

## Fluorous and Traceless Synthesis of Substituted Indole Alkaloids

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The fluorous traceless synthesis of substituted indole alkaloids is carried out first by attaching the 3-(perfluorooctyl)propanol with Boc protected L-tryptophan. The reaction of perfluoroalkyl (Rfh)-tagged tryptophan esters with various aldehydes undergoes Pictet-Spengler reaction to give cis and trans stereoisomers of tetrahydro- $\beta$ -carbolines. The nucleophilic addition of the piperidine nitrogen across various isocyanates is followed by the cyclization of ureas and simultaneous rupture of the fluorous tag to afford the hydantoin ring fused tetrahydro- $\beta$ -carbolines. All the fluorous-tag compounds are purified by solid-phase extraction (SPE) through Fluoro *Flash* cartridges.

Fluorous tag strategy<sup>1</sup> has received widespread attention as an efficient tool to simplify the separation and purification of reaction mixtures in the modern synthetic organic chemistry. The development of fluorous chemistry started in the early of 1990s that Horvath and Rabai introduced the fluorous biphasic catalysis for the recovery of catalysts,<sup>2</sup> and then Curran group as well as Fluorous Technologies, Inc. (FTI) developed the “light-fluorous” strategy.<sup>3,4</sup> One of the advantages of fluorous tag reactions is that reactions progress can be monitored by conventional analytical methods such as TLC, HPLC, MS, and NMR. The separation of fluorous reaction mixtures can be achieved by fluorous liquid–liquid extraction (F-LLE) or by fluorous silica gel in solid-phase extraction (F-SPE).<sup>5</sup> The schematic representation of F-SPE concept was shown in the supporting material. Crude compounds which contain fluorous and nonfluorous components are charged into fluorous silica gel. It is then followed by elution with fluorophobic solvents such as 80% of MeOH in H<sub>2</sub>O or 90% of DMF in H<sub>2</sub>O to remove nonfluorous (organic) compounds and other byproducts. Finally the fluorous fractions were eluted and collected with fluorophilic solvents such as MeOH, CH<sub>3</sub>CN and THF to deliver clean fluorous intermediates.

Design concept of currently constructed tetrahydro- $\beta$ -carbolinehydantoin scaffold has originated from the recognition of biological roles of hydantoin and tetrahydro- $\beta$ -carboline moiety. This generation of a combined tetracyclic skeleton containing two important pharmacophores thus, is a substantial intellectual appeal resembling drug-like molecules. They possess diverse array of biological activities and pharmacological profiles, such as CNS drugs,<sup>6</sup> CCK receptor antagonists,<sup>7</sup> and inhibitor of cGMP-phosphodiesterase.<sup>8</sup> For example, fumitremorgins have been isolated from the fungal species, which are shown to have antiviral<sup>9</sup> and cell-cycle inhibiting activities.<sup>10</sup> They are also

acted as topoisomerase II and protein kinase inhibitors<sup>11</sup> (Figure 1). Recent evidence has shown that carboline derivative HR22C16 played important roles in inducing mitotic arrest and blocking cell division in taxol-resistant cancer cells.<sup>12,13</sup> Another interesting molecule—tadalafil is a highly potent and orally active PDE5 inhibitor.<sup>14,15</sup> Traceless synthesis of tetrahydro- $\beta$ -carbolinethiohydantoin under microwave irradiation using soluble polymer support as a carrier was reported.<sup>19e,g</sup> The present paper demonstrated a successful application of fluorous tag and MW technology to assist rapid synthesis of hydantoin fused tetrahydro- $\beta$ -carboline small molecules.

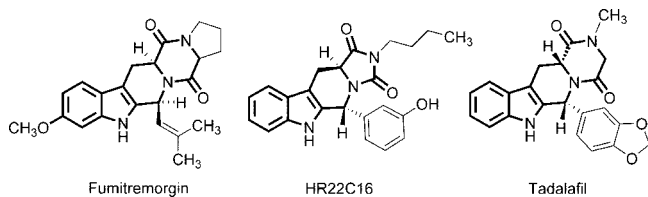
Fluorous and traceless synthesis of various tetrahydro- $\beta$ -carbolinehydantoin under microwave irradiation is described in Scheme 1. Esterification reaction was performed by using commercially available fluorous alcohol containing C<sub>8</sub>F<sub>17</sub> chain<sup>16</sup> and Boc protected L-tryptophan **2** with dicyclohexyl carbodiimide (DCC) and DMAP in dichloromethane at room temperature for 3 h. The fluorous tag of perfluoroalkyl portion is distanced from the hydroxyl group by three carbons spacer to decrease the electron-withdrawing effect of fluorous moiety. The perfluoro-tagged component **1** was used as the limiting agent with a slight excess of acid **2** to achieve the best SPE separation. Reaction progress was directly monitored by <sup>1</sup>H-NMR in each intermediate with attached fluorous tag molecule which was found their chemical shift at 1.8~2.0 and 4.0 ppm, respectively (Figure 2a). After completing reaction, it is followed by solid-phase extraction (SPE) over Fluoro *Flash* cartridges to remove nonfluorous byproducts by using eluent MeOH/H<sub>2</sub>O (4:1). The fluorous products were collected in the second fraction by washing cartridge with 100% MeOH.

