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Intramolecular *N*-aza-amidoalkylation in association with Witkop–Winterfeldt oxidation as the key step to synthesize Luotonin-A analogues

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ABSTRACT

An expedient four-step approach for the synthesis of a short library of original analogues of the Topo-I Luotonin-A inhibitor, substituted at their C_8- and N_{15}-positions, was investigated. This consists of Rutaecarpines formation, their Witkop–Winterfeldt oxidation followed ultimately with functional adjustment of the pyrroloquinolone intermediates. In the first step of these investigations, Rutaecarpines including the Topo-I poison Evodiamine were obtained via the new tandem N-acylation/aza-amidoalkylation using a nitrogen atom as an internal nucleophile with or without association with a decarboxylation.

1. Introduction

The quinazolinone skeleton is frequently encountered in numerous alkaloids[1] and synthetic structures all exhibiting biological properties.[1,2] Aromatic quinazolines have been shown to possess tyrosine kinase inhibiting effects,[3] inhibit tumour growth and display other biological profiles including anticonvulsant and antiepileptic activities.[4] They were used, for example, in the treatment of tuberculosis[5] as well as benign prostatic hyperplasia.[6] In addition, this skeleton fused to tetrahydro-*b*-carboline or pyrrolo[3,4-*b*] quinoline nuclei constitutes an important class of heterocycles belonging to quinazoline-type alkaloids both from an organic synthetic and pharmaceutical point of view. Both Luotonin-A (**1**) and Rutaecarpine (**2**) are members of this family whose extracts have long been used as remedies in Chinese traditional medicine for the treatment of various diseases.[7]

Despite the large spectra of activities of **2** and its derivatives, **2** has been reported as having a lower antitumour activity[8] than Camptothecin (CPT),[9] Luotonin-A (**1**) and their analogues.[10] In these cases, 10-bromo-, 11-methoxy- and 10,11-methylene-dioxyrutaecarpines are the most active derivatives in the series and numerous thiophene analogues have shown good anticancer activity in vitro but no activity in vivo.[8c] Importantly, the alkaloid Evodiamine (**3**, Scheme 1),[11] which could be considered as a reduced Rutaecarpine (**2**) and isolated along with it from *Evodia rutaecarpa*, seems to stabilize the topoisomerase-I (Topo-I)/DNA cleavable complex[12] effectively to inhibit the Topo-I activity with comparable level as Luotonin-A, CPT and other aromathecins (in which the chiral lactone as in CPT is replaced with an aryl group), such as Rosettacin and 22-hydroxyacuminatine.[13] Since the mode of action of CPTs is now well known via the X-ray crystal structure of the CPT/DNA/Topo-I ternary cleavage complex, outlining the pivotal role of the hydrogen bonds between C_{20}–OH function and quinoline-N_1 of CPT and Asp533 and Arg364 residues of Topo-I, respectively,[14] the possible similar mode of action of other compounds cited above is intriguing.

During the last two decades, the synthetic development of Luotonin **1** derivatives with different substituents on either **A**, **B**, **C** ring and/or **E** ring have outlined the importance of this class of products in the field of oncology (Scheme 1).[15,16] From these considerations, the development of new approaches into original Luotonins is still of interest in the search for other new lead compounds.

2. Results and discussion

We are interested in the development of short and effective methods towards aza-heterocyclic systems with promising pharmaceutical activities. Among these systems are pentacyclic Rutaecarpines,[17] aromathecins[18] and finally Luotonins substituted at the C_2-, C_7-, C_{10}- and/or C_{11}-positions.[19]

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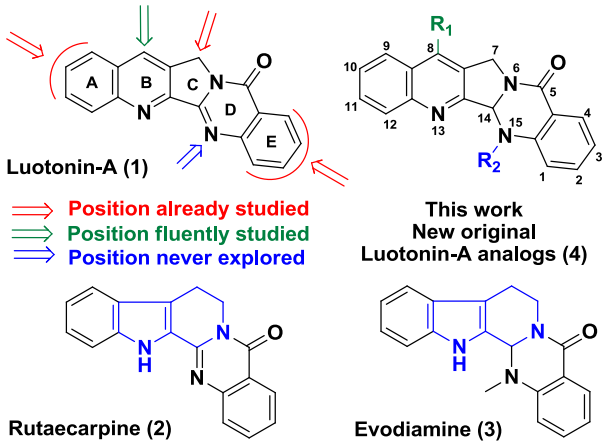
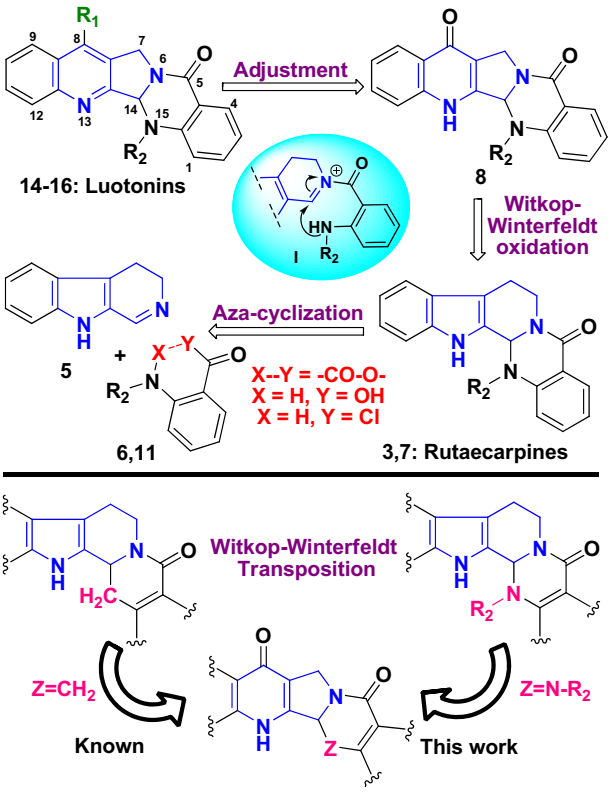


Scheme 1. Representative quinazoline-type alkaloids **1**–**3** with anticancer activity and the structure of our target compounds **4**.

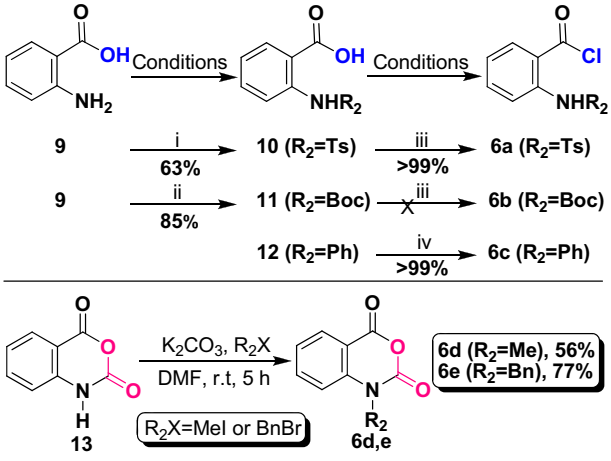
In association with our recent reports dealing with intramolecular α-thio-amidoalkylation,[20] α-oxo-amidoalkylation[21] and α-seleno-amidoalkylation,[20e] we reasoned that a suitably substituted *N*-acyliminium precursor of type **I** (see Scheme 2) could allow a facile approach to the reduced Rutaecarpine derivatives **3** and **7**. Their subjection further to the Witkop–Winterfeldt oxidation would lead to the pentacyclic cores **8** of the title targets **14**–**16**, which could be reached ultimately after rapid functional adjustments. To the best of our knowledge, the use of the present application in an intramolecular *N*-acyliminium mediated aza-cyclization reaction,[22] as depicted in Scheme 2, to form a six membered ring as a cyclic *N*,*N*-acetal structure, represents a novel illustration of this chemistry.



Scheme 2. Retrosynthetic scheme leading to *N*-substituted Luotonin-A analogues as the targets.

