibitors. To the best of our knowledge, the use of the present *N*-acyliminium precursors **12** to form a central six-membered ring as a piperidine ring fused to other nucleus represents a novel illustration of the α -amidoalkylation chemistry. In addition, no examples of intramolecular trapping of these π -cationic species was reported. But just now, only one example of such C—C bond forming reaction, using an enol function as internal nucleophile for trapping the *N*-acyliminium ion, is reported (Chiurato et al., 2010).

As shown in Scheme 4, treatment of hydroxy lactam **12aa** at the outset with BF₃·Et₂O in dichloromethane for 24 h was unsuccessful and even if the reaction time was prolonged for additional 48 h and the quantity of Lewis acid increased

Table 3 Reduction of imides **11** into hydroxyl lactams **12**.

Entry	Imide	R ₁	R ₂	R ₃	R ₄	Hydroxy lactam	Yield (%) ^a
1	11aa	H	H	H	H	12aa	85
2	11ab	H	H	MeO	H	12ab	77
3	11ac	H	H	MeO	MeO	12ac	69
4	11ba	H	Me	H	H	12ba	87
5	11bb	H	Me	MeO	H	12bb	83
6	11bc	H	Me	MeO	MeO	12bc	88
7	11ca	H	Ph	H	H	12ca	79
8	11cb	H	Ph	MeO	H	12cb	70
9	11cc	H	Ph	MeO	MeO	12cc	81
10	11da	Cl	Ph	H	H	12da	79
11	11db	Cl	Ph	MeO	H	12db	85
12	11dc	Cl	Ph	MeO	MeO	12dc	80

^a Yields obtained for isolated **12** after purification by chromatography.



Scheme 4 TFA-catalyzed intramolecular α -amidoalkylation of hydroxy lactams **12** into the targeted pentacyclic systems **6** analogous of aromathecines.

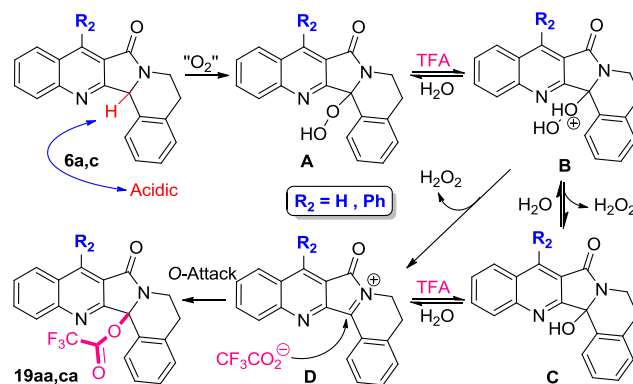
up to 6 equivalents relative the reactant **12aa**. In all these exploratory attempts, the starting hydroxyl lactam **12aa** was recovered intact after the reaction hydrolysis.

Also, the use of catalysts traditionally useful in this type of reaction such as TiCl_4 , SnCl_4 , SnCl_2 , AcOH , etc. (See for example: Yazici and Pyne, 2009a,b) was similarly ineffectual. However, the use of AlCl_3 , with high analytical purity of 99.99%, at reflux of dichloromethane resulted in the formation of only traces of the expected cyclized product **6aa**. Besides, when the hydroxy lactam **12aa** is reacted in neat TFA (5 mL of TFA for 1 mmol of hydroxy lactam **12aa**) at room temperature for 48 h according to our precedents reports (Saber et al., 2010; Fleury et al., 2011; Hucher et al., 2001, 2005; Pesquet et al., 2005), in our satisfaction, we isolated after a classical work up, a unique product identified to be the pentacyclic compound **6aa** in a good yield of 82% (Scheme 4). Given the slowness of this transformation, we thus carried out the reaction with same quantity of TFA but at reflux hopping to increase sensibly the reaction kinetic. Surprisingly, we isolate another cyclized product identified to be the pentacyclic compound **19aa** bearing a trifluoroacetate group at the angular carbon in appreciable yield of 66% after purification by chromatography on silica gel column.

Having demonstrated the power of TFA (in precise ratio to the reactant **12**), among others Brønsted or Lewis acids, to promote the intramolecular α -amidoalkylation reaction via the formal *N*-acyliminium cation **I** generated in situ from hydroxyl lactam **12aa**, we envisioned then to extend this reaction to hydroxy lactams bearing other aryl π -nucleophiles (Scheme 4). Thus, the use of both protocols different only by their reaction temperature and time (Method A and Method B) as in Scheme 4, demonstrates the effectiveness of the Method B in all cases. Under these conditions, hydroxy lactams **12** undergo the π -cationic cyclization again via the intermediate of type **I** to form the cyclized products **6**, surprisingly, in yields ranging from 59% up to 73% after purification except in the case of the hydroxy lactam **12ca**. In the latter case, the reaction delivers as for *N*-acyliminium precursor **12aa**, the angular substituted pentacyclic product **19ca** in 65% yield comparable to the one obtained for **19aa** (66%; See structures in last line of Scheme 4). It should be noticed here that only the hydroxy lactam **12ca** has required the use of the method A to reach the cyclized product **6ca** (72%) in which only the π -cationic cyclization was taken in consideration. Ultimately, from these results and as in the case of previous 'imidation' and reduction reactions, it seems that the nature and the position of the activated and/or deactivated substituents in left (electrophile) and right (nucleophile) parts of the hydroxyl lactams precursors, does not influence significantly the cyclization process.

Taking into account the less reactivity of hydroxy lactams **12**, their intramolecular arylation through cation intermediate into corresponding pentacyclic systems **6** require generally drastic conditions. The latter are generally justified with regard to the results obtained in pyridine series by Vernon's group (Hitchings and Vernon, 1988, 1990; Bahajaj et al., 1994, 2001). In these cases, PPA at high temperature (100–125 °C) or TFA at reflux were necessary to complete the cyclization reaction which accompanied in most cases with partial decomposition of the starting materials.

Besides compounds **6**, the formation of products **19aa** and **19ca**, in particular, can be explained if we consider the



Scheme 5 Plausible mechanism for the formation of the pentacyclic products **19aa** and **19ca**.

peroxidation in acidic medium with oxygen from air at the angular carbon of the pentacyclic systems **6aa,ca** to furnish the peroxide derivative **A** (Scheme 5). The latter, is transformed directly into **D** via **B** following protonation and loss of hydrogen peroxide. Alternatively, **B** can lead to **C** after H_2O_2 displacement with H_2O (generated from the intramolecular arylation leading to the cyclic system **6**) followed by dehydration of **C** in acid media. At this stage, an ultimate amidolactylation of the stable cation **D** using oxygen atom from CF_3CO_2^- group as external nucleophile occurred and delivered the cyclic trifluoroacetate derivatives **19aa** and **19ca** in comparable yields. This hypothesis can be corroborated also with the observations made by numerous authors, including members from our collaborators. The latter claim an easy peroxidation reaction in the presence of oxygen (Murahashi et al., 1991; Sánchez et al., 2001) of bicyclic keto-amides (Haeusler et al., 1978; Yates and McLachland, 1978), tricyclic keto-amides (Bourry et al., 2004, 2006; Chang et al., 2013), as well as tricyclic bis-keto-amides related to our systems (Godard et al., 1971).

The structure elucidation of the cyclized products **6** and **19** as well as all intermediates was based on their spectroscopic data (IR, ^1H NMR and ^{13}C NMR including NOE Difference and DEPT experiments) as well as their elemental analyses.