NH-Boc group in compound **3** was deprotected by using 30% TFA in CH<sub>2</sub>Cl<sub>2</sub> for 3 h to obtain the primary free amine. This reaction was confirmed by <sup>1</sup>H-NMR spectrum for the disappearance of *tert*-butyl group at 1.4 ppm (Figure 2 b). The in situ generated free amine was directly treated with appropriate aldehydes without any purification. It was

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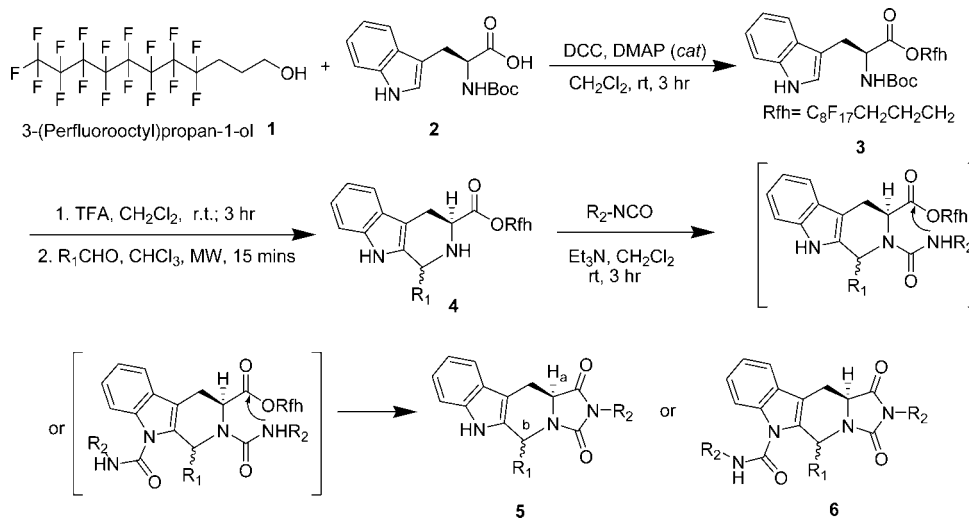


**Figure 1.** Pharmacologically active of tetrahydro- $\beta$ -carbolinehydantoin.

performed the intramolecular condensation in acidic condition between an iminium ion and an aromatic C-nucleophile. Same result was obtained to the construction of the six-membered  $\beta$ -carboline skeletons in one pot by the simultaneous addition of TFA and the aldehydes. This resulted in the sequential deprotection, nucleophilic addition, cyclization and induced the first point of structural diversity through the Pictet–Spengler reaction.<sup>17</sup> It was required 15 min to reach completion under microwave irradiation in chloroform and resulted in the formation of *cis* and *trans* diastereomers in various ratios.<sup>19</sup> It should be noted that under MW acidic harsh conditions, the fluorous tag-attached site still remains intact. Compared to the conventional Pictet–Spengler reaction which usually takes 1–2 days to reach completion in refluxing condition, the fluorous–microwave approach has more favorable reaction condition and has brought down reaction time within 20 min.<sup>20</sup> Purification of intermediate **4** was then performed by SPE through Fluoro cartridges to remove excess aldehydes and other nonfluorous byproducts (Figure 2c, 4a).

Finally, the  $\beta$ -carboline derivatives **4** were treated with various isocyanates in the presence of triethylamine to promote intramolecular cyclization that fluoro tag molecule cleavage and hydantoin ring formation were performed in one pot. Building up of the terminal hydantoin ring across the N-2/C-3 bond of the tetrahydro- $\beta$ -carboline skeleton was achieved at room temperature by the reaction of  $\beta$ -carboline derivatives **4** with  $R_2-N=C=O$ . This nucleophilic addition was achieved without the use of any metal salt or activating agents to reach spontaneous cyclization and to displace fluorous tag in 3 h with base. The reactive urea induced an acyl-oxygen bond cleavage of the ester to remove fluoro tag by a  $S_N1$  reaction via N–CO bond concomitant formation. It is leading to a traceless and stereoselective synthesis of substituted indole alkaloids **5**.

**Scheme 1.** Synthetic Route toward Tetrahydro- $\beta$ -Carbolinehydantoin **5** and **6**



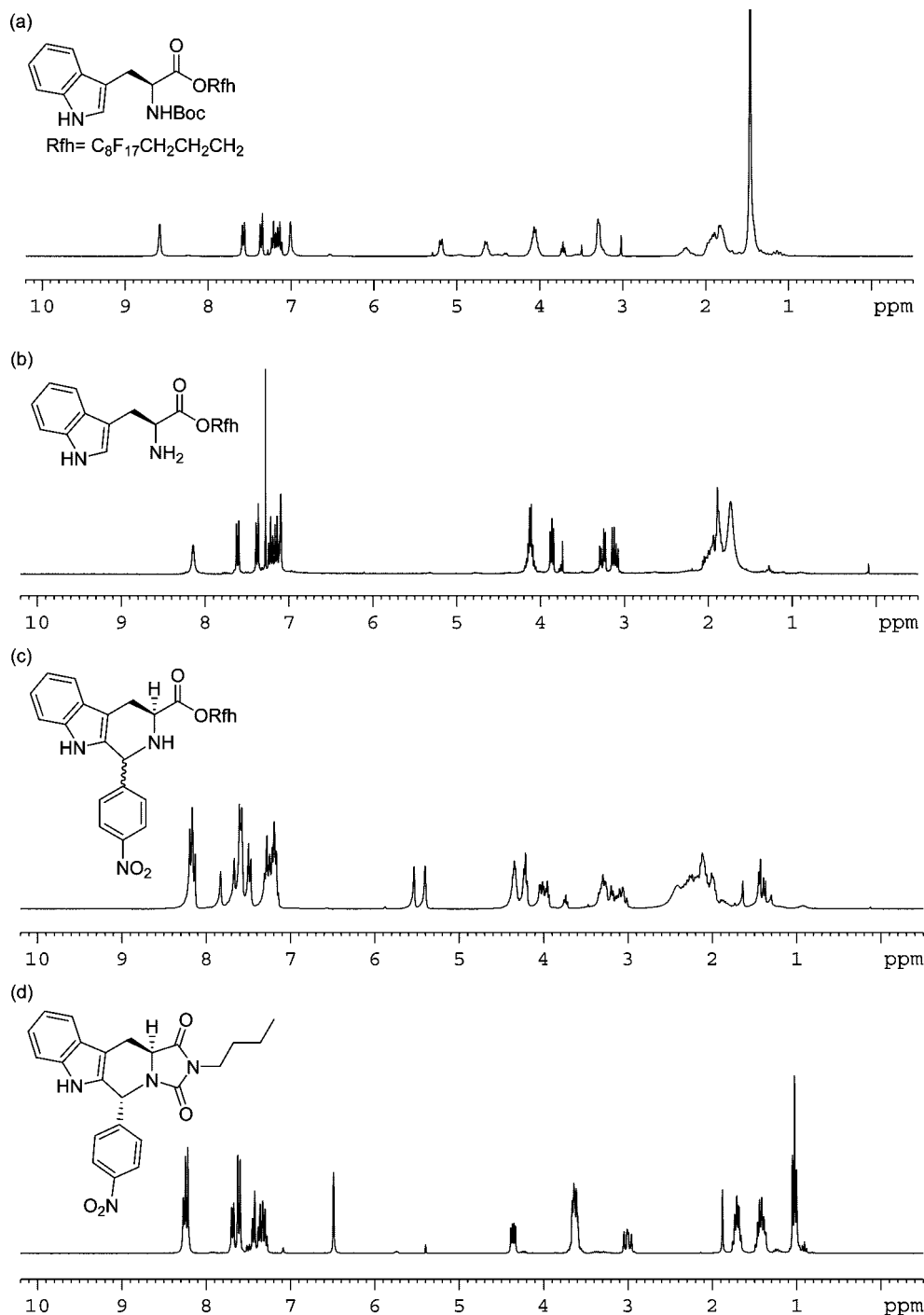
When the extra excess of isocyanates were added (such as 5 eq), the nitrogen of indole ring will further react with isocyanates to generate urea containing indole **6** and the final products were contaminated unreacted isocyanates.

