

Article

# Novel Approach to the Construction of Fused Indolizine Scaffolds: Synthesis of Rosettacin and the Aromathecin Family of Compounds

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**Abstract:** Camptothecin-like compounds are actively employed as anticancer drugs in clinical treatments. The aromathecin family of compounds, which contains the same indazolizidine core structure as the camptothecin family of compounds, is also expected to display promising anticancer activity. Therefore, the development of a suitable and scalable synthetic method of aromathecin synthesis is of great research interest. In this study, we report the development of a new synthetic approach for constructing the pentacyclic scaffold of the aromathecin family by forming the indolizidine moiety after synthesizing the isoquinolone moiety. Thermal cyclization of 2-alkynylbenzaldehyde oxime to the isoquinoline *N*-oxide, followed by a Reissert–Henze-type reaction, forms the key strategy in this isoquinolone synthesis. Under the optimum reaction conditions for the Reissert–Henze-type reaction step, microwave irradiation-assisted heating of the purified *N*-oxide in acetic anhydride at 50 °C reduced the formation of the 4-acetoxyisoquinoline byproduct to deliver the desired isoquinolone at a 73% yield after just 3.5 h. The eight-step sequence employed afforded rosettacin (simplest member of the aromathecin family) at a 23.8% overall yield. The synthesis of rosettacin analogs was achieved by applying the developed strategy and may be generally applicable to the production of other fused indolizidine compounds.

**Keywords:** acuminatine; 22-hydroxyacuminatine; benz[6,7]indolizino[1,2-*b*]quinolin-11(13*H*)-one; total synthesis; thermal cyclization



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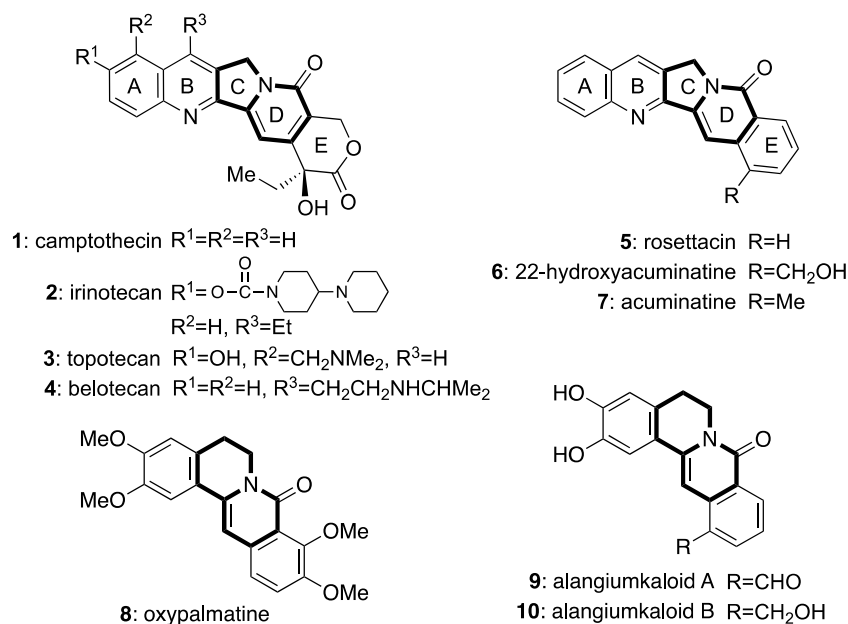


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## 1. Introduction

The indolizidine and quinolizidine moieties are important core structures that can be found in several biologically active compounds, such as camptothecin (**1**) [1], rosettacin (**5**) [2], and the 8-oxoprotoberberine alkaloids **8–10** [3,4] (Figure 1). The study of indolizidine- or quinolizidine-containing compounds has attracted the interest of many research groups because these compounds exhibit antitumor activity. Among such compounds, camptothecin (**1**) was isolated by Wani and co-workers in 1966 from the Chinese tree *Camptotheca acuminata* [1]. This alkaloid was shown to potently inhibit tumor growth by binding to the topoisomerase I enzyme (Top1). Subsequently, drug development studies were conducted with **1** as the lead compound. As a result, irinotecan (**2**) [5], topotecan (**3**) [6], and belotecan (**4**) [7], all compounds bearing substituents on the AB-ring, were developed for use in clinical studies. However, hydrolysis of the E-ring lactone moiety produces hydroxycarboxylates with a high affinity for human serum albumin protein; thus, the E-ring lactone hydrolysis product is responsible for attenuating the activity of **1** derivatives [8].

To address this drawback, the development novel anticancer drugs has focused on the aromathecins family of compounds (benz[6,7]indolizino[1,2-*b*]quinolin-11(13*H*)-ones), in which the lactone moiety of **1** is replaced with a benzene ring.

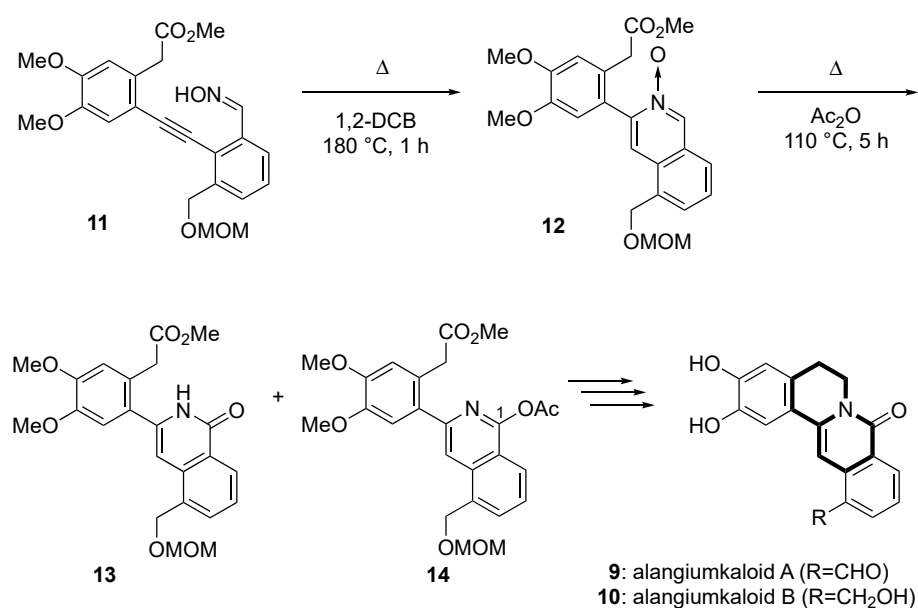


**Figure 1.** Structures of natural products containing the indolizino or quinolizino scaffold [1–7,9,10].

To date, three members of the aromathecins family are known: rosettacin (**5**), 22-hydroxyacuminatine (**6**) [6], and acuminatine (**7**) [7]. Together with **1**, **6** has been isolated at a very low yield from the seeds of *C. accuminata* [6]. Moreover, rosettacin, its derivatives, and **6** have been reported to display weak Top1 inhibitory activity [11–16]. Therefore, aromathecins can be considered as a new class of Top1 inhibitors which can replace camptothecins as candidates for therapeutic development. To date, many approaches have been reported for the synthesis of aromathecins. These routes primarily focus on a late-stage indolizidine moiety construction by either C- or D-ring formation [15,17–26]. Indeed, several synthetic procedures have been developed in recent years which enable the facile production of aromathecins. Eycken and co-workers reported the total synthesis of **5** via three synthetic strategies [17–19]. The first approach is based on using an intramolecular cascade annulation of *O*-substituted *N*-hydroxybenzamides, triggered by Rh(III)-catalyzed sequential C(sp<sup>2</sup>)-H activation and C(sp<sup>3</sup>)-H amination, for the synthesis of indolizinoquinolones [17]. The next method involves the intermolecular annulation of 2-acetylenic aldehydes with *O*-substituted *N*-hydroxybenzamides through Rh(III)-catalyzed C–H activation for the synthesis of indolizinoquinolones [18]. The third route comprised the construction of indolizinoquinolones by an intramolecular cascade annulation triggered by C–H activation via rhodium hydride intermediate [19]. Huang and co-workers reported the synthesis of **5** via the construction of isoquinolone using carbene-catalyzed aerobic oxidation of isoquinolinium salts, followed by a Pd-catalyzed intramolecular cyclization [20]. Reddy and co-workers developed the synthesis of **5** by a one-pot method for the synthesis of 7-hydroxyisoindolo[2,1-*b*]isoquinolin-5(7*H*)-ones from *N*-(pivaloyloxy)benzamides and 2-alkynyl aldehydes via Rh(III)-catalyzed C–H functionalization [21]. Furthermore, Evano and co-workers developed a method to assemble the indolizinoquinolone moiety by copper-catalyzed photoinduced radical domino cyclization of ynamides and applied this method to the synthesis of **5** [22]. Glorius and co-workers reported the synthesis of **5** and its derivatives via the construction of isoquinolones by the intramolecular annulation of a Cp\*Co<sup>III</sup>-catalyzed C–H activation approach for *N*-(pent-4-yn-1-yloxy)benzamide production as the key step [23].

