

Scaffold-Directed Traceless Synthesis of Tetrahydro- β -carbolinehydantoins

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Pharmacologically interesting tetrahydro- β -carbolinehydantoins have been prepared through four-step traceless synthesis by a combinatorial approach. Two-arm PEG **1** (MW \approx 4000) was used as a soluble polymer support and reacted with Fmoc-protected L-tryptophane **2** to form bis-ester **3**. The resulting polymer-supported amino ester **3** was deprotected, and amino ester **4** underwent Pictet–Spengler reaction with various ketones to form tricyclic indoles **5**. The nucleophilic piperidine in the tricyclic indole reacted with isocyanate to generate the urea intermediates and simultaneously intramolecular cyclization to release the target compounds **7** from the support in good yields.

Introduction

Combinatorial chemistry is a powerful tool for the rapid preparation of low-molecular weight heterocyclic libraries in the discovery of new chemical entities with a desired property. The development of novel synthetic routes to functionalized heterocycles is required for the construction of druglike molecular libraries.

Polymer-supported synthesis is a core technology of combinatorial chemistry. It was originated from solid-phase peptide synthesis (SPPS) which was first reported by Merrifield in 1963. This technique is a highly efficient method for the generation of thousands of individual compounds.¹ In 1992, Ellman reported solid-phase synthesis of small organic heterocycles and extended this methodology from SPPS to the solid-phase organic synthesis (SPOS).² Now, SPOS using an insoluble solid support is extensively used in different branches of chemistry, especially for small molecule drug discovery for medicinal chemistry. Despite being well developed, SPOS still exhibits some disadvantages including heterogeneous reaction conditions, hard to monitor the reaction, nonlinear kinetic behavior, solvation problems, etc. To overcome these problems, we and others^{3–4} used soluble polymer supports as the alternative complement to SPOS in combinatorial synthesis. It retained the advantages of classical and solid-phase organic synthesis, and avoided their disadvantages. For example, the liquid-phase method provided the homogeneous reaction condition that product formation is easily monitored by conventional TLC, IR, and ¹H NMR spectroscopy. Product isolation, as well as purification, in each step of reaction sequence can be achieved by precipitation and filtration.

The use of a linker in polymer-supported synthesis is required because the target compounds are attached to the polymer carrier through a polar functionality. However, the linker may be detrimental to the biological activities and can cause undesired side effects during the lead optimization.

The traceless linker strategy is an exciting aspect of polymer-supported synthesis because of the lack of an extraneous functionality of final compounds.^{5–6}

Tetrahydro- β -carboline (THBC) is a privileged core structure in naturally occurring alkaloids which often shows a wide range of pharmacological properties (Figure 1). Eudistomin was isolated from the caribbean tunicate *Eudistoma olivaceum* and elucidated by Kobayashi and Rinehart.⁷ This kind of analogue has potent antiviral activity against the herpes simplex virus, type 1 (HSV-1). Hamann⁸ had isolated Manadomanzamines A and B from an Indonesian sponge *Acanthostrongylophora* sp. which exhibited strong activity against *Mycobacterium tuberculosis* (Mtb). Manadomanzamines A and B also exhibit activities against human immunodeficiency virus (HIV-1) and AIDS opportunistic fungal infections. Rohloff⁹ proposed that Yohimbine can antagonize 5HT-induced contraction in the rat stomach fundus, and the results was confirmed by Audia.¹⁰ Substituted heterocycles provides a high degree of molecular diversity, and their broad utility as therapeutics has been proven. The design concept of the present library originated from the observation of the biological role of the hydantoin moiety. The generation of a combined tetracyclic skeleton with tetrahydro- β -carboline, thus, has a substantial intellectual appeal resembling druglike molecules. Therefore, we report here an efficient, traceless, soluble-support synthesis of tetrahydro- β -carbolinehydantoins as a part of our ongoing projects directed toward the soluble polymer-supported synthesis of a large number of structurally diverse molecules.^{11–15} The heterocyclic template of target compounds **7** has multiple sites to generate diversity, and it is a good candidate to design scaffold-based combinatorial libraries for drug discovery.

Results and Discussions

Several synthetic approaches have been developed to generate THBC core-containing molecules which are mainly based on the acid-catalyzed Pictet–Spengler reaction of tryptophane analogues with aldehydes or activated ketones such as 1,2-dicarbonyl series. These include an asymmetric

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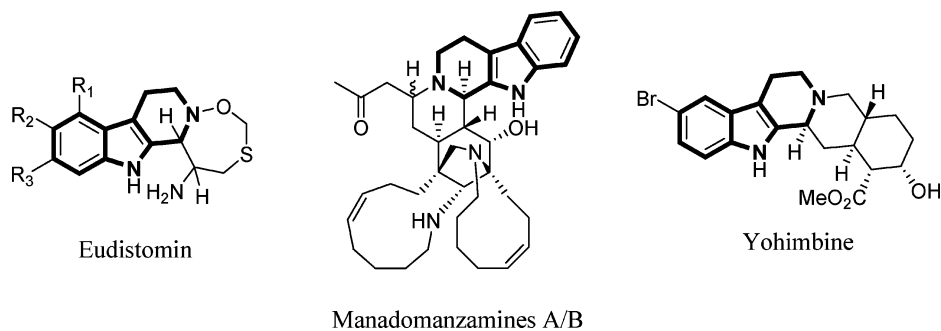
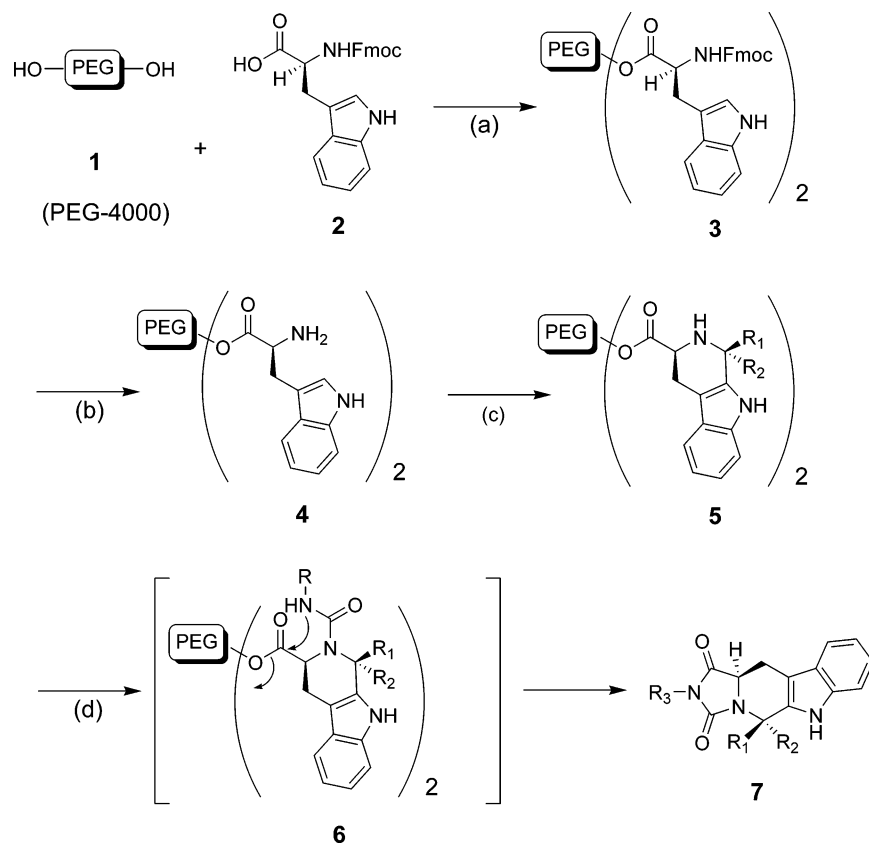


Figure 1. Natural occurring alkaloids with tetrahydro- β -carboline scaffold.

