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New synthetic technology for the construction of *N*-hydroxyindoles and synthesis of nocathiacin I model systems

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Abstract

A new synthetic method providing expedient access to a wide range of polyfunctionalized *N*-hydroxyindoles (**IV**) is reported. These unique constructs are assembled by nucleophilic additions to *in situ* generated α,β -unsaturated nitrones (**III**) through carbon–carbon and carbon–heteroatom bond formation. The new synthetic technology was applied to the synthesis of nocathiacin I (**1**) model systems (**2** and **3a–c**) containing the *N*-hydroxyindole structural motif.

Keywords

N-hydroxyindole; nitron; nocathiacin I; nucleophilic addition; synthetic methods

1. Introduction

Nocathiacin I (**1**, Figure 1), a complex thiopeptide antibiotic isolated from *Nocardia* sp. (ATCC-202099) and the fungus *Amiccolaptosis* sp., exhibits remarkably potent *in vitro* and *in vivo* activity against Gram-positive bacteria.^{1–3} One of the most striking structural motifs within the molecular framework of nocathiacin I (**1**) is the *N*-hydroxyindole moiety that carries the oxygen ether linkage and bridges the 15-membered depsipeptide ring with the 10-membered macrolide system of the molecule.⁴ Challenged by the daunting structure of nocathiacin I (**1**) and intrigued by the rarity of its *N*-hydroxyindole structural motif in nature and the relative scarcity of methods for its assembly,⁵ we initiated a program directed toward the development of synthetic technologies for the generation of substituted *N*-hydroxyindoles suitable for potential applications to complex molecule construction.

In this article, we describe a detailed account of our investigations in this area that culminated in a general method for the synthesis of highly substituted *N*-hydroxyindoles (**IV**, Scheme 1)⁶ from readily available aromatic precursors and a variety of nucleophiles through the trapping of *in situ* generated α,β -unsaturated nitrones and the application of the developed technology to the construction of certain nocathiacin I (**1**) model systems such as **2** and **3a–c** (Figure 1).⁷

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2. Results and discussion

2.1 Synthetic technology development

Based on certain precedents,^{5c–g} our general strategy for the construction of *N*-hydroxyindoles, shown in Scheme 1, was devised to take advantage of the ready availability of aromatic nitro compounds as starting materials and the perceived propensity of α,β -unsaturated nitrones to enter into reactions with suitable nucleophiles and give stable adducts. Thus, it was envisioned that reduction of nitro ketoesters **I** under appropriate conditions should produce hydroxylamines **II**, which were expected to undergo facile intramolecular condensation to afford the α,β -unsaturated nitrones **III**, whose existence in the presence of suitable nucleophiles should be transient, leading through 1,5-addition reactions, to *N*-hydroxyindoles **IV**.⁸ Having defined the general cascade for the projected synthesis of *N*-hydroxyindoles, the synthesis of the starting nitro ketoesters, the exploration of conditions for their reduction, and the range of capable nucleophiles to be employed in this scheme became the first objectives of the investigation.

Scheme 2 summarizes the synthesis of nitro ketoesters **6a–g** and nitro ketoacid **7a**, which were required for the present studies. Thus, reaction of the corresponding nitrotoluene compound with excess dimethyl oxalate in the presence of NaH in DMF at 0 °C furnished ketoesters **5a–g** in yields ranging from 60–85%.⁹ Exposure of each of these compounds to Eschenmoser's salt in the presence of NaH in THF at 0–25 °C then led to the desired α,β -unsaturated ketoesters **6a–g** in 50–98% yield.^{10,11} The α,β -unsaturated ketoacid **7a** was prepared from methyl ester **6a** through the action of Me₃SnOH in 1,2-dichloroethane at 70 °C (77% yield), as standard hydrolysis methods resulted in decomposition, as alluded to in a previous communication from our laboratories.¹²

The desired generation and trapping of the α,β -unsaturated nitrones was achieved under two sets of experimental conditions. Scheme 3 depicts the first procedure (method A) for this cascade sequence involving activated zinc [Zn] (prepared from zinc dust, 1,2-dibromoethane and TMSCl) as the reducing agent as demonstrated with nitro ketoester **6a**.¹³ Thus, refluxing zinc dust with 1,2-dibromoethane in THF, followed by cooling to 25 °C (refluxing/cooling process repeated three additional times) and subsequent addition of TMSCl, followed by a mixture of aqueous 1N NH₄Cl and **6a** resulted in the formation of *N*-hydroxyindoline **9** (56% yield) and hydroxylactam **14** (10% yield). The structure of the latter compound was unambiguously proven by X-ray crystallographic analysis (see ORTEP structure, Scheme 3).¹⁴ These results can be rationalized by envisioning ring closure within the structure of the initially formed hydroxylamine (**8**) leading to *N*-hydroxylamine tertiary alcohol **9** (path A, Scheme 3) on one hand, and 1,4-addition of NH₃ to the starting material **6a** followed by a lactamization/enolization sequence within the initially formed aminoketoester **13** to generate compound **14** (path B, Scheme 3) on the other. Tertiary alcohol **9** exhibited high reactivity, especially upon exposure to acidic conditions that resulted in the loss of a molecule of water, generating a reactive species presumed to be the α,β -unsaturated nitrone **10**, whose isolation proved elusive. The presence of the α,β -unsaturated nitrone **10** was supported by its trapping with a variety of nucleophiles. Thus, reaction of **9** with benzyl alcohol (5.0 equiv) or benzyl mercaptan (5.0 equiv) in DME at 40 °C in the presence of *p*TsOH led to the formation of *N*-hydroxyindoles **11** (55% yield) and **12** (90% yield), respectively. These reactions are presumed to proceed either directly from **9** by S_N2'-type displacement, or by 1,5-addition to the initially formed nitrone (**10**), or through both of the potential mechanistic pathways. It is interesting to note that the isolation of *N*-hydroxyindoles **11** and **12** stands in contrast to the observations of Myers and Herzon in which their initially formed products from 1,5-nucleophilic additions to a sterically congested α,β -unsaturated nitrone proved too labile for isolation, rapidly reverting back to their components instead.^{5d}

In search of a more direct and convenient access to the desired *N*-hydroxyindoles from the same starting materials, an alternative experimental procedure was explored and optimized as summarized in Scheme 4 and Table 1. According to this method (method B), nitro ketoester **6a** was treated with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.2 equiv) in the presence of benzyl alcohol (5.0 equiv) or benzyl mercaptan (5.0 equiv) and 4 Å molecular sieves in DME at 40 °C for 1–1.5 h, conditions that led, through path A₁, to the formation of adducts **11** (60% yield, see ORTEP drawing, Scheme 4)¹⁴ or **12** (55% yield), respectively. The optimum conditions described above were arrived at through a systematic study in which benzyl alcohol (BnOH) was employed as a nucleophile to trap the reactive species reductively generated from nitro ketoester **6a** (see Table 1) whereby the effects of stoichiometry, temperature (entries 1–4), water content (entry 9), molecular sieves (entries 9 and 10) and solvent (entries 11 and 12) were varied. It is interesting to note, in contrast to method A, the absence of the *N*-hydroxy tertiary alcohol **9** as an isolable intermediate in this procedure (method B), presumably due to the fleeting nature of the latter under the prevailing acidic conditions of the reaction medium which apparently promote its rapid conversion, first to nitrone **10** and subsequently to the observed *N*-hydroxyindole product **11** or **12**. The $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ -induced process, however, also leads to *N*-hydroxy ketoester **16** (15–17% yield), presumably originating from the initially formed hydroxylamine (**8**) through pathway A₂ (Scheme 4) via an intramolecular aza-Michael addition followed by oxidation/aromatization of the presumed enolic species (**15**). Another possible mechanism for the formation of *N*-hydroxy ketoester **16** may involve the corresponding nitroso compound, generated by partial reduction of **6a** (or its hydrated counterpart), which could similarly undergo, through its nitrogen atom, intramolecular 1,4-addition to the α,β -unsaturated site; such an event may then be followed by rearrangement (or elimination of H_2O) to the observed by-product **16**.

Having established the $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ procedure (method B) as the preferred method for the generation and trapping of the reactive α,β -unsaturated nitrones such as **10** (or its hydrated form, *N*-hydroxy tertiary alcohol **9**, Scheme 3), we set out to explore its generality and scope. Tables 2 and 3 summarize our initial findings employing various combinations of nitroaromatic ketoesters with oxygen (Table 2), sulfur (Table 3) and nitrogen (Table 3) nucleophiles. As seen in these tables, both primary and secondary alcohols, thiols and amines participate in these reactions to form the expected *N*-hydroxyindoles in moderate to excellent yields. Aside from by-product **16** (Scheme 4), another probable contributing factor to the moderate yields in certain cases is the possibility of dimerization/polymerization processes, in which the fleeting nitrone (**10**, Scheme 4) can be captured by the *N*-hydroxy group of the desired product.^{4b} Benzyl alcohol and benzyl mercaptan were the hetero-nucleophiles chosen to investigate varying substitutions around the aromatic nuclei of the employed ketoesters. As depicted in Tables 2 and 3 cyano (Table 2, entry 9, Table 3, entry 9), SEM-protected hydroxymethyl (Table 2, entry 5; Table 3, entry 5), and several fluorine-containing (Table 2, entries 6–8; Table 3, entries 6–8) nitro ketoesters successfully enter the reaction.

Finally, phenols (Scheme 5) were employed as nucleophiles with the anticipation that they would yield the oxygen–carbon bonded 1,5-addition products that had been observed with the other oxygen nucleophiles. However, we were somewhat surprised to discover that both phenol and 2,6-dimethoxyphenol led to compounds **35** (40% yield) and **36** (31% yield), respectively, which were formed through carbon–carbon bond forming reactions as the major products. An X-ray crystal structure (see ORTEP drawing, Scheme 5) of the latter compound (**36**) further confirmed this outcome.¹⁴

Intrigued by these initial results we then set out to explore the addition of various carbon nucleophiles to α,β -unsaturated nitrones generated from an array of α,β -unsaturated ketoesters employing the $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ -based reaction (method B). Our studies began with

silyl enol ethers as nucleophiles and 2-bromo-substituted ketoester **6a**; the results are shown in Table 4. Thus, in DME at 40 °C and in the presence of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$, both cyclic (entries 1–3) and acyclic (entries 4–13) silyl enol ethers, as well as ethyl vinyl ether (entry 14) entered the developed cascade reaction with varying yields, ranging from 30 to 75%. The *N*-hydroxyindoles formed possess substituents at the 3-position containing α -substituted ketones (or an aldehyde as in entry 14) carrying aliphatic, aromatic and heteroaromatic appendages. Of special interest are the fluoro-substituted indoles (entries 8–10), due to their often superior pharmacological properties,¹⁵ and those indoles endowed with synthetically fertile functional groups for further chemical manipulation. The *N*-hydroxy-3-substituted ketoester **16**, whose formation as a by-product has already been discussed above, was also observed in these reactions in small amounts (see Table 4).

Table 5 demonstrates the successful utilization of silanes and related compounds as well as stannanes as nucleophiles in this reaction. Thus, allyl silanes of varying structures serve well as partners with bromo-substituted nitro ketoester **6a**, furnishing novel *N*-hydroxyindoles (entries 1–4) while the allenyl trimethylsilane (entry 8) led to acetylenic compound **57**. Somewhat interestingly, the use of allyl trimethoxysilane in this reaction (entry 5) resulted in the formation of the methoxy *N*-hydroxyindole **55** (rather than the allyl substituted product). The same methoxy indole was observed when methoxytrimethylsilane was used (entry 6). X-Ray crystallographic analysis of *N*-hydroxyindole **55** confirmed its structure beyond doubt (see ORTEP drawing, Figure 2). The participation of triethylsilane (entry 7) in this process resulted in the formation of the methyl substituted *N*-hydroxyindole **56**, presumably through 1,5-reduction of the incipient α,β -unsaturated nitrone. The use of allyl stannanes (Table 5, entries 9 and 10) also proved successful, leading to the expected products and demonstrating their potential as partners in this cascade reaction. X-Ray crystallographic analysis of the gem-dimethyl compound **58** confirmed its structure (see ORTEP drawing, Figure 2).¹⁴

In order to explore further the generality and scope of the present methodology we proceeded to vary the nitroaromatic partner and combine the new substrates with a number of nucleophiles. Table 6 shows the results with nitroaromatic substrates **6a–g** (whose preparation has already been discussed above, Scheme 2) and silyl enol ethers **59–61**. Thus, *N*-hydroxyindoles **37**, **40**, **44**, and **62–79** were formed in moderate to good yields as shown in Table 6. It was of interest to observe that the process tolerates various substituents and substitution patterns, although somewhat higher yields were obtained with the *ortho*-substituted nitroaromatic substrates. The survival of the nitrile group under the reductive conditions (see Table 6, entry 7) is also of note and underscores the mildness of the process. Furthermore, the fact that fluoro-substituted nitroaromatic substrates enter the reaction (see Table 6, entries 4–6) bodes well for its potential applications in medicinal chemistry due to the special value of fluorinated compounds in pharmaceutical research.

Finally, a study was carried out to determine the optimum stoichiometry of the two partners. Table 7 shows the results using the bromo-substituted nitro ketoester **6a** and difluorosilyl enol ether **61** under the standard conditions with $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (method B).¹⁵ As seen from the table, the yields of product **44** increase from 50 to 75% as the number of equivalents of nucleophile increase from 1 to 5 and appear to plateau (74%) as 10 equivalents of nucleophile is reached. It is, indeed, reassuring that good yields are still possible with a 1:1 stoichiometry of the two partners, making the process viable in cases where the nucleophile is precious.

2.2. Application to the synthesis of nocathiacin I model systems

Having developed this synthetic technology to a comfortable level of practicality and scope, we then proceeded to test its applicability to the thiopeptide antibiotic nocathiacin I by

targeting suitable model systems. Scheme 6 summarizes the synthesis of the rather simple nocathiacin I model system **2** containing the *N*-hydroxyindole structural motif bridged to a thiazole moiety through an ether linkage. Thus, the *N*-Boc acetamide **80**, prepared as previously described from Boc-L-Ser-OH,¹⁶ was converted to the required *N*-Boc primary alcohol **81** by exposure to TFA (68% yield), a substrate that reacted smoothly with the *N*-hydroxy tertiary alcohol **9** under acidic conditions as prescribed above to afford the targeted *N*-hydroxyindole **2** in 44% yield.

This initial success led us to attempt the next hurdle of synthesizing the more advanced model systems **3a** and **3b** (Schemes 1 and 8), which contain not only the *N*-hydroxyindole structural motif of nocathiacin I, but also its 15-membered depsipeptide ether ring. The syntheses of these compounds featured a Yamaguchi macrolactonization as the final step of the macrocycle construction,¹⁷ while the ether bridge was formed at an earlier stage through intermolecular nucleophilic addition of a hydroxy component to an *in situ* generated α,β -unsaturated nitron. The requisite hydroxy substrate **85** was prepared from *N*-Boc acetamide **80**¹⁶ as shown in Scheme 7. Thus, exposure of **80** to DIBAL-H followed by treatment with NaH and MeI resulted in the formation of methoxy compound **82** in 74% overall yield. Concomitant removal of the Boc and acetamide groups from the latter compound was achieved by exposure to acid (TFA), leading, upon selective silylation (TBSCl, Et₃N) of the hydroxy group, to the primary amine **84** (85% yield for the two steps). Finally, coupling of this amine (**84**) to carboxylic acid **83** (generated by LiOH hydrolysis of ethyl ester **80**)¹⁶ in the presence of HATU, HOAt and *i*Pr₂NEt, furnished, after TBAF-induced desilylation, the targeted hydroxy substrate **85** in 87% overall yield.

Scheme 8 depicts the final stages of the synthesis of model systems **3a** and **3b** beginning with the preparation of hydroxy acetate **86** ready for the anticipated intermolecular *N*-hydroxyindole formation in partnership with nitro ketoester **6a** or *N*-hydroxy tertiary alcohol **9**. Thus, acetylation of **85** (Ac₂O, Et₃N, 4-DMAP) followed by TFA treatment furnished the desired hydroxy acetate **86** in 82% overall yield. This substrate performed well as a nucleophile in the crucial coupling with the precursor to the indole structural motif employing either of the two methods (A and B) described above. Thus, reaction of **86** with **6a** in the presence of SnCl₂·2H₂O according to method B (40 °C, 6 h) led to *N*-hydroxyindole **87** in 40% yield. Subsequent protection (SEMCl, *i*Pr₂NEt) of the *N*-hydroxy group of **87**, followed by exposure to LiOH, afforded the required hydroxy acid for the anticipated macrolactonization, which was brought about through the action of 2,4,6-trichlorobenzoyl chloride in the presence of Et₃N and 4-DMAP, furnishing the *N*-OSEM protected model system **3a** (38% yield for the three steps). The same substrate **86** underwent the key *N*-hydroxyindole forming reaction with the tertiary alcohol **9**, generated from **6a** through the [Zn]/NH₄Cl protocol (method A), in the presence of *p*TsOH in DME at 40 °C to yield the same *N*-hydroxyindole **87** in 56% yield. MOM protection (MOMCl, *n*Bu₄NI cat., *i*Pr₂NEt) of the latter compound followed by ester hydrolysis (LiOH) and Yamaguchi macrolactonization then led to the MOM-protected nocathiacin I model system **3b** in 44% overall yield for the three steps.

Our final investigation in these studies involved the challenging task of forming the relevant *N*-hydroxyindole ether macrocyclic system through intramolecular, rather than intermolecular, trapping of an incipient α,β -unsaturated nitron. To this end, and as shown in Scheme 9, the required precursor, hydroxy α,β -unsaturated ketoester **89**, was prepared from alcohol **85** and ketoacid **7a**, which were coupled through the intermediacy of the acid chloride produced from **7a** and oxalyl chloride. Proceeding in the presence of Et₃N, this coupling reaction furnished ester **88** (77% yield) which was then reacted with TFA in CH₂Cl₂:MeOH at 0 °C to afford hydroxy ester **89** in 72% yield. Much to our delight, both methods A and B were found productive in furnishing the desired *N*-hydroxy indole system

3c. Thus, method A ([Zn]/NH₄Cl) allowed first the generation of tertiary alcohol **90**, and thence, under the influence of *p*TsOH, formation of the nocathiacin I model system **3c** in 40% overall yield from **89**. The same model system **3c** was formed, albeit in lower yield (10%), directly from **89** by method B (SnCl₂·2H₂O), presumably through the fleeting intermediate **91** as shown in Scheme 9.

3. Conclusion

The described chemistry provides a versatile entry into substituted *N*-hydroxyindoles from readily available nitroaromatic systems and suitable partners carrying O-, S-, N- and carbon nucleophilic moieties. Proceeding through a cascade sequence involving trapping of incipient α,β -unsaturated nitrones and/or *N*-hydroxy tertiary alcohol species, these processes tolerate a variety of functionalities and substituents amenable to further chemical manipulations. Furthermore, the model studies performed in the area of nocathiacin I bode well for a potential application of the method to the construction of this natural product's most intriguing and challenging structural motif, its *N*-hydroxyindole moiety. Other applications of the present synthetic technology in chemical synthesis in general, and medicinal chemistry in particular, are also envisioned.

4. Experimental

4.1. General

All reactions were carried out under an argon atmosphere with dry solvents under anhydrous conditions, unless otherwise noted. Dry tetrahydrofuran (THF), toluene, 1,2-dimethoxyethane (DME), and methylene chloride (CH₂Cl₂) were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. Yields refer to chromatographically and spectroscopically (¹H NMR) homogenous materials, unless otherwise stated. Reagents were purchased at the highest commercial quality and used without further purification, unless otherwise stated. Difluorosilyl enol ethers were prepared according to literature procedures.¹³ Reactions were monitored by thin-layer chromatography (TLC) carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and an ethanolic solution of phosphomolybdic acid and cerium sulfate, and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography (PTLC) separations were carried out on 0.25 or 0.50 mm E. Merck silica gel plates (60F-254). Optical rotations were recorded on a Perkin-Elmer 343 polarimeter. NMR spectrum were recorded on Bruker DRX-600, DRX-500, AMX-500 or AMX-400 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, ½ABq = ½AB quartet, m = multiplet, quin = quintuplet, sext = sextet, sep = septet, hept = heptet, br = broad. IR spectra were recorded on a Perkin-Elmer 1600 or Spectrum 100 series FT-IR spectrometer. Electrospray ionization (ESI) mass spectrometry (MS) experiments were performed on an API 100 Perkin-Elmer SCIEX single quadrupole mass spectrometer at 4000V emitter voltage. High-resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer using MALDI (matrix-assisted laser-desorption ionization) or ESI (electrospray ionization).

4.1.1. Trimethyl(2-[(2-methyl-3-nitrobenzyl)oxy]methoxy)ethyl)silane (4c)—To 2-methyl-3-nitrobenzyl alcohol (20 g, 120 mmol) in DMF (600 mL) at 25 °C was added *i*Pr₂Net (62.5 mL, 359 mmol), SEMCl (42.2 mL, 239 mmol) and *n*Bu₄NI (442 mg, 1.20 mmol). After stirring for 12 h, the reaction mixture was diluted with EtOAc (500 mL), washed with H₂O (500 mL), brine (500 mL) and dried (Na₂SO₄). The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel,

Et₂O:hexanes, 20:80 → 60:40) to afford **4c** (35 g, 98%) as a yellow oil; *R*_f = 0.60 (silica gel, EtOAc:hexanes, 2:8); IR (film) ν_{max} 2953, 2886, 1527, 1465, 1352, 1248, 1189, 1155, 1105, 1057, 1028, 937, 920, 858, 834, 802, 759, 736, 715, 694, 666 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 7.69 (d, *J* = 8.0 Hz, 1 H), 7.62 (d, *J* = 8.0 Hz, 1 H), 7.34 (t, *J* = 8.0 Hz, 1 H), 4.73 (s, 2 H), 4.64 (s, 2 H), 3.63 (t, *J* = 8.5 Hz, 2 H), 2.39 (s, 3 H), 0.91 (t, *J* = 8.5 Hz, 2 H), 0.01 (s, 9 H); ¹³C NMR (125 MHz, CD₃CN) δ 152.7, 141.2, 134.0, 132.0, 128.0, 124.6, 95.9, 68.5, 66.5, 19.2, 15.1, -0.7 (3 C); HRMS (ESI-TOF) calcd for C₁₄H₂₃NO₄SiNa⁺ [*M* + Na⁺] 320.1288, found 320.1284.