After formation of terminal hydantoin ring, the crude products were purified over a Fluoro *Flash* cartridge contained fluorous silica gel and the nonfluorous final compounds **5** was collected in the first fraction of  $\text{CH}_3\text{OH}/\text{H}_2\text{O}(4/1)$  (Figure 2d, 5a).

The stepwise formation of tetrahydro- $\beta$ -carbolinehydantoin **5** was monitored by  $^1\text{H}$  NMR spectra shown in Figure 2a–d. However, the 3-(perfluorooctyl)propan-1-ol was not recovered in the MeOH fraction because the recycled  $\text{C}_8\text{F}_{17}$  chain of fluorous alcohol further reacted with excess of isocyanates which was confirmed by  $^1\text{H}$  NMR and MS. The application of fluorous, microwave-assisted synthesis was demonstrated by the synthesis of tetrahydro- $\beta$ -carbolinehydantoin derivatives with two points of diversity. The analytical data of *cis/trans* ratio and Lrms data are shown in Table 1. Assignment of *cis/trans* stereochemistry of final compounds **5** was identified by  $^{13}\text{C}$  NMR at  $\text{C}_b$  and  $\text{C}_a$  using the method described by Cook's research group.<sup>18</sup> These isomers were also determined by 1D NOE analysis after a proper separation. Experiments in which saturation of Ha of **5m'** caused the enhancement of the Hb signal, and other protons around indicated *cis* relationship of Ha and Hb (Figure 3). On the contrary, saturation of Ha of **5m** caused no enhancement of Hb signal. Furthermore, in single-crystal X-ray analysis of *trans* compound **5m** (Figure 4) confirms that the rings C and D are *trans* fused and nonplanar, which shows that the hydrogens of C-9 and C-10 are antiperiplanar.

In Table 1, the results show that thermodynamically more stable *trans* compounds are obtained in most of cases. However, the detailed mechanism regarding conversion of *cis/trans* mixtures **4** to only one *trans* product **5** is still under investigation. The *cis/trans* intermediates **4** have not been separated during the present work. We have confirmed the formation of stereoisomeric mixtures **4** by the crude proton NMR itself.

In conclusion, we have developed a novel fluorous and traceless synthesis of tetrahydro- $\beta$ -carbolinehydantoin libraries.



**Figure 2.** Formation of tetrahydro- $\beta$ -carbolinehydantoin **5a** is stepwise monitored by  $^1\text{H-NMR}$  spectra.

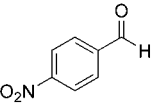
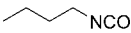
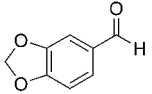

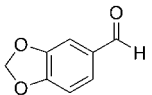
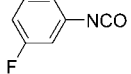
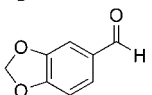
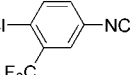
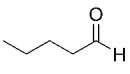
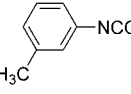
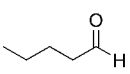
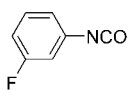
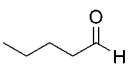
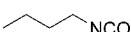
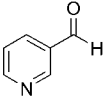
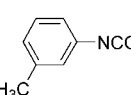
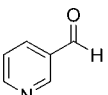
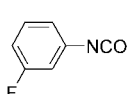
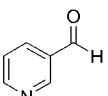

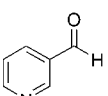
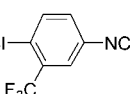
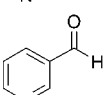
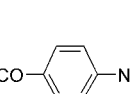
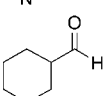
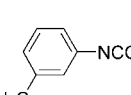
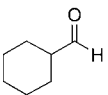

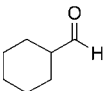
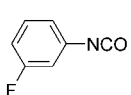
The key step of Pictet-Spengler reaction was highly accelerated under focused microwave irradiation<sup>20</sup> in reduced reaction time significantly from days to minutes. It should be noted that fluorous tag intermediates and tag itself are stable during the harsh MW irradiation. The fluorous tag synthesis strategy could enhance the rapid separation and purification of products after SPE cartridges are used. Further work involving biological evaluation of small molecule library is currently underway.