Scheme 1^a



^a Reagents and reaction conditions: (a) Fmoc-protected tryptophan, DCC, catalyst DMAP, CH₂Cl₂, room temp, stirred 15 h; (b) 10% piperidine, room temp, stirred, 30 min; (c) ketone, CHCl₃, reflux 15 h; (d) R₃-N=C=O, Et₃N, CH₂Cl₂, room temp, stirred 15 h

Pictet–Spengler reaction,¹⁶ the application of Pictet–Spengler reaction in total synthesis,¹⁷ a catalyzed Pictet–Spengler reaction,¹⁸ and a Pictet–Spengler reaction in ionic liquid.¹⁹ However, very few references^{21–22} regarding Pictet–Spengler reactions with ketones are known, probably, because of the slow imine formation of ketones and the production of a crowded tetrasubstituted C1 carbon of the tetrahydro- β -carboline. It should be noted that further attempts to functionalize the secondary nitrogen at the 2-position of the THBC ring system through reductive alkylation with aldehydes or reactions with acid halides, sulfonyl chlorides, and isocyanates were not successful in many examples because of steric congestion of that site.^{11,23}

Parallel synthesis of tetrahydro- β -carbolinehydantoins was carried out on a soluble polymer support, and liquid-phase reaction monitoring was performed by regular ¹H NMR. It is quiet clear that an NMR-based method that allows one to determine the extent of reaction progress would be superior

to other analytical methods or functional group spot checking which often gives ambiguous results. The synthetic sequence is illustrated in Scheme 1.

Two hydroxyl functional group PEG 1 (MW~4000) was employed as the soluble support and coupled with Fmoc-protected tryptophane 2 under the activated DCC/DMAP amino acid-coupling condition. The reaction progress was monitored by regular proton NMR once per hour, and when the reactions were completed, the reaction mixtures were subsequently purified by simple precipitation, filtration, and ether washing to remove unreacted reagents. In Figure 2, for example, we can observe the reaction progress by the ¹H NMR spectra after each stage of the synthetic sequence from starting material 3 to target compound 7. Compound 3 was characterized by two sets of featured chemical shift in spectrum A: (1) Ha and Hb represented the indole of the tryptophane and the aromatic protons of the Fmoc protecting group, respectively, and (2) the 4.1–4.9 ppm region repre-

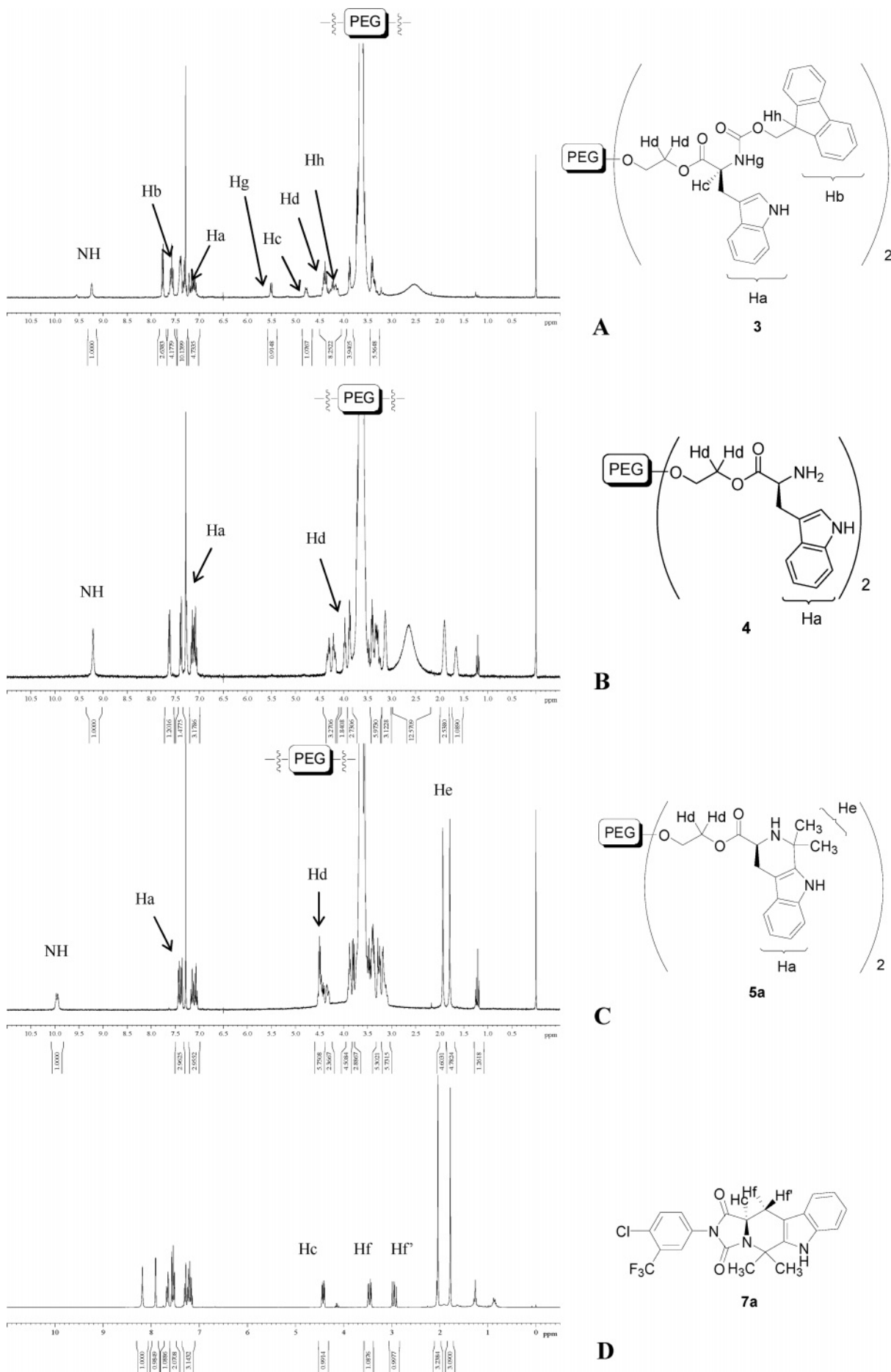


Figure 2. ^1H NMR monitoring of a stepwise tetrahydro- β -carbolines formation.