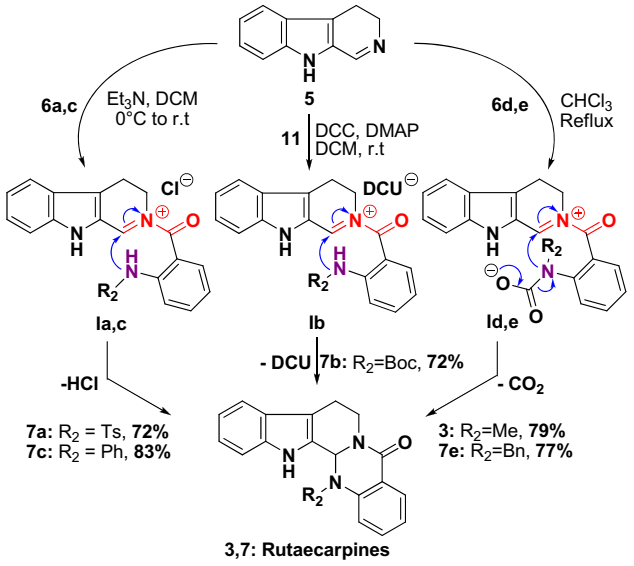
The cationic cyclization using a nitrogen atom as internal nucleophile has first been mentioned during the synthesis of 9a-phenyltetrahydroisoindolo[2,1-*a*]quinazoline-5,11-dione without isolation of the *N*-acyliminium precursor[23a] and then later for the production[23b] of diethyl dioxolo[4,5-*g*]pyrrolo[2,1-*b*]quinazoline-8,8-dicarboxylate. Its power was also illustrated in the total synthesis of (+/−)- and (−)-physostigmine, namely eserine, as the principal alkaloid of Calabar bean,[24] (+/−)-glochidine and (+/−)-glochidicine,[25] imidazoloindoline alkaloids,[26] oroidin-derived alkaloids[27] and more recently chiral (−)-decarbamoyloxysaxitoxin as a neurotoxin that blocks voltage-gated sodium channels, which are critical for depolarization and conduction in most excitable cells.[28] The reports of this process concern also its use: (1) in medicinal chemistry to access aldose reductase inhibitors,[29] (2) in solid-phase parallel synthesis of D^2-2-oxopiperazines,[30] (3) in asymmetric synthesis of Reissert compounds,[31] (4) in synthesis of lactam-based peptide-mimetics,[32] and finally (5) in sterically hindered *N*-substituted and fused g-lactams.[33]

In the context outlined above, we present herein our first findings from a related study dealing with the examination of the impact, during the cyclization process, of the nitrogen atom as internal nucleophile on the reactivity of *N*-acyliminium species **I**. Also for comparative reasons, a nitrogen atom bearing different R_2 groups is also considered (Schemes 2 and 3). The choice of R_2 group was based on two considerations: first, NHTs and NHBoc groups were rarely engaged in the intramolecular cationic cyclization, and we expected that both groups could be removed easily during or after the oxidative transposition of Rutaecarpines **3** and **7**. Second, both tosyl and Boc are electron-withdrawing groups, which could render the amino group less nucleophilic. This could consequently lead, after hydrolysis of cations **Ia**,**b**, to corresponding hydroxy lactams as isolable intermediates (not presented in the Schemes 2 and 4). Complementarily, the use of Ph, Me and Bn groups could lead to Rutaecarpines **7c**,**3** and **7e** with another stereoelectronic profile different from those, which could be obtained when R_2=Ts (**7a**) and R_2=Boc (**7b**).



Scheme 3. Synthesis of substrates **11**, **6a**,**c** and **6d**,**e**. Reaction conditions: (i) (Na_2CO_3, TsCl, H_2O, 70 °C, 50 min. (ii) Boc_2O, EtOH, 50 °C, 72 h. (iii) $(COCl)_2$, DCM, rt, 2 h. (iv) $SOCl_2$, Toluene, reflux, 30 min.

Our initial work concerns the preparation of three kinds of reagents **6a**,**c**, **6d**,**e** and **11**, partners of the known dihydro-*b*-carboline (**5**)[34] in the cyclocondensation reaction. These substrates are well described in the literature starting from anthranilic acid (**9**) and isatoic anhydride (**13**) by N-alkylation process using modified published procedures. The protection of **9** with tosyl and Boc groups afforded carboxylic acids **10**[35] and **11**,[36] respectively, which upon treatment with slight excess of oxalyl chloride in dry DCM provided acid chloride **6a**[37] in nearly quantitative yield and **6b**, which turned out to be unstable. By the same chlorination reaction but using harsher conditions (2 equiv of $SOCl_2$, toluene, reflux,



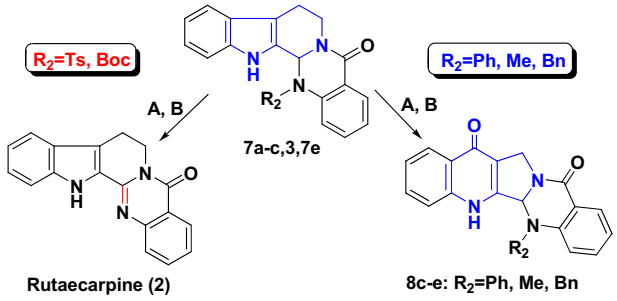
Scheme 4. Scheme leading to Rutaecarpines **7a**–**c**, **3** and **7e** including the Topo-I poison Evodiamine **3** (**3** correspond to the initial number **7d**).

30 min), the 2-(phenylamino)benzoyl chloride (**6c**) was isolated in quantitative yield starting from the commercially available 2-(phenylamino)benzoic acid (**12**).[38] Because it was difficult to prepare 2-(alkylamino)benzoyl chloride using the same protocol as for reagent **6a**,**b**, another approach using isatoic anhydride (**13**) as starting material was investigated to prepare **6d**,**e**. Thus, N-methylation and N-benzylation of the anhydride isatoic **13** using a modified known procedure afforded *N*-methylated and *N*-benzylated anhydride isatoic derivatives **6d**,**e** in acceptable yields of 56% for **6d** and 77% for **6e**, respectively.[39]

The operability of the crucial cyclocondensation leading to Rutaecarpines **3**,**7** was first tested by treatment of cyclic imine **5** with acid chloride **6a** (generated in situ) in DCM at 0 °C up to room temperature in the presence of NEt_3 as HCl scavenger. After 1.5 h of reaction, the resulting sole reaction product was identified to be **7a** in 72% yield (Scheme 4) after flash chromatography purification (i.e., SiO_2, cyclohexane/AcOEt: 7/3). This is the consequence of the cyclization of the presumed *N*-acyliminium cation **Ia** being formed as intermediate with a nitrogen atom as internal nucleophile. Under the same conditions, reaction of imine **5** with acid chloride **6c** proved successful and the *N*-phenyldihydrorutaecarpine (**7c**) was isolated in 83% yield in a similar manner. So far, these cyclization conditions were never used, but in the literature the reaction of isoquinoline and different chiral α-Cbz-amino acyl fluorides was reported.[31a,40] In the presence of Lewis acid, such as $AlCl_3$, that reaction sometimes provided the tricyclic imidazoisoquinolines as a consequence of the intramolecular *N*-acyliminium trapping of a nitrogen atom.

By the way, because it was difficult to isolate the acid chloride **6b** in pure form, the reaction of imine **5** with its carboxylic acid congener **11** was explored. Interestingly, under the peptide coupling conditions using DCC/DMAP (1.1 equiv peer 0.1 equiv) in DCM at room temperature for 4 h, the *N*-Boc-dihydrorutaecarpine (**7b**) was isolated in 72% yield. Mechanistically speaking, this process involves a tandem N-acylation/intramolecular aza-cyclization via the *N*-acyliminium cation **Ib** (Scheme 4). Herein the imine function of **5** is nucleophilic enough for the displacement of the reactive *O*-acyl-urea intermediate being obtained by the reaction of DCC with *N*-Boc-carboxylic acid **11**. This resulted also in the generation of the above species **Ib** and the dicyclohexyl-urea (DCU) carbanion as the counter-ion. Moreover, based on the few reports on reaction of isatoic anhydride (**13**) with linear[41] and cyclic[42] imines under neutral conditions, we anticipated that the reaction of **5** with *N*-alkylated isatoic anhydride could lead to the expected *N*-alkylrutaecarpines. Indeed, reaction of **5** with **6d** in $CHCl_3$ at reflux for 8 h provided *N*-methyldihydrorutaecarpine (**3**) in good yield (79%), which is commonly known as Evodiamine (**3**, Schemes 1 and 4). In the same manner, **5** and **6e** provided *N*-benzyldihydrorutaecarpine (**7e**) in 77% yield. Interestingly, here the tandem N-acylation/aza-cyclization via the *N*-acyliminium cation **Id**,**e** is also associated with the decarboxylation process (Scheme 4).

