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Synthesis of Lactams by Isomerization of Oxindoles Substituted at C-3 by an ω-Amino Chain

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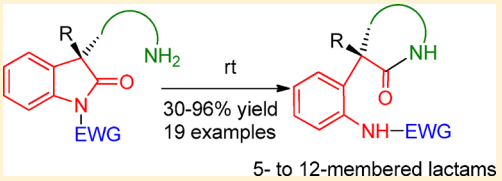
Supporting Information

ABSTRACT: Oxindoles substituted at N-1 by electron-withdrawing groups and at C-3 by ω-amino chains of various lengths undergo mild and easy isomerization to new 5- to 12-membered lactams in good yields (30−96%). As efficient asymmetric syntheses of diversely 3,3-disubstituted oxindoles are currently developed, this isomerization provides a new and valuable access to medium-sized lactams α-substituted with a quaternary asymmetric carbon bearing a 2-aminophenyl residue.

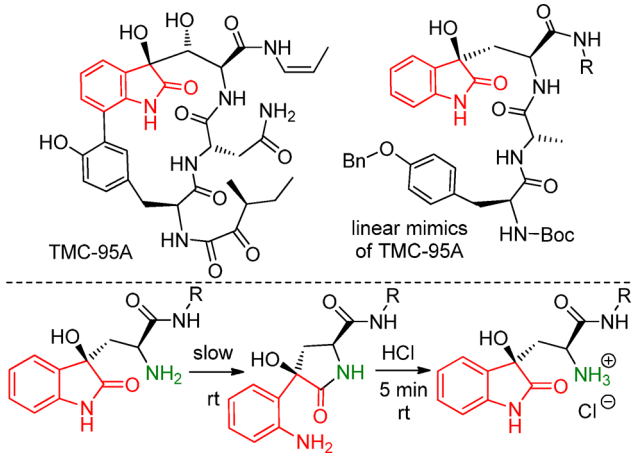


INTRODUCTION

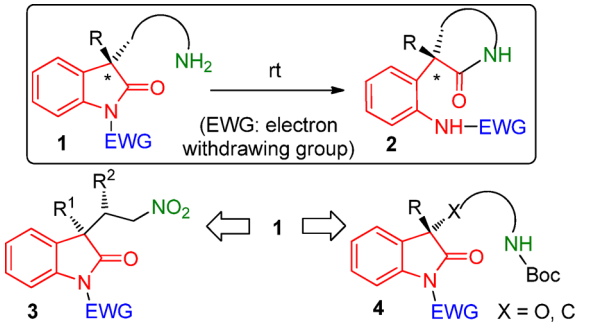
The 3,3-disubstituted oxindole scaffold, which is present in a large number of natural and synthetic compounds with significant biological activities, is currently an important target for the development of very efficient asymmetric synthesis methods.[1] Furthermore, these methods allow the introduction of a very wide diversity of substituents at C-3. Among the natural products bearing this scaffold, TMC-95A has attracted our interest[2] because it is a potent proteasome inhibitor (Scheme 1).[3]

We showed that linear mimics of TMC-95A, which contained the 3-hydroxyoxindolyl alanine residue, retained the proteasome inhibitory activity.[4] In the course of their synthesis, we observed that the 2-(3-oxindolyl)ethylamine core slowly isomerized to (2-aminophenyl)-2-butyrolactam (25% conversion after 18 h at room temperature, neat liquid, Scheme 1). Such an isomerization has occasionally been described[5,6] and has complicated the structure determination of the natural products donoxaridine[7] and chimonamidine.[7b,8] We also took advantage of the reported instability of the 2-(2-aminophenyl)-γ-lactam scaffold in acidic medium that rapidly led to the protonated form of the starting 2-(3-oxindolyl)ethylamine (Scheme 1).[5d,e,9] To the best of our knowledge, isomerization of oxindoles substituted at C-3 with longer ω-amino chains has not been studied. Since ring-closure reactions leading to 7- to 10-membered lactams are generally difficult, this isomerization may be valuable for the formation of medium-sized lactams that find widespread use in organic chemistry (key intermediates, core structures of natural products, or biologically active compounds).[10,11] We reasoned that substituting the oxindole nitrogen by an electron-withdrawing group (EWG) would enhance the electrophilicity of the oxindole carbonyl and favor the isomerization while disfavoring the reverse reaction in acidic medium due to poor nucleophilicity (Scheme 2).

Scheme 1. Structures of Some Proteasome Inhibitors and Isomerization of 3-(2-Aminoethyl)oxindole to 2-(2-Aminophenyl) γ-Lactam Followed by Acidic Transformation into Protonated Starting Material



Scheme 2. General Scheme for Isomerization of Oxindole 1 to Lactam 2 and Structures of Precursors 3 or 4



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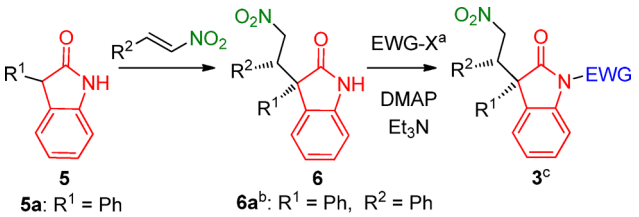
Herein we report the easy formation of 5- to 12-membered lactams **2** from oxindoles **1** substituted at N-1 by EWG and at C-3 by ω-amino chains of various lengths (Scheme 2). The isomerization of two families of oxindoles **1**, obtained from nitro compounds **3** or *N*-Boc-protected derivatives **4**, was studied (Scheme 2). Lactams **2** proved to be stable in acidic medium, provided EWG is also stable. Owing to the recent significant advances in the asymmetric synthesis of the 3,3-disubstituted oxindole scaffold,[1] this isomerization provides a new access to lactams, substituted with a α-quaternary asymmetric carbon.[10]

RESULTS AND DISCUSSION

We began our investigation by generating the amino group in **1** from the corresponding nitroethyl derivatives **3**, which were readily prepared by Michael addition of 3-oxindoles **5** to nitroolefins[12] followed by functionalization of **6** by EWG (Scheme 3).

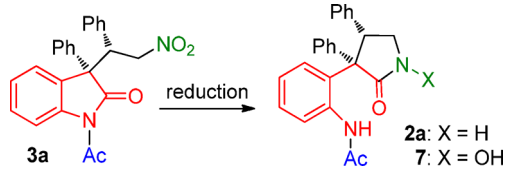
Scheme 3. Synthesis of Compounds 3



[a]EWG-X = Ac-Cl, Boc-OBoc, or Ms-Cl. [b]Compound **6a** (dr > 20/1)[12e] was prepared according to the literature. [c]See the formulas of R^1, R^2, and EWG in Table 2. Compound **3d**[12e] was prepared according to the literature. Nonracemic **3e**[12c] and **3f**[12b] have been described.

Reduction conditions were optimized using the *N*-acetyl compound **3a** (Table 1). Catalytic hydrogenation using palladium on charcoal was first carried out (entries 1 and 2).[12c,13] The crude product contained a 1/4 mixture of γ-lactam **2a** and cyclic hydroxamic acid derivative **7**, which was isolated in 74% yield. Compound **7** resulted from the isomerization of the intermediate hydroxylamine formed from the nitro group. Adding acetic acid did not favor its further reduction into **2a**.

Table 1. Reduction of Nitro Derivative 3a



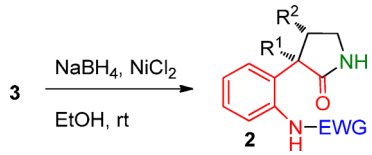
entry	conditions	2a/7 ratio[a]	2a[b] (%)	7[b] (%)
1	H_2, Pd/C, MeOH, 18h, rt	1/4	15	74
2	H_2, Pd/C, MeOH/AcOH, 18h, rt	1/4		
3	$NaBH_4$ (16 equiv), $NiCl_2$ (2 equiv), EtOH, 3h, rt	3/2		
4	$NaBH_4$ (16 equiv), $NiCl_2$ (2 equiv), EtOH, 3h, then $NaBH_4$ (6 equiv), rt	>20/1	56	

[a]Ratio determined by ^{1}H NMR analysis of the crude mixture (solvent DMSO). [b]Isolated yield.

We then used sodium borohydride in the presence of $NiCl_2$ (entries 3 and 4).[12a,i] Complete conversion of **3a** was observed after 3 h at room temperature, leading to a 3/2 mixture of **2a** and **7**. Adding an excess of sodium borohydride induced further reduction of **7** and allowed isolation of **2a** in 56% yield.

We then examined the substrate scope of different *N*-EWG-substituted nitrooxindoles **3a–g** using $NaBH_4/NiCl_2$ as the reducing agent (Table 2). Lactams **2a–f** (EWG = Ac or Boc)

Table 2. Synthesis of γ-Lactams 2a–g by Reduction of Oxindoles 3



entry	3	2	EWG	R^1	R^2	yield[a] (%)
1	**3a**	**2a**	Ac	Ph	Ph	56
2	**3b**	**2b**	Ac	Ph	H	64
3	**3c**	**2c**	Ac	Me	H	58
4	**3d**	**2d**	Boc	Ph	Ph	52
5	**3e**	**2e**	Boc	Ph	H	55
6	**3f**	**2f**	Boc	Me	H	57
7	**3g**	**2g**	Ms	Ph	Ph	71

[a]Isolated yield.

were isolated in 52–64% yield (entries 1–6). A higher yield in **2g** was obtained from **3g**, which was substituted by the better electron-withdrawing substituent Ms (entry 7).

These γ-lactams **2a–g** were characterized by ^{1}H NMR spectroscopy using CD_3SOCD_3 as solvent rather than $CDCl_3$. The NH-EWG chemical shifts were in the 9.1–10.2 ppm range. Noteworthy were the shape of the NH γ-lactam signal which appeared as a broad singlet instead of a triplet, a feature that has been generally observed in CD_3SOCD_3,[14] and the unusual chemical shift (1.24–1.38 ppm) of the *N*-Ac group in **2a**,**b**. Fortunately, the single-crystal X-ray structure of lactam **2b** was obtained and allowed interpretation of these apparent discrepancies (see the Supporting Information).

The structure showed the presence of the Ac group in the magnetic shielding region of the benzene ring at C-3. Lactam NH–CH dihedral angles were ca. 60°, leading to small vicinal coupling constants in the ^{1}H NMR. Finally, we noticed the stability of butyrolactams **2** in acidic medium: the ^{1}H NMR spectrum of **2b** (c = 0.05 M, CD_3SOCD_3) remained unchanged after 4 days at room temperature in the presence of excess trifluoracetic acid (3 equiv).

In order to study the influence of the ω-amino side chain length on the isomerization, we prepared Boc-amino precursors **4a–n** from 3-hydroxyoxindoles **8** (Table 3).

N-Boc-aminoalkanoic acids (n = 1–5) were efficiently coupled to hindered 3-hydroxyoxindole **8a** using the Steglich conditions, with DCC resulting in better yields than 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC) (entries 1–5).[15] Compounds substituted by donor or acceptor substituents on the aromatic ring were synthesized (entries 6–8). Different EWG groups (Ac, Cbz, and $CONMe_2$) were easily introduced[16] in 3-hydroxy-3-cyanomethyl derivatives **8d–f** (entries 9–12). Reaction of **8d–f** with DCC and *N*-Boc-β-alanine or *N*-Boc-aminohexanoic acid worked in good yields to give **4i–l** (entries 9–12). However, addition of DMAP in the

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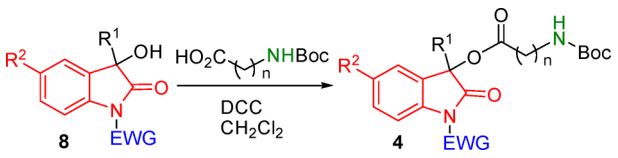
Table 3. Synthesis of Oxindoles 4 Substituted at C-3 by ω-Boc-amino Side Chains of Varying Lengths

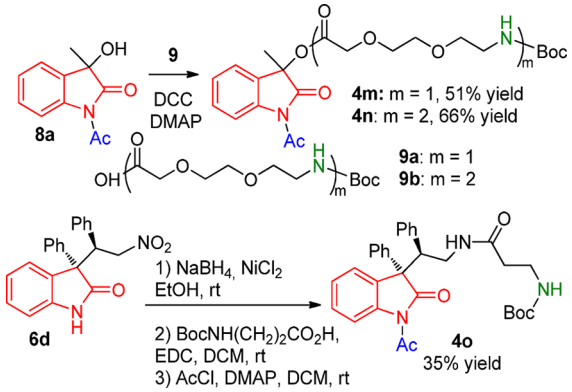


entry	8	4	EWG	R^2	R^1	n	yield[a] (%)
1	**8a**	**4a**	Ac	H	CH_3	1	69[b]
2	**8a**	**4b**	Ac	H	CH_3	2	95[b]
3	**8a**	**4c**	Ac	H	CH_3	3	78[b]
4	**8a**	**4d**	Ac	H	CH_3	4	95[b]
5	**8a**	**4e**	Ac	H	CH_3	5	97[b]
6	**8b**	**4f**	Ac	F	CH_3	2	60[b]
7	**8c**	**4g**	Ac	CH_3O	CH_3	2	91[b]
8	**8c**	**4h**	Ac	CH_3O	CH_3	5	78[b]
9	**8d**	**4i**	Ac	H	CH_2CN	2	59
10	**8d**	**4j**	Ac	H	CH_2CN	5	98
11	**8e**	**4k**	Cbz	H	CH_2CN	5	72
12	**8f**	**4l**	$CON(CH_3)_2$	H	CH_2CN	5	73

[a]Isolated yield. [b]DMAP was added.