sented three kinds of protons such as Hc, the methine proton of tryptophane, and Hd. The methylene protons (Hd) of PEG-OCH₂CH₂-OCO were shifted downfield to \sim 0.8 ppm compared to that of PEG-OCH₂CH₂-OH because the electron density was dispersed by the carbonyl group and Hh was assigned as the methine proton of Fmoc. Compound **3** was then deprotected by 10% piperidine in dichloromethane at room temperature to remove the Fmoc group. We were conscious of the disappearance of Hb and Hg; only Ha remained in the aromatic region of spectrum B in compound **4**. The transformation of these signals indicated that the deprotection was accomplished, and no cleavage of the ester bond of PEG linkage was observed under basic condition. The resulting amino ester compound **4** underwent Pictet–Spengler cyclization with various kinds of ketones in refluxing chloroform for 15 h. Compared to aldehyde,¹⁵ the reactivity of ketone was more sluggish which took a longer reaction time to reach completion. The first diversity was introduced by the Pictet–Spengler reaction, and spectrum C showed that Hd was shifted downfield from 4.0 to 4.5 ppm after cyclization. The primary amine of compound **4** reacted with ketone to form imine first; then the π electrons of the indole ring donated to the electrophilic carbon of the imine and formed tricyclic compound **5** which was further confirmed by the two methyl groups as the characteristic He in the C spectrum (Figure 2). The two methyl groups are clearly different because they are affected by the chiral center at the α position of carbonyl group and show two singlets instead of one singlet only. Toward this end, compound **5** was treated with diverse isocyanates (R–N=C=O) in the presence of triethylamine at room temperature to yield the terminal hydantoin ring tracelessly. The nucleophilic secondary amine attacked the electron-deficient carbon of isocyanate, and compound **6** was formed. It is shown that PEG linker provides the lower steric hindrance compared to that of solid support near the reaction center when the newly formed piperidine (N2) reacted with isocyanates. Without isolation of intermediate **6**, the secondary amide of the urea attacked the ester bond, and the products were released from the support simultaneously. Comparing spectra C and D in Figure 2, we found that the proton peaks of PEG (3.7 ppm) disappeared. This result indicated that the target product was released from PEG support after concomitant cleavage–cyclization. Doublet of doublets protons of three sets which represent the methine of chiral center (He) and the methylene adjacent to chiral center (Hf, Hf') appeared in spectrum D. Isothiocyanates (R–N=C=S) also reacted with compound **5**, but a longer reaction time and more harsh conditions were required to obtain similar results (data is shown in the Supporting Information). At this step, we introduced the second diversity point and released the target products from the support without an additional cleavage step. The total yields ranged from 65 to 83% after purification by silica gel chromatography through four-step synthesis. No attempts were made to optimize the reaction conditions, and all reagents were used directly without further purification. Products from validation libraries are characterized by mass spectrometry and ¹H NMR, confirming that in each reaction

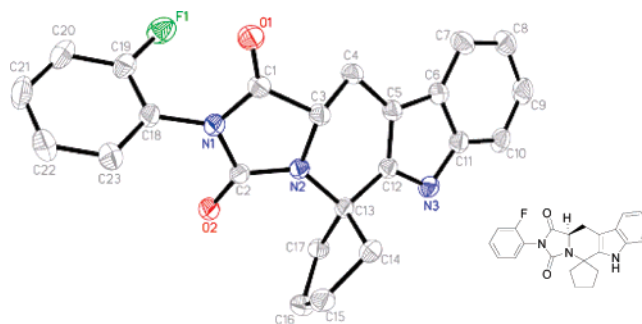


Figure 3. ORTEP diagram of **7i** (R, R₁ = $-(\text{CH}_2)_4-$) with crystallographic numbering system.

the major compound has a molecular ion corresponding to the appropriate product.

We also obtained the ORTEP diagram (Figure 3) of the corresponding spiro-fused tetrahydro- β -carboline **7i** from the X-ray diffraction studies to prove the absolute structure of the compound. It was shown that the plane of 2-fluorophenyl was slightly twisted with the plane of the fused tetracycle and that the plane of the cyclopentyl was perpendicular to the plane of the fused tetracycle. The fluorine atom F1 aligns close to the oxygen atom O1 but not to O2.

The stereochemistry of Pictet–Spengler cyclization is controlled by various factors,^{25–26} and literature about the asymmetric Pictet–Spengler reaction applied in natural products synthesis has been published.^{26–29} In our study, the substituents of the ketone are important to the stereochemistry. If the size difference of the two substituent groups of ketone is large, the intermediates prefer to align in the *trans* conformation to minimize the steric hindrance. If the size difference of the two alkyl group of ketone is small, two diastereomers were obtained, and *trans* form is the major product. 2-Butanone underwent Pictet–Spengler cyclization with compound **4** and subsequently reacted with isocyanate to release **7r** from the support. The mixtures could not be separated by column chromatography, and the ratio of *cis/trans* diastereomers was about 2/3, which was determined by ¹H NMR. However, the diastereomer mixtures tended to reach 1:1 ratio after storage of compounds at room temperature for a few days. This resulted from the small size difference between methyl and ethyl (Table 1, **7r**). 2-Heptanone (Table 1, **7k–7o**) was reacted with the same reaction sequence as 2-butanone, and we only observe the *trans* products by NMR and HPLC. The large size difference between the methyl and pentyl groups caused the formation of the thermodynamically more stable adducts.

Conclusions

In summary, a novel traceless combinatorial synthesis of biologically interesting 1,1-disubstituted tetrahydro- β -carbolinehydantoin at mild condition has been demonstrated. This strategy permits easy preparation of conformationally constrained tetracyclic (even pentacyclic) tetrahydro- β -carbolines backbone with two points of diversity which provides access to new tools for studying biology. It is worthy to note that, in contrast to the various restrictions on the analysis of reaction development in solid-phase synthesis, liquid-phase synthesis allows routine analytical instruments

Table 1. Synthesis of Tetrahydro- β -carboline **7** on the Soluble Support

Entry	Ketone	Isocyanate	LRMS	Yield
7a			447	67 %
7b			345	68 %
7c			370	80 %
7d			389	74 %
7e			359	78 %
7f			371	81 %
7g			473	72 %
7h			389	81 %
7i			389	83 %
7j			385	78 %
7k			415	67 % ^a
7l			415	77 % ^a
7m			419	74 % ^a
7n			503	65 % ^a
7o			401	70 % ^a
7p			487	68 %
7q			399	80 %
7r			384	70 % ^b

^a Product was isolated as the trans isomer only. ^b Product was isolated as diastereomers in a cis/trans ratio of 2:3.

such as conventional proton NMR to monitor reaction progress without following cleave-and-analyze method. Furthermore, integration of two privileged scaffolds into one molecule may create a more diverse range of pharmacophores for the drug discovery. Synthesis and screening of focused combinatorial library including the union of these two scaffolds such as hydantoin and tetrahydro- β -carbolin, may lead to the discovery of interesting biological activities.

Experimental Section

General. Dichloromethane was distilled from calcium hydride before use. All reactions were performed under an inert atmosphere with unpurified reagents and dry solvents.