Indeed, in the ^1H NMR spectra of compounds **6** the angular proton signals absorb downfield compared to the same protons of their hydroxyl lactams congeners **12** when R_3 and R_4 are H but absorb upfield, when at minimum, one of both groups R_3 and R_4 is equal to MeO group. Interestingly, these correlations are very good except for the sole pentacyclic product **6aa** while we observe no angular proton signals for compounds **19**. On the other hand, in the ^{13}C NMR spectra of **6**, we observe the appearance of an additional quaternary carbon in the aromatic region which disappears in the DEPT program spectra. In the case of trifluoroacetate derivatives **19**, we observe similarly two quaternary carbons which also disappear in the aromatic region in the DEPT program spectra. These facts are in agreement with these observed for related compounds thus attesting that the π -cationic cyclization occurs alone for the production of derivatives **6**. In both cases, this is associated with an oxidation reaction of the angular carbon followed by an intermolecular *O*-amidoalkylation via the trifluoroacetate anion present in the acid medium for the production of compounds **19aa** and **19ca**.

3. Conclusions

In summary, we have documented successfully a general five-step synthesis of a short library of benzo[7,8]indolizino-quinoline analogues of the potent topoisomerase-I (topo-I) poison rosettacin (**5a**) and 22-hydroxyacuminatine (**5c**) alkaloids. The sequence starts from readily available *ortho*-ketoanilines and dimethyl acetylenedicarboxylate (DMAD). Thus, methyl quinoline-2,3-dicarboxylates were generated by the effective tandem aza-Michael addition/cyclodehydration in appreciable yields and their hydrolysis provide corresponding *o*-dicarboxylic acids. The latter with various amines deliver *N*-substituted imides via the tandem intermolecular amidation/cyclodehydration reaction promoted by glacial acetic acid. The hydroxy lactams, obtained by the regioselective reduction using sodium borohydride in methanol under the promotion of Mg(ClO₄)₂ as Lewis acid, in turn, furnished in neat TFA an assembly of new benzo[7,8]indolizinoquinolines in acceptable to good yields. Among Lewis and Bönsted acids tested, only TFA promotes in quinoline series the π -cationic cyclization via stable *N*-acyliminium species as an important key step.

Ultimately, the power of this general practical approach was demonstrated by:

- (i) the four points of the diversification made,
- (ii) the generation of trifluoroacetate group at the angular position of certain pentacyclic systems could constitute a valuable *N*-acyliminium precursor for trapping further various nucleophiles, and
- (iii) many steps of the 'five-step' sequence we used could be conducted in large scale. These facts outline in part its potential applications in chemical synthesis necessary for the future QSAR studies.

4. Experimental section

4.1. General remarks

Unless otherwise specified, the chemical compounds were purchased from commercial suppliers (Sigma-Aldrich, Acros Organics, Alfa Aesar, NCI Chemicals) and were used without further purification. The reactions were carried out in standard glassware under argon atmosphere or in sealed tube in some cases where organometallic reagents were involved.

The advancement of reactions was monitored by thin-layer chromatography (TLC), which was carried out on Macherey-Nagel silica gel 60 F₂₅₄ aluminum plates. The spots were visualized under UV light at 254 and 380 nm. Otherwise, the following reagents were used as staining detectors:

- *p*-Anisaldehyde: 6.4 mL of *p*-anisaldehyde added to a mixture of glacial acetic acid (2.6 mL) and concentrated sulfuric acid (8.4 mL) dissolved in 232.0 mL of ethanol;
- Potassium permanganate: 0.05% aqueous KMnO₄;
- Ninhydrin: 0.2 g of ninhydrin were dissolved in 100 mL of ethanol.

Macherey-Nagel silica gel (40–63 μ m) was used for flash chromatography, and the elution was generally performed

with a mixture of cyclohexane/ethyl acetate or dichloromethane/ethyl acetate systems.

Infrared (IR) spectra were performed as neat on Perkin Elmer FT-IR spectrophotometer. For the cited compounds, only broad and strong signals are reported (wavenumbers, cm⁻¹). ¹H and ¹³C NMR spectroscopic data were recorded on a Bruker Avance 300 spectrometer at room temperature at 300 MHz and 75 MHz respectively by using broadband proton decoupling for ¹³C NMR. All spectra were calibrated using the residual solvent peaks as references: 7.26 and respectively 77.00 ppm for CDCl₃ or 2.50 and 39.50 respectively for DMSO-*d*₆. For ¹H NMR data, the multiplicities are reported using the following abbreviations: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), bs (broad singlet) or a suitable combination. The coupling constants (*J*) are displayed in Hz and the chemical shifts (δ) are expressed in ppm relative to tetramethylsilane as internal standard. The assignments of protons resonance were based on ¹H NMR, ¹H COSY, HMQC and HMBC analysis. High resolution mass spectra (HRMS) were recorded on a 6530 Q-TOF (Agilent System) apparatus and the electrospray ionization (ESI)-MS was measured in positive or negative ionization mode (ESI[±]) by using an Agilent Jet Stream or APCI pump: precision > 1 ppm, resolution (M/Z = 118) > 10,000 and resolution (M/Z = 1522) > 26,000. The melting points were taken in open capillary, recorded on a Stuart Scientific analyzer SMP 10 apparatus and are uncorrected and finally, the elemental analyses were carried out by the microanalysis of COBRA laboratory, CNRS UMR-6014, F-76130 Mont Saint-Aignan, France.

4.2. General procedure for reduction of imides (**11aa–11cd**)

Experimental protocol with the model imide 11aa. Magnesium perchlorate (0.32 g, 1.52 mmol) then sodium borohydride (34 mg, 0.84 mmol) were added to a solution of imide **11aa** (0.23 g, 0.76 mmol) in 20 mL of the mixture MeOH/CHCl₃ (1/1) under stirring at -20 °C. After the starting imide **11aa** was disappeared (approximately 2 h of the reaction as monitored by TLC using the mixture of cyclohexane/EtOAc (1/2) as the eluent). After warming slowly of the reaction at room temperature the reaction mixture was evaporated *in vacuo*. The residue was diluted with dichloromethane; the organic layer was washed with 2 \times 15 mL of water, brine and dried over MgSO₄. After evaporation of the solvent under reduced pressure, the resulting crude reaction was purified by flash chromatography on silica gel column by using the mixture of cyclohexane/EtOAc (1/2) as the eluent to provide expected hydro lactam **12aa** as the sole expected regioisomer product.

4.2.1. 3-Hydroxy-2-phenylethyl-2,3-dihydro-1H-pyrrolo[3,4-*b*]quinolin-1-one (**12aa**)

This product was obtained as a white-yellow solid in 85% yield starting from imide **11aa** according to the precedent protocol; Mp 242–244 °C (decomposition); IR (cm⁻¹) ν : 3312 (OH), 3012 (CH), 2995 (CH), 1705 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.05 (t, 2H, *J* = 7.43 Hz, CH₂), 3.77–3.88 (m, 2H, CH + OH), 4.09–4.23 (m, 1H, CH), 5.77 (s, 1H, CHOH), 7.09–7.21 (m, 5H, CHar), 7.68 (t, 1H, *J* = 7.04 Hz, CHar), 7.84 (t, 1H, *J* = 7.04 Hz, CHar), 7.94 (d, 1H, *J* = 7.83 Hz, CHar), 8.13 (d, 1H, *J* = 8.61 Hz, CHar), 8.53 (s, 1H, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 34.7 (CH₂),

40.8 (CH₂), 80.9 (CHOH), 122.8 (C^q), 126.0 (CHar), 127.3 (CHar), 127.7 (CHar), 128.1 (2 × CHar), 128.2 (2 × CHar), 129.7 (C^q), 130.6 (CHar), 131.4 (CHar), 132.4 (CHar), 138.2 (C^q), 148.6 (C^q), 156.6 (C^q), 164.5 (C=O). Anal. Calcd for C₁₉H₁₆N₂O₂ (304.34): C, 74.98; H, 5.30; N, 9.20. Found. C, 74.87; H, 5.21; N, 9.09.

