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Establishment of Substituent Effects in the DNA Binding Subunit of CBI Analogues of the Duocarmycins and CC-1065

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Abstract—An extensive series of CBI analogues of the duocarmycins and CC-1065 exploring substituent effects within the first indole DNA binding subunit is detailed. In general, substitution at the indole C5 position led to cytotoxic potency enhancements that can be ≥1000-fold providing simplified analogues containing a single DNA binding subunit that are more potent (IC_{50} = 2–3 pM) than CBI-TMI, duocarmycin SA, or CC-1065.

Introduction

CC-1065 (**1**),[1] duocarmycin A (**2**)[2] and duocarmycin SA (**3**)[3] constitute the parent members of a class of potent antitumor antibiotics[4] that derive their properties through a sequence-selective alkylation of duplex DNA, Figure 1.[5–10] Recent studies have established that the catalysis of the DNA alkylation reaction is derived from a DNA binding-induced conformational change in the agents which activate them for nucleophilic attack.[11–16] This conformational change twists the amide linking the alkylation subunit and attached DNA binding domain which disrupts the cross-conjugated vinylogous amide stabilization of the alkylation subunit activating the cyclopropane for nucleophilic attack. This ground-state destabilization of the cyclopropane upon DNA binding is consistent with the proposal that the DNA alkylation sequence selectivity originates in the noncovalent binding selectivity of the agents.[5]

Recent studies have indicated that the role of attached DNA binding domain goes beyond that of simply providing DNA binding affinity and selectivity, but that it contributes to and is largely responsible for the DNA alkylation catalysis.[11–19] Minor groove bound substituents on both the first DNA binding subunit[14–20] and the alkylation subunit[21–24] have been shown to have a pronounced effect on the rate and efficiency of DNA alkylation and the resulting biological potency of the compounds. These effects proved to be independent of the electronic properties of the substituent and their inherent effects on reactivity, but could be attributed to their simple presence and the fact that they extend the rigid length of the agent. In doing so, they increase the extent of the DNA binding-induced conformational

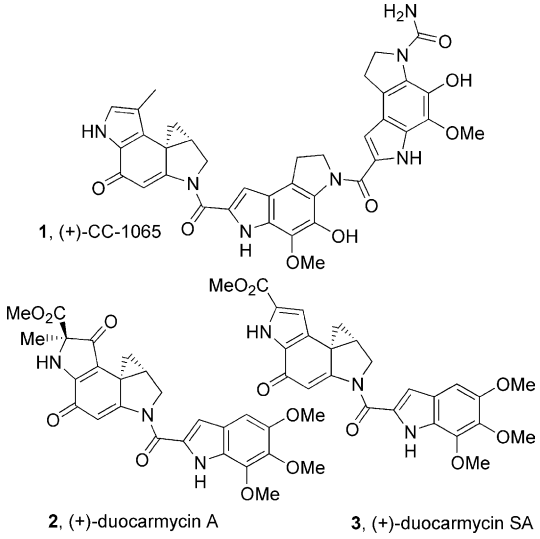

Figure 1.

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change, increase the degree of vinylogous amide disruption, and increase the rate of DNA alkylation.

For example, the contribution of each of the three methoxy groups of 5,6,7-trimethoxyindole (TMI) was established using the DNA alkylation subunits DSA[15] and CPI.[23] These studies demonstrated the predominant importance of the C5 methoxy substituent, which alone provided a fully active agent, with little or no contribution derived from the C6 and C7 methoxy groups. Moreover, the cytotoxic potency of these agents nicely correlated with their DNA alkylation rate and efficiency. The conclusion being that the agents bearing a C5 methoxy substituent were more effective and that this was due to the extended rigid length provided by the minor groove bound substituent. Subsequently, this was found to be consistent with the high resolution NMR structures of (+)-duocarmycin SA[25] and its derivative DSI (DSA-indole),[26] lacking the three methoxy groups, bound to DNA which confirmed that the presence of C5 methoxy group increased the twist in the DNA bound agent.[27] Moreover, the C5 methoxy group of **3** is found deeply embedded in the minor groove with methyl group extending into, not away from, the minor groove floor, potentially benefiting from hydrophobic contacts (Fig. 2).

Despite these studies and reports of limited series of agents,[28–30] no systematic examination of the DNA binding subunit C5 substituent has been disclosed. Following observations made in our recent preliminary study,[19] and utilizing the CBI alkylation subunit (1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one),[30–32] herein we describe an extensive library of nearly 80 derivatives designed to establish the impact of substituents placed on the first DNA binding subunit. The CBI subunit was chosen for the present study because it represents the synthetically most accessible simplified alkylation subunit in the series,[35] exhibits a potency and efficacy that surpasses that found in **1** and **2** while approaching that of **3**,[31] exhibits stability and reaction regioselectivity characteristics that are near optimal,[32] and constitutes a parent ring system that has been extensively employed, extended, or modified in both our work and that of many others.[17–24,30–60]

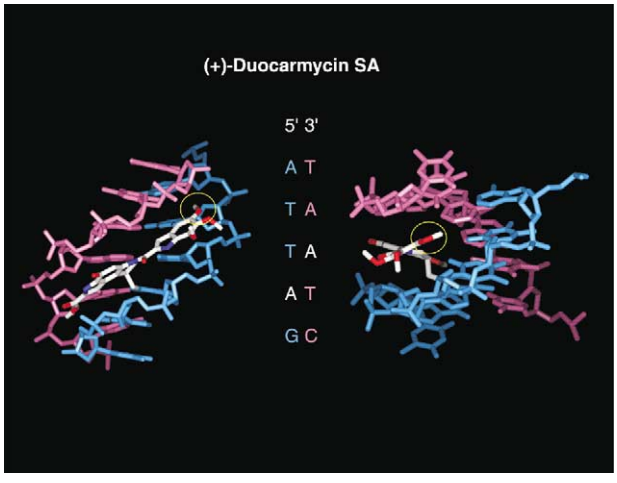


Figure 2. Front and groove view of the ^{1}H NMR derived solution structure of (+)-duocarmycin SA bound to a high affinity alkylation site within d(GACTAATTGAC)-d(GTCAATTAGTC) highlighting the minor groove embedded indole C5 methoxy group (ref. 25).

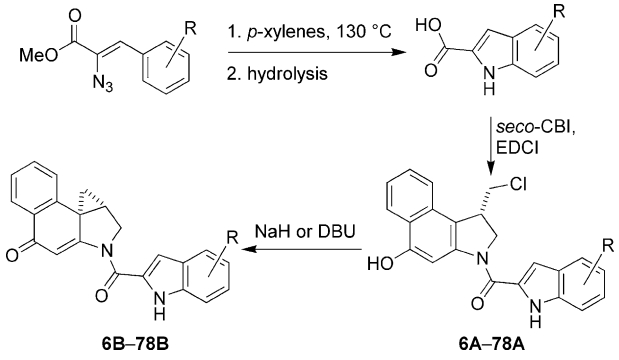
Synthesis

The compounds were prepared as shown in Scheme 1. The non-commercially available indole-2-carboxylic acids were obtained from the corresponding azido cinnamates derived from condensation of substituted benzaldehydes with methyl α-azidoacetate. The azidocinnamates were subjected to the Hemetsberger reaction[61] followed by saponification of the esters to provide the substituted indole-2-carboxylic acids. Acid-catalyzed deprotection of *seco*-*N*-BOC-CBI (natural or unnatural enantiomer) followed by coupling of the resulting hydrochloride salt with the indole-2-carboxylic acids (3 equiv EDCI, DMF, 25 °C, 14 h) in the absence of added base provided the *seco* agents.[31] Spirocyclization was effected by treatment with DBU[42] or NaH[31] providing **6B–78B**. In the case of **77–78**, both enantiomers of the compounds were examined, whereas in the case of **6–76** only the more potent natural enantiomers were examined.

Results and Discussion

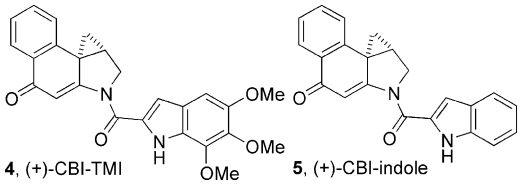
The comparison compounds for examining the effects of the indole substituents of the CBI analogues of duocarmycin SA (**3**) are CBI-TMI (**4**)[37] and CBI-indole (**5**, Table 1). The former contains the 5,6,7-trimethoxy substituents of duocarmycin SA (**3**) while the latter incorporates the parent unsubstituted indole. (+)-CBI-TMI (**4**) was found to be nearly 100-fold more potent than (+)-CBI-indole (**5**) with the 5,6,7-trimethoxyindole substitution increasing the L1210 cytotoxic potency 90 times. This effect of the 5,6,7-trimethoxy substitution is analogous, but more pronounced, than the 6–10-fold effect observed with duocarmycin SA[15] and CPI-TMI.[23]

The comparisons in Table 2 detail the systematic approach taken to establish the effects of the individual methoxy groups found on the indole. Although the CBI-based agents proved to be more sensitive to the removal of the TMI subunit methoxy groups than



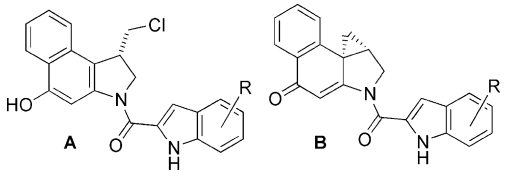
Scheme 1.

Table 1. Cytotoxic activity, L1210 (IC_{50}, pM)



Compd		IC_{50}, pM
(+)-duocarmycin SA	**3**	6–10
(+)-CC-1065	**1**	20
(+)-duocarmycin A	**2**	200
(+)-CBI-TMI	**4**	30
(+)-CBI-indole	**5**	2700

Table 2. Ether and thioether substituted indole derivatives



R	Compd	Yield **A**, **B** (%)	IC_{50}, pM[a]
4-OMe	**6A**,**B**	47, 92	500
5-OMe	**7A**,**B**	75, 73	50
6-OMe	**8A**,**B**	53, 98	300
7-OMe	**9A**,**B**	52, 94	300
4,5-OMe	**10A**,**B**	48, 35	>1000
5,6-OMe	**11A**,**B**	61, 82	30
6,7-OMe	**12A**,**B**	43, 65	200
5,7-OMe	**13A**,**B**	55, 98	40
5-OH	**14A**	43[b]	200
5-OEt	**15A**,**B**	54, 94	10
5-OPr	**16A**,**B**	63, 70	40
5-OBu	**17A**,**B**	46, 88	50
5-OBn	**18A**,**B**	31, 91	50
5-OCF_3	**19A**	53[b]	100
7-OCF_3	**20A**	65[b]	400
5-SMe	**21A**,**B**	39, 56	50
7-SMe	**22A**,**B**	55, 74	600
5-SEt	**23A**,**B**	62, 82	70

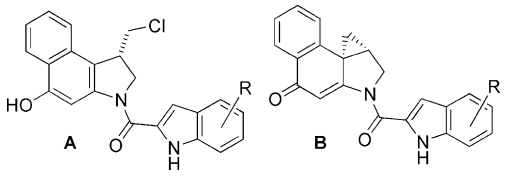
[a]L1210 cytotoxic activity, average of 2–7 determinations run in triplicate.
[b]Prepared and examined as the **A** *seco* derivative only.

the DSA- or CPI-based agents, analogous trends were observed. When the cytotoxic potency of CBI-TMI (**4**, IC_{50} = 30 pM)[9,37] was compared with the methoxy series **6** (C4 OMe), **7** (C5 OMe), **8** (C6 OMe), **9** (C7 OMe), decreases of 17×, 1.6×, 10×, and 10×, respectively, were observed. Thus, maintenance of the C5 methoxy group with removal of the C6 and C7 methoxy groups with analogue **7** maintained the cytotoxic potency, whereas its removal in **8** and **9** led to a ≥10× reduction in activity. Similar, but less pronounced, reductions in potency with the removal of the TMI methoxy substituents were observed with duocarmycin SA (6.5–10×) and CPI (7×). In the case of duocarmycin SA, the C7 methoxy substituent did not provide a contribution to cytotoxic potency and that of the C6 methoxy group was modest, whereas with CBI (**7** vs **8** and **9**) both the C7 and C6 methoxy group were found to improve potency significantly, but not nearly of the magnitude observed with the C5 methoxy group. Most surprising of the effects was the relatively potent behavior of **6**. Although it was 16–17-fold less active than CBI-TMI, it was 4-fold more active than CBI-indole despite the methoxy substitution at C4. A similar effect is seen with the dimethoxy derivatives **11** (C5,6 OMe), **12** (C6,7 OMe), and **13** (C5,7 OMe) where the potency of **11** (C5,6 OMe) and **13** (C5,7 OMe) were not distinguishable from that of **7** (C5 OMe) being only 1.0–1.3-fold from that of CBI-TMI, whereas **12** (C6,7 OMe) exhibited a more significant 6.6-fold reduction being essentially equivalent to the C6 or C7 monomethoxy derivatives **8** and **9**. Clearly, the C5 position is the most important site potentiating the cytotoxic activity (C5 OMe > C6 OMe ≥ C7 OMe > C4 OMe > H), and additional methoxy substitutions act in a more modest, but predictably additive manner. Interestingly, the C4,5 dimethoxy derivative **10** was much less active.

The effect of additional ether and thioether substituted indoles is also summarized in Table 2. Alterations in the C5 methoxy group providing longer, flexible, and more hydrophobic alkyl ethers (**15**–**18**) had little effect on the cytotoxic potency although a significant and optimal additional 5-fold increase was observed with the C5 ethoxy derivative (**15**, IC_{50} = 10 pM), and a 4-fold reduction in potency was observed with the corresponding C5 free phenol **14** versus C5 methyl ether. Notably, the trifluoromethyl ether series with substitutions at the C5 and C7 positions revealed a possible deleterious effect derived from fluorine substitution on the substituents that lie embedded in the minor groove. A substantial decrease of 2-fold in cytotoxic activity was seen with the C5 OCF_3 group relative to **7** (C5 OMe), whereas the C7 OCF_3 substitution proved essentially equivalent with **9** (C7 OMe). A thioether series provided similar observations. The derivative bearing a C5 thiomethyl group had the same cytotoxic activity as the corresponding C5 OCH_3 derivative (IC_{50} = 50 pM). Likewise, the C7 thiomethyl group was an order of magnitude less potent and comparable in activity to **9** (C7 OMe). Interestingly, the C5 thioethyl derivative did not exhibt the increased potency found with **15**.

As a consequence of these observations, a wide range of C5 indole substituents were examined. Many of these are summarized in Table 3 and those that provided the most potent derivatives or that were examined as a comparison series are summarized in subsequent tables. Although no single generalization is easily discerned from the comparisons summarized in Table 3, some important trends emerge that are discussed in more detail with the subsequent series. Addition of a single heavy atom substituent typically resulted in a modest 1.3–40× increase in potency which diminishes as the size of the substituent increased (potency: OH = NH_2 > Cl > Br > Me), unsaturated C5 substituents proved more potent than the corresponding saturated counterparts (potency: C≡CH=CH=CH_2 > Et) consistent with restrictions on the optimal size of the C5 substiuent, extension of the rigid length of the unsaturated C5 substiuents smoothly follows the trend 0 < 1 < 2 > 3 heavy atoms, and branching at the site of C5 attachment with a small hydrophobic group may

Table 3. Substituted indole derivatives



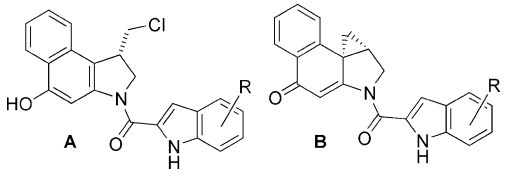
R	Compd	Yield **A**, **B** (%)	IC_{50}, pM[a]
5-H	**5A**,**B**	57, 93	2700
5-OMe	**7A**,**B**	75, 73	50
5-Me	**24A**,**B**	53, 87	2000
5-Et	**25A**,**B**	44, 61	2000
5-CH_2OCH_3	**26A**,**B**	53, 85	400
7-CH_2OCH_3	**27A**,**B**	44, 87	2000
5-Br	**28A**,**B**	56, 38	500
5-Cl	**29A**,**B**	74, 77	400
5-N_3	**30A**,**B**	60, 84	300
5-CN	**31A**,**B**	70, 21	30
7-CN	**32A**,**B**	35, 62	300
5-Vinyl	**33A**,**B**	54, 65	200
7-Vinyl	**34A**,**B**	41, 88	500
5-Isopropenyl	**35A**,**B**	51, 66	150
7-Isopropenyl	**36A**	64[b]	3500
5-C≡CH	**37A,B**	33, 87	300
5-C≡CMe	**38A,B**	33, 79	1000
4-Ph	**39A**	40[b]	400,000

[a]L1210 cytotoxic activity, average of 2–7 determinations run in triplicate.
[b]Prepared and examined as the **A** *seco* derivative only.

increase potency ($MeC{=}CH_2 > HC{=}CH_2$). In each case, a C5 substituent was more potent than the corresponding C7 substituent, and the impact of the C5 substituent on potency appears to be related simply to its presence and shape characteristics while being relatively independent of its electronic properties (e.g., OMe = CN). Most noteworthy in this series is the potency of the simple nitrile **31** (IC_{50} = 30 pM) which is equivalent with CBI-TMI and slightly more potent than **7** (C5 OMe, IC_{50} = 50 pM).

An important series examined early in the studies was the amine and amide derivatives of 5-aminoindole, Table 4. Not only does this represent the linking functionality and substitution found in the potent derivatives containing more than one DNA binding subunit (e.g., CBI indole$_2$ and **1**), but Lown has reported significant effects of such amides within a select set of (+)-CPI-*N*-methylpyrrole agents constituting hybrid stuructures of CPI linked with the DNA binding subunits of distamycin.[62] Notably the amide derivatives **44**–**47** proved to be potent cytotoxic agents (IC_{50} = 30 pM) being slightly more potent than **7** (C5 OMe, IC_{50} = 50 pM) and equivalent with (+)-CBI-TMI (IC_{50} = 30 pM) even though they contain a single C5 substituent. This activity was invariant within the range of the amides examined (**44** = **45** = **46**), and was unaffected by *N*-methylation (**44** = **47**) indicating H-bonding plays no role in their activity. Notably, this series did not exhibit the trends detailed by Lown for the CPI-pyrrole conjugates (NHCOPr > NHCOEt > NHCOMe). Most likely, this may be attributed to the intrinsically poorer properties of the CPI–pyrrole conjugates[18,62] reported by Lown and the greater influence such amide substituents may have.

Table 4. Amide substituted indole derivatives



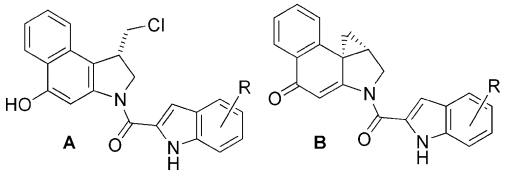
R	Compd	Yield **A**, **B** (%)	IC_{50}, pM[a]
5-NH_2	**40A,B**	87, 85	600
5-NMe_2	**41A**	23[b]	40
5-NEt_2	**42A**	20[b]	50
5-NHBoc	**43A**	55[b]	80
5-NHCOMe	**44A,B**	27, 76	30
5-NHCOEt	**45A,B**	30, 68	30
5-NHCOPr	**46A,B**	44, 99	30
5-N(Me)COMe	**47A,B**	48, 95	30
5-N(Et)COMe	**48A**	39[b]	80

[a]L1210 cytotoxic activity, average of 2–7 determinations run in triplicate.
[b]Prepared and examined as the **A** *seco* derivative only.

Interestingly, and analogous to observations made within the C5 alkoxy series (**7**, **14**, and **15**), the C5 amino derivative **40** was 5-fold more potent than CBI-indole and the corresponding C5 dimethylamino or diethylamino derivatives **41** and **42** were 12–15× more potent than **40**. The latter two derivatives (**41** and **42**) were equipotent with **7**, the C5 methoxy derivative.

An interesting and perhaps unprecedented series that was examined exploring the 5, 6, and 7-nitroindoles is summarized in Table 5. Consistent with the trends exhibited with the methoxy substitution pattern (C5 > C6 > C7; Table 2),[15,23] the smooth trend of **49** > **50** > **51** was observed. The distinction being that each was more potent than the corresponding methoxy derivative with **49** (C5 NO_2, IC_{50} = 20 pM) not only surpassing the potency of **7** (C5 OMe, IC_{50} = 50 pM) but also surpassing the potency of even (+)-CBI-TMI (**4**, IC_{50} = 30 pM). Nonetheless, the relatively small distinction between the strongly electron-withdrawing NO_2 versus electron-donating OMe substituent (C5 = 2.5×, C6 = 5×, C7 = 1.5×) suggest electronic effects[63] modulated through the indole ring may attenuate activity but only to minor extent.

Table 5. Nitro substituted indole derivatives



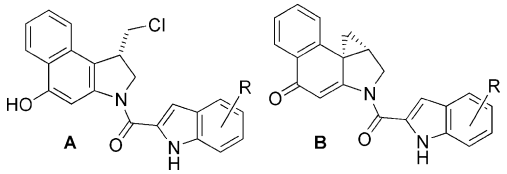
R	Compd	Yield **A**, **B** (%)	IC_{50}, pM[a]
5-NO_2	**49A**	49[b]	20
6-NO_2	**50A**	82[b]	60
7-NO_2	**51A**	29[b]	200

[a]L1210 cytotoxic activity, average of 2–7 determinations run in triplicate.
[b]Prepared and examined as the **A** *seco* derivative only.

One of the most interesting series that was explored in detail and that provided exceptionally potent derivatives was the C5 indole derivatives bearing a carbonyl group directly attached to the indole (Table 6). Most significant of the observations was the behavior of the C5 acyl derivatives **54** and **56**. A 1000-fold increase in potency over (+)-CBI-indole (**5**) was observed with **54** and **56** representing an additional $\geq$10-fold increase in potency beyond most C5 substituted derivatives described above. Analogues **54** and **56** are exceptionally potent cytotoxic compounds (IC_{50} = 2–3 pM) exceeding the activity of CBI-TMI (**4**, 30 pM), CC-1065 (**1**, 20 pM), and duocarmycin SA (**3**, 6–10 pM). Interestingly, the analogue **57** containing a propyl chain reverted to the potency characteristic of the C5 substituted analogues (IC_{50} = 20 pM), and did not show the further enhancement observed with **54** and **56**. As discussed later, this may reflect the adoption of a DNA bound conformation for **54** and **56** analogous to the angular fusion of a 5-membered ring (see Fig. 3) with the methyl or ethyl group of **54** and **56** deeply embedded in the minor groove. This bound conformation would not be accessible to **57** because of the extended chain length and its behavior reverts back to that of an extended, flexible C5 substituent. The analogous, but less pronounced, enhancement observed with **58** and **60** may reflect a similar behavior. Notably, the methyl group of the C5 methoxy substituent of duocarmycin SA has been shown to extend into and be deeply embedded in the minor groove[25–27] consistent with such a bound conformation (Fig. 2).

Consistent with this special role for the methyl and ethyl groups of **54**, **56**, **58**, and **60**, the C5 formyl analogue **52**, which would not benefit from such an interaction, proved to be 50-fold less potent. Although the corresponding ester derivatives **58** and **60** were significantly less potent with **58** > **60**, the former, but not the latter, may benefit from an analogous minor groove embedded methoxy versus precluded ethoxy group with the weaker

Table 6. Carbonyl substituted indole derivatives



R	Compd	Yield **A**, **B** (%)	IC_{50}, pM[a]
5-CHO	**52A**	39[b]	100
7-CHO	**53A,B**	20, 48	500
5-COMe	**54A,B**	66, 77	2
7-COMe	**55A,B**	57, 77	300
5-COEt	**56A,B**	63, 46	3
5-COPr	**57A,B**	64, 31	20
5-COOMe	**58A**	50[b]	50
7-COOMe	**59A**	53[b]	300
5-COOEt	**60A**	50[b]	200
5-$CONH_2$	**61A**	47[b]	20
5-CONHMe	**62A**	30[b]	10
5-$CONMe_2$	**63A**	45[b]	40

[a]L1210 cytotoxic activity, average of 2–7 determinations run in triplicate.
[b]Prepared and examined as the **A** *seco* derivative only.

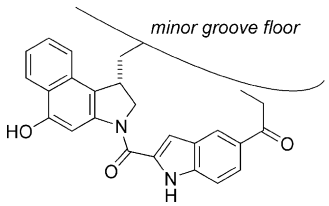


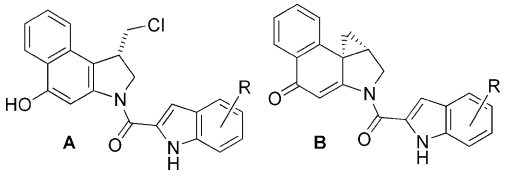
Figure 3.

potency reflecting the less hydrophobic character of the interacting group. Finally, the corresponding carboxamide C5 derivatives **61**–**63**, especially **61** and **62**, were potent derivatives and it is tempting to suggest the enhanced potency of **62** benefits from a similar minor groove interaction. Notably, **62** was only 5-fold less potent than **54** and 3-fold more potent than (+)-CBI-TMI also placing it among the more potent derivatives examined.

In an interesting extension of these observations, the sulfone derivatives **64** and **65** were examined, Table 7. Like **54**, the C5 methanesulfonyl derivative **64** proved exceptionally potent (IC_{50} = 3 pM) being 15–20 fold more active than the corresponding thiomethyl derivative **21** (IC_{50} = 50 pM) or methoxy derivative **7** (IC_{50} = 50 pM) and exceeding the activity of even **1**–**5**. Unlike **56**, the corresponding ethanesulfonyl derivative, while being a potent cytotoxic agent (IC_{50} = 40 pM), did not exhibit this exceptional activity, and was only slightly more active than the corresponding thioethyl derivative **23** (IC_{50} = 100 pM). This may reflect the larger size of S with **64**, not **65**, exhibiting shape characteristics closer to the potent ethyl ketone **54**, and uniquely benefiting from the embedded minor groove interactions within the sulfone series.