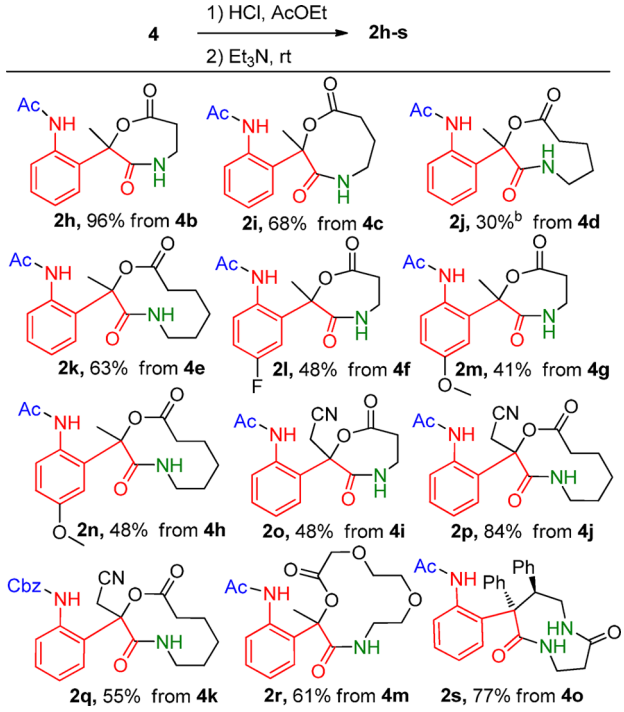
synthesis of **4i–l** resulted in the formation of unidentified products. Derivatives **4m–n** containing 10-amino or 19-amino oxyethylene chains were obtained using *N*-Boc-amino acids **9**[17] (Scheme 4). Boc-amino compound **4o** that did not bear an ester functionality at the quaternary junction was also prepared in three steps from nitroethyl compound **6d** (Scheme 4).

Scheme 4. Synthesis of Precursors 4m–o



Finally, Boc-amino precursors **4a–o** were deprotected using anhydrous hydrogen chloride (Scheme 5). Integration of the ^{1}H NMR signals of the resulting chlorhydrate (solvent CD_3SOCD_3) also showed the formation of up to 40% of the expected lactam **2**, indicating that the isomerization could occur even in acidic medium. Further treatment overnight by triethylamine at room temperature led to original 7- to 12-membered lactams **2h–r**, which were isolated in 30–96% yields (Scheme 5). Unidentified products were obtained from **4a** and **4l** after prolonged heating at 45 °C. The side chain in **4a** was probably too short to induce a favorable overlap of the amine HOMO and the carbonyl LUMO. As **4j** and **4k** successfully gave **2p** and **2q**, the failure of **4l** to react similarly may indicate that the electron-withdrawing effect of the carbamoyl group was not strength enough in order to promote the isomerization. The basic form of deprotected **4n** remained stable, failing to

Scheme 5. Synthesis of Lactams 2h–s



[a]Isolated yield. [b]Crude product was a 3/2 mixture of **2j** and δ-valerolactam.

give the corresponding 21-membered macrocycle. The competing attack of the carbonyl of the ester function instead of the oxindole one was observed only in the case of derivative **4d** leading to a 3/2 mixture of the nine-membered lactam **2j** and the six-membered δ-valerolactam. Fortunately, the nine-membered lactam **2s** featuring the cyclic core found in cyclic peptides that inhibit protein tyrosine phosphatase from *Mycobacterium tuberculosis*[18] was obtained in a good yield from **4o**. Similarly to γ-lactam **2b**, medium-sized lactam **2k** proved to be stable in the presence of trifluoroacetic acid (4 equiv, no change after 6 days at rt).

CONCLUSION

In summary, we have developed the easy transformation of oxindole derivatives **3** and **4** substituted at C-3 by an ω-amino chain of varying length into γ-lactams **2a–g** and medium-sized lactams **2h–s**. The reactions are easy to conduct and occur under mild conditions, and the yields are good. The use of building blocks **3** or **4** is a new route to lactam synthesis[10] and may allow configuration control of the quaternary carbon α to the carbonyl, using the asymmetric methods currently developed for the synthesis of C-3-disubstituted oxindoles.[1] As medium-sized lactams **2h–r** display unknown depsipeptide cores, this method may find applications in the discovery of new macrolactams of therapeutic interest.[10a,19]

EXPERIMENTAL SECTION

Methods and Materials. Commercially available reagents were used without further purification. Reagent-grade solvents were used for extraction and flash chromatography. DCM was stabilized with amylene. Dry solvents were distilled from the appropriate drying reagents immediately before use. Yields refer to chromatographically and spectroscopically homogeneous materials. Reactions were monitored by thin-layer chromatography carried out on silica gel

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aluminum sheets (60F-254) using UV light as a visualizing agent followed by 15% ethanolic phosphomolybdic acid and heat or 0.2% ethanolic ninhydrin and heat as developing agent. Column chromatography was performed on silica gel 60, 0.063−0.200 mm. ^{1}H NMR and ^{13}C NMR spectra were recorded at room temperature at, respectively, 300 and 75.5 MHz frequencies. Chemical shifts were reported in ppm (δ units), and residual nondeuterated solvent was used as internal reference. Assignments of ^{13}C signals were determined using DEPT experiments. Mass spectrometry accurate mass data (HRMS) were obtained from a Q-TOF spectrometer using an electrospray source (ESI). Melting points were determined using a Griffin melting point apparatus and are uncorrected. Compounds **5a,b** were commercially available.

Procedure for the Synthesis of Compounds 2a−g. To a mixture of nitro-oxindole **3a** (112.4 mg, 0.281 mmol) and $NiCl_2$ (69.1 mg, 0.53 mmol) in absolute ethanol (1 mL) was added sodium borohydride (170 mg, 4.5 mmol). The black mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. Three further portions of sodium borohydride (50 mg, 1.3 mmol) were added after stirring for 3, 5, and 7 h, respectively. After dilution by CH_2Cl_2 (30 mL), the mixture was washed by 10% aqueous ammonium chloride. The organic phase was concentrated in vacuo, and the residue was purified by chromatography over silica gel (3.5 g, eluent CH_2Cl_2) to afford lactam **2a** as a white solid (58.5 mg, 56% yield).

*N-(2-(rel-(3S,4S)-2-Oxo-3,4-diphenylpyrrolidin-3-yl)phenyl)-acetamide (**2a**):* ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.24 (s, 3H), 3.52 (dd, J = 10.5, 5 Hz, 1H), 3.81 (dd, J = 10.5, 6.5 Hz, 1H), 4.64 (t, J = 6 Hz, 1H), 6.62 (m, 2H), 6.78−6.82 (m, 2H), 6.87−7.01 (m, 6H), 7.25−7.36 (m, 2H), 7.51 (dd, J = 7.8 Hz, 1.8 Hz, 1H), 8.08 (d, J = 7.8 Hz, 1H), 8.92 (s, 1H), 10.03 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 3H), 3.66 (dd, J = 9.9, 5.4 Hz, 1H), 3.86 (dd, J = 9.9, 7.2 Hz, 1H), 4.49 (t, J = 6.2 Hz, 1H), 6.69 (m, 5H), 6.97 (m, 6H), 7.22 (dd, J = 7.8, 1.5 Hz, 1H), 7.31 (td, J = 7.6, 1.2 Hz, 1H), 7.60 (dd, J = 7.8, 1.5 Hz, 1H), 7.84 (d, J = 7.5 Hz, 1H), 9.64 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.2 (CH_3), 45.9 (CH_2), 50.0 (CH), 61.9(C), 124.6 (CH), 126.4 (CH), 126.8 (CH), 127.1 (CH), 127.7 (CH), 127.9 (CH), 128.0 (CH), 128.3 (CH), 128.6 (CH), 129.1 (CH), 132.5 (C), 137.80 (C), 137.85 (C), 138.7 (C), 168.1 (C), 179.1 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{24}H_{22}N_2O_2Na$ 393.1579, found 393.1579; R_f (AcOEt) 0.46; mp 242−246 °C.

*N-(2-(2-Oxo-3-phenylpyrrolidin-3-yl)phenyl)acetamide (**2b**):* yield 69 mg (64%); crystalline solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.38 (s, 3H), 2.35 (ddd, J = 13.5, 8 Hz, 8 Hz, 1H), 3.13 (ddd, J = 13.5, 6.0, 3 Hz, 1H), 3.29−3.49 (m, 2H), 7.04−7.07 (m, 2H), 7.23−7.41 (m, 5H), 7.58 (dd, J = 7.8, 1 Hz, 1H), 7.73 (dd, J = 7.8, 1 Hz, 1H), 8.60 (s, 1H), 10.19 (s, 1H); NMR signal attribution resulted from HMBC and HSQC experiments, see the Supporting Information for atom numbering; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.43 (s, 3H^{22}), 2.35 (ddd, J = 13, 8, 8 Hz, 1H^8), 3.04 (ddd, J = 13, 6, 3 Hz, 1H^8), 3.34 (m, 1H^9), 3.46 (m, 1H^9), 6.92 (br s, 1H^{10}), 7.02−7.04 (m, 2H^{1,5}), 7.12−7.23 (m, 4H^{15,3,2,4}), 7.29 (ddd, J = 7.8, 7.8, 1.2 Hz, 1H^{16}), 7.47 (d, J = 7.2 Hz, 1H^{14}), 7.62 (dd, J = 7.8, 1.2 Hz, 1H^{17}), 9.82 (s, 1H^{19}); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.4 (C^{22}), 38.6 (C^8), 39.8 (C^9), 56.7 (C^7), 124.7 (C^{15}), 126.0 (C^{1,5}), 126.2 (C^{14}), 126.8 (C^3), 127.5 (C^{17}), 128.6 (C^{16}), 128.7 (C^{2,4}), 131.1 (C^{13}), 137.5 (C^{18}), 143.4 (C^6), 168.3 (C^{20}), 179.7 (C^{11}); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{18}H_{18}N_2O_2Na$ 317.1266, found 317.1268; R_f (1/1 AcOEt/CH_2Cl_2) 0.28; mp 219−222 °C.

*N-(2-(3-Methyl-2-oxopyrrolidin-3-yl)phenyl)acetamide (**2c**):* yield 54 mg (58%); crystalline solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.45 (s, 3H), 2.03 (s, 3H), 2.09 (m, 1H), 2.63 (m, 1H), 3.22 (m, 1H), 3.29 (m, 1H), 7.14 (td, J = 7.8, 1.2 Hz, 1H), 7.25 (td, J = 7.8, 1.2 Hz, 1H), 7.41 (dd, J = 7.8, 1.2 Hz, 1H), 7.54 (dd, J = 7.8, 1.2 Hz, 1H), 8.09 (s, 1H), 10.39 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.60 (s, 3H), 2.18 (m, 4H), 2.87 (m, 1H), 3.45 (m, 2H), 6.02 (broad s, 1H), 7.06 (t, J = 7.8 Hz, 1H), 7.22−7.27 (m, 2H), 7.83 (d, J = 7.8 Hz, 1H), 10.35 (broad s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.4 (CH_3), 24.3 (CH_3), 36.7 (CH_2), 39.3 (CH_2), 47.5 (C), 125.1(CH), 126.0 (CH), 126.9 (CH), 128.1 (CH), 132.6 (C), 136.9 (C), 168.8 (C), 182.1 (C); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{13}H_{16}N_2O_2Na$ 255.1109, found 255.1108; R_f (MeOH/CH_2Cl_2 1/9) 0.50; mp 160−165 °C.