Furthermore, we next planned to investigate the reactivity of the reduced Rutaecarpines **3** and **7**, particularly by examining their behaviour in the Witkop–Winterfeldt oxidation.[43] These are of interest since their transformation could lead to the pentacyclic pyrroloquinolones **8** (Scheme 5), as the key intermediates in route to the Luotonins **14**–**16** as the targets (Scheme 1).



Scheme 5. Oxidative transposition conditions of Rutaecarpines **7a**–**c**, **3**, **7e**.

Two kinds of substrates **7a**,**b** and **7c**,**3** and three conditions **A**, **B** and **C** for the Witkop–Winterfeldt oxidation were chosen. For this purpose, conditions **A** (O_2, *t*-BuOK, DMF, room temperature) and **C** ($NaIO_4$, THF/MeOH/H_2O (1/1/1), reflux), which are classically used for this transformation[43] and conditions **B** (KO_2, 18-C-6, DMF, room temperature), introduced by Speier and Balogh-Hergovich in 1982[44] and extended by Sui et al.,[45] were tested.

Thus, the oxidation of the quinazolino-β-carbolines **7a**,**b** under conditions **A** or **B** led only to the deprotection of both electron-withdrawing groups followed spontaneously by the classical oxidation into the alkaloid Rutaecarpine (**2**). In both cases, no products **8a**,**b** as precursors of Luotonin-A (**1**) were detected (Scheme 5) but compound **2** was isolated as the sole reaction product in yields ranging from 37% up to 67%. The yield is better for *N*-Boc derivative **7b** in comparison to one for derivate **7a** (See entries 1–4 in Table 1). It is worth mentioning that when classical conditions **C** were used only traces of Rutaecarpine (**2**) were detected with the recovered starting material.

Table 1
Results of the oxidation of Rutaecarpines **7a**–**c**, **3** and **7e**[a,b]

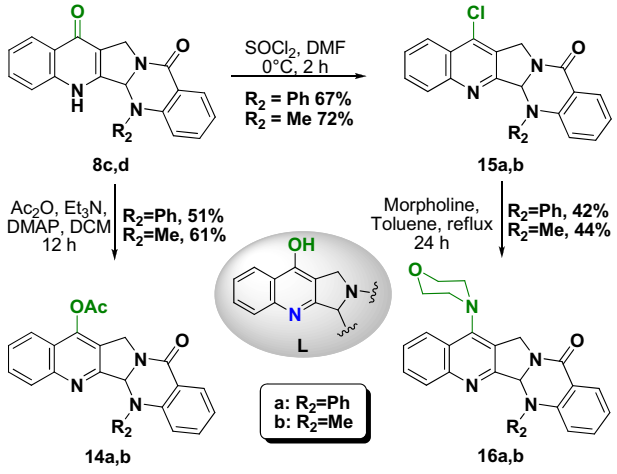
Entry	Substrate number	Conditions [a,b]	R_2 group	Product number	Yield (%)[c]
1	**7a**	**A**	Ts	**2**	48
2	**7a**	**B**	Ts	**2**	37
3	**7b**	**A**	Boc	**2**	67
4	**7b**	**B**	Boc	**2**	53
5	**7c**	**A**	Ph	**8c**	52
6	**7c**	**B**	Ph	**8c**	20
7	**3**	**A**	Me	**8d**	48
8	**3**	**B**	Me	**8d**	42
9	**7e**	**A**	Bn	**8e**	58
10	**7e**	**B**	Bn	**8e**	55

[a] Conditions **A**: O_2, *t*-BuOK, DMF, rt, 1 h; Conditions **B**: KO_2, 18-C-6, DMF, rt, 12 h.
[b] No reaction occurred or only traces of product were detected when conditions **C** ($NaIO_4$, THF/MeOH/H_2O (1/1/1), reflux, 12 h) were used.
[c] Isolated yield after silica gel chromatography purification.

Elsewhere, quinazolino-β-carbolines **7c**, **3** and **7e**, in which the Ewg group (Ts, Boc) was replaced, respectively, with the phenyl, methyl and benzyl substituent, were submitted to react under the oxidation conditions as above. To our satisfaction, the reaction provided products **8c**–**e** in yields ranging from 20% up to 61% (see Experimental section), better when conditions **A** were used (entries 5, 7, 9; Table 1). This is probably due to the balance between the high reactivity of KO_2 and its stability with regard to the reaction time (12 h) in comparison to O_2, which needed only 1 h of reaction.

Having in hand fused pyrroloquinolones **8c**,**d** as the oxidative transposition products of compounds **7c** and **3**, we then envisioned their diversification by substituting them at their C_8-position (the C_4-position of the quinolone nucleus). The principal objective here is to enhance the hydro-solubility of the ultimate Luotonin-A derivatives **14**–**16** as an important parameter in their further possible biological screening.

In this context, the esterification of condensed quinolin-4-ones **8c**,**d** was accomplished, via the presumed tautomer hydroxyl intermediates **L** in equilibrium with their congeners **8c**,**d** (Scheme 6). For this purpose, we have used the O-acylation conditions used earlier by us and others (i.e., Ac_2O, Et_3N, DMAP, DCM, 12 h).[46] Under these conditions, the expected acetate products **14a** and **14b** were isolated in 51% and 61% yields, respectively, after purification by flash chromatography on silica gel column using the mixture of cyclohexane/AcOEt (2/3) as the eluent.



Scheme 6. Diversification of the quinazolino-β-carboline scaffold of **8c**,**d**.

The chlorination of dihydroquinolinones **8c**,**d** via also the intermediacy of 4-hydroxyquinolines **L** was accomplished under mild conditions using $SOCl_2$ (10 equiv) in the presence of DMF as the solvent at 0 °C up to room temperature for 2 h.[47] The expected halide derivatives **15a** and **15b**, were isolated in yields of 67% and 72%, respectively. These derivatives were also purified by flash chromatography (i.e., SiO_2, cyclohexane/AcOEt (7/3 up to 4/1 ratio)). Ultimately, the chlorine atom of derivatives **15a** and **15b** was displaced easily with large excess of freshly distilled morpholine (10 equiv) in toluene at reflux for 24 h. Analytical pure compounds **16a** and **16b** were finally isolated by chromatography purification on silica gel column by using the mixture of cyclohexane/AcOEt in 1/1 up to 3/2 ratio in yields of 42% and 44%, respectively.

3. Conclusion

In this paper, we have successfully introduced an expedient synthetic entry to Rutaecarpines *N*-substituted of type **7** including the Topo-I inhibitor Evodiamine (**3**). This approach consists in using of the scarcely known tandem N-acylation/aza-cyclization of the *N*-acyliminium intermediates in association, in certain cases, with the decarboxylation process.

Rutaecarpines **7** obtained with this protocol were then used as valuable templates for the Witkop–Winterfeldt oxidation to provide successfully, and in the first time for these types of substrates, the oxidative transposition products **8** and the Topo-I Rutaecarpine poison **2** via the simple deprotection of Ts and Boc groups under the oxidative conditions of **7**. Further functionalisation of the obtained pyrroloquinolones using standard chemistry ultimately allow access to a small library of Luotonins **4** substituted at two points including the nitrogen atom at N_{15}-position for the first time.

Finally, we anticipate that the transformations developed in this project, particularly the access to new Luotonins, will find further applications in production of a large library for biological issues. These systems are currently under investigation in our laboratory and the results will be reported soon in full account.