4.2. General procedure for the synthesis of ketoesters 5a–g

To a suspension of NaH (60% dispersion in mineral oil, 4.0 equiv) in DMF (1.67 M) at 0 °C was added a solution of nitrotoluene (3.0–15.0 mmol) in DMF (0.74 M) via cannula. After stirring for 10 min, a solution of dimethyl oxalate (5.0 equiv) in DMF (0.96 M) was added via cannula and after stirring for 1 h at 0 °C, the reaction mixture was allowed to warm to 25 °C and stirring was continued for 12 h. The reaction mixture was then cooled to 0 °C, quenched with saturated aqueous NH₄Cl (5–25 mL) solution, diluted with EtOAc (20–100 mL), washed with H₂O (5–25 mL) and dried (Na₂SO₄). After concentration, the residue was subjected to flash column chromatography to give the ketoesters.

4.2.1. Methyl 3-(2-bromo-6-nitrophenyl)-2-oxopropanoate (5a)—*R*_f = 0.78 (silica gel, EtOAc:hexanes, 1:1); IR (film) ν_{max} 3093, 2956, 1735, 1598, 1527, 1436, 1403, 1349, 1274, 1201, 1059, 803, 736, 718 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 8.00–7.97 (m, 2 H), 7.46 (t, *J* = 8.3 Hz, 1 H), 4.67 (s, 2 H), 3.89 (s, 3 H); ¹³C NMR (125 MHz, CD₃CN) δ 189.6, 161.4, 151.6, 138.7, 130.9, 129.9, 128.4, 125.3, 53.9, 44.3; HRMS (ESI-TOF) calcd for C₁₀H₈BrNO₅Na⁺ [*M* + Na⁺] 323.9478, found 323.9475.

4.2.2. Methyl 3-(2-nitrophenyl)-2-oxopropanoate (5b)—*R*_f = 0.51 (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3441 (br), 2959, 2850, 1732, 1605, 1575, 1514, 1437, 1394, 1346, 1261, 1195, 1057, 966, 858, 786, 725, 664 cm⁻¹; ¹H NMR (500 MHz, CD₃CN) δ 8.10 (d, *J* = 8.1 Hz, 1 H), 7.71–7.64 (m, 1 H), 7.57–7.51 (m, 1 H), 7.42 (d, *J* = 7.7 Hz, 1 H), 4.53 (s, 2 H), 3.86 (s, 3 H); ¹³C NMR (125 MHz, CD₃CN) δ 190.9, 161.7, 149.6, 135.0, 134.8, 130.2, 129.9, 126.1, 53.8, 44.9; HRMS (ESI-TOF) calcd for C₁₀H₉NO₅Na⁺ [*M* + Na⁺] 246.0373, found 246.0363.

4.2.3. Methyl 3-[2-nitro-6-({[2-(trimethylsilyl)ethoxy]methoxy}methyl)phenyl]-2-oxopropanoate (5c)—*R*_f = 0.38 (silica gel, EtOAc:hexanes, 3:7); IR (film) ν_{max} 2953, 2892, 1735, 1612, 1528, 1438, 1349, 1247, 1188, 1155, 1104, 1056, 1031, 991, 136, 858, 833, 804, 767, 734, 692 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.02 (d, *J* = 8.4 Hz, 1 H), 7.67 (d, *J* = 7.2 Hz, 1 H), 7.46 (t, *J* = 8.0 Hz, 1 H), 4.63 (s, 2 H), 4.61 (s, 2 H), 4.59 (s, 2 H), 3.94 (s, 3 H), 3.59 (t, *J* = 8.4 Hz, 2 H), 0.94 (t, *J* = 8.4 Hz, 2 H), 0.01 (s, 9 H); ¹³C NMR (125 MHz, CD₃CN) δ 189.1, 161.2, 150.3, 140.1, 135.2, 128.8, 128.7, 125.4, 94.1, 67.4, 66.1, 53.7, 39.6, 18.5, -1.0 (3 C); HRMS (ESI-TOF) calcd for C₁₇H₂₅NO₇SiNa⁺ [*M* + Na⁺] 406.1292, found 406.1291.

4.2.4. Methyl 3-(2-fluoro-6-nitrophenyl)-2-oxopropanoate (5d)—*R*_f = 0.29 (silica gel, EtOAc:hexanes, 2:8); IR (film) ν_{max} 3459 (br), 3107, 2950, 1730, 1531, 1466, 1452, 1429, 1401, 1360, 1332, 1281, 1244, 1226, 1189, 1147, 1064, 971, 837, 800, 763, 735 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 7.91 (d, *J* = 7.9 Hz, 1 H), 7.58–7.50 (m, 2 H), 4.53 (s, 2 H), 3.87 (s, 3 H); ¹³C NMR (150 MHz, CD₃CN) δ 189.8, 162.0 (d, *J* = 247.3 Hz), 161.3, 150.4, 130.7 (d, *J* = 9.2 Hz), 121.8 (d, *J* = 3.4 Hz), 121.7 (d, *J* = 20.6 Hz), 118.4 (d, *J* = 19.5 Hz), 53.8, 36.6; HRMS (ESI-TOF) calcd for C₁₀H₈FNO₅Na⁺ [*M* + Na⁺] 264.0279, found 264.0269.

4.2.5. Methyl 3-(5-fluoro-2-nitrophenyl)-2-oxopropanoate (5e)— $R_f = 0.56$ (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3413 (br), 3083, 2958, 2919, 2849, 1736, 1590, 1525, 1343, 1249, 1062, 840, 751, 613 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 8.20 (dd, $J = 9.2, 4.1$ Hz, 1 H), 7.18–7.13 (m, 1 H), 7.03 (dd, $J = 8.7, 4.1$ Hz, 1 H), 4.51 (s, 2 H), 3.90 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 188.4, 164.8 (d, $J = 256.6$ Hz), 160.5, 144.2, 132.5 (d, $J = 9.1$ Hz), 128.3 (d, $J = 10.3$ Hz), 120.5 (d, $J = 22.8$ Hz), 115.8 (d, $J = 22.8$ Hz), 53.5, 44.4; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_8\text{FNO}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 264.0279, found 264.0276.

4.2.6. Methyl 3-(4-fluoro-2-nitrophenyl)-2-oxopropanoate (5f)— $R_f = 0.45$ (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3099, 2959, 1734, 1618, 1532, 1499, 1440, 1398, 1349, 1325, 1235, 1133, 1062, 949, 880, 819, 806, 747, 682 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 7.89 (dd, $J = 8.5, 2.5$ Hz, 1 H), 7.47–7.45 (m, 2 H), 4.53 (s, 2 H), 3.88 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 190.7, 162.4 (d, $J = 247.1$ Hz), 161.6, 150.0 (d, $J = 8.8$ Hz), 136.4 (d, $J = 7.9$ Hz), 126.3 (d, $J = 3.9$ Hz), 121.0 (d, $J = 21.1$ Hz), 113.5 (d, $J = 27.3$ Hz), 53.8, 44.3; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_8\text{FNO}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 264.0279, found 264.0269.

4.2.7. Methyl (2Z(E))-3-(4-cyano-2-nitrophenyl)-2-hydroxyacrylate (5g)— $R_f = 0.28$ (silica gel, EtOAc:hexanes, 1:1); IR (film) $\nu_{\max}$ 3372 (br), 3088, 2958, 2926, 2237, 1736, 1619, 1535, 1440, 1396, 1352, 1268, 1062, 912, 834, 795, 747, 677 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.44 (d, $J = 8.0$ Hz, 1 H), 8.17 (d, $J = 1.6$ Hz, 1 H), 7.84 (dd, $J = 8.0, 1.6$ Hz, 1 H), 6.96 (d, $J = 1.4$ Hz, 1 H), 6.92 (d, $J = 1.4$ Hz, 1 H), 3.98 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 161.3, 149.8, 137.8, 136.6, 135.9, 135.3, 129.9, 117.5, 113.7, 102.7, 53.9; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_7\text{N}_2\text{O}_5^- [\text{M} - \text{H}^-]$ 247.0360, found 247.0369.

4.3. General procedure for the synthesis of α,β -unsaturated ketoesters 6a–g

To a solution of ketoester (0.5–10 mmol) in THF (0.03 M) at 0 °C was added NaH (60% dispersion in mineral oil, 1.1 equiv) and, after stirring for 1 h, dimethylmethylen ammonium chloride (3.0 equiv) was added and the reaction mixture stirred for 12 h at 25 °C. After cooling to 0 °C, the reaction mixture was quenched with saturated aqueous NH_4Cl solution (1–20 mL), diluted with EtOAc (5–100 mL), washed with H_2O (1–20 mL) and dried (Na_2SO_4). After concentration, the residue was subjected to flash column chromatography to give the α,β -unsaturated ketoesters.

4.3.1. Methyl 3-(2-bromo-6-nitrophenyl)-2-oxobut-3-enoate (6a)— $R_f = 0.53$ (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3389 (br), 2954, 2913, 2861, 2355, 1719, 1672, 1526, 1472, 1431, 1349, 1237, 1026 cm^{-1} ; ^1H NMR (500 MHz, CDCl_3) δ 8.02 (dd, $J = 8.4, 1.3$ Hz, 1 H), 7.94 (dd, $J = 8.1, 1.3$ Hz, 1 H), 7.44 (dd, $J = 8.4, 8.1$ Hz, 1 H), 6.79 (s, 1 H), 6.17 (s, 1 H), 3.93 (s, 3 H); ^{13}C NMR (125 MHz, CDCl_3) δ 183.1, 162.5, 149.5, 141.8, 137.9, 134.8, 132.5, 130.5, 126.3, 123.8, 53.3; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_8\text{BrNO}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 335.9478, found 335.9477.

4.3.2. Methyl 3-(2-nitrophenyl)-2-oxobut-3-enoate (6b)— $R_f = 0.29$ (silica gel, EtOAc:hexanes, 3:7); IR (film) $\nu_{\max}$ 3474 (br), 3404 (br), 2953, 2906, 2849, 1740, 1688, 1601, 1567, 1531, 1514, 1433, 1410, 1341, 1271, 1236, 1132, 1028, 958, 859, 790, 761 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 8.10 (d, $J = 8.3$ Hz, 1 H), 7.77–7.74 (m, 1 H), 7.65–7.62 (m, 1 H), 7.45 (dd, $J = 7.5, 1.3$ Hz, 1 H), 6.55 (s, 1 H), 6.51 (s, 1 H), 3.89 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 186.5, 164.3, 148.7, 144.1, 135.2, 134.7, 133.4, 131.4, 131.1, 125.4, 53.7; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_{10}\text{NO}_5^+ [\text{M} + \text{H}^+]$ 236.0553, found 236.0550.

4.3.3. Methyl 3-[2-nitro-6-([2-(trimethylsilyl)ethoxy]methoxy)methyl]phenyl]-2-oxobut-3-enoate (6c)— $R_f = 0.55$ (silica gel, EtOAc:hexanes, 1:1); IR (film) $\nu_{\max}$ 2954,

2884, 1743, 1690, 1525, 1343, 1243, 1131, 1102, 1061, 1032, 938, 861, 832, 761, 732, 691 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 8.03 (d, J = 8.1 Hz, 1 H), 7.83 (d, J = 7.8 Hz, 1 H), 7.60 (dd, J = 8.1, 7.8 Hz, 1 H), 6.63 (s, 1 H), 6.26 (s, 1 H), 4.62 (s, 2 H), 4.46 (d, J = 3.5 Hz, 2 H), 3.87 (s, 3 H), 3.56 (t, J = 8.3 Hz, 2 H), 0.88 (t, J = 8.3 Hz, 2 H), -0.01 (s, 9 H); ^{13}C NMR (150 MHz, CD_3CN) δ 186.2, 164.2, 149.7, 140.8, 140.7, 134.9, 134.6, 130.8, 130.4, 124.7, 95.3, 67.3, 66.0, 53.7, 18.5, -1.4 (3 C); HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_7\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 418.1292, found 418.1297.

4.3.4. Methyl 3-(2-fluoro-6-nitrophenyl)-2-oxobut-3-enoate (6d)— R_f = 0.54 (silica gel, EtOAc:hexanes, 3:7); IR (film) ν_{max} 3473 (br), 3371 (br), 3096, 3954, 1738, 1687, 1621, 1524, 1447, 1345, 1294, 1248, 1182, 1121, 1065, 1024, 947, 881, 805, 729, 672 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 8.95 (d, J = 8.3 Hz, 1 H), 7.67–7.63 (m, 1 H), 7.59–7.56 (m, 1 H), 6.76 (s, 1 H), 6.50 (s, 1 H), 3.90 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 186.1, 164.1, 160.7 (d, J = 247.3 Hz), 149.8, 137.4 (d, J = 2.3 Hz), 136.5, 132.1 (d, J = 10.3 Hz), 122.4 (d, J = 22.9 Hz), 121.5 (d, J = 3.4 Hz), 119.9 (d, J = 20.6 Hz), 53.9; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_9\text{FNO}_5^+ [\text{M} + \text{H}^+]$ 254.0459, found 254.0452.

4.3.5. Methyl 3-(5-fluoro-2-nitrophenyl)-2-oxobut-3-enoate (6e)— R_f = 0.52 (silica gel, EtOAc:hexanes, 3:7); IR (film) ν_{max} 3083, 2959, 1743, 1695, 1585, 1526, 1436, 1347, 1218, 1132, 1036, 948, 843, 727, 611 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 8.24 (dd, J = 9.2, 5.3 Hz, 1 H), 7.27–7.24 (m, 1 H), 7.08 (dd, J = 8.3, 2.6 Hz, 1 H), 6.64 (s, 1 H), 6.29 (s, 1 H), 3.93 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 185.3, 165.4 (d, J = 253.2 Hz), 163.5, 144.5, 142.7, 134.6, 134.4 (d, J = 10.3 Hz), 128.1 (d, J = 10.3 Hz), 120.9 (d, J = 25.1 Hz), 117.3 (d, J = 22.8 Hz), 53.4; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_8\text{FNO}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 276.0279, found 276.0279.

4.3.6. Methyl 3-(4-fluoro-2-nitrophenyl)-2-oxobut-3-enoate (6f)— R_f = 0.33 (silica gel, EtOAc:hexanes, 2:8); IR (film) ν_{max} 3097, 2958, 1741, 1690, 1537, 1338, 1349, 1271, 1213, 1132, 1034, 947, 882, 812, 674 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.87 (dd, J = 8.3, 2.6 Hz, 1 H), 7.43–7.40 (m, 1 H), 7.37 (dd, J = 8.9, 5.7 Hz, 1 H), 6.59 (s, 1 H), 6.31 (s, 1 H), 3.92 (s, 3 H); ^{13}C NMR (150 MHz, CDCl_3) δ 183.9, 162.6, 161.7 (d, J = 252.0 Hz), 147.9 (d, J = 8.0 Hz), 142.7, 133.8 (d, J = 8.0 Hz), 132.5, 127.4 (d, J = 3.4 Hz), 121.2 (d, J = 20.5 Hz), 112.5 (d, J = 27.4 Hz), 52.9; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_8\text{FNO}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 276.0279, found 276.0274.

4.3.7. Methyl 3-(4-cyano-2-nitrophenyl)-2-oxobut-3-enoate (6g)— R_f = 0.55 (silica gel, EtOAc:hexanes, 1:1); IR (film) ν_{max} 2237, 1742, 1693, 1556, 1537, 1353, 1251, 1140, 1033 cm^{-1} ; ^1H NMR (400 MHz, CDCl_3) δ 8.45 (d, J = 1.6 Hz, 1 H), 7.98 (dd, J = 7.8, 1.6 Hz, 1 H), 7.54 (d, J = 1.6 Hz, 1 H), 6.75 (s, 1 H), 6.35 (s, 1 H), 3.94 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 185.6, 163.8, 148.8, 142.8, 138.4, 136.3, 135.9, 134.7, 129.4, 117.4, 114.8, 53.9; HRMS (ESI-TOF) calcd for $\text{C}_{12}\text{H}_8\text{N}_2\text{O}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 283.0325, found 283.0325.

4.5. General procedure for the synthesis of *N*-hydroxyindoles (method A)

A stirred suspension of Zn dust (4.9 equiv) and dibromoethane (0.33 equiv) in THF (0.20 M) was heated to reflux (70 °C) for approximately 5 min and then allowed to cool to 25 °C. The refluxing/cooling process was repeated three times. TMSCl (0.2 equiv) was then added and the resulting grey suspension was stirred at 25 °C for 10 min. A separate stirred solution containing a mixture of aqueous 1N NH_4Cl (2.2 equiv) and nitro ketoester (0.01–0.06 mmol, 1.0 equiv) in THF (0.10 M) was added via cannula to the activated Zn suspension and stirring was continued for 15–30 min in the absence of light at 25 °C. The crude reaction mixture was purified directly by PTLC to afford tertiary alcohol **9** which was added to a stirred solution of *p*TsOH (3.0 equiv), nucleophile (5.0 equiv) and 4 Å molecular sieves (20

wt%) in DME (0.05–0.10 M) at 25 °C. After 10 min, the reaction mixture was warmed to 40 °C, stirred for 1–3 h, cooled to room temperature and purified directly by PTLC to afford the targeted *N*-hydroxyindoles.

4.5.1. Methyl 4-bromo-1,2-dihydroxy-3-methyleneindoline-2-carboxylate (9)—

R_f = 0.53 (silica gel, EtOAc:hexanes, 6:4); IR (film) $\nu_{\max}$ 3389, 2954, 2849, 1737, 1596, 1566, 1460, 1431, 1290, 1255, 1231, 1184, 1155, 1096, 1026, 885, 802, 749 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 7.64 (s, 1 H), 7.14 (t, J = 7.9 Hz, 1 H), 7.11 (dd, J = 7.9, 1.3 Hz, 1 H), 6.85 (dd, J = 7.9, 1.3 Hz, 1 H), 6.32 (s, 1 H), 5.40 (s, 1 H), 5.08 (br s, 1 H), 3.61 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 170.3, 154.8, 144.3, 132.1, 127.3, 123.4, 117.9, 111.8, 111.7, 98.9, 53.6; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_{10}\text{BrNO}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 321.9685, found 321.9684.

4.5.2. Methyl 3-[(benzyloxy)methyl]-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (11)

Method A and B: R_f = 0.58 (silica gel, EtOAc:hexanes, 6:4); IR (film) $\nu_{\max}$ 3194, 2952, 2848, 1710, 1525, 1433, 1353, 1312, 1255, 1226, 1185, 1122, 1047, 1024, 909, 874, 771, 730, 690 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.49 (br s, 1 H), 7.45 (d, J = 8.1 Hz, 1 H), 7.39–7.23 (m, 6 H), 7.18 (t, J = 8.1 Hz, 1 H), 5.10 (s, 2 H), 4.61 (s, 2 H), 3.88 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.2, 139.9, 137.2, 129.2 (2 C), 128.9 (2 C), 128.3, 127.1, 126.9, 126.8, 121.0, 116.0, 115.9, 110.2, 72.7, 61.8, 52.9; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{16}\text{BrNO}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 412.0155, found 412.0155.

4.5.3. Methyl 3-[(benzylthio)methyl]-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (12)

Method A and B: R_f = 0.57 (silica gel, EtOAc:hexanes, 6:4); IR (film) $\nu_{\max}$ 3354 (br), 2955, 2908, 2837, 1708, 1672, 1608, 1514, 1484, 1442, 1390, 1255, 1232, 1185, 1120, 738, 692 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.30 (br s, 1 H), 7.45 (dd, J = 8.2, 0.7 Hz, 1 H), 7.33–7.23 (m, 5 H), 7.22–7.16 (m, 2 H), 4.45 (s, 2 H), 3.83 (s, 3 H), 3.79 (s, 2 H); ^{13}C NMR (100 MHz, CD_3CN) δ 162.4, 139.9, 137.8, 129.8 (2 C), 129.3 (2 C), 127.7, 127.4, 126.7, 125.6, 120.1, 117.8, 116.1, 110.4, 52.8, 37.2, 26.7; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{16}\text{BrNO}_3\text{SNa}^+$ [$\text{M} + \text{Na}^+$] 427.9926, found 427.9924.

4.5.4. 4-(2-Bromo-6-nitrophenyl)-3-hydroxy-1,5-dihydro-2*H*-pyrrol-2-one (14)—

R_f = 0.20 (silica gel, EtOAc:hexanes, 6:4); IR (film) $\nu_{\max}$ 3271 (br), 2955, 2919, 1684, 1525, 1455, 1414, 1349, 1220, 1108, 1037, 903, 803, 780 cm^{-1} ; ^1H NMR (600 MHz, CDCl_3) δ 7.99 (d, J = 8.3 Hz, 1 H), 7.95 (d, J = 8.3 Hz, 1 H), 7.49 (t, J = 8.3 Hz, 1 H), 6.85 (br s, 1 H), 4.05 (br s, 2 H); ^{13}C NMR (150 MHz, CD_3CN) δ 168.5, 154.2, 151.8, 145.1, 138.2, 131.8, 129.1, 126.7, 124.6, 45.1; HRMS (ESI-TOF) calcd for $\text{C}_{10}\text{H}_7\text{BrNO}_3^-$ [$\text{M} - \text{H}^-$] 279.9607, found 279.9615.