4.2.2. 3-Hydroxy-9-methyl-2-phenethyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12ba**)

This product was obtained as a white solid in 87% yield starting from imide **11ba** according to the precedent protocol used for the reduction of the imide **11aa**; Mp 190–192 °C; IR (cm⁻¹) v: 3343 (OH), 3006 (CH), 2990 (CH), 1697 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.05 (t, 2H, *J* = 7.43 Hz, CH₂), 3.21 (s, 3H, CH₃), 3.77–3.88 (m, 1H, CH), 4.09–4.23 (m, 2H, CH + OH), 5.72 (s, 1H, CHOH), 7.05–7.19 (m, 5H, CHar), 7.68 (t, 1H, *J* = 7.04 Hz, CHar), 7.84 (t, 1H, *J* = 7.04 Hz, CHar), 7.94 (d, 1H, *J* = 7.83 Hz, CHar), 8.13 (d, 1H, *J* = 8.61 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 12.3 (CH₃), 34.6 (CH₂), 41.1 (CH₂), 81.4 (CHOH), 123.2 (C^q), 125.0 (CHar), 126.5 (CHar), 127.8 (CHar), 128.5 (2 × CHar), 128.7 (2 × CHar), 128.8 (CHar), 129.7 (C^q), 132.9 (CHar), 138.7 (C^q), 146.9 (C^q), 149.1 (C^q), 162.0 (C^q), 165.0 (C=O). Anal. Calcd for C₂₀H₁₈N₂O₂ (318.37): C, 75.45; H, 5.70; N, 8.80. Found. C, 75.38; H, 5.62; N, 8.71.

4.2.3. 3-Hydroxy-9-phenyl-2-phenylethyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12ca**)

This product was obtained as a white solid in 79% yield starting from the imide **11ca** according to the precedent protocol used for the reduction of the imide **11aa**; Mp 170–172 °C (decomposition); IR (cm⁻¹) v: 3330 (OH), 3020 (CH), 2985 (CH), 1700 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.03–3.10 (t, 2H, *J* = 7.43 Hz, CH₂), 3.75–3.90 (m, 2H, CH + OH), 4.11–4.16 (m, 1H, CH), 5.91 (s, 1H, CHOH), 7.15–7.18 (m, 5H, CHar), 7.44–7.46 (m, 2H, CHar), 7.56–7.60 (m, 4H, CHar), 7.81 (2d, 2H, *J* = 8.6 Hz, CHar), 8.22 (d, 1H, *J* = 8.6 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 35.5 (CH₂), 42.3 (CH₂), 81.6 (CHOH), 127.4 (C^q), 127.8 (CHar), 128.0 (2 × CHar), 128.7 (2 × CHar), 129.0 (CHar), 129.3 (3 × CHar), 132.3 (CHar), 132.5 (C^q), 132.9 (CHar), 133.2 (2 × CHar), 138.1 (C^q), 139.6 (C^q), 142.9 (CHar), 149.1 (C^q), 156.1 (C^q), 146.2 (C^q), 170.8 (C=O). Anal. Calcd for C₂₅H₂₀N₂O₂ (380.44): C, 78.93; H, 5.30; N, 7.36. Found. C, 78.35; H, 5.41; N, 7.30.

4.2.4. 7-Chloro-3-hydroxy-2-phenylethyl-9-phenyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12da**)

This product was obtained as a white solid in 79% yield starting from imide **11da** according to the precedent protocol used for reduction of imide **11aa**; Mp 218–220 °C; IR (cm⁻¹) v: 3330 (OH), 3018 (CH), 2980 (CH), 1702 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.03 (t, 2H, *J* = 7.46 Hz, CH₂), 3.75–3.78 (m, 2H, CH + OH), 4.11–4.14 (m, 1H, CH), 5.86 (s, 1H, CHOH), 7.21–7.25 (m, 5H, CHar), 7.31–7.35 (m, 2H, CHar), 7.75–7.80 (m, 3H, CHar), 7.83–7.89 (m, 2H, CHar), 8.11 (d, 1H, *J* = 8.62 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 34.1 (CH₂), 42.0 (CH₂), 79.8 (CH), 120.2 (C^q), 126.2 (CHar), 126.6 (2 × CHar), 128.0 (CHar), 129.0 (2 × CHar), 129.1 (C^q), 129.5 (2 × CHar), 129.6 (2 × CHar), 129.9 (CHar), 130.3 (C^q), 130.7 (CHar), 130.9 (C^q), 131.2 (CHar), 131.7 (C^q),

134.0 (C^q), 145.1 (C^q), 158.3 (C^q), 166.9 (C=O). Anal. Calcd for C₂₅H₁₉ClN₂O₂ (414.88): C, 72.37; H, 4.62; N, 6.75. Found. C, 72.21; H, 4.58; N, 6.68.

4.2.5. 3-Hydroxy-2-(4-methoxyphenylethyl)-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12ab**)

This product was obtained as a yellow solid in 77% yield starting from the imide **11ab** according to the precedent protocol used for the reduction of the imide **11aa**; Mp 201–203 °C (decomposition); IR (cm⁻¹) v: 3345 (OH), 3012 (CH), 2988 (CH), 1707 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.04 (t, 2H, *J* = 7.06 Hz, CH₂), 3.75 (s, 3H, OCH₃), 3.77–3.86 (m, 2H, CH + OH), 4.11–4.23 (m, 1H, CH), 5.79 (s, 1H, CHOH), 6.70 (d, 2H, *J* = 8.48 Hz, CHar), 7.13 (d, 2H, *J* = 8.48 Hz, CHar), 7.64 (t, 1H, *J* = 7.44 Hz, CHar), 7.66 (t, 1H, *J* = 7.16 Hz, CHar), 7.96 (d, 1H, *J* = 7.91 Hz, CHar), 8.15 (d, 1H, *J* = 8.29 Hz, CHar), 8.54 (s, 1H, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 32.7 (CH₂), 40.4 (CH₂), 54.1 (OCH₃), 80.5 (CH), 112.9 (2 × CHar), 122.3 (C^q), 126.7 (CHar), 127.1 (C^q), 127.8 (CHar), 128.6 (3 × CHar), 129.7 (C^q), 130.8 (CHar), 131.9 (CHar), 148.1 (C^q), 157.2 (C^q), 161.1 (C^q), 166.0 (C=O). Anal. Calcd for C₂₀H₁₈N₂O₃ (334.37): C, 71.84; H, 5.43; N, 8.38. Found. C, 71.71; H, 5.31; N, 8.22.