Our research group has been interested in the unique structure and pharmacological action of condensed heteroaromatic compounds and we have been searching for highly active compounds based on these naturally occurring compounds and their derivatives. To date, we have achieved the total synthesis of several such compounds using various types of  $6\pi$ -electron system (hexatriene, 1- and 2-azahexatriene) electrocyclic reactions, such as asiaticumine [27], marinoquinolines [28], trigonoine B [29], girinimbine [30], and karnatakafuran B [31]. We have also published the total synthesis of (*R*)-(-)-pyridindolols using another synthetic approach that involved thermal cyclization of 3-alkynylindole-2-aldoxime to construct the key  $\beta$ -carboline *N*-oxide intermediate [32,33].

Recently, we developed a versatile synthetic route to produce 8-oxoprotoberberine alkaloids (alangiunkaloids A (9) and B (10)) through the synthesis of isoquinolone and via B-ring construction [34] (Scheme 1). The key step in this was the synthesis of isoquinolone 13 through the thermal cyclization of 2-alkynylbenzaldehyde oxime 11 to afford isoquinoline *N*-oxide 12, followed by a Reissert–Henze-type reaction. The lithium aluminum hydride ( $\text{LiAlH}_4$ ) reduction of both the obtained isoquinolone 13 and 1-acetoxyisoquinoline 14, followed by quinolizidine ring construction (B-ring formation), completed the first total synthesis of alangiunkaloids 9 and 10. Employing this strategy, we also synthesized a series of alangiunkaloid analogs and are currently conducting exploratory antitumor activity research into these compounds.

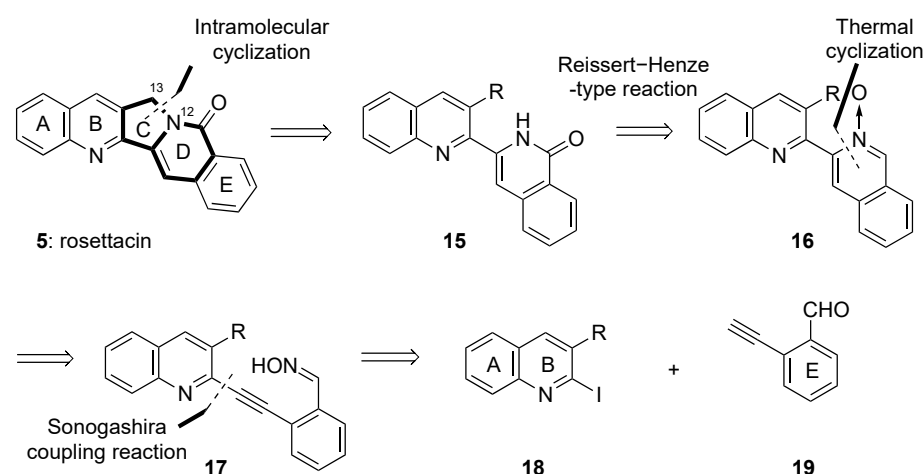


**Scheme 1.** Key synthetic transformations for the synthesis of alangiunkaloids A and B.

In this paper, we report on the synthesis of rosettacin (5) and its derivatives, a feat achieved by applying the synthetic strategies from our previous work to construction of a benz[6,7]indolizino[1,2-*b*]quinolin-11(13*H*)-one scaffold.

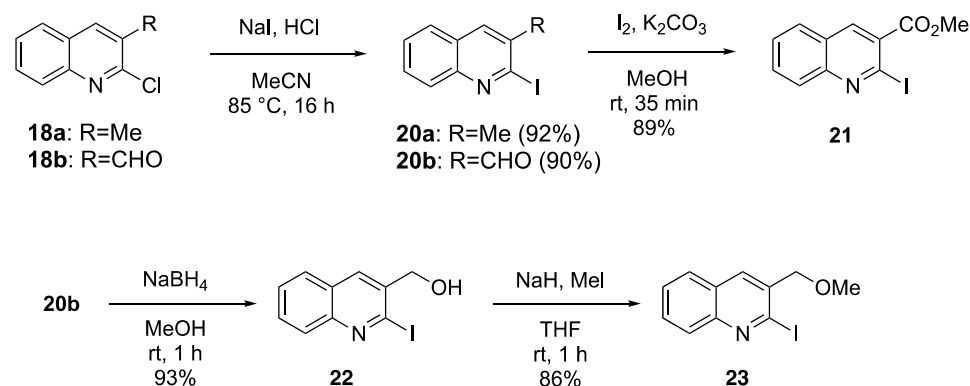
## 2. Results and Discussion

Our retrosynthetic analysis of 5 is presented in Scheme 2. The rosettacin scaffold can be synthesized by late-stage construction of the indolizine ring (CD-ring) moiety through bond formation between C13 and N12. The precursor isoquinolone 15 (DE-ring) can be obtained from a Reissert–Henze-type reaction of isoquinoline *N*-oxide 16, which can be formed from the thermal cyclization of 2-alkynylbenzaldehyde oxime 17. We envisioned that 17 could be synthesized from the Sonogashira reaction between 2-iodoquinoline 18 and 2-ethynylbenzaldehyde 19. The advantage of this synthetic strategy was that it allowed for easy access to rosettacin analogs by derivatizing both the starting quinolines and 2-ethynylbenzaldehydes.



**Scheme 2.** Retrosynthetic analysis of rosettacin (**5**).

We began the synthesis of three quinolines (AB-ring) in possession of the necessary substitutions, as shown in Scheme 3. The starting materials, 2-chloroquinolines **18a** and **18b**, were synthesized from acetanilide according to the method of Bhuyan and co-workers [35]. Subsequently, 2-chloroquinolines **18a** and **18b** were heated with NaI and concentrated HCl in acetonitrile (MeCN) to obtain 2-iodoquinolines **20a** and **20b** at 92% and 90% yields, respectively [36]. Treatment of **20b** with iodine and  $K_2CO_3$  in methanol (MeOH) provided methyl ester **21** at an 89% yield. Alternatively, the reduction of **20b** with  $NaBH_4$  followed by hydroxy group methylation provided 3-methoxymethylquinoline **23** at an 80% yield over 2 steps.

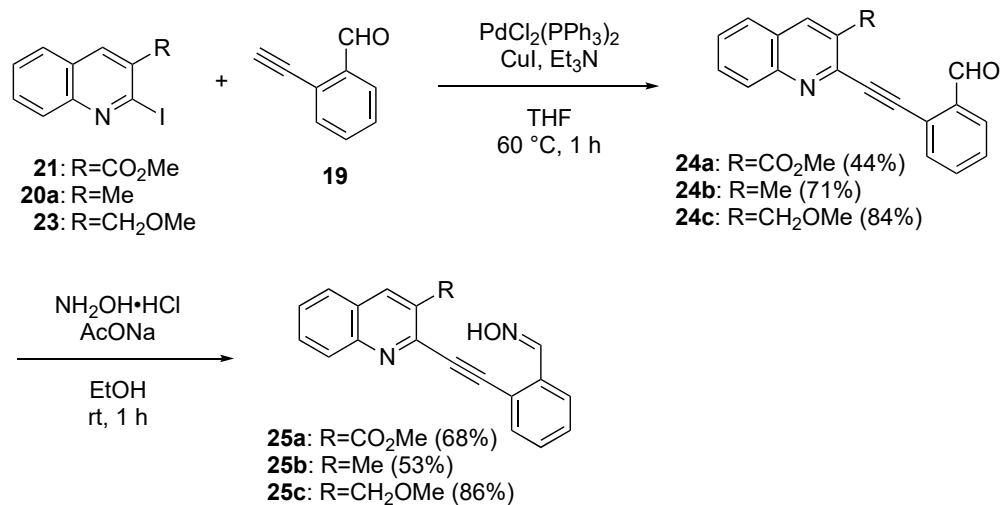


**Scheme 3.** Synthesis of 3-substituted 2-iodoquinolines **20a**, **21**, and **23**.

Next, we prepared the key isoquinolone synthesis precursors: 2-alkynylbenzaldehyde oximes **25** (Scheme 4). The Sonogashira reaction of 2-iodoquinolines **21**, **20a**, and **23** with 2-ethynylbenzaldehyde **19** in the presence of CuI, triethylamine ( $Et_3N$ ) and bis(triphenylphosphine) palladium(II) chloride ( $PdCl_2(PPh_3)_2$ ) provided 2-alkynylbenzaldehydes **24a**, **24b**, and **24c** at 44%, 71%, and 84% yields, respectively. The treatment of **24a–c** with hydroxylamine produced oximes **25a–c** at 68%, 53%, and 86% yields, respectively.