4.6. General procedure for the synthesis of *N*-hydroxyindoles (method B)

To a stirred solution of $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.2–2.5 equiv) and 4 Å molecular sieves (20 wt%) in DME (0.12–0.16 M) was added nucleophile (5.0 equiv) and nitro ketoester (0.03–0.10 mmol, 1.0 equiv) at 25 °C. The reaction mixture was warmed to 40–45 °C and stirring was continued for 1–72 h in the absence of light. Direct purification of the crude reaction mixture by PTLC afforded the desired *N*-hydroxyindoles.

4.6.1. Methyl 4-bromo-1-hydroxy-1*H*-indole-3-carboxylate (16)— R_f = 0.18 (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3149, 2914, 2855, 1722, 1634, 1553, 1370, 1311, 1258, 1199, 1164, 1123, 1070, 976, 841, 753, 729 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ

9.54 (br s, 1 H), 7.54 (d, $J = 8.2$ Hz, 1 H), 7.52 (d, $J = 7.9$ Hz, 1 H), 7.25 (dd, $J = 8.2, 7.9$ Hz, 1 H), 3.88 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 178.7, 165.7, 137.4, 137.0, 129.3, 126.1, 122.9, 114.9, 110.1, 109.0, 53.5; HRMS (ESI-TOF) calcd for $\text{C}_{11}\text{H}_8\text{BrNO}_4^+ [\text{M} + \text{H}^+]$ 297.9709, found 297.9709.

4.6.2. Methyl 4-bromo-3-[(hexyloxy)methyl]-1-hydroxy-1*H*-indole-2-carboxylate (17)— $R_f = 0.60$ (silica gel, EtOAc:hexanes, 6:4); IR (film) ν_{max} 3178 (br), 2955, 2920, 2849, 1714, 1531, 1437, 1396, 1355, 1314, 1255, 1226, 1185, 1149, 1120, 1073, 879, 773, 732 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.48 (br s, 1 H), 7.41 (dd, $J = 8.2, 0.7$ Hz, 1 H), 7.32 (dd, $J = 7.5, 0.7$ Hz, 1 H), 7.15 (dd, $J = 8.2, 7.5$ Hz, 1 H), 5.00 (s, 2 H), 3.91 (s, 3 H), 3.53 (t, $J = 6.4$ Hz, 2 H), 1.57–1.50 (m, 2 H), 1.35–1.21 (m, 6 H), 0.86–0.82 (m, 3 H); ^{13}C NMR (100 MHz, CD_3CN) δ 162.2, 137.3, 126.9, 126.8, 126.7, 121.0, 116.3, 116.0, 110.2, 70.7, 61.9, 52.9, 32.4, 30.5, 26.7, 23.4, 14.3; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{22}\text{BrNO}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 406.0624, found 406.0618.

4.6.3. Methyl 4-bromo-3-(ethoxymethyl)-1-hydroxy-1*H*-indole-2-carboxylate (18)— $R_f = 0.53$ (silica gel, EtOAc:hexanes, 6:4); IR (film) ν_{max} 3166 (br), 2978, 2861, 1713, 1531, 1355, 1249, 1226, 1185, 1126, 1073, 991, 732 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.36 (br s, 1 H), 7.40 (d, $J = 8.3$ Hz, 1 H), 7.32 (d, $J = 7.5$ Hz, 1 H), 7.15 (dd, $J = 8.3, 7.5$ Hz, 1 H), 5.02 (s, 2 H), 3.92 (s, 3 H), 3.60 (q, $J = 7.0$ Hz, 2 H), 1.17 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.8, 137.8, 127.7, 127.4, 121.5, 118.9, 116.9, 116.6, 110.7, 66.7, 62.4, 53.5, 16.2; HRMS (ESI-TOF) calcd for $\text{C}_{13}\text{H}_{14}\text{BrNO}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 349.9998, found 349.9996.

4.6.4. Methyl 4-bromo-3-[(cyclohexyloxy)methyl]-1-hydroxy-1*H*-indole-2-carboxylate (19)— $R_f = 0.58$ (silica gel, MeOH: CH_2Cl_2 , 5:95); IR (film) ν_{max} 3173 (br), 2922, 2853, 1713, 1530, 1433, 1348, 1256, 1228, 1188, 1148, 1125, 1057, 948, 771, 736 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.33 (s, 1 H), 7.40 (d, $J = 8.3$ Hz, 1 H), 7.32 (d, $J = 7.5$ Hz, 1 H), 7.14 (t, $J = 7.9$ Hz, 1 H), 5.05 (s, 2 H), 3.91 (s, 3 H), 3.52–3.49 (m, 1 H), 1.97–1.93 (m, 1 H), 1.73–1.69 (m, 2 H), 1.55–1.50 (m, 1 H), 1.34–1.21 (m, 6 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.2, 137.1, 127.1, 127.0, 126.7, 120.8, 116.6, 115.9, 110.1, 78.0, 59.3, 52.8, 33.0 (2 C), 26.6 (2 C), 25.8; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{20}\text{BrNO}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 404.0468, found 404.0469.

4.6.5. Methyl 3-[(benzyloxy)methyl]-1-hydroxy-4-([2-(trimethylsilyl)ethoxy]methoxy)-methyl)-1*H*-indole-2-carboxylate (20)— $R_f = 0.69$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 2950, 1718, 1439, 1248, 1057, 835 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.24 (s, 1 H), 7.46 (d, $J = 8.0$ Hz, 1 H), 7.36–7.26 (m, 6 H), 7.46 (d, $J = 7.0$ Hz, 1 H), 5.05 (s, 2 H), 5.02 (s, 2 H), 4.71 (s, 2 H), 4.56 (s, 2 H), 3.88 (s, 3 H), 3.61 (t, $J = 8.5$ Hz, 2 H), 0.88 (t, $J = 8.5$ Hz, 2 H), -0.01 (s, 9 H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.7, 139.9, 136.7, 133.6, 130.9, 130.4, 129.2 (2 C), 128.6 (2 C), 128.3, 126.3, 125.7, 122.9, 110.3, 94.9, 72.1, 68.2, 65.8, 63.2, 52.7, 18.6, -1.4 (3 C); HRMS (ESI-TOF) calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_6\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 494.1969, found 494.1969.

4.6.6. Methyl 3-[(benzyloxy)methyl]-4-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (21)— $R_f = 0.76$ (silica gel, MeOH: CH_2Cl_2 , 5:95); IR (film) ν_{max} 3194, 2939, 2862, 1711, 1628, 1523, 1434, 1362, 1318, 1263, 1229, 1135, 1097, 1044, 1025, 991, 936, 775, 731, 692 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.30 (br s, 1 H), 7.34–7.24 (m, 7 H), 6.84 (dd, $J = 11.4, 7.5$ Hz, 1 H), 4.97 (s, 2 H), 4.55 (s, 2 H), 3.88 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.2, 159.2 (d, $J = 249.1$ Hz), 140.6, 138.2 (d, $J = 10.3$ Hz), 129.8 (2 C), 129.3 (2 C), 128.9, 127.9 (d, $J = 8.4$ Hz), 126.2, 115.2 (d, $J = 4.0$ Hz), 112.3 (d, $J = 20.6$

(Hz), 107.5 (d, $J = 4.0$ Hz), 107.4 (d, $J = 19.3$ Hz), 73.7, 64.1, 53.4; HRMS (ESI-TOF) calcd for $C_{18}H_{16}FNO_4Na^+$ [$M + Na^+$] 352.0955, found 352.0952.

4.6.7. Methyl 3-[(benzyloxy)methyl]-5-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (22)— $R_f = 0.78$ (silica gel, EtOAc:hexanes, 1:1); IR (film) ν_{max} 3315 (br), 2954, 1708, 1528, 1444, 1259, 1192, 1105 cm^{-1} ; 1H NMR (500 MHz, CD_3CN) δ 9.22 (s, 1 H), 7.49–7.45 (m, 2 H), 7.36–7.30 (m, 5 H), 7.21–7.15 (m, 1 H), 4.96 (s, 2 H), 4.54 (s, 2 H), 3.88 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.3, 159.0 (d, $J = 234.0$ Hz), 139.8, 133.1, 129.2 (2 C), 128.7 (2 C), 128.4, 126.0, 123.2 (d, $J = 16.4$ Hz), 116.8 (d, $J = 2.3$ Hz), 115.6 (d, $J = 27.3$ Hz), 112.0 (d, $J = 9.8$ Hz), 106.4 (d, $J = 24.2$ Hz), 72.6, 63.6, 52.6; HRMS (ESI-TOF) calcd for $C_{18}H_{15}FNO_4^-$ [$M - H^-$] 328.0991, found 328.0995.

4.6.8. Methyl 3-[(benzyloxy)methyl]-6-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (23)— $R_f = 0.63$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3205 (br), 3032, 2951, 2860, 1714, 1628, 1529, 1438, 1355, 1177, 1054, 917, 832, 755 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 9.19 (s, 1 H), 7.81 (dd, $J = 8.4, 4.8$ Hz, 1 H), 7.36–7.23 (m, 5 H), 7.19 (dd, $J = 9.0, 1.8$ Hz, 1 H), 6.96 (dt, $J = 9.3, 2.4$ Hz, 1 H), 4.98 (s, 2 H), 4.54 (s, 2 H), 3.88 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.9 (d, $J = 240.3$ Hz), 162.3, 139.7, 136.5 (d, $J = 13.1$ Hz), 129.2 (2 C), 129.1, 128.7 (2 C), 128.4, 127.6, 124.2 (d, $J = 10.4$ Hz), 119.7, 111.1 (d, $J = 25.7$ Hz), 96.3 (d, $J = 27.2$ Hz), 72.7, 63.6, 52.5; HRMS (ESI-TOF) calcd for $C_{18}H_{16}FNO_4Na^+$ [$M + Na^+$] 352.0955, found 352.0949.

4.6.9. Methyl 3-[(benzyloxy)methyl]-6-cyano-1-hydroxy-1*H*-indole-2-carboxylate (24)— $R_f = 0.71$ (silica gel, EtOAc:hexanes, 1:1); IR (film) ν_{max} 2925, 1854, 2225, 1717, 1660, 1573, 1527, 1438, 1416, 1364, 1258, 1144, 1084, 1018, 867, 735, 698 cm^{-1} ; 1H NMR (500 MHz, CD_3CN) δ 9.38 (br s, 1 H), 7.94 (d, $J = 8.5$ Hz, 1 H), 7.93–7.91 (m, 1 H), 7.39 (dd, $J = 8.0, 1.5$ Hz, 1 H), 7.35–7.30 (m, 5 H), 4.99 (s, 2 H), 4.55 (s, 2 H), 3.91 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.4, 139.6, 129.2 (2 C), 128.7 (2 C), 128.5, 127.7, 125.5, 123.9, 123.5, 120.8, 120.4, 117.0, 115.9, 108.8, 72.8, 63.4, 52.9; HRMS (ESI-TOF) calcd for $C_{19}H_{15}N_2O_4^-$ [$M - H^-$] 335.1037, found 335.1049.

4.6.10. Methyl 4-bromo-3-[(hexylthio)methyl]-1-hydroxy-1*H*-indole-2-carboxylate (25)— $R_f = 0.63$ (silica gel, EtOAc:hexanes, 6:4); IR (film) ν_{max} 3349 (br), 2956, 2912, 2847, 1703, 1681, 1517, 1440, 1397, 1342, 1304, 1255, 1195, 1146, 1118, 982, 872, 774, 741 cm^{-1} ; 1H NMR (500 MHz, CD_3CN) δ 9.18 (s, 1 H), 7.46 (d, $J = 8.5$ Hz, 1 H), 7.34 (d, $J = 7.5$ Hz, 1 H), 7.22 (dd, $J = 8.5, 7.5$ Hz, 1 H), 4.44 (s, 2 H), 3.93 (s, 3 H), 2.48 (t, $J = 7.3$ Hz, 2 H), 1.52–1.46 (m, 2 H), 1.33–1.19 (m, 6 H), 0.84 (t, $J = 6.6$ Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.5, 137.9, 127.4, 126.7, 125.6, 120.0, 118.9, 116.2, 110.4, 52.8, 32.2, 32.1, 30.5, 29.3, 25.9, 23.2, 14.3; HRMS (ESI-TOF) calcd for $C_{17}H_{21}BrNO_3S^-$ [$M - H^-$] 398.0431 found 398.0420.

4.6.11. Methyl 4-bromo-1-hydroxy-3-[(phenylthio)methyl]-1*H*-indole-2-carboxylate (26)— $R_f = 0.60$ (silica gel, EtOAc:hexanes, 6:4); IR (film) ν_{max} 3342 (br), 2943, 1684, 1514, 1437, 1396, 1343, 1308, 1255, 1191, 1144, 1120, 1020, 979, 873, 773, 738, 691 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 9.18 (br s, 1 H), 7.46 (d, $J = 8.3$ Hz, 1 H), 7.35 (d, $J = 7.4$ Hz, 1 H), 7.28–7.19 (m, 6 H), 4.83 (s, 2 H), 3.69 (s, 3 H); ^{13}C NMR (100 MHz, CD_3CN) δ 162.0, 137.6, 136.4, 132.8 (2 C), 129.8 (2 C), 128.1, 127.3, 126.7, 125.8, 119.8, 116.6, 116.1, 110.4, 52.6, 30.1; HRMS (ESI-TOF) calcd for $C_{17}H_{14}BrNO_3SNa^+$ [$M + Na^+$] 413.9770 found 413.9761.

4.6.12. Methyl 3-[(cyclohexylthio)methyl]-4-bromo-1-hydroxy-1*H*-indole-2-carboxylate (27)— $R_f = 0.65$ (silica gel, EtOAc:hexanes, 6:4); IR (film) ν_{max} 3349 (br),

2956, 2912, 2847, 1703, 1681, 1517, 1440, 1397, 1342, 1304, 1255, 1195, 1146, 1118, 982, 872, 774, 741 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.17 (s, 1 H), 7.45 (d, $J = 9.7$ Hz, 1 H), 7.33 (d, $J = 9.0$ Hz, 1 H), 7.20 (dd, $J = 9.7, 9.0$ Hz, 1 H), 4.47 (s, 2 H), 3.94 (s, 3 H), 2.72–2.64 (m, 1 H), 1.95–1.88 (m, 1 H), 1.75–1.67 (m, 2 H), 1.59–1.54 (m, 1 H), 1.33–1.21 (m, 6 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.5, 137.9, 127.3, 126.6, 125.5, 120.0, 119.2, 116.1, 110.3, 52.8, 44.1, 34.7 (2 C), 26.9 (2 C), 26.5, 24.5; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{21}\text{BrNO}_3\text{S}^+ [\text{M} + \text{H}^+]$ 420.0239, found 420.0236.

4.6.13. Methyl 3-[(benzylthio)methyl]-1-hydroxy-4-[(2-(trimethylsilyl)ethoxy)methoxy]-methyl)-1*H*-indole-2-carboxylate (28)— $R_f = 0.65$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 2950, 1709, 1527, 1440, 1248, 1027, 859, 835, 753 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.20 (s, 1 H), 7.44 (dd, $J = 8.4, 1.2$ Hz, 1 H), 7.34–7.22 (m, 6 H), 7.13 (d, $J = 6.8$ Hz, 1 H), 4.95 (s, 2 H), 4.64 (s, 2 H), 4.38 (s, 2 H), 3.83 (s, 3 H), 3.80 (s, 2 H), 3.83 (t, $J = 7.6$ Hz, 2 H), 0.87 (t, $J = 7.6$ Hz, 2 H), -0.02 (s, 9 H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.8, 139.7, 137.1, 133.3, 129.6 (2 C), 129.3 (2 C), 127.7, 126.5, 124.6, 123.3, 120.6, 117.3, 110.7, 94.8, 68.7, 65.9, 52.5, 37.2, 27.6, 18.6, -1.4 (3 C); HRMS (ESI-TOF) calcd for $\text{C}_{25}\text{H}_{33}\text{NO}_5\text{SSiNa}^+ [\text{M} + \text{Na}^+]$ 510.1741, found 510.1731.

4.6.14. Methyl 3-[(benzylthio)methyl]-4-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (29)— $R_f = 0.65$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3356, 2950, 1700, 1630, 1532, 1451, 1355, 1321, 1262, 1236, 1137, 948, 924 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.22 (s, 1 H), 7.33–7.20 (m, 7 H), 6.81 (dd, $J = 10.5, 6.5$ Hz, 1 H), 4.25 (s, 2 H), 3.85 (s, 3 H), 3.77 (s, 2 H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.3, 158.4 (d, $J = 248.5$ Hz), 139.7, 138.5 (d, $J = 10.3$ Hz), 129.6 (2 C), 129.2 (2 C), 127.7, 127.5 (d, $J = 8.0$ Hz), 125.2, 116.5 (d, $J = 4.0$ Hz), 111.6 (d, $J = 20.0$ Hz), 106.9 (d, $J = 4.3$ Hz), 106.5 (d, $J = 19.3$ Hz), 52.6, 37.0, 27.9; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{15}\text{FNO}_3\text{S}^- [\text{M} - \text{H}^-]$ 344.0762, found 344.0765.

4.6.15. Methyl 3-[(benzylthio)methyl]-5-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (30)— $R_f = 0.52$ (silica gel, EtOAc:hexanes, 1:1); IR (film) ν_{max} 2956, 1718, 1522, 1442, 1262, 1180 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.13 (br s, 1 H), 7.45 (dd, $J = 8.5, 4.0$ Hz, 1 H), 7.34–7.22 (m, 6 H), 7.17 (dt, $J = 9.5, 2.5$ Hz, 1 H), 4.15 (s, 2 H), 3.84 (s, 3 H), 3.72 (s, 2 H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.3, 158.8 (d, $J = 233.8$ Hz), 139.7, 133.4, 129.6 (2 C), 129.3 (2 C), 127.7, 125.8, 122.9 (d, $J = 9.9$ Hz), 117.5, 115.7 (d, $J = 27.4$ Hz), 112.2 (d, $J = 9.5$ Hz), 106.0 (d, $J = 24.0$ Hz), 52.5, 37.0, 26.3; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{15}\text{FNO}_3\text{S}^- [\text{M} - \text{H}^-]$ 344.0762, found 344.0769.

4.6.16. Methyl 3-[(benzylthio)methyl]-6-fluoro-1-hydroxy-1*H*-indole-2-carboxylate (31)— $R_f = 0.53$ (silica gel, EtOAc:hexanes, 3:7); IR (film) ν_{max} 3315 (br), 2955, 1720, 1530, 1532, 1445, 1399, 1351, 1291, 1266, 1178, 1123 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.19 (br s, 1 H), 7.65 (dd, $J = 8.8, 5.2$ Hz, 1 H), 7.34–7.23 (m, 5 H), 7.16 (dd, $J = 9.2, 2.4$ Hz, 1 H), 6.95–6.90 (m, 1 H), 4.17 (s, 2 H), 3.82 (s, 3 H), 3.72 (s, 2 H); ^{13}C NMR (125 MHz, CD_3CN) δ 163.0 (d, $J = 240.4$ Hz), 162.3, 139.7, 136.8 (d, $J = 13.3$ Hz), 129.7 (2 C), 129.4, 128.3 (2 C), 128.0, 127.7, 123.8 (d, $J = 10.4$ Hz), 119.5, 110.8 (d, $J = 25.6$ Hz), 96.4 (d, $J = 27.0$ Hz), 52.4, 37.0, 26.3; HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{15}\text{FNO}_3\text{S}^- [\text{M} - \text{H}^-]$ 344.0762, found 344.0769.

4.6.17. Methyl 3-[(benzylthio)methyl]-6-cyano-1-hydroxy-1*H*-indole-2-carboxylate (32)— $R_f = 0.59$ (silica gel, EtOAc:hexanes, 1:1); IR (film) ν_{max} 2924, 2360, 2224, 1715, 1523, 1444, 1264, 1116 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.31 (s, 1 H), 7.89 (s, 1 H), 7.77 (d, $J = 8.5$ Hz, 1 H), 7.36 (d, $J = 8.5$ Hz, 1 H), 7.28–7.22 (m, 5 H), 4.18

(s, 2 H), 3.86 (s, 3 H), 3.72 (s, 2 H); ^{13}C NMR (125 MHz, CD_3CN) δ 161.9, 139.5, 134.9, 132.2, 129.6 (2 C), 129.3 (2 C), 127.7, 125.1, 123.6, 123.0, 120.4, 117.7, 115.9, 109.0, 52.8, 37.0, 26.0; HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{15}\text{N}_2\text{O}_3\text{S}^-$ [$\text{M} - \text{H}^-$] 351.0809, found 351.0813.

4.6.18. Methyl 4-bromo-1-hydroxy-3-(morpholin-4-ylmethyl)-1H-indole-2-carboxylate (33)— R_f = 0.13 (silica gel, EtOAc:hexanes, 6:4); IR (film) ν_{max} 3414 (br), 2923, 2858, 1713, 1642, 1604, 1549, 1517, 1462, 1435, 1353, 1260, 1244, 1221, 1184, 1113, 867, 769, 730 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 7.47 (d, J = 8.3 Hz, 1 H), 7.35 (d, J = 7.5 Hz, 1 H), 7.19 (t, J = 7.9 Hz, 1 H), 4.08 (s, 2 H), 3.93 (s, 3 H) 3.53 (br s, 4 H), 2.48 (br s, 4 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.7, 137.8, 127.7, 126.9, 126.8, 121.3, 116.4, 116.3, 110.2, 67.7 (2 C), 54.0 (2 C), 52.7, 51.1; HRMS (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{18}\text{BrN}_2\text{O}_4^+$ [$\text{M} + \text{H}^+$] 369.0444, found 369.0446.