As a consequence of these observations, we became interested in re-examining tricyclic DNA binding subunits that bear structural characteristics of the potent indole derivatives disclosed herein. In prior studies, we had already disclosed (+)-CBI-$CDPI_1$ (**68**) embodying the structural characteristics of the DNA binding subunit of CC-1065 and had shown that it was an exceptionally potent, simplified derivative (IC_{50} = 5 pM).[21] It contains a fused five-membered ring that may be regarded as a conformationally restricted and more rigid analogue of **44**–**48**. The results of our examination of

Table 7. Sulfone substituted indole derivatives

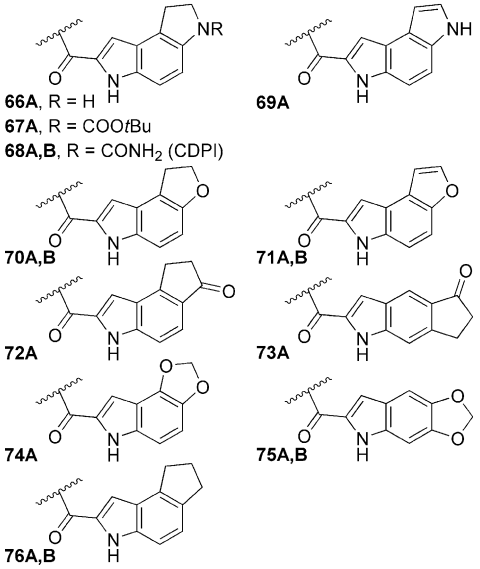


R	Compd	Yield **A**, **B** (%)	IC_{50}, pM[a]
5-SO_2Me	**64A**	38[b]	3
5-SO_2Et	**65A**	71[b]	40

[a]L1210 cytotoxic activity, average of 2–7 determinations run in triplicate.
[b]Prepared and examined as the **A** *seco* derivative only.

such alternative tricyclic systems that represent rigid or conformationally restricted analogues of the potent derivatives are summarized in Table 8. The cyclic structures representing substitutions at the 4,5 positions were expected to be superior to the 5,6 analogues due to their ability to adopt a conformation embodying the embedded minor groove substituent. Where examined, the 4,5-isomer was more potent than the corresponding 5,6-isomer (**72** vs **73** and **74** vs **75**), and introduction of unsaturation resulted in rather dramatic losses in activity (>10-fold, **66** vs **69** and **70** vs **71**). Most importantly, the 4,5 constrained analogues (but not the 5,6 constrained analogues) typically matched or exceeded the potency of the corresponding unconstrained analogue. For example, **72**, but not **73**, matched the potency of the C5 substituted methyl and ethyl ketones **54** and **56**. Similarly, **70** was slightly more potent than **7** (C5 OMe) and only slightly less potent than **15** (C5 OEt). Both CDPI and **67** were more potent than their corresponding C5 amine or amide derivatives (**40**–**48**, IC_{50} = 30–80 pM), and the fused cyclopentyl derivative **76** was more active than the corresponding C5 alkyl derivatives **24** and **25** (IC_{50} = 2000 pM). Analogously, **74** was much more active than the corresponding unconstrained 4,5 dimethoxy derivative **10** whereas the 5,6 isomer **75** was substantially less potent than the corresponding unconstrained C5,6 dimethoxy derivative **11**. Moreover, there was a pronounced difference in the relative potency of the constrained 4,5-derivatives that follows the trends observed with the analogous C5 substituent (–COR > –NCOR > –OR, $–NR_2$ > –R where R = alkyl). Importantly, this series provided some of the most potent derivatives of CBI being 6–8-fold more potent than CBI-TMI (IC_{50} = 30 pM) and ≥10-fold more potent than **5** (IC_{50} = 50 pM) and surpassing the activity of CC-1065 (IC_{50} = 20 pM) and duocarmycin SA (IC_{50} = 6–10 pM).

Table 8. Tricyclic indole derivatives



R	Compd	Yield **A**, **B** (%)	IC_{50}, pM[a]
4,5-CH_2CH_2NH	**66A**	100[b]	50[c]
4,5-$CH_2CH_2NCOOtBu$	**67A**	77[b]	6
4,5-$CH_2CH_2NCONH_2$	**68A**,**B** ($CDPI_1$)	86, 74	5[21]
4,5-CHCHNH–	**69A**	14[b]	800
4,5-CH_2CH_2O–	**70A**,**B**	53, 69	40
4,5-CHCHO–	**71A**,**B**	45, 55	600
4,5-CH_2CH_2CO–	**72A**	62[b]	4
5,6-$COCH_2CH_2$–	**73A**	46[b]	50
4,5-OCH_2O–	**74A**	57[b]	90
5,6-OCH_2O–	**75A**,**B**	42, 77	600
4,5-$(CH_2)_3$–	**76A**,**B**	62, 92	500

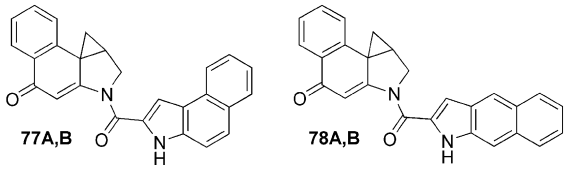
[a]L1210 cytotoxic activity, average of 2–7 determinations run in triplicate.
[b]Prepared and examined as the **A** *seco* derivative only.
[c]Unstable, rapidly oxidizes to **69A**.

As shown in Table 9, extending the rigid length of the DNA binding indole by adding a linear or angular fused benzene ring did not substantially alter the cytotoxic potency. The linear extension with (+)-**78** resulted in a modest 5-fold increase in potency whereas the angular extension with (+)-**77** resulted in a modest 2-fold reduction when compared to (+)-CBI-indole (R = H) and a more significant 6–8-fold reduction relative to the fused pyrrole **69** or the fused furan **71**. Consistent with expectations and past observations, the corresponding unnatural enantiomers (−)-**77** and (−)-**78** were found to be approximately 100–1000× less potent. The behavior of the angular derivatives (+)-**77** and (−)-**77** is especially striking in comparison with CBI-CDPI (**68**) and the related analogues in Table 8 which bear an angular fused saturated 5-membered ring. Presumably the increased sized and planar nature of the angularly fused benzene ring found in (+)-**77** and (−)-**77** hinders rather than facilitates minor groove binding and penetration required to observe DNA alkylation.

DNA alkylation selectivity, efficiency, and rate

Although a number of features of **6**–**78** can contribute to distinctions observed in a cellular functional assay for cytotoxic activity, the most prominent feature that we probed was the impact that the indole substituent had on the DNA alkylation properties. Thus, the DNA alkylation selectivity, efficiency, and rate of the simplest and most potent derivatives **54** and **64** were compared to duocarmycin SA (**3**), (+)-CBI-TMI (**4**), (+)-CBI-indole (**5**), and **7** in w794 DNA enlisting protocols previously introduced in our studies.[64] First, no alterations in the inherent DNA alkylation selectivity were observed with the new derivatives **54** and **64** consistent

Table 9.



R	Compd	Yield (%)	IC_{50}, pM[a]
(+)-CBI-benz[*e*]indole	(+)-**77A**,**B**	31	5000
(−)-CBI-benz[*e*]indole	(−)-**77A**,**B**	45	3×10^5
(+)-CBI-benz[*f*]indole	(+)-**78A**,**B**	20	500
(−)-CBI-benz[*f*]indole	(−)-**78A**,**B**	41	4×10^5

[a]L1210 cytotoxic activity, average of 2–7 determinations run in triplicate.

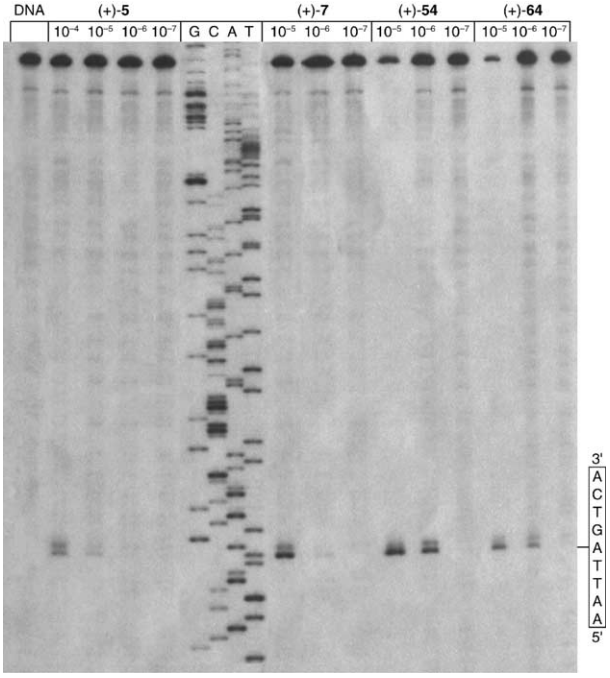


Figure 4. w794 DNA alkylation (24 h, 23 °C).[65]

Table 10. DNA alkylation properties[a]

Compd	Rel. Efficiency	Rel. Rate
3 (DSA)	2.0	(1.1–1.2)[b]
4 (CBI–TMI)	1.0	1.0
5 (CBI–Indole)	0.1	0.1
7 (C5 OMe)	0.95	1.0
54 (C5 COMe)	4.0	2.0
64 (C5 SO_2CH_3)	7.0	2.5

[a]w794 DNA,[64] following a procedure detailed in ref. 37.
[b]Taken from ref. 37.

with past observations now entailing a wide range of CBI-based analogues (e.g., CBI-TMI vs duocarmycin SA).[8,37] More importantly, the CBI analogues displayed significant distinctions in both their efficiencies in DNA alkylation (Fig. 4 and Table 10) and their rates of DNA alkylation (Table 10) that proved to correlate with the relative and absolute trends observed in their cytotoxic potency. Thus, in the case of the simplified and exceptionally potent derivatives **54** and **64**, their enhanced cytotoxic potency correlates with an enhanced rate and efficiency of DNA alkylation.

Conclusion

C5 substituents on the first indole DNA binding subunit have a pronounced effect on the activity of CBI analogues of the duocarmycins and CC-1065. This effect, which provides as large as a 1000-fold increase in cytotoxic potency with **54** and **64** that correlate well with accompanying increases in the rate and efficiency of DNA alkylation, is more pronounced with the CBI versus DSA or CPI based analogues. Moreover, this effect is largely insensitive to the electronic character of the C5 substituent but is sensitive to the size, rigid length, and shape (*sp*, sp^2, sp^3 hybridization) of this substituent consistent with expectation that the impact is due simply to its presence. With these substitutions, simplified CBI analogues were identified which surpass the potency of duocarmycin SA, CC-1065, and CBI-TMI. The comparison of these derivatives with a select set of conformationally constrained tricyclic indole derivatives suggest they additionally benefit from hydrophobic contacts in a pocket deeply imbedded in the minor groove. Thus, an indole C5 substituent may not only extend the rigid length of the compound enhancing the DNA binding induced disruption of the alkylation subunit vinylogous amide thereby accelerating the rate of DNA alkylation, but appropriate substituents may also benefit from stabilizing contacts within a minor groove hydrophobic pocket.

Experimental

General procedure for the synthesis of the *seco* agents: A solution of the natural enantiomer of *seco*-*N*-Boc-CBI (2.5 mg, 7.5 μmol) in 1 mL of 4 M HCl (EtOAc) was stirred for 1 h at 25 °C. The solvent was then removed under a stream of N_2. The residue was dried under high vacuum for 3 h and the indole-2-carboxylic acid[66] (8.3 μmol) was added. A solution of EDCI (22.5 μmol) in 200 μL DMF was added and the reaction mixture was stirred for 14 h at 25 °C. The reaction mixture was then diluted with CH_2Cl_2 (1 mL) and the solvent was removed under a stream of N_2. The product was purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1 or THF/hexane 1:1 to 3:1).

3-(4-Methoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (6A). (1.44 mg, 47%) as an off-white solid: $[\alpha]_D^{23}$ +33 (*c* 0.2, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.84 (1H, br s), 9.23 (1H, s), 8.25 (1H, d, *J* = 8.6 Hz), 8.10 (1H, br s), 7.90 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz), 7.39 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.17–7.24 (3H, m), 6.59 (1H, dd, *J* = 7.5, 1.1 Hz), 4.87 (1H, dd, *J* = 10.5, 8.8 Hz), 4.80 (1H, dd, *J* = 10.7, 2.6 Hz), 4.30–4.34 (1H, m), 4.11 (1H, dd, *J* = 11.1, 3.0 Hz), 3.97 (3H, s), 3.86 (1H, dd, *J* = 11.1, 8.1 Hz); MALDIFT-HRMS *m*/*z* 407.1162 ($M+H^+$, $C_{23}H_{20}ClN_2O_3$ requires 407.1157).

3-(5-Methoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (7A). (2.30 mg, 75%) as a white solid: $[\alpha]_D^{23}$ +14 (*c* 0.13, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.71 (1H, br s), 9.23 (1H, s), 8.25 (1H, d, *J* = 8.6 Hz), 8.08 (1H, br s), 7.89 (1H, d, *J* = 8.5 Hz), 7.55 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.49 (1H, d, *J* = 9.0 Hz), 7.39 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.19–7.20 (1H, m), 7.16 (1H, dd, *J* = 2.1, 0.9 Hz), 6.96 (1H, dd, *J* = 9.0, 2.6 Hz), 4.83 (1H, dd, *J* = 10.9, 8.3 Hz), 4.79 (1H, dd, *J* = 10.9, 2.4 Hz), 4.34–4.38 (1H, m), 4.08 (1H, dd, *J* = 11.1, 3.0 Hz), 3.84 (3H, s), 3.81 (1H, dd, *J* = 11.1, 8.6 Hz); MALDIFT-HRMS *m*/*z* 406.1070 (M^+, $C_{23}H_{19}ClN_2O_3$ requires 406.1084).

3-(6-Methoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (8A). (1.63 mg, 53%) as a pale yellow solid: $[\alpha]_D^{23}$ −45 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.67 (1H, br s), 9.25 (1H, s), 8.25 (1H, d, *J* = 8.5 Hz), 8.10 (1H, br s), 7.89 (1H, d, *J* = 8.5 Hz), 7.61 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.39 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.20 (1H, m), 7.08 (1H, d, *J* = 2.1 Hz), 6.79 (1H, dd, *J* = 8.8, 2.3 Hz), 4.82 (1H, dd, *J* = 10.5, 8.8 Hz), 4.77 (1H, dd, *J* = 10.7, 2.6 Hz), 4.27–4.31 (1H, m), 4.08 (1H, dd, *J* = 11.1, 3.4 Hz), 3.84 (3H, s), 3.82 (1H, dd, *J* = 11.5, 8.6 Hz); MALDIFT-HRMS *m*/*z* 406.1093 (M^+, $C_{23}H_{19}ClN_2O_3$ requires 406.1079).

3-(7-Methoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (9A). (1.59 mg, 52%) as a pale yellow solid: $[\alpha]_D^{23}$ +1 (*c* 0.2, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.27 (1H, br s), 9.25 (1H, s), 8.26 (1H, d, *J* = 8.6 Hz), 8.06 (1H, br s), 7.89 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.40 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.31 (1H, d, *J* = 8.1 Hz), 7.22 (1H, d, *J* = 2.6 Hz), 7.06 (1H, t, *J* = 7.9 Hz), 6.82 (1H, d, *J* = 7.7 Hz), 4.82 (1H, dd, *J* = 10.7, 8.5 Hz), 4.76 (1H, dd, *J* = 10.7, 2.1 Hz), 4.26–4.31 (1H, m), 4.08 (1H, dd, *J* = 11.1, 3.0 Hz), 3.99 (3H, s), 3.82 (1H, dd, *J* = 11.5, 8.5 Hz); MALDIFT-HRMS *m*/*z* 407.1170 ($M+H^+$, $C_{23}H_{19}ClN_2O_2$ requires 407.1157).

3-(4,5-Dimethoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (10A). (1.9 mg, 48%) as a white solid: $[\alpha]_D^{23}$ +43 (*c* 0.03, acetone); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 10.76 (1H, br s), 9.26 (1H, s), 8.24 (1H, d, *J* = 8.3 Hz), 8.08 (1H, s), 7.90 (1H, d, *J* = 8.2 Hz), 7.55 (1H, t, *J* = 7.0 Hz), 7.40 (1H, t, *J* = 7.5 Hz), 7.25 (1H, d, *J* = 8.8 Hz), 7.22 (1H, s), 7.11 (1H, d, *J* = 8.8 Hz), 4.86 (1H, t, *J* = 9.8 Hz), 4.79 (1H, d, *J* = 10.5 Hz), 4.30 (1H, m), 4.07 (1H, dd, *J* = 8.3, 3.1 Hz), 4.03 (3H, s), 3.87 (3H, s), 3.84 (1H, m); IR (film) ν_{max} 3749, 1684 1558, 1506 cm^{-1}, MALDIFT-HRMS *m*/*z* 437.1276 ($M+H^+$, $C_{24}H_{21}ClN_2O_4$ requires 437.1263).

3-(5,6-Dimethoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (11A). (2.01 mg, 61%) as a pale yellow solid: $[\alpha]_D^{23}$ +11 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.60 (1H, br s), 9.25 (1H, s), 8.25 (1H, d, *J* = 8.5 Hz), 8.11 (1H, br s), 7.88 (1H, d, *J* = 8.1 Hz), 7.54 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz), 7.38 (1H, ddd, *J* = 8.1, 6.8, 1.1 Hz), 7.18 (1H, s), 7.14 (1H, dd, *J* = 2.1, 0.9 Hz), 7.10 (1H, s), 4.81 (1H, dd, *J* = 10.7, 8.5 Hz), 4.76 (1H, dd, *J* = 10.7, 2.6 Hz), 4.26–4.30 (1H, m), 4.07 (1H, dd, *J* = 11.1, 3.0 Hz), 3.84 (6H, s), 3.80 (1H, dd, *J* = 11.1, 9.0 Hz); MALDIFT-HRMS *m*/*z* 436.1179 (M^+, $C_{24}H_{21}ClN_2O_4$ requires 436.1184).

3-(6,7-Dimethoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (12A). (1.41 mg, 43%) as a pale yellow solid: $[\alpha]_D^{23}$ +9 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.27 (1H, br s), 9.29 (1H, s), 8.25 (1H, d, *J* = 8.6 Hz), 8.06 (1H, br s), 7.89 (1H, d, *J* = 8.6 Hz), 7.55 (1H, m), 7.41 (1H, d, *J* = 8.1 Hz), 7.39 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.20 (1H, d, *J* = 2.6 Hz), 6.99 (1H, d, *J* = 8.6 Hz), 4.81 (1H, dd, *J* = 10.6, 9.0 Hz), 4.74 (1H, dd, *J* = 10.9, 2.4 Hz), 4.25–4.30 (1H, m), 4.07 (1H, dd, *J* = 11.1, 2.6 Hz), 3.97 (3H, s), 3.93 (3H, s), 3.81 (1H, dd, *J* = 11.1, 8.6 Hz); MALDIFT-HRMS *m*/*z* 437.1271 ($M+H^+$, $C_{24}H_{22}ClN_2O_4$ requires 437.1263).

3-(5,7-Dimethoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (13A). (1.81 mg, 55%) as an off-white solid: $[\alpha]_D^{23}$ +11 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.20 (1H, br s), 9.29 (1H, s), 8.25 (1H, d, *J* = 8.6 Hz), 8.04 (1H, br s), 7.88 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz), 7.39 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 7.12 (1H, d, *J* = 2.1 Hz), 6.76 (1H, d, *J* = 1.7 Hz), 6.47 (1H, d, *J* = 1.7 Hz), 4.80 (1H, dd, *J* = 10.7, 8.6 Hz), 4.74 (1H, dd, *J* = 10.9, 2.4 Hz), 4.25–4.29 (1H, m), 4.07 (1H, dd, *J* = 11.1, 3.0 Hz), 3.96 (3H, s), 3.92 (3H, s), 3.80 (1H, dd, *J* = 11.5, 9.0 Hz); MALDIFT-HRMS *m*/*z* 437.1259 ($M+H^+$, $C_{24}H_{22}ClN_2O_4$ requires 437.1263).

3-(5-Hydroxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (14A). (1.27 mg, 43%) as an off-white solid: $[\alpha]_D^{23}$ +11 (*c* 0.06, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.63 (1H, br s), 9.26 (1H, s), 8.25 (1H, d, *J* = 8.1 Hz), 8.07 (1H, br s), 7.92 (1H, s), 7.89 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz), 7.43 (1H, d, *J* = 8.6 Hz), 7.39 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.10 (1H, d, *J* = 2.6 Hz), 7.08 (1H, m), 6.91 (1H, dd, *J* = 9.0, 2.1 Hz), 4.82 (1H, dd, *J* = 11.1, 8.6 Hz), 4.77 (1H, dd, *J* = 10.7, 2.6 Hz), 4.26–4.30 (1H, m), 4.07 (1H, d, *J* = 10.7, 2.6 Hz), 3.82 (1H, dd, *J* = 11.3, 8.8 Hz); MALDIFT-HRMS *m*/*z* 393.0997 ($M+H^+$, $C_{22}H_{18}ClN_2O_3$ requires 393.1000).

3-(5-Ethoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (15A). (1.71 mg, 54%) as a white solid: $[\alpha]_D^{23}$ +19 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.70 (1H, br s), 9.22 (1H, s), 8.25 (1H, d, *J* = 8.5 Hz), 8.08 (1H, br s), 7.89 (1H, d, *J* = 8.1 Hz), 7.55 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.49 (1H, d, *J* = 9.0 Hz), 7.39 (1H, ddd, *J* = 8.3, 7.1, 1.1 Hz), 7.18 (1H, d, *J* = 2.6 Hz), 7.15 (1H, dd, *J* = 2.1, 0.9 Hz), 6.95 (1H, dd, *J* = 9.0, 2.6 Hz), 4.83 (1H, dd, *J* = 10.7, 8.6 Hz), 4.78 (1H, dd, *J* = 10.7, 2.6 Hz), 4.26–4.31 (1H, m), 4.08 (2H, q, *J* = 7.0 Hz), 4.07–4.08 (1H, m), 3.81 (1H, dd, *J* = 11.1, 8.5 Hz), 1.40 (3H, t, *J* = 7.1 Hz); MALDIFT-HRMS *m*/*z* 421.1295 ($M+H^+$, $C_{24}H_{22}ClN_2O_3$ requires 421.1313).

3-(5-Propyloxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (16A). (2.06 mg, 63%) as a beige solid: $[\alpha]_D^{23}$ +10 (*c* 0.2, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.70 (1H, br s), 9.22 (1H, s), 8.25 (1H, d, *J* = 8.1 Hz), 8.08 (1H, br s), 7.89 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 7.49 (1H, d, *J* = 9.0 Hz), 7.39 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 7.19 (1H, d, *J* = 2.6 Hz), 7.15 (1H, m), 6.97 (1H, dd, *J* = 8.8, 2.4 Hz), 4.83 (1H, dd, *J* = 10.7, 8.6 Hz), 4.78 (1H, dd, *J* = 11.1, 2.7 Hz), 4.26–4.31 (1H, m), 4.08 (1H, dd, *J* = 10.7, 3.0 Hz), 3.99 (2H, t, *J* = 6.4 Hz), 3.81 (1H, dd, *J* = 11.1, 8.6 Hz), 1.78–1.85 (2H, m), 1.06 (3H, t, *J* = 7.5 Hz); MALDIFT-HRMS *m*/*z* 434.1404 (M^+, $C_{25}H_{23}ClN_2O_3$ requires 434.1397).

3-(5-Butyloxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (17A). (1.53 mg, 46%) as a beige solid: $[\alpha]_D^{23}$ +20 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.70 (1H, br s), 9.23 (1H, s), 8.25 (1H, d, *J* = 8.5 Hz), 8.08 (1H, br s), 7.89 (1H, d, *J* = 8.1 Hz), 7.55 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz), 7.49 (1H, d, *J* = 9.0 Hz), 7.39 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.19 (1H, d, *J* = 2.1 Hz), 7.15 (1H, dd, *J* = 2.1, 0.9 Hz), 6.96 (1H, dd, *J* = 8.8, 2.4 Hz), 4.83 (1H, dd, *J* = 10.7, 8.1 Hz), 4.78 (1H, dd, *J* = 11.1, 2.6 Hz), 4.26–4.31 (1H, m), 4.07 (1H, dd, *J* = 11.1, 3.4 Hz), 4.03 (2H, t, *J* = 6.3 Hz), 3.81 (1H, dd, *J* = 11.1, 9.0 Hz), 1.76–1.81 (2H, m), 1.50–1.57 (2H, m), 0.99 (3H, t, *J* = 7.5 Hz); MALDIFT-HRMS *m*/*z* 449.1611 ($M+H^+$, $C_{26}H_{26}ClN_2O_3$ requires 449.1626).

3-(5-Benzyloxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (18A). (1.12 mg, 31%) as a white solid: $[\alpha]_D^{23}$ +36 (*c* 0.06, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.74 (1H, br s), 9.23 (1H, s), 8.25 (1H, d, *J* = 8.1 Hz), 8.08 (1H, br s), 7.89 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.51–7.54 (3H, m), 7.38–7.42 (3H, m), 7.31–7.35 (1H, m), 7.29 (1H, d, *J* = 2.6 Hz), 7.16 (1H, dd, *J* = 2.1, 0.9 Hz), 7.06 (1H, dd, *J* = 8.8, 2.2 Hz), 5.17 (2H, s), 4.82 (1H, dd, *J* = 10.7, 8.6 Hz), 4.78 (1H, dd, *J* = 10.7, 2.6 Hz), 4.26–4.31 (1H, m), 4.07 (1H, dd, *J* = 11.1, 3.4 Hz), 3.81 (1H, dd, *J* = 11.1, 8.6 Hz); MALDIFT-HRMS *m*/*z* 483.1466 ($M+H^+$, $C_{29}H_{24}ClN_2O_3$ requires 483.1470).