Analytical thin-layer chromatography (TLC) was performed using 0.25 mm silica gel-coated Kieselgel 60 F₂₅₄ plates. Flash chromatography was performed using the indicated solvent and silica gel 60 (Merck, 230-400 mesh). Microwave flash heating was performed in CEM Discovery equipment. ¹H NMR (300 MHz) and ¹³C NMR (75 MHz) spectra were recorded on a Bruker DX-300 spectrometer. Chemical shifts are reported in parts per million (ppm) on the δ scale from an internal standard. High-resolution mass spectra (HRMS) were recorded on a JEOL TMS-HX 110 mass spectrometer. Normal phase HPLC was performed on a Shimadzu LC-10AT series machine with a Hypersil (250 \times 4.6 mm) analytical column. PEG was purchased from SHOWA. Fmoc-protected amino acids were purchased from Advanced ChemTech.

General Procedure for the Synthesis of Tetracyclic Tetrahydro- β -carbolines 7a–7r. Polymer support **1** (PEG 4000, 1.0 g, 1.0 equiv, 0.25 mmol) in 5 mL of dichloromethane was coupled with Fmoc-tryptophan **2** (0.28 g, 2.6 equiv, 0.66 mmol) in 5 mL of dichloromethane, which was treated with DCC (2.4 equiv, 0.60 mmol) in presence of 4-dimethylaminomethyl pyridine (DMAP) (0.003 g), and the mixture was stirred for fifteen hours. Insoluble dicyclohexyl urea (DCU) was filtered off, and the reaction mixture was diluted with slow addition of cold ether (100 mL). The precipitated ester conjugate was filtered through a fritted funnel, washed with ether, and dried for the next step.

The crude ester conjugate **3** (1.1 g, 1.0 equiv, 0.25 mmol) in 5 mL of dichloromethane was treated with 5 mL of 10% piperidine in dichloromethane, and the mixture was stirred for 30 min. The reaction mixture was then treated with excess of ether (100 mL) to precipitate the deprotected polymer conjugate **4**. The separated solid was washed with ether (100 mL) to remove the piperidine and dried. The crude amino ester conjugate **4** (1.1 g, 1.0 equiv, 0.25 mmol) in 10 mL of chloroform was treated with a solution of excess ketone (5.0 eq, 1.25 mmol), and the mixture was refluxed for fifteen hours. The reaction mixture was then treated with ether (100 mL) to precipitate the polymer conjugate **5**. The separated solid was washed with ether (100 mL) to remove the unreacted ketone and dried. The tricyclic bis-ester conjugate **5** (1.1 g, 0.25 mmol) was dissolved in dichloroethane (10 mL), to which isocyanate (10.0 equiv, 2.5 mmol) and triethylamine (0.25 mL, 10.0 equiv, 2.5 mmol) were added, and the mixture was stirred for fifteen hours when the TLC showed complete release of the desired compound from the support. The reaction mixture was then diluted with cold ether to precipitate the polymer which was filtered through a fritted funnel, and the residue was again washed with cold ether. The combined filtrate was evaporated and checked for purity by NMR. The residual solid was then purified by silica gel column chromatography using a 4:1 mixture of hexane and ethyl acetate as eluent and gave the corresponding products in 65–83% yields.

2-(4-Chloro-3-trifluoromethyl-phenyl)-10,10-dimethyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (7a). The product was isolated as white solid in 67% yield. $[\alpha]_D^{25} = -102.4^\circ$ ($c = 0.1$). ¹H NMR (300 MHz, CDCl₃): δ 8.18 (s, 1H, NH), 7.91 (d, 1H, $J = 2.3$ Hz), 7.66

(dd, 1H, $J = 2.3, 8.6$ Hz), 7.58–7.51 (m, 2H), 7.31–7.14 (m, 3H), 4.42 (dd, 1H, $J = 11.3, 4.5$ Hz), 3.46 (dd, 1H, $J = 14.9, 4.5$ Hz), 2.94 (dd, 1H, $J = 14.9, 11.3$ Hz), 2.04 (s, 3H), 1.78 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.1 (C_q), 152.5 (C_q), 138.1 (C_q), 136.2 (C_q), 132.0 (CH), 131.5 (C_q), 130.4 (C_q), 130.1 (CH), 129.0 (C_q), 126.0 (C_q), 125.2 (CH), 124.1 (C_q), 122.7 (CH), 120.2 (CH), 118.4 (CH), 111.1(CH), 105.1 (C_q), 56.1 (CH), 56.0 (C_q), 28.2 (CH_3), 25.8 (CH_3), 22.9 (CH_2). IR (KBr): ν 3350, 1730, 1488, 1430, 1314, 1176 cm^{-1} . EI-MS: m/z 447 (M^+). HRMS Calcd for $\text{C}_{22}\text{H}_{17}\text{ClF}_3\text{N}_3\text{O}_2$: m/z 447.0961. Found: m/z 447.0964.

10,10-Dimethyl-2-phenyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (7b). The product was isolated as white solid in 68% yield. $[\alpha]_{\text{D}}^{25} = -37.2^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 7.95 (s, 1H, NH), 7.57–7.11 (m, 9H), 4.42 (dd, 1H, $J = 11.4, 4.4$ Hz), 3.48 (dd, 1H, $J = 15.0, 4.4$ Hz), 2.95 (dd, 1H, $J = 15.0, 11.4$ Hz), 2.07 (s, 3H), 1.81 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.6 (C_q), 153.4 (C_q), 138.5 (C_q), 136.1 (C_q), 131.5 (C_q), 129.0 (CH), 128.1 (CH), 126.3 (CH), 122.7 (CH), 120.4 (C_q), 120.3 (CH), 118.5 (CH), 111.1 (CH), 105.6 (C_q), 56.0 (CH), 55.7 (C_q), 28.3 (CH_3), 25.9 (CH_3), 23.0 (CH_2). IR (KBr): ν 3409, 1708, 1414 cm^{-1} . EI-MS: m/z 345 (M^+). HRMS Calcd for $\text{C}_{21}\text{H}_{19}\text{N}_3\text{O}_2$: m/z 345.1477. Found: m/z 345.1476.

3-(10,10-Dimethyl-1,3-dioxo-3a,4,9,10-tetrahydro-3H-2,9,10a-triaza-cyclopenta[b]fluorene-2-yl)-benzotrile (7c). The product was isolated as white solid in 80% yield. $[\alpha]_{\text{D}}^{25} = -111.1^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 7.99 (s, 1H, NH), 7.90 (s, 1H), 7.85–7.81 (m, 1H), 7.67–7.53 (m, 3H), 7.38 (d, 1H, $J = 7.9$ Hz), 7.27–7.18 (m, 2H), 4.44 (dd, 1H, $J = 11.3, 4.5$ Hz), 3.49 (dd, 1H, $J = 14.9, 4.5$ Hz), 2.95 (dd, 1H, $J = 14.9, 11.3$ Hz), 2.07 (s, 3H), 1.82 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.0 (C_q), 152.5 (C_q), 138.2 (C_q), 136.2 (C_q), 132.6 (C_q), 131.3 (CH), 130.1 (CH), 129.8 (CH), 129.3 (CH), 126.1 (C_q), 122.8 (CH), 120.3 (CH), 118.4 (CH), 117.9 (C_q), 113.2 (C_q), 111.1 (CH), 105.3 (C_q), 56.1 (CH), 56.0 (C_q), 28.3 (CH_3), 25.9 (CH_3), 23.0 (CH_2). IR (KBr): ν 3397, 2233, 1730, 1714, 1412 cm^{-1} . EI-MS: m/z 370 (M^+). HRMS Calcd for $\text{C}_{22}\text{H}_{18}\text{N}_4\text{O}_2$: 370.1430. Found: 370.1427.

