Synthesis of Indole Derivatives by Cyclization of Oxo *N*-Acyliminium Ions

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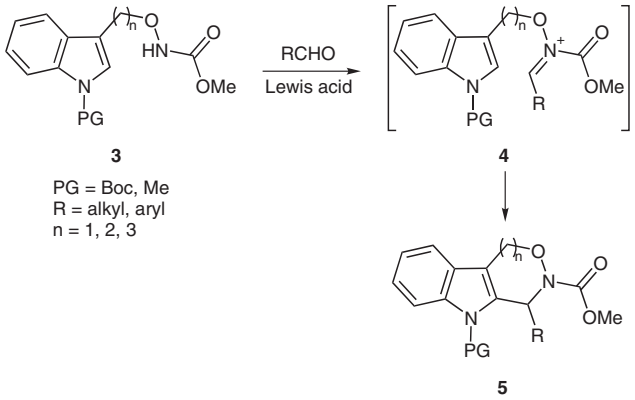
Abstract: The reaction of indole-containing hydroxamates with aldehydes in the presence of Lewis acid leads to oxo *N*-acyliminium ions, which cyclize to the corresponding N–O fused [1,2]oxazino[4,5-*b*]indole, [1,2]oxazepino[4,5-*b*]indole, and [1,2]oxazocino[4,5-*b*]indole derivatives in good yields.

Key words: oxo *N*-acyliminium ions, cyclization, hydroxamate, indole, Lewis acid

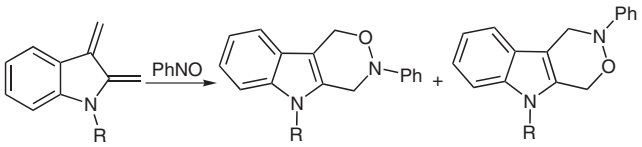
N-Acyliminium ions **1** (Figure 1) are important, reactive species in organic synthesis for the construction of carbon–carbon and carbon–heteroatom bonds.[1] Indeed, the well-known Pictet–Spengler[2] reaction is an excellent and extensively exploited method for the synthesis of tetrahydroisoquinolines (THIQ) and tetrahydrocarbolines, which are present in numerous natural products and synthetic medical compounds possessing biological activities. To the best of our knowledge, the cyclization of oxo *N*-acyliminium ions **2** has received less attention.[3] In attempting to extend the *N*-acyliminium ion chemistry, we observed and previously communicated that excellent yields of 1*H*-2,3-benzoxazines could be obtained from the Lewis acid catalyzed reaction of hydroxamates with aldehydes.[4] Due to the electronic feature of oxygen atom, the N–O fused 1*H*-2,3-benzoxazines, which appear to be structurally similar to THIQs, can dramatically change the electronic property of the nitrogen atom in the molecule, and may present interesting physical properties.[5]

Figure 1 *N*-Acyliminium ions **1** and oxo *N*-acyliminium ions **2**

In this context, we decided to extend our research focusing on developing a new approach to the preparation of N–O fused indole derivatives **5**, such as [1,2]oxazino[4,5-*b*]indoles (n = 1), [1,2]oxazepino[4,5-*b*]indoles (n = 2), and [1,2]oxazocino[4,5-*b*]indoles (n = 3), via cyclization of oxo *N*-acyliminium ions **4** (Scheme 1). Among these compounds, the [1,2]oxazino[4,5-*b*]indoles can be prepared from indole-2,3-quinodimethanes by Diels–Alder reaction with nitrosobenzene, but two isomers were obtained in this process (Scheme 2).[6]



Scheme 1



Scheme 2

Many polycyclic heteroarenes containing the indole nucleus exhibit important pharmacological properties and thus constitute synthetically interesting target molecules.[6,7] Therefore, we considered that the design of a novel access to [1,2]oxazino[4,5-*b*]indole series by indole-based oxo *N*-acyliminium ion cyclization would be desirable. The required hydroxamates **3** for this approach were conveniently prepared according to the reported process from commercial materials.[6,8]