3-(5-Trifluoromethoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (19A). (1.83 mg, 53%) as a beige solid: $[\alpha]_D^{23}$ +9 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.13 (1H, br s), 9.29 (1H, s), 8.26 (1H, d, *J* = 8.1 Hz), 8.08 (1H, br s), 7.90 (1H, d, *J* = 8.1 Hz), 7.72 (1H, m), 7.69 (1H, d, *J* = 9.0 Hz), 7.56 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz), 7.41 (1H, ddd, *J* = 8.4, 6.9, 1.4 Hz), 7.35 (1H, d, *J* = 1.3 Hz), 7.26 (1H, m), 4.86 (1H, dd, *J* = 10.7, 9.0 Hz), 4.80 (1H, dd, *J* = 10.7, 2.1 Hz), 4.29–4.33 (1H, m), 4.08 (1H, dd, *J* = 11.1, 3.0 Hz), 3.84 (1H, dd, *J* = 11.1, 8.6 Hz); ^{19}F NMR (acetone-d_6, 376 MHz) δ −57.5; ESI (negative) *m*/*z* 459 ($M-H^-$, $C_{23}H_{15}ClF_3N_2O_3$).

3-(7-Trifluoromethoxyindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (20A). (2.26 mg, 65%) as a pale yellow solid: $[\alpha]_D^{23}$ −7 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.26 (1H, br s), 9.32 (1H, s), 8.26 (1H, d, *J* = 7.7 Hz), 8.04 (1H, br s), 7.90 (1H, m), 7.77 (1H, dd, *J* = 8.1, 0.9 Hz), 7.56 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.41 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.37 (1H, s), 7.30 (1H, m), 7.20 (1H, t, *J* = 7.9), 4.85 (1H, t, *J* = 9.8 Hz), 4.76 (1H, dd, *J* = 10.9, 1.9 Hz), 4.26–4.31 (1H, m), 4.07 (1H, dd, *J* = 10.9, 3.2 Hz), 3.83 (1H, dd, *J* = 11.1, 8.5 Hz); ^{19}F NMR (acetone-d_6, 376 MHz) δ −57.4; MALDIFT-HRMS *m*/*z* 460.0799 (M^+, $C_{23}H_{16}ClF_3N_2O_3$ requires 460.0796).

3-(5-Thiomethylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (21A). (1.23 mg, 39%) as a yellow solid: $[\alpha]_D^{23}$ +28 (*c* 0.05, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.92 (1H, br s), 9.28 (1H, s), 8.25 (1H, d, *J* = 7.7 Hz), 8.08 (1H, br s), 7.90 (1H, d, *J* = 8.1 Hz), 7.71 (1H, m), 7.56 (1H, d, *J* = 9.0 Hz), 7.56 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.40 (1H, ddd, *J* = 8.3, 6.9, 1.3 Hz), 7.30 (1H, dd, *J* = 8.6, 1.7 Hz), 7.21 (1H, d, *J* = 2.1 Hz), 4.85 (1H, dd, *J* = 10.7, 8.6 Hz), 4.79 (1H, dd, *J* = 10.9, 2.4 Hz), 4.27–4.32 (1H, m), 4.08 (1H, dd, *J* = 11.1, 3.0 Hz), 3.83 (1H, dd, *J* = 11.1, 8.6 Hz), 2.52 (3H, s); MALDIFT-HRMS *m*/*z* 422.0845 (M^+, $C_{23}H_{19}ClN_2O_2S$ requires 422.0850).

3-(7-Thiomethylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (22A). (1.74 mg, 55%) as a yellow solid: $[\alpha]_D^{23}$ −19 (*c* 0.08, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.11 (1H, br s), 9.34 (1H, s), 8.26 (1H, d, *J* = 8.1 Hz), 8.06 (1H, br s), 7.90 (1H, d, *J* = 8.1 Hz), 7.66 (1H, d, *J* = 7.7 Hz), 7.56 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.41 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.36 (1H, dd, *J* = 7.5, 1.1 Hz), 7.31 (1H, d, *J* = 2.1 Hz), 7.16 (1H, t, *J* = 7.7 Hz), 4.84 (1H, t, *J* = 9.6 Hz), 4.76 (1H, dd, *J* = 10.7, 2.1 Hz), 4.27–4.31 (1H, m), 4.07 (1H, dd, *J* = 11.1, 3.0 Hz), 3.83 (1H, dd, *J* = 11.1, 8.5 Hz), 2.58 (3H, s); MALDIFT-HRMS *m*/*z* 422.0855 (M^+, $C_{23}H_{19}ClN_2O_2S$ requires 422.0850).

3-(5-Thioethylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (23A). (2.02 mg, 62%) as a pale yellow solid: $[\alpha]_D^{23}$ +8 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.95 (1H, br s), 9.27 (1H, s), 8.25 (1H, d, *J* = 7.7 Hz), 8.09 (1H, br s), 7.90 (1H, dd, *J* = 7.3, 0.9 Hz), 7.82 (1H, m), 7.57 (1H, dt, *J* = 8.5, 0.9 Hz), 7.55 (1H, ddd, *J* = 8.4, 7.0, 1.3 Hz), 7.40 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 7.36 (1H, dd, *J* = 8.6, 1.7 Hz), 7.23 (1H, dd, *J* = 2.1, 0.9 Hz), 4.85 (1H, dd, *J* = 10.5, 8.8 Hz), 4.79 (1H, dd, *J* = 10.7, 2.1 Hz), 4.28–4.32 (1H, m), 4.08 (1H, dd, *J* = 11.1, 3.4 Hz), 3.83 (1H, dd, *J* = 11.1, 8.6 Hz), 2.93 (2H, q, *J* = 7.3 Hz), 1.25 (3H, t, *J* = 7.3 Hz); MALDIFT-HRMS *m*/*z* 437.1086 ($M+H^+$, $C_{24}H_{22}ClN_2O_2S$ requires 437.1085).

3-(Indole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (5A, CBI-indole). (1.53 mg, 57%) as a white solid: $[\alpha]_D^{23}$ +10 (*c* 0.08, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.83 (1H, br s), 9.24 (1H, s), 8.25 (1H, d, *J* = 8.3 Hz), 8.09 (1H, br s), 7.89 (1H, d, *J* = 8.3 Hz), 7.74 (1H, d, *J* = 8.3 Hz), 7.60 (1H, dd, *J* = 8.2, 0.9 Hz), 7.55 (1H, ddd, *J* = 8.3, 6.9, 1.4 Hz), 7.40 (1H, ddd, *J* = 8.3, 6.9, 1.4 Hz), 7.29 (1H, ddd, *J* = 8.3, 6.9, 1.4 Hz), 7.26 (1H, dd, *J* = 2.3, 0.9 Hz), 7.12 (1H, ddd, *J* = 7.8, 6.9, 0.9 Hz), 4.86 (1H, dd, *J* = 10.8, 8.5 Hz), 4.80 (1H, dd, *J* = 10.7, 2.5 Hz), 4.27–4.32 (1H, m), 4.08 (1H, dd, *J* = 11.0, 3.2 Hz), 3.83 (1H, dd, *J* = 11.2, 8.5 Hz); MALDIFT-HRMS *m*/*z* 376.0987 (M^+, $C_{22}H_{17}ClN_2O_2$ requires 376.0978).

3-(5-Methylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (24A). (1.55 mg, 53%) as a white solid: $[\alpha]_D^{23}$ +6 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.71 (1H, br s), 9.23 (1H, s), 8.25 (1H, d, *J* = 8.6 Hz), 8.08 (1H, br s), 7.89 (1H, d, *J* = 8.6 Hz), 7.55 (1H, ddd, *J* = 8.1, 6.8, 1.3 Hz), 7.51 (1H, s), 7.48 (1H, d, *J* = 6.5 Hz), 7.39 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.16 (1H, dd, *J* = 2.1, 0.9 Hz), 7.13 (1H, dd, *J* = 8.1, 1.7 Hz), 4.83 (1H, dd, *J* = 10.7, 8.6 Hz), 4.78 (1H, dd, *J* = 10.7, 2.6 Hz), 4.26–4.30 (1H, m), 4.07 (1H,

dd, $J=10.9$, 3.2 Hz), 3.82 (1H, dd, $J=11.3$, 8.8 Hz), 2.42 (3H, s); MALDIFT-HRMS m/z 390.1149 (M^+, $C_{23}H_{19}ClN_2O_2$ requires 390.1135).

3-(5-Ethylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (25A). (1.35 mg, 44%) as a beige solid: $[\alpha]_D^{23}$ +20 (c 0.07, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.74 (1H, br s), 9.26 (1H, s), 8.25 (1H, d, $J=8.1$ Hz), 8.08 (1H, br s), 7.89 (1H, d, $J=8.5$ Hz), 7.55 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.54 (1H, m), 7.51 (1H, d, $J=8.1$ Hz), 7.39 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 7.17–7.19 (2H, m), 4.84 (1H, dd, $J=10.7$, 9.0 Hz), 4.79 (1H, dd, $J=10.7$, 2.1 Hz), 4.27–4.31 (1H, m), 4.08 (1H, dd, $J=11.3$, 3.2 Hz), 3.82 (1H, dd, $J=11.1$, 8.6 Hz), 2.74 (2H, q, $J=7.7$ Hz), 1.27 (3H, t, $J=7.5$ Hz); MALDIFT-HRMS m/z 405.1359 ($M+H^+$, $C_{24}H_{22}ClN_2O_2$ requires 405.1364).

3-(5-Methoxymethylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (26A). (1.66 mg, 53%) as a beige solid: $[\alpha]_D^{23}$ +3 (c 0.08, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.87 (1H, br s), 9.26 (1H, s), 8.25 (1H, d, $J=8.5$ Hz), 8.08 (1H, br s), 7.89 (1H, d, $J=8.1$ Hz), 7.69 (1H, s), 7.57 (1H, d, $J=7.7$ Hz), 7.55 (1H, ddd, $J=8.3$, 6.8, 1.4 Hz), 7.40 (1H, ddd, $J=8.1$, 7.1, 1.1 Hz), 7.30 (1H, dd, $J=8.3$, 1.5 Hz), 7.25 (1H, m), 4.85 (1H, dd, $J=10.7$, 9.0 Hz), 4.80 (1H, dd, $J=10.7$, 2.1 Hz), 4.52 (2H, s), 4.27–4.32 (1H, m), 4.08 (1H, dd, $J=11.3$, 3.2 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz), 3.33 (3H, s); MALDIFT-HRMS m/z 421.1332 ($M+H^+$, $C_{24}H_{22}ClN_2O_3$ requires 421.1313).

3-(7-Methoxymethylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (27A). (1.40 mg, 44%) as a pale yellow solid: $[\alpha]_D^{23}$ −9 (c 0.07, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.21 (1H, br s), 9.30 (1H, s), 8.26 (1H, d, $J=8.1$ Hz), 8.09 (1H, br s), 7.90 (1H, d, $J=8.1$ Hz), 7.70 (1H, d, $J=8.1$ Hz), 7.56 (1H, ddd, $J=8.5$, 7.0, 1.4 Hz), 7.40 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 7.28 (1H, d, $J=2.6$ Hz), 7.24 (1H, dd, $J=6.8$, 0.8 Hz), 7.11 (1H, dd, $J=8.1$, 7.3 Hz), 4.88 (2H, m), 4.85 (1H, dd, $J=10.5$, 9.2 Hz), 4.79 (1H, dd, $J=10.9$, 2.4 Hz), 4.28–4.32 (1H, m), 4.08 (1H, dd, $J=11.1$, 3.0 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz), 3.43 (3H, s); MALDIFT-HRMS m/z 420.1255 (M^+, $C_{24}H_{21}ClN_2O_3$ requires 420.1235).

3-(5-Bromoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (28A). (1.90 mg, 56%) as a beige solid: $[\alpha]_D^{23}$ +39 (c 0.06, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.05 (1H, br s), 9.25 (1H, s), 8.26 (1H, d, $J=8.6$ Hz), 8.06 (1H, br s), 7.93 (1H, m), 7.90 (1H, d, $J=8.1$ Hz), 7.57 (1H, d, $J=8.6$ Hz), 7.54–7.58 (1H, m), 7.41 (1H, ddd, $J=8.6$, 6.8, 1.1 Hz), 7.40 (1H, dd, $J=8.8$, 1.9 Hz), 7.25 (1H, dd, $J=2.2$, 0.9 Hz), 4.84 (1H, t, $J=10.8$ Hz), 4.78 (1H, dd, $J=10.7$, 2.1 Hz), 4.28–4.32 (1H, m), 4.08 (1H, dd, $J=11.3$, 3.2 Hz), 3.83 (1H, dd, $J=11.1$, 8.5 Hz); MALDIFT-HRMS m/z 454.0085 (M^+, $C_{22}H_{16}BrClN_2O_2$ requires 454.0084).

3-(5-Chloroindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (29A). (2.28 mg, 74%) as a beige solid: $[\alpha]_D^{23}$ +22 (c 0.13, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.04 (1H, br s), 9.26 (1H, s), 8.26 (1H, d, $J=8.5$ Hz), 8.07 (1H, br s), 7.89 (1H, d, $J=8.6$ Hz), 7.76–7.77 (1H, m), 7.61 (1H, d, $J=9.0$ Hz), 7.56 (1H, ddd, $J=8.6$, 6.8, 1.3 Hz), 7.40 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.28 (1H, dd, $J=8.6$, 2.1 Hz), 7.25 (1H, dd, $J=2.1$, 0.9 Hz), 4.84 (1H, dd, $J=10.5$, 8.8 Hz), 4.78 (1H, dd, $J=10.7$, 2.1 Hz), 4.28–4.32 (1H, m), 4.08 (1H, dd, $J=11.5$, 3.0 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 410.0594 (M^+, $C_{22}H_{16}Cl_2N_2O_2$ requires 410.0583).

3-(5-Azidoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (30A). (1.88 mg, 60%) as a beige solid: $[\alpha]_D^{23}$ +30 (c 0.07, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.98 (1H, br s), 9.26 (1H, s), 8.26 (1H, d, $J=8.1$ Hz), 8.08 (1H, br s), 7.89 (1H, m), 7. 65 (1H, d, $J=9.0$ Hz), 7.56 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.47 (1H, d, $J=2.1$ Hz), 7.40 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.25–7.26 (1H, m), 7.04 (1H, dd, $J=9.0$, 2.1 Hz), 4.85 (1H, dd, $J=10.7$, 8.6 Hz), 4.79 (1H, dd, $J=10.7$, 2.1 Hz), 4.28–4.23 (1H, m), 4.08 (1H, dd, $J=11.3$, 3.2 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz); MS (ESI negative) m/z 416 ($M-H^-$).

3-(5-Cyanoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (31A). (2.12 mg, 70%) as a beige solid: $[\alpha]_D^{23}$ +38 (c 0.08, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.38 (1H, br s), 9.27 (1H, s), 8.24–8.27 (2H, m), 8.08 (1H, br s), 7.91 (1H, d, $J=8.1$ Hz), 7.77 (1H, d, $J=8.6$ Hz), 7.58 (1H, dd, $J=8.6$, 1.7 Hz), 7.57 (1H, ddd, $J=8.6$, 6.8, 1.3 Hz), 7.39–7.43 (2H, m), 4.88 (1H, m), 4.80 (1H, dd, $J=10.7$, 2.1 Hz), 4.30–4.35 (1H, m), 4.08 (1H, dd, $J=11.3$, 3.2 Hz), 3.85 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 401.0927 (M^+, $C_{23}H_{16}ClN_3O_2$ requires 401.0931).

3-(7-Cyanoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (32A). (1.04 mg, 35%) as a yellow solid: $[\alpha]_D^{23}$ −12 (c 0.05, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.36 (1H, br s), 9.28 (1H, s), 8.26 (1H, d, $J=8.1$ Hz), 8.12 (1H, dd, $J=7.4$, 1.1 Hz), 8.04 (1H, br s), 7.90 (1H, d, $J=8.6$ Hz), 7.76 (1H, dd, $J=7.5$, 1.1 Hz), 7.56 (1H, ddd, $J=8.3$, 7.1, 1.3 Hz), 7.42–7.43 (1H, m), 7.41 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 7.32 (1H, t, $J=7.7$ Hz), 4.85 (1H, t, $J=9.6$ Hz), 4.76 (1H, dd, $J=10.7$, 2.1 Hz), 4.27–4.32 (1H, m), 4.07 (1H, dd, $J=11.3$, 3.2 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 402.1017 ($M+H^+$, $C_{23}H_{17}ClN_3O_2$ requires 402.1004).

3-(5-Vinylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (33A). (1.62 mg, 54%) as a pale yellow solid: $[\alpha]_D^{23}$ +33 (c 0.08, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.91 (1H, br s), 9.27 (1H, s), 8.25 (1H, d, $J=8.5$ Hz), 8.08 (1H, br s), 7.90 (1H, d, $J=8.6$ Hz), 7.76 (1H, m), 7.57 (1H, d, $J=8.6$ Hz), 7.56 (1H, dd, $J=8.1$, 1.3 Hz), 7.52 (1H, td, $J=8.3$, 1.3 Hz), 7.40 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 7.25 (1H, dd, $J=2.1$, 0.9 Hz), 6.86 (1H, dd, $J=17.5$, 10.7 Hz), 5.75 (1H, dd, $J=17.5$, 0.9 Hz), 5.14 (1H, dd, $J=10.9$, 1.1 Hz), 4.85 (1H, dd, $J=10.9$, 8.8 Hz), 4.79 (1H, dd, $J=10.9$, 2.4), 4.28–4.32 (1H, m), 4.08 (1H, dd, $J=11.1$,

3.0 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 403.1220 ($M+H^+$, $C_{24}H_{20}ClN_2O_2$ requires 403.1208).

3-(7-Vinylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (34A). (1.24 mg, 41%) as a pale yellow solid: $[\alpha]_D^{23}$ −12 (*c* 0.07, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.56 (1H, br s), 9.31 (1H, s), 8.26 (1H, d, $J=8.1$ Hz), 8.07 (1H, br s), 7.90 (1H, d, $J=8.1$ Hz), 7.69 (1H, d, $J=7.7$ Hz), 7.56 (1H, ddd, $J=8.4$, 6.9, 1.4 Hz), 7.54 (1H, d, $J=7.3$ Hz), 7.49 (1H, dd, $J=17.5$, 11.1 Hz), 7.40 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 7.28 (1H, d, $J=2.1$ Hz), 7.16 (1H, t, $J=7.7$ Hz), 5.96 (1H, dd, $J=17.5$, 0.9 Hz), 5.41 (1H, dd, $J=11.1$, 1.3 Hz), 4.85 (1H, dd, $J=10.9$, 8.8 Hz), 4.77 (1H, dd, $J=10.7$, 2.1 Hz), 4.27–4.31 (1H, m), 4.07 (1H, dd, $J=11.3$, 3.2 Hz), 3.82 (1H, dd, $J=11.1$, 8.1 Hz); ESI (positive) m/z 425 ($M+Na^+$, $C_{24}H_{19}ClN_2NaO_2$), 403 ($M+H^+$, $C_{24}H_{20}ClN_2O_2$); ESI (negative) m/z 401 ($M-H^-$, $C_{24}H_{18}ClN_2O_2$).

3-(5-Isopropenylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (35A). (1.58 mg, 51%) as a yellow solid: $[\alpha]_D^{23}$ +60 (*c* 0.07, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.88 (1H, br s), 9.27 (1H, s), 8.25 (1H, m), 8.09 (1H, br s), 7.90 (1H, d, $J=8.1$ Hz), 7.84 (1H, m), 7.53–7.57 (3H, m), 7.40 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 7.27 (1H, d, $J=2.1$ Hz), 5.41 (1H, m), 5.05–5.06 (1H, m), 4.85 (1H, dd, $J=10.7$, 8.6 Hz), 4.80 (1H, dd, $J=10.9$, 2.4 Hz), 4.28–4.32 (1H, m), 4.08 (1H, dd, $J=11.3$, 3.2 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz), 2.23 (3H, t, $J=1.1$ Hz); ESI (positive) m/z 417 ($M+H^+$, $C_{25}H_{22}ClN_2O_2$); ESI (negative) m/z 415 ($M-H^-$, $C_{25}H_{20}ClN_2O_2$).

3-(7-Isopropenylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (36A). (1.99 mg, 64%) as a white solid: $[\alpha]_D^{23}$ −10 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 9.89 (1H br s), 9.33 (1H, br s), 8.26 (1H, d, $J=8.1$ Hz), 8.08 (1H, br s), 7.90 (1H, d, $J=8.6$ Hz), 7.68 (1H, d, $J=8.1$ Hz), 7.56 (1H, ddd, $J=8.4$, 6.9, 1.4 Hz), 7.41 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 7.30 (1H, d, $J=2.1$ Hz), 7.29 (1H, dd, $J=7.3$, 1.3 Hz), 7.16 (1H, t, $J=7.5$ Hz), 5.44–5.45 (2H, m), 4.85 (1H, dd, $J=10.9$, 8.8 Hz), 4.78 (1H, dd, $J=10.7$, 2.1 Hz), 4.28–4.33 (1H, m), 4.08 (1H, dd, $J=11.1$, 3.0 Hz), 3.83 (1H, dd, $J=11.1$, 8.5 Hz), 2.28 (3H, t, $J=1.1$ Hz); ESI (positive) m/z 439 ($M+Na^+$, $C_{25}H_{21}ClN_2NaO_2$), 417 ($M+H^+$, $C_{25}H_{22}ClN_2O_2$); ESI (negative) m/z 415 ($M-H^-$, $C_{25}H_{20}ClN_2O_2$).

3-(5-Ethynylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (37A). (1.00 mg, 33%) as a beige solid: $[\alpha]_D^{23}$ +37 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.05 (1H, br s), 9.26 (1H, s), 8.26 (1H, d, $J=8.6$ Hz), 8.08 (1H, br s), 7.93 (1H, s), 7.90 (1H, d, $J=8.1$ Hz), 7.60 (1H, m), 7.56 (1H, ddd, $J=8.6$, 6.8, 1.3 Hz), 7.38–7.42 (1H, m), 7.39 (1H, dd, $J=8.3$, 1.5 Hz), 7.28–7.29 (1H, m), 4.85 (1H, t, $J=9.6$ Hz), 4.79 (1H, dd, $J=10.7$, 2.1 Hz), 4.28–4.33 (1H, m), 4.08 (1H, dd, $J=11.1$, 3.0 Hz), 3.84 (1H, dd, $J=11.1$, 8.5 Hz), 3.50 (1H, s); MALDIFT-HRMS m/z 401.1051 ($M+H^+$, $C_{24}H_{18}ClN_2O_2$ requires 401.1051).

3-[5-(1-Propynyl)indole-2-carbonyl]-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (38A). (1.02 mg, 33%) as a beige solid: $[\alpha]_D^{23}$ +39 (*c* 0.07, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.96 (1H, br s), 9.24 (1H, s), 8.25 (1H, d, $J=8.4$ Hz), 8.07 (1H, br s), 7.89 (1H, d, $J=8.4$ Hz), 7.79 (1H, s), 7.54–7.57 (2H, m), 7.40 (1H, ddd, $J=8.4$, 6.4, 1.1 Hz), 7.29 (1H, dd, $J=8.6$, 1.7 Hz), 7.24 (1H, m), 4.85 (1H, dd, $J=9.6$, 8.8 Hz), 4.78 (1H, dd, $J=9.6$, 2.2 Hz), 4.28–4.32 (1H, m), 4.08 (1H, dd, $J=11.4$, 3.3 Hz), 3.83 (1H, dd, $J=11.4$, 8.4 Hz), 2.03 (3H, s); MALDIFT-HRMS m/z 415.1203 ($M+H^+$, $C_{25}H_{20}ClN_2O_2$ requires 415.1208).

3-(4-Phenylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (39A). (1.42 mg, 42%) as an off-white solid: $[\alpha]_D^{23}$ +93 (*c* 0.07, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.05 (1H, br s), 9.28 (1H, s), 8.25 (1H, d, $J=8.1$ Hz), 8.07 (1H, br s), 7.88 (1H, d, $J=8.6$ Hz), 7.75–7.77 (2H, m), 7.62 (1H, m), 7.52–7.56 (3H, m), 7.38–7.56 (3H, m), 7.35 (1H, m), 7.22 (1H, dd, $J=7.3$, 0.9 Hz), 4.82 (1H, t, $J=9.6$ Hz), 4.75 (1H, dd, $J=10.9$, 2.4 Hz), 4.24–4.28 (1H, m), 4.05 (1H, dd, $J=11.1$, 3.4 Hz), 3.82 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 452.1288 (M^+, $C_{28}H_{21}ClN_2O_2$ requires 452.1286).

3-(5-Aminoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (40A). Prepared by treatment of **43A** (1.0 mg, 1.9 μmol) with 4 N HCl/EtOAc (500 μL) for 1 h at 23 °C, followed by solvent removal to afford **40A** (750 μg, 87%) as a pale yellow solid: ^1H NMR (acetone-d_6, 500 MHz) δ 10.48 (1H, br s), 9.70–9.90 (3H, br s), 8.13 (1H, d, $J=8.1$ Hz), 7.98 (1H, br s), 7.87 (1H, d, $J=8.6$ Hz), 7.68 (1H, app s), 7.59 (1H, d, $J=9.0$ Hz), 7.54 (1H, tm, $J=7.4$ Hz), 7.38 (1H, tm, $J=7.8$ Hz), 7.30 (1H, app s), 7.21 (1H, dd, $J=8.8$, 1.5 Hz), 4.81 (1H, dd, $J=10.5$, 9.2 Hz), 4.55 (1H, dd, $J=10.9$, 1.9 Hz), 4.23–4.27 (1H, m), 4.02 (1H, dd, $J=11.1$, 3.0 Hz), 3.88 (1H, dd, $J=11.1$, 7.3 Hz); ESI (positive) m/z 392 ($M+H^+$, $C_{22}H_{19}ClN_3O_2$); ESI (negative) m/z 390 ($M-H^-$, $C_{22}H_{17}ClN_3O_2$).