*tert-Butyl (2-(rel-(3S,4S)-2-oxo-3,4-diphenylpyrrolidin-3-yl)-phenyl)carbamate (**2d**):* yield 57 mg (52%); crystalline solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ (two rotamers, 57/43 mixture) 1.07 and 1.20 (two s, 9H),3.51 (m, 1H), 3.77 (m, 1H), 4.49 and 4.61 (two t, J = 4 Hz, 1H), 6.59−7.41 (m, 14 H), 8.04 (d, J = 8 Hz, 0.43 H), 8.57 (s, 0.57 H), 8.81 (s, 0.43 H), 9.13 (0.43 H); ^{1}H NMR (300 MHz, $CDCl_3$) δ (two rotamers, 57/43 mixture) 1.14 and 1.26 (9H, two s), 3.69 (m, 1H), 3.87 (m, 1H), 4.54 (t, J = 4 Hz, 1H), 6.33 (br s, 0.57 H), 6.70−7.67 (m, 14.43 H), 7.86 (d, J = 7.5 Hz, 0.57 H), 8.77 (s, 0.43 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ (two rotamers) 28.0 and 28.1 (CH_3), 45.8 and 45.9 (CH_2), 50.1 and 50.2 (CH), 61.2 and 61.8 (C), 78.7 and 79.2 (C), 123.0 (CH), 123.4 (CH), 126.3 (CH), 126.7 (CH), 127.0 (CH), 127.4 (CH), 127.5 (CH), 127.70 (CH), 127.75 (CH), 127.8 (CH), 127.9 (CH), 128.1 (CH), 128.2 (CH), 128.3 (CH), 128.8 (CH), 129.2 (CH), 130.0 (CH), 137.2 (C), 137.9 (C), 138.3 (C), 138.5 (C), 138.6 (C), 139.6 (C), 140.5 (C), 152.3 and 152.3 (C), 178.1 and 179.0 (C); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{27}H_{28}N_2O_3Na$ 451.1998, found 451.2000; R_f (AcOEt/CH_2Cl_2 1/9) 0.50; mp 189−192 °C.

*tert-Butyl (2-(2-oxo-3-phenylpyrrolidin-3-yl)phenyl)carbamate (**2e**):* yield 60 mg (55%); crystalline solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.13 (s, 9H), 2.23 (m, 1H), 3.06 (m, 1H), 3.23 (m, 1H), 3.38 (m, 1H), 6.99 (d, J = 7.2 Hz, 1H), 7.12−7.42 (m, 7H), 7.64 (d, J = 7.6 Hz, 1H), 8.50 (s, 1H), 9.32 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.14 (s, 9H), 2.41 (m, 1H), 3.03 (m, 1H), 3.34 (m, 1H), 3.46 (m, 1H), 5.81 (br s, 1H), 7.05−7.30 (m, 7H), 7.43 (d, J = 8 Hz, 1H), 7.56 (d, J = 8 Hz, 1H), 8.71 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.1 (CH_3), 38.4 (CH_2), 39.7 (CH_2), 56.6 (C), 79.0 (C), 123.7 (CH), 126.1 (CH), 126.2 (CH), 126.7 (CH), 128.4 (CH), 128.5 (CH), 128.5 (CH), 131.3 (C), 138.1 (C), 143.2 (C), 153.2 (C), 179.4 (C); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{21}H_{24}N_2O_3Na$ 375.1685, found 375.1688; R_f (1% Et_3N in 1/1 AcOEt/petroleum ether) 0.58; mp 182−185 °C.

*tert-Butyl (2-(3-methyl-2-oxopyrrolidin-3-yl)phenyl)carbamate (**2f**):* yield 59 mg (57%); crystalline solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.44 (s, 12 H), 2.08 (m, 1 H), 2.72 (m, 1H), 3.17−3.30 (m, 2 H), 7.09 (ddd, J = 7.8, 7.8, 1.5 Hz, 1H), 7.24 (ddd, J = 7.8, 7.8, 1.5 Hz, 1H), 7.37 (dd, J = 7.8, 1.5 Hz, 1H), 7.50 (dd, J = 7.8, 1.5 Hz, 1H), 8.11 (s, 1H), 9.86 (s, 1 H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18 (s, 3H), 1.44 (s, 9H), 2.17 (m, 1H), 2.73 (m, 1H), 3.46 (m, 2H), 5.69 (br s, 1H), 7.03 (t, J = 7.6 Hz, 1H), 7.29 (m, 2H), 7.62 (d, J = 8 Hz, 1H), 8.88 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.1 (CH_3), 28.4 (CH_3), 36.6 (CH_2), 39.3 (CH_2), 47.4 (C), 79.5 (C), 124.5 (CH), 126.1 (CH), 126.7 (CH), 127.9 (CH), 133.4 (C), 137.1 (C), 154.1 (C), 182.1 (C); HRMS (ESI, CH_3OH) calcd for $C_{16}H_{22}N_2O_3Na$ [(M + Na)$^+$] 313.1528, found 313.1525; R_f (1/1/0.01 AcOEt/petroleum ether/Et_3N) 0.22; mp 134−138 °C.

*N-(2-(rel-(3S,4S)-2-Oxo-3,4-diphenylpyrrolidin-3-yl)phenyl)-methanesulfonamide (**2g**):* yield 45 mg (71%); crystalline solid; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.85 (s, 3H), 3.47 (dd, J = 10.8, 2.5 Hz, 1H), 3.81 (dd, J = 10.8, 6.3 Hz, 1H), 4.63 (m, 1H), 6.74−6.75 (m, 2H), 6.81−6.85 (m, 2H), 7.00−7.07 (m, 6H), 7.29 (td, J = 7.8, 1.2 Hz, 1H), 7.39 (td, J = 8.4, 1.2 Hz, 1H), 7.63 (dd, J = 7.8, 1.2 Hz, 1H), 8.13 (d, J = 7.2 Hz, 1H), 9.06 (s, 1H), 10.49(s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 3H), 3.61 (dd, J = 10.2, 4.2 Hz, 1H), 3.87 (dd, J = 10.2, 6.6 Hz, 1H), 4.42 (dd, J = 6.3, 4.3 Hz, 1H), 6.48 (s, 1H), 6.71−6.79 (m, 4H), 6.95−6.99 (m, 6H), 7.18 (m, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.77 (d, J = 7.8 Hz, 1H), 7.86 (d, J = 8.1 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 38.8 (CH_3), 46.2 (CH_2), 51.1 (CH), 61.8 (C), 122.3 (CH), 123.8 (CH), 127.0 (CH), 127.1 (CH), 127.2 (CH), 128.0 (CH), 128.2 (CH), 128.5 (CH), 129.2 (CH), 129.3 (CH), 131.0 (C), 137.9 (C), 138.2 (C), 139.4 (C), 178.7 (C); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{23}H_{22}N_2O_3NaS$ 429.1249, found 429.1250; R_f (AcOEt/CH_2Cl_2 1/9) 0.30; mp 195−198 °C.

Procedure for the Synthesis of Compounds 2h−r. To a solution of Boc derivative **4b** (124.5 mg, 0.331 mmol) in AcOEt (0.2

mL) was added a 3 M solution of anhydrous HCl in AcOEt (0.35 mL, 1.05 mmol). The mixture was stirred at room temperature overnight. The solvent was removed in vacuo. To the resulting solid were added CH_2Cl_2 (0.6 mL) and trietylamine (90 μL, 0.65 mmol). The mixture was stirred for 8 h at room temperature, diluted with CH_2Cl_2 (10 mL), and washed with aqueous 10% citric acid. The organic phase was dried over sodium sulfate and concentrated in vacuo. Purification by chromatography over silica gel (6.3 g, eluent 1% MeOH in AcOEt) afforded lactam **2h** as a white solid (87.8 mg, yield 96%).

*N-(2-(2-Methyl-3,7-dioxo-1,4-oxazepan-2-yl)phenyl)acetamide (**2h**)*: ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48 (s, 3H), 1.76 (s, 3H), 2.47 (m, 2H), 3.14 (m, 2H), 6.83 (d, J = 9 Hz, 1H), 6.96 (t, J = 9 Hz, 1H), 7.19−7.23 (m, 2H), 7.90 (br s, 1H), 10.56 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$, c = 0.24 mol l^{-1}) δ 1.55 (s, 3H), 1.80 (s, 3H), 2.39−2.59 (m, 2H), 3.26−3.48 (m, 2H), 6.34 (br s, 1H), 6.81 (d, J = 7.8 Hz, 1H), 6.96 (t, J = 7.2 Hz, 1H), 7.12−7.20 (m, 2H), 8.93 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0 (CH_3), 23.2 (CH_3), 33.8 (CH_2), 34.9 (CH_2), 78.1 (C), 110.5 (CH), 122.3 (CH), 122.8 (CH), 129.3 (C), 129.7 (CH), 140.4 (C), 170.6 (C), 171.1 (C), 177.3 (C); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{14}H_{16}N_2O_4Na$ 299.1008, found 299.1008; R_f (MeOH/AcOEt 5/95) 0.26; mp 115−119 °C.

*N-(2-(2-Methyl-3,8-dioxo-1,4-oxazocan-2-yl)phenyl)acetamide (**2i**)*. Starting from Boc derivative **4c** (208.6 mg, 0.534 mmol), the general procedure afforded lactam **2i** as a viscous oil (105 mg, yield 68%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.48 (s, 3H), 1.55 (m, 2H), 1.77 (s, 3H), 2.32 (t, J = 7.2 Hz 2H), 2.97 (m, 2H), 6.83 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.20−7.26 (m, 2H), 7.82 (br s, 1H), 10.54 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$, c = 0.14 mol l^{-1}) δ 1.54 (s, 3H), 1.69 (m, 2H), 1.83 (s, 3H), 2.29 (m, 2H), 3.14 (m, 2H), 6.10 (br s, 1H), 6.80 (d, J = 7.8 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.10−7.17 (m, 2H), 8.82 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.1 (CH_3), 23.3 (CH_3), 24.3 (CH_2), 31.2 (CH_2), 38.7 (CH_2), 77.8 (C), 110.5 (CH), 122.3 (CH), 122.8 (CH), 129.4 (C), 129.7 (CH), 140.5 (C), 170.8 (C), 171.8 (C), 177.3 (C); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{15}H_{18}N_2O_4Na$ 313.1164, found 313.1159; R_f (AcOEt) 0.15

*N-(2-(2-Methyl-3,9-dioxo-1,4-oxazonan-2-yl)phenyl)acetamide (**2j**)*. Starting from Boc derivative **4d** (249 mg, 0.616 mmol), the general procedure afforded a crude product containing a 3/2 mixture of expected lactam **2j** and δ-valerolactam. Purification by chromatography over silica gel (8 g, eluent AcOEt) afforded lactam **2j** as a viscous oil (56.2 mg, yield 30%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.30−1.43 (m, 4H), 1.47 (s 3H), 1.77 (s, 3H), 2.31 (t, J = 6 Hz, 2H), 2.98 (m, 2H), 6.83 (d, J = 8 Hz, 1H), 6.95 (t, J = 7.5 Hz, 1H), 7.20 (m, 2H), 7.79 (broad s, 1H), 10.53 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$, c = 0.26 mol l^{-1}) δ 1.37−1.52 (m, 4H), 1.53 (s, 3H), 1.85 (s, 3H), 2.27 (m, 2H), 3.09 (m, 2H), 6.10 (br s, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.94 (t, J = 7.2 Hz, 1H), 7.10−7.18 (m, 2H), 8.99 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.9 (CH_2), 23.0 (CH_3), 23.2 (CH_3), 28.3 (CH_2), 33.1 (CH_2), 38.9 (CH_2), 77.6 (C), 110.5 (CH), 122.1 (CH), 122.6 (CH), 129.4 (CH), 129.5 (C), 140.6 (C), 170.6 (C), 171.8 (C), 177.3 (C); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{16}H_{20}N_2O_4Na$ [(M + Na)$^+$] 327.1320, found 327.1321; R_f (MeOH/AcOEt 1/9) 0.57.