Initial studies were directed toward finding a general set of reaction conditions that could be applied to a wide variety of indole-fused hydroxamates and aldehydes. Since the reaction conditions such as TMSCl/NaI in MeCN can promote the generation of 1*H*-2,3-benzoxazines successfully,[4] we turned our attention to optimizing that process. Firstly, the reaction of **3a** with benzaldehyde was carried out with three equivalents of TMSCl/NaI at –40 °C, and the cyclized product **5a** was obtained in 94% yield (Table 1, entry 1). Although the *N*-Boc group is sensitive to high acidity,[9] prolonged exposure of **5a** to these conditions did not promote the deprotection process.

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Table 1 Reaction of Hydroxamates **3** with Aldehydes in the Presence of Lewis Acid (Scheme 1)[a]

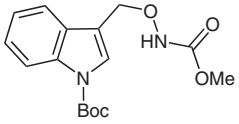
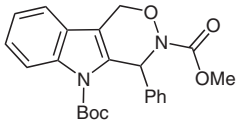
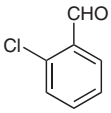
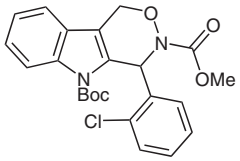
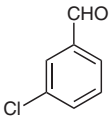
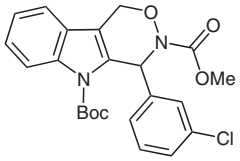
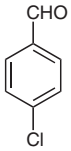
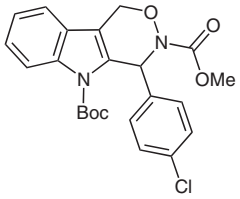
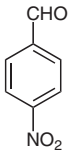
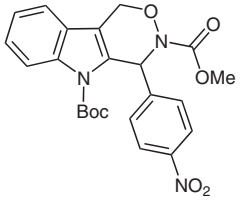
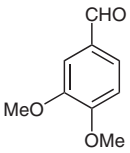
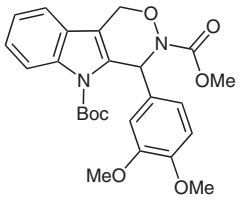
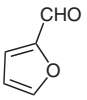
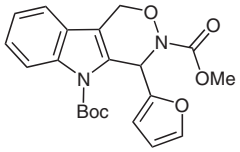
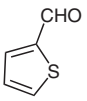
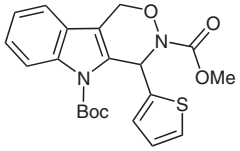
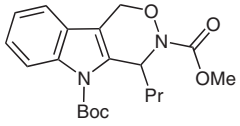
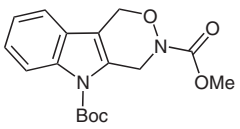
Entry	Hydroxamate	Aldehyde	Product	Yield (%)[b]
1	**3a** 	PhCHO	**5a** 	94
2	**3a**		**5b** 	82
3	**3a**		**5c** 	97
4	**3a**		**5d** 	95
5	**3a**		**5e** 	94
6	**3a**		**5f** 	99
7	**3a**		**5g** 	84
8	**3a**		**5h** 	85
9	**3a**	*n*-PrCHO	**5i** 	65
10	**3a**	$(HCHO)_n$	**5j** 	54

Table 1 Reaction of Hydroxamates **3** with Aldehydes in the Presence of Lewis Acid (Scheme 1)[a] (continued)

Entry	Hydroxamate	Aldehyde	Product	Yield (%)[b]
11	**3a**	*i*-PrCHO	**5k**	79
12	**3b**	PhCHO	**5l**	47
13	**3c**	PhCHO	**5m**	73
14	**3d**	PhCHO	**5n**	27

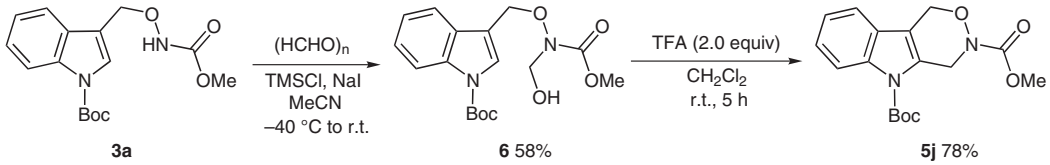
[a] Reaction conditions: see experimental section.
[b] Isolated yield.