3-(5-Dimethylaminoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (41A). (2.40 mg, 23%) as a yellow solid: $[\alpha]_D^{23}$ +15 (*c* 0.026, CH_2Cl_2); ^1H NMR ($CDCl_3$, 600 MHz) δ 9.26 (1H, br s), 8.28 (1H, d, $J=8.3$ Hz), 8.17 (1H, br s), 7.74 (1H, d, $J=8.3$ Hz), 7.58 (1H, t, $J=7.1$ Hz), 7.45 (2H, t, $J=7.1$ Hz), 7.09 (1H, br s), 4.84 (1H, d, $J=10.0$ Hz), 4.71 (1H, t, $J=9.0$ Hz), 4.17 (1H, m), 4.00 (1H, dd, $J=11.4$, 0.9 Hz), 3.55 (5H, m), 3.48 (1H, t, $J=11.0$ Hz), 3.02 (4H, m), 2.97 (1H, s), 2.90 (1H, s); IR (film) ν_{max} 3323, 2964, 2944, 1626, 1585, 1513, 1405, 1103 cm^{-1}; MALDIFT-HRMS m/z 420.1471 ($M+H^+$, $C_{24}H_{23}ClN_3O_2$ requires 420.1473).

3-(5-Diethylaminoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (42A). (2.80 mg, 20%) as a yellow solid: $[\alpha]_D^{23}$ +33 (*c* 0.015, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.30 (1H, br s), 8.94 (1H, br s), 8.36 (1H, s), 8.32 (1H, d, $J=8.4$ Hz), 7.72 (1H, d, $J=8.4$ Hz), 7.56 (1H, t, $J=7.0$ Hz), 7.44 (2H, m), 7.05 (2H, m), 4.84 (1H, d, $J=10.7$ Hz), 4.69

(1H, app t, $J=10.7$ Hz), 4.14 (1H, m), 3.99 (1H, dd, $J=11.4$, 2.9 Hz), 3.46 (1H, t, $J=11.0$ Hz), 3.37 (4H, m), 1.18 (6H, t, $J=6.6$ Hz); IR (film) ν_{max} 3247, 2967, 2917, 1610, 1581, 1417, 1391, 1254, 1148 cm^{-1}; MALDIFT-HRMS m/z 420.1471 ($M+H^+$, $C_{24}H_{23}ClN_3O_2$ requires 420.1473).

3-(5-*t*-Butyloxycarbonylaminoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (43A). (2.02 mg, 55%) as a pale yellow solid: $[\alpha]_D^{23}$ +40 (c 0.02, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.76 (1H, br s), 9.26 (1H, s), 8.29 (1H, br s), 8.25 (1H, d, $J=8.5$ Hz), 8.08 (1H, br s), 8.00 (1H, br s), 7.89 (1H, d, $J=8.6$ Hz), 7.55 (1H, ddd, $J=8.6$, 6.9, 1.4 Hz), 7.50 (1H, d, $J=9.0$ Hz), 7.42 (1H, dd, $J=8.6$, 1.7 Hz), 7.39 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.20 (1H, dd, $J=2.1$, 0.9 Hz), 7.21 (1H, dd, $J=8.8$, 1.5 Hz), 4.85 (1H, dd, $J=10.7$, 8.6 Hz), 4.80 (1H, dd, $J=10.7$, 2.6 Hz), 4.27–4.31 (1H, m), 4.07 (1H, dd, $J=11.1$, 3.4 Hz), 3.83 (1H, dd, $J=11.1$, 8.5 Hz), 1.50 (9H, s); MALDIFT-HRMS m/z 514.1501 ($M+Na^+$, $C_{27}H_{26}ClN_3NaO_4$ requires 514.1504).

3-(5-Acetylaminoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (44A). (0.89 mg, 27%) as a white solid: $[\alpha]_D^{23}$ +21 (c 0.033, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.75 (1H, br s), 9.23 (1H, s), 9.06 (1H, br s), 8.25 (1H, d, $J=8.6$ Hz), 8.19 (1H, s), 8.07 (1H, br s), 7.89 (1H, d, $J=8.1$ Hz), 7.55 (1H, ddd, $J=8.4$, 6.9, 1.4 Hz), 7.50 (1H, d, $J=8.5$ Hz), 7.38–7.42 (2H, m), 7.21 (1H, s), 4.85 (1H, dd, $J=10.9$, 8.8 Hz), 4.79 (1H, dd, $J=10.7$, 2.1 Hz), 4.27–4.32 (1H, m), 4.07 (1H, dd, $J=11.1$, 3.0 Hz), 3.83 (1H, dd, $J=11.3$, 8.3 Hz), 2.09 (3H, s); MALDIFT-HRMS m/z 434.1269 ($M+H^+$, $C_{24}H_{21}ClN_3O_3$ requires 434.1266).

3-(5-Propionylaminoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (45A). (1.00 mg, 30%) as a pale yellow solid: $[\alpha]_D^{23}$ +24 (c 0.05, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.76 (1H, br s), 9.24 (1H, s), 8.98 (1H, br s), 8.25 (1H, d, $J=8.6$ Hz), 8.21 (1H, m), 8.07 (1H, br s), 7.89 (1H, d, $J=8.6$ Hz), 7.55 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.50 (1H, d, $J=9.0$ Hz), 7.43 (1H, dd, $J=8.8$, 1.9 Hz), 7.39 (1H, ddd, $J=8.3$, 7.1, 1.1 Hz), 7.20–7.21 (1H, m), 4.85 (1H, dd, $J=10.7$, 8.6 Hz), 4.79 (1H, dd, $J=10.9$, 2.4 Hz), 4.27–4.32 (1H, m), 4.07 (1H, dd, $J=11.3$, 3.2 Hz), 3.83 (1H, dd, $J=11.3$, 8.3 Hz), 3.39 (2H, q, $J=7.6$ Hz), 1.17 (3H, t, $J=7.7$ Hz); MALDIFT-HRMS m/z 447.1350 (M^+, $C_{25}H_{22}ClN_3O_3$ requires 447.1350).

3-(5-Butyrylaminoindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (46A). (1.51 mg, 44%) as a white solid: $[\alpha]_D^{23}$ +43 (c 0.08, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.76 (1H, br s), 9.24 (1H, s), 9.00 (1H, br sCO), 8.25 (1H, d, $J=9.0$ Hz), 8.22 (1H, s), 8.07 (1H, br s), 7.89 (1H, d, $J=8.1$ Hz), 7.55 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.50 (1H, d, $J=9.0$ Hz), 7.43 (1H, dd, $J=8.8$, 1.9 Hz), 7.39 (1H, ddd, $J=8.3$, 6.8, 1.3 Hz), 7.20–7.21 (1H, m), 4.84 (1H, dd, $J=10.9$, 8.8 Hz), 4.79 (1H, dd, $J=10.9$, 2.4 Hz), 4.27–4.31 (1H, m), 4.07 (1H, dd, $J=11.3$, 3.2 Hz), 3.83 (1H, dd, $J=11.1$, 8.5 Hz), 2.35 (2H, t, $J=7.3$ Hz), 1.72 (2H, sextet, $J=7.5$ Hz), 0.98 (3H, t, $J=7.5$ Hz); MALDIFT-HRMS m/z 462.1565 (M^+, $C_{26}H_{24}ClN_3O_3$ requires 462.1579).

3-[5-(*N*-Acetyl-*N*-methyl)aminoindole-2-carbonyl]-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (47A). (1.60 mg, 48%) as a pale yellow solid: $[\alpha]_D^{23}$ +19 (c 0.2, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.04 (1H, br s), 9.26 (1H, s), 8.26 (1H, d, $J=8.6$ Hz), 8.11 (1H, br s), 7.90 (1H, d, $J=8.1$ Hz), 7.66–7.68 (2H, m), 7.56 (1H, ddd, $J=8.4$, 6.9, 1.4 Hz), 7.41 (1H, ddd, $J=8.1$, 6.9, 1.2 Hz), 7.31 (1H, s), 7.22 (1H, dd, $J=8.6$, 1.7 Hz), 4.87 (1H, dd, $J=10.7$, 8.6), 4.81 (1H, dd, $J=10.9$, 2.4 Hz), 4.29–4.33 (1H, m), 4.09 (1H, dd, $J=11.1$, 3.0 Hz), 3.84 (1H, dd, $J=11.3$, 8.3 Hz), 3.24 (3H, s), 1.78 (3H, s); MALDIFT-HRMS m/z 448.1420 ($M+H^+$, $C_{25}H_{23}ClN_3O_3$ requires 448.1420).

3-[5-(*N*-Acetyl-*N*-ethyl)aminoindole-2-carbonyl]-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (48A). (0.60 mg, 39%) as a pale yellow solid: $[\alpha]_D^{23}$ +35 (c 0.08, acetone); ^1H NMR (acetone-d_6, 600 MHz) δ 9.27 (1H, s), 8.26 (1H, d, $J=8.3$ Hz), 8.10 (1H, br s), 8.06 (1H, s), 7.90 (1H, d, $J=8.3$ Hz), 7.68–7.74 (2H, m), 7.56 (1H, t, $J=7.9$ Hz), 7.41 (1H, t, $J=8.3$ Hz), 7.39 (1H, s), 5.17 (1H, m), 4.88 (1H, t, $J=10.1$ Hz), 4.82 (1H, d, $J=10.5$ Hz), 4.32 (1H, m), 4.18 (1H, q, $J=7.0$ Hz), 4.09 (1H, dd, $J=7.9$, 3.5 Hz), 3.84 (1H, dd, $J=8.8$, 2.6 Hz), 2.52 (3H, s), 1.15 (3H, t, $J=7.0$ Hz); IR (film) ν_{max} 3276, 2933, 1664, 1610, 1583 cm^{-1}; MALDIFT-HRMS m/z 462.1597 ($M+H^+$, $C_{26}H_{24}ClN_3O_3$ requires 462.1579).

3-(5-Nitroindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (49A). (1.55 mg, 49%) as a yellow solid: $[\alpha]_D^{23}$ +45 (c 0.07, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.48 (1H, br s), 9.26 (1H, s), 8.78 (1H, d, $J=2.1$ Hz), 8.27 (1H, d, $J=8.6$ Hz), 8.19 (1H, dd, $J=9.2$, 2.4 Hz), 8.08 (1H, br s), 7.91 (1H, m), 7.77 (1H, d, $J=9.4$ Hz), 7.55–7.58 (2H, m), 7.42 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 4.88 (1H, dd, $J=10.5$, 8.8 Hz), 4.82 (1H, dd, $J=10.7$, 2.1 Hz), 4.31–4.36 (1H, m), 4.09 (1H, dd, $J=11.8$, 3.2 Hz), 3.85 (1H, dd, $J=11.3$, 8.3 Hz); MALDIFT-HRMS m/z 421.0824 (M^+, $C_{22}H_{16}ClN_3O_4$ requires 421.0824).

3-(6-Nitroindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (50A). (2.60 mg, 82%) as a yellow solid: $[\alpha]_D^{23}$ −26 (c 0.125, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.53 (1H, s), 9.30 (1H, s), 8.57 (1H, dd, $J=2.1$, 0.9 Hz), 8.27 (1H, d, $J=8.6$ Hz), 8.08 (1H, br s), 8.02 (1H, dd, $J=9.0$, 2.1 Hz), 7.96 (1H, d, $J=8.6$ Hz), 7.91 (1H, m), 7.57 (1H, ddd, $J=8.4$, 6.9, 1.2 Hz), 7.44–7.45 (1H, m), 7.42 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 4.89 (1H, t, $J=9.6$ Hz), 4.81 (1H, dd, $J=10.7$, 2.1 Hz), 4.30–4.35 (1H, m), 4.08 (1H, dd, $J=11.5$, 2.8 Hz), 3.85 (1H, dd, $J=11.1$, 8.5 Hz); ESI (positive) m/z 422 ($M+H^+$, $C_{22}H_{17}ClN_3O_4$); ESI (negative) m/z 420 ($M-H^-$, $C_{22}H_{15}ClN_3O_4$).

3-(7-Nitroindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (51A). (0.92 mg, 29%) as a yellow solid: $[\alpha]_D^{23}$ +9 (c 0.003, THF); ^1H

NMR (acetone-d_6, 500 MHz) δ 10.82 (1H, br s), 9.38 (1H, s), 8.27–8.34 (3H, m), 8.12 (1H, br s), 7.91 (1H, d, $J=8.3$ Hz), 7.57 (1H, ddd, $J=8.3$, 7.1, 1.2 Hz), 7.55 (1H, m), 7.43 (1H, ddd, $J=8.2$, 7.0, 1.1 Hz), 7.42 (1H, t, $J=8.1$ Hz), 4.89 (1H, t, $J=10.0$ Hz), 4.79 (1H, dd, $J=10.5$, 2.2 Hz), 4.31–4.36 (1H, m), 4.09 (1H, dd, $J=10.5$, 3.5 Hz), 3.86 (1H, dd, $J=11.2$, 8.3 Hz); ESI (positive) m/z 422 ($M+H^+$, $C_{22}H_{17}ClN_3O_4$); ESI (negative) m/z 420 ($M-H^-$, $C_{22}H_{15}ClN_3O_4$).

3-(5-Formylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (52A). (1.18 mg, 39%) as a beige solid: $[\alpha]_D^{23}$ +9 (*c* 0.03, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.34 (1H, br s), 10.07 (1H, s), 9.30 (1H, s), 8.39 (1H, m), 8.26 (1H, d, $J=7.7$ Hz), 8.09 (1H, br s), 7.91 (1H, d, $J=8.1$ Hz), 7.86 (1H, dd, $J=8.6$, 1.7 Hz), 7.75 (1H, d, $J=8.6$ Hz), 7.57 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.50 (1H, m), 7.41 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 4.90 (1H, dd, $J=10.7$, 9.0 Hz), 4.82 (1H, dd, $J=10.7$, 2.1 Hz), 4.30–4.35 (1H, m), 4.09 (1H, dd, $J=11.5$, 3.4 Hz), 3.85 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 405.1012 ($M+H^+$, $C_{23}H_{18}ClN_2O_3$ requires 405.1000).

3-(7-Formylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (53A). (1.46 mg, 20%) as a yellow solid: $[\alpha]_D^{23}$ −33 (*c* 0.54, 2:1 CH_2CH_2/$CDCl_3$); ^1H NMR ($CDCl_3$, 500 MHz) 11.46 (1H, br s), 10.21 (1H, s), 8.33 (1H, d, $J=8.4$ Hz), 8.15 (1H, br s), 8.06 (1H, d, $J=7.7$ Hz), 7.84 (1H, dd, $J=7.4$, 1.1 Hz), 7.74 (1H, d, $J=8.1$ Hz), 7.58 (1H, t, $J=7.1$ Hz), 7.47 (1H, t, $J=8.5$ Hz), 7.38 (1H, t, $J=7.7$ Hz), 7.21 (1H, d, $J=2.6$ Hz), 4.84 (1H, dd, $J=10.7$, 1.9 Hz), 4.73 (1H, t, $J=9.2$ Hz), 4.17 (1H, m), 4.01 (1H, dd, $J=11.4$, 2.6 Hz), 3.49 (1H, t, $J=11.0$ Hz); MALDIFT-HRMS m/z 405.1013 ($M+H^+$, $C_{23}H_{18}ClN_2O_3$ requires 405.1000).

3-(5-Acetylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (54A). (2.06 mg, 66%) as a pale yellow solid: $[\alpha]_D^{23}$ +33 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.17 (1H, br s), 9.26 (1H, s), 8.51 (1H, s), 8.26 (1H, d, $J=8.6$ Hz), 8.09 (1H, br s), 7.98 (1H, dd, $J=8.6$, 1.5 Hz), 7.90 (1H, d, $J=8.1$ Hz), 7.66 (1H, d, $J=8.6$ Hz), 7.56 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.43 (1H, m), 7.41 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 4.88 (1H, t, $J=9.6$ Hz), 4.81 (1H, dd, $J=10.7$, 2.1 Hz), 4.29–4.34 (1H, m), 4.09 (1H, dd, $J=11.1$, 3.0 Hz), 3.84 (1H, dd, $J=11.1$, 8.6 Hz); 2.64 (3H, s); MALDIFT-HRMS m/z 418.1089 (M^+, $C_{24}H_{19}ClN_2O_3$ requires 418.1084).

3-(7-Acetylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (55A). (1.79 mg, 57%) as a pale yellow solid: $[\alpha]_D^{23}$ −1 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.08 (1H, br s), 9.33 (1H, s), 8.27 (1H, d, $J=8.1$ Hz), 8.14 (1H, br s), 8.08–8.10 (2H, m), 7.90 (1H, d, $J=8.6$ Hz), 7.56 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.41 (1H, ddd, $J=8.3$, 6.8, 1.3 Hz), 7.39 (1H, d, $J=2.6$ Hz), 7.31 (1H, t, $J=7.7$ Hz), 4.88 (1H, dd, $J=10.5$, 8.8 Hz), 4.81 (1H, dd, $J=10.7$, 2.6 Hz), 4.20–4.34 (1H, m), 4.09 (1H, dd, $J=11.3$, 2.8 Hz), 3.85 (1H, dd, $J=11.1$, 8.5 Hz); 2.74 (3H, s); MALDIFT-HRMS m/z 419.1157 ($M+H^+$, $C_{24}H_{20}ClN_2O_3$ requires 419.1157).

3-(5-Propionylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (56A). (2.05 mg, 63%) as a pale yellow solid: $[\alpha]_D^{23}$ +33 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.18 (1H, br s), 9.27 (1H, s), 8.50 (1H, m), 8.26 (1H, d, $J=8.6$ Hz), 8.09 (1H, br s), 7.96 (1H, dd, $J=8.6$, 1.7 Hz), 7.90 (1H, d, $J=8.6$ Hz), 7.66 (1H, m), 7.56 (1H, ddd, $J=8.4$, 7.1, 1.1 Hz), 7.39–7.43 (2H, m), 4.88 (1H, dd, $J=10.7$, 9.0 Hz), 4.81 (1H, dd, $J=10.7$, 2.1 Hz), 4.29–4.34 (1H, m), 4.09 (1H, dd, $J=11.1$, 3.0 Hz), 3.84 (1H, dd, $J=11.1$, 8.6 Hz), 3.13 (2H, q, $J=7.3$ Hz), 1.20 (3H, t, $J=7.3$ Hz); MALDIFT-HRMS m/z 432.1232 (M^+, $C_{25}H_{21}ClN_2O_3$ requires 432.1235).

3-(5-Butyrylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (57A). (2.15 mg, 64%) as a pale yellow solid: $[\alpha]_D^{23}$ +35 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.17 (1H, br s), 9.27 (1H, s), 8.52 (1H, m), 8.26 (1H, d, $J=8.1$ Hz), 8.09 (1H, br s), 7.97 (1H, dd, $J=8.8$, 1.5 Hz), 7.90 (1H, m), 7.66 (1H, d, $J=9.0$ Hz), 7.56 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.42–7.43 (1H, m), 7.41 (1H, ddd, $J=8.6$, 6.8, 1.3 Hz), 4.88 (1H, dd, $J=10.7$, 9.0 Hz), 4.81 (1H, dd, $J=10.7$, 2.6 Hz), 4.29–4.34 (1H, m), 4.09 (1H, dd, $J=11.1$, 3.0 Hz), 3.87 (1H, dd, $J=11.1$, 8.6 Hz); 3.07 (2H, t, $J=7.3$ Hz), 1.77 (2H, sextet, $J=7.3$ Hz), 1.02 (3H, t, $J=7.5$ Hz); MALDIFT-HRMS m/z 446.1388 (M^+, $C_{26}H_{23}ClN_2O_3$ requires 446.1392).

3-(5-Methoxycarbonylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (58A). (1.64 mg, 50%) as a beige solid: $[\alpha]_D^{23}$ +25 (*c* 0.08, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.21 (1H, br s), 9.29 (1H, s), 8.51 (1H, m), 8.26 (1H, d, $J=8.6$ Hz), 8.08 (1H, br s), 7.96 (1H, dd, $J=8.8$, 1.5 Hz), 7.91 (1H, d, $J=8.1$ Hz), 7.67 (1H, d, $J=9.0$ Hz), 7.56 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.43–7.44 (1H, m), 7.41 (1H, ddd, $J=8.4$, 7.0, 1.4 Hz), 4.88 (1H, t, $J=9.3$ Hz), 4.81 (1H, dd, $J=10.7$, 2.1 Hz), 4.31–4.35 (1H, m), 4.08 (1H, dd, $J=11.1$, 3.0 Hz), 3.90 (3H, s), 3.85 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 435.1096 ($M+H^+$, $C_{24}H_{20}ClN_2O_4$ requires 435.1106).

3-(7-Methoxycarbonylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (59A). (1.72 mg, 53%) as a yellow solid: $[\alpha]_D^{23}$ −6 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.61 (1H, br s), 9.35 (1H, s), 8.27 (1H, d, $J=8.5$ Hz), 8.13 (1H, br s), 8.08 (1H, d, $J=7.7$ Hz), 8.02 (1H, dd, $J=7.5$, 1.1 Hz), 7.91 (1H, d, $J=8.6$ Hz), 7.56 (1H, ddd, $J=8.3$, 6.8, 1.3 Hz), 7.42 (1H, ddd, $J=8.3$, 6.8, 1.3 Hz), 7.41 (1H, d, $J=2.1$ Hz), 7.29 (1H, t, $J=7.7$ Hz), 4.88 (1H, dd, $J=10.5$, 8.8 Hz), 4.81 (1H, dd, $J=10.7$, 2.1 Hz), 4.30–4.35 (1H, m), 4.09 (1H, dd, $J=11.1$, 3.0 Hz), 4.03 (3H, s), 3.86 (1H, dd, $J=11.1$, 8.5 Hz); MALDIFT-HRMS m/z 435.1118 ($M+H^+$, $C_{24}H_{20}ClN_2O_4$ requires 435.1106).

3-(5-Ethoxycarbonylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (60A). (1.64 mg, 50%) as a pale yellow solid: $[\alpha]_D^{23}$ +31 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.20 (1H, br s), 9.29 (1H, s), 8.51 (1H, m), 8.26 (1H, d, $J=8.1$ Hz), 8.09 (1H, br s), 7.97 (1H, dd, $J=8.6$, 1.7 Hz), 7.91 (1H,

d, $J=8.6$ Hz), 7.67 (1H, d, $J=8.6$ Hz), 7.56 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.44 (1H, s), 7.41 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 4.88 (1H, t, $J=9.6$ Hz), 4.81 (1H, dd, $J=10.7$, 2.1 Hz), 4.37 (2H, q, $J=7.1$ Hz), 4.30–4.34 (1H, m), 4.08 (1H, dd, $J=11.1$, 3.0 Hz), 3.84 (1H, dd, $J=11.1$, 8.6 Hz), 1.39 (3H, t, $J=7.1$ Hz); MALDIFT-HRMS m/z 449.1246 ($M+H^+$, $C_{25}H_{22}ClN_2O_4$ requires 449.1263).

3-(5-Carbamoylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (61A). (1.49 mg, 47%) as a beige solid: $[\alpha]_D^{23}$ +18 (c 0.08, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.10 (1H, br s), 9.30 (1H, s), 8.39 (1H, m), 8.26 (1H, d, $J=8.6$ Hz), 8.08 (1H, br s), 7.96 (1H, br s), 7.91 (1H, dd, $J=8.5$, 1.7 Hz), 7.90 (1H, d, $J=7.7$ Hz), 7.63 (1H, dt, $J=8.6$, 0.9 Hz), 7.56 (1H, ddd, $J=8.4$, 6.9, 1.4 Hz), 7.40 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 7.36 (1H, d, $J=1.7$ Hz), 6.47 (1H, br s), 4.87 (1H, t, $J=9.6$ Hz), 4.80 (1H, dd, $J=10.7$, 2.1 Hz), 4.28–4.33 (1H, m), 4.08 (1H, dd, $J=11.1$, 3.4 Hz), 3.84 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 419.1029 (M^+, $C_{23}H_{18}ClN_3O_3$ requires 419.1031).

3-(5-Methylcarbamoylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (62A). (0.97 mg, 30%) as a pale yellow solid: $[\alpha]_D^{23}$ +34 (c 0.05, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.07 (1H, br s), 9.29 (1H, s), 8.32 (1H, m), 8.25 (1H, d, $J=8.1$ Hz), 8.08 (1H, br s), 7.90 (1H, d, $J=8.6$ Hz), 7.85 (1H, dd, $J=8.6$, 1.7 Hz), 7.63 (1H, br s), 7.62 (1H, d, $J=8.6$ Hz), 7.56 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.41 (1H, ddd, $J=8.6$, 7.0, 1.1 Hz), 7.35 (1H, s), 4.86 (1H, t, $J=9.6$ Hz), 4.80 (1H, dd, $J=11.1$, 2.1 Hz), 4.28–4.32 (1H, m), 4.08 (1H, dd, $J=11.3$, 3.2 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz), 2.93 (3H, d, $J=4.7$ Hz); MALDIFT-HRMS m/z 434.1276 ($M+H^+$, $C_{24}H_{21}ClN_3O_3$ requires 434.1266).