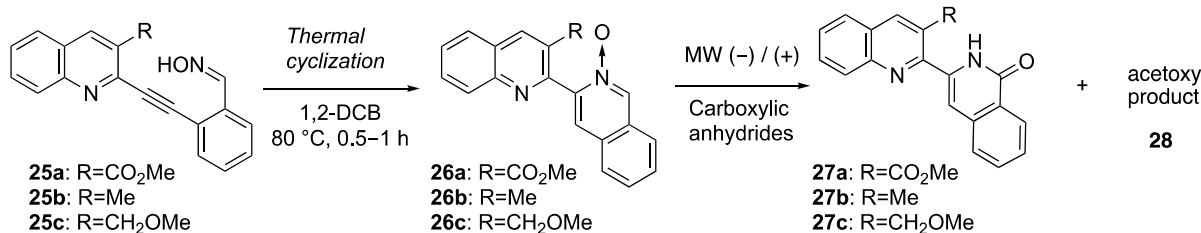
As shown in Table 1, we next investigated the synthesis of isoquinolone **27** via the construction of isoquinoline *N*-oxide **26** from oxime **25**. First, oxime **25a** was heated in 1,2-dichlorobenzene (1,2-DCB) at 180 °C until the starting material was no longer detectable by thin-layer chromatography (TLC) analysis. The reaction was quenched by the evaporation of 1,2-DCB in vacuo to obtain *N*-oxide **26**. Subsequently, without further purification, the crude *N*-oxide **26a** was heated in acetic anhydride ( $Ac_2O$ ) at 110 °C. Disappointingly, the desired isoquinolone **27a** was not obtained and an unidentifiable mixture of compounds was produced (entry 1). Reducing the cyclization temperature to 80 °C, the thermal cyclization of **25a** proceeded smoothly; however, the subsequent heating of the resulting

crude **26a** in Ac<sub>2</sub>O at 110 °C also did not afford isoquinoline **27a** (entry 2). Therefore, compounds containing an ester functional group were deemed to be unsuitable for the Reissert–Henze-type reaction and studies of oxime **25a** ceased.



**Scheme 4.** Synthesis of key isoquinolone precursor 2-alkynylbenzaldehyde oxime **25**.

**Table 1.** Optimization studies for the thermal cyclization synthesis of isoquinolone **27** starting from 2-alkynylbenzaldehyde oxime **25**.



| Entry            | Starting Material |                     | Method <sup>(1)</sup> | Carboxylic Anhydride                   | MW <sup>(2)</sup> | Temp. (°C) | Time (h) | Yield (%) |    |    |
|------------------|-------------------|---------------------|-----------------------|--|-------------------|------------|----------|-----------|----|----|
|                  | No.               | R                   |                       |  |                   |            |          | No.       | 27 | 28 |
| 1 <sup>(3)</sup> | <b>25a</b>        | CO <sub>2</sub> Me  | A                     | Ac <sub>2</sub> O                      | –                 | 110        | 2        | <b>a</b>  | –  | –  |
| 2                | <b>25a</b>        | CO <sub>2</sub> Me  | A                     | Ac <sub>2</sub> O                      | –                 | 110        | 1.5      | <b>a</b>  | –  | –  |
| 3                | <b>25b</b>        | Me                  | A                     | Ac <sub>2</sub> O                      | –                 | 110        | 3        | <b>b</b>  | 6  | 33 |
| 4                | <b>25c</b>        | CH <sub>2</sub> OMe | A                     | Ac <sub>2</sub> O                      | –                 | 110        | 3        | <b>c</b>  | 22 | 40 |
| 5                | <b>25c</b>        | CH <sub>2</sub> OMe | B                     | Ac <sub>2</sub> O                      | –                 | 110        | 2        | <b>c</b>  | 31 | 43 |
| 6                | <b>25c</b>        | CH <sub>2</sub> OMe | A                     | Ac <sub>2</sub> O                      | –                 | 50         | 24       | <b>c</b>  | 48 | 27 |
| 7                | <b>25c</b>        | CH <sub>2</sub> OMe | B                     | Ac <sub>2</sub> O                      | –                 | 50         | 41       | <b>c</b>  | 41 | 33 |
| 8                | <b>25c</b>        | CH <sub>2</sub> OMe | B                     | Ac <sub>2</sub> O                      | –                 | rt         | 51       | <b>c</b>  | 60 | 18 |
| 9                | <b>25c</b>        | CH <sub>2</sub> OMe | B                     | Ac <sub>2</sub> O                      | +                 | 110        | 2        | <b>c</b>  | 20 | 29 |
| 10               | <b>25c</b>        | CH <sub>2</sub> OMe | A                     | Ac <sub>2</sub> O                      | +                 | 50         | 14       | <b>c</b>  | 39 | 15 |
| 11               | <b>25c</b>        | CH <sub>2</sub> OMe | B                     | Ac <sub>2</sub> O                      | +                 | 50         | 3.5      | <b>c</b>  | 73 | 21 |
| 12               | <b>25c</b>        | CH <sub>2</sub> OMe | A                     | (CF <sub>3</sub> CO) <sub>2</sub> O    | –                 | rt         | 1        | <b>c</b>  | 14 | –  |
| 13               | <b>25c</b>        | CH <sub>2</sub> OMe | A                     | Ac <sub>2</sub> O, PTSA <sup>(4)</sup> | –                 | 50         | 39       | <b>c</b>  | 28 | 10 |

<sup>(1)</sup> Solutions of 2-alkynylbenzaldehyde oxime **25** in 1,2-dichlorobenzene (1,2-DCB) were heated at 80 °C until the starting material was no longer detectable by thin-layer chromatography (TLC) analysis. The reaction was quenched by evaporation of the solvent under reduced pressure. **Method A:** The obtained crude *N*-oxide **26** was used for the next reaction without further purification. The appropriate carboxylic anhydride was added to crude *N*-oxide **26** and heated to the desired study temperature. **Method B:** The obtained *N*-oxide **26** was purified by recrystallization (73% yield). Recrystallized *N*-oxide **26** was added to the appropriate carboxylic anhydride and heated to the desired study temperature. <sup>(2)</sup> MW: microwave; <sup>(3)</sup> the thermal cyclization of oxime **25a** was carried out at 180 °C; <sup>(4)</sup> PTSA: *p*-toluenesulfonic acid.

Next, we investigated the synthesis of isoquinolone **27b** from oxime **25b**. *N*-oxide **26b** was obtained by heating oxime **25b** in 1,2-DCB at 80 °C. Thereafter, crude **26b** was heated in Ac<sub>2</sub>O at 110 °C to afford the desired **27b** along with acetoxy **28b** at 6% and 33% yields, respectively (entry 3).

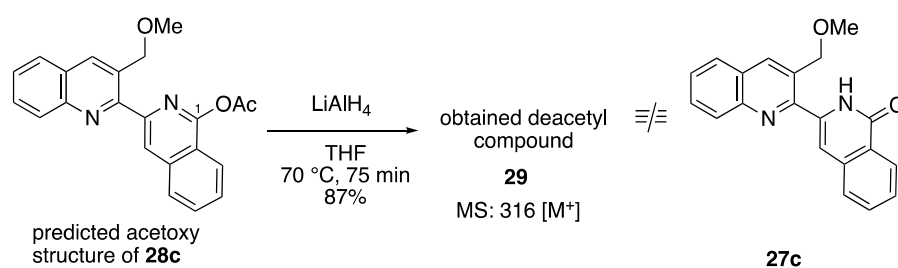
Subsequently, the synthesis of isoquinolone **27c** from oxime **25c** was investigated according to Method A (entry 4). Isoquinolone **27c** and the acetoxy product **28c** were obtained at 22% and 40% yields, respectively. From these exploratory results, oxime **25c** was selected for use in further optimization studies of the Reissert–Henze-type reaction to isoquinolone **27c**.

To examine the effect of *N*-oxide **26c** purity on the subsequent reaction, the crude *N*-oxide **26c** obtained by thermal cyclization was purified by crystallization (purification yield 73%). Purified *N*-oxide **26c** was heated in Ac<sub>2</sub>O at 110 °C (entry 5), resulting in slightly improved yields of **27c** (from 22% to 31%). When employing crude **26c**, lowering the Reissert–Henze-type reaction temperature to 50 °C further improved the yield of **27c** to 48% yield (entry 6). Notably, the production of acetoxy **28c** was reduced at the lower reaction temperature. Returning to Method B, the reaction of purified **26c** at 50 °C did not improve the yield of **27c** (entry 7). However, employing ambient temperature (rt) conditions, stirring purified **26c** in Ac<sub>2</sub>O improved the yield of **27c** to 60% and further reduced the production of **28c** to 18% (entry 8), although the reaction time required was significantly longer (51 h). From these early optimization studies, it may be asserted that the Reissert–Henze-type synthesis of isoquinolone **27c** produced better yields when starting from the purified *N*-oxide **26c**.