4.2.6. 3-Hydroxy-2-(4-methoxyphenethyl)-9-methyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12bb**)

This product was obtained as a yellow solid in 83% yield starting from imide **11bb** according to the precedent protocol used for reduction of imide **11aa**; Mp 252–254 °C; IR (cm⁻¹) v: 3352 (OH), 3014 (CH), 2992 (CH), 1712 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.00 (t, 2H, *J* = 6.92 Hz, CH₂), 3.23 (s, 3H, CH₃), 3.66 (s, 3H, OCH₃), 3.69–3.78 (m, 2H, CH + OH), 4.06–4.12 (m, 1H, CH), 6.01 (s, 1H, CHOH), 6.74 (d, 2H, *J* = 8.61 Hz, CHar), 7.15 (d, 2H, *J* = 8.61 Hz, CHar), 7.52 (t, 1H, *J* = 7.82 Hz, CHar), 7.79 (t, 1H, *J* = 7.82 Hz, CHar), 8.27 (dd, 2H, *J* = 7.61 and 2.32 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 10.7 (CH₃), 32.0 (CH₂), 39.5 (CH₂), 53.6 (OCH₃), 79.3 (CH), 112.4 (2 × CHar), 120.6 (C^q), 123.6 (CHar), 125.5 (CHar), 126.9 (C^q), 128.2 (2 × CHar), 128.4 (CHar), 129.3 (CHar), 129.5 (C^q), 143.2 (C^q), 147.2 (C^q), 156.6 (C^q), 160.9 (C^q), 164.6 (C=O). Anal. Calcd for C₂₁H₂₀N₂O₃ (348.40): C, 72.40; H, 5.79; N, 8.04. Found. C, 72.29; H, 5.68; N, 7.96.

4.2.7. 3-Hydroxy-2-(4-methoxyphenylethyl)-9-phenyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12cb**)

This product was obtained as a yellow solid in 70% yield starting from the imide **11cb** according to the precedent protocol used for the reduction of the imide **11aa**; Mp 195–197 °C (decomposition); IR (cm⁻¹) v: 3346 (OH), 3010 (CH), 2996 (CH), 1700 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.97–3.04 (t, 2H, *J* = 7.43 Hz, CH₂), 3.71 (s, 3H, OCH₃), 3.75–3.60 (m, 2H, CH + OH), 4.02–4.13 (m, 1H, CH), 5.91 (s, 1H, CHOH), 6.65 (d, 2H, *J* = 8.61 Hz, CHar), 7.10 (d, 2H, *J* = 8.61 Hz, CHar), 7.43–7.47 (m, 2H, CHar), 7.57–7.64 (m, 4H, CHar), 7.86 (t, 2H, *J* = 8.6 Hz, CHar), 8.22 (d, 1H, *J* = 8.6 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 34.6 (CH₂), 42.3 (CH₂), 55.9 (OCH₃), 81.1 (CH), 122.4 (C^q), 126.0 (CHar), 126.6 (CHar), 127.4 (2 × CHar), 127.8 (2 × CHar), 128.0 (C^q), 128.7 (2 × CHar), 129.0 (C^q), 129.3 (CHar),

130.7 (2 × CHar), 132.3 (CHar), 131.2 (CHar), 138.1 (C^q), 139.0 (C^q), 139.6 (C^q), 145.1 (C^q), 146.2 (C^q), 170.8 (C=O). Anal. Calcd for C₂₆H₂₂N₂O₃ (410.46): C, 76.08; H, 5.40; N, 6.82. Found. C, 76.00; H, 5.31; N, 6.74.

4.2.8. 7-Chloro-3-hydroxy-2-(4-methoxyphenethyl)-9-phenyl-2,3-dihydro-1H-pyrrolo[3,4-b]-quinolin-1-one (**12db**)

This product was obtained as a yellow solid in 70% yield starting from imide **11da** according to the precedent protocol used for reduction of imide **11aa**; Mp 205–207 °C; IR (cm⁻¹) v: 3352 (OH), 3016 (CH), 2990 (CH), 1703 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.96 (t, 2H, *J* = 7.43 Hz, CH₂), 3.74 (s, 3H, OCH₃), 3.74–3.76 (m, 2H, CH + OH), 4.01–4.05 (m, 1H, CH), 5.80 (s, 1H, CHOH), 6.66 (d, 2H, *J* = 8.61 Hz, CHar), 7.08 (d, 2H, *J* = 8.61 Hz, CHar), 7.41–7.44 (m, 2H, CHar), 7.53–7.77 (m, 3H, CHar), 7.79 (t, 2H, *J* = 8.6 Hz, CHar), 8.09 (d, 1H, *J* = 8.64 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 33.9 (CH₂), 41.8 (CH₂), 55.3 (CH₃), 80.6 (CH), 114.4 (2 × CHar), 120.2 (C^q), 126.2 (C^q), 126.6 (CHar), 127.2 (CHar), 128.3 (2 × CHar), 129.5 (CHar), 129.7 (2 × CHar), 129.9 (2 × CHar), 130.4 (CHar), 130.9 (C^q), 131.7 (C^q), 134.0 (C^q), 147.5 (C^q), 147.7 (C^q), 158.3 (C^q), 162.6 (C^q), 164.9 (C=O). Anal. Calcd for C₂₆H₂₁ClN₂O₃ (444.91): C, 70.19; H, 4.76; N, 6.30. Found. C, 70.08; H, 4.67; N, 6.21.

4.2.9. *N*-(3,4-Dimethoxyphenethyl)-3-hydroxy-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12ac**)

This product was obtained as a white solid in 69% yield starting from the imide **11ac** according to the precedent protocol used for the reduction of the imide **11aa**; Mp 192–194 °C (decomposition); IR (cm⁻¹) v: 3348 (OH), 3009 (CH), 2988 (CH), 1702 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.06 (t, 2H, *J* = 7.43 Hz, CH₂), 3.79 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.85–3.89 (m, 2H, CH + OH), 4.07–4.18 (m, 1H, CH), 5.87 (s, 1H, CHOH), 6.74–6.80 (m, 3H, CHar), 7.61 (t, 1H, *J* = 7.43 Hz, CHar), 7.80 (t, 1H, *J* = 7.43 Hz, CHar), 7.94 (d, 1H, *J* = 7.82 Hz, CHar), 8.13 (d, 1H, *J* = 7.82 Hz, CHar), 8.51 (s, 1H, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 34.8 (CH₂), 40.1 (CH₂), 56.6 (2 × OCH₃), 82.3 (CHar), 112.0 (CHar), 112.6 (CHar), 121.3 (2 × CHar), 123.7 (C^q), 128.5 (CHar), 128.9 (C^q), 130.4 (CHar), 131.8 (C^q), 132.7 (CHar), 148.4 (C^q), 149.7 (C^q), 150.9 (C^q), 152.2 (C^q), 165.7 (C=O). Anal. Calcd for C₂₁H₂₀N₂O₄ (364.39): C, 69.22; H, 5.53; N, 7.69. Found. C, 69.09; H, 5.48; N, 7.58.

4.2.10. *N*-(3,4-Dimethoxyphenethyl)-3-hydroxy-9-methyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12bc**)

This product was obtained as a yellow solid in 88% yield starting from imide **11bc** according to the precedent protocol used for reduction of imide **11aa**; Mp 195–197 °C (decomposition); IR (cm⁻¹) v: 3349 (OH), 3014 (CH), 2997 (CH), 1700 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.99 (s, 3H, CH₃), 3.05 (t, 2H, *J* = 8.61 Hz, CH₂), 3.76 (s, 3H, OCH₃), 3.79 (s, 3H, OCH₃), 3.86–3.94 (m, 2H, CH + OH), 4.13–4.20 (m, 1H, CH), 5.88 (s, 1H, CHOH), 6.73–6.85 (m, 3H, CHar), 7.63 (t, 1H, *J* = 7.43 Hz, CHar), 7.76 (t, 1H, *J* = 7.43 Hz, CHar), 8.09 (dd, 2H, *J* = 8.61 and 2.33 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 12.5 (CH₃), 34.3 (CH₂), 41.4 (CH₂), 55.9 (2 × OCH₃), 80.5 (CH), 111.3 (CHar), 111.9 (CHar), 120.3 (C^q), 120.7 (CHar), 125.2 (CHar), 127.6 (CHar), 127.9

(C^q), 128.8 (CHar), 130.6 (C^q), 131.6 (CHar), 147.2 (C^q), 147.5 (C^q), 147.8 (C^q), 149.0 (C^q), 162.0 (C^q), 167.9 (C=O). Anal. Calcd for C₂₂H₂₂N₂O₄ (378.42): C, 69.83; H, 5.86; N, 7.40. Found. C, 69.71; H, 5.79; N, 7.30.