*N-(2-(2-Methyl-3,10-dioxo-1,4-oxazecan-2-yl)phenyl)acetamide (**2k**)*. Starting from Boc derivative **4e** (140.4 mg, 0.335 mmol), the general procedure afforded lactam **2k** as an amorphous solid (67.2 mg, yield 63%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.18 (m, 2H), 1.34 (m, 2H), 1.42(m, 2H), 1.47 (s, 3H), 1.78 (s, 3H), 2.29 (t, J = 7.2 Hz, 2H), 2.94, 2.99 (ABq, J_{AB} = 6.7 Hz, 2H), 6.83 (dd, J = 8.1, 1 Hz, 1H), 6.96 (td, J = 8, 1 Hz, 1H), 7.20−7.26 (m, 2H), 7.76 (br s, 1H), 10.53 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$, c = 0.31 mol l^{-1}) δ 1.24 (m, 2H), 1.38 (m, 2H), 1.38 (m, 2H), 1.41 (s, 3H), 1.86 (s, 3H), 2.25 (m, 2H), 3.09, 3.14 (ABq, J_{AB} = 6.5 Hz, 2H), 6.20 (br s, 1H), 6.79 (d, J = 7.8 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 7.10−7.17 (m, 2H), 9.03 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.1 (CH_3), 23.3 (CH_3), 24.2 (CH_2), 25.8 (CH_2), 28.7 (CH_2), 33.5 (CH_2), 39.1 (CH_2), 77.7 (C), 110.6 (CH), 122.2 (CH), 122.6 (CH), 129.6 (C), 129.6 (CH), 140.7 (C), 170.7 (C), 171.9 (C), 177.3 (C); HRMS (ESI-TOF, CH_3OH) m/z [M + Na]$^+$ calcd for $C_{17}H_{22}N_2O_4Na$ 341.1477, found 341.1475; R_f (AcOEt) 0.23.

*N-(4-Fluoro-2-(2-methyl-3,7-dioxo-1,4-oxazepan-2-yl)phenyl)-acetamide (**2l**)*. Starting from Boc derivative **4f** (105.7 mg, 0.268 mmol), the general procedure afforded lactam **2l** as an amorphous solid (37.86 mg, yield 48%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.49 (s, 3H), 1.76 (s, 3H), 2.49−2.53 (m, 2H), 3.13−3.23 (m, 2H), 6.82 (dd, J = 8.4, 4.2 Hz, 1H), 7.06 (ddd, J = 11.1, 8.4, 2.7 Hz, 1H), 7.22 (dd, J = 8.1, 2.7 Hz, 1H), 7.91 (t, J = 5.3 Hz, 1H), 10.59 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.55 (s, 3H), 1.83 (s, 3H), 2.42−2.62 (m, 2H), 3.29−3.49 (m, 2H), 6.28 (t, J = 5.6 Hz, 1H), 6.78 (dd, J = 9.3, 4.2 Hz, 1H), 6.75−6.90 (m, 2H), 8.97 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0 (CH_3), 23.2 (CH_3), 33.8 (CH_2), 35.0 (CH_2), 78.2 (d, J = 2 Hz, C), 110.5 (d, J = 25 Hz, CH), 111.3 (d, J = 8 Hz, CH), 116.1 (d, J = 23 Hz, CH), 130.8 (d, J = 8 Hz, C), 136.3 (d, J = 3 Hz, C), 159.2 (d, J = 242 Hz, C), 170.7 (C), 171.2 (C), 177.2 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{14}H_{15}FN_2O_4Na$ 317.0914, found 317.0913; R_f (AcOEt) 0.14.

*N-(4-Methoxy-2-(2-methyl-3,7-dioxo-1,4-oxazepan-2-yl)phenyl)-acetamide (**2m**)*. Starting from Boc derivative **4g** (183.0 mg, 0.450 mmol), the general procedure afforded lactam **2m** as an amorphous solid (56.5 mg, yield 41%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.47 (s, 3H), 1.76 (s, 3H), 2.47 (m, 2H), 3.18 (m, 2H), 3.71 (s, 3H), 6.73−6.81 (m, 2H), 6.91 (s, 1H), 7.90 (broad s, 1H), 10.36 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$, c = 0.12 mol l^{-1}) δ 1.55 (s, 3H), 1.82 (s, 3H), 2.39−2.62 (m, 2H), 2.28−2.50 (m, 2H), 3.71 (s, 3H), 6.30 (broad s, 1H), 6.69−6.74 (m, 3H), 8.62 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.1 (CH_3), 23.4 (CH_3), 33.9 (CH_2), 35.0 (CH_2), 55.8 (CH_3), 78.5 (C), 109.6 (CH), 111.0 (CH), 114.0 (CH), 130.7 (C), 133.5 (C), 156.1 (C), 170.6 (C), 171.2 (C), 177.2 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{15}H_{18}N_2O_5Na$ 329.1113, found 329.1112; R_f (1% MeOH in AcOEt) 0.10.

*N-(4-Methoxy-2-(2-methyl-3,10-dioxo-1,4-oxazecan-2-yl)-phenyl)acetamide (**2n**)*. Starting from Boc derivative **4h** (181.9 mg, 0.405 mmol), the general procedure afforded lactam **2n** as a gum (68.4 mg, yield 48%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21−1.47 (m, 9H), 1.77 (s, 3H), 2.30 (m, 2H), 2.97 (m, 2H), 3.70 (s, 3H), 6.73−6.81 (m, 2H), 6.88 (s, 1H), 7.78 (broad s, 1H), 10.36 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$, c = 0.32 mol l^{-1}) δ 1.18−1.55 (m, 9H), 1.87 (s, 3H), 2.20 (m, 2H), 3.12 (m, 2H), 3.69 (s, 3H), 6.28 (broad s, 1H), 6.66−6.71 (m, 3H), 8.99 (broad s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0 (CH_3), 23.4 (CH_3), 24.1 (CH_2), 25.8 (CH_2), 28.7 (CH_2), 33.4 (CH_2), 39.1 (CH_2), 55.7 (CH_3), 78.0 (C), 109.5 (CH), 111.0 (CH), 113.8 (CH), 130.9 (C), 133.9 (C), 155.9 (C), 170.8 (C), 171.9 (C), 177.3 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{18}H_{24}N_2O_5Na$ 371.1583, found 371.1583; R_f (MeOH/AcOEt 5/95) 0.28.

*N-(2-(2-(Cyanomethyl)-3,7-dioxo-1,4-oxazepan-2-yl)phenyl)-acetamide (**2o**)*. Starting from Boc derivative **4i** (101.8 mg, 0.254 mmol), the general procedure afforded lactam **2o** as a white solid (36.7 mg, yield 48%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.76 (s, 3H), 2.54 (m,2H), 3.17 (m, 2H), 3.29 (s, 2H), 6.89 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 7.30 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 7.91 (br s, 1H), 10.88 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.84 (s, 3H), 2.54 (m,2H), 2.69, 3.00 (ABq, J_{AB} = 16.8 Hz, 2H), 3.39 (m, 2H), 6.26 (t, J = 6.5 Hz, 1H), 6.88 (d, J = 7.5 Hz, 1H), 7.04 (t, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.38 (d, J = 7.5 Hz, 1H), 9.09 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.1 (CH_3), 26.2 (CH_2), 33.7 (CH_2), 34.9 (CH_2), 75.7 (C), 111.1 (CH), 114.5 (C), 123.5 (CH), 123.6 (CH), 125.0 (C), 131.3 (CH), 140.8 (C), 170.2 (C), 170.9 (C), 173.5 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{15}H_{15}N_3O_4Na$ 324.0960, found 324.0961; R_f (AcOEt) 0.67; mp 66−70 °C.

*N-(2-(2-(Cyanomethyl)-3,10-dioxo-1,4-oxazecan-2-yl)phenyl)-acetamide (**2p**)*. Starting from Boc derivative **4j** (197.3 mg, 0.445 mmol), the general procedure afforded lactam **2p** as an amorphous solid (127.6 mg, yield 84%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21−1.47 (m, 6H), 1.77 (s, 3H), 2.35 (m, 2H), 2.98 (m, 2H), 3.28 (s, 2H), 6.90 (d, J = 8 Hz, 1H), 7.06 (t, J = 8 Hz, 1H), 7.30−7.35 (m, 2H), 7.77 (s, 1H), 10.86 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.53 (m,

6H), 1.89 (s, 3H), 2.30 (m, 2H), 2.64, 2.99 (ABq, J_{AB} = 17.5 Hz, 2H), 3.13 (m, 2H), 6.10 (br s, 1H), 6.86 (d, J = 8 Hz, 1H), 7.01 (t, J = 8 Hz, 1H), 7.24 (t, J = 8 Hz, 1H), 7.37 (d, J = 8 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.1 (CH_3), 24.2 (CH_2), 25.8 (CH_2), 26.2 (CH_2), 28.7 (CH_2), 33.3 (CH_2), 39.2 (CH_2), 75.3 (C), 111.1 (CH), 114.8 (C), 123.2 (CH), 123.3 (CH), 125.3 (C), 131.0 (CH), 141.1 (C), 170.9 (C), 171.2 (C), 173.6 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{18}H_{21}N_3O_4Na$ 366.1430, found 366.1431; R_f (AcOEt) 0.10.

*Benzyl (2-(2-(Cyanomethyl)-3,10-dioxo-1,4-oxazecan-2-yl)-phenyl)carbamate (**2q**).* Starting from Boc derivative **4k** (134.7 mg, 0.251 mmol), the general procedure afforded lactam **2q** as an amorphous solid (60 mg, yield 55%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.21−1.49 (m, 6H), 2.32 (m, 2H), 2.92 (m, 2H), 3.28 (s, 2H), 5.00 (s, 2H), 6.89 (d, J = 7.8 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.8 Hz, 1H), 7.29−7.38 (m, 7H), 10.86 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ (two rotamers 15/85) 1.18−1.54 (m, 6H), 2.31 (m, 2H), 2.55 (d, J = 16.8 Hz, 1H), 2.97−3.11 (m, 3H), 4.90 (br s, 0.85 H), 5.01−5.07 (br s, 2H), 5.21 (br s, 0.15 H), 6.80 (d, J = 7.8 Hz, 1H), 6.98 (t, J = 7.2 Hz, 1H), 7.19−7.27 (m, 6H), 7.38 (d, J = 7.2 Hz, 1H), 8.70 (s, 0.85 H), 8.82 (s, 0.15 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2 (CH_2), 25.8 (CH_2), 26.1 (CH_2), 29.4 (CH_2), 33.3 (CH_2), 40.7 (CH_2), 66.6 (CH_2), 75.2 (C), 111.0 (CH), 114.7 (C), 123.4 (CH), 125.2 (C), 128.1 (CH), 131.1 (CH), 136.6 (C), 140.7 (C), 156.5 (C), 171.1 (C), 173.7 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{24}H_{25}N_3O_5Na$ 458.1692, found 458.1690; R_f (AcOEt/petroleum ether 2/3) 0.20.

*N-(2-(8-Methyl-6,9-dioxo-1,4,7-trioxa-10-azacyclododecan-8-yl)-phenyl)acetamide (**2r**).* Starting from Boc derivative **4m** (82.8 mg, 0.184 mmol), the general procedure afforded lactam **2r** as an amorphous solid (39.3 mg, yield 61%): ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.50 (s, 3H), 1.78 (s, 3H), 3.14 (m, 2H), 3.30−3.49 (m, 6H), 4.17 (s, 2H), 6.86 (d, J = 7.5 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 7.22−7.26 (m, 2H), 7.87 (s, 1H), 10.62 (s, 1H); ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.57 (s, 3H), 1.78 (s, 3H), 3.28−3.53 (m, 8H), 4.10, 4.13 (ABq, J_{AB} = 16.8 Hz, 2H), 6.45 (br s, 1H), 6.82 (d, J = 7.5 Hz, 1H), 6.96 (t, J = 7.5 Hz, 1H), 7.22−7.26 (m, 2H), 9.03 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.0 (CH_3), 23.2 (CH_3), 39.2 (CH_2), 68.0 (CH_2), 69.7 (CH_2), 69.8 (CH_2), 70.9 (CH_2), 78.3 (C), 110.7 (CH), 122.4 (CH), 122.7 (CH), 129.0 (C), 129.9 (CH), 140.8 (C), 168.8 (C), 170.8 (C), 176.5 (C); HRMS (ESI, MeOH) m/z [M + Na]$^+$ calcd for $C_{17}H_{22}N_2O_6Na$ 373.1376, found 373.1379; R_f (AcOEt/MeOH 9/1) 0.25.