We subjected the hydroxamates **3** and a wide range of aldehydes to this process to determine its scope and limitations. As indicated in Table 1, this approach to N–O fused indole derivatives **5** is very versatile. A wide variety of aromatic aldehydes have been reacted successfully (entries 1–8). We have been able to obtain high yields using benzaldehydes with electron-withdrawing or electron-donating groups on benzene ring. However, when the hindered 2-chlorobenzaldehyde was employed, a slightly lower yield of **5b** was observed (entry 2). It is particularly noteworthy that **3a** undergoes this cyclization process with furan-2-carbaldehyde and thiophen-2-carbaldehyde to afford the corresponding **5g** and **5h** in good yields (entries 7 and 8).

When aliphatic aldehydes were employed, the results were generally inferior to those of aromatic aldehydes. The reaction of **3a** with *n*-butyraldehyde dramatically lowers the yield of **5i** (entry 9). The reaction proceeded well when paraformaldehyde was employed, but only the α-hydroxy intermediate **6** was obtained in 58% yield (Scheme 3), which can be cyclized to the desired compound **5j** in 78% yield by treatment with TFA. Reasonable yield of **5j** was also obtained by the reaction of **3a** with paraformaldehyde using just TFA at room temperature (entry 10). However, complicated result was obtained when hindered isobutyraldehyde was used, and no desired product was isolated. $BF_3{\cdot}Et_2O$ was found to efficiently promote the reaction, and a deprotected compound **5k** was obtained in 79% yield (entry 11).

Next, in order to investigate the scope of the presented methodology, the hydroxamates **3b**, **3c**, and **3d** were prepared with different side chains. Formation of seven-membered rings in arene cyclization can be troublesome,[10] but the cyclized product **5l** was readily obtained from **3b** in a moderate 47% yield after treatment with TMSCl/NaI (entry 12). Given the higher reactivity of *N*-methyl indole (compared to *N*-Boc indole), dramatic improvement in yield was observed when the reaction of **3c** with benzaldehyde was carried out in the same conditions, and the corresponding **5m** was isolated in 73% yield. In this approach, it is possible for the cyclization of **3d** with benzaldehyde to produce a new eight-membered ring **5n** in 27% yield (entry 14).

In summary, a synthesis of diverse N–O fused indole derivatives **5** via the cyclization of oxo *N*-acyliminium ions methodology has been developed. The TMSCl/NaI system proved to be efficient for the cyclization of hydroxamates **3** and aromatic aldehydes regardless of the



Scheme 3

substitution on benzene ring. Aliphatic aldehydes can be used in the cyclization in the presence of $BF_3{\cdot}Et_2O$. A series of novel [1,2]oxazino[4,5-*b*]indoles (**5a**–**k**, n = 1), [1,2]oxazepino[4,5-*b*]indoles (**5l**, **5m**, n = 2), and [1,2]oxazocino[4,5-*b*]indoles (**5n**, n = 3) were obtained by application of this procedure.

MeCN and CH_2Cl_2 were distilled from CaH_2. TMSCl, $BF_3{\cdot}Et_2O$, TFA and all aldehydes were commercially available. All the hydroxamates **3** were prepared according to the literature. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) spectra were recorded on Varian Inova 500 MHz instrument. Melting point was not corrected. High-resolution mass spectra (HRMS) were recorded on a Q-TOF micro (water) apparatus.