4. Experimental section

4.1. General remarks

All melting points were measured on a Boetius micro-hotstage and are uncorrected. The infrared spectra of solids (potassium bromide) and liquids (neat) were recorded on a Perkin–Elmer FT-IR paragon 1000 spectrometer and are reported in terms of frequency of absorption (n, cm^{-1}). The ^1H and ^{13}C NMR spectra were recorded on a Bruker 300 MHz instrument in deuteriochloroform unless other indicated solvent and chemical shifts (δ) are expressed in parts per million (ppm) relative to TMS (Tetramethylsilane) as internal standard and/or referenced to residual chloroform (δ=7.27 ppm). Ascending thin layer chromatography was performed on precoated plates of silica gel 60 F_{254} (Merck) and the spots visualized using an ultraviolet lamp or iodine vapour. The solvents used were purified by standard protocols. The elemental analyses were carried out by the microanalysis of COBRA laboratory, CNRS UMR-6014, F-76130 Mont Saint-Aignan, France.

*4.1.1. 2-(Tosylamino)benzoyl chloride (**6a**).* To a solution of a freshly prepared known carboxylic acid **10**[35] (2.91 g, 10 mmol) in dry dichloromethane (30 mL) was added oxalyl chloride (1.875 g, 1.275 mL, 15 mmol) at 0–5 °C. The mixture was stirred at room temperature for 2 h and then evaporated under reduced pressure. The crude product identified as acid chloride **6a**[37] was obtained in quantitative yield (3.09 g) and was used in the next without other purification.

*4.1.2. 2-(Phenylamino)benzoyl chloride (**6c**).* To a solution of a commercially available 2-(phenylamino)-benzoic acid **12** (2.13 g, 10 mmol) in dry toluene (25 mL) was added dropwise thionyl chloride (2 equiv, 2.36 g, 1.44 mL, 20 mmol) at 0–5 °C. The mixture was stirred at reflux for 30 min and then evaporated under reduced pressure. The crude product identified as acid chloride **6c**[38] was obtained in quantitative yield (2.30 g) and was used in the next without other purification.

4.2. General procedure for the synthesis of *N*-substituted tetrahydroindolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-5-ones (7a,c)

To a stirred solution of 3,4-dihydro-β-carboline (**5**, 340 mg, 2.00 mmol) in 16 mL of dry dichloromethane containing triethylamine (560 μL, 4 mmol, 2 equiv) was added at 0 °C a solution of freshly prepared acid chloride **6a** (640 mg, 2.20 mmol, 1.1 equiv) or **6c** (510 mg, 2.20 mmol, 1.1 equiv) dissolved in 16 mL of dichloromethane. The reaction mixture was stirred at 0 °C for 30 min then an additional 1 h at room temperature, after which saturated

aqueous solution of $NaHCO_3$ was added. The organic phase after separation was washed with brine, dried over anhydrous $MgSO_4$, filtered, and evaporated under reduced pressure. The resulting crude product was purified by flash chromatography on silica gel column using the mixture of cyclohexane/AcOEt as the eluent to provide the title following compounds **7a** and **7c**.

*4.2.1. N_{14}-Tosyl-7,8,13,13b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-b] quinazolin-5-one (**7a**).* This product was isolated as a white solid after chromatography purification (i.e., SiO_2, cyclohexane/AcOEt (7/3)) in 72% yield: mp 242 °C; R_f 0.50 (cyclohexane/AcOEt: 1/1); IR (KBr, cm^{-1}) ν: 3460 (NH), 1665 (C=O), 1604 (NH), 1466 (CH), 1410 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.34 (s, 3H, CH_3), 2.59 (d, 1H, $1CH_{2\beta}$, J=12.5 Hz), 3.00–3.29 (m, 2H, $1CH_{2\alpha}$–NCO and $1CH_{2\beta}$), 4.67–4.77 (m, 1H, $1CH_{2\alpha}$–NCO), 7.00–1.18 (m, 6H, $5H_{aro}$ and CH), 7.24–7.32 (m, 1H, H_{aro}), 7.39 (d, 3H, H_{aro}, J=8.6 Hz), 7.49 (dd, 1H, H_{aro}, J=8.6 and 7.0 Hz), 7.83 (d, 2H, H_{aro}, J=7.8 Hz), 8.30 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 19.7 (CH_2), 21.9 (CH_3), 44.8 (CH_2), 69.2 (CH), 111.7 (CH_{aro}), 113.2 ($C_{q/aro}$), 118.8 (CH_{aro}), 120.2 (CH_{aro}), 123.1 (CH_{aro}), 123.8 ($C_{q/aro}$), 126.5 (CH_{aro}), 127.3 ($C_{q/aro}$), 127.8 ($3CH_{aro}$), 128.8 (CH_{aro}), 130.0 ($2CH_{aro}$ and $C_{q/aro}$), 133.4 (CH_{aro}), 134.0 ($C_{q/aro}$), 135.8 ($C_{q/aro}$), 135.9 ($C_{q/aro}$), 145.4 ($C_{q/aro}$), 163.4 (C=O); Anal. Calcd for $C_{25}H_{21}N_3O_3S$ (443.13): C, 67.70; H, 4.77; N, 9.47. Found: C, 67.59; H, 4.65; N, 9.37.

*4.2.2. N_{14}-Phenyl-7,8,13,13b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-b]quinazolin-5-one (**7c**).* This product was isolated as a white solid after chromatography purification (i.e., SiO_2, cyclohexane/AcOEt (4/1)) in 83% yield: mp 211 °C; R_f 0.50 (cyclohexane/AcOEt: 7/3); IR (cm^{-1}) ν: 1652 (C=O), 1605 (C=C), 1591 (C=C), 1495 (C=C), 1471 (C=C), 1416 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.65–2.78 (m, 1H, $1CH_{2\beta}$), 2.68–3.29 (m, 2H, $1CH_{2\beta}$ and $1CH_{2\alpha}$–NCO), 4.85–4.95 (m, 1H, $1CH_{2\alpha}$–NCO), 6.37 (s, 1H, CH), 6.94–7.36 (m, 11H, H_{aro}), 7.45 (d, 1H, H_{aro}, J=7.8 Hz), 8.03 (dd, 1H, H_{aro}, J=7.8 and 1.6 Hz), 8.09 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.0 (CH_2), 43.2 (CH_2), 72.9 (CH), 111.5 (CH_{aro}), 113.8 ($C_{q/aro}$), 119.0 (CH_{aro}), 120.2 (CH_{aro}), 120.6 (CH_{aro}), 121.3 ($C_{q/aro}$), 122.8 (CH_{aro}), 123.0 (CH_{aro}), 124.7 ($2CH_{aro}$), 125.7 (CH_{aro}), 127.2 ($C_{q/aro}$), 129.2 (CH_{aro}), 129.8 ($2CH_{aro}$), 131.2 ($C_{q/aro}$), 133.3 (CH_{aro}), 136.2 ($C_{q/aro}$), 145.2 ($C_{q/aro}$), 146.7 ($C_{q/aro}$), 165.3 (C=O); Anal. Calcd for $C_{24}H_{19}N_3O$ (365.15): C, 78.88; H, 5.24; N, 11.50. Found: C, 78.65; H, 5.09; N, 11.41.