*rel-N-(2-((7S,8R)-2,6-Dioxo-7,8-diphenyl-1,5-diazonan-7-yl)-phenyl)acetamide (**2s**).* To a solution of Boc derivative **4o** (32.0 mg, 0.059 mmol) in AcOEt (0.2 mL) was added a 3 M solution of anhydrous HCl in AcOEt (61 μL, 0.18 mmol). The mixture was stirred at room temperature for 1 h. The solvent was removed in vacuo. To the resulting solid were added CH_2Cl_2 (0.6 mL) and diisopropylethylamine (20 μL, 0.11 mmol). The mixture was stirred overnight at room temperature and then diluted with ether (2 mL). The precipitate was collected on a sintered glass funnel, washed with ether (1 mL), and chromatographed over silica gel (2.2 g, eluent AcOEt) to afford compound **2s** (19.4 mg, 77% yield) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.80 (s, 3H), 1.92−2.09 (m, 2H), 3.25, 3.29 (ABq, J_{AB} = 6 Hz, 2H), 3.77 (t, J = 6 Hz, 2H), 4.10 (t, J = 7.5 Hz, 1H), 5.56 (t, J = 5.7 Hz, 1H), 6.06 (br s, 1H), 6.56 (d, J = 7.2 Hz, 1H), 6.84−7.04 (m, 7H), 7.13−7.32 (m, 5H), 7.50 (br s 1H), 7.57−7.60 (m, 2H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 22.5 (CH_3), 36.5 (CH_2), 37.0 (CH_2), 40.1 (CH_2), 52.0 (CH), 62.2 (C), 110.8 (CH), 123.0 (CH), 126.3 (CH), 128.0 (CH), 128.3 (CH), 128.4 (CH), 128.6 (CH), 128.9 (CH), 129.8 (CH), 131.0 (CH), 134.1(C), 138.2 (C), 140.7 (C), 141.9 (C), 173.2 (C), 173.6 (C), 181.5 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{27}H_{27}N_3O_3Na$ 464.1950, found 464.1950; R_f (AcOEt/MeOH 9/1) 0.52; mp 191−197 °C.

Procedures for the Synthesis of Compounds 3 and 6. Nitroethylene,[20] and compounds **3d**[12e,f] and **6a** (dr >20/1)[12e,c] were prepared according to the literature. Nonracemic compounds **3e**[12c] and **3f**[12b] were previously described.

*3-(2-Nitroethyl)-3-phenylindolin-2-one (**6b**).* To a solution of oxindole **5a** (1.00 g, 4.78 mmol) and triethylamine (60 μL, 0.48 mmol) in dry CH_2Cl_2 (28 mL) at 0 °C and under argon atmosphere was added using a syringe pump (1.5 mL per hour) a solution of nitroethylene (0.65 mL, 9.57 mmol) in dry CH_2Cl_2 (20 mL). The resulting mixture was stirred overnight at 0 °C and then concentrated in vacuo. After purification by chromatography over silica gel (54.5 g, eluent CH_2Cl_2), the nitro compound **6b** was afforded as a beige solid (1.03 g, 82% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.82−2.92 (m, 1H), 3.02−3.11 (m, 1H), 4.09−4.30 (m, 2H), 6.92 (d, J = 7.5 Hz, 1H), 7.04 (td, J = 7.5, 1.2 Hz, 1H), 7.12−7.32 (m, 7H), 9.09 (broad s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 33.8 (CH_2), 54.6 (C), 71.4 (CH_2), 110.8 (CH), 123.3 (CH), 124.8 (CH), 126.5 (CH), 128.0 (CH), 129.0 (CH), 129.1 (CH), 130.8 (C), 138.0 (C), 140.5 (C), 179.7 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{16}H_{14}N_2O_3Na$ 305.0902, found 305.0899; R_f (AcOEt/petroleum ether 1/1) 0.67; mp 114−116 °C.

*3-Methyl-3-(2-nitroethyl)indolin-2-one (**6c**).* Similarly, compound **6c** (192 mg, 85%) was obtained from **5b**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 3H), 2.50−2.71 (m, 2H), 4.09−4.18 (m, 1H), 4.26−4.36 (m, 1H), 7.00 (d, J = 7.8 Hz, 1H), 7.11 (t, J = 7.3 Hz, 1H), 7.21−7.31 (m, 2H), 9.15 (broad s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8 (CH_3), 34.5 (CH_2), 46.8 (C), 71.5 (CH_2), 110.7 (CH), 123.1 (CH), 123.3 (CH), 128.9 (CH), 132.2 (C), 140.2 (C), 181.8 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{11}H_{12}N_2O_3Na$ 243.0745, found 243.0745; R_f (AcOEt/petroleum ether 1/1) 0.47; mp 94−98 °C.

*rel-(R)-3-((S)-2-Nitro-1-phenylethyl)-3-phenylindolin-2-one (**6d**).* Compound **6d** was obtained according to the literature[12e] and was recrystallized from a 3/2 2-propanol−water mixture: dr >25/1; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.73−4.78 (m, 2H), 3.02−3.11 (dd, J = 14.1, 12.3 Hz, 1H), 6.66 (d, J = 8.1 Hz, 1H), 7.03−7.19 (m, 7H), 7.28−7.47 (m, 4H), 7.69 (d, J = 6.0 Hz, 2H), 8.86 (s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 50.2 (CH), 60.5 (C), 75.6 (CH_2), 110.1 (CH), 122.8 (CH), 124.8 (CH), 126.6 (CH), 128.07 (CH), 128.10 (CH), 128.15 (CH), 128.5 (CH), 129.0 (CH), 129.6 (CH), 131.6 (C), 133.9 (C), 137.8 (C), 139.4 (C), 179.2 (C); HRMS (ESI-TOF, MeOH/CH_2Cl_2) m/z [M + Na]$^+$ calcd for $C_{22}H_{18}N_2O_3Na$ 381.1215, found 381.1215; R_f (AcOEt/petroleum ether 1/1) 0.64; mp 204−211 °C.

*rel-(S)-1-Acetyl-3-((S)-2-nitro-1-phenylethyl)-3-phenylindolin-2-one (**3a**).* To a solution of oxindole **6a** (248 mg, 0.694 mmol), DMAP (8.5 mg, 0.069 mmol), and triethylamine (110 μL, 0.76 mmol) in dry CH_2Cl_2 (1 mL) at 0 °C was added acetyl chloride (54 μL, 0.76 mmol). The mixture was stirred at room temperature overnight and then washed with 10% aqueous citric acid. After aqueous workup, the resulting product was chromatographed over silica gel (8.2 g, eluent CH_2Cl_2) to afford nitro compound **3a** as a white solid (243 mg, 88% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.31 (s, 3H), 4.75−5.04 (m, 3H), 6.80 (d, J = 7.5 Hz, 2H), 7.07−7.21 (m, 3H), 7.39−7.52 (m, 6H), 7.63−7.66 (m, 2H), 8.11 (dd, J = 7.5, 1.8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.3 (CH_3), 50.9 (CH), 60.2 (C), 76.0 (CH_2), 117.2 (CH), 125.1 (CH), 125.6 (CH), 126.5 (C), 127.8 (CH), 128.3 (CH), 128.8 (CH), 128.8 (CH), 128.9 (CH), 129.4 (CH), 129.9 (CH), 132.8 (C), 135.3 (C), 141.2 (C), 170.3 (C), 176.6 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{24}H_{20}N_2O_4Na$ 423.1321, found 423.1320; R_f (CH_2Cl_2) 0.68; mp 195−200 °C; IR 1746, 1710, 1554 cm^{-1}.

*1-Acetyl-3-(2-nitroethyl)-3-phenylindolin-2-one (**3b**).* To a solution of oxindole **6b** (158.1 mg, 0.560 mmol), DMAP (6.84 mg, 0.056 mmol), and triethylamine (80 μL, 0.62 mmol) in dry CH_2Cl_2 (0.7 mL) at 0 °C was added a solution of acetyl chloride (80 μL, 1.12 mmol) in dry CH_2Cl_2 (0.7 mL). The mixture was stirred at room temperature for 5 h and then washed by 10% aqueous citric acid. After aqueous workup, the resulting product was dissolved in CH_2Cl_2 (2 mL) and treated with pentane (5 mL). The filtrate was concentrated in vacuo to give nitro compound **3b** as a white solid (126 mg, 70% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.59 (s, 3H), 2.82−2.92 (m, 1H), 3.11−3.21 (m, 1H), 4.05−4.25 (m, 2H), 7.18−7.40 (m, 8H), 8.27 (d, J = 8.1 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.6 (CH_3), 34.4 (CH_2), 54.6 (C), 71.4 (CH_2), 117.3 (CH), 124.4 (CH), 125.8 (CH),

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126.5 (CH), 128.4 (CH), 128.8 (C), 129.1 (CH), 129.6 (CH), 137.8 (C), 140.0 (C), 170.7 (C), 177.9 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{18}H_{16}N_2O_4Na$ 347.1008, found 347.1010; R_f (AcOEt/petroleum ether 1/1) 0.72; mp 147−150 °C.

*1-Acetyl-3-methyl-3-(2-nitroethyl)indolin-2-one (**3c**).* To a solution of oxindole **6c** (97.2 mg, 0.441 mmol), DMAP (5.66 mg, 0.046 mmol), and triethylamine (72 μL, 0.51 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added acetyl chloride (35 μL, 0.48 mmol). The mixture was stirred at room temperature overnight and then diluted with CH_2Cl_2, washed with 10% aqueous citric acid, and dried over magnesium sulfate. After concentration in vacuo and purification by chromatography over silica gel (10 g, eluent CH_2Cl_2/petroleum ether 4/1), oxindole **3c** was afforded as a white amorphous solid (84.3 mg, 73% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.48 (s, 3H), 2.46−2.57 (m, 1H), 2.64−2.67 (m, 4H), 4.10−4.29 (m, 2H), 7.23−7.29 (m, 2H), 7.31−7.39 (m, 1H), 8.23 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.6 (CH_3), 26.5 (CH_3), 35.0 (CH_2), 46.6 (C), 71.0 (CH_2), 116.9 (CH), 122.2 (CH), 125.7 (CH), 129.1 (CH), 130.7 (C), 139.1 (C), 170.7 (C), 179.8 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{13}H_{14}N_2O_4Na$ 285.0851, found 285.0852; R_f (CH_2Cl_2) 0.37.

*tert-Butyl 3-(2-Nitroethyl)-2-oxo-3-phenylindoline-1-carboxylate (**3e**).* To a solution of oxindole **6b** (142.2 mg, 0.500 mmol) and DMAP (5.66 mg, 0.046 mmol) in dry CH_2Cl_2 (8 mL) at 0 °C was added *tert*-butyl pyrocarbonate (120 mg, 0.55 mmol). The mixture was stirred at room temperature for 2.5 h and then diluted with CH_2Cl_2, washed with 10% aqueous citric acid, and dried over magnesium sulfate. After concentration in vacuo and purification by chromatography over silica gel (10 g, eluent 1% triethylamine in CH_2Cl_2), oxindole **3e** was afforded as a white solid (96.3 mg, 53% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.49 (s, 9H), 2.80−2.90 (m, 1H), 3.08−3.18 (m, 1H), 4.05−4.15 (m, 1H), 4.20−4.30 (m, 1H), 7.19−7.38 (m, 8H), 7.88 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.0 (CH_3), 34.6 (CH_2), 54.4 (C), 71.4 (CH_2), 85.1 (C), 115.7 (CH), 124.6 (CH), 125.1 (CH), 126.7 (CH), 128.3 (CH), 128.7 (C), 129.1 (CH), 129.5 (CH), 138.0 (C), 139.6 (C), 148.9 (C), 175.4 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{21}H_{22}N_2O_5Na$ 405.1426, found 405.1425; R_f (AcOEt/petroleum ether 1/6) 0.80; mp 56−60 °C.

*tert-Butyl 3-Methyl-3-(2-nitroethyl)-2-oxoindoline-1-carboxylate (**3f**).* Similarly, compound **3f** (733 mg, 64% yield) was obtained as a white solid from **6c**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 3H), 1.59 (s, 9H), 2.38−2.48 (m, 1H), 2.55−2.64 (m, 1H), 4.00−4.10 (m, 1H), 4.18−4.28 (m, 1H), 7.14−7.20 (m, 2H), 7.28−7.32 (m, 1H), 7.80 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.3 (CH_3), 27.8 (CH_3), 34.8 (CH_2), 46.3 (C), 70.9 (CH_2), 84.6 (C), 115.2 (CH), 122.3 (CH), 124.8 (CH), 128.7 (CH), 130.4 (C), 138. Six (C), 148.7 (C), 177.3 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{16}H_{20}N_2O_5Na$ 343.1270, found 343.1266; R_f (CH_2Cl_2) 0.33; mp 106−109 °C.