4.6.19. Methyl 3-(anilinomethyl)-4-bromo-1-hydroxy-1H-indole-2-carboxylate (34)— R_f = 0.76 (silica gel, MeOH: CH_2Cl_2 , 3:97); IR (film) ν_{max} 3385 (br), 2927, 2843, 1706, 1599, 1496, 1435, 1351, 1309, 1253, 1225, 1183, 1127, 1061, 1024, 767, 739 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.24 (br s, 1 H), 7.48 (d, J = 8.3 Hz, 1 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.22 (dd, J = 8.3, 7.5 Hz, 1 H), 7.12 (dd, J = 8.5, 7.6 Hz, 2 H), 6.69 (d, J = 7.6 Hz, 2 H), 6.65–6.60 (m, 1 H), 4.83 (s, 2 H), 3.91 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.4, 149.6, 137.6, 130.0 (2 C), 127.3, 126.7, 120.8, 117.8, 117.5, 115.9, 115.3, 114.0 (2 C), 110.4, 52.9, 38.1; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{16}\text{BrN}_2\text{O}_3^+$ [$\text{M} + \text{H}^+$] 375.0339, found 375.0327.

4.6.20. Methyl 4-bromo-1-hydroxy-3-(4-hydroxybenzyl)-1H-indole-2-carboxylate (35)— R_f = 0.41 (silica gel, EtOAc:hexanes, 6:4); IR (film) ν_{max} 3342 (br), 2943, 1690, 1614, 1508, 1443, 1343, 1249, 1173, 1120, 873, 756, 732 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.16 (br s, 1 H), 7.49 (d, J = 8.3 Hz, 1 H), 7.30 (d, J = 7.4 Hz, 1 H), 7.19 (dd, J = 8.3, 7.4 Hz, 1 H), 6.92 (d, J = 8.5 Hz, 2 H), 6.65 (d, J = 8.5 Hz, 2 H), 4.62 (s, 2 H), 3.86 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.5, 155.6, 137.8, 133.5, 129.9 (2 C), 127.2, 126.4, 126.0, 120.6, 120.3, 116.0, 115.6 (2 C), 110.3, 52.5, 29.3; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{14}\text{BrNO}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 397.9998, found 397.9987.

4.6.21. Methyl 4-bromo-1-hydroxy-3-(3-hydroxy-2,4-dimethoxybenzyl)-1H-indole-2-carboxylate (36)— R_f = 0.42 (silica gel, EtOAc:hexanes, 6:4); IR (film) ν_{max} 3414, 2934, 2835, 1708, 1675, 1615, 1489, 1440, 1396, 1347, 1287, 1249, 1085, 1030, 894, 746 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.21 (s, 1 H), 7.51 (d, J = 7.9 Hz, 1 H), 7.28 (d, J = 7.9 Hz, 1 H), 7.21 (t, J = 7.9 Hz, 1 H), 6.46 (d, J = 8.6 Hz, 1 H), 6.38 (s, 1 H), 5.92 (d, J = 8.6 Hz, 1 H), 4.62 (s, 2 H), 3.86 (s, 3 H), 3.82 (s, 3 H), 3.74 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.5, 147.5, 146.0, 139.7, 138.0, 128.6, 127.3, 126.5, 126.4, 121.2, 119.2, 118.6, 116.3, 110.4, 107.5, 60.4, 56.7, 52.6, 24.7; HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{18}\text{BrNO}_6\text{Na}^+$ [$\text{M} + \text{Na}^+$] 458.0210, found 458.0200.

4.6.22. Methyl 4-bromo-1-hydroxy-3-[(2-oxocyclohexyl)methyl]-1H-indole-2-carboxylate (37)— R_f = 0.38 (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3319, 2928, 2855, 1705, 1515, 1436, 1399, 1341, 1304, 1251, 1230, 1120, 882, 756, 729 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.14 (br s, 1 H), 7.45 (d, J = 8.0 Hz, 1 H), 7.30 (d, J = 8.0 Hz, 1 H), 7.17 (t, J = 8.0 Hz, 1 H), 3.90 (s, 3 H), 3.73 (dd, J = 14.2, 4.4 Hz, 1 H), 3.18 (dd, J = 14.2, 9.2 Hz, 1 H), 2.83–2.75 (m, 1 H), 2.37–2.26 (m, 2 H), 2.02–1.96 (m, 1 H), 1.90–1.84 (m, 1 H), 1.78–1.71 (m, 1 H), 1.68–1.58 (m, 1 H), 1.57–1.42 (m, 2 H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.7, 162.9, 138.1, 127.1, 126.7, 126.5, 120.8, 120.0, 116.2, 110.4, 53.6, 52.6,

42.7, 33.6, 28.8, 25.8, 24.5; HRMS (ESI-TOF) calcd for $C_{17}H_{18}BrNO_4Na^+$ [$M + Na^+$] 402.0311, found 402.0299.

4.6.23. Methyl 4-bromo-1-hydroxy-3-[(2-oxocyclopentyl)methyl]-1*H*-indole-2-carboxylate (38)— R_f = 0.32 (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3318, 2954, 2872, 1713, 1689, 1531, 1437, 1396, 1349, 1307, 1243, 1184, 1143, 1119, 1078, 978, 884, 773, 737 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 9.29 (br s, 1 H), 7.45 (d, J = 7.9 Hz, 1 H), 7.29 (d, J = 7.9 Hz, 1 H), 7.17 (t, J = 7.9 Hz, 1 H), 3.89 (s, 3 H), 3.68 (dd, J = 13.8, 6.2 Hz, 1 H), 3.25 (dd, J = 13.8, 9.2 Hz, 1 H), 2.63–2.54 (m, 1 H), 2.20–2.09 (m, 1 H), 1.97–1.91 (m, 2 H), 1.90–1.83 (m, 1 H), 1.74–1.65 (m, 2 H); ^{13}C NMR (150 MHz, CD_3CN) δ 200.0, 162.7, 137.9, 127.1, 126.3, 125.8, 120.4, 120.2, 116.1, 110.3, 52.5, 51.6, 38.5, 29.6, 24.7, 21.0; HRMS (ESI-TOF) calcd for $C_{16}H_{16}BrNO_4Na^+$ [$M + Na^+$] 388.0155, found 388.0148.

4.6.24. Methyl 4-bromo-1-hydroxy-3-[(1-oxo-1,2,3,4-tetrahydronaphthalen-2-yl)methyl]-1*H*-indole-2-carboxylate (39)— R_f = 0.35 (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3310, 2944, 2850, 1708, 1676, 1598, 1519, 1451, 1399, 1352, 1300, 1242, 1221, 1116, 1022, 980, 881, 776, 734 cm^{-1} ; 1H NMR (400 MHz, CD_3CN) δ 9.27 (br s, 1 H), 7.92 (d, J = 7.7 Hz, 1 H), 7.51–7.43 (m, 2 H), 7.31 (t, J = 7.7 Hz, 2 H), 7.26 (d, J = 7.7 Hz, 1 H), 7.18 (t, J = 7.7 Hz, 1 H), 4.06 (br s, 1 H), 3.74 (s, 3 H), 3.39 (br s, 1 H), 3.02–2.92 (m, 2 H), 2.91–2.80 (m, 1 H), 2.07–1.97 (m, 1 H), 1.95 (s, 1 H); ^{13}C NMR (125 MHz, CD_3CN) δ 199.7, 162.8, 145.4, 138.0, 134.1, 133.4, 129.9, 127.7, 127.4, 127.2, 126.5, 126.2, 120.8, 119.8, 116.2, 110.4, 52.5, 50.6, 29.0, 28.7, 24.9; HRMS (ESI-TOF) calcd for $C_{21}H_{18}BrNO_4Na^+$ [$M + Na^+$] 450.0311, found 450.0297.

4.6.25. Methyl 4-bromo-1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (40)— R_f = 0.37 (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3300, 2965, 2923, 1708, 1680, 1514, 1441, 1341, 1247, 1184, 1148, 1116, 1090, 1033, 975, 881, 771, 734 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 9.22 (br s, 1 H), 7.45 (d, J = 7.9 Hz, 1 H), 7.32 (d, J = 7.9 Hz, 1 H), 7.19 (t, J = 7.9 Hz, 1 H), 3.91 (s, 3 H), 3.49 (br s, 1 H), 3.35 (br s, 1 H), 3.03–2.97 (m, 1 H), 2.51–2.43 (m, 1 H), 2.34–2.26 (m, 1 H), 0.99 (d, J = 7.0 Hz, 3 H), 0.89 (d, J = 7.2 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 215.2, 162.6, 138.0, 127.2, 126.6, 126.3, 120.6, 119.4, 116.1, 110.4, 52.6, 48.9, 35.3, 27.7, 15.9, 7.9; HRMS (ESI-TOF) calcd for $C_{16}H_{18}BrNO_4Na^+$ [$M + Na^+$] 390.0311, found 390.0307.

4.6.26. Methyl 4-bromo-1-hydroxy-3-(3-oxo-3-phenylpropyl)-1*H*-indole-2-carboxylate (41)— R_f = 0.35 (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3357, 2914, 1708, 1674, 1594, 1520, 1441, 1395, 1310, 1242, 1146, 1117, 771, 737, 686 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 9.29 (br s, 1 H), 7.99–7.94 (m, 2 H), 7.60–7.55 (m, 1 H), 7.49–7.43 (m, 3 H), 7.30 (br s, 1 H), 7.18 (t, J = 7.7 Hz, 1 H), 3.85 (s, 3 H), 3.63 (br s, 2 H), 3.35 (t, J = 7.7 Hz, 2 H); ^{13}C NMR (150 MHz, CD_3CN) δ 200.1, 162.5, 137.8, 133.9, 129.5, 128.7, 128.6, 127.1, 126.2, 125.5, 121.0, 120.4, 116.0, 110.3, 52.5, 41.7, 20.2 (3 C); HRMS (ESI-TOF) calcd for $C_{19}H_{16}BrNO_4Na^+$ [$M + Na^+$] 424.0155, found 424.0154.

4.6.27. Methyl 4-bromo-3-(4,4-dimethyl-3-oxopentyl)-1-hydroxy-1*H*-indole-2-carboxylate (42)— R_f = 0.46 (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3283, 2942, 2872, 1725, 1707, 1519, 1437, 1396, 1349, 1243, 1178, 1149, 1119, 984, 884, 779, 737 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 9.34 (br s, 1 H), 7.44 (br s, 1 H), 7.29 (br s, 1 H), 7.17 (t, J = 7.4 Hz, 1 H), 3.90 (s, 3 H), 3.40 (br s, 2 H), 2.87 (t, J = 7.9 Hz, 2 H), 1.09 (s, 9 H); ^{13}C NMR (150 MHz, CD_3CN) δ 215.7, 162.6, 138.6, 127.2, 126.3, 124.8, 121.5, 120.5, 116.1, 110.3, 52.7, 44.6, 39.7, 26.6, 20.1 (3 C); HRMS (ESI-TOF) calcd for $C_{17}H_{20}BrNO_4Na^+$ [$M + Na^+$] 404.0468, found 404.0456.

4.6.28. Methyl 4-bromo-1-hydroxy-3-(2,2,4-trimethyl-3-oxopentyl)-1H-indole-2-carboxylate (43)— R_f = 0.45 (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3309, 2972, 2868, 1712, 1689, 1515, 1464, 1440, 1379, 1346, 1271, 1234, 1182, 1140, 1117, 1042, 1000, 878, 798, 775, 742 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.49 (br s, 1 H), 7.49 (br s, 1 H), 7.33 (br s, 1 H), 7.18 (t, J = 7.2 Hz, 1 H), 3.90 (s, 3 H), 3.67 (br s, 2 H), 3.30 (hept, J = 6.6 Hz, 1 H), 1.04 (d, J = 6.6 Hz, 6 H), 0.97 (s, 6 H); ^{13}C NMR (150 MHz, CD_3CN) δ 220.1, 162.9, 137.6, 128.1, 127.2, 126.6, 121.8, 116.1, 115.6, 110.4, 52.6, 50.6, 35.0, 29.5, 23.0 (2 C), 20.4 (2 C); HRMS (ESI-TOF) calcd for $\text{C}_{18}\text{H}_{22}\text{BrNO}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 418.0624, found 418.0620.

4.6.29. Methyl 4-bromo-3-(2,2-difluoro-3-oxo-3-phenylpropyl)-1-hydroxy-1H-indole-2-carboxylate (44)— R_f = 0.47 (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3360, 2955, 2919, 1698, 1520, 1449, 1311, 1264, 1184, 1127, 914, 764, 716 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.24 (br s, 1 H), 8.04–8.02 (m, 2 H), 7.68 (t, J = 7.3 Hz, 1 H), 7.53–7.50 (m, 3 H), 7.38–7.36 (m, 1 H), 7.24–7.21 (m, 1 H), 4.46 (t, J = 17.7 Hz, 2 H), 3.80 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 190.5, 162.1, 137.2, 135.4, 133.0, 130.7 (t, J = 3.4 Hz, 2 C), 129.7 (2 C), 127.4, 127.2, 127.1, 121.1, 119.1, 115.9, 110.4, 108.9, 52.7, 29.7 (t, J = 23.8 Hz); HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{15}\text{BrF}_2\text{NO}_4^+ [\text{M} + \text{H}^+]$ 438.0147, found 438.0145.

4.6.30. Methyl 4-bromo-3-[3-(4-chlorophenyl)-2,2-difluoro-3-oxopropyl]-1-hydroxy-1H-indole-2-carboxylate (45)— R_f = 0.31 (silica gel, EtOAc:hexanes, 2:8); IR (film) $\nu_{\max}$ 1702, 1588, 1448, 1401, 1265, 1091, 762 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.24 (br s, 1 H), 7.96 (d, J = 8.8 Hz, 2 H), 7.53–7.50 (m, 3 H), 7.37 (d, J = 7.5 Hz, 1 H), 7.23 (t, J = 8.8 Hz, 1 H), 4.45 (t, J = 17.5 Hz, 2 H), 3.82 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 189.0, 161.6, 140.8, 136.8, 132.0 (t, J = 3.6 Hz, 2 C), 131.2, 129.5 (2 C), 129.4, 128.5, 126.8, 126.7, 120.6, 115.4, 110.0, 108.3, 52.2, 29.3 (t, J = 23.8 Hz); HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{14}\text{BrClF}_2\text{NO}_4^+ [\text{M} + \text{H}^+]$ 471.9757, found 471.9752.

4.6.31. Methyl 4-bromo-3-(2,2-difluoro-3-oxo-3-thien-2-ylpropyl)-1-hydroxy-1H-indole-2-carboxylate (46)— R_f = 0.25 (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3335 (br), 3105, 2954, 1714, 1679, 1614, 1517, 1447, 1411, 1345, 1311, 1266, 1186, 1148, 1127, 1058, 932, 879, 839, 761, 733 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.36 (br s, 1 H), 7.95 (dd, J = 4.5, 1.3 Hz, 1 H), 7.86–7.84 (m, 1 H), 7.51 (d, J = 8.5 Hz, 1 H), 7.38 (d, J = 7.0 Hz, 1 H), 7.26–7.18 (m, 2 H), 4.44 (t, J = 17.0 Hz, 2 H), 3.84 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 183.8, 162.1, 139.3, 138.3, 137.2, 137.1 (t, J = 5.4 Hz), 130.1, 127.5, 127.3, 127.1, 121.1, 118.9, 115.9, 110.5, 108.8, 52.7, 30.0 (t, J = 23.8 Hz); HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{13}\text{BrF}_2\text{NO}_4\text{S}^+ [\text{M} + \text{H}^+]$ 443.9711, found 443.9711.

4.6.32. Methyl 4-bromo-1-hydroxy-3-(3-oxobutyl)-1H-indole-2-carboxylate (47)— R_f = 0.37 (silica gel, EtOAc:hexanes, 1:1); IR (film) $\nu_{\max}$ 3342, 2942, 1707, 1519, 1437, 1396, 1354, 1243, 1184, 1119, 879, 773, 737 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.36 (br s, 1 H), 7.45 (d, J = 8.2 Hz, 1 H), 7.30 (d, J = 8.2 Hz, 1 H), 7.18 (t, J = 8.2 Hz, 1 H), 3.91 (s, 3 H), 3.44 (t, J = 8.0 Hz, 2 H), 2.78 (t, J = 8.0 Hz, 2 H), 2.11 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 208.7, 162.5, 137.9, 127.2, 126.3, 125.6, 121.1, 120.4, 116.0, 110.4, 52.7, 46.3, 29.9, 19.8; HRMS (ESI-TOF) calcd for $\text{C}_{14}\text{H}_{14}\text{BrNO}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 361.9998, found 361.9990.

4.6.33. Methyl 3-(2-acetyl-3-oxobutyl)-4-bromo-1-hydroxy-1H-indole-2-carboxylate (48)— R_f = 0.23 (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3392, 2956, 1710, 1697, 1617, 1519, 1433, 1353, 1243, 1180, 1140, 1117, 870, 773, 733 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.11 (br s, 1 H), 7.47 (d, J = 7.0 Hz, 1 H), 7.35 (d, J = 7.0 Hz, 1 H),

7.21 (t, $J = 7.0$ Hz, 1 H), 4.26 (t, $J = 6.0$ Hz, 1 H), 3.90 (s, 3 H), 3.71 (d, $J = 6.0$ Hz, 2 H), 2.04 (s, 6 H); ^{13}C NMR (125 MHz, CD_3CN) δ 205.1 (2 C), 162.3, 137.9, 127.3, 126.7, 126.6, 120.4, 117.4, 115.8, 110.5, 69.6, 52.7, 30.7, 23.7 (2 C); HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{16}\text{BrNO}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 404.0104, found 404.0100.

4.6.34. Methyl 4-bromo-1-hydroxy-3-(3-methoxy-2,2-dimethyl-3-oxopropyl)-1H-indole-2-carboxylate (49)— $R_f = 0.36$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3323, 2944, 1714, 1513, 1433, 1393, 1347, 1249, 1180, 1134, 1025, 985, 865, 773, 733 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.12 (br s, 1 H), 7.48 (d, $J = 7.5$ Hz, 1 H), 7.33 (d, $J = 7.5$ Hz, 1 H), 7.18 (t, $J = 7.5$ Hz, 1 H), 3.89 (s, 3 H), 3.72 (s, 2 H), 3.51 (s, 3 H), 1.11 (s, 6 H); ^{13}C NMR (125 MHz, CD_3CN) δ 178.3, 162.8, 137.7, 127.8, 127.2, 126.7, 121.8, 116.6, 116.3, 110.5, 52.7, 52.3, 44.7, 32.7, 25.1 (2 C); HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{18}\text{BrNO}_5\text{Na}^+ [\text{M} + \text{Na}^+]$ 406.0260, found 406.0243.

4.6.35. Methyl 4-bromo-1-hydroxy-3-(3-oxopropyl)-1H-indole-2-carboxylate (50)— $R_f = 0.20$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3471, 1701, 1695, 1537, 1437, 1384, 1237, 1190, 1172, 1149, 1119, 920, 873, 773, 737 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.77 (s, 1 H), 9.31 (br s, 1 H), 7.46 (d, $J = 7.9$ Hz, 1 H), 7.32 (d, $J = 7.9$ Hz, 1 H), 7.20 (t, $J = 7.9$ Hz, 1 H), 3.91 (s, 3 H), 3.56 (t, $J = 7.7$ Hz, 2 H), 2.80 (t, $J = 7.7$ Hz, 2 H); ^{13}C NMR (125 MHz, CD_3CN) δ 203.0, 162.4, 137.9, 127.3, 126.3, 125.5, 120.6, 120.4, 115.9, 110.4, 52.7, 46.7, 18.2; HRMS (ESI-TOF) calcd for $\text{C}_{13}\text{H}_{11}\text{BrNO}_4^- [\text{M} - \text{H}^-]$ 323.9877, found 323.9863.

4.6.36. Methyl 4-bromo-3-but-3-enyl-1-hydroxy-1H-indole-2-carboxylate (51)— $R_f = 0.67$ (silica gel, MeOH: CH_2Cl_2 , 3:97); IR (film) ν_{max} 3360, 2953, 1679, 1638, 1615, 1516, 1440, 1341, 1312, 1254, 1143, 1120, 911, 876, 771, 736 cm^{-1} ; ^1H NMR (400 MHz, CD_3CN) δ 9.23 (br s, 1 H), 7.44 (d, $J = 7.9$ Hz, 1 H), 7.30 (d, $J = 7.9$ Hz, 1 H), 7.18 (t, $J = 7.9$ Hz, 1 H), 6.00–5.89, (m, 1 H), 5.03 (dd, $J = 17.2$, 1.9 Hz, 1 H), 4.95 (d, $J = 10.2$ Hz, 1 H), 3.91 (s, 3 H), 3.39–3.33 (m, 2 H), 2.38 (q, $J = 7.5$ Hz, 2 H); ^{13}C NMR (125 MHz, CD_3CN) δ 162.8, 139.2, 137.9, 127.2, 126.4, 125.4, 122.2, 120.5, 116.2, 115.3, 110.3, 52.6, 37.3, 24.7; HRMS (ESI-TOF) calcd for $\text{C}_{14}\text{H}_{15}\text{BrNO}_3^+ [\text{M} + \text{H}^+]$ 324.0230, found 324.0234.

4.6.37. Methyl 4-bromo-1-hydroxy-3-(3-methylbut-3-enyl)-1H-indole-2-carboxylate (52)— $R_f = 0.69$ (silica gel, MeOH: CH_2Cl_2 , 1:99); IR (film) ν_{max} 3346, 2960, 2925, 1679, 1511, 1440, 1398, 1342, 1271, 1257, 1239, 1117, 986, 882, 775, 737 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.19 (br s, 1 H), 7.44 (d, $J = 7.9$ Hz, 1 H), 7.30 (d, $J = 7.9$ Hz, 1 H), 7.17 (t, $J = 7.9$ Hz, 1 H), 4.75 (s, 2 H), 3.92 (s, 3 H), 3.41–3.35 (m, 2 H), 2.35–2.30 (m, 2 H), 1.81 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.7, 146.8, 137.7, 127.1, 126.2, 125.0, 122.4, 120.3, 116.1, 110.6, 110.2, 52.5, 41.2, 24.2, 22.5; HRMS (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{15}\text{BrNO}_3^- [\text{M} - \text{H}^-]$ 336.0241, found 336.0238.