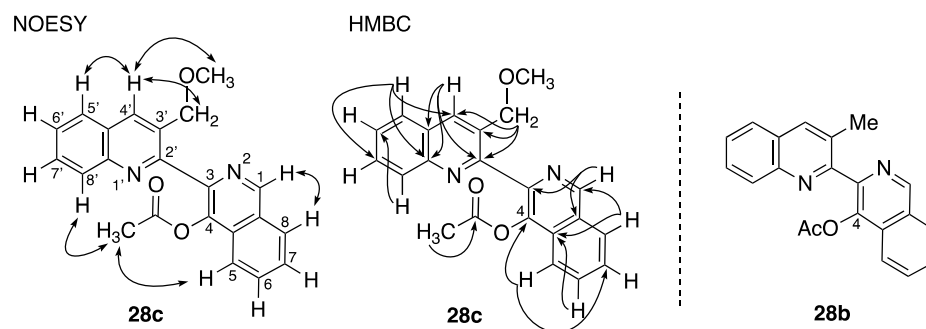
Next, the effect of microwave (MW) technology on the Reissert–Henze-type reaction was studied. Unfortunately, the yield of **27c** decreased to 20% when purified **26c** was heated in Ac<sub>2</sub>O at 110 °C under MW irradiation (entry 9). To directly compare the effects of MW irradiation (entry 6 vs. entry 10), crude **26c** was heated in Ac<sub>2</sub>O at 50 °C under MW, the reaction time required was greatly reduced from 24 h to 14 h and the production of **28c** was further reduced. Gratifyingly, using the same conditions of entry 10, purified **26c** was transformed into **27c** with a greatly improved yield of 73% in a short 3.5 h reaction time. Briefly, the use of trifluoroacetic anhydride in place of Ac<sub>2</sub>O and the addition of an acid catalyst were investigated; however, the yield of **27c** did not improve further (entries 12 and 13). Therefore, the conditions of entry 11 were deemed optimal for the Reissert–Henze-type synthesis of isoquinolone **27c** from **25c**.

During our Reissert–Henze-type reaction optimization studies, because of our work on the synthesis of alangiumkaloids (Scheme 1), we predicted that the obtained acetoxy **28c** was the 1-acetoxyisoquinoline product (Scheme 5). Therefore, we attempted to remove the acetyl group of **28c** by LiAlH<sub>4</sub> reduction. However, the <sup>1</sup>H-NMR spectra of the obtained compound **29** did not match that of isoquinolone **27c**. Further 2D-NMR studies (heteronuclear multiple-bond correlation (HMBC) and nuclear Overhauser effect spectroscopy (NOESY) measurements) were performed to verify the structure of the obtained **28c**. The through-space proton interaction correlations are shown in Figure 2. In particular, **28c** was identified as 4-acetoxyisoquinoline because the NOESY correlation of the methyl protons (2.13 ppm) of the acetyl group to C5-H (7.98 ppm) and C8'-H (8.13 ppm) was observed. Consequently, compound **29**, obtained from **28c** reduction, was confirmed to be 4-hydroxy-3-(3-methoxymethylquinolin-2-yl)isoquinoline and compound **28b** was also confirmed to be 4-acetoxyisoquinoline. The formation of both the 4-acetoxyisoquinoline product together with the isoquinolone product has been reported by Robison and co-workers [37]. However, why the Reissert–Henze-type reaction of our *N*-oxide **26** afforded 4-acetoxyisoquinoline remains to be elucidated. In the future, we will investigate this phenomenon in greater detail.



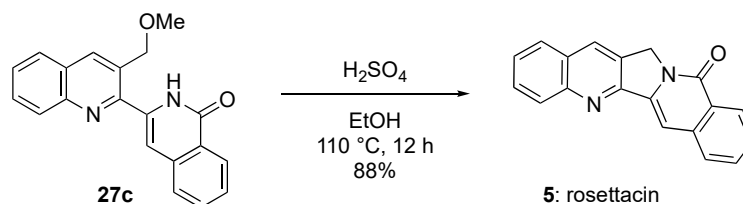


**Scheme 5.** Synthesis of deacetyl compound **29** from predicted acetoxy compound **28c**.



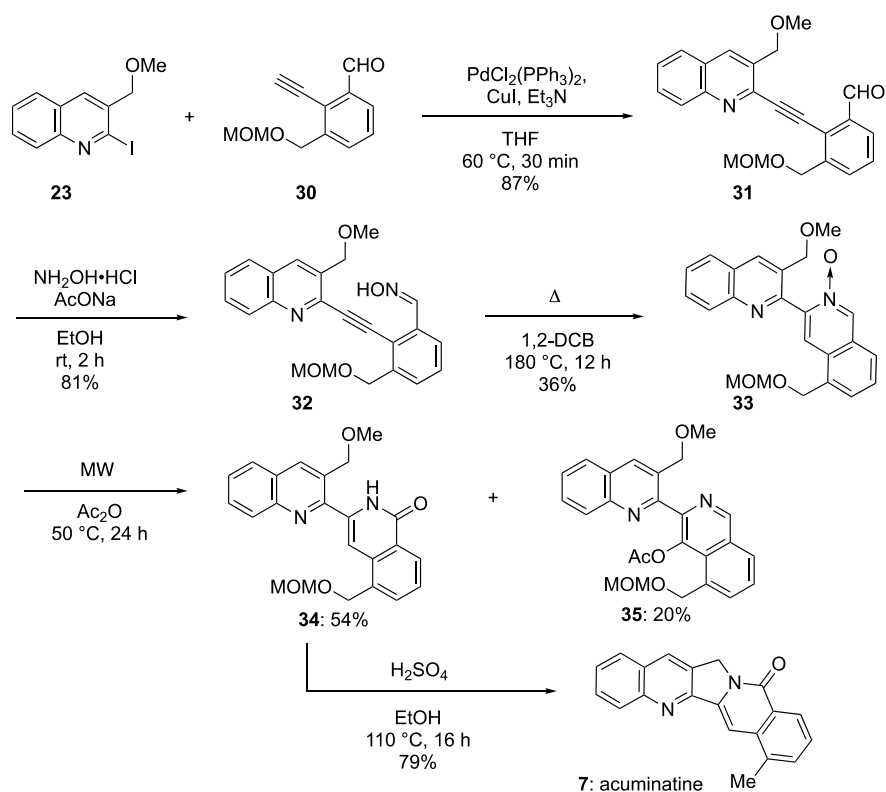
**Figure 2.** The NOESY and HMBC correlations of acetoxyisoquinoline **28c**, and structure of **28b**.

To complete the synthesis of rosettacin (**5**), we applied the conditions reported by Ciufolini and co-workers for C-ring formation [38]. Heating **27c** with H<sub>2</sub>SO<sub>4</sub> in ethanol (EtOH) produced **5** at an 88% yield (Scheme 6). Thus, the total synthesis of rosettacin (**5**) was achieved through an eight-step sequence at a 23.8% overall yield.



**Scheme 6.** Synthesis of rosettacin (**5**) by construction of C-ring.

As described above, we established a method for the synthesis of benz[6,7]indolizino[1,2-*b*]quinolin-11(13*H*)-one, which is the core structure of compounds in the aromathecin family. Next, we tried to synthesize 22-hydroxyacuminatin (**6**) by applying the same methodology (Scheme 7). Sonogashira coupling of 2-iodoquinoline **23** and 2-ethynylbenzaldehyde **30** in the presence of CuI, Et<sub>3</sub>N and PdCl<sub>2</sub>(PPh<sub>3</sub>)<sub>2</sub> produced 2-alkynylbenzaldehyde **31** at an 87% yield. The treatment of **31** with hydroxylamine in EtOH produced 2-alkynylbenzaldehyde oxime **32** at an 81% yield. Subsequently, heating **32** in 1,2-DCB at 80 °C did not deliver the isoquinoline *N*-oxide cyclization product **33**. Instead, the treatment of **32** in 1,2-DCB at 180 °C produced **33** at a 36% yield. Next, heating **33** in Ac<sub>2</sub>O at 50 °C under MW irradiation produced the desired isoquinolone **34** and 4-acetoxyisoquinoline **35** at yields of 54% and 20%, respectively. Finally, when **34** was heated with H<sub>2</sub>SO<sub>4</sub> in EtOH, the desired 22-hydroxyacuminatine (**6**) was not produced, but acuminatine (**7**) was isolated at a 79% yield. The formation of **7** is believed to have proceeded with dehydroxylation after the removal of the MOM group along with scaffold formation. The physical and spectroscopic data for our synthetic rosettacin (**5**) were consistent with previously reported values in all respects [26]. Furthermore, <sup>1</sup>H-NMR, <sup>13</sup>C-NMR, and mass spectroscopy characterization of all our synthetic compounds supported the identified structures, the details of which can be found in the Supporting Information section.