Cyclization of Hydroxamates 3 and Aldehydes in the Presence of TMSCl/NaI; General Procedure

To a solution of hydroxamate **3** (500 mg) in anhyd MeCN (10 mL per 1.0 mmol of **3**) was added the appropriate aldehyde (1.5 equiv) in one portion followed by NaI (3.0 equiv). The resulting mixture was chilled to –40 °C and TMSCl (3.0 equiv) was added dropwise under N_2. The mixture was allowed to warm to r.t. slowly and treated with aq 20% $NaHSO_3$ (20 mL) and extracted with EtOAc (3 × 20 mL). The organic phases were collected, washed with aq sat. $NaHCO_3$ (20 mL) and brine (20 mL), dried (Na_2SO_4), and evaporated under reduced pressure. The residue was chromatographed on a silica gel column to afford the desired N–O fused indole derivatives **5**.

5-*tert*-Butyl 3-Methyl 4-Phenyl-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5a)

Colorless solid; mp 121–123 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 3.86 (s, 3 H), 5.06, 5.38 (AB, *J* = 13.5 Hz, 2 H), 6.82 (s, 1 H), 7.22–7.24 (m, 2 H), 7.27–7.30 (m, 4 H), 7.36 (dd, *J* = 8.5, 1.0 Hz, 1 H), 7.40 (d, *J* = 8.5 Hz, 1 H), 8.26 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.74, 53.43, 58.09, 67.19, 84.70, 114.50, 116.01, 117.96, 123.16, 124.96, 125.89, 128.05, 128.23, 128.33, 130.38, 136.24, 138.59, 149.31, 155.59.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{24}N_2O_5$ + Na [M + Na]$^+$: 431.1577; found: 431.1586.

5-*tert*-Butyl 3-Methyl 4-(2-Chlorophenyl)-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5b)

Colorless solid; mp 88–91 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.37 (s, 9 H), 3.87 (s, 3 H), 5.99, 5.45 (AB, *J* = 13.3 Hz, 2 H), 6.78 (dd, *J* = 7.5, 1.5 Hz, 1 H), 6.99 (br, 1 H), 7.10 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.25 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.29 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.39 (td, *J* = 8.0, 1.5 Hz, 2 H), 7.44 (dd, *J* = 8.0, 1.0 Hz, 1 H), 8.29 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.79, 53.68, 56.33, 66.34, 84.82, 114.78, 116.17, 117.98, 123.25, 125.24, 125.85, 126.43, 129.49, 129.99, 130.02, 134.46, 135.87, 136.30, 149.29, 156.00.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}ClN_2O_5$ + Na [M + Na]$^+$: 465.1188; found: 465.1188.

5-*tert*-Butyl 3-Methyl 4-(3-Chlorophenyl)-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5c)

Colorless solid; mp 181–183 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 3.86 (s, 3 H), 5.07, 5.38 (AB, *J* = 14.0 Hz, 2 H), 6.78 (s, 1 H), 7.15 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.23 (td, *J* = 7.5, 0.5 Hz, 1 H), 7.25–7.26 (m, 2 H), 7.29 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.37 (dd, *J* = 8.5, 1.0 Hz, 1 H), 7.40 (td, *J* = 7.5, 1.5 Hz, 1 H), 8.23 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.85, 53.56, 57.62, 67.22, 84.94, 114.69, 116.10, 118.09, 123.26, 125.16, 125.81, 126.64, 128.25, 128.51, 129.46, 129.83, 134.16, 136.14, 140.60, 149.26, 155.47.

5-*tert*-Butyl 3-Methyl 4-(4-Chlorophenyl)-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5d)

Colorless solid; mp 76–78 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.43 (s, 9 H), 3.85 (s, 3 H), 5.05, 5.36 (AB, *J* = 13.5 Hz, 2 H), 6.79 (s, 1 H), 7.19–7.20 (m, 2 H), 7.25–7.30 (m, 3 H), 7.35–7.40 (m, 2 H), 8.21 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.87, 53.51, 57.54, 67.25, 84.87, 114.64, 116.06, 118.06, 123.25, 125.11, 125.82, 128.38, 129.78, 130.15, 133.93, 136.11, 137.16, 149.23, 155.49.