4.6.38. Methyl 4-bromo-3-[3-(chloromethyl)but-3-enyl]-1-hydroxy-1H-indole-2-carboxylate (53)— $R_f = 0.70$ (silica gel, MeOH: CH_2Cl_2 , 1:99); IR (film) ν_{max} 3377, 2954, 2907, 1678, 1513, 1443, 1396, 1343, 1313, 1255, 1119, 908, 879, 787, 732 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.20 (s, 1 H), 7.45 (d, $J = 8.0$ Hz, 1 H), 7.32 (d, $J = 8.0$ Hz, 1 H), 7.19 (t, $J = 8.0$ Hz, 1 H), 5.20 (s, 1 H), 5.05 (s, 1 H), 4.19 (s, 2 H), 3.93 (s, 3 H), 3.42 (t, $J = 8.4$ Hz, 2 H), 2.49 (t, $J = 8.4$ Hz, 2 H); ^{13}C NMR (150 MHz, CD_3CN) δ 162.7, 146.5, 137.8, 127.2, 126.3, 125.2, 121.7, 120.3, 116.1, 115.4, 110.3, 52.7, 49.0, 36.0, 24.2; HRMS (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{14}\text{BrClNO}_3^- [\text{M} - \text{H}^-]$ 369.9851, found 369.9852.

4.6.39. Methyl 4-bromo-3-(cyclopenta-2,4-dien-1-ylmethyl)-1-hydroxy-1H-indole-2-carboxylate (54)— $R_f = 0.75$ (silica gel, MeOH:CH₂Cl₂, 1:99); IR (film) $\nu_{\max}$ 3356, 2943, 1675, 1614, 1515, 1445, 1398, 1342, 1304, 1257, 1121, 986, 878, 775, 737 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 9.38 (br s, 1 H), 7.47 (d, $J = 7.9$ Hz, 1 H), 7.28 (d, $J = 7.9$ Hz, 1 H), 7.18 (t, $J = 7.9$ Hz, 1 H), 6.34–6.29 (m, 1 H), 6.24–6.19 (m, 1 H), 5.83 (br s, 1 H), 4.43 (br s, 2 H), 3.89 (s, 3 H), 2.93 (s, 2 H); ¹³C NMR (150 MHz, CD₃CN) δ 162.6, 150.3, 138.0, 133.2, 131.7, 127.7, 127.2, 126.4, 125.7, 120.5, 120.4, 116.3, 110.4, 52.6, 44.1, 26.4; HRMS (ESI-TOF) calcd for C₁₆H₁₃BrNO₃⁻ [M - H⁻] 346.0084, found 346.0072.

4.6.40. Methyl 4-bromo-1-hydroxy-3-(methoxymethyl)-1H-indole-2-carboxylate (55)— $R_f = 0.32$ (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3175, 2937, 2887, 1709, 1525, 1436, 1404, 1346, 1311, 1257, 1227, 1187, 1123, 1073, 934, 879, 775, 736, 666 cm⁻¹; ¹H NMR (400 MHz, CD₃CN) δ 9.38 (br s, 1 H), 7.44 (dd, $J = 8.3, 0.7$ Hz, 1 H), 7.34 (dd, $J = 7.6, 0.7$ Hz, 1 H), 7.18 (dd, $J = 8.3, 7.6$ Hz, 1 H), 4.97 (s, 2 H), 3.93 (s, 3 H), 3.35 (s, 3 H); ¹³C NMR (125 MHz, CD₃CN) δ 162.3, 137.3, 127.1, 127.0, 126.8, 121.0, 116.0, 115.9, 110.2, 63.4, 57.7, 52.9; HRMS (ESI-TOF) calcd for C₁₂H₁₂BrNO₄Na⁺ [M + Na⁺] 335.9842, found 335.9834.

4.6.41. Methyl 4-bromo-1-hydroxy-3-methyl-1H-indole-2-carboxylate (56)— $R_f = 0.58$ (silica gel, MeOH:CH₂Cl₂, 1:99); IR (film) $\nu_{\max}$ 3436, 2919, 1672, 1613, 1519, 1443, 1272, 1184, 1119, 978, 873, 761, 726, 679, 608, 561 cm⁻¹; ¹H NMR (400 MHz, CD₃CN) δ 9.09 (s, 1 H), 7.43 (d, $J = 7.9$ Hz, 1 H), 7.29 (d, $J = 7.9$ Hz, 1 H), 7.17 (t, $J = 7.9$ Hz, 1 H), 3.92 (s, 3 H), 2.78 (s, 3 H); ¹³C NMR (125 MHz, CD₃CN) δ 162.9, 138.2, 127.3, 126.1, 125.7, 121.4, 118.5, 116.7, 110.3, 52.6, 12.0; HRMS (ESI-TOF) calcd for C₁₁H₉BrNO₃⁻ [M - H⁻] 281.9771, found 281.9770.

4.6.42. Methyl 4-bromo-1-hydroxy-3-pent-3-ynyl-1H-indole-2-carboxylate (57)— $R_f = 0.68$ (silica gel, MeOH:CH₂Cl₂, 1:99); IR (film) $\nu_{\max}$ 3360, 2942, 2907, 2848, 1689, 1513, 1443, 1396, 1255, 1119, 1025, 879, 802, 767, 732, 667 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 9.13 (br s, 1 H), 7.46 (d, $J = 7.9$ Hz, 1 H), 7.32 (d, $J = 7.9$ Hz, 1 H), 7.19 (t, $J = 7.9$ Hz, 1 H), 3.93 (s, 3 H), 3.48 (t, $J = 7.4$ Hz, 2 H), 2.46–2.41 (m, 2 H), 1.69 (t, $J = 2.4$ Hz, 3 H); ¹³C NMR (150 MHz, CD₃CN) δ 162.6, 137.8, 127.1, 126.4, 126.2, 120.3, 120.2, 116.0, 110.2, 79.1, 77.3, 52.6, 24.6, 22.2, 3.4; HRMS (ESI-TOF) calcd for C₁₅H₁₃BrNO₃⁻ [M - H⁻] 334.0084, found 334.0083.

4.6.43. Methyl 4-bromo-3-(2,2-dimethylbut-3-enyl)-1-hydroxy-1H-indole-2-carboxylate (58)— $R_f = 0.53$ (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3366, 2951, 2917, 1686, 1519, 1439, 1387, 1306, 1254, 1122, 1018, 903, 868, 793, 770, 742, 684 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 9.08 (s, 1 H), 7.46 (s, 1 H), 7.31 (s, 1 H), 7.16 (t, $J = 7.2$ Hz, 1 H), 5.87 (dd, $J = 17.4, 10.8$ Hz, 1 H), 4.77 (d, $J = 10.8$ Hz, 1 H), 4.69 (d, $J = 17.4$ Hz, 1 H), 3.88 (s, 3 H), 3.49 (br s, 2 H), 0.97 (s, 6 H); ¹³C NMR (150 MHz, CD₃CN) δ 163.2, 149.0, 137.7, 128.0, 127.2, 126.6, 121.8, 117.2, 116.4, 110.9, 110.3, 52.5, 40.1, 34.8, 26.5 (2 C); HRMS (ESI-TOF) calcd for C₁₆H₁₇BrNO₃⁻ [M - H⁻] 350.0397, found 350.0396.

4.6.44. Methyl 1-hydroxy-3-[(2-oxocyclohexyl)methyl]-1H-indole-2-carboxylate (62)— $R_f = 0.26$ (silica gel, EtOAc:hexanes, 2:8); IR (film) $\nu_{\max}$ 3020, 1742, 1702, 1528, 1447, 1214 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 9.03 (br s, 1 H), 7.68 (d, $J = 9.6$ Hz, 1 H), 7.44 (d, $J = 9.6$ Hz, 1 H), 7.36 (t, $J = 9.0$ Hz, 1 H), 7.12 (t, $J = 9.0$ Hz, 1 H), 3.91 (s, 3 H), 3.45 (dd, $J = 16.5, 5.7$ Hz, 1 H), 2.89 (dd, $J = 11.1, 5.7$ Hz, 1 H), 2.75–2.70 (m, 1 H), 2.37–2.33 (m, 2 H), 2.03–1.97 (m, 1 H), 1.86–1.83 (m, 1 H), 1.77–1.73 (m, 1 H), 1.67–1.63 (m, 1

H), 1.54 (ddt, $J = 30.0, 14.4, 4.2$ Hz, 1 H), 1.47–1.39 (ddd, $J = 30.0, 14.4, 4.2$ Hz, 1 H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.7, 163.1, 136.8, 126.8, 124.5, 123.7, 121.9, 121.4, 121.3, 110.5, 52.4, 52.3, 42.5, 34.3, 28.7, 25.5, 25.1; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{20}\text{NO}_4^+ [\text{M} + \text{H}^+]$ 302.1387, found 302.1387.

4.6.45. Methyl 1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (63)

— $R_f = 0.63$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 2929, 1700, 1540, 1507, 1457, 1259, 119 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.06 (br s, 1 H), 7.66 (d, $J = 8.5$ Hz, 1 H), 7.44 (d, $J = 8.5$ Hz, 1 H), 7.38–7.35 (m, 1 H), 7.15–7.12 (m, 1 H), 3.93 (s, 3 H), 3.30–3.26 (m, 1 H), 3.01–2.94 (m, 2 H), 2.50–2.42 (m, 1 H), 2.34–2.26 (m, 1 H), 1.01 (d, $J = 7.0$ Hz, 3 H), 0.86 (t, $J = 7.5$ Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.2, 162.3, 126.9, 124.2, 123.4, 122.3, 121.8, 121.5, 120.6, 110.5, 52.3, 47.8, 35.4, 28.8, 16.7, 7.9; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{19}\text{NO}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 312.1206, found 312.1199.

4.6.46. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-1-hydroxy-1*H*-indole-2-carboxylate (64)

— $R_f = 0.52$ (silica gel, EtOAc:hexanes, 2:8); IR (film) ν_{max} 3375, 1697, 1598, 1535, 1448, 1264, 1122 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.12 (br s, 1 H), 8.04–7.99 (m, 2 H), 7.72–7.68 (m, 2 H), 7.55–7.51 (m, 3 H), 7.4 (t, $J = 3.0$ Hz, 1 H), 7.2 (t, $J = 3.0$ Hz, 1 H), 4.1 (t, $J = 21.3$ Hz, 2 H), 3.8 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 190.5 (t, $J = 28.5$ Hz), 162.4, 136.2, 135.4, 135.1, 130.7 (t, $J = 3.2$ Hz), 130.6 (t, $J = 3.2$ Hz), 129.8, 129.7, 126.9, 125.8, 123.8, 122.1, 121.9, 110.5, 52.4, 31.1 (t, $J = 24.4$ Hz); HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{16}\text{F}_2\text{NO}_4^+ [\text{M} + \text{H}^+]$ 360.1042, found 360.1039.

4.6.47. Methyl 1-hydroxy-3-[(2-oxocyclohexyl)methyl]-4-([2-(trimethylsilyl)ethoxy]methoxy)methyl)-1*H*-indole-2-carboxylate (65)

— $R_f = 0.25$ (silica gel, EtOAc:hexanes, 2:8); IR (film) ν_{max} 3240 (br), 2936, 2860, 1709, 1438, 1396, 1235, 1125, 1037 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.11 (br s, 1 H), 7.43 (d, $J = 7.0$ Hz, 1 H), 7.31–7.30 (m, 1 H), 7.11 (d, $J = 6.5$ Hz, 1 H), 4.85 (br s, 2 H), 4.67 (s, 2 H), 3.90 (s, 3 H), 3.65–3.56 (m, 3 H), 3.12–3.05 (m, 1 H), 2.65–2.63 (m, 1 H), 2.35–2.30 (m, 2 H), 2.05–1.97 (m, 1 H), 1.88–1.84 (m, 1 H), 1.80–1.73 (m, 1 H), 1.65–1.61 (m, 1 H), 1.53–1.42 (m, 2 H), 0.88 (dd, $J = 9.0, 8.0$ Hz, 2 H), -0.01 (s, 9 H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.7, 163.3, 137.5, 133.5, 129.6, 126.2, 125.5, 123.2, 120.7, 110.7, 94.7, 68.3, 65.8, 53.3, 52.3, 42.5, 33.7, 28.6, 25.7, 18.6, -1.4 (3 C); HRMS (ESI-TOF) calcd for $\text{C}_{23}\text{H}_{36}\text{NO}_6\text{Si}^+ [\text{M} + \text{H}^+]$ 462.2306, found 462.2304.

4.6.48. Methyl 1-hydroxy-3-(2-methyl-3-oxopentyl)-4-([2-(trimethylsilyl)ethoxy]methoxy)methyl)-1*H*-indole-2-carboxylate (66)

— $R_f = 0.50$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3240 (br), 2950, 1714, 1520, 1456, 1398, 1248, 1128, 1102, 1028, 859, 836 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.14 (br s, 1 H), 7.44 (d, $J = 8.0$ Hz, 1 H), 7.32–7.29 (m, 1 H), 7.13 (d, $J = 6.5$ Hz, 1 H), 4.94 (d, $J = 12.0$ Hz, 1 H), 4.90 (d, $J = 12.0$ Hz, 1 H), 4.70 (s, 2 H), 3.92 (s, 3 H), 3.59 (dd, $J = 9.0, 8.0$ Hz, 2 H), 3.42 (dd, $J = 14.0, 6.0$ Hz, 1 H), 3.19 (dd, $J = 14.0, 7.0$ Hz, 1 H), 2.93 (dd, $J = 14.0, 7.0$ Hz, 1 H), 2.47–2.37 (m, 1 H), 2.25–2.18 (m, 1 H), 1.01 (d, $J = 7.0$ Hz, 3 H), 0.90–0.83 (m, 5 H), -0.01 (s, 9 H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.2, 163.1, 133.4, 126.2, 125.0, 124.5, 123.3, 120.9, 120.0, 110.7, 94.7, 68.4, 65.9, 52.4, 48.6, 35.6, 29.3, 18.6, 16.3, 7.8, -1.4 (3 C); HRMS (ESI-TOF) calcd for $\text{C}_{23}\text{H}_{35}\text{NO}_6\text{SiNa}^+ [\text{M} + \text{Na}^+]$ 472.2126, found 472.2126.

4.6.49. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-1-hydroxy-4-([2-(trimethylsilyl)ethoxy]methoxy)methyl)-1*H*-indole-2-carboxylate (67)

— $R_f = 0.36$ (silica gel, EtOAc:hexanes, 1:5); IR (film) ν_{max} 2951, 1700, 1449, 1251, 1096, 1028 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.21 (br s, 1 H), 8.07–8.03 (m, 2 H), 7.71–7.68 (m, 1 H), 7.55–7.49 (m, 3 H), 7.36–7.33 (m, 1 H), 7.16 (d, $J = 6.5$ Hz, 1 H), 4.95 (d, $J = 16.0$ Hz,

2 H), 4.66 (s, 2 H), 4.32 (t, $J = 18.0$ Hz, 2 H), 3.79 (s, 3 H), 3.54 (t, $J = 8.0$ Hz, 2 H), 0.81 (t, $J = 8.0$ Hz, 2 H), -0.04 (s, 9 H); ^{13}C NMR (125 MHz, CD_3CN) δ 196.2, 159.9, 136.2, 136.1, 133.6, 131.5 (t, $J = 3.0$ Hz, 2 C), 130.6, 130.5 (2 C), 130.4, 126.9, 126.5, 124.5, 120.7, 114.4, 100.6, 95.3, 69.2, 66.6, 53.2, 32.1, 19.2, -0.8 (3 C); HRMS (ESI-TOF) calcd for $\text{C}_{26}\text{H}_{31}\text{F}_2\text{NO}_6\text{SiNa}^+$ [$\text{M} + \text{Na}^+$] 542.1781, found 542.1767.

4.6.50. Methyl 4-fluoro-1-hydroxy-3-[(2-oxocyclohexyl)methyl]-1H-indole-2-carboxylate (68)— $R_f = 0.47$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3295 (br), 2931, 2849, 1702, 1631, 1566, 1531, 1443, 1401, 1361, 1314, 1255, 1231, 1131, 937, 785, 732 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.19 (br s, 1 H), 7.29–7.23 (m, 2 H), 6.77 (dd, $J = 11.4, 7.4$ Hz, 1 H), 3.92 (s, 3 H), 3.50 (dd, $J = 14.0, 4.8$ Hz, 1 H), 2.99 (dd, $J = 14.0, 5.7$ Hz, 1 H), 2.72–2.66 (m, 1 H), 2.35–2.27 (m, 2 H), 2.00–1.93 (m, 1 H), 1.87–1.85 (m, 1 H), 1.75–1.72 (m, 1 H), 1.67–1.59 (m, 1 H), 1.56–1.49 (m, 1 H), 1.46–1.39 (m, 1 H); ^{13}C NMR (150 MHz, CD_3CN) δ 212.8, 162.7, 158.8 (d, $J = 248.4$ Hz), 138.8 (d, $J = 10.3$ Hz), 127.3 (d, $J = 8.0$ Hz), 125.0, 118.8 (d, $J = 3.4$ Hz), 112.4 (d, $J = 19.5$ Hz), 106.9 (d, $J = 3.4$ Hz), 106.2 (d, $J = 20.6$ Hz), 52.7, 52.5, 42.5, 33.7, 28.6, 26.3, 25.5; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{18}\text{FNO}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 342.1112, found 342.1102.

4.6.51. Methyl 4-fluoro-1-hydroxy-3-(2-methyl-3-oxopentyl)-1H-indole-2-carboxylate (69)— $R_f = 0.46$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3299 (br), 2970, 1714, 1633, 1538, 1455, 1404, 1361, 1318, 1235, 1137 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.18 (br s, 1 H), 7.31–7.26 (m, 2 H), 6.80 (dd, $J = 12.0, 7.5$ Hz, 1 H), 3.97 (s, 3 H), 3.35 (dd, $J = 13.5, 5.5$ Hz, 1 H), 3.09 (dd, $J = 13.5, 9.0$ Hz, 1 H), 2.97–2.91 (m, 1 H), 2.53–2.43 (m, 1 H), 2.41–2.35 (m, 1 H), 0.99 (d, $J = 7.0$ Hz, 3 H), 0.92 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 214.9, 162.6, 158.6 (d, $J = 248.0$ Hz), 138.6, 132.1, 127.3 (d, $J = 8.3$ Hz), 124.8, 112.6, 106.9 (d, $J = 3.9$ Hz), 106.2 (d, $J = 19.8$ Hz), 52.5, 48.1, 34.9, 29.6, 15.8, 7.9; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{18}\text{FNO}_4\text{Na}^+$ [$\text{M} + \text{Na}^+$] 330.1112, found 330.1109.

4.6.52. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-4-fluoro-1-hydroxy-1H-indole-2-carboxylate (70)— $R_f = 0.52$ (silica gel, EtOAc:hexanes, 4:6); IR (film) ν_{max} 3364 (br), 2956, 2926, 2848, 1700, 1636, 1540, 1450, 1323, 1269, 1240, 1142, 1091, 946, 764, 716 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.21 (br s, 1 H), 8.02 (d, $J = 7.8$ Hz, 2 H), 7.69–7.66 (m, 1 H), 7.52 (dd, $J = 8.0, 7.3$ Hz, 2 H), 7.33–7.28 (m, 2 H), 6.85–6.81 (m, 1 H), 4.12 (t, $J = 17.3$ Hz, 2 H), 3.97 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 190.4, 161.8, 137.3, 136.4, 135.4, 132.9, 130.6 (t, $J = 3.8$ Hz, 2 C), 129.6 (2 C), 127.2 (d, $J = 8.6$ Hz), 126.1, 117.3, 113.0, 107.1, 106.8 (d, $J = 3.8$ Hz), 106.6 (d, $J = 20.0$ Hz), 52.4, 32.8 (t, $J = 26.7$ Hz); HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{NO}_4^+$ [$\text{M} + \text{H}^+$] 378.0948, found 378.0943.

4.6.53. Methyl 5-fluoro-1-hydroxy-3-[(2-oxocyclohexyl)methyl]-1H-indole-2-carboxylate (71)— $R_f = 0.65$ (silica gel, EtOAc:hexanes, 1:1); IR (film) ν_{max} 3311 (br), 2937, 2855, 1707, 1577, 1532, 1447, 1403, 1342, 1251, 1192, 1169, 849, 799, 757 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.04 (s, 1 H), 7.43 (dd, $J = 9.0, 4.5$ Hz, 1 H), 7.40 (dd, $J = 9.5, 2.5$ Hz, 1 H), 7.15 (dt, $J = 9.5, 2.5$ Hz, 1 H), 3.89 (s, 3 H), 3.39 (dd, $J = 14.0, 5.0$ Hz, 1 H), 2.85 (dd, $J = 14.0, 8.5$ Hz, 1 H), 2.73–2.68 (m, 1 H), 2.39–2.27 (m, 2 H), 2.04–1.98 (m, 1 H), 1.89–1.83 (m, 1 H), 1.77–1.73 (m, 1 H), 1.68–1.50 (m, 2 H), 1.44–1.40 (m, 1 H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.8, 162.7, 158.8 (d, $J = 233.1$ Hz), 133.6, 126.1, 123.8 (d, $J = 9.5$ Hz), 120.8 (d, $J = 5.4$ Hz), 115.6 (d, $J = 26.9$ Hz), 112.0 (d, $J = 9.4$ Hz), 106.3 (d, $J = 24.0$ Hz), 52.4, 52.3, 42.5, 34.4, 28.7, 25.6, 25.2; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{19}\text{FNO}_4^+$ [$\text{M} + \text{H}^+$] 320.1293, found 320.1289.