*(S)-1-(Methylsulfonyl)-3-((S)-2-nitro-1-phenylethyl)-3-phenylindolin-2-one (**3g**).* To a solution of oxindole **6a** (121.4 mg, 0.339 mmol), DMAP (4.70 mg, 0.038 mmol), and triethylamine (56 μL, 0.40 mmol) in dry CH_2Cl_2 (2 mL) at 0 °C was added methanesulfonyl chloride (30 μL, 0.39 mmol). The mixture was stirred at room temperature overnight. After aqueous workup, the resulting product was chromatographed over silica gel (22 g, eluent CH_2Cl_2) to afford nitro compound **3g** as a white solid (78 mg, 53% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.54 (s, 3H), 4.73−4.99 (m, 3H), 6.79−6.81 (m, 2H), 7.10−7.21 (m, 3H), 7.40−7.53 (m, 6H), 7.60−7.64 (m, 2H), 7.72 (d, J = 7.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 40.1 (CH_3), 51.2 (CH), 59.7 (C), 76.3 (CH_2), 114.2 (CH), 125.0 (CH), 126.0 (C), 126.4 (CH), 127.6 (CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 129.4 (CH), 129.5 (CH), 130.3 (CH), 133.4 (C), 134.3 (C), 140.1 (C), 174.4 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{23}H_{20}N_2O_5SNa$ 459.0991, found 459.0993; R_f (CH_2Cl_2) 0.74; mp dec 160 °C.

Synthesis of Compound 7. A mixture of nitro compound **3a** (42.25 mg, 0.105 mmol) and 10% Pd on C (30.3 mg) in MeOH (2 mL) was stirred at room temperature under an H_2 balloon overnight. After filtration through a pad of Celite, concentration in vacuo, and purification by chromatography over silica gel (2g, eluent 80/20 CH_2Cl_2/AcOEt), hydroxamic acid **7** (30.0 mg, yield 74%) and lactam **2a** (5.80 mg, yield 15%) were afforded as white amorphous solids: ^{1}H NMR (300 MHz, DMSO-d_6) 1.24 (s, 3H), 3.79 (dd, J = 9.9, 4.5 Hz, 1H), 4.11 (dd, J = 9.9, 6.6 Hz, 1H), 4.63 (dd, J = 6 Hz, J = 4.5 Hz, 1H), 6.57 (m, 2H), 6.81−6.84 (m, 2H), 6.96−7.00 (m, 6 H), 7.37 (m, 2 H), 7.51 (dd, J = 7.8, 1.8 Hz, 1H), 8.09 (d, J = 7.5 Hz, 1H), 10.00 (s, 1H),10.64 (br s, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 23.1 (CH_3), 46.3 (CH), 54.3 (CH_2), 62.4 (C), 126.6 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 128.9 (CH), 129.1 (CH), 129.4 (CH), 129.4 (CH), 129.5 (CH), 130.3 (CH), 134.5 (C), 138.5 (C), 139.4 (C), 140.9 (C), 170.5 (C), 173.0 (C); HRMS (ESI-TOF, CH_3OH) m/z $[M + Na]^+$ calcd for $C_{24}H_{22}N_2O_3Na$ 409.1523, found 409.1521; R_f = 0.08 (AcOEt).

Procedures for the Synthesis of Compounds 8. Compound **8d** was prepared according to the literature.[16]

*1-Acetyl-3-hydroxy-3-methylindolin-2-one (**8a**).* Under argon atmosphere, a 2.5 M solution of methylmagnesium bromide in ether (2.8 mL, 7 mmol) was added using a syringe pump (0.5 mL per hour) to a mixture of acetylisatin (1.23 g, 6.53 mmol) and THF (33 mL) at −60 °C. The resulting mixture was stirred overnight at −60 °C, quenched with 1 M chlorhydric acid (8 mL) at −60 °C, and then concentrated in vacuo. The aqueous phase was extracted with AcOEt (3 × 8 mL). The organic phase was dried over sodium sulfate, concentrated in vacuo, and purified by chromatography over silica gel (42 g, eluent CH_2Cl_2). Hydroxyoxindole **8a** was afforded as a pale yellow solid (0.528 g, 45% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.67 (s, 3H), 2.70 (s, 3H), 3.15 (broad s, 1H), 7.17 (td, J = 7.5, 1.2 Hz, 1H), 7.29 (td, J = 7.9, 1.5 Hz, 1H), 7.37 (dd, J = 7.5, 1.2 Hz, 1H), 8.11 (d, J = 7.9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.6 (CH_3), 26.4 (CH_3), 73.6 (C), 116.9 (CH), 123.2 (CH), 125.8 (CH), 130.1 (CH), 130.5 (C), 139.0 (C), 170.9 (C), 179.1 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{11}H_{11}NO_3Na$ 228.0636, found 228.0643; R_f (AcOEt) 0.77; mp 119−121 °C (lit.[21] mp 102−103 °C).

*1-Acetyl-5-fluoro-3-hydroxy-3-methylindolin-2-one (**8b**).* Similarly, compound **8b** (0.155 g, 21% yield) was afforded as a light yellow solid from 1-acetyl-5-fluoroisatin (0.677 g, 3.27 mmol) and 2.5 M MeMgBr in ether (1.7 mL, 4.2 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.65 (s, 3H), 2.66 (s, 3H), 3.15 (s, 1H), 7.08 (td, J = 9, 2.7 Hz, 1H), 7.18 (dd, J = 7.5, 2.7 Hz, 1H), 8.22 (dd, J = 9, 4.5 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.7 (CH_3), 26.4 (CH_3), 73.6 (d, J = 1.7 Hz, C), 110.8 (d, J = 24.4 Hz, CH), 116.6 (d, J = 22.7 Hz, CH), 118.5 (d, J = 7.8 Hz, CH), 132.3 (d, J = 7.9 Hz, C), 134.9 (d, J = 2.6 Hz, C), 160.6 (d, J = 246 Hz, C), 170.6 (C), 178.8 (C); HRMS (ESI-TOF, MeOH) m/z $[M - H]^-$ calcd for $C_{11}H_9NO_3F$ 222.0572, found 222.0570; R_f (AcOEt/petroleum ether 1/1) 0.56; mp 112−116 °C.

*1-Acetyl-3-hydroxy-5-methoxy-3-methylindolin-2-one (**8c**).* Similarly, compound **8c** (0.345 g, 29% yield) was afforded as a light yellow solid from 1-acetyl-5-methoxyisatin (1.117 g, 5.09 mmol) and 2.5 M MeMgBr in ether (2.50 mL, 6.2 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.53 (s, 3H), 2.49 (s, 3H), 3.53 (s, 1H), 3.73 (s, 3H), 6.77 (dd, J = 8.7, 2.7 Hz, 1H), 6.89 (d, J = 2.7 Hz, 1H), 8.00 (d, J = 8.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 25.6 (CH_3), 26.2 (CH_3), 55.6 (CH_3), 73.7 (C), 109.0 (CH), 114.9 (CH), 118.0 (CH), 131.9 (C), 132.2 (C), 157.7 (C), 170.7 (C), 179.2 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{12}H_{13}NO_4Na$ 258.0742, found 258.0741; R_f (AcOEt/petroleum ether 1/1) 0.63; mp 118−120 °C.

*Benzyl 3-Hydroxy-3-(cyanomethyl)-2-oxoindoline-1-carboxylate (**8e**).* A mixture of *N*-benzyloxycarbonyl isatin[22] (0.485 g, 1.73 mmol), cyanoacetic acid (0.170 g, 2.00 mmol), and triethylamine (0.050 mL, 0.10 mmol) in DMF (8.5 mL) was heated at 70 °C for 3 h. DMF was removed in vacuo. Water was added and extracted three times with diethyl ether. After drying of the organic phases over sodium sulfate and concentration in vacuo, purification by chromatography over silica gel (16 g, eluent DCM) gave product **8e** as a beige solid (0.305 g, 54% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.65, 2.95 (ABq, J_{AB} = 18 Hz, 2H), 3.59 (br s, 1H), 5.34 (m, 2H), 7.18−7.39 (m, 7H), 7.58 (dd, J = 7.5, 1 Hz, 1H), 7.84 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.9 (CH_2), 69.3 (CH_2), 72.3 (C), 114.8 (C), 115.8 (CH),

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124.2 (CH), 125.9 (CH), 126.3 (C), 128.4 (CH), 128.7 (CH), 128.8 (CH), 131.4 (CH), 134.3 (C), 138.5 (C), 150.1 (C), 173.7 (C); HRMS (ESI-TOF, acetone) m/z $[M + Na]^+$ calcd for $C_{18}H_{14}N_2O_4Na$ 345.0851, found 345.0849; R_f (AcOEt/DCM 1/9) 0.42; mp 59−68 °C.

*3-Hydroxy-3-(cyanomethyl)-N,N-dimethyl-2-oxoindoline-1-carboxamide (**8f**).* A mixture of *N*-dimethylcarbamoyl isatin[23] (0.472 g, 2.17 mmol), cyanoacetic acid (0.213 g, 2.39 mmol), and triethylamine (0.060 mL, 0.43 mmol) in DMF (11 mL) was heated at 70 °C for 3 h. DMF was removed in vacuo. Water was added and extracted three times with diethyl ether. After drying of the organic phases over sodium sulfate and concentration in vacuo, purification by chromatography over silica gel (11 g, eluent DCM) gave product **8f** as a beige solid (0.405 g, 72% yield): ^{1}H NMR (300 MHz, DMSO-d_6) δ 2.98 (s, 3H), 3.05 (s, 3H), 3.20 (s, 2H), 6.97 (s, 1H), 7.09 (d, J = 7.8 Hz, 1H), 7.21 (td, J = 7.8, 1.2 Hz, 1H), 7.40 (td, J = 7.8, 1.2 Hz, 1H), 7.57 (d, J = 7.2 Hz, 1H). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.84−3.18 (m, 8H), 3.66 (br s, 1H), 7.16 (d, J = 8.1 Hz, 1H), 7.22 (td, J = 7.8, 1.2 Hz, 1H), 7.40 (td, J = 7.8, 1.2 Hz, 1H), 7.58 (d, J = 8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.20 (CH_2), 36.87 (CH_3), 38.41 (CH_3), 73.24 (C), 113.28 (CH), 115.05 (C), 123.94 (CH), 124.79 (CH), 127.37 (C), 131.06 (CH), 139.75 (C), 150.89 (C), 173.58 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{13}H_{13}N_3O_3Na$ 282.0855, found 282.0858; R_f (AcOEt) 0.55; mp 132−139 °C.

General Procedure for the Synthesis of Compounds 4. To a solution of 3-hydroxyoxindole **8a** (205.5 mg, 1.00 mmol) in CH_2Cl_2 (1 mL) were successively added Boc-β-alanine (227 mg, 1.2 mmol), DCC (227 mg, 1.1 mmol), and DMAP (147 mg, 1.2 mmol). The resulting mixture was stirred for 5 h at room temperature and then diluted with CH_2Cl_2 (10 mL) and filtered. The filtrate was successively washed with aqueous 10% citric acid, aqueous 10% sodium carbonate, and water. After drying over magnesium sulfate and concentration in vacuo, the residue was chromatographed over silica gel (11 g, eluant: 1% Et_3N in CH_2Cl_2) to yield Boc derivative **4b** (359 mg) as an amorphous solid: yield 95%.

*1-Acetyl-3-methyl-2-oxoindolin-3-yl (tert-Butoxycarbonyl)-glycinate (**4a**).* According to the general procedure, **4a** was obtained as a viscous liquid (132 mg, yield: 69%) from 3-hydroxyoxindole **8a** (108 mg, 0.526 mmol), Boc-Gly-OH (101.4 mg, 0.579 mmol), DCC (119.5 mg, 0.579 mmol), and DMAP (77.1 mg, 0.631 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.61 (s, 3H), 2.62 (s, 3H), 3.91 (d, J = 6 Hz, 2H), 4.77 (br s, 1H), 7.20−7.26 (m, 2H), 7.32 (t, J = 6 Hz, 1H), 8.19 (d, J = 6 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8 (CH_3), 26.5 (CH_3), 28.2 (CH_3), 42.0 (CH_2), 77.9 (C), 80.1 (C), 116.8 (CH), 122.1 (CH), 125.6 (C), 130.4 (CH), 139.5 (C), 155.3 (C), 168.9 (C), 170. Seven (C), 175.0 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{18}H_{22}N_2O_6Na$ 385.1376, found 385.1375; R_f (AcOEt/petroleum ether) 0.38.