3-(5-Dimethylcarbamoylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (63A). (1.5 mg, 45%) as a pale yellow solid: $[\alpha]_D^{23}$ +25 (c 0.08, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.05 (1H, br s), 9.30 (1H, s), 8.25 (1H, d, $J=8.1$ Hz), 8.09 (1H, br s), 7.90 (1H, m), 7.85–7.86 (1H, m), 7.62 (1H, d, $J=8.1$ Hz), 7.56 (1H, ddd, $J=8.4$, 6.9, 1.4 Hz), 7.40 (1H, ddd, $J=8.6$, 6.8, 1.3 Hz), 7.39 (1H, dd, $J=8.6$, 1.7 Hz), 7.33 (1H, m), 4.86 (1H, t, $J=9.6$ Hz), 4.80 (1H, dd, $J=10.7$, 2.1 Hz), 4.28–4.32 (1H, m), 4.08 (1H, dd, $J=11.1$, 3.2 Hz), 3.84 (1H, dd, $J=11.1$, 8.6 Hz), 2.83 (3H, s), 2.80 (3H, s); MALDIFT-HRMS m/z 448.1422 ($M+H^+$, $C_{25}H_{23}ClN_3O_3$ requires 448.1422).

3-(5-Methylsulfonylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (64A). (1.29 mg, 38%) as a yellow solid: $[\alpha]_D^{23}$ +26 (c 0.05, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.37 (1H, br s), 9.28 (1H, s), 8.40–8.41 (1H, m), 8.26 (1H, d, $J=7.7$ Hz), 8.08 (1H, br s), 7.91 (1H, d, $J=8.1$ Hz), 7.83 (1H, dd, $J=8.8$, 1.5 Hz), 7.80 (1H, m), 7.57 (1H, ddd, $J=8.1$, 6.8, 1.3 Hz), 7.51 (1H, d, $J=1.3$ Hz), 7.42 (1H, ddd, $J=8.3$, 6.8, 1.3 Hz), 4.89 (1H, t, $J=9.6$ Hz), 4.81 (1H, dd, $J=11.1$, 2.1 Hz), 4.30–4.35 (1H, m), 4.08 (1H, dd, $J=11.1$, 3.0 Hz), 3.84 (1H, dd, $J=11.5$, 8.6 Hz), 3.13 (3H, s); ESI (positive) m/z 455 ($M+H^+$, $C_{23}H_{20}ClN_2O_4S$); ESI (negative) m/z 453 ($M-H^-$, $C_{23}H_{18}ClN_2O_4S$).

3-(5-Ethylsulfonylindole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (65A). (2.51 mg, 71%) as a pale yellow solid: $[\alpha]_D^{23}$ +30 (c 0.13, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.40 (1H, br s), 9.31 (1H, s), 8.37 (1H, s), 8.26 (1H, d, $J=8.1$ Hz), 8.09 (1H, br s), 7.91 (1H, d, $J=8.1$ Hz), 7.81 (1H, m), 7.78 (1H, dd, $J=8.6$, 1.7 Hz), 7.57 (1H, ddd, $J=8.3$, 7.1, 1.3 Hz), 7.51 (1H, s), 7.41 (1H, ddd, $J=8.2$, 6.9, 1.2 Hz), 4.89 (1H, t, $J=9.6$ Hz), 4.81 (1H, dd, $J=10.7$, 1.7 Hz), 4.30–4.35 (1H, m), 4.08 (1H, dd, $J=11.3$, 3.2 Hz), 3.85 (1H, dd, $J=11.1$, 8.5 Hz), 3.21 (2H, q, $J=7.3$ Hz), 1.21 (3H, t, $J=7.5$ Hz); MALDIFT-HRMS m/z 469.0966 ($M+H^+$, $C_{24}H_{22}ClN_2O_4S$ requires 469.0983).

3-(1,2-Dihydro-3*H*-pyrrolo[3,2-*e*]indole-7-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (66A). Prepared from **67A** (6.3 mg, 12.1 μmol) by treatment with 4 N HCl/EtOAc (0.25 mL), followed by exposure to Et_3N (13.0 μL) in THF (1 mL) for 1 h which afforded **66A** (5.0 mg, 100%) as a brown solid: $[\alpha]_D^{23}$ +34 (c 0.01, CH_2Cl_2); ^1H NMR (CD_3CN, 600 MHz) δ 9.84 (1H, br s), 8.16 (1H, d, $J=8.3$ Hz), 8.05 (1H, m), 7.83 (1H, s), 7.81 (1H, d, $J=8.3$ Hz), 7.70 (1H, m), 7.54 (1H, t, $J=8.3$ Hz), 7.39 (1H, t, $J=7.9$ Hz), 7.22 (1H, d, $J=9.2$ Hz), 6.95 (1H, s), 6.79 (1H, d, $J=8.3$ Hz), 4.71 (2H, m), 4.23 (2H, m), 3.99 (1H, dd, $J=11.4$, 3.0 Hz), 3.76 (1H, m), 3.58 (1H, m), 3.18 (1H, m); IR (film) ν_{max} 3292, 2964, 2923, 2851, 1605, 1585, 1400 1256, 1092, 1021, 800 cm^{-1}; MALDIFT-HRMS m/z 417.1244 (M^+, $C_{24}H_{20}ClN_3O_2$ requires 417.1244).

3-(*N*-*t*-Butyloxycarbonyl-1,2-dihydro-3*H*-pyrrolo[3,2-*e*]-indole-7-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (67A). (6.3 mg, 67%) as a yellow solid: $[\alpha]_D^{23}$ −23 (c 0.04, CH_2Cl_2); ^1H NMR ($CDCl_3$, 500 MHz) δ 9.71 (1H, br s), 9.41 (1H, br s), 8.33 (1H, s), 8.27 (1H, d, $J=7.0$ Hz), 8.10 (1H, br s), 7.52 (1H, m), 7.43 (1H, t, $J=6.6$ Hz), 7.25 (1H, br s), 6.81 (1H, s), 4.66 (1H, d, $J=7.3$ Hz), 4.57 (1H, t, $J=7.7$ Hz), 4.12 (2H, br m), 3.92 (1H, m), 3.87 (1H, d, $J=9.9$ Hz), 3.36 (1H, t, $J=8.8$ Hz), 3.25 (1H, m), 3.15 (1H, m), 1.63 (9H, m); IR (film) ν_{max} 3426, 3272, 2964, 2913, 1692, 1605, 1580, 1502, 1410, 1339, 1251, 1139, 800 cm^{-1}; ESI (positive) m/z 518 ($M+H^+$, $C_{29}H_{29}ClN_3O_4$); ESI (negative) m/z 516 ($M-H^-$, $C_{29}H_{27}ClN_3O_4$).

3-(Pyrrolo[3,2-*e*]indole-7-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (69A). (0.43 mg, 14%) as a pale yellow solid: $[\alpha]_D^{23}$ +184 (c 0.01, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.79 (1H, br s), 10.37 (1H, br s), 9.22 (1H, s), 8.25 (1H, d, $J=8.5$ Hz), 8.10 (1H, br s), 7.89 (1H, m), 7.55 (1H, ddd, $J=8.4$, 6.9, 1.4 Hz), 7.49 (1H, m), 7.44 (1H, m), 7.38 (1H, ddd, $J=8.3$, 7.0, 1.3 Hz), 7.37 (1H, d, $J=9.0$ Hz), 7.33 (1H, t, $J=2.8$ Hz), 6.78–6.79 (1H, m), 4.90 (1H, dd, $J=10.9$, 8.3 Hz), 4.86 (1H, dd, $J=10.9$, 2.8 Hz), 4.28–4.33 (1H, m), 4.09 (1H, dd, $J=11.1$, 3.0 Hz), 3.83 (1H, dd, $J=11.1$, 8.6 Hz); MALDIFT-HRMS m/z 416.1156 ($M+H^+$, $C_{24}H_{19}ClN_3O_2$ requires 416.1160).

3-(1,2-Dihydropyrrolo[3,2-*e*]benzofuran-7-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (70A). (0.8 mg, 53%) as a white solid: $[\alpha]_D^{23}$ +25 (*c* 0.2, acetone); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.40 (1H, br s), 8.30 (1H, d, *J* = 8.3 Hz), 8.27 (1H, s), 7.73 (1H, d, *J* = 8.3 Hz), 7.58 (1H, t, *J* = 7.9 Hz), 7.46 (1H, t, *J* = 7.9 Hz), 7.31 (1H, d, *J* = 8.3 Hz), 6.99 (1H, d, *J* = 8.3 Hz), 6.95 (1H, s), 4.85 (1H, d, *J* = 10.5 Hz), 4.72 (2H, t, *J* = 10.1 Hz), 4.16 (1H, t, *J* = 9.7 Hz), 4.00 (1H, dd, *J* = 8.8, 2.6 Hz), 3.75 (1H, m), 3.41–3.52 (3H, m); IR (film) ν_{max} 3406, 1428, 1048 cm^{-1}; MALDIFT-HRMS *m*/*z* 418.1094 (M^+, $C_{11}H_9NO_5$ requires 418.1079).

3-(Pyrrolo[3,2-*e*]benzofuran-7-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (71A). (1.7 mg, 45%) as a white solid: $[\alpha]_D^{23}$ +42 (*c* 0.2, acetone); ^{1}H NMR ($CDCl_3$, 600 MHz) δ 9.27 (1H, s), 8.25 (1H, d, *J* = 7.9 Hz), 8.10 (1H, s), 7.90 (2H, m), 7.56 (5H, m), 7.40 (1H, t, *J* = 7.5 Hz), 7.23 (1H, d, *J* = 0.9 Hz), 4.86 (2H, m), 4.31 (1H, m), 4.07 (1H, dd, *J* = 8.4, 3.0 Hz), 3.84 (1H, dd, *J* = 8.7, 2.6 Hz); IR (film) ν_{max} 3735, 3675, 1684, 1647, 1558, 1507, 1457 cm^{-1}; MALDIFT-HRMS *m*/*z* 416.0945 (M^+, $C_{24}H_{17}ClN_2O_3$ requires 416.0928).

3-(6-Oxo-cyclopenten[*e*]indole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (72A). (2.0 mg, 62%) as a pale yellow solid: $[\alpha]_D^{23}$ +75 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.43 (1H, br s), 9.30 (1H, s), 8.26 (1H, d, *J* = 8.1 Hz), 8.10 (1H, br s), 7.91 (1H, d, *J* = 8.6 Hz), 7.63 (1H, d, *J* = 8.6 Hz), 7.56 (1H, ddd, *J* = 8.4, 7.0, 1.4 Hz), 7.56 (1H, d, *J* = 9.0 Hz), 7.55 (1H, m), 7.41 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 4.92 (1H, t, *J* = 9.6 Hz), 4.84 (1H, dd, *J* = 10.7, 2.1 Hz), 4.30–4.35 (1H, m), 4.08 (1H, dd, *J* = 11.3, 3.2 Hz), 3.86 (1H, dd, *J* = 11.3, 8.3 Hz), 3.33–3.34 (2H, m), 2.70 (2H, t, *J* = 6.0 Hz); MALDIFT-HRMS *m*/*z* 431.1157 ($M+H^+$, $C_{25}H_{20}ClN_2O_3$ requires 431.1157).

3-(6-Oxo-cyclopenten[*f*]indole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (73A). (1.5 mg, 46%) as a pale yellow solid: $[\alpha]_D^{23}$ +46 (*c* 0.08, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.27 (1H, br s), 9.32 (1H, s), 8.21 (1H, d, *J* = 8.3 Hz), 8.08 (1H, s), 8.02 (1H, br s), 7.80 (1H, d, *J* = 8.2 Hz), 7.47–7.50 (2H, m), 7.30–7.33 (2H, m), 4.76–4.81 (2H, m), 4.17–4.22 (1H, m), 4.01 (1H, dd, *J* = 11.2, 3.4 Hz), 3.61–3.63 (1H, m), 3.22 (2H, t, *J* = 6.4 Hz), 2.62–2.64 (2H, m); MALDIFT-HRMS *m*/*z* 430.1063 (M^+, $C_{25}H_{19}ClN_2O_3$ requires 430.1079).

3-([1,3]Dioxolo[*e*]indole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (74A). (1.0 mg, 57%) as a yellow solid: $[\alpha]_D^{23}$ +30 (*c* 0.0065, CH_2Cl_2); ^{1}H NMR ($CDCl_3$, 500 MHz) δ 10.94 (1H, br s), 9.34 (1H, s), 8.33 (1H, d, *J* = 8.1 Hz), 8.15 (1H, br s), 7.98 (1H, d, *J* = 8.4 Hz), 7.63 (1H, t, *J* = 7.0 Hz), 7.47 (2H, t, *J* = 7.0 Hz), 7.18 (2H, t, *J* = 8.5 Hz), 7.05 (1H, d, *J* = 8.5 Hz), 6.15 (1H, s), 4.94 (1H, m), 4.86 (1H, m), 4.38 (1H, m), 4.16 (1H, m), 3.92 (1H, t, *J* = 8.3 Hz); IR (film) ν_{max} 3415, 2943, 2862, 1605, 1580, 1241, 1041 cm^{-1}; MALDI-FTMS *m*/*z* 420.0869 (M^+, $C_{23}H_{17}ClN_2O_4$ requires 420.0871).

3-([1,3]Dioxolo[*f*]indole-2-carbonyl)-1-(*S*)-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (75A). (1.28 mg, 42%) as an off-white solid: $[\alpha]_D^{23}$ +1 (*c* 0.08, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.75 (1H, br s), 9.24 (1H, s), 8.24 (1H, d, *J* = 8.1 Hz), 8.09 (1H, br s), 7.88 (1H, d, *J* = 8.1 Hz), 7.54 (1H, ddd, *J* = 8.4, 6.8, 1.3 Hz), 7.38 (1H, ddd, *J* = 8.3, 7.1, 1.1 Hz), 7.14 (1H, m), 7.09 (1H, s), 7.03 (1H, s), 5.99 (2H, s), 4.80 (1H, dd, *J* = 10.5, 8.8 Hz), 4.75 (1H, dd, *J* = 10.7, 2.1 Hz), 4.26-4.30 (1H, m), 4.07 (1H, dd, *J* = 11.1, 3.4 Hz), 3.81 (1H, dd, *J* = 11.1, 8.5 Hz); MALDIFT-HRMS *m*/*z* 420.0888 (M^+, $C_{23}H_{17}ClN_2O_4$ requires 420.0871).

76A: (3.8 mg, 62%) as a yellow solid: $[\alpha]_D^{23}$ −39 (*c* 0.02, CH_2Cl_2); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.66 (1H, br s), 10.58 (1H, br s), 9.26 (1H, d, *J* = 13.6 Hz), 8.24 (1H, d, *J* = 8.1 Hz), 8.09 (1H, br s), 7.88 (1H, d, *J* = 8.4 Hz), 7.54 (2H, m), 7.38 (2H, m), 7.25 (1H, m), 7.15 (1H, m), 7.05 (1H, d, *J* = 8.1 Hz), 4.80 (2H, m), 4.27 (1H, m), 4.07 (1H, m), 3.80 (1H, m), 3.18 (1H, t, *J* = 7.3 Hz), 3.02 (1H, t, *J* = 7.3 Hz), 2.97 (1H, pent, *J* = 7.4 Hz), 2.19 (1H, t, *J* = 7.3 Hz), 2.09 (1H, t, *J* = 7.3 Hz); MALDIFT-HRMS *m*/*z* 417.1371 ($M+H^+$, $C_{25}H_{21}ClN_2O_2$ requires 417.1364).

3-[Benz[*e*]indole-2-carbonyl]-1-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (77A). (1.60–2.30 mg, 37–54%) as a beige solid: (natural enantiomer $[\alpha]_D^{23}$ +100 (*c* 0.08, THF); unnatural enantiomer $[\alpha]_D^{23}$ −108 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.27 (1H, br s), 9.23 (1H, s), 8.42 (1H, d, *J* = 8.7 Hz), 8.26 (1H, d, *J* = 8.3 Hz), 8.12 (1H, br s), 7.95 (1H, m), 7.94 (1H, d, *J* = 2.0 Hz), 7.91 (1H, m), 7.74–7.77 (2H, m), 7.59 (1H, ddd, *J* = 8.3, 7.2, 1.2 Hz), 7.56 (1H, ddd, *J* = 8.5, 7.0, 1.6 Hz), 7.46 (1H, ddd, *J* = 8.1, 7.0, 1.2 Hz), 7.40 (1H, ddd, *J* = 8.5, 6.8, 1.0 Hz), 4.98 (1H, dd, *J* = 10.7, 8.7 Hz), 4.91 (1H, dd, *J* = 10.7, 2.4 Hz), 4.31–4.36 (1H, m), 4.09 (1H, dd, *J* = 11.3, 3.4 Hz), 3.86 (1H, dd, *J* = 11.1, 8.3 Hz); MALDI-HRMS *m*/*z* 426.1143 (M^+, $C_{26}H_{19}ClN_2O_2$ requires 426.1135).

3-[Benz[*f*]indole-2-carbonyl]-1-(chloromethyl)-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (78A). (1.00–3.02 mg, 23–71%) as a yellow solid: (natural enantiomer) $[\alpha]_D^{23}$ +32 (*c* 0.05, THF); (unnatural enantiomer) $[\alpha]_D^{23}$ −40 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.80 (1H, br s), 9.32 (1H, s), 8.35 (1H, s), 8.27 (1H, d, *J* = 8.4 Hz), 8.09 (1H, br s), 8.06 (1H, s), 7.98 (1H, m), 7.95 (1H, m), 7.92 (1H, d, *J* = 8.4 Hz), 7.57 (1H, ddd, *J* = 8.3, 6.9, 1.4 Hz), 7.43–7.44 (1H, m), 7.42 (1H, ddd, *J* = 8.3, 7.0, 1.2 Hz), 7.38 (1H, ddd, *J* = 8.3, 6.3, 1.5 Hz), 7.32 (1H, ddd, *J* = 8.2, 6.7, 1.4 Hz), 4.92 (1H, t, *J* = 10.2 Hz), 4.86 (1H, dd, *J* = 10.6, 2.2 Hz), 4.30–4.35 (1H, m), 4.09 (1H, dd, *J* = 10.8, 3.1 Hz), 3.86 (1H, dd, *J* = 11.4, 8.4 Hz); MALDIFT-HRMS *m*/*z* 426.1149 (M^+, $C_{26}H_{19}ClN_2O_2$ requires 426.1135).

Data for spirocyclized compounds

***N*^{2}-[(4-Methoxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (6B).** A solution of **6A** (0.98 mg, 2.4 μmol) and DBU (0.73 mg, 4.8 μmol) in 480 μL of CH_3CN/THF was stirred for 1 h at

0 °C. The reaction mixture was allowed to reach 25 °C over 2 h, and then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **6B** (0.82 mg, 92%) as a white solid: $[\alpha]_D^{23}$ +90 (*c* 0.04, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.96 (1H, br s), 8.11 (1H, dd, *J*=8.1, 1.3 Hz), 7.58 (1H, ddd, *J*=8.0, 7.2, 1.2 Hz), 7.43 (1H, td, *J*=7.6, 1.1 Hz), 7.22-7.25 (2H, m), 7.21 (1H, d, *J*=6.8 Hz), 7.17 (1H, m), 7.13 (1H, s), 6.58 (1H, d, *J*=7.3 Hz), 4.72 (1H, dd, *J*=10.0, 4.9 Hz), 4.62 (1H, d, *J*=9.8 Hz), 3.96 (3H, s), 3.23 (1H, dt, *J*=7.7, 4.9 Hz), 1.79 (1H, dd, *J*=7.9, 4.5 Hz), 1.71 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 3183, 2915, 2848, 1634, 1592, 1578, 1357, 1366, 1247, 1100, 775 cm^{-1}; MALDIFT-HRMS *m*/*z* 371.1398 (M+H$^+$, $C_{23}H_{19}N_2O_3$ requires 371.1390).

N^2-[(5-Methoxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (7B). A solution of **7A** (2.28 mg, 5.6 μmol) and DBU (1.7 mg, 11.2 μmol) in 700 μL of CH_3CN was stirred for 1 h at 0 °C and 3 h at 25 °C. The reaction mixture was purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **7B** (1.52 mg, 73%) as white solid: $[\alpha]_D^{23}$ +122 (*c* 0.08, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.82 (1H, br s), 8.11 (1H, dd, *J*=7.9, 1.1 Hz), 7.58 (1H, td, *J*=7.6, 1.3 Hz), 7.49 (1H, d, *J*=9.0 Hz), 7.43 (1H, td, *J*=7.5, 1.3 Hz), 7.20 (1H, d, *J*=8.1 Hz), 7.17–7.18 (1H, m), 7.15 (1H, d, *J*=2.6 Hz), 7.09 (1H, s), 6.98 (1H, dd, *J*=9.0, 2.1 Hz), 4.68 (1H, dd, *J*=10.0, 4.9 Hz), 4.59 (1H, d, *J*=9.8 Hz), 3.82 (3H, s), 3.21 (1H, dt, *J*=7.8, 4.8 Hz), 1.78 (1H, dd, *J*=7.7, 4.7 Hz), 1.71 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 2915, 1647, 1624, 1595, 1517, 1403, 1387, 1266, 1235 cm^{-1}; MALDIFT-HRMS *m*/*z* 371.1405 (M+H$^+$, $C_{23}H_{19}N_2O_3$ requires 371.1390).

N^2-[(6-Methoxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (8B). A solution of **8A** (1.40 mg, 3.4 μmol) in 680 μL of CH_3CN/THF was treated with DBU (1.05 mg, 6.9 μmol) and then stirred for 1 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 1 h, and then purified by preparative TLC (10×20 cm, THF/hexane 3:2) to afford **8B** (1.25 mg, 98%) as an off-white solid: $[\alpha]_D^{23}$ +147 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.76 (1H, br s), 8.10 (1H, dd, *J*=7.9, 1.1 Hz), 7.56–7.59 (2H, m), 7.43 (1H, m), 7.22 (1H, dd, *J*=2.1, 0.9 Hz), 7.20 (1H, d, *J*=7.3 Hz), 7.13 (1H, s), 7.07 (1H, d, *J*=2.1 Hz), 6.79 (1H, dd, *J*=8.6, 2.1 Hz), 4.68 (1H, dd, *J*=10.0, 4.9 Hz), 4.59 (1H, d, *J*=9.8 Hz), 3.84 (3H, s), 3.21 (1H, dt, *J*=8.0, 4.9 Hz), 1.77 (1H, dd, *J*=7.7, 4.3 Hz), 1.69 (1H, t, *J*=4.5 Hz); IR (film) ν_{max} 3321, 2900, 1644, 1624, 1599, 1505, 1275 cm^{-1}; MALDIFT-HRMS *m*/*z* 371.1392 (M+H$^+$, $C_{23}H_{19}N_2O_3$ requires 371.1390).

N^2-[(7-Methoxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (9B). A solution of **9A** (1.30 mg, 3.2 μmol) and DBU (0.97 mg, 6.4 μmol) in 320 μL of CH_3CN and 320 μL of THF were stirred for 1.5 h at 0 °C and 1 h from 0 to 25 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **9B** (1.11 mg, 94%) as a pale yellow solid: $[\alpha]_D^{23}$ +170 (*c* 0.05, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.47 (1H, br s), 8.10 (1H, dd, *J*=7.7, 0.9 Hz), 7.58 (1H, ddd, *J*=8.1, 7.1, 1.3 Hz), 7.43 (1H, td, *J*=7.6, 1.0 Hz), 7.28 (1H, d, *J*=8.3 Hz), 7.22 (1H, d, *J*=2.1 Hz), 7.20 (1H, m), 7.05 (1H, t, *J*=7.9 Hz), 7.00 (1H, s), 4.66 (1H, dd, *J*=10.0, 4.9 Hz), 4.56 (1H, d, *J*=10.3 Hz), 3.97 (3H, s), 3.20 (1H, dt, *J*=7.7, 4.9 Hz), 1.79 (1H, dd, *J*=7.7, 4.2 Hz), 1.73 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 2960, 2868, 1651, 1626, 1600, 1529, 1489, 1393, 1371, 1342, 1312, 1263, 1126, 732 cm^{-1}; MALDIFT-HRMS *m*/*z* 371.1395 (M+H$^+$, $C_{23}H_{19}N_2O_3$ requires 371.1390).

N^2 - [(4,5 - Dimethoxyindole - 2 - yl)carbonyl] - (8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (10B). A solution of **10A** (1.3 mg, 2.9 μmol) and DBU (2.7 mg, 17.8 μmol) in 500 μL of CH_3CN–THF was stirred for 1 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 1 h, and then purified by preparative TLC (10×20 cm, EtOAc/hexane 1:1) to afford **10B** (0.42 mg, 35%) as a beige solid: $[\alpha]_D^{23}$ +225 (*c* 0.06, acetone); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.8 (1H, br s), 8.10 (1H, d, *J*=6.6 Hz), 7.59 (1H, t, *J*=6.2 Hz), 7.43 (1H, t, *J*=7.0 Hz), 7.12–7.25 (5H, m), 4.72 (1H, m), 4.63 (1H, d, *J*=9.9 Hz), 4.01 (3H, s), 3.87 (3H, s), 3.23 (1H, m), 1.70–1.80 (2H, m); IR (film) ν_{max} 2321, 1656, 1600, 1380, 1267; MALDIFT-HRMS *m*/*z* 401.1499 (M+H$^+$, $C_{24}H_{20}N_2O_4$ requires 401.1496).