### Experimental Section

**General Procedure for the Synthesis of Tetracyclic Tetrahydro- $\beta$ -Carbolines. 5a-5o.** The 3-(perfluorooctyl)propan-1-ol **1** 0.2 g (1 eq 0.2 mmol) and Boc-Trp-OH **2** (1.5

eq 0.30 mmol) in 5 mL of dichloromethane was added DCC (2.5 eq 0.5 mmol) and 4-dimethylamino pyridine (DMAP, 0.002 g). The mixture was stirred at room temperature for 3 h and the reaction progress was monitored by TLC and  $^1\text{H NMR}$ . After completion, dicyclohexyl urea (DCU) was filtered off and concentrated residue was loaded onto a Fluoro Flash cartridge containing 10 g of fluorosilica gel. The cartridge was eluted with 20 mL of MeOH/H<sub>2</sub>O (80:20) followed by 20 mL of MeOH. The MeOH fraction was concentrated to give product **3**, and subsequently treated with 30% TFA in dichloromethane at room temperature for three hours. After deprotection of Boc-group, aldehyde was added (0.3 mmol) in 10 mL CHCl<sub>3</sub> under microwave irradiation

**Table 1.** Fluorous Traceless Synthesis of Tetrahydro- $\beta$ -Carbolinehydantoin

Entry	R <sub>1</sub> CHO	R <sub>2</sub> NCO	LR-MS	Yield ( <i>trans/cis</i> )
5a			418	92 ( <i>trans</i> only)
5b			417	90 ( <i>trans</i> only)
5c			455	88 ( <i>trans</i> only)
5d			539	85 ( <i>trans</i> only)
5e			387	92 ( <i>trans</i> only)
5f			391	86 ( <i>trans</i> only)
5g			353	84 (3/1)
5h			408	80 ( <i>trans</i> only)
5i			412	88 ( <i>trans</i> only)
5j			374	92 (1/1)
5k			496	90 ( <i>trans</i> only)
5l			424	80 ( <i>trans</i> only)
5m			413	92 (1/1)
5n			379	89 (3/1)
5o			417	86 ( <i>trans</i> only)

(CEM Discover) at 240W for 15 min in open vessel system. Upon completion of the reaction, isocyanate (0.3 mmol) and triethylamine (0.37 mmol) in 8 mL of dichloromethane was added to solution of **4** and resulted in simultaneous release of the fluorous tag with formation of tetracyclic hydantoin **5** in three hours. The reaction mixture was directly loaded on a Fluoro *Flash* cartridge containing 10 g of fluorous silica gel. The cartridge was eluted with 20 mL of MeOH/H<sub>2</sub>O(4/

1). The fractions were collected and concentrated to give the analytical pure tetrahydro- $\beta$ -carbolinehydantoin **5**. The crude product was then further purified by silica gel column chromatography using a 1:2 mixture of ethyl acetate and hexane as an eluent.

***trans*-2-Butyl-10-(4-nitro-phenyl)-3,4,9,10-tetrahydro-2,9,10-triaza-cyclopenta[*b*]fluorine-1,3-dion (5a).** <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>):  $\delta$  8.26 (s, 1H), 8.23 (d, *J* = 8.5 Hz,

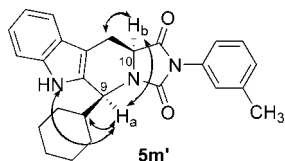


Figure 3. Some important NOE interactions in *cis* isomer **5m'**.

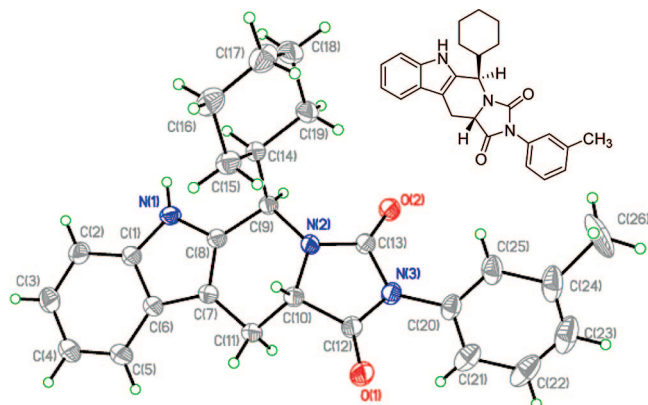
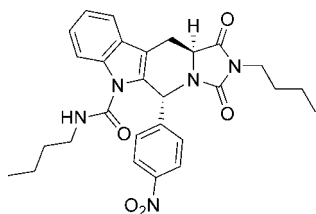


Figure 4. Single crystal X-ray structural elucidation of compound **5m**.

2H), 7.68 (d,  $J = 7.6$  Hz, 1H), 7.61 (d,  $J = 8.5$  Hz, 2H), 7.43 (d,  $J = 7.6$  Hz, 1H), 7.38–7.27 (m, 2H), 6.48 (s, 1H), 4.38–4.33 (dd,  $J = 11.0, 5.4$  Hz, 1H), 3.68–3.59 (m, 3H), 3.04–2.95 (dd,  $J = 15.2, 11.0$  Hz, 1H), 1.75–1.65 (m, 2H), 1.48–1.36 (m, 2H), 1.02 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.8, 155.5, 148.2, 146.4, 137.2, 129.6, 129.1, 126.3, 124.6, 123.7, 120.8, 119.0, 111.8, 109.1, 53.5, 51.5, 39.1, 30.5, 23.7, 20.3, 14.0; IR ( $\text{cm}^{-1}$ , neat): 3337, 2957, 2934, 2870, 1711, 1695, 1453, 1548, 1494;  $[\alpha]_{\text{D}}^{20} = -36.2^\circ$  ( $c = 0.5$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 418 ( $\text{M}^+$ ); Hrms: calcd for  $\text{C}_{23}\text{H}_{22}\text{N}_4\text{O}_4$ ;  $m/z$  418.1641; Found 418.1642.