Scheme 7. Synthesis of acuminatine (7).

### 3. Materials and Methods

All non-aqueous reactions were carried out under an atmosphere of nitrogen in dried glassware unless otherwise noted. Solvents were dried and distilled according to standard protocols. Analytical thin-layer chromatography was performed with silica gel 60PF<sub>254</sub> (Merck). Silica gel column chromatography was performed with silica gel 60 (70–230 mesh, Kanto Chemical Co. Lit., Nihonbashi, Tokyo, Japan). All melting points were determined on Yanagimoto micromelting point apparatus MP-500D (Yanaco Technical Sciences Co. Lit., Taito-ku, Tokyo, Japan) and are uncorrected. Proton nuclear magnetic resonance (<sup>1</sup>H-NMR) spectra were recorded on a JEOL JNM-ECZ400S (JEOL Resonance Co. Lit., Akishima, Tokyo, Japan). Chemical shifts were reported relative to Me<sub>4</sub>Si ( $\delta$  0.00). Multiplicity is indicated by one or more of the following: s (singlet); d (doublet); t (triplet); q (quartet); m (multiplet); br (broad). Carbon nuclear magnetic resonance (<sup>13</sup>C-NMR) spectra were recorded on a JEOL JNM-ECZ400S z at 100 MHz. Chemical shifts were reported relative to CDCl<sub>3</sub> ( $\delta$  77.0) and DMSO-*d*<sub>6</sub> ( $\delta$  39.7). Infrared spectra were recorded with ATR method using a Horiba FT-720 FREEXACT-II spectrophotometer (Horiba Ltd., Kyoto, Japan) and Technologies DuraScop (ST. Japan Inc., Chuo-ku, Tokyo, Japan). Low- and high-resolution mass spectra were recorded on JEOL JMS-700 spectrometers (JEOL Resonance Co.Lit., Akishima, Tokyo, Japan) via the use of a direct inlet system. The microwave-assisted reaction was carried out at 180 W and 2450 MHz with Discover (CEM corporation, Matthews NC, USA).

#### 3.1. 2-Iodo-3-methylquinoline (20a)

We added dropwise conc. HCl (0.12 mL) to a solution of 2-chloroquinoline **18a** (685 mg, 3.86 mol) and NaI (1.74 × 10<sup>3</sup> mg, 11.61 mmol) in MeCN (16 mL); then, these were stirred at 85 °C for 16 h. After cooling at ambient temperature, we added H<sub>2</sub>O (15 mL) and saturated Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> (15 mL) to the reaction mixture. The resulting precipitate was filtrated in vacuo. The filtrate was extracted with EtOAc. The organic layer was washed with H<sub>2</sub>O and brine, dried with Na<sub>2</sub>SO<sub>4</sub>, and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:4 *v/v*) to give 2-iodoquinoline **20a** (958 mg,



92%) as a yellow solid. mp 181–183 °C (EtOAc-hexane).  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  2.46 (s, 3H), 7.61 (t,  $J = 8.2$  Hz, 1H), 7.71 (t,  $J = 8.2$  Hz, 1H), 7.89–7.93 (m, 2H), 8.17 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  25.8, 127.2, 127.3, 127.5, 127.6, 128.2, 129.6, 135.11, 135.14, 147.1. MS  $m/z$ : 269 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{10}\text{H}_8\text{NI}$  268.9701; found 268.9711.

### 3.2. 2-Iodoquinoline-3-carbaldehyde (20b)

The same procedure as above was carried out with 2-chloroquinoline **18b** ( $1.0 \times 10^4$  mg, 52.35 mmol) to give 2-iodoquinoline **20b** (13.3 g, 90%) as a white solid. mp 150–151 °C (EtOH). IR (ATR)  $\nu = 1685$   $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  7.67 (t,  $J = 8.2$  Hz, 1H), 7.88 (t,  $J = 8.2$  Hz, 1H), 7.97 (d,  $J = 8.2$  Hz, 1H), 8.11 (d,  $J = 8.2$  Hz, 1H), 8.56 (s, 1H), 10.29 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  120.5, 126.5, 128.3, 128.7, 128.9, 129.7, 133.4, 138.7, 151.6, 194.7. MS  $m/z$ : 283 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{10}\text{H}_6\text{NOI}$  282.9494; found 282.9485.

### 3.3. Methyl 2-Iodoquinoline-3-carboxylate (21)

A suspension of quinoline-3-carbaldehyde **20b** (200 mg 0.71 mmol),  $\text{I}_2$  (683 mg, 2.69 mmol) and  $\text{K}_2\text{CO}_3$  (345 mg, 2.50 mmol) in MeOH (6 mL) was stirred at rt for 35 min. After quenching with  $\text{H}_2\text{O}$  (5 mL) and saturated  $\text{Na}_2\text{S}_2\text{O}_3$  (5 mL), the resulting precipitate was filtered in vacuo to give methyl ester **21** (198 mg, 89%) as a yellow solid. mp 93–94 °C (EtOH). IR (ATR)  $\nu = 1716$   $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.02 (s, 3H), 7.64 (t,  $J = 8.2$  Hz, 1H), 7.82 (t,  $J = 8.2$  Hz, 1H), 7.87 (d,  $J = 8.2$  Hz, 1H), 8.10 (d,  $J = 8.2$  Hz, 1H), 8.49 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  52.9, 115.7, 125.6, 128.0, 128.5, 128.8, 129.0, 132.3, 138.9, 149.8, 166.0. MS  $m/z$ : 313 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{11}\text{H}_8\text{NO}_2\text{I}$  312.9600; found 312.9605.

### 3.4. 2-Iodoquinolin-3-ylmethanol (22)

A solution of quinoline-3-carbaldehyde **20b** (900 mg, 3.18 mmol) in MeOH (20 mL) was added dropwise to a suspension of  $\text{NaBH}_4$  (182 mg, 4.77 mmol) in MeOH (10 mL) under ice cooling conditions. After stirring at rt for 1 h, the reaction mixture was quenched with  $\text{H}_2\text{O}$ . The resulting precipitate was filtrated in vacuo to give alcohol **22** (848 mg, 93%) as a yellow solid. mp 177–179 °C ( $\text{CHCl}_3$ ). IR (ATR)  $\nu = 3745$   $\text{cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  4.53 (d,  $J = 8.2$  Hz, 2H), 5.74 (t,  $J = 8.2$  Hz, 1H), 7.64 (t,  $J = 8.2$  Hz, 1H), 7.74 (t,  $J = 8.2$  Hz, 1H), 7.95 (d,  $J = 8.2$  Hz, 1H), 8.04 (d,  $J = 8.2$  Hz, 1H), 8.22 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  65.5, 123.1, 127.1, 127.3, 127.6, 128.0, 129.9, 133.5, 137.7, 147.9. MS  $m/z$ : 285 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{10}\text{H}_8\text{NOI}$  284.9651; found 284.9663.

### 3.5. 2-Iodo-3-methoxymethylquinoline (23)

A solution of alcohol **22** (600 mg, 2.11 mmol) in THF (10 mL) was added dropwise to a suspension of 60% NaH (336 mg, 8.42 mmol) in THF (5 mL) under ice cooling. After stirring at the same temperature for 15 min, MeI (710 mg, 5.00 mmol) was added to the reaction mixture and this was then stirred at rt for 1 h. After quenching with  $\text{H}_2\text{O}$ , the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried with  $\text{Na}_2\text{SO}_4$ , and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:9  $v/v$ ) to produce 3-methoxymethylquinoline **23** (543 mg, 86%) as a yellow solid. mp 45–46 °C (EtOAc-hexane).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.58 (s, 3H), 4.55 (s, 2H), 7.57 (t,  $J = 8.1$  Hz, 1H), 7.70 (t,  $J = 8.1$  Hz, 1H), 7.82 (d,  $J = 8.1$  Hz, 1H), 8.04–8.06 (m, 2H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  58.9, 76.4, 122.2, 127.3, 127.6, 128.4, 129.9, 134.2, 134.3 (2C), 148.7. MS  $m/z$ : 299 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{11}\text{H}_{10}\text{NOI}$  298.9807; found 298.9807.