*1-Acetyl-3-methyl-2-oxoindolin-3-yl 3-((tert-butoxycarbonyl)-amino)propanoate (**4b**):* ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.59 (s, 3H), 2.50 (m, 2H), 2.62 (s, 3H), 3.25 (m, 2H), 4.77 (br s, 1H), 7.12−7.22 (m, 2H), 7.31 (t, J = 7.8 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.9 (CH_3), 26.5 (CH_3), 28.4 (CH_3), 34.1 (CH_2), 36.0 (CH_2), 77.3 (C), 79.5 (C), 116.8 (CH), 121.8 (CH), 125.5 (CH), 128.1 (C), 130.2 (CH), 139.5 (C), 155.7 (C), 170.7 (C), 170. Nine (C), 175.4 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{19}H_{24}N_2O_6Na$ 399.1532, found 399.1532; R_f (AcOEt/petroleum ether 1/1) 0.77.

*1-Acetyl-3-methyl-2-oxoindolin-3-yl 4-((tert-Butoxycarbonyl)-amino)butanoate (**4c**).* According to the general procedure, **4c** was obtained as a viscous oil (210 mg, yield: 78%) from 3-hydroxyoxindole **8a** (142.0 mg, 0.692 mmol), Boc-NH-$(CH_2)_3$-COOH (168.6 mg, 0.830 mmol), DCC (157.5 mg, 0.761 mmol), and DMAP (101.2 mg, 0.830 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.34 (s, 9H), 1.56 (s, 3H), 1.62 (m, 2H), 2.29 (m, 2H), 2.58 (s, 3H), 3.00 (m, 2H), 4.75 (br s, 1H), 7.12 (t, J = 6.8 Hz, 1H), 7.19−7.27 (m, 2H), 8.16 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.7 (CH_3), 24.9 (CH_2), 26.3 (CH_3), 28.2 (CH_3), 30.6 (CH_2), 39.3 (CH_2), 76.8 (C), 78.9 (C), 116.5 (CH), 121.6 (CH), 125.3 (CH), 128.1 (C), 129.9 (CH), 139.3 (C), 155.8 (C), 170.5 (C), 171.4 (C), 175.3 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{20}H_{26}N_2O_6Na$ 413.1688, found 413.1689; R_f (AcOEt/CH_2Cl_2 1/4): 0.71.

*1-Acetyl-3-methyl-2-oxoindolin-3-yl 5-((tert-butoxycarbonyl)-amino)pentanoate (**4d**).* According to the general procedure, **4d** was obtained as a white solid (251 mg, yield: 95%) from 3-hydroxyoxindole **8a** (134.8 mg, 0.656 mmol), Boc-NH-$(CH_2)_4$-COOH (170.9 mg, 0.787 mmol), DCC (148.8 mg, 0.721 mmol), and DMAP (96.1 mg, 0.787 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36−1.42 (m, 11H), 1.47−1.58 (m, 5H), 2.29 (m, 2H), 2.62 (s, 3H), 3.01 (m, 2H), 4.46 (br s, 1H), 7.11−7.21 (m, 2H), 7.28 (td, J = 7.8, 1.8 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 21.8 (CH_3), 23.9 (CH_2), 26.5 (CH_3), 28.4 (CH_3), 29.2 (CH_2), 33.0 (CH_2), 39.9 (CH_2), 76.9 (C), 79.2 (C), 116.8 (CH), 121.7 (CH), 125.4 (CH), 128.3 (C), 130.1 (CH), 139.5 (C), 155.9 (C), 170.8 (C), 171.8 (C), 175.6 (C); HRMS (ESI, MeOH) m/z $[M + Na]^+$ calcd for $C_{21}H_{28}N_2O_6Na$ 427.1845, found 427.1844; R_f (AcOEt/CH_2Cl_2 1/4) 0.78; mp 98−102 °C.

*1-Acetyl-3-methyl-2-oxoindolin-3-yl 6-((tert-Butoxycarbonyl)-amino)hexanoate (**4e**).* According to the general procedure, **4e** was obtained as a solid (406.8 mg, yield: 97%) from 3-hydroxyoxindole **8a** (199.5 mg, 0.972 mmol), Boc-NH-$(CH_2)_5$-COOH (269 mg, 1.170 mmol), DCC (221 mg, 1.07 mmol), and DMAP (143 mg, 1.17 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.16−1.26 (m, 2H), 1.32−1.42 (m, 2H), 1.36 (s, 9H), 1.44−1.56 (m, 2H), 1.58 (s, 3H), 2.26 (m, 2H), 2.62 (s, 3H), 3.00 (m, 2H), 4.48 (br s, 1H), 7.11−7.26 (m, 2H), 7.29 (t, J = 7.6 Hz, 1H), 8.19 (d, J = 8.4 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8 (CH_3), 24.3 (CH_2), 26.0 (CH_2), 26.5 (CH_3), 28.4 (CH_3), 29.6 (CH_2), 33.9 (CH_2), 40.3 (CH_2), 76.9 (C), 79.0 (C), 116.8 (CH), 121.6 (CH), 125.4 (CH), 128.3 (C), 130.0 (CH), 139.5 (C), 155.9 (C), 170.7 (C), 171.9 (C), 175.5 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{22}H_{30}N_2O_6Na$ 441.2001, found 441.1998; R_f (AcOEt/CH_2Cl_2 1/9) 0.64; mp 67−72 °C.

*1-Acetyl-5-fluoro-3-methyl-2-oxoindolin-3-yl 3-((tert-Butoxycarbonyl)amino)propanoate (**4f**).* According to the general procedure, compound **4f** was obtained as a pale yellow solid (140 mg, yield: 60%) from 3-hydroxyoxindole **8b** (132 mg, 0.595 mmol), Boc-NH-$(CH_2)_2$-COOH (135 mg, 0.714 mmol), DCC (135 mg, 0.655 mmol), and DMAP (87.2 mg, 0.714 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.58 (s, 3H), 2.52 (t, J = 6 Hz, 2H), 2.61 (s, 3H), 3.25 (m, 2H), 4.75 (broad s, 1H), 6.92 (dd, J = 7.2, 2.7 Hz, 1H), 7.00 (td, J = 9, 2.7 Hz, 1H), 8.20 (dd, J = 9, 4.8 Hz, 1H); ^{13}C NMR (75.5 MHz, CD_3OD) δ 23.9 (CH_3), 26.4 (CH_3), 28.7 (CH_3), 34.7 (CH_2), 37.02(CH_2), 78.3 (d, J = 1.7 Hz, C), 80.3 (C), 110.9 (d, J = 25 Hz, CH), 117.2 (d, J = 23 Hz, CH), 119.2 (d, J = 7.8 Hz, CH), 132.0 (d, J = 8.2 Hz, C), 137.1 (d, J = 2.6 Hz, C), 158.2 (C), 161.8 (d, J = 244 Hz, C), 171.9 (C), 171.9 (C), 176.6 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{19}H_{23}FN_2O_6Na$ 417.1438, found 417.1439; R_f (AcOEt/petroleum ether 1/1) 0.65; mp 118−121 °C.

*1-Acetyl-5-methoxy-3-methyl-2-oxoindolin-3-yl 3-((tert-Butoxycarbonyl)amino)propanoate (**4g**).* According to the general procedure, **4g** was obtained as a solid (195.1 mg, yield: 91%) from hydroxyoxindole **8c** (124.6 mg, 0.529 mmol), Boc-NH-$(CH_2)_2$-COOH (120.2 mg, 0.636 mmol), DCC (120 mg, 0.582 mmol), and DMAP (77 mg, 0.64 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 1.57 (s, 3H), 2.50 (m, 2H), 2.60 (s, 3H), 3.25 (m, 2H), 3.74 (s, 3H), 4.80 (br s, 1H), 6.74 (d, J = 2.4 Hz, 1H), 6.81 (dd, J = 8.7, 2.4 Hz, 1H), 8.13 (d, J = 8.7 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.0 (CH_3), 26.4 (CH_3), 28.3 (CH_3), 34.0 (CH_2), 36.0 (CH_2), 55.6 (CH_3), 77.3 (C), 79.5 (C), 108.2 (CH), 114.3 (CH), 117.9 (CH), 129.5 (C), 132.8 (C), 155.7 (C), 157.5 (C), 170.4 (C), 170.9 (C), 175.4 (C); HRMS (ESI-TOF, MeOH) m/z $[M + Na]^+$ calcd for $C_{20}H_{26}N_2O_7Na$ 429.1637, found 429.1635; R_f (AcOEt/CH_2Cl_2 1/9) 0.67; mp 112−114 °C.

*1-Acetyl-5-methoxy-3-methyl-2-oxoindolin-3-yl 6-((tert-Butoxycarbonyl)amino)hexanoate (**4h**).* According to the general procedure, **4h** was obtained as a solid (185.68 mg, yield: 78%) from hydroxyoxindole **8c** (125.9 mg, 0.535 mmol), Boc-NH-$(CH_2)_5$-COOH (148.5 mg, 0.642 mmol), DCC (121.4 mg, 0.588 mmol), and DMAP (78.4 mg, 0.642 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.17−1.27 (m, 2H), 1.34−1.43 (m, 11 H), 1.46−1.50 (m, 5H), 2.18−

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2.37 (m, 2H), 2.59 (s, 3H), 2.98−3.04 (m, 2H), 3.74 (s, 3H), 4.50 (broad s, 1H), 6.73 (d, J = 2.7 Hz, 1H),), 6.79 (dd, J = 9, 2.7 Hz, 1H), 8.12 (d, J = 9 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.9 (CH_3), 24.3 (CH_2), 26.0 (CH_3), 26.4 (CH_2), 28.4 (CH_3), 29.6 (CH_2), 33.4 (CH_2), 40.3 (CH_2), 55.6 (CH_3), 77.2 (C), 79.1 (C), 108.2 (CH), 114.1 (CH), 117.9 (CH), 129.8 (C), 132.9 (C), 156.0 (C), 157.4 (C), 170.5 (C), 171.9 (C), 175.6 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{23}H_{32}N_2O_7Na$ 471.2107, found 471.2102; R_f (AcOEt/CH_2Cl_2 1/9) 0.64; mp 109−112 °C.

1-Acetyl-3-(cyanomethyl)-2-oxoindolin-3-yl 3-((tert-Butoxycarbonyl)amino)propanoate (4i). According to the general procedure, **4i** was obtained as a solid (110.5 mg, yield: 59%) from 3-hydroxyoxindole **8d** (108 mg, 0.469 mmol), Boc-NH-$(CH_2)_2$-COOH (106 mg, 0.56 mmol), and DCC (106 mg, 0.516 mmol) after 5 days at 40 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.35 (s, 9H), 2.57 (m, 2H), 2.62 (s, 3H), 2.74, 3.05 (ABq, J_{AB} = 16.5 Hz, 2H), 4.75 (br s, 1H), 7.23 (t, J = 8 Hz, 1H), 7.39−7.49 (m, 2H), 8.23 (d, J = 8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 26.5 (CH_3), 26.7 (CH_2), 28.3 (CH_3), 34.0 (CH_2), 35.9 (CH_2), 75.1 (C), 79.7 (C), 113.8 (C), 117.2 (CH), 122.8 (CH), 123.7 (C), 126.1 (CH), 131.8 (CH), 140.0 (C), 155.6 (C), 170.2 (C), 172.4 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{20}H_{23}N_3O_6Na$ 424.1485, found 424.1486; R_f (AcOEt) 0.71; mp 74−77 °C.

1-Acetyl-3-(cyanomethyl)-2-oxoindolin-3-yl 6-((tert-Butoxycarbonyl)amino)hexanoate (4j). According to the general procedure, **4j** was obtained (222 mg, yield: 98%) as a vitreous solid from hydroxyoxindole **8d** (117.8 mg, 0.511 mmol), Boc-NH-$(CH_2)_6$-COOH (142 mg, 0.614 mmol), and DCC (116 mg, 0.562 mmol) after 5 days at 40 °C: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.25 (m, 2H), 1.28−1.39 (m, 11 H), 1.53 (m, 2H), 2.32 (m, 2H), 2.61 (s, 3H), 2.72 (d, J = 17.5 Hz, 1H), 3.00−3.08 (m, 3H), 4.48 (br s, 1H), 7.23 (t, J = 8 Hz, 1H), 7.39−7.49 (m, 2H), 8.23 (d, J = 8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2 (CH_2), 25.9 (CH_2), 26.5 (CH_3), 26.7 (CH_2), 28.4 (CH_3), 29.6 (CH_2), 33.2 (CH_2), 40.2 (CH_2), 74.7 (C), 79.1 (C), 113.9 (C), 117.1 (CH), 122.7 (CH), 124.0 (C), 126.0 (CH), 131.6 (CH), 140.0 (C), 155.9 (C), 170.2 (C), 171.2 (C), 172.6 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{23}H_{29}N_3O_6Na$ 466.1954, found 466.1953; R_f (AcOEt/petroleum ether 1/1) 0.60.