***trans*-2-Butyl-10-(4-nitro-phenyl)-1,3-dioxo-1,2,3,3s,4,10-hexahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-9-carboxylic acid butylamide (**6a**).**

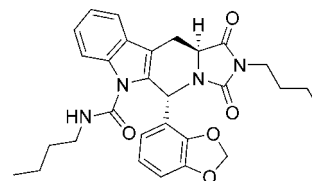


Yield: 5 %;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.10 (d,  $J = 8.6$  Hz, 2H), 7.58 (t,  $J = 9.1$  Hz, 2H), 7.41 (d,  $J = 8.6$  Hz, 2H), 7.33–7.28 (m, 2H), 6.94 (s, 1H), 5.92 (s, 1H), 4.16–4.10 (dd,  $J = 10.1, 5.8$  Hz, 1H), 3.51 (t,  $J = 7.2$  Hz, 2H), 3.46–3.39 (dd,  $J = 15.5, 5.8$  Hz, 1H), 3.30–3.13 (m, 2H), 2.83–2.74 (dd,  $J = 15.5, 11.2$  Hz, 1H), 1.61–1.57 (m, 2H), 1.35–1.25 (m, 4H), 1.14–1.09 (m, 2H), 0.91 (t,  $J = 7.1$  Hz, 3H), 0.79 (t,  $J = 7.1$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.6, 154.7, 151.3, 147.9, 147.0, 135.3, 131.0, 129.0, 128.0, 125.1, 124.3, 122.9, 119.6, 113.2, 112.4, 51.9, 51.8, 41.1, 39.1, 31.8, 30.5, 23.2, 20.3, 20.1, 14.0, 13.9; IR ( $\text{cm}^{-1}$ , neat): 2960, 2933, 2872, 1712, 1693, 1451, 1548, 1490;  $[\alpha]_{\text{D}}^{20} = -92.0^\circ$  ( $c = 1.1$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 517 ( $\text{M}^+$ ); Hrms: calcd for  $\text{C}_{28}\text{H}_{31}\text{N}_5\text{O}_5$ ;  $m/z$  517.2325; Found 517.2369.

***trans*-10-Benzo[1,3]dioxol-4-yl-2-butyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*] fluorene-1,3-dione (**5b**).**

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.43 (s, 1H), 7.57 (d,  $J = 7.2$  Hz, 1H), 7.31 (d,  $J = 7.2$  Hz, 1H), 7.27–7.16 (m, 2H), 6.83–6.71 (m, 3H), 6.17 (s, 1H), 5.89–5.85 (m, 2H), 4.26–4.20 (dd,  $J = 11.0, 5.4$  Hz, 1H), 3.57–3.42 (m, 3H), 2.89–2.80 (ddd,  $J = 15.2, 11.0, 1.7$  Hz, 1H), 1.67–1.57 (m, 2H), 1.40–1.30 (m, 2H), 0.92 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.2, 155.3, 148.5, 148.3, 137.0, 133.5, 130.9, 126.4, 123.2, 122.3, 120.4, 118.8, 111.6, 108.9, 108, 8, 108.3, 101.7, 53.4, 52.1, 38.9, 32.0, 30.6, 20.4, 14.0; IR ( $\text{cm}^{-1}$ , neat): 3327, 2958, 2932, 2872, 1703, 1622, 1449;  $[\alpha]_{\text{D}}^{20} = -36.3^\circ$  ( $c = 0.3$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 417 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{24}\text{H}_{23}\text{N}_3\text{O}_4$ ;  $m/z$  417.1689; Found 417.1661.

***trans*-10-Benzo[1,3]dioxol-4-yl-2-butyl-1,3-dioxo-1,2,3,3a,4,10-hexahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-9-carboxylic acid butylamide (**6b**).**



Yield: 5 %;  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  7.62 (d,  $J = 7.8$  Hz, 1H), 7.52 (d,  $J = 7.0$  Hz, 1H), 7.31–7.25 (m, 2H), 6.79–6.65 (m, 4H), 5.92 (s, 2H), 5.70 (s, 1H), 4.19–4.13 (dd,  $J = 11.0, 5.8$  Hz, 1H), 3.50 (t,  $J = 7.2$  Hz, 2H), 3.37–3.17 (m, 3H), 2.83–2.74 (dd,  $J = 15.5, 11.0$  Hz, 1H), 1.62–1.57 (m, 2H), 1.39–1.26 (m, 4H), 1.17–1.12 (m, 2H), 0.92 (t,  $J = 7.2$  Hz, 3H), 0.86 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.0, 154.5, 151.4, 148.4, 148.0, 135.6, 133.7, 132.1, 127.8, 124.7, 122.6, 121.6, 119.3, 112.6, 112.5, 108.8, 108.7, 52.0, 51.8, 41.0, 39.0, 31.8, 30.6, 23.3, 20.3, 20.1, 14.1, 14.0; IR ( $\text{cm}^{-1}$ , neat): 2959, 2933, 2871, 1709, 1629, 1449;  $[\alpha]_{\text{D}}^{20} = -12.1^\circ$  ( $c = 0.4$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 516 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{29}\text{H}_{32}\text{N}_4\text{O}_5$ ;  $m/z$  516.2373; Found 516.2360.