5-*tert*-Butyl 3-Methyl 4-(4-Nitrophenyl)-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5e)

Pale yellow solid; mp 100–102 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.46 (s, 9 H), 3.87 (s, 3 H), 5.09, 5.41 (AB, *J* = 14.0 Hz, 2 H), 6.89 (s, 1 H), 7.31 (td, *J* = 7.5, 0.5 Hz, 1 H), 7.30 (td, *J* = 7.5, 1.5 Hz, 1 H), 7.42 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.46–7.48 (m, 2 H), 7.14–7.18 (m, 3 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.95, 53.71, 57.51, 67.36, 85.17, 114.97, 116.14, 118.26, 123.42, 125.37, 125.77, 129.42, 129.54, 135.92, 145.69, 147.62, 149.24, 155.39.

HRMS (ESI): *m*/*z* calcd for $C_{23}H_{23}N_3O_7$ + Na [M + Na]$^+$: 476.1428; found: 476.1425.

5-*tert*-Butyl 3-Methyl 4-(3,4-Dimethoxyphenyl)-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5f)

Colorless solid; mp 144–146 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.42 (s, 9 H), 3.82 (s, 3 H), 3.83 (s, 3 H), 3.86 (s, 3 H), 5.06, 5.37 (AB, *J* = 13.5 Hz, 2 H), 6.62 (dd, *J* = 8.0, 2.0 Hz, 1 H), 6.73 (d, *J* = 8.0 Hz, 1 H), 6.77 (s, 1 H), 6.93 (d, *J* = 2.0 Hz, 1 H), 7.28 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.36 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.39 (td, *J* = 7.5, 1.0 Hz, 1 H), 8.25 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.84, 53.44, 55.86, 55.98, 57.92, 67.18, 84.64, 110.52, 111.79, 114.35, 115.99, 117.97, 120.66, 123.14, 124.95, 125.86, 130.64, 131.20, 136.21, 148.86, 148.95, 149.32, 155.71.

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{28}N_2O_7$ + Na [M + Na]$^+$: 491.1789; found: 491.1797.

5-*tert*-Butyl 3-Methyl 4-(Furan-2-yl)-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5g)

Colorless solid; mp 132–134 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.48 (s, 9 H), 3.88 (s, 3 H), 5.06 (d, *J* = 13.5 Hz, 1 H), 5.35 (dd, *J* = 13.5, 1.0 Hz, 1 H), 6.02 (td, *J* = 7.5, 1.0 Hz, 1 H), 6.30 (ddd, *J* = 3.5, 2.0, 0.5 Hz, 1 H), 6.80 (s, 1 H), 7.28 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.36–7.39 (m, 2 H), 7.40 (dd, *J* = 2.0, 1.0 Hz, 1 H), 8.28 (d, *J* = 8.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.79, 52.96, 53.62, 67.14, 84.77, 109.49, 110.52, 114.61, 115.98, 118.04, 123.18, 125.18, 125.72, 128.53, 136.30, 142.24, 149.22, 151.21, 155.61.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{22}N_2O_6$ + Na [M + Na]$^+$: 421.1370; found: 421.1371.

5-*tert*-Butyl 3-Methyl 4-(Thiophen-2-yl)-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5h)

Colorless solid; mp 102–104 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.49 (s, 9 H), 3.87 (s, 3 H), 5.10 (d, *J* = 13.5 Hz, 1 H), 5.36 (dd, *J* = 13.5, 1.5 Hz, 1 H), 6.87 (dd, *J* = 3.5, 1.0 Hz, 1 H), 6.90 (dd, *J* = 5.0, 3.5 Hz, 1 H), 6.96 (s, 1 H), 7.23 (dd, *J* = 5.0, 1.5 Hz, 1 H), 7.28 (td, *J* = 7.5, 1.0 Hz, 1 H), 7.36 (dd, *J* = 7.5, 1.5 Hz, 1 H), 7.38–7.40 (m, 1 H), 8.22 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 27.84, 53.53, 54.31, 67.45, 84.83, 114.32, 115.99, 118.15, 123.17, 125.12, 125.68, 126.32, 127.23, 130.91, 136.19, 141.00, 149.28, 155.42.