*4.2.3. N_{14}-Tertiobutoxycarbonyl-7,8,13,13b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-b]quinazolin-5-one (**7b**).* To a solution of 3,4-dihydro-β-carboline (**5**, 340 mg, 2.00 mmol) and *N*-Boc-anthralinic acid (**11**,[36] 512 mg, 2 mmol, 1 equiv) in dry dichloromethane (20 mL), was added under stirring 4-dimethylaminopyridine (DMAP, 24.0 mg, 0.20 mmol, 0.1 equiv) and *N*,*N*-dicyclohexylcarbodiimide (DCC, 454 mg, 2.20 mmol, 1.1 equiv) at room temperature. After 4 h of the reaction, the mixture was filtered on Celite-545 with washing twice by dichloromethane. The combined organic filtrate was treated with saturated solution of $NaHCO_3$, separated, dried over anhydrous $MgSO_4$, filtered again and evaporated under reduced pressure. The ultimate residue was purified by flash column chromatography (silica gel, eluted with the mixture cyclohexane/AcOEt (3/2)) to provide the *N*-Boc-dihydro-rutaecarpine (**7b**) in 72% yield as a white solid. Mp 221 °C; R_f 0.30 (cyclohexane/AcOEt: 3/2); IR (KBr, cm^{-1}) ν: 3319 (NH), 2989 (CH), 1702 (C=O), 1643 (C=O), 1606 (NH), 1488 (C=C), 1470 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 1.58 (s, 9H, N-Boc), 2.66 (d, 1H, $1CH_{2\beta}$, J=13.3 Hz), 3.12–3.46 (m, 2H, $1CH_{2\beta}$ and $1CH_{2\alpha}$–NCO), 4.91–5.1 (m, 1H, $1CH_{2\alpha}$–NCO), 7.02–7.17 (m, 4H, $3H_{aro}$ and CH), 7.22–7.28 (m, 1H, H_{aro}), 7.35–7.46 (m, 2H, H_{aro}), 7.53 (d, 1H, H_{aro}, J=8.6 Hz), 7.98 (d, 1H, H_{aro}, J=7.8 Hz), 8.15 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.0 (CH_2), 28.4 ($3CH_3$), 45.1 (CH_2), 67.0 (CH), 84.0 (C_q), 111.4 (CH_{aro}), 113.1 ($C_{q/aro}$), 118.8 (CH_{aro}), 120.1 (CH_{aro}), 121.8 ($C_{q/aro}$), 122.8 (CH_{aro}); 124.2 (CH_{aro}), 125.3 (CH_{aro}); 127.4 ($C_{q/aro}$), 128.5 (CH_{aro}); 131.2 ($C_{q/aro}$), 132.5 (CH_{aro}); 135.9 ($C_{q/aro}$), 137.6 ($C_{q/aro}$), 153.4 ($C{=}O_{carbamate}$), 164.8 ($C{=}O_{lactam}$); Anal. Calcd for $C_{23}H_{23}N_3O_3$ (389.45): C, 70.93; H, 5.95; N, 10.79. Found: C, 70.78; H, 5.69; N, 10.54.

4.3. General procedure for the synthesis of *N*-substituted tetrahydroindolo[2′,3′:3,4]pyrido[2,1-*b*]quinazolin-5-ones (3 and 7e)

The solution of 3,4-dihydro-β-carboline (**5**, 340 mg, 2 mmol) and *N*-methyl isatoic anhydride (**6d**, 355 mg, 2 mmol) (or *N*-benzyl isatoic anhydride **6e**, 506.5 mg, 2 mmol), prepared by N-alkylation of isatoic anhydride, in 10 mL of chloroform was refluxed for 8 h. After cooling of the reaction solution at room temperature then −10 °C, the precipitated formed was filtered off, dried and recrystallized from diethyl ether/ethyl acetate (3/2).

*4.3.1. N_{14}-Methyl-7,8,13,13b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-b]quinazolin-5-one (**3**).* This product was isolated as a rose solid in 79% yield: mp 268 °C (lit.[11b] 268–270 °C); R_f 0.50 (cyclohexane/AcOEt: 1/1); IR (KBr, cm^{-1}) ν: 3222 (NH), 1645 (C=O), 1628 (NH), 1509 (C=C), 1494 (C=C), 1449 (C=C), 1408 (CH), 1390 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.79–3.03 (m, 2H, $CH_{2\beta}$), 2.92 (s, 3H, CH_3), 3.17–3.29 (m, 1H, $1CH_{2\alpha}$–NCO), 4.67 (dd, 1H, $1CH_{2\alpha}$–NCO, J=13.2 and 3.5 Hz), 6.17 (s, 1H, CH), 6.96–7.19 (m, 4H, H_{aro}), 7.40 (d, 1H, H_{aro}, J=7.9 Hz), 7.48–7.55 (m, 2H, H_{aro}), 7.83 (d, 1H, H_{aro}, J=7.9 Hz), 11.12 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 19.5 (CH_2), 36.4 (CH_3), 40.8 (CH_2), 69.7 (CH), 111.5 ($C_{q/aro}$), 111.6 (CH_{aro}), 117.5 (CH_{aro}), 118.2 (CH_{aro}), 118.9 (CH_{aro}), 119.3 ($C_{q/aro}$), 120.3 (CH_{aro}), 121.8 (CH_{aro}), 125.9 ($C_{q/aro}$), 128.0 (CH_{aro}), 130.6 ($C_{q/aro}$), 133.4 (CH_{aro}), 136.5 ($C_{q/aro}$), 148.8 ($C_{q/aro}$), 164.2 (C=O); Anal. Calcd for $C_{19}H_{17}N_3O$ (303.36): C, 75.23; H, 5.65; N, 13.85. Found: C, 75.09; H, 5.42; N, 13.66.

*4.3.2. N_{14}-Benzyl-7,8,13,13b-tetrahydroindolo-[2′,3′:3,4]pyrido[2,1-b] quinazolin-5-one (**7e**).* This product was isolated as a white solid in 77% yield: mp 224 °C (Decomposition); R_f 0.57 (cyclohexane/AcOEt: 3/2); IR (cm^{-1}) ν: 3209 (NH), 1658 (C=O), 1619 (NH), 1512(C=C), 1489 (C=C), 1451 (C=C), 1412 (CH), 1395 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.20–2.97 (m, 2H, $CH_{2\beta}$), 3.20–3.30 (m, 1H, $1CH_{2\alpha}$–NCO), 4.04 (d, 1H, $1PhCH_2$–N, J=14.8 Hz), 4.27 (d, 1H, $1PhCH_2$–N, J=14.8 Hz), 4.81–4.88 (m, 1H, $1CH_{2\alpha}$–NCO), 6.06 (s, 1H, CH), 6.82 (d, 1H, H_{aro}, J=7.8 Hz), 7.02–7.45 (m, 9H, H_{aro}), 7.48 (t, 1H, H_{aro}, J=7.9 Hz), 7.55 (d, 1H, H_{aro}, J=7.8 Hz), 8.01 (br s, 1H, NH), 8.11 (dd, 1H, H_{aro}, J=7.8 and 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 19.2 (CH_2), 41.7 (CH_2–NCO), 52.7 (CH_2Ph), 70.1 (CH), 111.4 ($C_{q/aro}$), 111.6 (CH_{aro}), 117.1 (CH_{aro}), 118.1 (CH_{aro}), 118.8 (CH_{aro}), 119.7 (CH_{aro}), 121.8 (CH_{aro}), 126.2 ($C_{q/aro}$), 127.1 (CH_{aro} and $C_{q/aro}$), 127.5 ($2CH_{aro}$), 128.1 (CH_{aro}), 128.3 ($2CH_{aro}$), 131.5 ($C_{q/aro}$), 133.1 (CH_{aro}), 136.2 ($C_{q/aro}$), 138.2 ($C_{q/aro}$), 146.7 ($C_{q/aro}$), 164.7 (C=O); Anal. Calcd for $C_{25}H_{21}N_3O$ (379.45): C, 79.13; H, 5.58; N, 11.07. Found: C, 79.01; H, 5.38; N, 10.88.

4.4. The procedures for the oxidation reaction of *N*-substituted dihydrorutaecarpines 7a–c, 3 and 7e

Method A (O_2, *t*-BuOK, DMF). A mixture of *N*-substituted dihydrorutaecarpines (**7a**–**c**,**3** and **7e**, 1 mmol) and potassium *tert*-butanoate (KO*t*-Bu, 2.50 mmol, 2.5 equiv) in 5 mL of dry DMF at room temperature was stirred slowly under constant oxygen bubble for 2 h. After an additional stirring for 5 h, the reaction mixture was diluted with ethyl acetate (30 mL) and water (30 mL). The collected organic layers were washed with aqueous HCl (1 N) solution (50 mL) and brine (50 mL) and, then dried and concentrated under reduced pressure. Ultimately, the crude product **8** was

purified by silica gel column chromatography by using the mixture of EtOAc/cyclohexane as the eluent (See Table 1 for yields).