2-(4-Ethoxy-phenyl)-10,10-dimethyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (7d). The product was isolated as white solid in 74% yield. $[\alpha]_{\text{D}}^{25} = -119.8^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 8.11 (s, 1H, NH), 7.54 (d, 1H, $J = 7.0$ Hz), 7.38–7.12 (m, 5H), 6.98–6.94 (m, 2H), 4.39 (dd, 1H, $J = 11.3, 4.5$ Hz), 4.04 (q, 2H, $J = 7.0$ Hz), 3.46 (dd, 1H, $J = 14.9, 4.5$ Hz), 2.93 (dd, 1H, $J = 14.9, 11.3$ Hz), 2.05 (s, 3H), 1.79 (s, 3H), 1.42 (t, 3H, $J = 7.0$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 170.9 (C_q), 158.6 (C_q), 153.8 (C_q), 138.5 (C_q), 136.2 (C_q), 127.6 (CH), 126.2 (C_q), 124.0 (C_q), 122.6 (CH), 120.1 (CH), 118.4 (CH), 114.9 (CH), 111.1 (CH), 105.4 (C_q), 63.7 (CH_2), 56.0 (CH), 55.7 (C_q), 28.3 (CH_3), 25.9 (CH_3), 23.0 (CH_2), 14.7 (CH_3). IR (KBr): ν 3339, 1723, 1714, 1516, 1254 cm^{-1} . EI-MS: m/z 389 (M^+). HRMS Calcd for $\text{C}_{23}\text{H}_{23}\text{N}_3\text{O}_3$: 389.1739. Found: 389.1737.

10,10-Dimethyl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (7e). The product

was isolated as white solid in a 78% yield. ^1H NMR (300 MHz, CDCl_3): δ 7.94 (s, 1H, NH), 7.55 (d, 1H, $J = 7.5$ Hz), 7.39–7.09 (m, 7H), 4.41 (dd, 1H, $J = 10.7, 3.5$ Hz), 3.48 (dd, 1H, $J = 15.5, 3.5$ Hz), 2.94 (dd, 1H, $J = 15.5, 10.7$ Hz), 2.40 (s, 3H), 2.06 (s, 3H), 1.80 (s, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.7 (C_q), 153.5 (C_q), 139.1 (C_q), 138.5 (C_q), 136.1 (C_q), 131.3 (C_q), 129.1 (CH), 128.9 (CH), 127.0 (CH), 126.3 (C_q), 123.5 (CH), 122.7 (CH), 120.3 (CH), 118.5 (CH), 111.1 (CH), 105.6 (C_q), 56.0 (CH), 55.7 (C_q), 28.3 (CH_3), 25.9 (CH_3), 23.0 (CH_2), 21.4 (CH_3). IR (KBr): ν 3329, 1697, 1638 cm^{-1} . EI-MS: m/z : 359 (M^+). HRMS Calcd for $\text{C}_{22}\text{H}_{21}\text{N}_3\text{O}_2$: m/z 359.1634. Found: m/z 359.1634.

(11a'R)-2'-Phenyl-11',11a'-dihydrospiro[cyclopentane-1,5'-imidazo[1',5':1,6]pyrido[3,4-b]indole]-1',3'(2'H,6'H)-dione (7f). The product was isolated as black solid in 81% yield. $[\alpha]_{\text{D}}^{25} = -71.6^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 7.92 (s, 1H, NH), 7.55–7.12 (m, 9H), 4.40 (dd, 1H, $J = 11.4, 4.7$ Hz), 3.45 (dd, 1H, $J = 15.0, 4.7$ Hz), 3.28–3.18 (m, 1H), 2.96 (dd, 1H, $J = 15.0$ Hz, $J = 11.4$ Hz), 2.43–1.84 (m, 7H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.7 (C_q), 153.3 (C_q), 138.5 (C_q), 136.3 (C_q), 131.5 (C_q), 129.0 (CH), 128.2 (CH), 126.3 (CH), 126.1 (C_q), 122.6 (CH), 120.2 (CH), 118.3 (CH), 111.0 (CH), 105.8 (C_q), 65.7 (C_q), 56.9 (CH), 42.1 (CH_2), 37.8 (CH_2), 27.4 (CH_2), 26.3 (CH_2), 23.3 (CH_2). IR (KBr): ν 3343, 1705, 1413 cm^{-1} . EI-MS: m/z 371 (M^+). HRMS Calcd for $\text{C}_{23}\text{H}_{21}\text{N}_3\text{O}_2$: 371.1634. Found: 371.1637.

(11a'R)-2'-[4-Chloro-3(trifluoromethyl)phenyl]-11',11a'-dihydrospiro[cyclopentane-1,5'-imidazo[1',5':1,6]pyrido[3,4-b]indole]-1',3'(2'H,6'H)-dione (7g). The product was isolated as yellow solid in 72% yield. $[\alpha]_{\text{D}}^{25} = -53.8^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 7.90 (d, 1H, $J = 2.2$ Hz), 7.85 (s, 1H, NH), 7.70–7.59 (m, 2H), 7.53 (d, 1H, $J = 7.2$ Hz), 7.37 (d, 1H, $J = 7.9$ Hz), 7.27–7.15 (m, 2H), 4.44 (dd, 1H, $J = 11.4, 4.7$ Hz), 3.47 (dd, 1H, $J = 15.1, 4.7$ Hz), 3.27–3.17 (m, 1H), 2.98 (dd, 1H, $J = 15.1$ Hz, $J = 11.4$ Hz), 2.46–1.88 (m, 7H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.1 (C_q), 152.4 (C_q), 138.3 (C_q), 136.3 (C_q), 132.0 (CH), 131.6 (C_q), 130.5 (C_q), 130.1 (CH), 129.3 (C_q), 126.0 (C_q), 125.2 (CH), 124.1 (C_q), 122.8 (CH), 120.3 (CH), 118.3 (CH), 111.1 (CH), 105.7 (C_q), 65.9 (C_q), 57.0 (CH), 42.1 (CH_2), 37.8 (CH_2), 27.4 (CH_2), 26.4 (CH_2), 23.3 (CH_2). IR (KBr): ν 3374, 1733, 1465, 1179 cm^{-1} . EI-MS: m/z 473 (M^+). HRMS Calcd for $\text{C}_{24}\text{H}_{19}\text{ClF}_3\text{N}_3\text{O}_2$: m/z 473.1118. Found: m/z 473.1114.