4.2.11. *N*-(3,4-Dimethoxyphenethyl)-3-hydroxy-9-phenyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12cc**)

This product was obtained as a yellow solid in 88% yield starting from imide **11cc** according to the precedent protocol used for reduction of imide **11aa**; Mp 187–189 °C; IR (cm⁻¹) v: 3353 (OH), 3010 (CH), 2990 (CH), 1700 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.00–3.08 (t, 2H, *J* = 7.43 Hz, CH), 3.74 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 3.80–3.99 (m, 2H, CH + OH), 4.06–4.13 (m, 1H, CH), 6.06 (s, 1H, CHOH), 6.70–6.81 (m, 3H, CHar), 7.48–7.43 (m, 2H, CHar), 7.55–7.62 (m, 4H, CHar), 7.83 (t, 2H, *J* = 6.70 Hz, CHar), 8.19 (d, 1H, *J* = 7.8 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 34.3 (CH₂), 41.6 (CH₂), 55.8 (OCH₃), 55.8 (OCH₃), 80.4 (CH), 111.3 (CHar), 111.9 (CHar), 119.5 (C^q), 120.6 (CHar), 127.6 (2 × CHar), 128.1 (CHar), 128.5 (CHar), 128.8 (CHar), 129.2 (C^q), 129.8 (2 × CHar), 131.3 (CHar), 131.6 (CHar), 132.2 (C^q), 147.6 (C^q), 148.6 (C^q), 148.7 (C^q), 149.0 (C^q), 146.2 (C^q), 157.8 (C^q), 164.5 (C=O). Anal. Calcd for C₂₇H₂₄N₂O₄ (378.42): C, 73.62; H, 5.49; N, 6.36. Found. C, 73.51; H, 5.37; N, 6.28.

4.2.12. 7-Chloro-2-(3,4-dimethoxyphenethyl)-3-hydroxy-9-phenyl-2,3-dihydro-1H-pyrrolo[3,4-b]quinolin-1-one (**12dc**)

This product was obtained as a yellow solid in 80% yield starting from imide **11dc** according to the precedent protocol used for the reduction of imide **11aa**; Mp 203–205 °C (decomposition); IR (cm⁻¹) v: 3346 (OH), 3021 (CH), 2987 (CH), 1704 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 3.00 (t, 2H, *J* = 7.82 Hz, CH₂), 3.72 (s, 3H, OCH₃), 3.76 (s, 3H, OCH₃), 3.75–3.78 (m, 1H, CH), 4.02–4.10 (m, 1H, CH), 6.00 (s, 1H, CHOH), 6.72–6.77 (m, 3H, CHar), 7.30–7.35 (m, 2H, CHar), 7.55–7.59 (m, 3H, CHar), 7.77–7.82 (m, 2H, CHar), 8.08 (d, 1H, *J* = 8.6 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 34.1 (CH₂), 41.9 (CH₂), 55.9 (OCH₃), 56.0 (OCH₃), 80.8 (CH), 111.3 (CHar), 111.9 (CHar), 119.5 (C^q), 120.6 (2 × CHar), 126.6 (CHar), 128.3 (2 × CHar), 128.5 (CHar), 128.8 (CHar), 129.2 (C^q), 129.8 (2 × CHar), 132.2 (C^q), 134.6 (C^q), 147.6 (C^q), 147.8 (C^q), 148.6 (C^q), 148.7 (C^q), 149.0 (C^q), 156.4 (C^q), 167.5 (C=O). Anal. Calcd for C₂₇H₂₃ClN₂O₄ (474.94): C, 68.28; H, 4.88; N, 5.90. Found. C, 68.19; H, 4.75; N, 5.82.

4.3. General procedure for the π-cationic cyclization of α-hydroxy lactams **12aa–12cd** into cyclized products **6aa–6cd** and **19**

Experimental protocol with the model hydroxy lactam 12aa. To a solution of hydroxy lactam **12aa** (0.15 g, 0.49 mmol) in 8 mL of TFA (we use in general 16 mL of TFA for 1 mmol of reactant **12**) was stirred vigorously at room temperature for 48 h (**Method A**) or at reflux during 24 h (**Method B**). After cooling in the case of Method B, the reaction mixture was evaporated *in vacuo* and the residue diluted with 35 mL of dichloromethane then neutralized with saturated aqueous NaHCO₃. After the separation, the organic layer was washed with water, brine, dried over MgSO₄, filtered and concentrated under

reduced pressure. The resulting oily mixture obtained ultimately was purified by column chromatography using the mixture of cyclohexane/EtOAc in 1/1 ratio as the eluent to provide the cyclized products **6aa** or **19aa**.

4.3.1. 5,14b-Dihydrobenzo[7,8]indolizino[1,2-b]-quinolin-8(6H)-one (**6aa**)

This product was obtained as a white solid in 82% yield starting from hydroxy lactam **12aa** according to the **Method A**; Mp 201–203 °C; IR (cm⁻¹) v: 3015 (CH), 2990 (CH), 1689 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.91–2.98 (m, 1H, CH), 3.01–3.21 (m, 1H, CH), 3.51–3.60 (m, 1H, CH), 4.64–4.71 (m, 1H, CH), 5.81 (s, 1H, CHN), 7.17–7.30 (m, 3H, CHar), 7.60 (t, 1H, *J* = 7.34 Hz, CHar), 7.82 (t, 1H, *J* = 7.63 Hz, CHar), 7.97 (d, 1H, *J* = 8.1 Hz, CHar), 8.27 (d, 1H, *J* = 8.67 Hz, CHar), 8.40 (d, 1H, *J* = 7.73 Hz, CHar), 8.62 (s, 1H, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 29.1 (CH₂), 37.8 (CH₂), 59.8 (CH), 123.7 (C^q), 126.8 (CHar), 126.9 (CHar), 127.1 (CHar), 127.7 (CHar), 128.7 (C^q), 129.2 (CHar), 129.6 (CHar), 129.7 (CHar), 131.4 (CHar), 132.5 (C^q), 132.6 (CHar), 133.9 (C^q), 149.9 (C^q), 162.4 (C^q), 165.9 (C=O). Anal. Calcd for C₁₉H₁₄N₂O (286.33): C, 79.70; H, 4.93; N, 9.78. Found. C 79.59; H 4.87; N 9.61.

4.3.2. 14b-Trifluoroacetyloxy-5,6-dihydrobenzo-[7,8]indolizino[1,2-b]quinolin-8-one (**19aa**)

This product was obtained as a white solid in 66% yield starting from hydroxy lactam **12aa** according to the **Method B**; Mp 213–215 °C (ethyl acetate/cyclohexane, decomposition); IR (cm⁻¹) v: 3020 (CH), 2987 (CH), 1694 (C=O), 1722 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.90–2.95 (m, 1H, CH), 3.29–3.32 (m, 1H, CH), 3.53–3.60 (m, 1H, CH), 4.32–4.39 (m, 1H, CH), 7.17–7.33 (m, 3H, CHar), 7.69 (t, 1H, *J* = 7.34 Hz, CHar), 7.90 (t, 1H, *J* = 7.16 Hz, CHar), 8.19 (d, 1H, *J* = 7.91 Hz, CHar), 8.24 (d, 1H, *J* = 8.67 Hz, CHar), 8.47 (d, 1H, *J* = 7.54 Hz, CHar), 8.77 (s, 1H, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 28.4 (CH₂), 33.7 (CH₂), 118.7 (C^q), 119.4 (q, ¹*J* = 284.5 Hz, C^q CF₃), 122.2 (C^q), 126.1 (CHar), 127.4 (C^q), 127.6 (CHar), 128.2 (CHar), 128.6 (CHar), 128.8 (CHar), 129.3 (CHar), 129.7 (CHar), 131.7 (CHar), 132.2 (CHar), 134.3 (2 × C^q), 144.7 (C^q), 149.1 (C^q), 163.3 (q, ²*J* = 33.5 Hz, C^q C=O), 164.5 (C=O). Anal. Calcd for C₂₁H₁₃F₃N₂O₃ (398.08): C, 63.32; H, 3.29; N, 7.03. Found. C, 63.21; H, 3.14; N, 6.89.