Method B (KO_2, 18-C-6, DMF). To a solution of *N*-substituted dihydrorutaecarpines (**7a**–**c**, **3** and **7e**, 1 mmol) and 18-crown-6 (264 mg, 1 mmol) in dry DMF (6 mL) was added potassium superoxide (KO_2, 284 mg, 4.00 mmol) in one portion at room temperature. The reaction mixture turned red and was stirred for 16 h at the same temperature. After the end of the reaction, the excess of KO_2 was consumed by adding several drops of water. The mixture was then extracted with ethyl acetate and decanted. The aqueous phase was extracted three times with ethyl acetate. The combined organic layer was washed with brine, dried over anhydrous $MgSO_4$, filtered and concentrated under reduced pressure to provide the crude product **8**, which was purified by silica gel column chromatography by using the mixture of EtOAc/cyclohexane as the eluent (See Table 1 for yields).

*4.4.1. 14-Phenyl-1,2-dihydroquinolino[2′,3′:3,4]-pyrrolo[2,1-b]quinazoline-5,8(13H)-dione (**8c**).* This product was isolated as a brown solid in yields of 52% (*Method A*) and 20% (*Method B*). Mp 200 °C (Decomposition); R_f 0.11 (cyclohexane/AcOEt: 0.5/9.5); IR (KBr, cm^{-1}) ν: 1662 (C=O), 1630 (C=O), 1592 (C=C), 1567 (C=C), 1410 (CH); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.48 (d, 1H, $1CH_{1\alpha}$, J=14.9 Hz), 4.55 (d, 1H, $1CH_{1\beta}$, J=14.9 Hz), 6.74 (s, 1H, CH), 7.03–7.27 (m, 6H, H_{aro}), 7.32–7.42 (m, 2H, H_{aro}), 7.59 (dd, 1H, H_{aro}, J=7.9 and 7.0 Hz), 7.69–7.75 (m, 2H, H_{aro}), 8.07 (d, 2H, H_{aro}, J=7.0 Hz), 12.8 (s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 47.0 (CH_2), 77.6 (CH), 115.7 ($C_{q/aro}$), 118.6 (CH_{aro}), 123.5 (CH_{aro}), 124.3 (CH_{aro}), 124.6 (CH_{aro}), 125.0 (CH_{aro}), 125.1 ($C_{q/aro}$), 126.6 ($C_{q/aro}$), 126.9 (CH_{aro}), 127.7 (CH_{aro}), 128.0 ($2CH_{aro}$), 129.0 ($2CH_{aro}$), 132.0 (CH_{aro}), 133.6 (CH_{aro}), 140.2 ($C_{q/aro}$), 143.3 ($C_{q/aro}$), 144.4 ($C_{q/aro}$), 148.3 ($C_{q/aro}$), 160.8 ($C{=}O_{lactam}$), 173.2 ($C{=}O_{ketone}$); Anal. Calcd for $C_{24}H_{17}N_3O_2$ (379.41): C, 75.97; H, 4.52; N, 11.08. Found: C, 75.76; H, 4.43; N, 10.90.

*4.4.2. 14-Methyl-1,2-dihydroquinolino[2′,3′:3,4]-pyrrolo[2,1-b]quinazoline-5,8(13H)-dione (**8d**).* This product was isolated as a white solid in yields of 48% (*Method A*) and 42% (*Method B*). Mp 240 °C (Decomposition); R_f 0.21 (cyclohexane/AcOEt: 0.5/9.5); IR (cm^{-1}) ν: 3100 (CH), 2924 (CH), 1649 (C=O), 1607 (NH), 1575 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.64 (s, 3H, CH_3), 4.56 (d, 1H, $1CH_{1\alpha}$, J=14.4 Hz), 4.73 (d, 1H, $1CH_{1\beta}$, J=14.4 Hz), 6.32 (s, 1H, CH), 7.29–7.48 (m, 3H, H_{aro}), 7.64 (dd, 1H, H_{aro}, J=7.4 and 7.1 Hz), 7.73–7.80 (m, 2H, H_{aro}), 7.95 (d, 1H, H_{aro}, J=7.4 Hz), 8.22 (d, 1H, H_{aro}, J=7.9 Hz), 12.78 (br s, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 37.3 (CH_3), 47.0 (CH_2), 76.7 (CH), 115.8 ($C_{q/aro}$), 118.9 (CH_{aro}), 123.5 (CH_{aro}), 124.4 (CH_{aro}), 124.7 (CH_{aro}), 125.1 ($C_{q\ aro}$), 127.5 ($2CH_{aro}$), 131.9 (CH_{aro}), 133.3 (CH_{aro}), 140.7 ($C_{q/aro}$), 144.0 ($C_{q/aro}$), 150.4 ($2C_{q/aro}$), 160.3 ($C{=}O_{lactam}$), 173.3 ($C{=}O_{ketone}$); Anal. Calcd for $C_{19}H_{15}N_3O_2$ (317.34): C, 71.91; H, 4.76; N, 13.24. Found: C, 71.77; H, 4.59; N, 13.05.

*4.4.3. 14-Benzyl-1,2-dihydroquinolino[2′,3′:3,4]-pyrrolo[2,1-b]quinazoline-5,8(13H)-dione (**8e**).* This product was isolated as a white-yellow solid in yields of 58% (*Method A*) and 55% (*Method B*): mp 202 °C (Decomposition); R_f 0.27 (cyclohexane/AcOEt: 1/9); IR (cm^{-1}) ν: 3089 (CH), 2936 (CH), 16,454 (C=O), 1600 (NH), 1566 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ (ppm) 3.41 (br s, 1H, NH), 3.92 (d, 1H, $1CH_{2\alpha}$–Ph, J=14.1 Hz), 4.18 (dd, 1H, $1CH_{1\alpha}$–N, J=14.4 and 3.3 Hz), 4.32 (d, 1H, $1CH_{1\beta}$–N, J=14.4 Hz), 4.43 (d, 1H, $1CH_{2\alpha}$–Ph, J=14.1 Hz), 6.38 (d, 1H, CH, J=3.3 Hz), 6.71–6.75 (m, 2H, H_{aro}), 7.01–7.15 (m, 3H, H_{aro}), 7.23 (d, 1H, H_{aro}, J=7.2 Hz), 7.30 (t, 1H, H_{aro}, J=6.8 Hz), 7.37–7.42 (m, 1H, H_{aro}), 7.51 (t, 1H, H_{aro}, J=8.6 Hz), 7.65–7.76 (m, 2H, H_{aro}), 7.87 (d, 1H, H_{aro}, J=7.8 Hz), 8.18 (d, 1H, H_{aro}, J=8.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 46.6 (CH_2–NCO), 53.9 (CH_2Ph), 76.3 (CH), 115.7 ($C_{q/aro}$), 119.6 (CH_{aro}), 122.9 (CH_{aro}), 123.7 (CH_{aro}), 124.0 (CH_{aro}), 124.6 (CH_{aro}), 125.0 ($C_{q/aro}$), 125.5 ($C_{q/aro}$), 127.0 (CH_{aro}), 127.5 (CH_{aro}), 127.8 ($2CH_{aro}$), 128.1 ($2CH_{aro}$), 131.8 (CH_{aro}), 132.9 (CH_{aro}), 136.7 ($C_{q/aro}$), 141.9 ($C_{q/aro}$), 145.2 ($C_{q/aro}$), 148.3 ($C_{q/aro}$), 160.6 ($C{=}O_{lactam}$), 173.5 ($C{=}O_{ketone}$); Anal. Calcd for $C_{25}H_{19}N_3O_2$ (393.44): C, 76.32; H, 4.87; N, 10.68. Found: C, 76.18; H, 4.64; N, 10.49.

4.5. Procedure for the esterification reaction of *N*-substituted-quinolines 8c,d. formation of the pentacyclic acetates 14a,b

To a suspension mixture of *N*-substituted-quinoline (**8c** or **8d**, 1 mmol) dissolved in 15 mL of dry dichloromethane was added successively dry triethylamine (280 μL, 2 mmol, 2 equiv), acetic anhydride (188 μL, 2 mmol, 2 equiv) and catalytic amounts of 4-dimethylaminopyridine (DMAP, 12 mg, 0.1 mmol, 0.1 equiv). After stirring at room temperature for 12 h, a cold saturated solution of $NaHCO_3$ (15 mL) was added to the reaction mixture. The organic layers separated were combined, washed with brine, dried over anhydrous $MgSO_4$ and evaporated under reduced pressure. The residue was ultimately purified by silica gel column chromatography by using the mixture of cyclohexane/AcOEt as the eluent to provide the expected ester derivatives **14**.