HRMS (ESI): *m*/*z* calcd for $C_{21}H_{22}N_2O_5S$ + Na [M + Na]$^+$: 437.1142; found: 437.1147.

5-*tert*-Butyl 3-Methyl 4-Propyl-[1,2]oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5i)
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 0.98 (t, *J* = 7.5 Hz, 3 H), 1.52–1.64 (m, 2 H), 1.71 (s, 9 H), 1.88–1.97 (m, 2 H), 3.81 (s, 3 H), 4.95 (d, *J* = 13.5 Hz, 1 H), 5.31 (br, 1 H), 5.62 (br, 1 H), 7.22 (td, *J* = 7.0, 1.0 Hz, 1 H), 7.28–7.32 (m, 2 H), 8.14 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 13.84, 17.90, 28.24, 35.22, 53.27, 55.70, 66.74, 84.53, 112.06, 115.98, 117.73, 123.02, 124.51, 126.25, 134.14, 135.77, 149.69, 156.27.

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{27}N_2O_5$ [M + H]$^+$: 375.1914; found: 375.1928.

5-*tert*-Butyl 3-Methyl [1,2]Oxazino[4,5-*b*]indole-3,5(1*H*,4*H*)-dicarboxylate (5j)
To a solution of hydroxamate **3a** (500 mg, 1.56 mmol) in anhyd CH_2Cl_2 (20 mL) was added paraformaldehyde (70 mg, 2.33 mmol) in one portion. TFA (0.24 mL, 3.12 mmol) was added dropwise at r.t. After stirring for 10 h, the solvent was evaporated under reduced pressure and the residue was chromatographed on silica gel column to afford **5j** as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.69 (s, 9 H), 3.84 (s, 3 H), 5.05 (s, 2 H), 5.12 (t, *J* = 1.5 Hz, 2 H), 7.23 (td, *J* = 7.0, 1.0 Hz, 1 H), 7.30–7.33 (m, 2 H), 8.15 (d, *J* = 8.0 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.24, 46.38, 53.45, 67.30, 84.67, 113.43, 115.70, 117.71, 123.04, 124.49, 126.28, 129.44, 135.60, 149.77, 156.22.

HRMS (ESI): *m*/*z* calcd for $C_{17}H_{20}N_2O_5$ + Na [M + Na]$^+$: 355.1264; found: 355.1273.

Methyl 4-Isopropyl-[1,2]oxazino[4,5-*b*]indole-3(1*H*,4*H*,5*H*)-carboxylate (5k)
To a solution of hydroxamate **3a** (500 mg, 1.56 mmol) in anhyd CH_2Cl_2 (20 mL) was added isobutyraldehyde (0.21 mL, 2.34 mmol) in one portion. The resulting mixture was cooled to –78 °C and $BF_3{\cdot}OEt_2$ (0.4 mL, 3.12 mmol) was added dropwise under N_2. The mixture was allowed to warm to r.t. slowly and quenched with Et_3N (0.5 mL). The solvent was evaporated under reduce pressure and the residue was chromatographed on silica gel column to afford **5k** as a colorless solid; mp 202–204 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.03 (d, *J* = 6.5 Hz, 3 H), 1.12 (d, *J* = 7.0 Hz, 3 H), 2.26 (td, *J* = 13.5, 6.5 Hz, 1 H), 3.82 (s, 3 H), 4.98 (br, 1 H), 5.02 (d, *J* = 13.5 Hz, 1 H), 5.31 (d, *J* = 12.5 Hz, 1 H), 7.10 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.18 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.35 (dt, *J* = 8.0, 1.0 Hz, 1 H), 7.38 (d, *J* = 8.0 Hz, 1 H), 8.26 (br, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.22, 19.47, 32.91, 53.39, 59.77, 67.74, 106.80, 111.23, 117.92, 119.95, 122.20, 124.19, 130.79, 135.87, 156.60.