4.3.3. 9-Methyl-5,14b-dihydrobenzo[7,8]indolizino[1,2-b]quinolin-8(6H)-one (**6ba**)

This product was obtained as a white solid in 65% yield starting from hydroxy lactam **12ba** according to the **Method B**; Mp 175–177 °C; IR (cm⁻¹) v: 3010 (CH), 2987 (CH), 1708 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.85–2.97 (m, 1H, CH), 2.99–3.38 (m, 1H, CH), 3.23 (s, 3H, CH₃), 3.44–3.58 (m, 1H, CH), 4.60–4.65 (m, 1H, CH), 5.72 (s, 1H, CHN), 7.15–7.35 (m, 4H, CHar), 7.63 (t, 1H, *J* = 7.82 Hz, CHar), 7.85 (t, 1H, *J* = 7.82 Hz, CHar), 8.23 (d, 1H, *J* = 7.82 Hz, CHar), 7.85 (d, 1H, *J* = 7.04 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 12.2 (CH₃), 28.9 (CH₂), 37.6 (CH₂), 58.9 (CH), 120.7 (C^q), 124.9 (CHar), 126.7 (CHar), 126.9 (CHar), 127.5 (CHar), 128.2 (C^q), 129.1 (CHar), 130.2 (CHar), 130.8 (CHar), 132.8 (C^q), 134.0 (CHar), 146.0 (C^q), 149.0 (C^q), 158.3 (C^q), 161.2

(C^q), 166.6 (C=O). Anal. Calcd for C₂₀H₁₆N₂O (300.35): C, 79.98; H, 5.37; N, 9.33. Found. C 79.77; H 5.21; N 9.19.

4.3.4. 9-Phenyl-5,14b-dihydrobenzo[7,8]indolizino[1,2-b]quinolin-8(6H)-one (**6ca**)

This product was obtained as a white solid in 72% yield starting from hydroxy lactam **12ca** according to the **Method A**; Mp 169–171 °C; IR (cm⁻¹) v: 3014 (CH), 2986 (CH), 1702 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.84–2.92 (m, 1H, CH), 3.03–3.20 (m, 1H, CH), 3.46–3.53 (m, 1H, CH), 4.53–4.64 (m, 1H, CH), 5.80 (s, 1H, CHN), 7.16 (t, 1H, *J* = 6.26 Hz, CHar), 7.29–7.55 (m, 8H, CHar), 7.79–7.86 (m, 2H, CHar), 8.45 (d, 1H, *J* = 7.82 Hz, CHar), 8.49 (d, 1H, *J* = 7.82 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 29.0 (CH₂), 37.5 (CH₂), 58.8 (CH), 119.7 (C^q), 126.7 (CHar), 126.9 (CHar), 127.0 (CHar), 127.4 (2 × CHar), 127.6 (CHar), 128.0 (CHar), 128.2 (C^q), 128.8 (CHar), 129.3 (CHar), 129.8 (2 × CHar), 130.0 (CHar), 131.0 (CHar), 132.7 (C^q), 132.9 (C^q), 134.1 (C^q), 147.8 (C^q), 149.8 (C^q), 162.6 (C^q), 165.5 (C=O). Anal. Calcd for C₂₅H₁₈N₂O (362.42): C, 82.85; H, 5.01; N, 7.73. Found. C, 82.76; H, 4.91; N, 7.58.

4.3.5. 9-Phenyl-14b-trifluoroacetyloxy-5,6-dihydrobenzo[7,8]indolizino[1,2-b]quinolin-8-one (**19ca**)

This product was obtained as a white solid in 65% yield starting from hydroxy lactam **12ca** according to the **Method A**; Mp 182–184 °C; IR (cm⁻¹) v: 3021 (CH), 2982 (CH), 1706 (C=O), 1730 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.86–2.92 (m, 1H, CH), 3.04–3.16 (m, 1H, CH), 3.62–3.72 (m, 1H, CH), 4.47–4.53 (m, 1H, CH), 7.16 (d, 1H, *J* = 7.54 Hz, CHar), 7.29–7.39 (m, 4H, CHar), 7.50–7.74 (m, 4H, CHar), 7.77 (d, 1H, *J* = 8.66 Hz, CHar), 7.82 (t, 1H, *J* = 7.53 Hz, CHar), 8.32 (d, 1H, *J* = 8.29 Hz, CHar), 8.67 (d, 1H, *J* = 7.91 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 29.0 (CH₂), 37.5 (CH₂), 118.3 (C^q), 127.0 (CHar), 127.6 (2 × CHar), 127.7 (q, ¹*J* = 283.5 Hz, C^q CF₃), 128.1 (2 × CHar), 128.8 (CHar), 129.0 (2 × CHar), 129.3 (CHar), 129.8 (CHar), 129.9 (CHar), 130.0 (CHar), 131.4 (CHar), 131.7 (C^q), 132.4 (C^q), 132.6 (C^q), 134.7 (C^q), 134.9 (C^q), 139.9 (C^q), 148.2 (C^q), 149.7 (C^q), 163.8 (q, ²*J* = 34.0 Hz, C^q C=O), 164.2 (C=O). Anal. Calcd for C₂₇H₁₇F₃N₂O₃ (474.43): C, 68.35; H, 3.61; N, 5.90. Found. C, 68.28; H, 3.58; N, 5.81.

4.3.6. 11-Chloro-9-phenyl-5,14b-dihydrobenzo-[7,8]indolizino[1,2-b]quinolin-8(6H)-one (**6da**)

This product was obtained as a yellow solid in 71% yield starting from hydroxy lactam **12da** according to the **Method B**; Mp 183–185 °C; IR (cm⁻¹) v: 3012 (CH), 2989 (CH), 1698 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.81–2.84 (m, 1H, CH), 3.00–3.06 (m, 1H, CH), 3.40–3.45 (m, 1H, CH), 4.49–4.53 (m, 1H, CH), 5.72 (s, 1H, CHN), 7.11–7.16 (m, 3H, CHar), 7.28–7.31 (m, 3H, CHar), 7.56–7.59 (m, 4H, CHar), 8.17 (d, 1H, *J* = 8.72 Hz, CHar), 8.37 (d, 1H, *J* = 7.82 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 28.9 (CH₂), 37.2 (CH₂), 58.9 (CH), 120.4 (C^q), 126.1 (CHar), 126.7 (2 × CHar), 127.6 (CHar), 128.1 (2 × CHar), 129.1 (CHar), 129.2 (CHar), 129.7 (CHar), 129.8 (CHar), 130.1 (C^q), 131.3 (CHar), 131.8 (CHar), 132.2 (C^q), 132.4 (C^q), 133.0 (C^q), 134.1 (C^q), 146.9 (C^q), 148.1 (C^q), 162.8 (C^q), 164.9 (C=O). Anal. Calcd for C₂₅H₁₇ClN₂O (396.87): C, 75.66; H, 4.32; N, 7.06. Found. C, 75.57; H, 4.19; N, 7.00.