N^2 - [(5,6 - Dimethoxyindole - 2 - yl)carbonyl] - (8b*R*,9a*S*) - 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (11B). A solution of **11A** (1.72 mg, 3.9 μmol) in 390 μL CH_3CN was treated with DBU (1.2 mg, 7.9 μmol) and stirred for 1 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 1 h, and then purified by preparative TLC (10×20 cm, THF/hexane 2:1) to afford **11B** (1.29 mg, 82%) as a pale yellow solid: $[\alpha]_D^{23}$ +165 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.69 (1H, br s), 8.10 (1H, dd, *J*=7.9, 1.5 Hz), 7.58 (1H, ddd, *J*=8.0, 7.2, 1.2 Hz), 7.43 (1H, m), 7.19 (1H, m), 7.15 (1H, m), 7.13 (1H, s), 7.12 (1H, s), 7.09 (1H, s), 4.66 (1H, dd, *J*=10.3, 5.1 Hz), 4.56 (1H, d, *J*=9.8 Hz), 3.86 (3H, s), 3.83 (3H, s), 3.21 (1H, dt, *J*=7.8, 4.9 Hz), 1.77 (1H, dd, *J*=7.7, 4.3 Hz), 1.68 (1H, t, *J*=4.5 Hz); IR (film) ν_{max} 3325, 2916, 1634, 1600, 1515, 1498, 1386, 1280, 1262, 1130 cm^{-1}; MS (ESI positive) *m*/*z* 399 (M+H$^+$).

N^2 - [(6,7 - Dimethoxyindole - 2 - yl)carbonyl] - (8b*R*,9a*S*) - 1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (12B). A solution of **12A** (1.15 mg, 2.6 μmol) in 260 μL CH_3CN was treated with DBU (0.80 mg, 5.3 μmol) and then stirred for 2 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, THF/hexane 1:1) to afford **12B** (0.68 mg, 65%) as a white solid: $[\alpha]_D^{23}$ +168 (*c* 0.025, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.47 (1H, br s), 8.10 (1H, dd, *J*=8.3, 1.1 Hz), 7.58 (1H, td, *J*=7.5, 1.3 Hz), 7.43 (1H, m), 7.39 (1H, d, *J*=8.5 Hz), 7.22 (1H, d, *J*=2.6 Hz), 7.20 (1H, d, *J*=7.3 Hz), 7.03 (1H, s), 6.99 (1H, d, *J*=9.0 Hz), 4.66 (1H, dd, *J*=10.0, 4.9 Hz), 4.55 (1H, d, *J*=10.3 Hz), 3.94 (3H, s), 3.93 (3H, s), 3.20 (1H, dt, *J*=7.7, 4.9 Hz), 1.78 (1H, dd, *J*=7.9, 4.1 Hz), 1.71 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 3271, 2917, 2848, 1627, 1598, 1379, 1269, 1252 cm^{-1}; MALDIFT-HRMS *m*/*z* 401.1509 (M+H$^+$, $C_{24}H_{21}N_2O_4$ requires 401.1496).

N^2-[(5,7-Dimethoxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (13B). A solution of **13A** (1.0 mg, 2.3 μmol) in 230 μL CH_3CN was treated with DBU (0.70 mg, 4.6 μmol) and stirred for 1.5 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 2 h, and then purified by preparative TLC (10×20 cm, THF/hexane 1:1) to afford **13B** (0.90 mg, 98%) as a pale yellow solid: $[\alpha]_D^{23}$ −58 (*c* 0.14, $CHCl_3$); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.41 (1H, br s), 8.10 (1H, dd, *J* = 7.9, 1.5 Hz), 7.58 (1H, ddd, *J* = 8.1, 7.1, 1.3 Hz), 7.43 (1H, td, *J* = 7.6, 1.1 Hz), 7.19 (1H, m), 7.12 (1H, d, *J* = 2.6 Hz), 6.97 (1H, s), 6.71 (1H, d, *J* = 2.1 Hz), 6.47 (1H, d, *J* = 2.1 Hz), 4.63 (1H, dd, *J* = 10.0, 4.9 Hz), 4.52 (1H, d, *J* = 10.3 Hz), 3.95 (3H, s), 3.81 (3H, s), 3.19 (1H, dt, *J* = 7.7, 4.9 Hz), 1.79 (1H, dd, *J* = 7.7, 4.3 Hz), 1.73 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 3292, 2916, 1652, 1645, 1627, 1598, 1532, 1394, 1312, 1267, 1250 cm^{-1}; MALDIFT-HRMS *m*/*z* 423.1317 ($M+Na^+$, $C_{24}H_{20}N_2NaO_4$ requires 423.1315).

N^2-[(5-Ethoxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (15B). A solution of **15A** (1.56 mg, 3.7 μmol) and DBU (1.13 mg, 7.4 μmol) in 370 μL of CH_3CN and 370 μL of THF was stirred for 1 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **15B** (1.35 mg, 94%) as a pale yellow solid: $[\alpha]_D^{23}$ +144 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.81 (1H, br s), 8.11 (1H, dd, *J* = 7.7, 1.3 Hz), 7.58 (1H, td, *J* = 7.5, 1.1 Hz), 7.48 (1H, d, *J* = 8.6 Hz), 7.43 (1H, td, *J* = 7.5, 1.4 Hz), 7.20 (1H, m), 7.16 (1H, dd, *J* = 2.6, 0.9 Hz), 7.14 (1H, d, *J* = 2.6 Hz), 7.09 (1H, s), 6.98 (1H, dd, *J* = 9.0, 2.6 Hz), 4.68 (1H, dd, *J* = 10.3, 5.1 Hz), 4.59 (1H, d, *J* = 9.8 Hz), 4.06 (2H, q, *J* = 7.0 Hz), 3.21 (1H, dt, *J* = 7.7, 4.9 Hz), 1.78 (1H, dd, *J* = 7.7, 4.3 Hz), 1.71 (1H, t, *J* = 4.7 Hz), 1.39 (3H, t, *J* = 7.1 Hz); IR (film) ν_{max} 2975, 1651, 1622, 1597, 1515, 1386, 1266, 1236, 1184, 1118 cm^{-1}; MALDIFT-HRMS *m*/*z* 384.1483 (M^+, $C_{24}H_{21}N_2O_3$ requires 384.1474).

N^2-[(5-Propyloxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (16B). A solution of **16A** (1.80 mg, 4.1 μmol) and DBU (1.26 mg, 8.2 μmol) in 410 μL of CH_3CN and 205 μL of THF was stirred for 1.5 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **16B** (1.15 mg, 70%) as a pale yellow solid: $[\alpha]_D^{23}$ +139 (*c* 0.06, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.80 (1H, br s), 8.11 (1H, dd, *J* = 7.7, 1.3 Hz), 7.58 (1H, ddd, *J* = 8.0, 7.2, 1.2 Hz), 7.49 (1H, d, *J* = 9.0 Hz), 7.43 (1H, m), 7.20 (1H, d, *J* = 7.7 Hz), 7.16 (1H, dd, *J* = 2.1, 0.9 Hz), 7.15 (1H, d, *J* = 2.6 Hz), 7.09 (1H, s), 6.99 (1H, dd, *J* = 9.0, 2.6 Hz), 4.68 (1H, dd, *J* = 10.0, 4.9 Hz), 4.59 (1H, d, *J* = 9.8 Hz), 3.97 (2H, t, *J* = 6.4 Hz), 3.21 (1H, dt, *J* = 7.7, 4.9 Hz), 1.77–1.84 (3H, m), 1.71 (1H, t, *J* = 4.7 Hz), 1.05 (3H, t, *J* = 7.5 Hz); IR (film) ν_{max} 2963, 1651, 1622, 1597, 1515, 1386, 1266, 1236, 1184 cm^{-1}; MALDIFT-HRMS *m*/*z* 384.1483 (M^+, $C_{25}H_{21}N_2O_3$ requires 384.1474).

N^2-[(5-Butyloxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (17B). A solution of **17A** (1.26 mg, 2.8 μmol) and DBU (0.86 mg, 5.6 μmol) in 330 μL of CH_3CN and 100 μL of THF was stirred for 1.5 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **17B** (1.02 mg, 88%) as a beige solid: $[\alpha]_D^{23}$ +124 (*c* 0.05, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.82 (1H, br s), 8.11 (1H, dd, *J* = 7.7, 1.1 Hz), 7.58 1H, (ddd, *J* = 8.3, 6.9, 1.0 Hz), 7.48 (1H, m), 7.43 (1H, td, *J* = 7.5, 1.1 Hz), 7.20 (1H, dd, *J* = 7.3, 0.7 Hz), 7.16 (1H, dd, *J* = 2.2, 0.7 Hz), 7.15 (1H, d, *J* = 2.6 Hz), 7.09 (1H, s), 6.98 (1H, dd, *J* = 9.0, 2.4 Hz), 4.68 (1H, dd, *J* = 10.1, 5.0 Hz), 4.59 (1H, d, *J* = 9.9 Hz), 4.01 (2H, t, *J* = 6.4 Hz), 3.21 (1H, dt, *J* = 7.8, 4.9 Hz), 1.75–1.80 (3H, m), 1.71 (1H, t, *J* = 4.6 Hz), 1.49–1.56 (2H, m), 0.98 (3H, t, *J* = 7.3 Hz); IR (film) ν_{max} 2975, 1651, 1622, 1597, 1515, 1386, 1266, 1236, 1183 cm^{-1}; MALDIFT-HRMS *m*/*z* 413.1855 ($M+H^+$, $C_{26}H_{24}N_2O_3$ requires 413.1860).

N^2-[(5-Benzyloxyindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (18B). A solution of **18A** (0.88 mg, 1.8 μmol) and DBU (0.55 mg, 3.6 μmol) in 180 μL of CH_3CN and 180 μL of THF was stirred for 2.5 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **18B** (0.74 mg, 91%) as a pale yellow solid: $[\alpha]_D^{23}$ +92 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.83 (1H, br s), 8.11 (1H, dd, *J* = 7.7, 0.9 Hz), 7.58 (1H, td, *J* = 7.6, 1.4 Hz), 7.50–7.52 (3H, m), 7.38–7.45 (3H, m), 7.31–7.34 (1H, m), 7.25 (1H, d, *J* = 2.1 Hz), 7.20 (1H, d, *J* = 7.7 Hz), 7.17 (1H, dd, *J* = 2.1, 0.9 Hz), 7.09 (1H, s), 7.08 (1H, dd, *J* = 9.0, 2.3 Hz), 5.15 (2H, s), 4.68 (1H, dd, *J* = 9.8, 4.9 Hz), 4.59 (1H, d, *J* = 10.3 Hz), 3.21 (1H, dt, *J* = 7.7, 4.9 Hz), 1.78 (1H, dd, *J* = 7.7, 4.7 Hz), 1.70 (1H, t, *J* = 4.5 Hz); IR (film) ν_{max} 2923, 1651, 1623, 1597, 1515, 1388, 1265, 1236, 1171 cm^{-1}; MALDIFT-HRMS *m*/*z* 447.1693 ($M+H^+$, $C_{29}H_{22}N_2O_3$ requires 447.1703).

N^2-[(5-Thiomethylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (21B). A solution of **21A** (1.0 mg, 2.4 μmol) and DBU (0.72 mg, 4.7 μmol) in 240 μL of CH_3CN was stirred for 1 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 2 h, and then purified by preparative TLC (10×20 cm, THF/hexane 2:1) to afford **21B** (0.51 mg, 56%) as a beige solid: $[\alpha]_D^{23}$ +136 (*c* 0.025, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.00 (1H, br s), 8.10 (1H, m), 7.67 (1H, d, *J* = 1.7 Hz), 7.58 (1H, td, *J* = 7.5, 1.1 Hz), 7.55 (1H, d, *J* = 8.6 Hz), 7.43 (1H, td, *J* = 7.6, 1.1 Hz), 7.32 (1H, dd, *J* = 8.8, 1.9 Hz), 7.22 (1H, d, *J* = 1.7 Hz), 7.21 (1H, d, *J* = 8.6 Hz), 7.10 (1H, s), 4.71 (1H, dd, *J* = 9.8, 5.1 Hz), 4.61 (1H, d, *J* = 10.3 Hz), 3.23 (1H, dt, *J* = 7.8, 4.9 Hz), 2.51 (3H, s), 1.77–1.80 (1H, m), 1.72 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 3224, 2916, 1651, 1622, 1598, 1403, 1386, 1281, 1265 cm^{-1}; MALDIFT-HRMS *m*/*z* 387.1164 ($M+H^+$, $C_{23}H_{19}N_2O_2S$ requires 387.1162).

N^2-[(7-Thiomethylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (22B). A solution of **22A** (1.5 mg, 3.6 μmol) and DBU (1.08 mg, 7.1 μmol) in 360 μL of CH_3CN was stirred for 1 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 1 h, and then purified by preparative TLC (10×20 cm,

THF/hexane 1:1) to afford **22B** (1.01 mg, 74%) as a beige solid: $[\alpha]_D^{23}$ +184 (*c* 0.05, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.27 (1H, br s), 8.10 (1H, dd, *J* = 7.7, 1.3 Hz), 7.63 (1H, d, *J* = 8.1 Hz), 7.58 (1H, td, *J* = 7.6, 1.7 Hz), 7.43 (1H, td, *J* = 7.5, 1.3 Hz), 7.37 (1H, dd, *J* = 7.3, 0.8 Hz), 7.31 (1H, d, *J* = 2.1 Hz), 7.20 (1H, d, *J* = 8.6 Hz), 7.16 (1H, t, *J* = 7.7 Hz), 7.03 (1H, s), 4.68 (1H, dd, *J* = 10.0, 4.9 Hz), 4.58 (1H, d, *J* = 9.8 Hz), 3.21 (1H, dt, *J* = 7.8, 4.8 Hz), 2.57 (3H, s), 1.80 (1H, dd, *J* = 7.7, 4.3 Hz), 1.74 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 2916, 2848, 1626, 1592, 1568, 1386, 770, 733 cm^{-1}; MALDIFT-HRMS *m*/*z* 387.1176 (M + H$^+$, $C_{23}H_{19}N_2O_2S$ requires 387.1162).

N^2-[(5-Thioethylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (23B). A solution of **23A** (1.7 mg, 3.9 μmol) and DBU (1.18 mg, 7.8 μmol) in 390 μL of CH_3CN was stirred for 1.5 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 1.5 h, and then purified by preparative TLC (10×20 cm, THF/hexane 1:1) to afford **23B** (1.28 mg, 82%) as a pale yellow solid: $[\alpha]_D^{23}$ +135 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.04 (1H, br s), 8.11 (1H, dd, *J* = 7.9, 1.1 Hz), 7.78 (1H, d, *J* = 1.7 Hz), 7.58 (1H, td, *J* = 7.5, 1.1 Hz), 7.57 (1H, d, *J* = 8.6 Hz), 7.43 (1H, m), 7.38 (1H, dd, *J* = 8.6, 1.7 Hz), 7.24 (1H, dd, *J* = 2.1, 0.9 Hz), 7.21 (1H, d, *J* = 7.3 Hz), 7.11 (1H, s), 4.70 (1H, dd, *J* = 10.0, 4.9 Hz), 4.62 (1H, d, *J* = 9.8 Hz), 3.23 (1H, dt, *J* = 8.0, 4.9 Hz), 2.93 (2H, q, *J* = 7.3 Hz), 1.79 (1H, dd, *J* = 8.1, 4.3 Hz), 1.72 (1H, t, *J* = 4.7 Hz), 1.24 (3H, t, *J* = 7.3 Hz); IR (film) ν_{max} 3231, 2964, 2916, 1646, 1621, 1595, 1380, 1262 cm^{-1}; MALDIFT-HRMS *m*/*z* 423.1131 (M + Na$^+$, $C_{24}H_{20}N_2NaO_2S$ requires 423.1138).

N^2-[(Indole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (5B, CBI-indole). A solution of **5A** (1.50 mg, 4 μmol) and DBU (1.2 mg, 8 μmol) in 400 μL of CH_3CN was stirred for 1 h at 0 °C and the reaction mixture was purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **5B** (1.25 mg, 93%) as a white solid: $[\alpha]_D^{23}$ +159 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.95 (1H, br s, 1H), 8.12 (1H, dd, *J* = 7.5, 1.1 Hz), 7.72 (1H, dd, *J* = 8.1, 0.9 Hz), 7.57–7.61 (2H, m), 7.44 (1H, td, *J* = 7.6, 1.1 Hz), 7.32 (1H, ddd, *J* = 8.2, 6.9, 1.2 Hz), 7.29 (1H, dd, *J* = 2.1, 0.9 Hz), 7.21 (1H, d, *J* = 7.3 Hz), 7.13 (1H, ddd, *J* = 8.0, 6.9, 1.0 Hz), 4.72 (1H, dd, *J* = 9.8, 5.1 Hz), 4.63 (1H, d, *J* = 9.8 Hz), 3.23 (1H, dt, *J* = 7.8, 4.8 Hz), 1.80 (1H, dd, *J* = 7.3, 4.7 Hz), 1.73 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 2924, 1651, 1622, 1597, 1403, 1389, 1343, 1309, 1270, 1252, 744 cm^{-1}; MALDIFT-HRMS *m*/*z* 341.1276 (M + H$^+$, $C_{22}H_{17}N_2O_2$ requires 341.1284).

N^2-[(5-Methylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (24B). A solution of **24A** (1.52 mg, 3.9 μmol) and DBU (1.18 mg, 7.8 μmol) in 390 μL of CH_3CN was stirred for 1.5 h at 0 °C and the reaction mixture was purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **24B** (1.20 mg, 87%) as a white solid: $[\alpha]_D^{23}$ +149 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.81 (1H, br s), 8.11 (1H, dd, *J* = 7.5, 1.1 Hz), 7.58 (1H, td, *J* = 7.6, 1.7 Hz), 7.49 (1H, m), 7.48 (1H, d, *J* = 6.4 Hz), 7.43 (1H, td, *J* = 7.6, 1.1 Hz), 7.20 (1H, d, *J* = 8.6 Hz), 7.17–7.18 (1H, m), 7.15 (1H, dd, *J* = 8.3, 1.5 Hz), 7.10 (1H, s), 4.69 (1H, dd, *J* = 10.3, 5.1 Hz), 4.60 (1H, d, *J* = 10.3 Hz), 3.21 (1H, dt, *J* = 7.7, 4.9 Hz), 2.41 (3H, s), 1.78 (1H, dd, *J* = 7.7, 4.4 Hz), 1.71 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 2921, 1641, 1619, 1594, 1557, 1405, 1388 cm^{-1}; MALDIFT-HRMS *m*/*z* 355.1441 (M + H$^+$, $C_{23}H_{19}N_2O_2$ requires 355.1441).

N^2-[(5-Ethylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (25B). A solution of **25A** (1.1 mg, 2.7 μmol) and DBU (1.18 mg, 7.8 μmol) in 270 μL of CH_3CN was stirred for 1 h at 0 °C and 1 h at 25 °C. The reaction mixture was purified by preparative TLC (10×20 cm, THF/hexane 1:1) to afford **25B** (0.61 mg, 61%) as a white solid: $[\alpha]_D^{23}$ +188 (*c* 0.025, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.85 (1 h, br s), 8.10 (1H, dd, *J* = 7.7, 0.9 Hz), 7.58 (1H, t, *J* = 7.6, 1.7 Hz), 7.51 (1H, s), 7.50 (1H, d, *J* = 9.0 Hz), 7.43 (1H, td, *J* = 7.6, 1.1 Hz), 7.19–7.21 (3H, m), 7.10 (1H, s), 4.70 (1H, dd, *J* = 10.3, 5.1 Hz), 4.61 (1H, d, *J* = 9.8 Hz), 3.22 (1H, dt, *J* = 7.7, 4.9 Hz), 2.72 (2H, q, *J* = 7.6 Hz), 1.78 (1H, dd, *J* = 7.5, 4.5 Hz), 1.71 (1H, t, *J* = 4.7 Hz), 1.26 (3H, t, *J* = 7.5 Hz); IR (film) ν_{max} 3241, 2944, 2913, 2862, 1641, 1615, 1595, 1518, 1385, 1267 cm^{-1}; MALDIFT-HRMS *m*/*z* 369.1585 (M + H$^+$, $C_{24}H_{20}N_2O_2$ requires 369.1597).

N^2-[(5-Methoxymethylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (26B). A solution of **26A** (1.4 mg, 3.3 μmol) and DBU (1.01 mg, 6.6 μmol) in 330 μL of CH_3CN was stirred for 1 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, THF/hexane 3:2) to afford **26B** (1.09 mg, 85%) as a beige solid: $[\alpha]_D^{23}$ +128 (*c* 0.05, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.97 (1H, br s), 8.11 (1H, dd, *J* = 7.7, 0.9 Hz), 7.67 (1H, m), 7.58 (1H, ddd, *J* = 8.0, 7.0, 1.3 Hz), 7.57 (1H, d, *J* = 8.1 Hz), 7.43 (1H, td, *J* = 7.5, 1.4 Hz), 7.31 (1H, dd, *J* = 8.6, 1.7 Hz), 7.27 (1H, dd, *J* = 2.1, 0.9 Hz), 7.20 (1H, d, *J* = 7.3 Hz), 7.12 (1H, s), 4.71 (1H, dd, *J* = 10.0, 4.9 Hz), 4.62 (1H, d, *J* = 10.3 Hz), 4.51 (2H, s), 3.32 (3H, s), 3.23 (1H, dt, *J* = 7.8, 5.0 Hz), 1.79 (1H, dd, *J* = 7.9, 4.5 Hz), 1.72 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 3217, 2918, 1651, 1622, 1598, 1403, 1392, 1289, 760 cm^{-1}; MALDIFT-HRMS *m*/*z* 385.1558 (M + H$^+$, $C_{24}H_{21}N_2O_3$ requires 385.1547).

N^2-[(7-Methoxymethylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (27B). A solution of **27A** (1.15 mg, 2.7 μmol) and DBU (0.83 mg, 5.5 μmol) in 270 μL of CH_3CN was stirred for 1 h at 0 °C, and then purified by preparative TLC (10×20 cm, THF/hexane 3:2) to afford **27B** (0.91 mg, 87%) as a white solid: $[\alpha]_D^{23}$ +125 (*c* 0.04, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.31 (1H, br s), 8.11 (1H, dd, *J* = 7.9, 1.5 Hz), 7.67 (1H, d, *J* = 7.7 Hz), 7.58 (1H, td, *J* = 7.6, 1.7 Hz), 7.43 (1H, td, *J* = 7.6, 1.1 Hz), 7.30 (1H, d, *J* = 2.1 Hz), 7.26 (1H, m), 7.21 (1H, d, *J* = 7.3 Hz), 7.11 (1H, dd, *J* = 8.1, 6.8 Hz), 7.11 (1H, s), 4.86 (2H, s), 4.71 (1H, dd, *J* = 10.0, 4.9 Hz), 4.61 (1H, d, *J* = 10.3 Hz), 3.41 (3H, s), 3.22 (1H, dt, *J* = 7.7, 4.9 Hz), 1.79 (1H, dd, *J* = 8.1, 4.3 Hz), 1.72 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max}

3450, 3269, 2825, 1651, 1626, 1599, 1386, 1265, 749 cm^{-1}; MALDIFT-HRMS *m/z* 385.1547 ($M+H^+$, $C_{24}H_{21}N_2O_2$ requires 385.1547).

N^2-[(5-Bromoindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (28B). A solution of **28A** (1.72 mg, 3.8 μmol) in 860 μL of THF was treated with NaH (0.18 mg, 7.6 μmol) and was stirred for 2 h at 0 °C, then warmed to 25 °C over 1 h and stirred for 3 h. The reaction mixture was purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **28B** (0.60 mg, 38%) as a beige solid: $[\alpha]_D^{23}$ +66 (*c* 0.03, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.13 (1H, br s), 8.11 (1H, dd, *J*=7.9, 1.1 Hz), 7.90 (1H, d, *J*=1.3 Hz), 7.59 (1H, ddd, *J*=8.1, 6.8, 1.1 Hz), 7.56 (1H, m), 7.41–7.45 (1H, m), 7.42 (1H, dd, *J*=9.0, 2.1 Hz), 7.26–7.27 (1H, m), 7.20 (1H, d, *J*=7.7 Hz), 7.10 (1H, s), 4.70 (1H, dd, *J*=10.0, 4.9 Hz), 4.62 (1H, d, *J*=9.8 Hz), 3.23 (1H, dt, *J*=7.7, 4.7 Hz), 1.79 (1H, dd, *J*=7.9, 4.5 Hz), 1.73 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 2925, 1651, 1645, 1633, 1593, 1563, 1557, 1505, 1393 cm^{-1}; MALDIFT-HRMS *m/z* 419.0408 ($M+H^+$, $C_{22}H_{16}BrN_2O_2$ requires 419.0390).

N^2-[(5-Chloroindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (29B). A solution of **29A** (1.53 mg, 3.8 μmol) in 380 μL of DMF was treated with NaH (0.18 mg, 7.6 μmol) and was stirred for 1.5 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **29B** (1.08 mg, 77%) as a beige solid: $[\alpha]_D^{23}$ +108 (*c* 0.05, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.12 (1H, br s), 8.11 (1H, dd, *J*=7.9, 1.5 Hz), 7.74 (1H, d, *J*=2.3 Hz), 7.61 (1H, m), 7.58 (1H, td, *J*=7.5, 1.1 Hz), 7.43 (1H, td, *J*=7.7, 1.5 Hz), 7.30 (1H, dd, *J*=8.5, 2.1 Hz), 7.26 (1H, dd, *J*=2.1, 0.9 Hz), 7.20 (1H, d, *J*=7.3 Hz), 7.10 (1H, s), 4.70 (1H, dd, *J*=10.3, 5.1 Hz), 4.62 (1H, d, *J*=9.8 Hz), 3.23 (1H, dt, *J*=7.8, 4.9 Hz), 1.79 (1H, dd, *J*=7.7, 4.7 Hz), 1.73 (1H, t, *J*=4.5 Hz); IR (film) ν_{max} 2917, 1644, 1619, 1592, 1508, 1402, 1393, 1267 cm^{-1}; MALDIFT-HRMS *m/z* 375.0901 ($M+H^+$, $C_{22}H_{16}ClN_2O_2$ requires 375.0895).