(11a'R)-2'-(3-Fluorophenyl)-11',11a'-dihydrospiro[cyclopentane-1,5'-imidazo[1',5':1,6]pyrido[3,4-b]indole]-1',3'(2'H,6'H)-dione (7h). The product was isolated as yellow solid in 81% yield. $[\alpha]_{\text{D}}^{25} = -106.2^\circ$ ($c = 0.5$). ^1H NMR (300 MHz, CDCl_3): δ 7.95 (s, 1H, NH), 7.61–7.03 (m, 8H), 4.41 (dd, 1H, $J = 11.3, 4.5$ Hz), 3.46 (dd, 1H, $J = 14.9, 4.5$ Hz), 3.28–3.18 (m, 1H), 2.98 (dd, 1H, $J = 14.9, 11.3$ Hz), 2.50–1.85 (m, 7H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.4 (C_q), 164.2 (C_q), 160.9 (C_q), 152.8 (C_q), 138.4 (C_q), 136.3 (C_q), 132.9 (C_q , $J_{\text{CF}} = 10.2$ Hz), 130.1 (CH, $J_{\text{CF}} = 8.9$ Hz), 126.0 (C_q), 122.6 (CH), 121.7 (CH, $J_{\text{CF}} = 3.3$ Hz), 120.2 (CH), 118.3 (CH), 115.0 (CH, $J_{\text{CF}} = 20.8$ Hz), 113.7 (CH, $J_{\text{CF}} = 24.5$ Hz), 111.0 (CH), 105.7 (C_q), 65.8 (C_q), 56.8 (CH), 42.1 (CH_2), 37.8 (CH_2), 27.3 (CH_2), 26.3 (CH_2), 23.3 (CH_2).

IR (KBr): ν 3381, 1729, 1494 cm^{-1} . EI-MS: m/z 389 (M^+). HRMS Calcd for $\text{C}_{23}\text{H}_{20}\text{FN}_3\text{O}_2$: m/z 389.1540. Found: m/z 389.1540.

(11a'R)-2'-(2-Fluorophenyl)-11',11a'-dihydrospiro[cyclopentane-1,5'-imidazo[1',5':1,6]pyrido[3,4-b]indole]-1',3'-(2'H,6'H)-dione (7i). The product was isolated as white solid in 83% yield. $[\alpha]_{\text{D}}^{25} = -86.4^\circ$ ($c = 0.5$). ^1H NMR (300 MHz, CDCl_3): δ 8.00 (s, 1H, NH), 7.54–7.14 (m, 8H), 4.45 (dd, 1H, $J = 11.0, 4.5$ Hz), 3.46 (dd, 1H, $J = 15.0, 4.5$ Hz), 3.25–3.16 (m, 1H), 3.01 (dd, 1H, $J = 15.0, 11.0$ Hz), 2.45–1.84 (m, 7H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.3 (C_q), 159.4 (C_q), 156.1 (C_q), 152.6 (C_q), 138.2 (C_q), 136.3 (C_q), 131.6 (CH, $J_{\text{CF}} = 8.0$ Hz), 130.8 (CH, $J_{\text{CF}} = 8.0$ Hz), 126.0 (C_q), 124.6 (CH, $J_{\text{CF}} = 3.8$ Hz), 122.5 (CH), 120.1 (CH), 118.2 (CH), 116.7 (CH, $J_{\text{CF}} = 19.4$ Hz), 111.0 (CH), 105.7 (C_q), 65.9 (C_q), 57.2 (CH), 42.2 (CH_2), 37.6 (CH_2), 27.2 (CH_2), 26.2 (CH_2), 23.4 (CH_2). IR (KBr): ν 3349, 1724, 1400 cm^{-1} . EI-MS: m/z 389 (M^+). HRMS Calcd for $\text{C}_{23}\text{H}_{20}\text{FN}_3\text{O}_2$: m/z 389.1540. Found: m/z 389.1537.

(11a'R)-2'-(3-Methylphenyl)-11',11a'-dihydrospiro[cyclopentane-1,5'-imidazo[1',5':1,6]pyrido[3,4-b]indole]-1',3'-(2'H,6'H)-dione (7j). The product was isolated as yellow solid in 78% yield. $[\alpha]_{\text{D}}^{25} = -106.4^\circ$ ($c = 0.5$). ^1H NMR (300 MHz, CDCl_3): δ 8.02 (s, 1H, NH), 7.53 (d, 1H, $J = 7.2$ Hz), 7.35 (d, 2H, $J = 7.5$ Hz), 7.26–7.13 (m, 5H), 4.40 (dd, 1H, $J = 11.4, 4.7$ Hz), 3.46 (dd, 1H, $J = 15.0, 4.7$ Hz), 3.28–3.18 (m, 1H), 2.97 (dd, 1H, $J = 15.0, 11.4$ Hz), 2.39 (s, 1H), 2.37–2.07 (m, 7H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.9 (C_q), 153.4 (C_q), 139.1 (C_q), 138.5 (C_q), 136.3 (C_q), 131.3 (C_q), 129.1 (CH), 128.9 (CH), 127.0 (CH), 126.0 (C_q), 123.5 (CH), 122.5 (CH), 120.1 (CH), 118.2 (CH), 111.0 (CH), 105.7 (C_q), 65.8 (C_q), 56.9 (CH), 42.9 (CH_2), 37.7 (CH_2), 27.3 (CH_2), 26.3 (CH_2), 23.3 (CH_2), 21.3 (CH_3); IR (KBr): 3379, 1721, 1719 cm^{-1} . EI-MS: m/z 385 (M^+). HRMS Calcd for $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_2$: m/z 385.1790. Found: m/z 385.1788.

2-Benzyl-10-pentyl-10-methyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (7k). The product was isolated as yellow solid in 67% yield. ^1H NMR (300 MHz, CDCl_3): δ 7.84 (s, 1H, NH), 7.53–7.12 (m, 9H), 4.71 (s, 2H), 4.23 (dd, 1H, $J = 11.4, 4.4$ Hz), 3.36 (dd, 1H, $J = 14.9, 4.4$ Hz), 3.21–3.09 (m, 1H), 2.75 (dd, 1H, $J = 14.9, 11.4$ Hz), 1.71 (m, 4H), 1.29–1.05 (m, 6H), 0.73 (t, 3H, $J = 6.5$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 171.6 (C_q), 154.3 (C_q), 137.4 (C_q), 136.3 (C_q), 136.1 (C_q), 128.7 (CH), 128.4 (CH), 127.8 (CH), 126.3 (C_q), 122.5 (CH), 120.1 (CH), 118.3 (CH), 111.1 (CH), 106.7 (C_q), 58.7 (C_q), 57.9 (CH), 42.1 (CH_2), 39.9 (CH_2), 31.9 (CH_2), 29.7 (CH_2), 27.9 (CH_3), 24.8 (CH_2), 22.8 (CH_2), 22.4 (CH_2), 13.9 (CH_3). IR (KBr): ν 3354, 1701, 1441 cm^{-1} . EI-MS: m/z 415 (M^+). HRMS Calcd for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_2$: m/z 415.2260. Found: m/z 415.2257.