4.3.7. 2-Methoxy-5,14b-dihydrobenzo[7,8]-indolizino[1,2-b]quinolin-8(6H)-one (**6ab**)

This product was obtained as a white solid in 69% yield starting from hydroxy lactam **12ab** according to the **Method B**; Mp 172–174 °C; IR (cm⁻¹) v: 3012 (CH), 2985 (CH), 1704 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.75–2.85 (m, 1H, CH), 2.92–2.98 (m, 1H, CH), 3.39–3.46 (m, 1H, CH), 3.78 (s, 3H, OCH₃), 4.54–4.61 (m, 1H, CH), 5.67 (s, 1H, CHN), 6.68 (d, 1H, *J* = 8.29 Hz, CHar), 6.98 (d, 1H, *J* = 8.29 Hz, CHar), 7.50 (t, 1H, *J* = 7.34 Hz, CHar), 7.81 (t, 1H, *J* = 7.34 Hz, CHar), 7.88 (d, 1H, *J* = 8.29 Hz, CHar), 7.93 (s, 1H, CHar), 8.15 (d, 1H, *J* = 8.29 Hz, CHar), 8.53 (s, 1H, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 27.8 (CH₂), 34.6 (CH₂), 55.7 (OCH₃), 77.2 (CH), 111.0 (2 × CHar), 113.9 (C^q), 122.1 (CHar), 126.1 (C^q), 127.0 (C^q), 127.5 (CHar), 127.9 (C^q), 129.4 (CHar), 129.8 (CHar), 131.6 (CHar), 132.7 (CHar), 147.9 (C^q), 149.5 (C^q), 149.8 (C^q), 164.5 (C=O). Anal. Calcd for C₂₀H₁₆N₂O₂ (316.35): C, 75.93; H, 5.10; N, 8.86. Found. C, 75.88; H, 5.01; N, 8.69.

4.3.8. 2-Methoxy-9-methyl-5,14b-dihydrobenzo-[7,8]indolizino[1,2-b]quinolin-8(6H)-one (**6bb**)

This product was obtained as a white-yellow solid in 68% yield starting from hydroxy lactam **12bb** according to the **Method B**; Mp 171–173 °C; IR (cm⁻¹) v: 3016 (CH); 2989 (CH); 1700 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.82–2.88 (m, 1H, CH), 3.00–3.10 (m, 1H, CH), 3.14 (s, 3H, CH₃), 3.43–3.50 (m, 1H, CH), 3.87 (s, 3H, OCH₃), 4.63–4.67 (m, 1H, CH), 5.67 (s, 1H, CHN), 6.78 (d, 1H, *J* = 8.28 Hz, CHar), 7.06 (d, 1H, *J* = 8.28 Hz, CHar), 7.60 (t, 1H, *J* = 7.35 Hz, CHar), 7.78 (t, 1H, *J* = 7.35 Hz, CHar), 8.03 (s, 1H, CHar), 8.16 (dd, 2H, *J* = 8.47 and 2.31 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 12.7 (CH₃), 27.9 (CH₂), 37.7 (CH₂), 55.4 (OCH₃), 77.2 (CH), 111.3 (2 × CHar), 120.6 (C^q), 123.6 (CHar), 125.5 (CHar), 126.9 (C^q), 128.2 (CHar + C^q), 128.4 (CHar), 129.3 (CHar), 133.5 (C^q), 145.9 (C^q), 148.8 (C^q), 158.1 (C^q), 162.1 (C^q), 167.0 (C=O). Anal. Calcd for C₂₁H₁₈N₂O₂ (330.37): C 76.34, H 5.49, N 8.48. Found. C 76.16, H 5.32, N 8.31.

4.3.9. 2-Methoxy-9-phenyl-5,14b-dihydrobenzo-[7,8]indolizino[1,2-b]quinolin-8(6H)-one (**6cb**)

This product was obtained as a white solid in 59% yield starting from hydroxy lactam **12cb** according to the **Method B**, Mp 189–191 °C; IR (cm⁻¹) v: 3012 (CH), 2993 (CH), 1705 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.77–2.85 (m, 1H, CH), 2.95–3.12 (m, 1H, CH), 3.36–3.50 (m, 1H, CH), 3.91 (s, 3H, OCH₃), 4.53–4.64 (m, 1H, CH), 5.78 (s, 1H, CHN), 6.79 (d, 1H, *J* = 7.83 Hz, CHar), 7.07 (d, 1H, *J* = 7.83 Hz, CHar), 7.41–7.56 (m, 7H, CHar), 7.82–7.86 (m, 2H, CHar), 8.36 (d, 1H, *J* = 7.82 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 28.0 (CH₂), 37.6 (CH₂), 55.4 (OCH₃), 58.8 (CH), 114.1 (CHar), 119.6 (C^q), 125.8 (C^q), 126.8 (CHar), 127.4 (CHar), 127.8 (CHar), 127.7 (C^q), 127.9 (CHar), 128.7 (CHar), 129.7 (2 × CHar), 129.8 (2 × CHar), 130.9 (CHar), 130.1 (C^q), 131.3 (CHar), 132.8 (C^q), 133.6 (C^q), 149.6 (C^q), 158.2 (C^q), 162.3 (C^q), 165.3 (C=O). Anal. Calcd for C₂₆H₂₀N₂O₂ (392.45): C 79.57, H 5.14, N 7.14. Found. C 79.40, H 5.04, N 7.00.

4.3.10. 11-Chloro-2-methoxy-9-phenyl-5,14b-dihydrobenzo[7,8]indolizino[1,2-b]quinolin-8(6H)-one (**6db**)

This product was obtained as a white solid in 73% yield starting from hydroxy lactam **12db** according to the **Method B**, Mp 183–185 °C; IR (cm⁻¹) v: 3012 3014 (CH), 2988 (CH), 1700 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.77–2.80 (m, 1H, CH), 2.97–3.02 (m, 1H, CH), 3.44–3.48 (m, 1H, CH), 3.88 (s, 3H, OCH₃), 4.54–4.58 (m, 1H, CH), 5.73 (s, 1H, CHN), 6.77 (d, 1H, *J* = 7.82 Hz, CHar), 6.84 (d, 1H, *J* = 7.82 Hz, CHar), 7.36–7.42 (m, 2H, CHar), 7.53–7.62 (m, 3H, CHar), 7.76 (m, 2H, CHar), 8.09 (d, 1H, *J* = 2.36 Hz, CHar), 8.23 (d, 1H, *J* = 8.6 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 28.7 (CH₂), 37.5 (CH₂), 58.7 (OCH₃), 60.7 (CH), 116.4 (C^q), 120.5 (C^q), 126.9 (CHar), 127.4 (CHar), 127.5 (2 × CHar), 127.7 (C^q), 127.9 (CHar), 128.3 (CHar), 128.5 (C^q), 128.6 (CHar), 128.9 (2 × CHar), 129.7 (CHar), 129.8 (CHar), 130.1 (C^q), 132.6 (C^q), 133.9 (C^q), 135.1 (C^q), 146.2 (C^q), 162.0 (C^q), 167.0 (C=O). Anal. Calcd for C₂₀H₁₆N₂O₂ (3426.89): C 73.15, H 4.49, N 6.56. Found. C 73.06, H 4.39, N 6.58.