*4.5.1. 8-Acetyloxy-14-phenyl-1,2-dihydroquinolino-[2′,3′:3,4]pyrrolo [2,1-b]quinazolin-5-one (**14a**).* This product was isolated as an orange oil in 51% yield; R_f 0.48 (cyclohexane/AcOEt: 3/2); IR (neat, cm^{-1}) ν: 1777 (C=O), 1651 (C=O), 1607 (C=N), 1491 (C=C), 1473 (C=C), 1434 (CH); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.47 (s, 3H, OAc), 4.82 (d, 1H, $1CH_{1\alpha}$, J=16.4 Hz), 5.03 (dd, 1H, $1CH_{1\beta}$, J=16,4 Hz and 1.6 Hz), 6.53 (s, 1H, CH), 6.73 (d, 1H, H_{aro}, J=8.6 Hz), 7.09 (dd, 1H, H_{aro}, J=7.8 and 7.0 Hz), 7.17–7.38 (m, 6H, H_{aro}), 7.54 (ddd, 1H, H_{quino}, J=7.8, 7.0 and 1.6 Hz), 7.66 (ddd, 1H, H_{quino}, J=8.6, 7.0 and 1.6 Hz), 7.83 (d, 1H, H_{quino}, J=8.6 Hz), 7.86 (d, 1H, H_{aro}, J=7.8 Hz), 8.11 (dd, 1H, H_{quino}, J=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.8 (CH_3), 46.7 (CH_2), 76.7 (CH), 120.0 (CH_{aro}), 120.8 ($C_{q/aro}$), 121.1 (CH_{aro}), 122.1 ($C_{q/aro}$), 122.2 ($C_{q/aro}$), 122.3 (CH_{aro}), 127.3 (CH_{aro}), 127.8 (CH_{aro}), 128.5 (CH_{aro}), 129.2 ($2CH_{aro}$), 129.9 (CH_{aro}), 130.1 ($2CH_{aro}$), 130.3 (CH_{aro}), 133.8 (CH_{aro}), 142.8 ($C_{q/aro}$), 149.5 ($C_{q/aro}$), 149.6 ($C_{q/aro}$), 150.0 ($C_{q/aro}$), 157.7 (C=N), 162.8 ($C{=}O_{lactam}$), 167.0 ($C{=}O_{ester}$); Anal. Calcd for $C_{26}H_{19}N_3O_3$ (421.45): C, 74.10; H, 4.54; N, 9.97. Found: C, 74.00; H, 4.39; N, 9.80.

*4.5.2. 8-Acetyloxy-14-methyl-1,2-dihydroquinolino-[2′,3′:3,4]pyrrolo [2,1-b]quinazolin-5-one (**14b**).* This product was isolated as an orange solid in 61% yield; Mp 182 °C (Decomposition); R_f 0.50 (cyclohexane/AcOEt: 2/3); IR (KBr, cm^{-1}) ν: 1778 (C=O), 1653 (C=O), 1608 (C=N), 1480 (C=C), 1442 (CH); ^{1}H NMR (300 MHz, $CDCl_3$): δ (ppm) 2.50 (s, 3H, OAc), 3.21 (s, 3H, NMe), 4.79 (d, 1H, $1CH_{1\alpha}$, J=16.4 Hz), 5.10 (d, 1H, $1CH_{1\beta}$, J=16.4 Hz), 5.97 (s, 1H, CH), 7.02–7.10 (m, 1H, H_{aro}), 7.07 (d, 1H, H_{aro}, J=7.8 Hz), 7.44–7.53 (m, 1H, H_{aro}), 7.62 (dd, 1H, H_{quino}, J=7.8 Hz and 7.0 Hz), 7.82 (dd, 1H, H_{quino}, J=7.8 and 7.0 Hz), 7.95 (d, 1H, H_{quino}, J=7.8 Hz), 8.04 (dd, 1H, H_{quino}, J=7.8 and 1.6 Hz), 8.21 (d, 1H, H_{aro}, J=8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 20.8 (CH_3), 34.2 (NCH_3), 46.5 (CH_2), 75.9 (CH), 116.8 (CH_{aro}), 120.6 ($C_{q/aro}$), 121.0 ($C_{q/aro}$), 121.3 (CH_{aro}), 121.4 (CH_{aro}), 122.4 ($C_{q/aro}$), 128.0 (CH_{aro}), 128.5 (CH_{aro}), 130.0 (CH_{aro}), 130.6 (CH_{aro}), 134.0 (CH_{aro}), 149.9 ($C_{q/aro}$), 150.2 ($C_{q/aro}$), 150.6 ($C_{q/aro}$), 159.0 (C=N), 162.5 ($C{=}O_{lactam}$), 167.1 ($C{=}O_{ester}$); Anal. Calcd for $C_{21}H_{17}N_3O_3$ (359.38): C, 70.18; H, 4.77; N, 11.69. Found: C, 70.03; H, 4.49; N, 11.52.

4.6. Procedure for the chlorination reaction of *N*-substituted-quinolines 8c,d. Formation of the pentacyclic halides 15a,b

To a suspension mixture of *N*-substituted-quinoline (**8c** or **8d**, 1 mmol) dissolved in 10 mL of dry *N*,*N*-dimethylformamide was added at 0 °C, was added under stirring dropwise thionyl chloride (725 μL, 10.0 mmol, 10 equiv). The reaction mixture was then

stirred for an additional 2 h at room temperature and hydrolyzed by adding slowly a saturated solution of $NaHCO_3$. The reaction mixture was extracted twice with ethyl acetate and the combined organic layers were washed with water, brine and decanted. The organic phase was dried over $MgSO_4$ and evaporated under reduced pressure. The residue was purified by silica gel column chromatography by using the mixture of cyclohexane/AcOEt as the eluent to provide the expected halides **15**.

*4.6.1. 8-Chloro-14-phenyl-1,2-dihydroquinolino-[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-5-one (**15a**).* This product was isolated as a yellow solid in 67% yield; mp 190 °C (Decomposition); R_f 0.67 (cyclohexane/AcOEt: 7/3); IR (KBr, cm^{-1}) ν: 1654 (C=O), 1607 (C=N), 1562 (C=C), 1488 (C=C), 1434 (CH), 1385 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 4.97 (d, 1H, $1CH_{1\alpha}$, J=17.2 Hz), 5.16 (d, 1H, $1CH_{1\beta}$, J=17.2 Hz), 6.55 (s, 1H, CH), 6.74 (d, 1H, H_{aro}, J=8.6 Hz), 7.08–7.28 (m, 6H, H_{aro}), 7.32–7.41 (m, 1H, H_{aro}), 7.59–7.75 (m, 2H, H_{quino}), 7.85 (d, 1H, H_{aro}, J=7.8 Hz), 8.13 (d, 1H, H_{quino}, J=7.8 Hz), 8.17 (d, 1H, H_{quino}, J=7.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 48.1 (C_1), 77.4 (C_2), 120.2 (CH_{aro}), 122.4 ($C_{q/aro}$), 122.5 (CH_{aro}), 123.7 (CH_{aro}), 125.9 ($C_{q/aro}$), 127.3 (CH_{aro}), 128.0 ($C_{q/aro}$), 128.4 (CH_{aro}), 128.5 (CH_{aro}), 129.3 ($2CH_{aro}$), 130.1 ($2CH_{aro}$), 130.2 (CH_{aro}), 130.5 (CH_{aro}), 133.8 (CH_{aro}), 137.9 ($C_{q/aro}$), 142.9 ($C_{q/aro}$), 149.0 ($C_{q/aro}$), 149.6 ($C_{q/aro}$), 156.1 (C=N), 162.8 (C=O); Anal. Calcd for $C_{24}H_{16}ClN_3O$ (397.86): C, 72.45; H, 4.05; N, 10.56. Found: C, 72.18; H, 3.86; N, 10.37.