N^2-[(5-Azidoindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (30B). A solution of **30A** (1.07 mg, 2.6 μmol) and DBU (0.78 mg, 5.1 μmol) in 260 μL of CH_3CN was stirred for 1 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **30B** (0.82 mg, 84%) as a beige solid: $[\alpha]_D^{23}$ +100 (*c* 0.05, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.07 (1H, br s), 8.11 (1H, m), 7.64 (1H, d, *J*=7.6 Hz), 7.64 (1H, ddd, *J*=7.9, 7.3, 1.3 Hz), 7.42–7.45 (2H, m), 7.26 (1H, dd, *J*=2.1, 0.9 Hz), 7.20 (1H, d, *J*=7.3 Hz), 7.10 (1H, s), 7.06 (1H, dd, *J*=8.6, 2.1 Hz), 4.70 (1H, dd, *J*=10.0, 4.9 Hz), 4.61 (1H, d, *J*=9.8 Hz), 3.22 (1H, dt, *J*=7.7, 4.9 Hz), 1.79 (1H, dd, *J*=7.9, 4.5 Hz), 1.73 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 2917, 2104, 1636, 1621, 1593, 1511, 1403, 1386, 1277, 1228, 1129 cm^{-1}; MS (ESI positive) *m/z* 382 ($M+H^+$); MS (ESI negative) *m/z* 380 ($M-H^-$).

N^2-[(5-Cyanoindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (31B). A solution of **31A** (2.10 mg, 5.2 μmol) in 520 μL of DMF was treated with NaH (0.25 mg, 10.5 μmol) and was stirred for 1.5 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **31B** (0.41 mg, 21%) as a beige solid: $[\alpha]_D^{23}$ +80 (*c* 0.025, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.45 (1H, br s), 8.22–8.23 (1H, m), 8.11 (1H, dd, *J*=8.3, 1.1 Hz), 7.77 (1H, dt, *J*=8.5, 0.9 Hz), 7.60 (1H, dd, *J*=8.6, 1.3 Hz), 7.57–7.61 (1H, m), 7.42–7.46 (2H, m), 7.21 (1H, d, *J*=7.3 Hz), 7.11 (1H, s), 4.74 (1H, dd, *J*=10.0, 4.9 Hz), 4.65 (1H, d, *J*=10.3 Hz), 3.24 (1H, dt, *J*=7.8, 4.9 Hz), 1.80 (1H, dd, *J*=7.7, 4.7 Hz), 1.75 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 2916, 2219, 1656, 1651, 1644, 1625, 1621, 1598, 1563, 1519, 1407, 1389, 1341, 1292, 1275, 1237 cm^{-1}; MALDIFT-HRMS *m/z* 366.1235 ($M+H^+$, $C_{23}H_{16}N_3O_2$ requires 366.1237).

N^2-[(7-Cyanoindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (32B). A solution of **32A** (0.69 mg, 1.7 μmol) in 170 μL of DMF was treated with NaH (0.08 mg, 3.4 μmol) and was stirred for 1.5 h at 0 °C. The reaction mixture was purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **32B** (0.39 mg, 62%) as a pale yellow solid: $[\alpha]_D^{23}$ +124 (*c* 0.05, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.55 (1H, br s), 8.11 (1H, dd, *J*=7.3, 0.9 Hz), 8.09 (1H, dd, *J*=8.1, 1.3 Hz), 7.78 (1H, dd, *J*=7.5, 1.1 Hz), 7.59 (1H, ddd, *J*=7.9, 7.1, 1.3 Hz), 7.44 (1H, td, *J*=7.5, 1.3 Hz), 7.43 (1H, s), 7.31 (1H, dd, *J*=8.1, 7.3 Hz), 7.21 (1H, dd, *J*=7.3, 1.3 Hz), 7.00 (1H, s), 4.70 (1H, dd, *J*=10.3, 5.1 Hz), 4.59 (1H, d, *J*=10.3 Hz), 3.22 (1H, dt, *J*=7.7, 5.0 Hz), 1.81 (1H, dd, *J*=7.7, 4.7 Hz), 1.76 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 2923, 2222, 1719, 1657, 1626, 1599, 1404, 1389, 1301, 1270, 1252 cm^{-1}; MALDIFT-HRMS *m/z* 365.1169 (M^+, $C_{23}H_{15}N_3O_2$ requires 365.1164).

N^2-[(5-Vinylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (33B). A solution of **33A** (1.35 mg, 3.4 μmol) and DBU (1.02 mg, 6.7 μmol) in 600 μL of CH_3CN/THF was stirred for 1 h at 0 °C and 1 h at 25 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, THF/hexane 1:1) to afford **33B** (0.80 mg, 65%) as a beige solid: $[\alpha]_D^{23}$ +159 (*c* 0.03, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.10 (1H, br s), 8.11 (1H, dd, *J*=7.7, 0.9 Hz), 7.73 (1H, s), 7.58 (1H, td, *J*=7.6, 1.7 Hz), 7.57 (1H, d, *J*=8.6 Hz), 7.54 (1H, dd, *J*=8.8, 1.5 Hz), 7.43 (1H, td, *J*=7.6, 1.1 Hz), 7.27 (1H, dd, *J*=2.1, 0.9 Hz), 7.21 (1H, d, *J*=7.3 Hz), 7.12 (1H, s), 6.85 (1H, dd, *J*=17.7, 10.9 Hz), 5.75 (1H, dd, *J*=17.7, 1.1 Hz), 5.15 (1H, dd, *J*=10.9, 1.1 Hz), 4.71 (1H, dd, *J*=9.8, 5.1 Hz), 4.62 (1H, d, *J*=10.3 Hz), 3.23 (1H, dt, *J*=7.7, 4.9 Hz), 1.79 (1H, dd, *J*=7.9, 4.5 Hz), 1.72 (1H, t, *J*=4.7 Hz); IR (film) ν_{max} 3208, 2917, 1651, 1622, 1597, 1520, 1403, 1386, 1271 cm^{-1}; MALDIFT-HRMS *m/z* 367.1442 ($M+H^+$, $C_{24}H_{19}N_2O_2$ requires 367.1441).

N^2-[(7-Vinylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (34B). A solution of **34A** (0.95 mg, 2.4 μmol) and DBU (0.72 mg, 4.7 μmol) in 400 μL of CH_3CN/THF was stirred for 1 h at 0 °C and 1 h at 25 °C. The reaction mixture was purified by preparative TLC (10×20 cm, THF/hexane 1:1) to

afford **34B** (0.76 mg, 88%) as a beige solid: $[\alpha]_D^{23}$ +198 (*c* 0.03, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.69 (1H, br s), 8.11 (1H, dd, *J* = 7.9, 1.5 Hz), 7.67 (1H, d, *J* = 8.1 Hz), 7.56–7.60 (2H, m), 7.48 (1H, dd, *J* = 17.5, 11.1 Hz), 7.43 (1H, td, *J* = 7.5, 1.3 Hz), 7.30 (1H, d, *J* = 2.1 Hz), 7.21 (1H, d, *J* = 7.3 Hz), 7.15 (1H, t, *J* = 7.7 Hz), 7.08 (1H, s), 5.95 (1H, dd, *J* = 17.5, 1.3 Hz), 5.40 (1H, dd, *J* = 11.1, 1.3 Hz), 4.70 (1H, dd, *J* = 10.0, 4.9 Hz), 4.60 (1H, d, *J* = 9.8 Hz), 3.22 (1H, dt, *J* = 7.7, 4.9 Hz), 1.79 (1H, dd, *J* = 7.7, 4.3 Hz), 1.72 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 3230, 1652, 1622, 1598, 1401, 1386, 1300, 1263, 1250, 744 cm^{-1}; MALDIFT-HRMS *m*/*z* 367.1440 ($M+H^+$, $C_{24}H_{19}N_2O_2$ requires 367.1441).

N^2-[(5-Isopropenylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (35B). A solution of **35A** (1.3 mg, 3.1 μmol) and DBU (0.95 mg, 6.2 μmol) in 310 μL of CH_3CN was stirred for 1 h at 0 °C and warmed over 1.5 h to 25 °C. The reaction mixture was purified by preparative TLC (10×20 cm, THF/hexane 1:1) to afford **35B** (0.79 mg, 66%) as an off-white solid: $[\alpha]_D^{23}$ +116 (*c* 0.05, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.97 (1H, br s), 8.11 (1H, dd, *J* = 7.7, 0.9 Hz), 7.81 (1H, s), 7.57–7.60 (2H, m), 7.55 (1H, d, *J* = 9.0 Hz), 7.43 (1H, *J* = 7.6 Hz), 7.28 (1H, d, *J* = 1.7 Hz), 7.21 (1H, d, *J* = 7.3 Hz), 7.11 (1H, s), 5.40 (1H, m), 5.05–5.06 (1H, m), 4.71 (1H, dd, *J* = 10.0, 4.9 Hz), 4.62 (1H, d, *J* = 9.8 Hz), 3.23 (1H, dt, *J* = 7.8, 4.9 Hz), 1.79 (1H, dd, *J* = 7.7, 4.3 Hz), 1.72 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 3219, 2916, 1652, 1622, 1598, 1404, 1386, 1275 cm^{-1}; MALDIFT-HRMS *m*/*z* 381.1591 ($M+H^+$, $C_{25}H_{21}N_2O_2$ requires 381.1597).

N^2-[(5-Ethynylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (37B). A solution of **37A** (1.52 mg, 3.9 μmol) and DBU (1.18 mg, 7.8 μmol) in 390 μL of CH_3CN was stirred for 1.5 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **37B** (1.20 mg, 87%) as a white solid: $[\alpha]_D^{23}$ +149 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.14 (1H, br s), 8.11 (1H, dd, *J* = 7.7, 1.1 Hz), 7.90 (1H, s), 7.57–7.60 (1H, m), 7.59 (1H, d, *J* = 8.6 Hz), 7.40–7.45 (1H, m), 7.41 (1H, dd, *J* = 8.8, 1.5 Hz), 7.29–7.30 (1H, m), 7.21 (1H, d, *J* = 7.3 Hz), 7.12 (1H, s), 4.71 (1H, dd, *J* = 10.0, 4.9 Hz), 4.63 (1H, d, *J* = 9.8 Hz), 3.51 (1H, s), 3.23 (1H, dt, *J* = 7.7, 4.9 Hz), 1.78 (1H, dd, *J* = 7.7, 4.7 Hz), 1.73 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 2923, 1642, 1619, 1596, 1561, 1515, 1406, 1386, 1270 cm^{-1}; MALDIFT-HRMS *m*/*z* 365.1278 ($M+H^+$, $C_{24}H_{17}N_2O_2$ requires 365.1284).

N^2-{5-[1-(Propynyl)indole-2-yl]carbonyl}-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (38B). A solution of **38A** (1.00 mg, 2.4 μmol) and DBU (0.73 mg, 4.8 μmol) in 240 μL of CH_3CN was stirred for 1 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **38B** (0.72 mg, 79%) as a beige solid: $[\alpha]_D^{23}$ +106 (*c* 0.07, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.05 (1H, br s), 8.10 (1H, dd, *J* = 7.9, 1.1 Hz), 7.76 (1H, s), 7.58 (1H, td, *J* = 7.5, 1.3 Hz), 7.54 (1H, m), 7.43 (1H, td, *J* = 7.5, 1.3 Hz), 7.31 (1H, dd, *J* = 8.5, 1.3 Hz), 7.25 (1H, dd, *J* = 2.1, 0.9 Hz), 7.20 (1H, d, *J* = 7.5 Hz), 7.11 (1H, s), 4.70 (1H, dd, *J* = 10.0, 4.9 Hz), 4.62 (1H, d, *J* = 9.8 Hz), 3.22 (1H, dt, *J* = 8.0, 4.9 Hz), 2.03 (3H, s), 1.79 (1H, dd, *J* = 7.5, 4.1 Hz), 1.72 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 2971, 1651, 1622, 1598, 1519, 1404, 1386, 1269, 1249 cm^{-1}; MALDIFT-HRMS *m*/*z* 378.1362 (M^+, $C_{25}H_{18}N_2O_2$ requires 378.1368).

N^2-[(5-Aminoindole-2-yl)-carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (40B). A sample of **43A** (0.75 mg, 1.5 μmol) was treated with 4 M HCl in EtOAc for 1 h at 25 °C and then the solvent was evaporated. Crude **40A** was dissolved in 300 μL of CH_3CN/THF and treated with DBU (0.69 mg, 2 μmol) for 1 h at 0 °C and then allowed to reach 25 °C over 30 min. The reaction mixture was purified by preparative TLC (10×20 cm, THF) to afford **40B** (0.46 mg, 85%) as a yellow solid: $[\alpha]_D^{23}$ +92 (*c* 0.025, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.77 (1H, br s), 8.10 (1H, dd, *J* = 7.8, 0.9 Hz), 7.48 (1H, td, *J* = 7.6, 1.2 Hz), 7.43 (1H, m), 7.18 (1H, d, *J* = 8.7 Hz), 7.12 (1H, s), 7.06 (1H, d, *J* = 7.8 Hz), 6.87 (1H, d, *J* = 1.8 Hz), 6.75 (1H, d, *J* = 2.3 Hz), 6.71 (1H, dd, *J* = 8.7, 2.3 Hz), 4.53 (1H, dd, *J* = 10.1, 4.6 Hz), 4.49 (1H, d, *J* = 9.6 Hz), 3.03 (1H, dt, *J* = 7.6, 4.6 Hz), 1.66 (1H, dd, *J* = 7.8, 4.1 Hz), 1.56 (1H, t, *J* = 4.6 Hz); IR (film) ν_{max} 3325, 2927, 1652, 1622, 1598, 1520, 1386, 1267, 1246 cm^{-1}; MALDIFT-HRMS *m*/*z* 356.1398 ($M+H^+$, $C_{22}H_{18}N_3O_2$ requires 356.1393).

N^2-[(5-Acetylaminoindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (44B). A solution of **44A** (1.37 mg, 3.2 μmol) and DBU (0.96 mg, 6.3 μmol) in 320 μL of CH_3CN and 320 μL of THF was stirred for 1 h at 0 °C and 2 h from 0 to 25 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **44B** (0.95 mg, 76%) as a pale yellow solid: $[\alpha]_D^{23}$ +90 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.85 (1H, br s), 9.07 (1H, br s), 8.21 (1H, d, *J* = 1.8 Hz), 8.11 (1H, m), 7.58 (1H, ddd, *J* = 8.3, 6.9, 1.0 Hz), 7.49 (1H, d, *J* = 8.8 Hz), 7.43 (1H, ddd, *J* = 8.1, 7.2, 1.1 Hz), 7.40 (1H, dd, *J* = 8.8, 2.2 Hz), 7.21–7.22 (1H, m), 7.20 (1H, d, *J* = 7.7 Hz), 7.12 (1H, s), 4.70 (1H, dd, *J* = 10.1, 5.0 Hz), 4.62 (1H, d, *J* = 9.9 Hz), 3.22 (1H, dt, *J* = 7.7, 4.8 Hz), 2.08 (3H, s), 1.78 (1H, dd, *J* = 7.7, 4.4 Hz), 1.71 (1H, t, *J* = 4.6 Hz); IR (film) ν_{max} 2971, 2930, 2872, 1658, 1652, 1644, 1634, 1622, 1596, 1563, 1558, 1519, 1487, 1463, 1404, 1386, 1316, 1292, 1264, 1251, 1237, 1207, 1127, 1066 cm^{-1}; MALDIFT-HRMS *m*/*z* 398.1512 ($M+H^+$, $C_{24}H_{20}N_3O_3$ requires 398.1499).

N^2-[(5-Propionylaminoindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (45B). A solution of **45A** (0.89 mg, 2 μmol) and DBU (0.60 mg, 4 μmol) in 200 μL of CH_3CN and 200 μL of THF was stirred for 1 h at 0 °C and 2 h from 0 to 25 °C. The reaction mixture was purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **45B** (0.56 mg, 68%) as a pale yellow solid: $[\alpha]_D^{23}$ +56 (*c* 0.05, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.87 (1H, br s), 9.01 (1H, br s), 8.24 (1H, br s), 8.11 (1H, dd, *J* = 7.9, 1.5 Hz), 7.58 (1H, td, *J* = 7.6, 1.6 Hz), 7.50 (1H, d, *J* = 8.6 Hz), 7.43 (1H, td, *J* = 7.6, 1.0 Hz), 7.42 (1H, dd, *J* = 9.0, 2.1

Hz), 7.22–7.23 (1H, m), 7.21 (1H, d, $J=7.7$ Hz), 7.13 (1H, s), 4.71 (1H, dd, $J=10.0$, 4.9 Hz), 4.63 (1H, d, $J=10.3$ Hz), 3.23 (1H, dt, $J=7.6$, 4.9 Hz), 2.38 (2H, q, $J=7.6$ Hz), 1.78 (1H, dd, $J=7.7$, 4.3 Hz), 1.71 (1H, t, $J=4.7$ Hz), 1.17 (3H, t, $J=7.7$ Hz); IR (film) ν_{max} 2921, 1650, 1621, 1590, 1552, 1515, 1386, 1265, 1250, 1236 cm^{-1}; MALDIFT-HRMS m/z 412.1658 ($M+H^+$, $C_{25}H_{22}N_3O_3$ requires 412.1656).

N^2-[(5-Butyrylaminoindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (46B). A solution of **46A** (1.22 mg, 2.6 μmol) and DBU (0.80 mg, 5.3 μmol) in 260 μL of CH_3CN and 260 μL of THF was stirred for 1.5 h at 0 °C and 2 h from 0 to 25 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **46B** (1.10 mg, 99%) as a pale yellow solid: $[\alpha]_D^{23}$ +92 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 10.85 (1H, br s), 9.01 (1H, br s), 8.23 (1H, d, $J=1.7$ Hz), 8.11 (1H, dd, $J=7.9$, 1.1 Hz), 7.58 (1H, td, $J=7.5$, 1.1 Hz), 7.50 (1H, d, $J=9.0$ Hz), 7.41–7.45 (1H, m), 7.42 (1H, dd, $J=9.0$, 2.1 Hz), 7.22 (1H, m), 7.20 (1H, d, $J=7.3$ Hz), 7.12 (1H, s), 4.71 (1H, dd, $J=10.0$, 4.9 Hz), 4.62 (1H, d, $J=10.3$ Hz), 3.22 (1H, dt, $J=7.8$, 4.8 Hz), 2.34 (2H, t, $J=7.3$ Hz), 1.78 (1H, dd, $J=7.9$, 4.5 Hz), 1.72 (2H, sextet, $J=7.4$ Hz), 1.71 (1H, t, $J=4.7$ Hz), 0.97 (3H, t, $J=7.5$ Hz); IR (film) ν_{max} 3292, 2964, 2931, 2873, 1682, 1673, 1667, 1661, 1651, 1644, 1633, 1626, 1622, 1615, 1598, 1563, 1556, 1553, 1548, 1538, 1520, 1515, 1463, 1403, 1386, 1291, 1266, 1252, 1237, 1128 cm^{-1}; MALDIFT-HRMS m/z 426.1819 ($M+H^+$, $C_{26}H_{23}N_3O_3$ requires 426.1812).

N^2-{[5-(*N*-Acetyl-*N*-methyl)aminoindole-2-yl]carbonyl}-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclo propa[*c*]benz[*e*]indol-4-one (47B). A solution of **47A** (1.20 mg, 2.7 μmol) and DBU (0.82 mg, 5.4 μmol) in 270 μL of CH_3CN and 270 μL of THF was stirred for 2 h at 0 °C and 1 h from 0 to 25 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **47B** (1.05 mg, 95%) as a pale yellow solid: $[\alpha]_D^{23}$ +80 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.14 (1H, br s), 8.11 (1H, dd, $J=7.7$, 1.3 Hz), 7.66–7.68 (2H, m), 7.59 (1H, td, $J=7.5$, 1.3 Hz), 7.44 (1H, m), 7.32 (1H, m), 7.21 (1H, d, $J=7.7$ Hz), 7.12 (1H, s), 4.72 (1H, dd, $J=10.1$, 4.9 Hz), 4.64 (1H, d, $J=9.8$ Hz), 3.24 (1H, dt, $J=7.9$, 4.8 Hz), 3.22 (3H, s), 1.80 (1H, dd, $J=7.3$, 4.3 Hz), 1.76 (3H, s), 1.73 (1H, t, $J=4.7$ Hz); IR (film) ν_{max} 2924, 1621, 1598, 1518, 1383, 1273, 1121, 1021, 897, 8.13, 782, 764, 742 cm^{-1}; MALDIFT-HRMS m/z 412.1664 ($M+H^+$, $C_{25}H_{22}N_3O_3$ requires 412.1656).

N^2-[(7-Formylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (53B). A solution of **53A** (940 μg, 2.3 μmol) and DBU (1.9 μL, 12.3 μmol) in 50 μL of CH_3CN was stirred for 2 h at 23 °C and then purified by preparative TLC (10×20 cm, EtOAc) to afford **53B** (0.41 mg, 48%) as a yellow solid: $[\alpha]_D^{23}$ +226 (*c* 0.0023, $CHCl_3$); ^1H NMR ($CDCl_3$, 600 MHz) δ 10.77 (1H, br s), 10.16 (1H, s), 8.25 (1H, d, $J=7.9$ Hz), 7.99 (1H, d, $J=7.9$ Hz), 7.84 (1H, d, $J=7.0$ Hz), 7.55 (1H, t, $J=7.4$ Hz), 7.44 (1H, t, $J=8.4$ Hz), 7.35 (1H, t, $J=7.9$ Hz), 7.18 (1H, m), 7.04 (1H, s), 6.95 (1H, d, $J=7.4$ Hz), 4.50 (2H, m), 4.42 (1H, d, $J=10.0$ Hz), 2.90 (1H, m), 2.23 (1H, t, $J=7.5$ Hz), 1.80 (1H, dd, $J=7.4$, 4.9 Hz), 1.66 (1H, t, $J=4.8$ Hz); MALDIFT-HRMS m/z 369.1242 ($M+H^+$, $C_{23}H_{16}N_2O_3$ requires 369.1234).

N^2-[(5-Acetylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (54B). A solution of **54A** (1.6 mg, 3.8 μmol) in 380 μL of DMF was treated with NaH (0.18 mg, 7.6 μmol) and was stirred for 1.5 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **54B** (1.08 mg, 77%) as a pale yellow solid: $[\alpha]_D^{23}$ +48 (*c* 0.05, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.26 (1H, br s), 8.47 (1H, m), 8.11 (1H, dd, $J=7.9$, 1.1 Hz), 7.97 (1H, dd, $J=8.5$, 2.1 Hz), 7.66 (1H, m), 7.59 (1H, td, $J=7.5$, 1.1 Hz), 7.45 (1H, dd, $J=2.1$, 0.9 Hz), 7.44 (1H, td, $J=7.6$, 1.1 Hz), 7.21 (1H, d, $J=7.3$ Hz), 7.11 (1H, s), 4.74 (1H, dd, $J=10.0$, 4.9 Hz), 4.65 (1H, d, $J=10.3$ Hz), 3.24 (1H, dt, $J=7.7$, 4.9 Hz), 2.63 (3H, s), 1.80 (1H, dd, $J=7.7$, 4.3 Hz), 1.74 (1H, t, $J=4.7$ Hz); IR (film) ν_{max} 2959, 1661, 1651, 1600, 1386, 1359, 1272, 1195, 1127 cm^{-1}; MALDIFT-HRMS m/z 383.1391 ($M+H^+$, $C_{24}H_{19}N_2O_3$ requires 383.1390).

N^2-[(7-Acetylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (55B). A solution of **55A** (1.55 mg, 3.7 μmol) in 370 μL of DMF was treated with NaH (0.18 mg, 7.4 μmol) and was stirred for 1 h at 0 °C. The reaction mixture was purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **55B** (1.08 mg, 77%) as a white solid: $[\alpha]_D^{23}$ +196 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.03 (1H, br s), 8.10–8.12 (2H, m), 8.07 (1H, d, $J=8.1$ Hz), 7.59 (1H, td, $J=7.6$, 1.3 Hz), 7.44 (1H, td, $J=7.6$, 1.1 Hz), 7.39 (1H, d, $J=2.6$ Hz), 7.32 (1H, t, $J=7.7$ Hz), 7.21 (1H, d, $J=8.6$ Hz), 7.15 (1H, s), 4.73 (1H, dd, $J=9.8$, 5.1 Hz), 4.64 (1H, d, $J=9.8$ Hz), 3.24 (1H, dt, $J=8.0$, 4.9 Hz), 2.79 (3H, s), 1.80 (1H, dd, $J=7.7$, 4.3 Hz), 1.76 (1H, t, $J=4.7$ Hz); IR (film) ν_{max} 3434, 2918, 2846, 1661, 1651, 1621, 1594, 1557, 1515, 1386, 1307, 1263, 1123 cm^{-1}; MALDIFT-HRMS m/z 383.1392 ($M+H^+$, $C_{24}H_{19}N_2O_3$ requires 383.1390).

N^2-[(5-Propionylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (56B). A solution of **56A** (1.95 mg, 4.5 μmol) in 450 μL of DMF was treated with NaH (0.22 mg, 9.0 μmol) and was stirred for 1.5 h at 0 °C. The reaction mixture was purified by preparative TLC (10′ 20 cm, CH_2Cl_2/acetone 1:1) to afford **56B** (0.86 mg, 46%) as a pale yellow solid: $[\alpha]_D^{23}$ +120 (*c* 0.1, THF); ^1H NMR (acetone-d_6, 500 MHz) δ 11.27 (1H, br s), 8.48 (1H, d, $J=0.9$ Hz), 8.11 (1H, dd, $J=8.3$, 1.1 Hz), 7.99 (1H, dd, $J=8.5$, 1.7 Hz), 7.66 (1H, m), 7.59 (1H, td, $J=7.6$, 1.4 Hz), 7.44 (1H, dd, $J=2.4$, 1.1 Hz), 7.44 (1H, td, $J=7.6$, 1.1 Hz), 7.21 (1H, d, $J=8.6$ Hz), 7.12 (1H, s), 4.74 (1H, dd, $J=10.0$, 4.9 Hz), 4.65 (1H, d, $J=10.3$ Hz), 3.24 (1H, dt, $J=7.8$, 4.9 Hz), 3.11 (2H, q, $J=7.3$ Hz), 1.80 (1H, dd, $J=7.7$, 4.3 Hz), 1.74 (1H, t, $J=4.7$ Hz), 1.18 (3H, t, $J=7.3$ Hz); IR (film) ν_{max} 2974, 2934, 2868, 1655, 1621, 1599, 1563, 1404, 1388, 1348, 1321, 1290, 1272, 1250, 1180, 1125 cm^{-1}; MALDIFT-HRMS m/z 397.1546 ($M+H^+$, $C_{25}H_{21}N_2O_3$ requires 397.1547).