### 3.6. Methyl 2-(2-Formylphenyl)ethynylquinoline-3-carboxylate (24a)

We added a solution of 2-ethynylbenzaldehyde **19** (62 mg, 0.48 mmol) in THF (1 mL) to a solution of 2-iodoquinoline **21** (100 mg, 0.32 mmol), CuI (6 mg, 0.032 mmol),  $\text{PdCl}_2(\text{PPh}_3)_2$  (7 mg, 0.0096 mmol) and  $\text{Et}_3\text{N}$  (2 mL, 14.47 mmol) in THF (5 mL). The reaction mixture was stirred at 60 °C for 1 h. After cooling to ambient temperature, the reaction mixture was

filtrated through Celite pad, washed with EtOAc, and the filtrate was evaporated in vacuo. The residue was purified using column chromatography (EtOAc/hexane 1:4 *v/v*) to give 2-alkynylbenzaldehyde **24a** (43 mg, 44%) as a yellow solid. mp 131–132 °C (EtOAc-hexane). IR (ATR)  $\nu = 1689, 1709 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  4.03 (s, 3H), 7.53 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.62–7.68 (m, 2H), 7.85–7.89 (m, 2H), 7.93 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.01 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.19 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.87 (s, 1H), 10.86 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  52.8, 88.5, 94.6, 125.1, 125.9, 126.0, 127.0, 128.4, 128.6, 129.3, 129.6, 132.5, 133.7, 134.0, 136.9, 140.0, 141.0, 149.1, 165.2, 192.4. MS  $m/z$ : 315 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{20}\text{H}_{13}\text{NO}$  315.0895; found 315.0887.

### 3.7. 2-(3-Methylquinolin-2-yl)ethynylbenzaldehyde (**24b**)

The same procedure as above was carried out with 2-iodoquinoline **20a** (700 mg, 2.60 mmol) to give 2-alkynylbenzaldehyde **24b** (500 mg, 71%) as a white solid. mp 129–131 °C (EtOAc-hexane). IR (ATR)  $\nu = 1689 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.71 (s, 3H), 7.52–7.57 (m, 2H), 7.64 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.69 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.76 (d,  $J = 7.8 \text{ Hz}$ , 1H), 7.83 (d,  $J = 7.8 \text{ Hz}$ , 1H), 7.99–8.02 (m, 2H), 8.11 (d,  $J = 7.8 \text{ Hz}$ , 1H), 10.75 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.8, 88.2, 94.3, 125.5, 126.8, 127.4, 127.7 (2C), 128.9, 129.2, 129.4, 132.5, 133.7, 134.0, 135.5, 136.2, 143.6, 146.7, 191.1. MS  $m/z$ : 271 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{19}\text{H}_{13}\text{NO}$  271.0997; found 271.0988.

### 3.8. 2-(3-Methoxymethylquinolin-2-yl)ethynylbenzaldehyde (**24c**)

The same procedure as above was carried out with 2-iodoquinoline **23** (612 mg, 2.05 mmol) to give 2-alkynylbenzaldehyde **24c** (519 mg, 84%) as a white solid. mp 97–98 °C (EtOAc-hexane). IR (ATR)  $\nu = 1693 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.57 (s, 3H), 4.87 (s, 2H), 7.52–7.61 (m, 2H), 7.65 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.74 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.76–7.82 (m, 2H), 8.01 (t,  $J = 7.8 \text{ Hz}$ , 1H), 8.14 (t,  $J = 8.6 \text{ Hz}$ , 1H), 8.27 (s, 1H), 10.72 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  59.0, 71.7, 88.6, 93.2, 125.3, 127.5, 127.6, 127.7, 127.8, 129.1, 129.6, 130.0, 132.9, 133.8, 134.1, 134.6, 136.5, 141.7, 147.6, 191.3. MS  $m/z$ : 301 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{20}\text{H}_{15}\text{NO}_2$  301.1103; found 301.1121.

### 3.9. Methyl 2-(2-Hydroxyiminomethylphenyl)ethynylquinoline-3-carboxylate (**25a**)

A mixture of benzaldehyde **24a** (70 mg, 0.22 mmol),  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (30 mg, 0.44 mmol), and  $\text{AcONa}$  (36 mg, 0.44 mmol) in EtOH (5 mL) was stirred at rt for 1 h. After the removal of the solvent, the residue was diluted with  $\text{H}_2\text{O}$  and then filtrated off to give crude oxime **25a** (50 mg, 68%) as a yellow solid. The product was recrystallized from EtOAc-hexane. mp 171–173 °C (EtOAc-hexane). IR (ATR)  $\nu = 3047, 1709 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  3.99 (s, 3H), 7.43–7.52 (m, 2H), 7.71–7.77 (m, 2H), 7.91–7.97 (m, 2H), 8.11 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.20 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.73 (s, 1H), 9.03 (s, 1H), 11.67 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  53.3, 89.6, 93.8, 121.1, 125.1, 125.7, 126.2, 128.9, 129.0, 129.7, 130.1, 130.7, 133.4, 133.6, 135.3, 140.2, 140.6, 146.6, 148.9, 165.7. MS  $m/z$ : 330 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}_3$  330.1004; found 330.1011.

### 3.10. 2-(3-Methylquinolin-2-yl)ethynylbenzaldehyde Oxime (**25b**)

The same procedure as above was carried out with benzaldehyde **24b** (500 mg, 1.84 mmol) to give oxime **25b** (280 mg, 53%) as a red solid. mp 179–181 °C (EtOAc-hexane). IR (ATR)  $\nu = 3051 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  2.65 (s, 3H), 7.50–7.52 (m, 2H), 7.61 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.72–7.76 (t,  $J = 7.8 \text{ Hz}$ , 2H), 7.89–7.93 (m, 2H), 8.01 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.29 (s, 1H), 8.64 (s, 1H), 11.71 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  19.8, 89.9, 93.6, 121.0, 125.4, 127.80, 127.83, 128.1, 128.9, 130.0, 130.2, 130.6, 132.9, 133.6, 134.9, 136.1, 143.9, 146.4, 146.8. MS  $m/z$ : 286 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}$  286.1106; found 286.1115.

### 3.11. 2-(3-Methoxymethylquinolin-2-yl)ethynylbenzaldehyde Oxime (**25c**)

The same procedure as above was carried out with benzaldehyde **24c** (150 mg, 0.50 mmol) to give oxime **25c** (137 mg, 86%) as a red solid. mp 151–153 °C (EtOAc-

hexane). IR (ATR)  $\nu = 3055 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  3.47 (s, 3H), 4.79 (s, 2H), 7.48–7.55 (m, 2H), 7.65 (t,  $J = 7.5 \text{ Hz}$ , 1H), 7.74–7.76 (m, 1H), 7.80 (t,  $J = 7.5 \text{ Hz}$ , 1H), 7.90 (d,  $J = 7.5 \text{ Hz}$ , 1H), 8.02–8.05 (m, 2H), 8.41 (s, 1H), 8.66 (s, 1H), 11.72 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  58.2, 71.0, 89.4, 92.1, 120.3, 124.9, 126.9, 127.7, 128.0, 128.4, 129.6, 130.1, 130.2, 132.7, 133.1, 134.5, 134.7, 141.6, 145.9, 146.9. MS  $m/z$ : 316 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2$  316.1212; found 316.1216.

### 3.12. 3-(3-Methylquinolin-2-yl)isoquinolin-1-one (27b) and 4-Acetoxy-3-(3-methylquinolin-2-yl)isoquinoline (28b)

A solution of oxime **25b** (40 mg, 0.14 mmol) in 1,2-dichlorobenzene (4 mL) was stirred at 80 °C for 1 h. After the removal of the solvent,  $\text{Ac}_2\text{O}$  (4 mL) was added to the residue, and the mixture was stirred at 110 °C for 3 h. After the removal of the solvent, the residue was purified by column chromatography (EtOAc/hexane 1:1  $v/v$ ) to give isoquinolone **27b** (2 mg, 6%) and the 4-acetoxyisoquinoline **28b** (15 mg, 33%).

**27b**: a white solid. mp 214–215 °C (EtOAc-hexane). IR (ATR)  $\nu = 1628 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.88 (s, 3H), 7.55–7.60 (m, 2H), 7.68–7.76 (m, 3H), 7.80 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.10 (s, 1H), 8.13 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.50 (d,  $J = 8.2 \text{ Hz}$ , 1H), 10.64 (br s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  22.5, 108.8, 126.6, 126.7, 127.4, 127.6, 127.7, 127.8, 128.9, 129.1, 129.7, 132.6, 136.2, 137.6, 139.3, 145.7, 148.7, 162.6. MS  $m/z$ : 286 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{19}\text{H}_{14}\text{N}_2\text{O}$  286.1106; found 286.1109.

**28b**: an orange oil. IR (ATR)  $\nu = 1770 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.09 (s, 3H), 2.48 (s, 3H), 7.55 (t,  $J = 7.5 \text{ Hz}$ , 1H), 7.65–7.72 (m, 2H), 7.77–7.82 (m, 2H), 7.97 (d,  $J = 7.5 \text{ Hz}$ , 1H), 8.08–8.12 (m, 3H), 9.28 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.4, 20.5, 121.2, 126.8, 126.9, 127.5, 128.0, 128.7, 129.2, 129.5, 131.0, 131.1, 137.0, 140.5, 143.9, 146.1, 149.4, 156.2, 168.7. MS  $m/z$ : 328 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{21}\text{H}_{16}\text{N}_2\text{O}_2$  328.1212; found 328.1222.