10-Methyl-10-pentyl-2-m-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (7l). The product was isolated as white solid in 77% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.03 (s, 1H, NH), 7.55 (d, 1H, $J = 7.5$ Hz), 7.40–7.05 (m, 7H), 4.45 (dd, 1H, $J = 11.3, 4.5$ Hz), 3.51 (dd, 1H, $J = 14.9, 4.5$ Hz), 2.91 (dd, 1H, $J = 14.9, 11.3$ Hz), 2.43–2.31 (m, 4H), 1.99–1.87 (m, 4H), 1.46–1.26 (m, 6H), 0.85 (t, 3H, $J = 6.5$ Hz). ^{13}C NMR (75 MHz,

CDCl_3): δ 170.9 (C_q), 153.5 (C_q), 139.1 (C_q), 137.3 (C_q), 136.2 (C_q), 131.4 (C_q), 129.1 (CH), 128.9 (CH), 127.0 (CH), 126.3 (C_q), 123.5 (CH), 122.5 (CH), 120.1 (CH), 118.3 (CH), 111.1 (CH), 106.7 (C_q), 59.1 (C_q), 57.9 (CH), 39.7 (CH_2), 31.9 (CH_2), 28.1 (CH_3), 25.0 (CH_2), 23.0 (CH_2), 22.5 (CH_2), 21.3 (CH_3), 14.0 (CH_3). IR (KBr): ν 3346, 1727, 1416 cm^{-1} . EI-MS: m/z 415 (M^+). HRMS Calcd for $\text{C}_{26}\text{H}_{29}\text{N}_3\text{O}_2$: m/z 415.2260. Found: 415.2260.

2-(2-Fluorophenyl)-10-methyl-10-pentyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (7m). The product was isolated as yellow solid in 74% yield. $[\alpha]_{\text{D}}^{25} = -130.0^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 8.11 (s, 1H, NH), 7.55 (d, 1H, $J = 7.3$ Hz), 7.44–7.17 (m, 7H), 4.52 (dd, 1H, $J = 11.3, 4.3$ Hz), 3.51 (dd, 1H, $J = 14.9, 4.3$ Hz), 2.96 (dd, 1H, $J = 14.9, 11.3$ Hz), 2.52–2.42 (m, 1H), 2.01–1.89 (m, 4H), 1.46–1.18 (m, 6H), 0.87 (t, 3H, $J = 6.5$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 170.4 (C_q), 159.5 (C_q), 156.2 (C_q), 152.9 (C_q), 137.4 (C_q), 136.3 (C_q), 130.9 (CH, $J_{\text{CF}} = 7.9$ Hz), 129.9 (CH), 126.4 (C_q), 124.7 (CH, $J_{\text{CF}} = 3.8$ Hz), 122.6 (CH), 120.2 (CH), 118.4 (CH), 116.8 (CH, $J_{\text{CF}} = 19.4$ Hz), 111.2 (CH), 106.6 (C_q), 59.3 (C_q), 58.3 (CH), 39.8 (CH_2), 32.0 (CH_2), 28.0 (CH_3), 25.0 (CH_2), 23.2 (CH_2), 22.6 (CH_2), 14.0 (CH_3). IR (KBr): ν 3353, 1728, 1413 cm^{-1} . EI-MS: m/z 419 (M^+). HRMS Calcd for $\text{C}_{25}\text{H}_{26}\text{FN}_3\text{O}_2$: 419.2009. Found: 419.2005.

2-(4-Chloro-3-trifluoromethyl-phenyl)-10-methyl-10-pentyl-1-thioxo-1,2,3a,4,9,10-hexahydro-2,9,10a-triaza-cyclopenta[b]fluorene-3-one (7n). The product was isolated as yellow solid in 65% yield. $[\alpha]_{\text{D}}^{25} = -130.4^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 7.94 (d, 1H, $J = 2.3$ Hz), 7.91 (s, 1H, NH), 7.71 (dd, 1H, $J = 8.6, 2.3$ Hz), 7.63–7.54 (m, 2H), 7.39 (d, 1H, $J = 7.9$ Hz), 7.29–7.15 (m, 2H), 4.48 (dd, 1H, $J = 11.3, 4.5$ Hz), 3.51 (dd, 1H, $J = 14.9, 4.5$ Hz), 2.92 (dd, 1H, $J = 14.9, 11.3$ Hz), 2.55–2.45 (m, 1H), 2.01–1.88 (m, 4H), 1.43–1.15 (m, 6H), 0.85 (t, 3H, $J = 6.8$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 170.1 (C_q), 152.5 (C_q), 137.0 (C_q), 136.2 (C_q), 132.0 (CH), 131.5 (C_q), 130.5 (C_q), 130.0 (CH), 129.1 (C_q), 126.2 (C_q), 125.1 (CH), 124.2 (C_q), 122.8 (CH), 120.3 (CH), 118.3 (CH), 111.2 (CH), 106.5 (C_q), 59.3 (C_q), 57.9 (CH), 39.7 (CH_2), 31.9 (CH_2), 28.1 (CH_3), 25.0 (CH_2), 23.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3). IR (KBr): 3364, 1726, 1426 cm^{-1} . EI-MS: m/z 503 (M^+). HRMS Calcd for $\text{C}_{26}\text{H}_{25}\text{ClF}_3\text{N}_3\text{O}_2$: 503.1587. Found: 503.1591.

10-Methyl-10-pentyl-2-phenyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (7o). The product was isolated as yellow solid in 70% yield. $[\alpha]_{\text{D}}^{25} = -105.0^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 7.95 (s, 1H, NH), 7.64–7.11 (m, 9H), 4.46 (dd, 1H, $J = 11.3, 4.4$ Hz), 3.51 (dd, 1H, $J = 14.8, 4.4$ Hz), 2.92 (dd, 1H, $J = 14.8, 11.3$ Hz), 2.54–2.41 (m, 1H), 1.99–1.87 (m, 4H), 1.48–1.11 (m, 6H), 0.85 (t, 3H, $J = 6.8$ Hz). ^{13}C NMR (75 MHz, CDCl_3): δ 170.7 (C_q), 153.4 (C_q), 137.3 (C_q), 136.2 (C_q), 131.6 (C_q), 129.0 (CH), 126.2 (CH), 124.5 (CH), 122.6 (CH), 120.6 (C_q), 120.2 (CH), 118.3 (CH), 111.1 (CH), 106.7 (C_q), 59.1 (C_q), 57.9 (CH), 39.7 (CH_2), 31.9 (CH_2), 28.1 (CH_3), 25.0 (CH_2), 23.0 (CH_2), 22.5 (CH_2), 14.0 (CH_3). IR (KBr): ν 3356, 1712, 1418 cm^{-1} . EI-MS: m/z 401 (M^+). HRMS Calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_2$: m/z 401.2103. Found: 401.2106.