N^2-[(5-Butyrylindole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (57B). A solution of **57A** (1.92 mg, 4.3 μmol) in 430 μL of DMF was treated with NaH (0.21 mg, 8.6 μmol) and was stirred for 1.5 h at 0 °C. The reaction mixture was then purified by preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **57B** (0.55 mg, 31%) as a pale yellow solid: $[\alpha]_D^{23}$ +96 (*c* 0.1, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.27 (1H, br s), 8.48–8.49 (1H, m), 8.11 (1H, dd, *J* = 7.9, 1.5 Hz), 7.99 (1H, dd, *J* = 8.6, 1.7 Hz), 7.66 (1H, m), 7.59 (1H, ddd, *J* = 8.1, 7.1, 1.3 Hz), 7.45 (1H, dd, *J* = 2.1, 0.9 Hz), 7.44 (1H, td, *J* = 7.6, 1.1 Hz), 7.21 (1H, d, *J* = 8.5 Hz), 7.12 (1H, s), 4.74 (1H, dd, *J* = 10.0, 4.9 Hz), 4.65 (1H, d, *J* = 10.3 Hz), 3.25 (1H, dt, *J* = 7.7, 4.9 Hz), 3.06 (2H, t, *J* = 7.3 Hz), 1.80 (1H, dd, *J* = 7.7, 4.3 Hz), 1.76 (2H, sextet, *J* = 7.3 Hz), 1.74 (1H, t, *J* = 4.7 Hz), 1.00 (3H, t, *J* = 7.5 Hz); IR (film) ν_{max} 2959, 2927, 1655, 1619, 1599, 1405, 1388, 1363, 1341, 1291, 1273, 1128 cm^{-1}; MALDIFT-HRMS *m*/*z* 411.1708 (M + H$^+$, $C_{26}H_{22}N_2O_3$ requires 411.1703).

N^2-[(1,2-Dihydropyrrolo[3,2-*e*]benzofuran-7-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (70B). A solution of **70A** (0.8 mg, 1.9 μmol) and DBU (1.7 mg, 11.5 μmol) in 500 μL of CH_3CN–THF was stirred for 1 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 1 h, and then purified by preparative TLC (10×20 cm, EtOAc/hexane 1:1) to afford **70B** (0.5 mg, 69%) as a beige solid: $[\alpha]_D^{23}$ +90 (*c* 0.07, acetone); ^{1}H NMR (acetone-d_6, 600 MHz) δ 8.10 (1H, d, *J* = 7.9 Hz), 7.58 (1H, t, *J* = 7.5 Hz), 7.43 (1H, t, *J* = 7.9 Hz), 7.36 (1H, d, *J* = 8.8 Hz), 7.20 (1H, d, *J* = 7.5 Hz), 7.11 (2H, m), 6.85 (1H, d, *J* = 9.2 Hz), 4.70 (1H, m), 4.61 (3H, m), 3.39 (1H, t, *J* = 8.8 Hz), 3.21 (1H, m), 1.78 (1H, m), 1.71 (1H, m); MALDIFT-HRMS *m*/*z* 383.1417 (M + H$^+$, $C_{24}H_{18}N_2O_3$ requires 383.1396).

N^2-[(Pyrrolo[3,2-*e*]benzofuran-7-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (71B). A solution of **71A** (0.6 mg, 1.4 μmol) and DBU (1.3 mg, 8.6 μmol) in 500 μL of CH_3CN-THF was stirred for 1 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 1 h, and then purified by preparative TLC (10×20 cm, EtOAc/hexane 1:1) to afford **71B** (0.30 mg, 55%) as a beige solid: $[\alpha]_D^{23}$ +185 (*c* 0.04, acetone); ^{1}H NMR (acetone-d_6, 400 MHz) δ 8.11 (1H, dd, *J* = 6.8, 1.0 Hz), 7.90 (1H, d, *J* = 2.1 Hz), 7.55–7.61 (4H, m), 7.44 (1H, t, *J* = 8.1 Hz), 7.21 (2H, m), 7.15 (1H, s), 4.66–4.77 (2H, m), 3.25 (1H, m), 1.72-1.81 (2H, m); IR (film) ν_{max} 2914, 1647, 1595, 1277, 739; MALDIFT-HRMS *m*/*z* 381.1231 (M + H$^+$, $C_{24}H_{16}N_2O_3$ requires 381.1234).

N^2-[([1,3]Dioxolo[*f*]indole-2-yl)carbonyl]-(8b*R*,9a*S*)-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (75B). A solution of **75A** (1.25 mg, 3.1 μmol) in 310 μL of CH_3CN was treated with DBU (0.93 mg, 6.1 μmol) and then stirred for 1 h at 0 °C. The reaction mixture was allowed to reach 25 °C over 1 h, and then purified by preparative TLC (10×20 cm, THF/hexane 2:1) to afford **75B** (0.90 mg, 77%) as a pale yellow solid: $[\alpha]_D^{23}$ +153 (*c* 0.04, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.81 (1H, br s), 8.10 (1H, dd, *J* = 7.7, 0.9 Hz), 7.57 (1H, m), 7.42 (1H, td, *J* = 7.6, 1.1 Hz), 7.19 (1H, d, *J* = 7.3 Hz), 7.16 (1H, dd, *J* = 2.1, 0.9 Hz), 7.12 (1H, s), 7.05 (1H, s), 7.01 (1H, s), 6.00–6.01 (2H, m), 4.66 (1H, dd, *J* = 10.0, 4.9 Hz), 4.56 (1H, d, *J* = 10.3 Hz), 3.21 (1H, dt, *J* = 7.7, 4.9 Hz), 1.77 (1H, dd, *J* = 7.7, 4.3 Hz), 1.68 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 3321, 2917, 1634, 1594, 1426, 1284, 1262 cm^{-1}; MALDIFT-HRMS *m*/*z* 385.1196 (M + H$^+$, $C_{23}H_{17}N_2O_4$ requires 385.1183).

76B: A solution of **76A** (700 μg, 1.7 μmol) and DBU (1.4 mg, 8.9 μmol) in 60 μL of CH_3CN was stirred for 2 h at 23 °C and then purified by preparative TLC (10×20 cm, THF/hexane 1:1) to afford **76B** (590 μg, 92%) as a yellow solid: $[\alpha]_D^{23}$ +26 (*c* 0.004, CH_2Cl_2); ^{1}H NMR (acetone-d_6, 600 MHz) δ 11.21 (1H, br s), 8.10 (1H, d, *J* = 7.9 Hz), 7.58 (1H, t, *J* = 7.4 Hz), 7.49 (1H, t, *J* = 8.3 Hz), 7.42 (1H, m), 7.25 (1H, s), 7.20 (1H, d, *J* = 7.9 Hz), 7.11 (1H, d, *J* = 7.0 Hz), 7.09 (1H, s), 7.05 (1H, d, *J* = 7.9 Hz), 4.68 (2H, m), 4.58 (1H, d, *J* = 10.0 Hz), 3.21 (1H, m), 3.16 (1H, t, *J* = 7.4 Hz), 3.01 (1H, t, *J* = 7.4 Hz), 2.97 (1H, m), 2.94 (1H, t, *J* = 7.4 Hz), 2.20 (1H, t, *J* = 7.3 Hz), 1.77 (1H, m), 1.70 (1H, dd, *J* = 10.5, 5.3 Hz; MALDIFT-HRMS *m*/*z* 381.1599 (M + H$^+$, $C_{25}H_{20}N_2O_2$ requires 381.1597).

N^2-[(Benz[*e*]indole-2-yl)carbonyl]-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (77B). A solution of **77A** (2.05 mg, 4.8 μmol) and NaH (0.23 mg, 9.6 μmol) in 480 μL of THF was stirred for 1 h at 0 °C and the reaction mixture was separated by preparative TLC (10×20 cm, THF) and (10×20 cm, CH_2Cl_2/acetone 3:1) to afford **77B** (1.50 mg, 80%) as a beige solid: (natural enantiomer) $[\alpha]_D^{23}$ +114 (*c* 0.07, THF); (unnatural enantiomer) $[\alpha]_D^{23}$ −111 (*c* 0.06, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 11.37 (1H, br s), 8.41 (1H, d, *J* = 8.1 Hz), 8.12 (1H, dd, *J* = 7.7, 0.9 Hz), 7.95–8.01 (2H, m), 7.77 (1H, d, *J* = 9.0 Hz), 7.75 (1H, d, *J* = 9.0 Hz), 7.57–7.61 (2H, m), 7.46 (1H, ddd, *J* = 8.0, 6.9, 1.2 Hz), 7.42–7.45 (1H, m), 7.22 (1H, d, *J* = 7.3 Hz), 7.19 (1H, s), 4.82 (1H, dd, *J* = 10.0, 4.9 Hz), 4.75 (1H, d, *J* = 10.3 Hz), 3.26 (1H, dt, *J* = 7.7, 4.9 Hz), 1.80 (1H, dd, *J* = 7.7, 4.7 Hz), 1.74 (1H, t, *J* = 4.7 Hz); IR (film) ν_{max} 2922, 1647, 1623, 1595, 1381, 1289, 1264 cm^{-1}; MALDIFT-HRMS *m*/*z* 391.1454 (M + H$^+$, $C_{26}H_{19}N_2O_2$ requires 391.1441).

N^2-[(Benz[*f*]indole-2-yl)carbonyl]-1,2,9,9a-tetrahydrocyclopropa[*c*]benz[*e*]indol-4-one (78B). A solution of **78A** (1.00 mg, 2.3 μmol) and DBU (0.71 mg, 4.7 μmol) in 240 μL of CH_3CN was stirred for 1 h at 0 °C and the reaction mixture was separated by two consecutive preparative TLC (10×20 cm, CH_2Cl_2/acetone 1:1) to afford **78B** (0.53 mg, 58%) as a yellow solid: (natural enantiomer) $[\alpha]_D^{23}$ +126 (*c* 0.03, THF); (unnatural enantiomer) $[\alpha]_D^{23}$ −136 (*c* 0.025, THF); ^{1}H NMR (acetone-d_6, 500 MHz) δ 10.83 (1H, br s), 8.33 (1H, s), 8.12 (1H, dd, *J* = 7.5, 1.3 Hz), 8.05 (1H, s), 7.97 (1H, d, *J* = 7.7 Hz), 7.94 (1H, d, *J* = 8.8 Hz), 7.59 (1H, td, *J* = 7.5, 1.5 Hz), 7.42–7.46 (1H, m), 7.44 (1H, s), 7.38 (1H, ddd, *J* = 8.4, 6.6, 1.1 Hz), 7.31 (1H, ddd, *J* = 8.3, 6.8, 1.3 Hz), 7.22 (1H, d, *J* = 7.3 Hz), 7.13 (1H, s), 4.77 (1H, dd, *J* = 10.0, 5.0 Hz), 4.69 (1H, d, *J* = 9.9 Hz), 3.25 (1H, dt, *J* = 7.7, 5.0 Hz), 1.81 (1H, dd, *J* = 7.7, 4.4 Hz), 1.77 (1H, t, *J* = 4.6 Hz); IR (film) ν_{max} 2919, 1645, 1622, 1597, 1406, 1372, 1303, 1270, 1243 cm^{-1}; MALDIFT-HRMS *m*/*z* 391.1430 (M + H$^+$, $C_{26}H_{19}N_2O_2$ requires 391.1441).

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References and Notes

1. Chidester, C. G.; Krueger, W. C.; Mizsak, S. A.; Duchamp, D. J.; Martin, D. G. *J. Am. Chem. Soc.* **1981**, *103*, 7629.
2. Takahashi, I.; Takahashi, K.; Ichimura, M.; Morimoto, M.; Asano, K.; Kawamoto, I.; Tomita, F.; Nakano, H. *J. Antibiot.* **1988**, *41*, 1915.
3. Ichimura, M.; Ogawa, T.; Takahashi, K.; Kobayashi, E.; Kawamoto, I.; Yasuzawa, T.; Takahashi, I.; Nakano, H. *J. Antibiot.* **1990**, *43*, 1037.
4. Yasuzawa, T.; Muroi, K.; Ichimura, M.; Takahashi, I.; Ogawa, T.; Takahashi, K.; Sano, H.; Saitoh, Y. *Chem. Pharm. Bull.* **1995**, *43*, 378.
5. Boger, D. L.; Johnson, D. S. *Angew. Chem., Int. Ed. Engl.* **1996**, *35*, 1438. For earlier reviews, see: Boger, D. L. *Acc. Chem. Res.* **1995**, *28*, 20. Boger, D. L.; Johnson, D. S. *Proc. Natl. Acad. Sci. U.S.A.* **1995**, *92*, 3642. Boger, D. L. *Chemtracts: Org. Chem.* **1991**, *4*, 329. Synthesis: Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Goldberg, J. *Chem. Rev.* **1997**, *97*, 787.
6. Boger, D. L.; Johnson, D. S.; Yun, W.; Tarby, C. M. *Bioorg. Med. Chem.* **1994**, *2*, 115. Boger, D. L.; Coleman, R. S.; Invergo, B. J.; Sakya, S. M.; Ishizaki, T.; Munk, S. A.; Zarrinmayeh, H.; Kitos, P. A.; Thompson, S. C. *J. Am. Chem. Soc.* **1990**, *112*, 4623.
7. Boger, D. L.; Ishizaki, T.; Zarrinmayeh, H.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1990**, *112*, 8961. Boger, D. L.; Ishizaki, T.; Zarrinmayeh, H. *J. Am. Chem. Soc.* **1991**, *113*, 6645.
8. Boger, D. L.; Johnson, D. S.; Yun, W. *J. Am. Chem. Soc.* **1994**, *116*, 1635.
9. Warpehoski, M. A.; Hurley, L. H. *Chem. Res. Toxicol.* **1988**, *1*, 315.
10. Sugiyama, H.; Hosoda, M.; Saito, I.; Asai, A.; Saito, H. *Tetrahedron Lett.* **1990**, *31*, 7197.
11. Boger, D. L.; Garbaccio, R. M. *Bioorg. Med. Chem.* **1999**, *5*, 263.
12. Boger, D. L.; Garbaccio, R. M. *Acc. Chem. Res.* **1999**, *32*, 1043.
13. Wolkenberg, S. E.; Boger, D. L. *Chem. Rev.* **2002**, *102*, 2477.
14. Boger, D. L.; Bollinger, B.; Hertzog, D. L.; Johnson, D. S.; Cai, H.; Mesini, P.; Garbaccio, R. M.; Jin, Q.; Kitos, P. A. *J. Am. Chem. Soc.* **1997**, *119*, 4987.
15. Boger, D. L.; Hertzog, D. L.; Bollinger, B.; Johnson, D. S.; Cai, H.; Goldberg, J.; Turnbull, P. *J. Am. Chem. Soc.* **1997**, *119*, 4977.
16. Ambroise, Y.; Boger, D. L. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 303.
17. For an alternative source of catalysis, see: Ellis, D. A.; Wolkenberg, S. E.; Boger, D. L. *J. Am. Chem. Soc.* **2001**, *123*, 9299. Boger, D. L.; Wolkenberg, S. E.; Boyce, C. W. *J. Am. Chem. Soc.* **2000**, *122*, 6325. Boger, D. L.; Boyce, C. W. *J. Org. Chem.* **2000**, *65*, 4088. For an alternative source of activation, see: Boger, D. L.; Garbaccio, R. M. *J. Org. Chem.* **1999**, *64*, 8350.
18. Boger, D. L.; Schmitt, H.; Fink, B. E.; Hedrick, M. P. *J. Org. Chem.* **2001**, *66*, 6654.
19. Boger, D. L.; Stauffer, F.; Hedrick, M. P. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 2021.
20. Boger, D. L.; Bollinger, B.; Johnson, D. S. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2207.
21. Boger, D. L.; Han, N.; Tarby, C. M.; Boyce, C. W.; Cai, H.; Jin, Q.; Kitos, P. A. *J. Org. Chem.* **1996**, *61*, 4894.
22. Boger, D. L.; McKie, J. A.; Cai, H.; Cacciari, B.; Baraldi, P. G. *J. Org. Chem.* **1996**, *61*, 1710.
23. Boger, D. L.; Santillán, A.; Searcey, M.; Brunette, S. R.; Wolkenberg, S. E.; Hedrick, M. P.; Jin, Q. *J. Org. Chem.* **2000**, *65*, 4101.
24. Boger, D. L.; Hughes, T. V.; Hedrick, M. P. *J. Org. Chem.* **2001**, *66*, 2207.
25. Eis, P. S.; Smith, J. A.; Rydzewski, J. M.; Case, D. A.; Boger, D. L.; Chazin, W. J. *J. Mol. Biol.* **1997**, *272*, 237.
26. Schnell, J. R.; Ketchem, R. R.; Boger, D. L.; Chazin, W. J. *J. Am. Chem. Soc.* **1999**, *121*, 5645.
27. Smith, J. A.; Bifulco, G.; Case, D. A.; Boger, D. L.; Gomez-Paloma, L.; Chazin, W. J. *J. Mol. Biol.* **2000**, *300*, 1195.
28. Warpehoski, M. A.; Gebhard, I.; Kelly, R. C.; Krueger, W. C.; Li, L. H.; McGovren, J. P.; Prairie, M. D.; Wicnienski, N.; Wierenga, W. *J. Med. Chem.* **1988**, *31*, 590.
29. Atwell, G. J.; Milbank, J. J. B.; Wilson, W. R.; Hogg, A.; Denny, W. A. *J. Med. Chem.* **1999**, *42*, 3400.
30. Boger, D. L.; Yun, W.; Cai, H.; Han, N. *Bioorg. Med. Chem.* **1995**, *3*, 761.
31. Boger, D. L.; Ishizaki, T.; Wysocki, R. J.; Munk, S. A.; Kitos, P. A.; Suntornwat, O. *J. Am. Chem. Soc.* **1989**, *111*, 6461. Boger, D. L.; Ishizaki, T.; Kitos, P. A.; Suntorwat, O. *J. Org. Chem.* **1990**, *55*, 5823. Boger, D. L.; Ishizaki, T. *Tetrahedron Lett.* **1990**, *31*, 793. Boger, D. L.; Ishizaki, T.; Sakya, S. A.; Munk, S. A.; Kitos, P. A.; Jin, Q.; Besterman, J. M. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 115.
32. Boger, D. L.; Munk, S. A.; Ishizaki, T. *J. Am. Chem. Soc.* **1991**, *113*, 2779.
33. Drost, K. J.; Cava, M. P. *J. Org. Chem.* **1991**, *56*, 2240.
34. Boger, D. L.; Munk, S. A. *J. Am. Chem. Soc.* **1992**, *114*, 5487.
35. Boger, D. L.; Yun, W.; Teegarden, B. R. *J. Org. Chem.* **1992**, *57*, 2873. Boger, D. L.; McKie, J. A. *J. Org. Chem.* **1995**, *60*, 1271. Boger, D. L.; McKie, J. A.; Boyce, C. W. *Synlett* **1997**, 515. Boger, D. L.; Boyce, C. W.; Garbaccio, R. M. *Tetrahedron Lett.* **1998**, *39*, 2227.
36. Aristoff, P. A.; Johnson, P. D. *J. Org. Chem.* **1992**, *57*, 6234. Aristoff, P. A.; Johnson, P. D.; Sun, D.; Hurley, L. H. *J. Med. Chem.* **1993**, *36*, 1956.
37. Boger, D. L.; Yun, W. *J. Am. Chem. Soc.* **1994**, *116*, 7996.
38. Boger, D. L.; Yun, W.; Han, N. *Bioorg. Med. Chem.* **1995**, *3*, 1429.
39. Boger, D. L.; Yun, W.; Han, N.; Johnson, D. S. *Bioorg. Med. Chem.* **1995**, *3*, 611. Boger, D. L.; Yun, W.; Cai, H.; Han, N. *Bioorg. Med. Chem.* **1995**, *3*, 761. Boger, D. L.; Han, N. *Bioorg. Med. Chem.* **1997**, *5*, 233.
40. C3-substituted CBI analogues: Boger, D. L.; Brunette, S. R.; Garbaccio, R. M. *J. Org. Chem.* **2001**, *66*, 5163. Iso-CBI: Boger, D. L.; Garbaccio, R. M.; Jin, Q. *J. Org. Chem.* **1997**, *62*, 8875. C_2BI: Boger, D. L.; Palanki, M. S. S. *J. Am. Chem. Soc.* **1992**, *114*, 9318. Boger, D. L.; Johnson, D. L.; Palanki, M. S. S.; Kitos, P. A.; Chang, J.; Dowell, P. *Bioorg. Med. Chem.* **1993**, *1*, 27. CBQ: Boger, D. L.; Mesini, P. *J. Am. Chem. Soc.* **1995**, *117*, 11647. Boger, D. L.; Mesini, P. *J. Am. Chem. Soc.* **1994**, *116*, 11335. CNA: Boger, D. L.; Turnbull, P. *J. Org. Chem.* **1997**, *62*, 5849. CBI: Boger, D. L.; Turnbull, P. *J. Org. Chem.* **1998**, *63*, 8004.
41. Boger, D. L.; Boyce, C. W.; Garbaccio, R. M.; Searcey, M.; Jin, Q. *Synthesis* **1999**, 1505.

42. Boger, D. L.; Santillan, A.; Searcey, M.; Jin, Q. *J. Am. Chem. Soc.* **1998**, *120*, 11554. Boger, D. L.; Santillan, A.; Searcey, M.; Jin, Q. *J. Org. Chem.* **1999**, *64*, 5241.
43. Boger, D. L.; Garbaccio, R. M. *J. Org. Chem.* **1999**, *64*, 5666. Boger, D. L.; Boyce, C. W.; Johnson, D. S. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 233.
44. Chang, A. Y.; Dervan, P. B. *J. Am. Chem. Soc.* **2000**, *122*, 4856.
45. Kumar, R.; Lown, J. W. *Org. Lett.* **2002**, *4*, 1851.
46. Reddy, B. S. P.; Sharma, S. K.; Lown, J. W. *Curr. Med. Chem.* **2001**, *8*, 475.
47. Denny, W. A. *Curr. Med. Chem.* **2001**, *8*, 533.
48. Jia, G. F.; Lown, J. W. *Bioorg. Med. Chem.* **2000**, *8*, 1607.
49. Jia, G. F.; Iida, H.; Lown, J. W. *Synlett* **2000**, 603.
50. Wang, Y. Q.; Yuan, H. L.; Ye, W. Q.; Wright, S. C.; Wang, H.; Larrick, J. W. *J. Med. Chem.* **2000**, *43*, 1541.
51. Jia, G. F.; Iida, H.; Lown, J. W. *Heterocyclic Commun.* **1999**, *5*, 497.
52. Hay, M. P.; Sykes, B. M.; Denny, W. A.; Wilson, W. R. *Brit. J. Cancer.* **1999**, *Suppl 2*, P65.
53. Hay, M. P.; Sykes, B. M.; Denny, W. A.; Wilson, W. R. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 2237.
54. Gieseg, M. A.; Matejovic, J.; Denny, W. A. *Anti-Cancer Drug Des.* **1999**, *14*, 77.
55. Jia, G. F.; Iida, H.; Lown, J. W. *Heterocyclic Commun.* **1998**, *4*, 557.
56. Jia, G. F.; Iida, H.; Lown, J. W. *Chem. Commun.* **1999**, 119.
57. Atwell, G. J.; Tercel, M.; Boyd, M.; Wilson, W. R.; Denny, W. A. *J. Org. Chem.* **1998**, *63*, 9414.
58. Atwell, G. J.; Wilson, W. R.; Denny, W. A. *Bioorg. Med. Chem. Lett.* **1997**, *7*, 1493.
59. Chari, R. V. J.; Jackel, K. A.; Bourret, L. A.; Derr, S. M.; Tadayoni, B. M.; Mattocks, K. M.; Shah, S. A.; Liu, C.; Blättler, W. A.; Goldmacher, V. S. *Cancer Res.* **1995**, *55*, 4079.
60. Wang, Y.; Wright, S. C.; Larrick, J. L. *U.S. Patent* **1998**, 5843937.
61. Hemetsberger, H.; Knittel, D.; Weidmann, H. *Montash. Chem.* **1969**, *100*, 1599.
62. Wang, Y.; Gupta, R.; Huang, L.; Luo, W.; Lown, J. W. *Anti-Cancer Drug Des.* **1996**, *11*, 15.
63. Boger, D. L.; Yun, W. *J. Am. Chem. Soc.* **1994**, *116*, 5523.
64. Boger, D. L.; Munk, S. A.; Zarrinmayeh, H.; Ishizaki, T.; Haught, J.; Bina, M. *Tetrahedron* **1991**, *47*, 2661.
65. The extent of DNA alkylation is measured by the disappearance of full length DNA (top band) and not by relative intensities of the alkylation cleavage band (bottom band). A second short alkylation cleavage band immediately adjacent to the 5′ end label is observed (only at the higher compound concentrations) which results from a second, subsequent alkylation reaction. For details, see reference 37.
66. Details of the preparation and characterization of all non-commercially available and new indole-2-carboxylic acids are available and can be provided upon request.