***trans*-10-Benzo[1,3]dioxol-4-yl-2-(3-fluoro-phenyl)-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (**5c**).**  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  10.8 (s, 1H), 7.58–7.52 (m, 2H), 7.37–7.26 (m, 4H), 7.14–7.01 (m, 2H), 6.94–6.87 (m, 3H), 6.21 (s, 1H), 6.01 (s, 2H), 4.81–4.75 (dd,  $J = 10.9, 5.6$  Hz, 1H), 3.54–3.47 (m, 1H), 3.11–3.00 (ddd,  $J = 15.0, 10.9, 1.7$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  172.2, 164.1, 160.9, 153.8, 148.3, 148.0, 137.5, 134.5, 134.3, 134.2, 132.0, 131.2, 131.1, 126.6, 123.8, 123.7, 122.6, 122.5, 119.7, 119.1, 115.7, 115.4, 114.9, 114.6, 112.2, 109.1, 106.9, 102.0, 53.8, 52.5, 23.3; IR ( $\text{cm}^{-1}$ , neat): 3344, 2919, 2852, 1716, 1600, 1492, 1420;  $[\alpha]_{\text{D}}^{20} = -64.8^\circ$  ( $c = 0.2$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 455 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{26}\text{H}_{18}\text{FN}_3\text{O}_4$ ;  $m/z$  455.1281; Found 455.1278.

***trans*-10-Benzo[1,3]dioxol-4-yl-2-(3-fluoro-phenyl)-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (**5d**).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.6 (s, 1H), 7.88 (d,  $J = 2.3$  Hz, 1H), 7.67–7.63 (dd,  $J = 8.7, 2.3$  Hz, 1H), 7.59 (s, 1H), 7.56 (s, 1H), 7.36–7.16 (m, 3H), 6.88–6.76 (m, 3H), 6.31 (s, 1H), 5.93 (s, 2H), 4.51–4.45 (ddd,  $J = 11.1, 5.6, 2.8$  Hz, 1H), 3.60–3.53 (dd,  $J = 15.1, 5.6$  Hz,



1H), 3.07–2.98 (dd,  $J = 15.1, 11.1$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.3, 153.1, 148.7, 148.5, 137.1, 132.9, 132.4, 132.2, 131.8, 130.8, 130.5, 130.1, 129.2, 126.3, 125.3, 125.2, 123.3, 122.5, 120.5, 118.7, 111.8, 109.0, 107.9, 101.8, 53.4, 52.5, 23.9; IR ( $\text{cm}^{-1}$ , neat): 3345, 2924, 2850, 1721, 1605, 1486, 1429, 745;  $[\alpha]_{\text{D}}^{20} = -46.2^\circ$  ( $c = 0.3$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 539 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{27}\text{H}_{17}\text{ClN}_3\text{O}_4\text{F}_3$ :  $m/z$  539.0860; Found 539.0859.

**trans-10-Butyl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (5e).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.59 (s, 1H), 7.51 (d,  $J = 8.5$  Hz, 1H), 7.41–7.14 (m, 7H), 5.34–5.31 (dd,  $J = 6.9, 4.0$  Hz, 1H), 4.51–4.45 (dd,  $J = 10.8, 5.7$  Hz, 1H), 3.52–3.45 (dd,  $J = 15.2, 5.7$  Hz, 1H), 2.97–2.82 (ddd,  $J = 15.2, 10.8, 1.3$  Hz, 1H), 2.40 (s, 3H), 2.09–2.00 (m, 1H), 1.90–1.76 (m, 1H), 1.58–1.40 (m, 4H), 0.92 (t,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.7, 155.0, 139.6, 136.8, 133.0, 129.6, 129.4, 129.1, 127.3, 126.6, 123.8, 122.8, 120.3, 118.5, 111.6, 105.9, 53.3, 49.4, 42.1, 36.0, 28.1, 23.1, 21.8, 14.4; IR ( $\text{cm}^{-1}$ , neat): 3324, 2957, 2932, 2872, 1702, 1608, 1453;  $[\alpha]_{\text{D}}^{20} = -42.6^\circ$  ( $c = 0.9$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 387 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{24}\text{H}_{25}\text{N}_3\text{O}_2$ :  $m/z$  387.1947; Found 387.1985.

**trans-10-Butyl-2-(3-fluoro-phenyl)-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (5f).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.08 (s, 1H), 7.54–7.39 (m, 2H), 7.35–7.33 (m, 3H), 7.25–7.08 (m, 3H), 5.39–5.35 (dd,  $J = 7.4, 4.5$  Hz, 1H), 4.52–4.46 (dd,  $J = 10.8, 5.7$  Hz, 1H), 3.54–3.47 (dd,  $J = 15.3, 5.7$  Hz, 1H), 2.99–2.90 (ddd,  $J = 15.3, 10.8, 1.6$  Hz, 1H), 2.08–1.88 (m, 2H), 1.72–1.62 (m, 2H), 1.62–1.60 (m, 2H), 0.96–0.92 (m, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.0, 164.6, 161.3, 154.3, 136.7, 133.4, 132.7, 130.5, 126.6, 123.1, 120.5, 118.6, 115.6, 115.3, 114.0, 111.5, 106.3, 54.1, 49.3, 36.0, 28.1, 24.1, 23.1, 13.3; IR ( $\text{cm}^{-1}$ , neat): 3359, 2957, 2929, 2856, 1716, 1597, 1493, 1420;  $[\alpha]_{\text{D}}^{20} = -91.8^\circ$  ( $c = 0.08$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 391 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{23}\text{H}_{22}\text{FN}_3\text{O}_2$ :  $m/z$  391.1696; Found 391.1697.