### 3.13. 3-(3-Methoxymethylquinolin-2-yl)isoquinoline N-Oxide (26c)

A solution of oxime **25c** (150 mg, 0.47 mmol) in 1,2-dichlorobenzene (10 mL) was stirred at 80 °C for 1 h. After the removal of the solvent, the residue was crystallized from  $\text{Et}_2\text{O}$  to give *N*-oxide **26c** (109 mg, 73%) as a white solid. mp 222–223 °C ( $\text{CHCl}_3$ ).  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.32 (s, 3H), 4.56 (d,  $J = 12.8 \text{ Hz}$ , 1H), 4.84 (d,  $J = 12.8 \text{ Hz}$ , 1H), 7.60–7.69 (m, 3H), 7.74 (t,  $J = 8.2 \text{ Hz}$ , 1H), 7.79 (d,  $J = 8.2 \text{ Hz}$ , 1H), 7.86 (d,  $J = 8.2 \text{ Hz}$ , 1H), 7.92 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.01 (s, 1H), 8.15 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.37 (s, 1H), 8.90 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  58.6, 71.5, 124.6, 125.7, 127.2, 127.5, 127.6, 128.2, 129.0, 129.4, 129.6 (3C), 129.7, 132.4, 134.9, 136.3, 146.4, 147.2, 151.2. MS  $m/z$ : 316 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2$  316.1212; found 316.1222.

### 3.14. 3-(3-Methoxymethylquinolin-2-yl)isoquinolin-1-one (27c) and 4-Acetoxy-3-(3-methoxymethylquinolin-2-yl)isoquinoline (28c)

A solution of *N*-oxide **26c** (30 mg, 0.095 mmol) in  $\text{Ac}_2\text{O}$  (2 mL) was heated at 50 °C under microwave irradiation for 3.5 h. After the removal of the solvent, the residue was purified by column chromatography (EtOAc/hexane 1:1  $v/v$ ) to give isoquinolone **27c** (22 mg, 73%) and 4-acetoxyisoquinoline **28c** (7 mg, 21%).

**27c**: a white solid. mp 156–157 °C (EtOAc-hexane). IR (ATR)  $\nu = 1624 \text{ cm}^{-1}$ .  $^1\text{H NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.62 (s, 3H), 4.79 (s, 2H), 7.34 (s, 1H), 7.54–7.63 (m, 2H), 7.68–7.73 (m, 2H), 7.79 (t,  $J = 8.2 \text{ Hz}$ , 1H), 7.88 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.16 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.35 (s, 1H), 8.49 (d,  $J = 8.2 \text{ Hz}$ , 1H), 10.50 (br s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  58.2, 72.6, 108.9, 126.7, 127.3, 127.4, 127.5 (2C), 127.7, 127.8, 128.2, 129.2, 130.7, 132.6, 135.9, 137.7, 139.5, 146.7, 150.0, 162.6. MS  $m/z$ : 316 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{20}\text{H}_{16}\text{N}_2\text{O}_2$  316.1212; found 316.1208.

**28c**: a yellow solid. mp 106–108 °C (EtOAc-hexane). IR (ATR)  $\nu = 1774 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.13 (s, 3H), 3.41 (s, 3H), 4.73 (s, 2H), 7.58 (t,  $J = 8.2 \text{ Hz}$ , 1H), 7.69–7.73 (m, 2H), 7.80 (t,  $J = 8.2 \text{ Hz}$ , 1H), 7.90 (d,  $J = 8.2 \text{ Hz}$ , 1H), 7.99 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.09 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.13 (d,  $J = 8.2 \text{ Hz}$ , 1H), 8.46 (s, 1H), 9.25 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  20.6, 58.6, 71.7, 121.4, 126.9, 127.5, 127.6, 127.7, 128.2, 129.1, 129.3, 129.5, 131.1,

131.2, 131.9, 134.6, 140.7, 143.0, 146.5, 149.1, 154.2, 168.7. MS  $m/z$ : 358 ( $M^+$ ). HRMS (EI): calcd for  $C_{22}H_{18}N_2O_3$  358.1317; found 358.1323.

### 3.15. 4-Hydroxy-3-(3-methoxymethylquinolin-2-yl)isoquinoline (29)

A solution of 4-acetoxyisoquinoline **28c** (28 mg, 0.078 mmol) in THF (3 mL) was added dropwise to a suspension of  $LiAlH_4$  (8 mg, 0.20 mmol) in THF (3 mL) under ice cooling, and then stirred at 70 °C for 75 min. After quenching with  $H_2O$ , the reaction mixture was filtrated through a Celite pad and washed with  $H_2O$  and EtOAc. Next, the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried with  $Na_2SO_4$ , and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 3:15  $v/v$ ) to give 4-hydroxyquinoline **29** (22 mg, 87%) as an orange solid. mp 139–140 °C (EtOH). IR (ATR)  $\nu = 3055\text{ cm}^{-1}$ .  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  1.25 (br s, 1H), 3.66 (s, 3H), 5.47 (s, 2H), 7.56 (t,  $J = 7.8\text{ Hz}$ , 1H), 7.67–7.75 (m, 3H), 7.88 (d,  $J = 7.8\text{ Hz}$ , 1H), 7.94 (d,  $J = 7.8\text{ Hz}$ , 1H), 8.06 (d,  $J = 7.8\text{ Hz}$ , 1H), 8.51 (d,  $J = 7.8\text{ Hz}$ , 1H), 8.66 (s, 1H), 8.81 (s, 1H).  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  58.8, 73.3, 123.0, 125.6, 126.6, 126.7, 126.7, 127.6, 128.8, 128.9, 129.1, 129.6, 130.1, 132.6, 135.6, 139.9, 141.7, 156.2, 156.3. MS  $m/z$ : 316 ( $M^+$ ). HRMS (EI): calcd for  $C_{20}H_{16}N_2O_2$  316.1212; found 316.1216.

### 3.16. Rosettacin (5)

We added dropwise conc.  $H_2SO_4$  (0.5 mL) under ice cooling to a suspension of isoquinolone **27c** (13 mg, 0.041 mmol) in EtOH (1 mL) and the solution was stirred at 110 °C for 12 h. After cooling to ambient temperature, the solvent was evaporated in vacuo. The residue was diluted with  $H_2O$  (1 mL), and then was alkalinized with 1 M aqueous NaOH. The resulting mixture was extracted with  $CH_2Cl_2$ . The organic layer was washed with brine, dried with  $Na_2SO_4$ , and evaporated in vacuo. The residue was washed with  $Et_2O$  and filtrated in vacuo to give rosettacin (**5**) (10 mg, 88%) as a yellow solid. mp 292–294 °C (EtOAc-hexane, lit. [26] mp 288 °C). IR (ATR)  $\nu = 1651\text{ cm}^{-1}$ .  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  5.39 (s, 2H), 7.57–7.65 (m, 2H), 7.68 (s, 1H), 7.74 (t,  $J = 8.2\text{ Hz}$ , 1H), 7.79–7.83 (m, 2H), 7.92 (d,  $J = 8.2\text{ Hz}$ , 1H), 8.23 (d,  $J = 8.2\text{ Hz}$ , 1H), 8.35 (s, 1H), 8.56 (d,  $J = 8.2\text{ Hz}$ , 1H).  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  49.5, 101.1, 126.1, 127.3 (2C), 127.5 (2C), 128.0 (2C), 128.8, 129.5, 130.2, 130.7, 132.5, 137.5, 140.0, 148.9, 153.7, 161.1 MS  $m/z$ : 284 ( $M^+$ ). HRMS (EI): calcd for  $C_{19}H_{12}N_2O$  284.0950; found 284.0952.

### 3.17. 3-Methoxymethyloxymethyl-2-[(3-methoxymethylquinolin-2-yl)ethynyl]benzaldehyde (31)

We added a solution of 2-ethynylbenzaldehyde **30** (82 mg, 0.40 mmol) in THF (1 mL) to a solution of 2-iodoquinoline **23** (100 mg, 0.33 mmol), CuI (3.0 mg, 0.016 mmol),  $PdCl_2(PPh_3)_2$  (23 mg, 0.033 mmol) and  $Et_3N$  (1 mL, 21.63 mmol) in THF (2 mL). The reaction mixture was stirred at 60 °C for 30 min. After cooling to ambient temperature, the reaction mixture was filtrated through Celite pad, washed with EtOAc, and the filtrate was evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 1:9  $v/v$ ) to give 2-alkynylbenzaldehyde **31** (109 mg, 87%) as a yellow solid. mp 87–88 °C (EtOAc-hexane). IR (ATR)  $\nu = 1693\text{ cm}^{-1}$ .  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  3.43 (s, 3H), 3.56 (s, 3H), 4.84 (s, 2H), 4.87 (s, 2H), 5.01 (s, 2H), 7.54–7.61 (m, 2H), 7.74 (t,  $J = 7.8\text{ Hz}$ , 1H), 7.85 (d,  $J = 7.8\text{ Hz}$ , 2H), 7.95 (d,  $J = 7.8\text{ Hz}$ , 1H), 8.12 (d,  $J = 7.8\text{ Hz}$ , 1H), 8.28 (s, 1H), 10.77 (s, 1H).  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  55.6, 58.8, 67.1, 71.6, 85.5, 96.4, 98.2, 123.7, 126.6, 127.5, 127.6, 127.8, 129.2, 129.4, 130.0, 132.8, 132.9, 134.4, 136.7, 141.4, 142.1, 147.6, 191.5. MS  $m/z$ : 375 ( $M^+$ ). HRMS (EI): calcd for  $C_{23}H_{21}NO_4$  375.1471; found 375.1477.