4.6.54. Methyl 5-fluoro-1-hydroxy-3-(2-methyl-3-oxopentyl)-1H-indole-2-carboxylate (72)— R_f = 0.58 (silica gel, EtOAc:hexanes, 1:1); IR (film) $\nu_{\max}$ 3300 (br), 2934, 1699, 1540, 1522, 1456, 1250, 1178, 1110 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.08 (br s, 1 H), 7.44 (dd, J = 9.0, 4.5 Hz, 1 H), 7.36 (dd, J = 9.5, 2.5 Hz, 1 H), 7.18–7.14 (m, 1 H), 3.93 (s, 3 H), 3.26–3.21 (m, 1 H), 2.97–2.92 (m, 2 H), 2.54–2.43 (m, 1 H), 2.32–2.26 (m, 1 H), 1.02 (d, J = 7.5 Hz, 3 H), 0.86 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.2, 162.6, 158.9 (d, J = 233.3 Hz), 133.4, 125.8, 123.5 (d, J = 9.6 Hz), 120.1 (d, J = 5.1 Hz), 115.6 (d, J = 27.5 Hz), 112.1 (d, J = 9.5 Hz), 106.2 (d, J = 23.8 Hz), 52.4, 47.7, 35.3, 28.7, 16.7, 7.8; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{19}\text{FNO}_4^+ [\text{M} + \text{H}^+]$ 330.1112, found 330.1104.

4.6.55. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-5-fluoro-1-hydroxy-1H-indole-2-carboxylate (73)— R_f = 0.50 (silica gel, EtOAc:hexanes, 4:6); IR (film) $\nu_{\max}$ 3383 (br), 2922, 2851, 1700, 1598, 1580, 1528, 1438, 1402, 1379, 1337, 1304, 1251, 1190, 1169, 1108, 1079, 1015, 970, 952, 936, 913, 850, 794, 785, 762, 732, 707, 682 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.11 (s, 1 H), 8.00 (d, J = 7.8 Hz, 2 H), 7.70 (t, J = 7.2 Hz, 1 H), 7.53 (t, J = 7.82 Hz, 2 H), 7.48 (dd, J = 9.0, 4.2 Hz, 1 H), 7.40 (d, J = 9.6 Hz, 1 H), 7.20 (dt, J = 9.6, 2.4 Hz, 1 H), 4.04 (t, J = 17.4 Hz, 2 H), 3.76 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 191.1, 162.7, 158.9 (d, J = 233.9 Hz), 136.2, 133.7, 131.4 (t, J = 3.3 Hz, 2 C), 131.2, 130.5 (2 C), 127.9, 124.7 (d, J = 10.4 Hz), 120.4, 120.2, 116.5 (d, J = 27.3 Hz), 112.8 (d, J = 9.6 Hz), 106.8 (d, J = 24.3 Hz), 53.2, 31.8 (t, J = 24.5 Hz); HRMS (ESI-TOF) calcd for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{NO}_4^+ [\text{M} + \text{H}^+]$ 378.0948, found 378.0943.

4.6.56. Methyl 6-fluoro-1-hydroxy-3-[(2-oxocyclohexyl)methyl]-1H-indole-2-carboxylate (74)— R_f = 0.44 (silica gel, EtOAc:hexanes, 3:7, eluted 2 $\times$); IR (film) $\nu_{\max}$ 3286 (br), 2924, 2854, 1706, 1629, 1537, 1446, 1402, 1352, 1264, 1219, 1177, 1110, 1034, 924, 834, 809 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.06 (s, 1 H), 7.68 (dd, J = 8.8, 4.8 Hz, 1 H), 7.13 (dd, J = 9.6, 2.2 Hz, 1 H), 7.91 (dt, J = 9.6, 2.5 Hz, 1 H), 3.87 (s, 3 H), 3.42 (dd, J = 14.0, 4.8 Hz, 1 H), 2.86 (dd, J = 14.0, 9.2 Hz, 1 H), 2.72–2.67 (m, 1 H), 2.37–2.23 (m, 2 H), 2.01–1.98 (m, 1 H), 1.86–1.84 (m, 1 H), 1.76–1.72 (m, 1 H), 1.65–1.58 (m, 1 H), 1.56–1.49 (m, 1 H), 1.44–1.37 (m, 1 H); ^{13}C NMR (150 MHz, CD_3CN) δ 213.0, 163.2 (d, J = 239.5 Hz), 163.0, 135.6, 125.3, 124.2 (d, J = 11.4 Hz), 122.0, 120.7, 110.8 (d, J = 25.1 Hz), 96.5 (d, J = 27.4 Hz), 52.7, 52.6, 42.8, 34.7, 29.0, 25.9, 25.4; HRMS (ESI-TOF) calcd for $\text{C}_{17}\text{H}_{19}\text{FNO}_4^+ [\text{M} + \text{H}^+]$ 320.1293, found 320.1282.

4.6.57. Methyl 6-fluoro-1-hydroxy-3-(2-methyl-3-oxopentyl)-1H-indole-2-carboxylate (75)— R_f = 0.56 (silica gel, EtOAc:hexanes, 1:1); IR (film) $\nu_{\max}$ 3313, 2924, 2877, 1698, 1539, 1456, 1396, 1260, 1223, 1175, 1110 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN) δ 9.10 (br s, 1 H), 7.68–7.65 (m, 1 H), 7.15 (dd, J = 9.5, 2.5 Hz, 1 H), 6.95–6.91 (m, 1 H), 3.92 (s, 3 H), 3.30–3.24 (m, 1 H), 3.00–2.93 (m, 2 H), 2.51–2.43 (m, 1 H), 2.33–2.25 (m, 1 H), 1.02 (d, J = 6.5 Hz, 3 H), 0.86 (t, J = 7.5 Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.2, 163.0 (d, J = 239.8 Hz), 162.6, 132.9, 124.9, 123.8 (d, J = 10.5 Hz), 121.0, 120.2, 110.7 (d, J = 25.6 Hz), 96.3 (d, J = 27.1 Hz), 52.4, 47.8, 35.4, 28.7, 16.7, 7.9; HRMS (ESI-TOF) calcd for $\text{C}_{16}\text{H}_{18}\text{FNO}_4\text{Na}^+ [\text{M} + \text{Na}^+]$ 330.1112, found 330.1110.

4.6.58. Methyl 3-(2,2-difluoro-3-oxo-3-phenylpropyl)-6-fluoro-1-hydroxy-1H-indole-2-carboxylate (76)— R_f = 0.52 (silica gel, EtOAc:hexanes, 3:7, eluted 2 $\times$); IR (film) $\nu_{\max}$ 3362, 2962, 2923, 2853, 1699, 1632, 1598, 1537, 1449, 1401, 1355, 1264, 1223, 1177, 1112, 1063, 924, 907, 880, 834, 812 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN) δ 9.12 (br s, 1 H), 7.99 (d, J = 7.9 Hz, 2 H), 7.71–7.67 (m, 2 H), 7.51 (t, J = 7.9 Hz, 2 H), 7.18 (dd, J = 9.1, 1.7 Hz, 1 H), 6.98 (dt, J = 9.1, 1.7 Hz, 1 H), 4.06 (t, J = 17.5 Hz, 2 H), 3.74 (s, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 191.0, 163.3 (d, J = 240.6 Hz), 162.5, 136.8 (d, J = 14.7 Hz),

135.9, 133.5, 131.1 (t, $J = 3.4$ Hz, 2 C), 130.3, 130.2 (2 C), 126.9 (d, $J = 3.4$ Hz), 124.4 (d, $J = 10.3$ Hz), 121.0, 120.1, 111.9 (d, $J = 26.2$ Hz), 96.7 (d, $J = 27.4$ Hz), 52.8, 31.5 (t, $J = 23.9$ Hz); HRMS (ESI-TOF) calcd for $C_{19}H_{15}F_3NO_4^+$ [$M + H^+$] 378.0948, found 378.0941.

4.6.59. Methyl 6-cyano-1-hydroxy-3-[(2-oxocyclohexyl)methyl]-1*H*-indole-2-carboxylate (77)— $R_f = 0.42$ (silica gel, EtOAc:hexanes, 6:4); IR (film) $\nu_{\max}$ 3300 (br), 2930, 2856, 2359, 2221, 1711, 1519, 1446, 1263, 1117 cm^{-1} ; 1H NMR (500 MHz, CD_3CN) δ 9.22 (br s, 1 H), 7.88 (s, 1 H), 7.85 (d, $J = 8.5$ Hz, 1 H), 7.36 (dd, $J = 8.5, 1.0$ Hz, 1 H), 3.92 (s, 3 H), 3.45 (dd, $J = 14.0, 5.0$ Hz, 1 H), 2.88 (dd, $J = 14.0, 9.0$ Hz, 1 H), 2.72–2.68 (m, 1 H), 2.38–2.26 (m, 2 H), 2.03–1.99 (m, 1 H), 1.89–1.84 (m, 1 H), 1.77–1.73 (m, 1 H), 1.67–1.50 (m, 2 H), 1.46–1.38 (m, 1 H); ^{13}C NMR (125 MHz, CD_3CN) δ 212.6, 162.3, 135.0, 127.5, 126.0, 123.3, 123.2, 120.7, 120.5, 115.8, 108.8, 52.7, 52.4, 42.5, 34.5, 28.7, 25.6, 25.0; HRMS (ESI-TOF) calcd for $C_{18}H_{18}N_2O_4Na^+$ [$M + Na^+$] 349.1159, found 349.1149.

4.6.60. Methyl 6-cyano-1-hydroxy-3-(2-methyl-3-oxopentyl)-1*H*-indole-2-carboxylate (78)— $R_f = 0.55$ (silica gel, EtOAc:hexanes, 6:4); IR (film) $\nu_{\max}$ 3242 (br), 2969, 2357, 2224, 1712, 1537, 1445, 1259, 1233, 1117 cm^{-1} ; 1H NMR (500 MHz, CD_3CN) δ 9.31 (br s, 1 H), 7.87 (s, 1 H), 7.81 (d, $J = 8.5$ Hz, 1 H), 7.36 (dd, $J = 8.5, 1.5$ Hz, 1 H), 3.95 (s, 3 H), 3.28 (m, 1 H), 3.00–2.93 (m, 2 H), 2.51–2.43 (m, 1 H), 2.32–2.24 (m, 1 H), 0.86 (d, $J = 7.0$ Hz, 3 H), 1.01 (t, $J = 7.0$ Hz, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 215.1, 162.2, 134.8, 127.3, 125.7, 123.4, 123.1, 120.4, 120.0, 115.8, 108.8, 52.7, 47.7, 35.4, 28.4, 16.8, 7.9; HRMS (ESI-TOF) calcd for $C_{17}H_{19}N_2O_4^+$ [$M + H^+$] 315.1339, found 315.1331.

4.6.61. Methyl 6-cyano-3-(2,2-difluoro-3-oxo-3-phenylpropyl)-1-hydroxy-1*H*-indole-2-carboxylate (79)— $R_f = 0.47$ (silica gel, EtOAc:hexanes, 1:1); IR (film) $\nu_{\max}$ 2930, 2846, 2358, 2222, 1711, 1560, 1437, 1260, 1117 cm^{-1} ; 1H NMR (500 MHz, CD_3CN) δ 9.38 (br s, 1 H), 8.00 (d, $J = 8.0$ Hz, 2 H), 7.92 (s, 1 H), 7.85 (d, $J = 8.5$ Hz, 1 H), 7.71–7.68 (m, 1 H), 7.54–7.51 (m, 2 H), 7.41 (dd, $J = 8.5, 1.0$ Hz, 1 H), 4.08 (t, $J = 17.5$ Hz, 2 H), 3.79 (s, 3 H); ^{13}C NMR (125 MHz, CD_3CN) δ 203.1, 170.7, 135.6, 135.3, 133.7, 133.6, 130.8 (t, $J = 3.1$ Hz, 2 C), 129.8, 129.7 (2 C), 126.0, 123.8, 123.4, 120.8, 114.6, 105.9, 105.6, 54.3, 31.4; HRMS (ESI-TOF) calcd for $C_{20}H_{13}F_2N_2O_4^-$ [$M - H^-$] 383.0849, found 383.0850.

4.7. Synthesis of nocathiacin I model systems 2 and 3a–c

4.7.1. Ethyl 2-[(1*S*)-1-[(*tert*-butoxycarbonyl)amino]-2-hydroxyethyl]-1,3-thiazole-4-carboxylate (81)—Thiazole ethyl ester **80** (150 mg, 0.42 mmol) was dissolved in CH_2Cl_2 (2.8 mL) and MeOH (1.4 mL) and cooled to 0 °C. Trifluoroacetic acid (4.2 mL) was added dropwise over 5 min to the reaction mixture, and after stirring at 0 °C for 2.5 h, toluene (5 mL) was added and the reaction mixture was concentrated. The residue was dissolved in CH_2Cl_2 and washed with saturated aqueous $NaHCO_3$ solution (5 mL), brine (5 mL) and dried over Na_2SO_4 . The solution was then concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc:hexanes, 1:1 $\rightarrow$ 80:20) to afford primary alcohol **81** (91 mg, 68%) as a yellow foam; $R_f = 0.40$ (silica gel, MeOH: CH_2Cl_2 , 5:95); IR (film) $\nu_{\max}$ 3354 (br), 2978, 2919, 1707, 1502, 1484, 1390, 1361, 1337, 1231, 1167, 1091, 1055, 1020, 856, 756 cm^{-1} ; 1H NMR (600 MHz, CD_3CN) δ 8.17 (s, 1 H), 6.04 (s, 1 H), 4.93 (s, 1 H), 4.31 (ddd, $J = 7.8, 3.1, 0.9$ Hz, 2 H), 3.88 (t, $J = 6.1$ Hz, 2 H), 3.22 (t, $J = 5.7$ Hz, 1 H), 1.42 (br s, 9 H), 1.33 (t, $J = 6.1$ Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 173.9, 162.0, 156.4, 147.8, 129.0, 80.4, 64.5, 62.0, 56.0, 28.5, 14.5 (3 C); HRMS (ESI-TOF) calcd for $C_{13}H_{20}N_2O_5SNa^+$ [$M + Na^+$] 339.0985, found 339.0985.

4.7.2. Methyl 4-bromo-3-[[{(2S)-2-[(*tert*-butoxycarbonyl)amino]-2-[4-(ethoxycarbonyl)-1,3-thiazol-2-yl]ethyl]oxy)methyl]-1-hydroxy-1*H*-indole-2-carboxylate (2)—Primary alcohol **81** (16.9 mg, 0.05 mmol) was dissolved in DME (350 μ L) and to this solution was added 4 Å molecular sieves (20 wt%), *p*TsOH (7.6 mg, 0.04 mmol) and tertiary alcohol **9** (4.0 mg, 0.013 mmol) at 25 °C. After stirring for 10 min, the reaction mixture was heated to 40 °C for 2 h after which the crude reaction mixture was allowed to cool to room temperature and purified directly by PTLC (silica gel, EtOAc:hexanes, 7:3) to afford model system **2** (3.5 mg, 44%) as a yellow oil; R_f = 0.43 (silica gel, EtOAc:hexanes, 7:3); $[\alpha]_D^{32}$ = -3.0 (CHCl_3 , c = 0.50); IR (film) ν_{max} 3354, 2978, 2919, 1707, 1490, 1460, 1437, 1390, 1360, 1255, 1231, 1161, 1119, 1090, 1025, 879, 773, 743 cm^{-1} ; ^1H NMR (600 MHz, CD_3CN , 66 °C) δ 9.22 (s, 1 H), 8.06 (s, 1 H), 7.50 (d, J = 7.7 Hz, 1 H), 7.36 (d, J = 7.7 Hz, 1 H), 7.22 (t, J = 7.7 Hz, 1 H), 5.81 (br s, 1 H), 5.17 ($\frac{1}{2}\text{ABq}$, J = 11.4 Hz, 1 H), 5.14 ($\frac{1}{2}\text{ABq}$, J = 11.4 Hz, 1 H), 5.04 (dt, J = 7.4, 4.8 Hz, 1 H), 4.33 (q, J = 7.0 Hz, 2 H), 3.97 (s, 3 H), 3.96 (dd, J = 10.0, 4.8 Hz, 1 H), 3.93 (dd, J = 10.0, 4.8 Hz, 1 H), 1.39 (s, 9 H), 1.35 (t, J = 7.0 Hz, 3 H); ^{13}C NMR (150 MHz, CD_3CN) δ 174.0, 162.2, 162.0, 156.2, 147.7, 137.2, 128.9, 127.2, 127.0, 126.9, 120.9, 115.9, 115.2, 110.2, 80.4, 71.2, 62.1, 61.9, 54.2, 53.1, 28.4 (3 C), 14.5; HRMS (ESI-TOF) calcd for $\text{C}_{24}\text{H}_{28}\text{BrN}_3\text{O}_8\text{SNa}^+ [\text{M} + \text{Na}^+]$ 620.0673, found 620.0674.

4.7.3. *tert*-Butyl (4S)-4-[4-(methoxymethyl)-1,3-thiazol-2-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (82)—Thiazole ethyl ester **80** (530 mg, 1.49 mmol) was dissolved in toluene (6.0 mL) and cooled to 0 °C. DIBAL-H (2.0 mL, 3.0 mmol, 1.5 M in toluene) was then added dropwise and the reaction mixture stirred for 2.5 h after which the reaction was slowly quenched at 0 °C with MeOH (2 mL) and the resulting mixture was warmed to 25 °C and stirred for 12 h with saturated aqueous sodium potassium tartrate solution (5 mL). The mixture was extracted with EtOAc (3 $\times$ 20 mL) and the combined organic layers were dried over Na_2SO_4 and the resulting solution was concentrated. The residue was taken up in THF (6.0 mL) and cooled to 0 °C and to this solution was added NaH (150 mg, 3.7 mmol, 60% dispersion in mineral oil) and MeI (649 μ L, 10.43 mmol). The reaction mixture was allowed to warm to room temperature over 12 h at which time the reaction mixture was poured over ice water (10 mL), extracted with EtOAc (20 mL), washed with brine (10 mL) and dried (Na_2SO_4). The solution was then concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc:hexanes, 60:40 $\rightarrow$ 80:20) to afford methyl ether **82** (360 mg, 74% over two steps) as a yellow oil; R_f = 0.52 (silica gel, EtOAc:hexanes, 7:3); $[\alpha]_D^{33}$ = -24.1 (CHCl_3 , c = 0.60); IR (film) ν_{max} 3383 (br), 2971, 1874, 1698, 1455, 1371, 1255, 1116, 1092, 1049 cm^{-1} ; ^1H NMR (500 MHz, CD_3CN , 66 °C) δ 7.22 (s, 1 H), 5.19 (dd, J = 6.2, 1.9 Hz, 1 H), 4.47 (d, J = 0.7 Hz, 2 H), 4.29 (dd, J = 9.2, 6.2 Hz, 1 H), 4.07 (dd, J = 9.2, 1.9 Hz, 1 H), 3.37 (s, 3 H), 1.69 (s, 3 H), 1.52 (s, 3 H), 1.38 (br s, 9 H); ^{13}C NMR (150 MHz, CD_3CN , 66 °C) δ 174.6, 155.2, 147.8, 117.2, 95.3, 81.2, 71.2 (2 C), 70.1, 60.7, 58.8 (2 C), 28.9 (3 C); HRMS (ESI-TOF) calcd for $\text{C}_{15}\text{H}_{25}\text{N}_2\text{O}_4\text{S}^+ [\text{M} + \text{H}^+]$ 329.1529, found 329.1518.

4.7.4. (1S)-2-[[*tert*-Butyl(dimethyl)silyl]oxy]-1-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethanamine (84)—Methyl ether **82** (50 mg, 0.152 mmol) was dissolved in CH_2Cl_2 (761 μ L) and cooled to 0 °C. TFA (761 μ L) was then added dropwise and the reaction mixture stirred for 10 min at 0 °C and then 1 h at 25 °C at which time the reaction was diluted with toluene (2 mL) and concentrated (3 $\times$). After drying under high vacuum for 30 min, the crude amino alcohol was dissolved in CH_2Cl_2 (317 μ L) and cooled to 0 °C. Et_3N (70 μ L, 0.50 mmol), and TBSCl (50 mg, 0.33 mmol) were then added and the reaction mixture was warmed to 25 °C. After 3 h, the mixture was washed with saturated aqueous NaHCO_3 solution (1 mL), brine (1 mL) and then dried over Na_2SO_4 . The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel,

EtOAc:hexanes, 80:20 → 100:0) to afford primary amine **84** (39.0 mg, 85% over two steps) as a yellow oil; R_f = 0.57 (silica gel, MeOH:CH₂Cl₂, 5:95); $[\alpha]_D^{31}$ = -7.6 (CH₂Cl₂, c = 1.23); IR (film) $\nu_{\max}$ 3378 (br), 2931, 2848, 1461, 1255, 1091, 838, 764, 602 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 7.19 (s, 1 H), 4.44 (s, 2 H), 4.19 (dd, J = 6.1, 4.3 Hz, 1 H), 3.88 (dd, J = 9.9, 4.3 Hz, 1 H), 3.78 (dd, J = 9.9, 6.1 Hz, 1 H), 3.33 (s, 3 H), 0.85 (s, 9 H), 0.03 (s, 3 H), 0.01 (s, 3 H); ¹³C NMR (150 MHz, CD₃CN) δ 177.1, 154.9, 117.5, 71.2, 69.1, 58.8, 56.9, 26.3 (3 C), 19.0, -4.87, -4.94; HRMS (ESI-TOF) calcd for C₁₃H₂₇N₂O₂SSi⁺ [M + H⁺] 303.1484, found 303.1487.