**trans-2,10-Dibutyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (5g).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.09 (s, 1H), 7.50 (d,  $J = 7.8$  Hz, 1H), 7.36 (d,  $J = 7.8$  Hz, 1H), 7.25–7.13 (m, 2H), 5.30–5.26 (dd,  $J = 6.4, 4.5$  Hz, 1H), 4.32–4.27 (dd,  $J = 10.9, 5.7$  Hz, 1H), 3.58 (td,  $J = 7.1, 1.5$  Hz, 2H), 3.44–3.37 (dd,  $J = 15.2, 5.7$  Hz, 1H), 2.83–2.73 (ddd,  $J = 15.2, 10.9, 1.6$  Hz, 1H), 2.05–1.99 (m, 1H), 1.84–1.73 (m, 1H), 1.69–1.61 (m, 4H), 1.41–1.33 (m, 4H), 0.97–0.88 (m, 6H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  173.3, 155.7, 136.3, 132.7, 126.3, 122.6, 120.1, 118.3, 111.1, 106.1, 53.8, 48.6, 38.6, 35.8, 30.2, 27.8, 23.6, 22.7, 20.0, 14.0, 13.7; IR ( $\text{cm}^{-1}$ , neat): 3344, 2958, 2929, 2857, 1705, 1620, 1454;  $[\alpha]_{\text{D}}^{20} = -87.7^\circ$  ( $c = 0.1$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 353 ( $\text{M}^+$ ). Hrms calcd for  $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_2$ :  $m/z$  353.2103; Found 353.2109.

**cis-2,10-Dibutyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (5g').**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.14 (s, 1H), 7.55 (d,  $J = 7.4$  Hz, 1H), 7.38 (d,  $J = 7.4$  Hz, 1H), 7.25–7.15 (m, 2H), 5.09 (d,  $J = 1.4$  Hz, 1H), 4.20–4.15 (dd,  $J = 11.4, 4.3$  Hz, 1H), 3.58 (t,  $J = 7.2$  Hz, 2H), 3.43–3.37 (ddd,  $J = 14.8, 4.3, 1.1$  Hz, 1H), 2.84–2.75 (ddd,  $J = 14.8, 11.4, 1.9$  Hz, 1H), 1.93–1.83 (m,

2H), 1.71–1.60 (m, 4H), 1.45–1.39 (m, 4H), 0.96 (t,  $J = 7.3$  Hz, 3H), 0.80 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.3, 155.5, 136.7, 133.4, 126.6, 122.8, 120.4, 118.5, 111.5, 108.5, 58.3, 52.8, 38.8, 32.5, 30.6, 25.0, 22.9, 22.8, 20.3, 14.3, 14.0; IR ( $\text{cm}^{-1}$ , neat): 3345, 2956, 2929, 2871, 1709, 1622, 1456;  $[\alpha]_{\text{D}}^{20} = -69.0^\circ$  ( $c = 0.2$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 353 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{21}\text{H}_{27}\text{N}_3\text{O}_2$ :  $m/z$  353.2103; Found 353.2102.

**trans-10-Pyridin-3-yl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (5h).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.54 (d,  $J = 11.7$  Hz, 1H), 8.48 (s, 2H), 7.67–7.60 (m, 2H), 7.38–7.18 (m, 8H), 6.36 (s, 1H), 4.47–4.42 (dd,  $J = 10.8, 5.4$  Hz, 1H), 3.65–3.58 (dd,  $J = 15.2, 5.4$  Hz, 1H), 3.11–3.02 (m, 1H), 2.38 (s, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.7, 154.4, 149.8, 149.5, 139.6, 137.4, 136.7, 135.7, 131.5, 129.6, 129.4, 129.3, 127.1, 126.3, 124.7, 123.6, 123.4, 120.5, 118.8, 111.9, 108.5, 53.6, 50.5, 23.8, 21.7; IR ( $\text{cm}^{-1}$ , neat): 3326, 2957, 2930, 2871, 1702, 1602, 1453;  $[\alpha]_{\text{D}}^{20} = -19.6^\circ$  ( $c = 0.2$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 408 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_2$ :  $m/z$  408.1586; Found 408.1590.

**trans-2-(3-Fluoro-phenyl)-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (5i).**  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  11.20 (s, 1H), 8.75 (s, 1H), 8.58 (d,  $J = 4.3$  Hz, 1H), 7.80 (d,  $J = 7.9$  Hz, 1H), 7.61 (d,  $J = 7.6$  Hz, 1H), 7.59–7.49 (m, 1H), 7.44–7.39 (m, 4H), 7.29–7.24 (m, 1H), 7.16–7.04 (m, 2H), 6.41 (s, 1H), 4.89–4.84 (dd,  $J = 10.7, 5.6$  Hz, 1H), 3.50–3.44 (dd,  $J = 15.1, 5.6$  Hz, 1H), 3.12–3.04 (dd,  $J = 13.1, 11.3$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  172.2, 164.1, 160.9, 154.0, 150.2, 150.1, 137.7, 136.4, 134.3, 131.2, 131.1, 126.6, 124.7, 123.7, 122.7, 119.8, 119.2, 115.6, 114.7, 112.3, 107.3, 54.0, 50.7, 23.2; IR ( $\text{cm}^{-1}$ , neat): 3352, 2935, 2853, 1715, 1610, 1412, 1257;  $[\alpha]_{\text{D}}^{20} = -36.0^\circ$  ( $c = 0.5$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 412 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{24}\text{H}_{17}\text{FN}_4\text{O}_2$ :  $m/z$  412.1336; Found 412.1330.