### 3.18. 3-Methoxymethyloxymethyl-2-[(3-methoxymethylquinolin-2-yl)ethynyl]benzaldehyde Oxime (32)

A mixture of benzaldehyde **31** (247 mg, 0.66 mmol),  $NH_2OH \cdot HCl$  (92 mg, 1.32 mmol), and  $AcONa$  (108 mg, 1.32 mmol) in EtOH (7 mL) was stirred at rt for 2 h. After removal of solvent, the residue was diluted with  $H_2O$ , and then filtrated off to give crude oxime **32** (208 mg, 81%) as a red solid. The product was recrystallized from EtOAc-hexane. mp

130–131 °C (EtOAc-hexane). IR (ATR)  $\nu = 3734 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{DMSO-}d_6$ )  $\delta$  3.35 (s, 3H), 3.47 (s, 3H), 4.77 (s, 2H), 4.83 (s, 2H), 4.87 (s, 2H), 7.51–7.55 (m, 1H), 7.59 (d,  $J = 7.8 \text{ Hz}$ , 1H), 7.66 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.79–7.86 (m, 2H), 8.04–8.06 (m, 2H), 8.44 (s, 1H), 8.70 (s, 1H), 11.71 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{DMSO-}d_6$ )  $\delta$  54.9, 58.1, 67.0, 70.9, 86.6, 95.8, 96.8, 118.9, 123.8, 127.0, 127.8, 128.0, 128.4, 129.8, 130.2, 132.7, 134.6, 135.0, 141.3, 141.5, 146.0, 146.9. MS  $m/z$ : 390 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4$  390.1580; found 390.1590.

### 3.19. 5-Methoxymethyloxymethyl-3-(3-methoxymethylquinolin-2-yl)isoquinoline N-Oxide (33)

A solution of oxime **32** (60 mg, 0.15 mmol) in 1,2-dichlorobenzene (4 mL) was stirred at 180 °C for 12 h. After removal of solvent, the residue was purified by column chromatography (MeOH) to give *N*-oxide **33** (21 mg, 36%). The obtained **33** contained a small amount of impurity and could not be further purified.

### 3.20. 5-Methoxymethyloxymethyl-3-(3-methoxymethylquinolin-2-yl)isoquinolin-1-one (34) and 4-Acetoxy-5-methoxymethyloxymethyl-3-(3-methoxymethylquinolin-2-yl)isoquinoline (35)

A solution of *N*-oxide **33** (15 mg, 0.038 mmol) in  $\text{Ac}_2\text{O}$  (1 mL) was heated at 50 °C under microwave irradiation for 24 h. After removal of the solvent, the residue was purified by column chromatography (EtOAc/hexane 1:1 *v/v*) to give isoquinolone **34** (8 mg, 54%) and the 4-acetoxyisoquinoline **35** (3 mg, 20%).

**34**: a yellow solid. mp 113–114 °C (EtOAc-hexane). IR (ATR)  $\nu = 1628 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.42 (s, 3H), 3.62 (s, 3H), 4.77 (s, 2H), 4.82 (s, 2H), 4.97 (s, 2H), 7.54 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.62 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.67 (s, 1H), 7.75–7.82 (m, 2H), 7.89 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.17 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.36 (s, 1H), 8.49 (d,  $J = 7.8 \text{ Hz}$ , 1H), 10.61 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  29.7, 55.5, 58.4, 66.9, 72.7, 95.7, 105.4, 127.2, 127.3, 127.4, 127.7, 127.8, 128.3, 129.3, 130.7, 133.2, 133.8, 136.1, 136.5, 139.6, 146.8, 150.1, 162.8. MS  $m/z$ : 390 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_2\text{O}_4$  390.1580; found 390.1574.

**35**: an orange oil. IR (ATR)  $\nu = 1770 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  1.95 (s, 3H), 3.35 (s, 3H), 3.44 (s, 3H), 4.63 (s, 2H), 4.71 (s, 2H), 5.19 (s, 2H), 7.58 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.65 (d,  $J = 7.8 \text{ Hz}$ , 1H), 7.71 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.87 (d,  $J = 7.8 \text{ Hz}$ , 1H), 7.90 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.04 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.13 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.48 (s, 1H), 9.23 (s, 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  21.0, 55.4, 58.7, 67.8, 70.9, 94.8, 126.9, 127.66, 127.71, 127.8, 128.1, 129.0, 129.2, 129.9, 130.9, 132.3, 132.4, 132.6, 134.4, 140.7, 145.0, 146.2, 149.8, 154.4, 168.7. MS  $m/z$ : 432 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{25}\text{H}_{24}\text{N}_2\text{O}_5$  432.1685; found 432.1694.

### 3.21. Acuminatine (7)

We added dropwise conc.  $\text{H}_2\text{SO}_4$  (2 mL) under ice cooling to a suspension of isoquinolone **34a** (30 mg, 0.077 mmol) in EtOH (4 mL) and then stirred the mixture at 110 °C for 16 h. After cooling to an ambient temperature, the solvent was evaporated in vacuo. The residue was diluted with  $\text{H}_2\text{O}$  (2 mL) and then was alkalinified with 1 M aqueous NaOH. The resulting mixture was extracted with  $\text{CH}_2\text{Cl}_2$ . The organic layer was washed with water and brine, dried with  $\text{Na}_2\text{SO}_4$ , and evaporated in vacuo. The residue was purified by column chromatography (EtOAc/hexane 4:6 *v/v*) to give acuminatine (**7**) (18 mg, 79%). mp 290–292 °C (EtOAc-hexane). IR (ATR)  $\nu = 1770 \text{ cm}^{-1}$ .  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ )  $\delta$  2.74 (s, 3H), 5.38 (s, 2H), 7.47 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.58 (d,  $J = 7.8 \text{ Hz}$ , 1H), 7.62 (t,  $J = 7.8 \text{ Hz}$ , 1H), 7.79–7.83 (m, 2H), 7.91 (d,  $J = 7.8 \text{ Hz}$ , 1H), 8.24 (d,  $J = 8.7 \text{ Hz}$ , 1H), 8.35 (s, 1H), 8.43 (d,  $J = 7.8 \text{ Hz}$ , 1H).  $^{13}\text{C-NMR}$  (100 MHz,  $\text{CDCl}_3$ )  $\delta$  19.6, 49.4, 98.1, 125.5, 126.4, 127.1, 127.3, 128.0, 128.1, 128.9, 129.4, 130.3, 130.9, 133.3, 135.0, 136.6, 139.6, 148.9, 153.9, 161.3. MS  $m/z$ : 298 ( $\text{M}^+$ ). HRMS (EI): calcd for  $\text{C}_{20}\text{H}_{14}\text{N}_2\text{O}$  298.1106; found 298.1111.

## 4. Conclusions

We developed a synthetic route to create the pentacyclic scaffold of the aromathecin family by constructing the indolizidine moiety after isoquinolone synthesis. The key step of our isoquinolone synthesis employed a thermal cyclization of 2-alkynylbenzaldehyde oxime to the isoquinoline *N*-oxide, followed by the performance of a Reissert–Henze-type

reaction. Under the optimum reaction conditions for the Reissert–Henze-type reaction step, microwave irradiation-assisted heating of the purified *N*-oxide in Ac<sub>2</sub>O at 50 °C reduced the formation of the 4-acetoxyisoquinoline byproduct to deliver the desired isoquinolone at a moderate yield. The employed eight-step sequence afforded rosettacin at a 23.8% overall yield. Furthermore, the synthesis of acuminatine was achieved by applying the developed strategy. Future research will focus on the use of this strategy to efficiently synthesize a variety of polycyclic compounds, including alkaloids with promising therapeutic profiles.

**Supplementary Materials:** The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/molecules28104059/s1>, Copies of the <sup>1</sup>H NMR and <sup>13</sup>C NMR spectra for compounds 20–35, rosettacin (5), and acuminatine (7).

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