*4.6.2. 8-Chloro-14-methyl-1,2-dihydroquinolino-[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-5-one (**15b**).* This product was isolated as a yellow solid in 72% yield; mp 189 °C (Decomposition); R_f 0.31 (cyclohexane/AcOEt: 4/1); IR (KBr, cm^{-1}) ν: 1654 (C=O), 1608 (C=N), 1561 (C=C), 1479 (C=C), 1441 (CH), 1370 and 1387 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.20 (s, 3H, CH_3), 4.92 (d, 1H, $1CH_{1\alpha}$, J=17.2 Hz), 5.25 (d, 1H, $1CH_{1\beta}$, J=17.2 Hz), 5.98 (s, 1H, CH), 7.03–7.11 (m, 1H, H_{aro}), 7.08 (d, 1H, H_{aro}, J=7.8 Hz), 7.50 (ddd, 1H, H_{aro}, J=8.6, 7.0 and 1.6 Hz), 7.71 (ddd, 1H, H_{quino}, J=7.8, 7.0 and 1.6 Hz), 7.81 (dd, 1H, H_{quino}, J=8.6 and 7.0 Hz), 8.07 (dd, 1H, H_{aro}, J=7.0 and 1.6 Hz), 8.19–8.24 (m, 1H, H_{quino}), 8.26 (d, 1H, H_{quino}, J=8.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 34.2 (CH_3), 48.0 (CH_2), 76.5 (CH), 116.8 (CH_{aro}), 120.7 ($C_{q/aro}$), 121.6 (CH_{aro}), 123.8 (CH_{aro}), 126.1 ($C_{q/aro}$), 128.2 ($C_{q/aro}$), 128.6 ($2CH_{aro}$), 130.3 (CH_{aro}), 130.8 (CH_{aro}), 134.1 (CH_{aro}), 138.4 ($C_{q/aro}$), 149.2 ($C_{q/aro}$), 150.6 ($C_{q/aro}$), 157.4 (C=N), 162.5 (C=O); Anal. Calcd for $C_{19}H_{14}ClN_3O$ (335.79): C, 67.96; H, 4.20; N, 12.51. Found: C, 67.79; H, 4.06; N, 12.35.

4.7. Procedure for amination of *N*-substituted chloroquinolines 8c,d. formation of the pentacyclic amines 16a,b

A mixture of pentacyclic halide **15** (0.5 mmol) and morpholine (440 μL, 5.0 mmol, 10 equiv) in dry toluene (5 mL) was heated at reflux under stirring. After 48 h of the reaction the mixture was evaporated under reduced pressure. The residue was taken up into ethyl acetate and the organic solution was washed with saturated solution of NH_4Cl, water, brine, dried over anhydrous $MgSO_4$ and filtered. The organic solution was evaporated under reduced pressure and the residue was purified by column chromatography using the mixture of cyclohexane/AcOEt as the eluent to afford the expected pentacyclic tertiary amines **16a**,**b**.

*4.7.1. 8-Morpholino-14-phenyl-1,2-dihydroquinol-ino[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-5-one (**16a**).* This product was isolated as a viscous yellow oil in 42% yield; R_f 0.32 (cyclohexane/AcOEt: 3/2); IR (neat, cm^{-1}) ν: 2987 (CH), 2889 (CH), 2855 (CH), 1679 (C=O), 1607 (C=N), 1487 (C=C), 1467 (C=C), 1430 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.20–3.28 (m, 2H, $2NCH_{\alpha,\beta}$–CH_2O), 3.31–3.38 (m, 2H, $2NCH_{\alpha,\beta}$–CH_2O), 3.87–3.95 (m, 4H, $2NCH_{\alpha,\beta}$–CH_2O), 5.04 (d, 1H, $1CH_{1\alpha}$–N, J=15.4 Hz), 5.25 (dd, 1H, $1CH_{1\beta}$–N, J=15.4 and 1.6 Hz), 6.40 (s, 1H, CH), 6.77 (d, 1H, H_{aro}, J=8.3 Hz), 7.09–7.18 (m, 6H, H_{aro}), 7.32–7.38 (m, 1H, H_{aro}), 7.47 (dd, 1H, H_{aro}, J=7.2 and 6.8 Hz), 7.60 (t, 1H, H_{aro}, J=7.2 Hz), 7.79 (d, 1H, H_{aro}, J=8.3 Hz), 8.02 (d, 1H, H_{aro}, J=7.9 Hz), 8.12 (dd, 1H, H_{aro}, J=7.9 and 1.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 48.2 (CH_2N), 51.9 ($2NCH_2$–CH_2O), 67.5 ($2NCH_2$–CH_2O), 76.2 (CH), 119.3 ($C_{q/aro}$), 120.6 (CH_{aro}), 122.5 (CH_{aro}), 122.8 ($C_{q/aro}$), 124.1 ($C_{q/aro}$), 124.2 (CH_{aro}), 124.3 ($C_{q/aro}$), 126.6 (CH_{aro}), 127.0 (CH_{aro}), 128.4 (CH_{aro}), 129.1 ($2CH_{aro}$), 129.6 (CH_{aro}), 130.0 ($2CH_{aro}$), 130.2 (CH_{aro}), 133.7 (CH_{aro}), 143.3 ($2C_{q/aro}$), 149.7 ($C_{q/aro}$), 157.3 (C=N), 162.6 (C=O); Anal. Calcd for $C_{28}H_{24}N_4O_2$ (448.62): C, 74.98; H, 5.39; N, 12.49. Found: C, 74.69; H, 5.10; N, 12.25.

*4.7.2. 8-Morpholino-14-methyl-1,2-dihydroquinol-ino[2′,3′:3,4]pyrrolo[2,1-b]quinazolin-5-one (**16b**).* This product was isolated as a yellow solid in 44% yield; mp 170 °C (Decomposition); R_f 0.37 (cyclohexane/AcOEt: 1/1); IR (KBr, cm^{-1}) ν: 2971 (CH), 2894 (CH), 2859 (CH), 1651 (C=O), 1607 (C=N), 1571 (C=C), 1479 (CH), 1378, 1364 (CH); ^1H NMR (300 MHz, $CDCl_3$): δ (ppm) 3.16 (s, 3H, NMe), 3.32–3.39 (m, 4H, $2NCH_2$–CH_2O), 3.92–4.01 (m, 4H, $2NCH_2$–CH_2O), 5.01 (d, 1H, $1CH_{1\alpha}$–N, J=15.7 Hz), 5.37 (d, 1H, $1CH_{1\beta}$–N, J=15.7 Hz), 5.84 (s, 1H, CH), 7.03–7.11 (m, 2H, H_{aro}), 7.48 (td, 1H, H_{aro}, J=7.3 and 1.1 Hz), 7.55 (t, 1H, H_{aro}, J=7.8 Hz), 7.70 (dd, 1H, H_{aro}, J=8.1 and 7.3 Hz), 8.04 (dd, 1H, H_{aro}, J=7.7 Hz), 8.13 (d, 2H, H_{aro}, J=8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ (ppm) 34.3 (CH_3), 48.0 (CH_2N), 51.9 ($2NCH_2$–CH_2O), 67.5 ($2NCH_2$–CH_2O), 74.1 (CH), 117.2 (CH_{aro}), 119.4 ($C_{q/aro}$), 121.0 ($C_{q/aro}$), 121.5 (CH_{aro}), 124.2 ($C_{q/aro}$), 124.3 (CH_{aro}), 126.8 (CH_{aro}), 128.5 (CH_{aro}), 129.9 (CH_{aro}), 130.2 (CH_{aro}), 134.0 (CH_{aro}), 149.8 ($C_{q/aro}$), 150.8 ($C_{q/aro}$), 151.9 ($C_{q/aro}$), 158.6 (C=N), 162.6 (C=O); Anal. Calcd for $C_{23}H_{22}N_4O_2$ (486.45): C, 71.48; H, 5.74; N, 14.50. Found: C, 71.422; H, 5.59; N, 14.17.

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