4.3.11. 2,3-Dimethoxy-5,14b-dihydrobenzo[7,8]-indolizino[1,2-b]quinolin-8(6H)-one (**6ac**)

This product was obtained as a white-yellow solid in 61% yield starting from hydroxy lactam **12ac** according to the **Method B**, Mp 182–184 °C; IR (cm⁻¹) v: 3014 (CH), 2984 (CH), 1705 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.77–2.85 (m, 1H, CH), 2.97–3.10 (m, 1H, CH), 3.61–3.79 (m, 1H, CH), 3.83 (s, 3H, OCH₃), 4.00 (s, 3H, OCH₃), 4.52–4.61 (m, 1H, CH), 5.59 (s, 1H, CHN), 7.24 (s, 1H, CHar), 7.57 (t, H, *J* = 7.42 Hz, CHar), 7.79 (t, 1H, *J* = 7.42 Hz, CHar), 7.88 (d, 1H, *J* = 7.82 Hz, CHar), 8.21 (s, 1H, CHar), 8.23 (d, 1H, *J* = 7.82 Hz, CHar), 8.46 (s, 1H, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 27.8 (CH₂), 34.6 (CH₂), 55.4 (OCH₃), 55.7 (OCH₃), 84.6 (CH), 111.0 (2 × CHar), 113.9 (C^q), 122.1 (C^q), 126.1 (C^q), 127.0 (C^q), 127.5 (CHar), 127.9 (C^q), 129.4 (CHar), 129.8 (CHar), 131.6 (CHar), 132.7 (CHar), 147.9 (C^q), 149.5 (C^q), 149.8 (C^q), 164.5 (C=O). Anal. Calcd for C₂₀H₁₆N₂O₂ (346.38): C 72.82, H 5.24, N 8.09. Found. C 72.77, H 5.15, N 7.99.

4.3.12. 2,3-Dimethoxy-9-methyl-5,14b-dihydrobenzo[7,8]indolizino[1,2-b]quinolin-8(6H)-one (**6bc**)

This product was obtained as a yellow solid in 69% yield starting from hydroxy lactam **12bc** according to the **Method B**, Mp 180–182 °C; IR (cm⁻¹) v: 3013 (CH), 2989 (CH), 1681 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.77–2.84 (m, 1H, CH), 3.02–3.13 (m, 1H, CH), 3.15 (s, 3H, CH₃), 3.37–3.52 (m, 1H, CH), 3.84 (s, 3H, OCH₃), 4.00 (s, 3H, OCH₃), 4.69–4.77 (m, 1H, CH), 5.65 (s, 1H, CHN), 6.62 (s, 1H, CHar), 7.63 (t, 1H, *J* = 7.53 Hz, CHar), 7.78 (t, 1H, *J* = 7.34 Hz, CHar), 8.04 (s, 1H, CHar), 8.20 (dd, 2H, *J* = 7.91 and 2.16 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 12.1 (CH₃), 28.4 (CH₂), 37.5 (CH₂), 56.0 (OCH₃), 56.1 (OCH₃), 58.5 (CH), 109.7 (CHar), 111.4 (CHar), 124.5 (C^q), 124.8 (CHar), 125.8 (C^q), 126.5 (CHar), 128.1 (C^q), 129.9 (CHar), 130.7 (CHar), 146.0 (C^q), 147.7 (C^q), 148.3 (C^q), 148.3 (C^q), 148.9 (C^q), 162.5 (C^q), 167.0 (C=O). Anal. Calcd for C₂₀H₁₆N₂O₂ (360.40): C 73.32, H 5.59, N 7.77. Found. C 73.21, H 5.44, N 7.59.

4.3.13. 2,3-Dimethoxy-9-phenyl-5,14b-dihydro-benzo[7,8]indolino[1,2-b]quinolin-8(6H)-one (**6cc**)

This product was obtained as a white-yellow solid in 67% yield starting from hydroxy lactam **12cc** according to the **Method B**, Mp 215–217 °C (ethyl acetate/cyclohexane, decomposition); IR (cm⁻¹) v: 3010 (CH), 2988 (CH), 1692 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.69–2.81 (m, 1H, CH), 2.97–3.11 (m, 1H, CH), 3.35–3.94 (m, 1H, CH), 3.85 (s, 3H, OCH₃), 4.04 (s, 3H, OCH₃), 4.59–4.68 (m, 1H, CH), 5.78 (s, 1H, CHN), 6.64 (s, 1H, CHar), 7.43–7.53 (m, 6H, CHar), 7.80–7.81 (m, 2H, CHar), 8.09 (s, 1H, CHar), 8.27 (d, 1H, *J* = 8.6 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 28.0 (CH₂), 34.3 (CH₂), 56.0 (OCH₃), 56.2 (OCH₃), 83.9 (CH), 116.6 (C^q), 112.2 (CHar), 116.8 (CHar), 120.6 (C^q), 126.5 (C^q), 126.6 (CHar), 128.3 (CHar), 128.4 (C^q), 128.6 (2 × CHar), 129.5 (CHar), 130.5 (2 × CHar), 131.8 (CHar), 130.1 (C^q), 131.3 (CHar), 132.5 (C^q), 134.6 (C^q), 134.7 (C^q), 148.1 (C^q), 149.6 (C^q), 164.5 (C=O). Anal. Calcd for C₂₀H₁₆N₂O₂ (422.47): C 76.76, H 5.25, N 6.63. Found. C 76.83, H 5.23, N 6.69.

4.3.14. 11-Chloro-2,3-dimethoxy-9-phenyl-5,14b-dihydrobenzo[7,8]indolino[1,2-b]quinolin-8(6H)-one (**6dc**)

This product was obtained as a white-yellow solid in 69% yield starting from hydroxy lactam **12dc** according to the **Method B**, Mp 200–202 °C (ethyl acetate/cyclohexane, decomposition); IR (cm⁻¹) v: 3018 (CH), 2996 (CH), 1692 (C=O); ¹H NMR (300 MHz, CDCl₃): δ (ppm) 2.66–2.70 (m, 1H, CH), 2.94–2.99 (m, 1H, CH), 3.31–3.35 (m, 1H, CH), 3.78 (s, 3H, OCH₃), 3.96 (s, 3H, OCH₃), 4.53–4.58 (m, 1H, CH), 5.66 (s, 1H, CHN), 6.56 (s, 1H, CHar), 7.35–7.39 (m, 2H, CHar), 7.47–7.50 (m, 3H, CHar), 7.66–7.70 (m, 2H, CHar), 7.99 (s, 1H, CHar), 8.12 (d, 1H, *J* = 8.66 Hz, CHar); ¹³C NMR (75 MHz, CDCl₃): δ (ppm) 28.3 (CH₂); 37.6 (CH₂); 56.0 (OCH₃); 56.2 (OCH₃); 58.7 (CH); 109.9 (CHar); 111.7 (CHar); 118.6 (C^q); 120.6 (C^q); 126.5 (C^q); 126.6 (CHar); 128.3 (2 × CHar); 129.2 (CHar); 129.8 (CHar); 129.9 (2 × CHar); 130.3 (C^q); 132.0 (CHar); 132.5 (C^q); 134.6 (C^q); 134.7 (C^q); 136.1 (C^q); 148.0 (C^q); 148.6 (C^q); 157.6 (C^q); 163.3 (C=O). Anal. Calcd for C₂₇H₂₁ClN₂O₃ (456.92): C 70.97, H 4.63, N 6.13. Found. C 71.02, H 4.57, N 6.17.

Acknowledgments

The authors are grateful to the Libyan Government for a Post-doctoral Fellowship attributed to one of us A. Hamid. We thank also very warmly the Region of 'Normandie', 'Normandie Université-COMUE' and the 'Université Le Have Normandie' for technical support and material help.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.arabjc.2018.03.009>.

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