4.7.5. *tert*-butyl (4*S*)-4-{4-[(1*S*)-2-hydroxy-1-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethyl]amino}carbonyl-1,3-thiazol-2-yl}-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (85**)**—Amine **84** (846 mg, 2.80 mmol) was dissolved in DMF (7 mL), cooled to 0 °C and then *i*Pr₂NEt (974 μ L, 5.59 mmol) was added followed by cannula addition of thiazole acid **83** (918 mg, 2.80 mmol) dissolved in DMF (7 mL). HATU (1.17 g, 3.08 mmol) and HOAt (419 mg, 3.08 mmol) were then added and the reaction mixture stirred for 1 h at 0 °C and 2 h at 25 °C after which EtOAc (25 mL) was added and the reaction mixture was washed with aqueous 5% HCl solution (10 mL), H₂O (10 mL), saturated aqueous NaHCO₃ solution (10 mL), brine (10 mL) and dried over Na₂SO₄. The resulting solution was concentrated and the residue was taken up in THF (75 mL) and cooled to 0 °C. TBAF (3.36 mL, 1.0 M in THF) was added dropwise and after 30 min, the reaction mixture was quenched with saturated aqueous NH₄Cl solution (20 mL), extracted with EtOAc (2 × 25 mL), washed with brine (20 mL) and dried over Na₂SO₄. The resulting solution was concentrated and the residue was subjected to flash column chromatography (silica gel, EtOAc:hexanes, 20:80 → 90:10) affording complex alcohol **85** (1.21 g, 87% over two steps) as a light yellow foam; R_f = 0.42 (silica gel, MeOH:CH₂Cl₂, 5:95); $[\alpha]_D^{32}$ = -10.9 (CH₂Cl₂, c = 0.80); IR (film) $\nu_{\max}$ 3389 (br), 2966, 2731, 2872, 1696, 1467, 1531, 1472, 1373, 1249, 1167, 1091, 1049, 761 cm⁻¹; ¹H NMR (500 MHz, CD₃CN, 66 °C) δ 8.13 (d, J = 5.5 Hz, 1 H), 8.07 (d, J = 1.0 Hz, 1 H), 7.26 (d, J = 1.0 Hz, 1 H), 5.41–5.37 (m, 1 H), 5.24 (d, J = 6.6 Hz, 1 H), 4.51 (s, 2 H), 4.34–4.31 (m, 1 H), 4.16–4.13 (m, 1 H), 4.10–4.04 (m, 2 H), 3.97 (dd, J = 11.4, 4.8 Hz, 1 H), 3.39 (s, 3 H), 1.72 (s, 3 H), 1.57 (s, 3 H), 1.39 (br s, 9 H); ¹³C NMR (150 MHz, CD₃CN, 66 °C) δ 175.9, 171.9, 162.3, 155.9, 155.8, 151.0, 125.6, 118.3, 71.6, 70.3, 65.8, 65.7, 61.1, 61.0, 59.4, 55.0 (2 C), 29.3 (3 C); HRMS (ESI-TOF) calcd for C₂₁H₃₁N₄O₆S₂⁺ [M + H⁺] 499.1679, found 499.1670.

4.7.6. (2*S*)-2-[(2-[(1*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-hydroxyethyl]-1,3-thiazol-4-yl)carbonyl]amino-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]EtOAc (86**)**—A solution of complex alcohol **85** (95 mg, 0.19 mmol) in CH₂Cl₂ (1.0 mL) was cooled to 0 °C and Et₃N (80 μ L, 0.57 mmol) and 4-DMAP (2.3 mg, 0.02 mmol) were added followed by Ac₂O (90 μ L, 0.95 mmol). After 10 min at 0 °C, the reaction mixture was diluted with CH₂Cl₂ (3 mL) and washed with aqueous 5% HCl solution (3 mL), saturated aqueous NaHCO₃ solution (3 mL), brine (3 mL) and dried over Na₂SO₄. The resulting solution was concentrated and the residue was taken up in CH₂Cl₂ (1.26 mL) and MeOH (630 μ L) and cooled to 0 °C. TFA (1.88 mL) was then added dropwise and after 30 min the reaction mixture was diluted with toluene (5 mL) and concentrated (3×). The residue was subjected to flash column chromatography (silica gel, EtOAc:hexanes, 1:1 → 100:0) affording hydroxy acetate **86** (78 mg, 82% over two steps) as a yellow oil; R_f = 0.17 (silica gel, EtOAc:hexanes, 8:2); $[\alpha]_D^{31}$ = -6.8 (CHCl₃, c = 0.50); IR (film) $\nu_{\max}$ 3309 (br), 2930, 1712, 1661, 1533, 1460, 1382, 1248, 1165, 1059, 797, 679, 590 cm⁻¹; ¹H NMR (600 MHz, CD₃CN, 66 °C) δ 8.16 (d, J = 4.8 Hz, 1 H), 8.10 (s, 1 H), 7.30 (s, 1 H), 5.41–5.37 (m, 1 H), 5.92 (br s, 1 H), 5.62–5.64 (m, 1 H), 4.99–4.96 (m, 1 H), 4.62 (ddd, J = 11.8, 4.8, 1.3 Hz, 1 H), 4.57 (ddd, J = 11.8, 6.5, 0.8 Hz, 1 H), 4.51 (s, 2 H), 3.97–3.95 (m, 2 H), 3.39 (s, 3 H), 2.00 (s, 3 H), 1.45 (s, 9 H); ¹³C NMR (150 MHz, CD₃CN) δ 173.7, 171.4, 169.4, 161.6,

156.4, 154.8, 149.8, 125.4, 118.1, 80.3, 70.5, 65.5, 64.4, 58.4, 55.9, 51.3, 28.4 (3 C), 20.8; HRMS (ESI-TOF) calcd for $C_{20}H_{29}N_4O_7S_2^+$ [M + H⁺] 501.1472, found 501.1459.

4.7.7. Methyl 3-[(2S)-2-{4-[(1S)-2-(acetyloxy)-1-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethyl]amino}carbonyl]-1,3-thiazol-2-yl]-2-[(tert-butoxycarbonyl)amino]ethyl]oxy)-methyl]-4-bromo-1-hydroxy-1H-indole-2-carboxylate (87)—Method A: To a stirred solution of *p*TsOH (13.3 mg, 0.07 mmol), and 4 Å molecular sieves (20 wt%) in DME (470 µL) was added hydroxy acetate **86** (23 mg, 0.046 mmol) and tertiary alcohol **9** (7 mg, 0.023 mmol) at 25 °C. After 10 min, the reaction mixture was warmed to 40 °C, stirred for 3 h, allowed to cool to room temperature and purified directly by PTLC (silica gel, EtOAc:hexanes, 80:20) to afford *N*-hydroxyindole **87** (10 mg, 56%) as a yellow oil; **Method B:** To a stirred solution of SnCl₂·2H₂O (10.4 mg, 0.046 mmol) and 4 Å molecular sieves (20 wt%) in DME (110 µL) was added hydroxy acetate **86** (41 mg, 0.082 mmol) in DME (100 µL) and ketoester **6a** (6.6 mg, 0.021 mmol) at 25 °C. The reaction mixture was warmed immediately to 40 °C and stirring was continued for 6 h in the absence of light at which time the reaction mixture was allowed to cool to room temperature and purified directly by PTLC (silica gel, MeOH:Et₂O, 2:98) to afford *N*-hydroxyindole **87** (6.6 mg, 40%) as a yellow oil; *R*_f = 0.26 (silica gel, EtOAc:hexanes, 7:3); [α]_D³¹ = +1.7 (CH₂Cl₂, *c* = 0.20); IR (film) ν_{max} 3331 (br), 2919, 2849, 1725, 1708, 1400, 1531, 1449, 1431, 1378, 1249, 1061, 761 cm⁻¹; ¹H NMR (600 MHz, CD₃CN, 66 °C) δ 9.30 (br s, 1 H), 8.09–8.05 (m, 1 H), 7.97 (d, *J* = 9.6 Hz, 1 H), 7.48 (d, *J* = 8.3 Hz, 1 H), 7.34 (d, *J* = 7.8 Hz, 1 H), 7.31 (d, *J* = 6.1 Hz, 1 H), 7.20 (t, *J* = 7.7 Hz, 1 H), 5.84 (br s, 1 H), 5.66–5.63 (m, 1 H), 5.19–5.14 (m, 2 H), 5.07–5.03 (m, 1 H), 4.61–4.55 (m, 2 H), 4.52 (s, 2 H), 4.01 (dd, *J* = 10.1, 5.2 Hz, 1 H), 3.97–3.94 (m, 4 H), 3.39 (s, 3 H), 1.99 (s, 3 H), 1.40 (s, 9 H); ¹³C NMR (150 MHz, CD₃CN) δ 173.8, 171.4, 169.3, 162.0 (2 C), 161.5, 156.2, 154.8, 149.7, 137.3, 127.0, 126.8, 126.2, 125.2, 120.7, 115.8, 115.1, 110.1, 80.4, 71.3, 70.4, 65.5, 64.7, 58.4, 54.1 52.9, 51.3, 28.4 (3 C), 20.8; HRMS (ESI-TOF) calcd for C₃₁H₃₆BrN₅O₁₀S₂Na⁺ [M + Na⁺] 804.0979, found 804.0979.

4.7.8. tert-Butyl (4S,11S)-15-bromo-4-[4-(methoxymethyl)-1,3-thiazol-2-yl]-1,6-dioxo-19-[[2-(trimethylsilyl)ethoxy]methoxy]-3,4,5,6,11,12,14,19-octahydro-1H-7,10-epiazeno[1,12,8,4]dioxathiazacyclohexadecino[15,14-b]indol-11-ylcarbamate (3a)—*N*-hydroxyindole **87** (34 mg, 0.043 mmol) was dissolved in DMF (1.5 mL) and cooled to 0 °C at which time *i*Pr₂NEt (23 µL, 0.130 mmol), SEMCl (15 µL, 0.087 mmol) and *n*Bu₄NI (1.6 mg, 0.004 mmol) were added and the reaction mixture was warmed to 25 °C. After 10 min, the reaction mixture was diluted with EtOAc (5 mL), washed with aqueous 5% HCl solution (3 mL) and dried over Na₂SO₄. The resulting solution was concentrated and the residue was taken up in THF (2.58 mL), MeOH (860 µL) and H₂O (860 µL) and then cooled to 0 °C. LiOH (3 mg, 0.129 mmol) was added and, after warming to 25 °C over 4 h, the reaction mixture was diluted with EtOAc (5 mL), cooled to 0 °C, quenched with aqueous 5% HCl solution, separated, and the organic layer dried with Na₂SO₄. After azeotroping with toluene (3 × 5 mL), the residue was dissolved in toluene (4.3 mL) and Et₃N (240 µL, 1.72 mmol) and 2,4,6-trichlorobenzoyl chloride (202 µL, 1.29 mmol) were added. After stirring for 12 h at 25 °C, the reaction mixture was added dropwise over the course of 12 h (syringe pump) to a solution of 4-DMAP (158 mg, 1.29 mmol) in toluene (80 mL). After addition was complete, the resulting mixture was stirred at 25 °C for a further 12 h, then cooled to 0 °C and acidified to pH ~ 3 with an aqueous 10 mg/mL solution of KHSO₄. The layers were separated and the aqueous layer was re-extracted with EtOAc (2 × 40 mL). The combined organic layers were then washed with a 1:1 solution of saturated aqueous NaHCO₃:brine (40 mL) and the aqueous layer was re-extracted with EtOAc (2 × 40 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by PTLC (silica gel, EtOAc:hexanes, 60:40) to give macrocycle **3a**

(14 mg, 38% over three steps) as a yellow oil; $R_f = 0.37$ (silica gel, EtOAc:hexanes, 8:2); $[\alpha]_D^{33} = -12.3$ (CH₂Cl₂, $c = 0.72$); IR (film) $\nu_{\max}$ 3353 (br), 2924, 2854, 2086, 1712, 1536, 1494, 1366, 1214, 1170, 1105, 859, 836, 777 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 8.44 (d, $J = 7.5$ Hz, 1 H), 8.04 (s, 1 H), 7.51 (dd, $J = 8.3, 0.9$ Hz, 1 H), 7.41 (dd, $J = 7.4, 0.9$ Hz, 1 H), 7.30 (s, 1 H), 7.24 (t, $J = 7.9$ Hz, 1 H), 6.00 (d, $J = 7.9$ Hz, 1 H), 5.66–5.62 (m, 1 H), 5.34 (d, $J = 3.9$ Hz, 1 H), 5.21 (d, $J = 10.1$ Hz, 1 H), 5.18 (dd, $J = 11.4, 3.9$ Hz, 1 H), 5.14–5.12 (m, 2 H), 5.08 (d, $J = 7.5$ Hz, 1 H), 5.04 (dd, $J = 11.4, 5.7$ Hz, 1 H), 4.48 (s, 2 H), 4.17–4.14 (m, 1 H), 3.94 (dd, $J = 9.6, 2.6$ Hz, 1 H), 3.80–3.70 (m, 2 H), 3.36 (s, 3 H), 1.40 (br s, 9 H), 0.86 (t, $J = 7.0$ Hz, 2 H), –0.02 (s, 9 H); ¹³C NMR (150 MHz, CD₃CN) δ 170.9, 170.1, 163.0, 162.0, 161.7, 155.3, 149.4, 138.1, 128.0, 127.8, 127.5, 126.7, 122.1, 119.2, 116.3, 113.2, 111.5, 103.3, 72.2, 70.8, 69.6, 65.6, 65.2, 62.7, 58.8, 52.7, 52.6, 28.6 (3 C), 18.9, –1.3 (3 C); HRMS (ESI-TOF) calcd for C₃₄H₄₅BrN₅O₉S₂Si⁺ [M + H⁺] 838.1606, found 838.1604.

4.7.9. *tert*-butyl (4*S*,11*S*)-15-bromo-19-(methoxymethoxy)-4-[4-(methoxymethyl)-1,3-thiazol-2-yl]-1,6-dioxo-3,4,5,6,11,12,14,19-octahydro-1*H*-7,10-epiazeno[1,12,8,4]dioxathiazacyclohexadecino[15,14-*b*]indol-11-ylcarbamate (3b**)**—*N*-hydroxyindole **87** (30 mg, 0.038 mmol) was dissolved in DMF (1.9 mL) and cooled to 0 °C at which time *i*Pr₂NEt (20 μ L, 0.114 mmol), MOMCl (6 μ L, 0.076 mmol) and *n*Bu₄NI (1.4 mg, 0.004 mmol) were added and the reaction mixture was warmed to 25 °C. After 10 min, the reaction mixture was diluted with EtOAc (5 mL), washed with aqueous 5% HCl solution (3 mL) and dried over Na₂SO₄. The resulting solution was concentrated and the residue was taken up in THF (2.28 mL), MeOH (760 μ L) and H₂O (760 μ L) and then cooled to 0 °C. LiOH (2.7 mg, 0.114 mmol) was added and after warming to 25 °C over 4 h, the reaction mixture was diluted with EtOAc (5 mL), cooled to 0 °C, quenched with aqueous 5% HCl solution, separated, and the organic layer dried with Na₂SO₄. After azeotroping with toluene (3 $\times$ 5 mL), the residue was dissolved in toluene (4.0 mL) and Et₃N (212 μ L, 1.52 mmol) and 2,4,6-trichlorobenzoyl chloride (178 μ L, 1.14 mmol) were added. After stirring for 12 h at 25 °C, the reaction mixture was added dropwise over the course of 12 h (syringe pump) to a solution of 4-DMAP (139 mg, 1.14 mmol) in toluene (71 mL). After addition was complete, the resulting mixture was stirred at 25 °C for a further 12 h, then cooled to 0 °C and acidified to pH ~ 3 with an aqueous 10 mg/mL solution of KHSO₄. The layers were separated and the aqueous layer was re-extracted with EtOAc (2 $\times$ 40 mL). The combined organic layers were then washed with a 1:1 solution of saturated aqueous NaHCO₃:brine (40 mL) and the aqueous layer was re-extracted with EtOAc (2 $\times$ 40 mL). The combined organic layers were dried (Na₂SO₄) and concentrated. The residue was purified by PTLC (silica gel, EtOAc:hexanes, 80:20) to give macrocycle **3b** (12.7 mg, 44% over three steps) as a yellow oil; $R_f = 0.36$ (silica gel, EtOAc:hexanes, 8:2); $[\alpha]_D^{32} = -10.5$ (CH₂Cl₂, $c = 0.68$); IR (film) $\nu_{\max}$ 3330 (br), 2919, 2849, 1725, 1713, 1608, 1531, 1449, 1384, 1260, 1067, 803 cm⁻¹; ¹H NMR (600 MHz, CD₃CN) δ 8.45 (d, $J = 7.9$ Hz, 1 H), 8.04 (s, 1 H), 7.52 (dd, $J = 8.3, 0.9$ Hz, 1 H), 7.42 (dd, $J = 7.5, 0.9$ Hz, 1 H), 7.30 (s, 1 H), 7.26 (dd, $J = 8.3, 7.5$ Hz, 1 H), 6.00 (d, $J = 8.3$ Hz, 1 H), 5.66–5.62 (m, 1 H), 5.36–5.33 (m, 1 H), 5.22–5.18 (m, 2 H), 5.13 (d, $J = 10.1$ Hz, 1 H), 5.09 (d, $J = 7.5$ Hz, 1 H), 5.05 (d, $J = 7.5$ Hz, 1 H), 5.02 (dd, $J = 11.4, 5.2$ Hz, 1 H), 4.48 (s, 2 H), 4.18–4.14 (m, 1 H), 3.95 (dd, $J = 10.1, 3.1$ Hz, 1 H), 3.52 (s, 3 H), 3.36 (s, 3 H), 1.40 (br s, 9 H); ¹³C NMR (150 MHz, CD₃CN, 66 °C) δ 171.0, 170.1, 163.0, 162.0, 161.7, 155.3, 149.4, 138.2, 128.2, 127.9, 127.7, 126.8, 122.2, 119.3, 116.3, 113.2, 111.5, 105.3, 80.7, 72.2, 70.8, 65.2, 62.8, 59.0, 58.8, 52.7, 52.6, 28.7 (3 C); HRMS (ESI-TOF) calcd for C₃₀H₃₄BrN₅O₉S₂Na⁺ [M + Na⁺] 774.0873, found 774.0869.

4.7.10. *tert*-Butyl (4*S*)-4-[4-[(1*S*)-2-[3-(2-bromo-6-nitrophenyl)-2-oxobut-3-enoyl]oxy]-1-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethyl]amino)carbonyl]-1,3-

thiazol-2-yl]-2,2-dimethyl-1,3-oxazolidine-3-carboxylate (88)—Complex alcohol **85** (10 mg, 0.02 mmol) was dissolved in THF (80 μ L), cooled to 0 °C, and oxalyl chloride (3.5 μ L, 0.04 mmol) was added followed by DMF (1 drop). After 45 min at 0 °C, Et₃N (11 μ L, 0.08 mmol) and acid **7a** (18 mg, 0.06 mmol) in THF (80 μ L) were added and the reaction mixture was allowed to warm to 25 °C over 2 h. THF was concentrated in vacuo and the residue was dissolved in CH₂Cl₂ (5 mL), washed with ice H₂O (5 mL) and dried (Na₂SO₄). The resulting solution was concentrated and the residue was purified by PTLC (silica gel, EtOAc:hexanes, 80:20) to afford α -ketoester **88** (12 mg, 77%) as a yellow oil; *R*_f = 0.71 (silica gel, EtOAc:hexanes, 8:2); [α]_D³² = −3.5 (CHCl₃, *c* = 0.34); IR (film) ν_{max} 3377 (br), 3119, 2978, 2919, 1754, 1689, 1666, 1531, 1443, 1372, 1255, 1149, 1091, 1049, 961, 908, 808, 755 cm^{−1}; ¹H NMR (600 MHz, CD₃CN, 70 °C) δ 8.17 (d, *J* = 8.8 Hz, 1 H), 8.10 (d, *J* = 1.7 Hz, 1 H), 8.00 (dd, *J* = 8.3, 1.3 Hz, 1 H), 7.97 (dd, *J* = 7.8, 0.8 Hz, 1 H), 7.50 (t, *J* = 8.3 Hz, 1 H), 7.32 (d, *J* = 0.9 Hz, 1 H), 6.61 (s, 1 H), 6.25 (dd, *J* = 10.1, 0.9 Hz, 1 H), 5.84–5.80 (m, 1 H), 5.24–5.21 (m, 1 H), 4.95–4.87 (m, 2 H), 4.50 (s, 2 H), 4.32–4.29 (m, 1 H), 4.16 (dd, *J* = 9.1, 1.7 Hz, 1 H), 3.38 (s, 3 H), 1.69 (s, 3 H), 1.56 (s, 3 H), 1.28 (br s, 9 H); ¹³C NMR (150 MHz, CD₃CN, 66 °C) δ 175.9, 169.2, 163.7, 162.2, 156.1, 150.3, 143.1, 139.1, 137.1, 133.0, 132.5, 126.9, 125.9, 125.2 (2 C), 119.0, 96.4, 81.5, 71.3 (2 C), 68.1, 60.60, 60.59, 59.2, 51.8 (2 C), 29.1 (3 C); HRMS (ESI-TOF) calcd for C₃₁H₃₅BrN₅O₁₀S₂⁺ [*M* + *H*⁺] 780.1003, found 780.1001.