Benzyl 3-((6-((tert-Butoxycarbonyl)amino)hexanoyl)oxy)-3-(cyanomethyl)-2-oxoindoline-1-carboxylate (4k). According to the general procedure, **4k** was obtained (153 mg, yield: 72%) after 3 days at 45 °C as an amorphous solid from hydroxyoxindole **8e** (128.6 mg, 0.399 mmol), Boc-NH-$(CH_2)_5$-COOH (121.3 mg, 0.520 mmol), and DCC (92 mg, 0.45 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15−1.26 (m, 2H), 1.32−1.42 (m, 11H), 1.46−1.56 (m, 2H), 2.31 (m, 2H), 2.63 (d, J = 17.4 Hz, 1H), 2.96−3.08 (m, 3H), 4.48 (br s, 1H), 5.33, 5.39 (ABq, J_{AB} = 12.3 Hz, 2H), 7.19 (t, J = 7.7 Hz, 1H), 7.29−7.43 (m, 7H), 7.92 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.2 (CH_2), 25.9 (CH_2), 26.6 (CH_2), 28.4 (CH_3), 29.6 (CH_2), 33.2 (CH_2), 40.3 (CH_2), 69.1 (CH_2), 74.5 (C), 79.1 (C), 114.1 (C), 115.9 (CH), 123.0 (CH), 124.0 (C), 125.6 (CH), 128.2 (CH), 128.6 (CH), 128.7 (CH), 131.6 (CH), 134.6 (C), 139.3 (C), 150.1 (C), 156.0 (C), 170.0 (C), 171.1 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{29}H_{33}N_3O_7Na$ 558.2216, found 558.2221; R_f (AcOEt/CH_2Cl_2 5/95) 0.53.

1-(Dimethylcarbamoyl)-3-(cyanomethyl)-2-oxoindolin-3-yl 6-((tert-Butoxycarbonyl)amino)hexanoate (4l). According to the general procedure, **4l** was obtained as an amorphous solid (170 mg, yield: 73%) after 3 days at 45 °C from hydroxyoxindole **8f** (127.1 mg, 0.49 mmol), Boc-NH-$(CH_2)_5$-COOH (138 mg, 0.60 mmol) and DCC (111 mg, 0.539 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.18−1.26 (m, 2H), 1.32−1.40 (m, 11H), 1.42−1.55 (m, 2H), 2.31 (m, 2H), 2.6−3.06 (m, 10H), 4.69 (br s, 1H), 7.08−7.15 (m, 2H), 7.33 (dd, J = 8, 1.5 Hz, 1H), 7.43 (d, J = 7.2 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.00 (CH_2), 25.67 (CH_2), 26.18 (CH_2), 28.17 (CH_3), 29.28 (CH_2), 33.07 (CH_2), 36.62 (CH_3), 37.88 (CH_3), 39.96 (CH_2), 74.77 (C), 78.70 (C), 112.95, 114.16 (C), 122.89, 124.09 (C), 124.29, 131.07, 139.82 (C), 150.31 (C), 155.74 (C), 169.20 (C), 170.92 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{24}H_{32}N_4O_6Na$ 495.2219, found 495.2221; R_f (AcOEt/petroleum ether 1/1) 0.50.

1-Acetyl-3-methyl-2-oxoindolin-3-yl 8-(tert-Butoxycarbonyl)-amino)-3,6-dioxaoctanoate (4m). According to the general procedure, **4m** was obtained (59.1 mg, yield: 51%) as a viscous oil from hydroxyoxindole **8a** (53 mg, 0.258 mmol), Boc-NH-$(CH_2)_2$O-$(CH_2)_2OCH_2COOH$ **9a**[17] (0.284 mmol), DCC (70.8 mg, 0.343 mmol), and DMAP (31.5 mg, 0.258 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.36 (s, 9H), 1.61 (s, 3H), 2.61 (s, 3H), 3.22 (m, 2H), 3.42 (t, J = 5 Hz, 2H), 3.50−3.59 (m, 4H), 4.07, 4.14 (ABq, J_{AB} = 17 Hz, 2H), 4.91 (br s, 1H), 7.14 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 8.19 (d, J = 8 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8 (CH_3), 26.5 (CH_3), 28.4 (CH_3), 40.3 (CH_2), 68.0 (CH_2), 70.2 (CH_2), 70.3 (CH_2), 70.9 (CH_2), 77.5 (C), 79.2 (C), 116.9 (CH), 121.9 (CH), 125.5 (CH), 127.7 (C), 130.3 (CH), 139.6 (C), 155.9 (C), 168.8 (C), 170.7 (C), 175.1 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{22}H_{30}N_2O_8Na$ 473.1900, found 473.1901; R_f (AcOEt/petroleum ether 1/1) 0.47.

Compound 4n. According to the general procedure, **4n** was obtained (123 mg, yield: 66%) as a viscous oil from hydroxyoxindole **8a** (64 mg, 0.312 mmol), Boc-[NH-$(CH_2)_2$O-$(CH_2)_2OCH_2CO]_2$OH **9b**[17] (155 mg, 0.374 mmol), DCC (70.8 mg, 0.343 mmol), and DMAP (45.8 mg, 0.374 mmol): ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (s, 9H), 1.61 (s, 3H), 2.62 (s, 3H), 3.20−3.25 (m, 2H), 3.38−3.60 (m, 14H), 3.90 (s, 2H), 4.06, 4.15 (ABq, J_{AB} = 16.8 Hz, 2H), 5.15 (br s, 1H), 7.11−7.26 (m, 3H), 7.31 (t, J = 7.89 Hz, 1H), 8.19 (d, J = 8.1 Hz, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 23.8 (CH_3), 26.6 (CH_3), 28.4 (CH_3), 38.5 (CH_2), 40.3 (CH_2), 68.0 (CH_2), 67.0 (CH_2), 70.1 (CH_2), 70.4 (CH_2), 70.5 (CH_2), 70.8, (CH_2) 70.9 (CH_2), 77.5 (C), 79.2 (C), 116.9 (CH), 121.9 (CH), 125.5 (CH), 127.7 (C), 130.4 (CH), 139.6 (C), 156.0 (C), 168.7 (C), 170.0 (C), 170.7 (C), 175.1 (C); HRMS (ESI-TOF, CH_2Cl_2/MeOH 95/5) m/z [M + Na]$^+$ calcd for $C_{28}H_{41}N_3O_{11}Na$ 618.2633, found 618.2633; R_f (AcOEt/MeOH 9/1): 0.51.

tert-Butyl rel-(3-(((S)-2-(R-1-Acetyl-2-oxo-3-phenylindolin-3-yl)-2-phenylethyl)amino)-3-oxopropyl)carbamate (4o). Step 1: To a mixture of nitro-oxindole **6d** (130 mg, 0.364 mmol) and $NiCl_2$ (96 mg, 0.74 mmol) in absolute ethanol (0.7 mL) was added sodium borohydride (233 mg, 6.16 mmol). The black mixture was stirred at room temperature. The progress of the reaction was monitored by TLC. Three further portions of sodium borohydride (50 mg, 1.3 mmol) were added after stirring for 3, 5, and 7 h, respectively. After dilution with CH_2Cl_2 (30 mL), the mixture was washed with 10% aqueous sodium carbonate. The organic phase was dried over sodium sulfate and then concentrated in vacuo. Step 2: To the resulting residue in CH_2Cl_2 (0.7 mL) were added 1-ethyl-3-(3-(dimethylamino)propyl)carbodiimide (EDC) (64 μL, 0.364 mmol) and Boc-NH$(CH_2)_2CO_2H$ (69.6 mg, 0.368 mmol). The mixture was stirred overnight, diluted with CH_2Cl_2 (20 mL), and washed with 10% aqueous citric acid and then water. After drying on sodium sulfate and concentration in vacuo, the residue was chromatographed over silica gel (5 g, eluent 7/3 CH_2Cl_2/AcOEt) to afford *tert*-butyl *rel*-(3-oxo-3-(((*S*)-2-((*R*)-2-oxo-3-phenylindolin-3-yl)-2-phenylethyl)amino)-propyl)carbamate (100 mg, 55% yield from **6d**) as a white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.33 (s, 9H), 1.94−2.05 (m, 2H), 3.13, 3.17 (ABq, J_{AB} = 6 Hz, 2H), 3.73 (t, J = 6 Hz, 2H), 4.13 (t, J = 7.8 Hz, 1H), 4.99 (br s, 1H), 5.74 (t, J = 5.7 Hz, 1H), 6.61 (d, J = 7.5 Hz, 1H), 6.84−7.26 (m, 11H), 7.57 (d, J = 7.5 Hz, 2H), 8.50 (br s, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 28.4 (CH_3), 36.1 (CH_2), 36.7 (CH_2), 38.9 (CH_2), 51.4 (CH), 60.2 (C), 79.3 (C), 109.8 (CH), 122.2 (CH), 125.9 (CH), 127.2 (CH), 127.3 (CH), 127.5 (CH), 127.8 (CH), 128.1 (CH), 128.7 (CH), 129.5 (CH), 131.3 (C), 136.7 (C), 138.3 (C), 139.9 (C), 156.1 (C), 171.5 (C), 179.7 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{30}H_{33}N_3O_4Na$ 522.2369, found 522.2369; R_f (AcOEt/petroleum ether 1/1) 0.18; mp 125−132 °C. Step 3: To *tert*-butyl *rel*-(3-oxo-3-(((*S*)-2-((*R*)-2-oxo-3-phenylindolin-3-yl)-2-phenylethyl)amino)propyl)carbamate (48.5 mg, 0.097 mmol) in CH_2Cl_2 (0.2 mL) were added DMAP (14.3 mg, 0.012 mmol), Et_3N (31 μL, 0.21 mmol) and acetyl chloride (16 μL, 0.21 mmol). The resulting mixture was stirred for 2.5 h at room temperature, diluted by CH_2Cl_2, and washed by water. After drying on sodium sulfate, concentration in vacuo, and chromatography over silica gel (6g, eluent

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95/5 CH_2Cl_2/AcOEt), the expected product **4o** (32.9 mg, 63% yield) was obtained as a white amorphous solid: ^{1}H NMR (300 MHz, $CDCl_3$, 1/9 mixture of Boc rotamers) δ 1.18, 1.32 (two s, 9H), 2.02 (t, J = 6 Hz, 2H), 2.64 (s, 3H), 3.13, 3.17 (ABq, J_{AB} = 6 Hz, 2H), 3.65−3.82 (m, 1H), 3.85−3.94 (m, 1H), 4.12 (dd, J = 11.1, 4.5 Hz, 1H), 4.88 (br s, 1H), 5.32 (br s, 1H), 6.84−6.87 (m, 2H), 6.97−7.11 (m, 5H), 7.15−7.25 (m, 2H), 7.30−7.35 (m, 2H), 7.50−7.54 (m, 2H), 7.85−7.88 (m, 1H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 27.0 (CH_3), 27.8 (minor CH_3), 28.4 (CH_3), 36.1 (CH_2), 36.5 (CH_2), 38.8 (CH_2), 51.7 (CH), 60.6 (C), 79.3 (C), 116.3 (CH), 124.7 (CH), 124.9 (CH), 127.1 (CH), 127.8 (CH), 128.1 (CH), 128.4 (CH), 129.1 (CH), 129.2 (CH), 130.6 (C), 135.6 (C), 138.0 (C), 138.8 (C), 155.9 (C), 170.4 (C), 171.6 (C), 178.9 (C); HRMS (ESI-TOF, MeOH) m/z [M + Na]$^+$ calcd for $C_{32}H_{35}N_3O_5Na$ 564.2474, found 564.2470; R_f (AcOEt/petroleum ether 1/1) 0.40.

■ ASSOCIATED CONTENT

Supporting Information

X-ray data of **2b** and copies of ^{1}H and ^{13}C spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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