HRMS (ESI): *m*/*z* calcd for $C_{15}H_{18}N_2O_3$ + Na [M + Na]$^+$: 297.1210; found: 297.1216.

10-*tert*-Butyl 2-Methyl 1-Phenyl-4,5-dihydro-1*H*-[1,2]oxazepino[4,5-*b*]indole-2,10-dicarboxylate (5l)
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.41 (s, 9 H), 3.07–3.19 (m, 2 H), 3.86 (s, 3 H), 4.29–4.31 (m, 2 H), 7.13 (s, 1 H), 7.14 (d, *J* = 1.5 Hz, 1 H), 7.24–7.36 (m, 5 H), 7.50 (d, *J* = 8.0 Hz, 1 H), 7.62 (s, 1 H), 8.17 (d, *J* = 8.0 Hz, 1 H).

HRMS (ESI): *m*/*z* calcd for $C_{24}H_{26}N_2O_5$ + Na [M + Na]$^+$: 445.1734; found: 445.1749.

Methyl 10-Methyl-1-phenyl-4,5-dihydro-1*H*-[1,2]oxazepino[4,5-*b*]indole-2(10*H*)-carboxylate (5m)
Colorless solid; mp 155–157 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 3.18 (dt, *J* = 16.5, 4.0 Hz, 1 H), 3.25–3.31 (m, 1 H), 3.51 (s, 9 H), 3.84 (s, 3 H), 4.27–4.32 (m, 1 H), 4.44–4.49 (m, 1 H), 6.83 (s, 1 H), 7.15–7.30 (m, 8 H), 7.57 (d, *J* = 7.5 Hz, 1 H).

HRMS (ESI): *m*/*z* calcd for $C_{20}H_{20}N_2O_3$ + Na [M + Na]$^+$: 359.1366; found: 359.1377.

11-*tert*-Butyl 2-Methyl 1-Phenyl-5,6-dihydro-[1,2]oxazocino[4,5-*b*]indole-2,11(1*H*,4*H*)-dicarboxylate (5n)
Colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.56 (s, 9 H), 1.83–1.90 (m, 1 H), 1.98–2.06 (m, 1 H), 2.82–2.91 (m, 2 H), 3.70 (td, *J* = 12.0, 4.5 Hz, 1 H), 3.89 (s, 3 H), 4.31 (dd, *J* = 13.0, 5.0 Hz, 1 H), 7.27–7.33 (m, 6 H), 7.38 (td, *J* = 7.0, 1.0 Hz, 1 H), 7.55 (d, *J* = 7.5 Hz, 1 H), 7.81 (s, 1 H), 8.17 (d, *J* = 7.5 Hz, 1 H).

HRMS (ESI): *m*/*z* calcd for $C_{25}H_{28}N_2O_5$ + Na [M + Na]$^+$: 459.1890; found: 459.1890.

Methyl [*N*-(1-*tert*-Butoxycarbonylindol-3-yl)]methoxy(hydroxymethyl)carbamate (6)
Colorless solid; mp 136–137 °C.

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.67 (s, 9 H), 3.18 (t, *J* = 7.5 Hz, 1 H, OH), 3.81 (s, 3 H), 4.87 (d, *J* = 7.5 Hz, 2 H), 5.07 (d, *J* = 0.5 Hz, 2 H), 7.28 (td, *J* = 8.0, 1.0 Hz, 1 H), 7.34 (td, *J* = 8.0, 1.5 Hz, 1 H), 7.65 (s, 1 H), 7.74 (d, *J* = 7.5 Hz, 1 H), 8.13 (d, *J* = 7.5 Hz, 1 H).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 28.17, 53.45, 68.18, 73.88, 84.07, 115.09, 115.30, 119.47, 123.06, 124.83, 126.50, 129.59, 135.61, 149.51, 157.39.

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