4.7.11. (2*S*)-2-[(2-[(1*S*)-1-[(*tert*-Butoxycarbonyl)amino]-2-hydroxyethyl]-1,3-thiazol-4-yl)carbonyl]amino)-2-[4-(methoxymethyl)-1,3-thiazol-2-yl]ethyl 3-(2-bromo-6-nitrophenyl)-2-oxobut-3-enoate (89)— α -ketoester **88** (10 mg, 0.013 mmol) was dissolved in CH₂Cl₂ (330 μ L) and MeOH (170 μ L) and cooled to 0 °C. TFA (500 μ L) was added dropwise and, after stirring for 1 h at 0 °C, the reaction mixture was diluted with toluene (3 mL) and concentrated (2 $\times$). The residue was purified by PTLC (silica gel, EtOAc:hexanes, 80:20) to afford *N*-Boc amino alcohol **89** (6.8 mg, 72%) as a yellow oil; *R*_f = 0.29 (silica gel, EtOAc:hexanes, 8:2); [α]_D³³ = −0.4 (CH₂Cl₂, *c* = 0.78); IR (film) ν_{max} 3383 (br), 3109, 2971, 2923, 2850, 1746, 1698, 1686, 1649, 1528, 1346, 1243, 1158, 1031, 740, 595 cm^{−1}; ¹H NMR (600 MHz, CD₃CN) δ 8.19 (d, *J* = 7.0 Hz, 1 H), 8.09 (s, 1 H), 8.01–7.98 (m, 1 H), 7.98–7.96 (m, 1 H), 7.52–7.48 (m, 1 H), 7.32 (s, 1 H), 6.62 (dd, *J* = 2.2, 0.9 Hz, 1 H), 6.25 (dd, *J* = 6.1, 1.3 Hz, 1 H), 5.87–5.80 (m, 2 H), 4.98–4.90 (m, 3 H), 4.51 (s, 2 H), 4.95–4.85 (m, 2 H), 3.39 (s, 3 H), 1.43 (br s, 9 H); ¹³C NMR (150 MHz, CD₃CN) δ 185.3, 174.0, 171.8, 168.9, 163.4, 161.9, 155.5, 151.2, 150.1, 142.6, 138.8, 136.9, 132.5, 132.1, 126.5, 125.8, 124.9, 120.5, 118.6, 80.8, 70.9, 67.6, 64.8, 58.8, 51.3, 28.8 (3 C); HRMS (ESI-TOF) calcd for C₂₈H₃₁BrN₅O₁₀S₂⁺ [*M* + *H*⁺] 740.0690, found 740.0687.

4.7.12. *tert*-butyl (4*S*,11*S*)-15-bromo-19-hydroxy-4-[4-(methoxymethyl)-1,3-thiazol-2-yl]-1,6-dioxo-3,4,5,6,11,12,14,19-octahydro-1*H*-7,10-epiazeno[1,12,8,4]dioxathiaza-cyclohexadecino[15,14-*b*]indol-11-ylcarbamate (3c)—**Method A:** A stirred suspension of Zn dust (5.0 mg, 0.078 mmol) and dibromoethane (0.46 μ L, 0.005 mmol) in THF (79 μ L) was heated to reflux (70 °C) for approximately 5 min and then allowed to cool to 25 °C. The refluxing/cooling process was repeated three times. TMSCl (0.41 μ L, 0.003 mmol) was then added and the resulting grey suspension was stirred at 25 °C for 10 min. A separate stirred solution containing a mixture of aqueous 1 N NH₄Cl (36 μ L, 0.036 mmol) and *N*-Boc amino alcohol **89** (12 mg, 0.016 mmol) in THF (153 μ L) was added via cannula to the activated Zn suspension and stirring was continued for 15 min at 25 °C. The crude reaction mixture was diluted with EtOAc (5 mL) and washed with saturated aqueous NaHCO₃ solution (1 mL) filtered through celite and dried (Na₂SO₄). The resulting solution was concentrated and the residue was dissolved in DME (16 mL). 4 Å Molecular sieves (20 wt%), and *p*TsOH (9 mg, 0.048 mmol) were added and, after 10 min at 25 °C and 12 h at 40 °C, the reaction mixture was cooled to room temperature and purified

by PTLC (silica gel, MeOH:Et₂O, 5:95) to give *N*-hydroxyindole macrocycle **3c** (4.6 mg, 40%) as a yellow oil; **Method B**: To a stirred solution of SnCl₂·2H₂O (5.2 mg, 0.022 mmol) and 4 Å molecular sieves (20 wt%) in DME (50 µL) was added *N*-Boc amino alcohol **89** (5.3 mg, 0.007 mmol) in DME (50 µL) at 25 °C. The reaction mixture was warmed immediately to 45 °C and stirring was continued for 3 h in the absence of light at which time the reaction mixture was allowed to cool to room temperature and purified directly by PTLC (silica gel, MeOH:Et₂O, 7:93) to afford *N*-hydroxyindole macrocycle **3c** (0.51 mg, 10%) as a yellow oil; **3c** (+ **3c'**) [*ca* 1:1 mixture of *N*-Boc rotamers (¹H NMR)] *R*_f = 0.63 (silica gel, MeOH:Et₂O, 5:95); [α]_D³³ = +1.0 (CH₂Cl₂, *c* = 0.23); IR (film) ν_{max} 3346, 2924, 2850, 1709, 1668, 1534, 1494, 1458, 1365, 1251, 1223, 1185, 1163, 1122, 1100, 778, 743 cm⁻¹; ¹H NMR (600 MHz, CD₃CN, 67 °C) δ 9.05 (s, 1 H), 8.97 (s, 1 H), 8.47 (d, *J* = 8.3 Hz, 1 H), 8.47 (d, *J* = 6.1 Hz, 1 H), 8.01 (s, 1 H), 7.97 (s, 1 H), 7.48 (dd, *J* = 8.3, 2.6 Hz, 1+1 H), 7.39 (dd, *J* = 7.8, 2.1 Hz, 1+1 H), 7.34 (s, 1 H), 7.32 (s, 1 H), 7.23 (dd, *J* = 8.3, 7.8 Hz, 1+1 H), 5.85 (br s, 1+1 H), 5.68–5.63 (m, 1+1 H), 5.43 (d, *J* = 10.5 Hz, 1 H), 5.37–5.35 (m, 1+1 H), 5.33–5.31 (m, 1+1 H), 5.26 (d, *J* = 10.1 Hz, 1 H), 5.23 (d, *J* = 10.1 Hz, 1 H), 5.18–5.14 (m, 1 H), 5.08–5.04 (m, 1 H), 5.01 (dd, *J* = 11.8, 4.3 Hz, 1 H), 5.01 (dd, *J* = 11.8, 4.9 Hz, 1 H), 4.54 (d, *J* = 0.8 Hz, 2 H), 4.53 (d, *J* = 0.8 Hz, 2 H), 4.37 (dd, *J* = 10.1, 3.5 Hz, 1 H), 4.37 (dd, *J* = 10.1, 3.5 Hz, 1 H), 4.02 (dd, *J* = 9.6, 3.0 Hz, 1 H), 3.41 (s, 3 H), 3.40 (s, 3 H), 1.46 (s, 9 H), 1.44 (s, 9 H); ¹³C NMR (150 MHz, CD₃CN) δ = 169.6, 167.6, 162.4, 162.3, 156.3, 149.1, 137.7, 130.9, 127.8, 127.7, 127.2, 125.9, 121.4, 121.3, 116.2, 111.7, 110.6, 70.7, 64.4, 62.6, 62.0, 48.7, 53.1, 52.8, 52.6, 28.6 (3 C); HRMS (ESI-TOF) calcd for C₂₈H₃₁BrN₅O₈S₂⁺ [*M* + *H*⁺] 708.0792, found 708.0786.

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Figure 1. Structures of nocathiacin I (1) and *N*-hydroxyindole model systems 2 and 3a–c. SEM, 2-(trimethylsilyl)ethoxymethyl; MOM, methoxymethyl.

Figure 2.
ORTEP drawings of compounds **55** and **58** drawn at the 50% probability level.

Scheme 1.

General route for the construction of 3-substituted *N*-hydroxyindoles (IV).

Scheme 2.

Synthesis of nitro ketoesters **6a–g** and acid **7a**. Reagents and conditions: a) NaH (4.0 equiv), (CO₂Me)₂ (5.0 equiv), DMF, 0 °C, 1 h; then 25 °C, 12 h, **5a** (60%), **5b** (60%), **5c** (85%), **5d** (80%), **5e** (75%), **5f** (75%), **5g** (65%); b) NaH (1.1 equiv), THF, 0 °C, 1 h; then CH₂=N⁺Me₂Cl[−] (3.0 equiv), 25 °C, 12 h, **6a** (80%), **6b** (67%), **6c** (98%), **6d** (74%), **6e** (55%), **6f** (75%), **6g** (50%); c) Me₃SnOH (3.0 equiv), 1,2-DCE, 80 °C, 20 min, 77%. DMF, *N,N*-dimethylformamide; DCE, 1,2-dichloroethane.

Scheme 3.

Zn/NH₄Cl-induced generation and trapping of isolable tertiary alcohol **9** and *in situ* generated α,β -unsaturated nitron **10** to form *N*-hydroxyindoles (method A). Reagents and conditions: a) Zn dust (4.9 equiv), BrCH₂CH₂Br (0.33 equiv), THF, reflux 5 min, then cool to 25 °C (repeat refluxing/cooling process 3 $\times$); then TMSCl (0.2 equiv); and then a mixture of aq. NH₄Cl (1.0 N; 2.2 equiv) and **6a** (1.0 equiv), 25 °C, 15 min, **9** (56%), **14** (10%); b) **9** (1.0 equiv), *p*TsOH (3.0 equiv), 4 Å molecular sieves (20 wt%), BnOH (5.0 equiv), DME, 40 °C, 3 h, **11** (55%); c) **9** (1.0 equiv), *p*TsOH (3.0 equiv), 4 Å molecular sieves (20 wt%), BnSH (5.0 equiv), DME, 40 °C, 1 h, **12** (90%). TMS, trimethylsilyl; *p*TsOH, *p*-toluenesulfonic acid; Bn, benzyl; DME, 1,2-dimethoxyethane.

Scheme 4.

$\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ -induced generation and trapping of *in situ* generated α,β -unsaturated nitron **10** to form *N*-hydroxyindoles (method B). Reagents and conditions: a,b) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.2 equiv), 4 Å molecular sieves (20 wt%), BnOH (5.0 equiv), **6a** (1.0 equiv), DME, 40 °C, 1.5 h, **11** (60%), **16** (17%); a,c) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.2 equiv), 4 Å molecular sieves (20 wt%), BnSH (5.0 equiv), **6a** (1.0 equiv), DME, 40 °C, 1 h, **12** (55%), **16** (15%).

Scheme 5.

Initial observations of C–C bond formation via 1,5-addition of phenolic nucleophiles.

Reagents and conditions: a) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.2 equiv), 4 Å molecular sieves (20 wt%), phenol (5.0 equiv), DME, 40 °C, 2.0 h, 40%; b) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.2 equiv), 4 Å molecular sieves (20 wt%), 2,6-dimethoxyphenol (5.0 equiv), DME, 50 °C, 3.0 h, 31%. ORTEP drawing of **36** drawn at the 50% probability level.

Scheme 6.

Construction of *N*-hydroxyindole nocathiacin I model system **2**. Reagents and conditions: a) TFA:CH₂Cl₂:MeOH (3:2:1), 25 °C, 30 min, 68%; b) *p*TsOH (3.0 equiv), 4 Å molecular sieves (20 wt%), **81** (4.0 equiv), **9** (1.0 equiv), DME, 25 °C, 10 min; then 40 °C, 2 h, 44%. TFA, trifluoroacetic acid.

Scheme 7.

Synthesis of Complex Alcohol **85**. Reagents and conditions: a) DIBAL-H (2.0 equiv), toluene, 0 °C, 2 h; b) NaH (2.5 equiv), MeI (7.0 equiv), THF, 0–25 °C, 12 h, 74% (two steps); c) LiOH (1.5 equiv), THF:EtOH:H₂O (3:1:1), 25 °C, 12 h, 90%; d) TFA:CH₂Cl₂ (1:1), 0 °C, 10 min; then 25 °C, 1 h; e) TBSCl (2.2 equiv), Et₃N (3.3 equiv), CH₂Cl₂, 25 °C, 3 h, 85% (two steps); f) **83** (1.0 equiv), HATU (1.1 equiv), HOAt (1.1 equiv), *i*Pr₂NEt (2.0 equiv), DMF, 0 °C, 1 h; then 25 °C, 2 h; g) TBAF (1.2 equiv), THF, 30 min, 0 °C, 87% (two steps). DIBAL-H, diisobutylaluminum hydride; TBSCl, *tert*-butyldimethylsilyl chloride; HATU, *O*-(7-azabenzotriazol-1-yl)-*N,N,N',N'*-tetramethyluronium hexafluorophosphate; HOAt, 1-hydroxy-7-azabenzotriazole; TBAF, tetrabutylammonium fluoride.

Scheme 8.

Construction of nocathiacin I model systems **3a** (N-OSEM) and **3b** (N-OMOM) via intermolecular *N*-hydroxyindole formation. Reagents and conditions: a) Ac_2O (5.0 equiv), Et_3N (3.0 equiv), 4-DMAP (0.1 equiv), CH_2Cl_2 , 0 °C, 10 min; b) TFA: CH_2Cl_2 :MeOH (3:2:1), 0 °C, 30 min, 82% (two steps); c) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (2.2 equiv), 4 Å molecular sieves (20 wt%), **86** (4.0 equiv), **6a** (1.0 equiv), DME, 40 °C, 6 h, 40%; d) SEMCl (2.0 equiv), $i\text{Pr}_2\text{NEt}$ (3.0 equiv), $n\text{Bu}_4\text{NI}$ (0.1 equiv), DMF, 25 °C, 10 min; e) LiOH (3.0 equiv), THF:MeOH: H_2O (3:1:1), 0–25 °C, 4 h; f) 2,4,6-trichlorobenzoyl chloride (30 equiv), Et_3N (40 equiv), toluene, 25 °C, 12 h; then 4-DMAP (30 equiv), toluene (0.5 mM), 25 °C, 24 h, 38% (three steps); g) $p\text{TsOH}$ (3.0 equiv), 4 Å molecular sieves (20 wt%), **86** (2.0 equiv), **9** (1.0 equiv), DME, 25 °C, 10 min; then 40 °C, 3 h, 56%; h) MOMCl (2.0 equiv), $i\text{Pr}_2\text{NEt}$ (3.0 equiv), $n\text{Bu}_4\text{NI}$ (0.1 equiv), DMF, 25 °C, 10 min; i) LiOH (3.0 equiv), THF:MeOH: H_2O (3:1:1), 0–25 °C, 4 h; j) 2,4,6-trichlorobenzoyl chloride (30 equiv), Et_3N (40 equiv), toluene, 25 °C, 12 h; then 4-DMAP (30 equiv), toluene (0.5 mM), 25 °C, 24 h, 44% (three steps). 4-DMAP, 4-dimethylaminopyridine; SEMCl, 2-(trimethylsilyl)ethoxymethyl chloride; MOMCl, chloromethyl methyl ether.

Scheme 9.

Construction of nocathiacin I model system **3c** (N-OH) via intramolecular *N*-hydroxyindole formation. Reagents and conditions: a) **7a** (2.0 equiv), oxalyl chloride (2.0 equiv), DMF (cat.), THF, 0 °C, 45 min; then Et_3N (4.0 equiv), **85** (1.0 equiv), 0–25 °C, 2 h, 77%; b) TFA: CH_2Cl_2 :MeOH (3:2:1), 0 °C, 1 h, 72%; c) Zn dust (4.9 equiv), $\text{BrCH}_2\text{CH}_2\text{Br}$ (0.33 equiv), THF, reflux 5 min, then cool to 25 °C (repeat refluxing/cooling process 3×); then TMSCl (0.2 equiv); and then a mixture of aq. NH_4Cl (1.0 N; 2.2 equiv) and **89** (1.0 equiv), 25 °C, 15 min; d) $p\text{TsOH}$ (3.0 equiv), 4 Å molecular sieves (20 wt%), DME (1.0 mM), 25 °C, 10 min; then 40 °C, 12 h, 40% (two steps); e) $\text{SnCl}_2 \cdot 2\text{H}_2\text{O}$ (3.2 equiv), 4 Å molecular sieves (20 wt%), DME (0.05 M), 45 °C, 3 h, 10%.

Yield [%] ^c	Product VI	t [h]
47		1.3

Tetrahedron. Author manuscript; available in PMC 2010 July 2.

Yield [%] ^c	Product VI	t [h]
41	<p>19</p>	3.0

Tetrahedron. Author manuscript; available in PMC 2010 July 2.

Yield [%] ^c	Product VI	t [h]
60		1.5

Tetrahedron. Author manuscript; available in PMC 2010 July 2.

Yield [%] ^c	Product VI	t [h]
37		1.0

Tetrahedron. Author manuscript; available in PMC 2010 July 2.

Yield [%] ^c	Product VI	t [h]
87		1.0

Tetrahedron. Author manuscript; available in PMC 2010 July 2.

Yield [%] ^c	Product VI	t [h]
56		1.5

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Yield [%]	Product VI	t [h]
55		1.0

23

Yield [%] ^c	Product VI	t [h]
47		1.0

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<p>iv)</p>	<p>2.0</p>	<p>75</p>	<p>Product VI</p>
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Yield [%] ^c	Product VI	t [h]
68		0.7

t [h]	Product VI	Yield [%] ^c
(iv)	2.5		73

Yield [%] ^c	Product VI	t [h]
55		1.0

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Product VI	t [h]	Yield [%] ^c
	1.0	54

	iv)	S		VI		t [h]	Yield [%] ^c
				1.0	75

t [h]	Product VI	Yield [%] ^c
	1.5		60

	Yield [%] ^c	Product VI	t [h]
61		1.0

Yield [%] ^c	Product VI	t [h]
57		1.0

Yield [%] ^c	Product VI	t [h]
27	 <chem>COC(=O)c1c(O)c2c(c1)c3ccccc3c2CCN4CCCCC4</chem>	6.0

33

Yield [%] ^c	Product VI	t [h]
18		3.0

Isolated yield.

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Table 4

ed nitron derived from **6a**.^a

t [h]	Product	Yield [%] ^b	Yield (16) [%] ^b
1.5		61	17

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Product	Yield [%] ^b	Yield (16) [%] ^b
t [h]	1.5			70	17

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16	39	Yield [%] ^b	Yield (16) [%] ^b
t [h]	Product OH	Product	66	11
1.2

Product	Yield [%] ^b	Yield (16) [%] ^b
t [h]		60	10
1.3

Product	Yield [%] ^b	Yield (16) [%] ^b
t [h]	2			63	10

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$\xrightarrow[\text{DME, 4 \AA MS, 40 } ^\circ\text{C}]{\text{SnCl}_2 \cdot 2\text{H}_2\text{O (2.5 equiv)}}$ $\xrightarrow[\text{DME, 4 \AA MS, 40 } ^\circ\text{C}]{\text{Enol ether (5.0 equiv)}}$	Product OH	Product OH	Product OH	Product OH	Product OH	Yield [%] ^b	Yield (16) [%] ^b	Yield (16) [%] ^b	Yield (16) [%] ^b
t [h]						75			c
1.5					Product OH	75			c
1.5					Product OH	63			c

t [h]		Product		Yield [%] ^b		Yield (16) [%] ^b		Yield [%] ^b		Yield [%] ^b		Yield [%] ^b	
1.0				51		14		33		20		14	
14				33		20		14		14		14

Product	Yield [%] ^b	Yield (16) [%] ^b
t [h]	3.0	30	19

t [h]	Product	Product	Yield [%] ^b	Yield (16) [%] ^b	
1.5			31	10	

Tetrahedron, Author manuscript; available in PMC 2010 July 2.

urified by PTLC (silica gel).

saturated nitron derived from **6a**.^a

t [h]	Product	Yield [%] ^b	Yield (16) [%] ^b
2.5		57	20

$\text{CH}_3\text{CO}_2\text{Me}$ $\xrightarrow[\text{DME, 4 \AA MS, 40 }^\circ\text{C}]{\text{SnCl}_2 \cdot 2\text{H}_2\text{O (2.5 equiv)}}$ $\text{silane/stannane (5.0 equiv)}$		Product	Yield [%] ^b	Yield (16) [%] ^b
Product OH	16 OH	52	61	15
t [h]	1.5

Product		Yield [%] ^b		Yield (16) [%] ^b	
t [h]							
1.5		54		57		15	
1.5		55		53		12	
2		55		50		15	

$\text{CH}_3\text{CO}_2\text{CH}_2\text{CO}_2\text{Me}$ $\xrightarrow[\text{DME, 4 \AA MS, 40 }^\circ\text{C}]{\text{SnCl}_2 \cdot 2\text{H}_2\text{O (2.5 equiv)}}$ $\text{silane/stannane (5.0 equiv)}$	16	Product	Yield [%]^b	Yield (16) [%]^b
t [h]	3.5		50	16

56

Product	Yield [%] ^b	Yield (16) [%] ^b
4.5			62	14

^aReactions were carried out on a scale of 0.06–0.10 mmol in anhydrous DME (concentration: 0.12–0.16 M), and the products were purified by PTLC (silica gel).

^bIsolated yield.

^cTrace amount not isolated.

Table 6

Product	Yield [%] ^c	Product	Yield [%] ^c
61		75
			73

Product	Yield [%] ^c	Product	Yield [%] ^c	Product	Yield [%] ^c

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^b In each case an additional compound corresponding to **16** (see Tables 1 and 2) was formed as a minor by-product, not isolated.
^c Isolated yield.

Table 7Effect of varying the stoichiometry in the *N*-hydroxyindole reaction.^a

Nucleophile (equiv)	Yield [%] ^b
1	50
3	59
5	75
10	74

^a Reactions were carried out on a scale of 0.06~0.10 mmol in anhydrous DME (concentration: 0.12~0.16 M), and the products were purified by PTLC (silica gel).

^b Isolated yield.