(11a'R)-2'-[4-Chloro-3-(trifluoromethyl)phenyl]-11',-11a'-dihydrospiro[cyclohexane-1,5'-imidazo[1',5':1,6]pyrido[3,4-b]indole]-1',3'(2'H,6'H)-dione (7p). The product was isolated as black solid in 68% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.16 (s, 1H, NH), 7.90 (d, 1H, $J = 2.1$ Hz), 7.70–7.54 (m, 2H), 7.41 (d, 1H, $J = 7.9$ Hz), 7.28–7.16 (m, 2H), 6.98 (s, 1H), 4.71 (dd, 1H, $J = 11.1, 4.8$ Hz), 3.48 (dd, 1H, $J = 15.0, 4.8$ Hz), 3.43–3.35 (m, 1H), 2.97 (dd, 1H, $J = 15.0, 11.1$ Hz), 2.49–2.37 (m, 1H), 2.10–1.65 (m, 8H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.1 (C_q), 152.5 (C_q), 138.9 (C_q), 135.6 (C_q), 131.9 (CH), 131.5 (C_q), 130.5 (C_q), 130.1 (CH), 129.1 (C_q), 125.7 (C_q), 125.3 (CH), 122.8 (CH), 120.5 (C_q), 120.4 (CH), 118.6 (C_q), 118.3 (CH), 111.1 (CH), 105.9 (C_q), 59.5 (C_q), 56.3 (CH), 35.0 (CH_2), 33.5 (CH_2), 24.0 (CH_2), 23.8 (CH_2), 23.5 (CH_2), 23.5 (CH_2). EI-MS: m/z 487 (M^+). IR (KBr): ν 3380, 1726, 1485 cm^{-1} . HRMS Calcd for $\text{C}_{25}\text{H}_{21}\text{ClF}_3\text{N}_3\text{O}_2$: m/z 487.1274. Found: m/z 487.1267.

(11a'R)-2'-(3-Methylphenyl)-11',11a'-dihydrospiro[cyclohexane-1,5'-imidazo[1',5':1,6]pyrido[3,4-b]indole]-1',3'(2'H,6'H)-dione (7q). The product was isolated as yellow solid in 70% yield. $[\alpha]_{\text{D}}^{25} = -72.8^\circ$ ($c = 0.1$). ^1H NMR (300 MHz, CDCl_3): δ 8.19 (s, 1H, NH), 7.56 (d, 1H, $J = 7.7$ Hz), 7.43–7.34 (m, 2H), 7.28–7.10 (m, 5H), 4.46 (dd, 1H, $J = 11.1, 4.7$ Hz), 3.48 (dd, 1H, $J = 15.0, 4.7$ Hz), 3.45–3.38 (m, 1H), 2.98 (dd, 1H, $J = 15.0, 11.4$ Hz), 2.49–2.40 (m, 4H), 2.13–1.55 (m, 8H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.9 (C_q), 153.5 (C_q), 139.2 (C_q), 139.1 (C_q), 135.6 (C_q), 131.4 (C_q), 129.1 (CH), 128.8 (CH), 127.0 (CH), 125.8 (C_q), 123.5 (CH), 122.6 (CH), 120.2 (CH), 118.3 (CH), 111.1 (CH), 106.1 (C_q), 59.1 (C_q), 56.2 (CH), 35.2 (CH_2), 33.5 (CH_2), 24.1 (CH_2), 23.7 (CH_2), 23.6 (CH_2), 23.5 (CH_2), 21.3 (CH_3). IR (KBr): ν 3299, 1721, 1702 cm^{-1} . EI-MS: m/z 399 (M^+). HRMS Calcd for $\text{C}_{25}\text{H}_{25}\text{N}_3\text{O}_2$: m/z 399.1947. Found: m/z 399.1944.

trans-3-(10-Ethyl-10-methyl-1,3-dioxo-3a,4,9,10-tetrahydro-3H-2,9,10a-triaza-cyclopenta[b]fluoren-2-yl)-benzotriazole (7r-trans). The product was isolated as white solid in 63% yield. ^1H NMR (300 MHz, CDCl_3): δ 8.02 (s, 1H, NH), 7.92–7.81 (m, 2H), 7.67–7.54 (m, 3H), 7.43–7.35 (m, 1H), 7.27–7.15 (m, 2H), 4.49 (dd, 1H, $J = 11.4, 4.5$ Hz), 3.52 (dd, 1H, $J = 14.9, 4.5$ Hz), 2.92 (dd, 1H, $J = 14.9, 11.4$ Hz), 2.61–2.46 (m, 1H), 2.10–1.95 (m, 4H), 0.97 (t, $J = 7.4$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.1 (C_q), 152.5 (C_q), 136.7 (C_q), 136.3 (C_q), 132.7 (C_q), 131.2 (CH), 130.2 (CH), 129.8 (CH), 129.3 (CH), 126.2 (C_q), 122.7 (CH), 120.2 (CH), 118.3 (CH), 117.9 (C_q), 113.2 (C_q), 111.2 (CH), 106.7 (C_q), 59.8 (C_q), 58.0 (CH), 32.4 (CH_2), 27.7 (CH_3), 23.0 (CH_2), 9.7 (CH_3). IR (KBr): ν 3396, 2231, 1728, 1411 cm^{-1} . EI-MS: m/z 384 (M^+). HRMS Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2$: 384.1586. Found: 384.1583.

cis-3-(10-Ethyl-10-methyl-1,3-dioxo-3a,4,9,10-tetrahydro-3H-2,9,10a-triaza-cyclopenta[b]fluoren-2-yl)-benzotriazole (7r-cis). The product was isolated as white solid in 70% yield. ^1H NMR (300 MHz, CDCl_3): δ 7.98 (s, 1H, NH), 7.92–7.81 (m, 2H), 7.67–7.54 (m, 3H), 7.43–7.35 (m, 1H), 7.27–7.15 (m, 2H), 4.44 (dd, 1H, $J = 11.4, 4.4$ Hz), 3.48 (dd, 1H, $J = 14.9, 4.4$ Hz), 2.91 (dd, 1H, $J = 11.4, 14.9$ Hz), 2.61–2.46 (m, 1H), 1.90–1.81 (m, 4H), 0.63 (t, $J = 7.2$ Hz, 3H). ^{13}C NMR (75 MHz, CDCl_3): δ 170.1 (C_q),

152.1 (C_q), 136.3 (C_q), 135.9 (C_q), 132.6 (C_q), 131.2 (CH), 130.1 (CH), 129.8 (CH), 129.2 (CH), 126.0 (C_q), 122.7 (CH), 120.2 (CH), 118.3 (CH), 117.9 (C_q), 113.2 (C_q), 111.2 (CH), 107.7 (C_q), 60.0 (C_q), 56.1 (CH), 32.4 (CH_2), 25.8 (CH_3), 22.9 (CH_2), 8.3 (CH_3). IR (KBr): ν 3396, 2231, 1728, 1708, 1411, 747 cm^{-1} . EI-MS: m/z 384 (M^+). HRMS Calcd for $\text{C}_{23}\text{H}_{20}\text{N}_4\text{O}_2$: m/z 384.1586. Found: m/z 384.1583.

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Supporting Information Available. Spectral data for **7t** and **7u**, ^1H and ^{13}C NMR spectra of **7a–7r**, X-ray structural data, and HPLC of **7k–7n** and **7r**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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