**trans-2-Butyl-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (5j).**  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  10.93 (s, 1H), 8.65 (s, 1H), 8.55 (d,  $J = 4.6$  Hz, 1H), 7.73 (d,  $J = 7.8$  Hz, 1H), 7.56 (d,  $J = 7.8$  Hz, 1H), 7.41–7.37 (dd,  $J = 7.8, 4.8$  Hz, 1H), 7.29 (d,  $J = 7.8$  Hz, 1H), 7.12–7.00 (m, 2H), 6.29 (s, 1H), 4.71–4.66 (dd,  $J = 10.7, 5.5$  Hz, 1H), 3.54–3.43 (m, 3H), 2.85–2.76 (dd,  $J = 13.5, 11.0$  Hz, 1H), 1.55–1.42 (m, 2H), 1.30–1.18 (m, 2H), 0.86 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  173.5, 155.4, 150.1, 149.9, 137.6, 136.5, 136.2, 131.3, 126.5, 124.7, 122.7, 119.8, 119.1, 112.2, 107.1, 54.0, 50.4, 38.5, 30.4, 23.4, 20.2, 14.3; IR ( $\text{cm}^{-1}$ , neat): 3347, 2932, 2850, 1707, 1599, 1422;  $[\alpha]_{\text{D}}^{20} = -158.5^\circ$  ( $c = 0.3$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 374 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_2$ :  $m/z$  374.1743; Found 374.1744.

**cis-2-Butyl-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (5j').**  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO-d}_6$ ):  $\delta$  10.84 (s, 1H), 8.64 (d,  $J = 1.9$  Hz, 1H), 8.47–8.45 (dd,  $J = 4.7, 1.5$  Hz, 1H), 7.65–7.61 (dd,  $J = 7.8, 1.5$  Hz, 1H), 7.56 (d,  $J = 7.3$  Hz, 1H), 7.31–7.22 (m, 2H), 7.06–7.00 (m, 2H), 5.96 (s, 1H), 4.59–4.54 (dd,  $J = 11.3, 4.3$  Hz, 1H), 3.40–3.30 (m, 3H), 3.11–3.02 (ddd,  $J = 14.5, 9.9, 1.5$  Hz, 1H), 1.52–1.43 (m, 2H), 1.31–1.23 (m,

2H), 0.86 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz, DMSO- $d_6$ ):  $\delta$  172.5, 155.2, 149.9, 149.4, 137.6, 137.0, 135.7, 134.7, 126.6, 124.3, 122.4, 119.7, 119.1, 112.1, 106.4, 58.2, 54.2, 38.3, 30.5, 22.5, 20.1, 14.3; IR ( $\text{cm}^{-1}$ , neat): 3345, 2929, 2864, 1711, 1588, 1424;  $[\alpha]_{\text{D}}^{20} = -44.5^\circ$  ( $c = 0.3$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 374 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{22}\text{H}_{22}\text{N}_4\text{O}_2$ :  $m/z$  374.1743; Found 374.1737.

**trans-2-(4-Chloro-3-trifluoromethyl-phenyl)-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (5k).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.0 (s, 1H), 8.58 (s, 1H), 8.51 (d,  $J = 4.3$  Hz, 1H), 7.89 (s, 1H), 7.69–7.58 (m, 4H), 7.36–7.21 (m, 4H), 6.42 (s, 1H), 4.51–4.45 (dd,  $J = 10.8, 5.4$  Hz, 1H), 3.66–3.59 (dd,  $J = 15.3, 5.4$  Hz, 1H), 3.12–3.03 (dd,  $J = 14.9, 11.5$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.9, 153.4, 150.1, 149.5, 137.5, 136.7, 135.2, 132.5, 132.1, 130.6, 130.1, 129.8, 139.3, 128.9, 126.3, 125.2, 124.6, 123.7, 120.8, 118.9, 112.0, 108.6, 53.8, 50.7, 23.8; IR ( $\text{cm}^{-1}$ , neat): 3342, 2922, 2852, 1720, 1602, 1484, 1429, 748;  $[\alpha]_{\text{D}}^{20} = -163.4^\circ$  ( $c = 0.3$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 496 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{25}\text{H}_{16}\text{ClF}_3\text{N}_4\text{O}_2$ :  $m/z$  496.0914; Found 496.0911.

**trans-2-(4-Methoxy-phenyl)-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (5l).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  9.55 (s, 1H), 8.55 (s, 1H), 7.64–7.58 (m, 2H), 7.38–7.17 (m, 6H), 7.02–6.90 (m, 3H), 6.37 (s, 1H), 4.44–4.39 (dd,  $J = 10.9, 5.4$  Hz, 1H), 3.79 (s, 3H), 3.60–3.53 (dd,  $J = 15.1, 5.4$  Hz, 1H), 3.05–2.96 (dd,  $J = 15.1, 11.2$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  171.6, 160.4, 154.3, 149.6, 149.4, 137.5, 136.8, 135.8, 132.6, 130.2, 124.6, 123.4, 120.5, 118.8, 118.6, 114.6, 112.2, 111.9, 108.4, 55.8, 53.6, 50.4, 23.7; IR ( $\text{cm}^{-1}$ , neat): 3338, 2936, 2836, 1716, 1605, 1421;  $[\alpha]_{\text{D}}^{20} = -126.1^\circ$  ( $c = 0.3$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 424 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{25}\text{H}_{20}\text{N}_4\text{O}_3$ :  $m/z$  424.1535; Found 424.1534.

**trans-10-Cyclohexyl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (5m).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.08 (s, 1H), 7.52 (d,  $J = 7.6$  Hz, 1H), 7.38–7.34 (m, 2H), 7.29–7.26 (m, 2H), 7.24–7.14 (m, 3H), 5.22 (d,  $J = 2.8$  Hz, 1H), 4.55–4.49 (dd,  $J = 10.7, 6.0$  Hz, 1H), 3.54–3.47 (dd,  $J = 15.4, 6.0$  Hz, 1H), 2.98–2.89 (ddd,  $J = 15.4, 10.7, 1.7$  Hz, 1H), 2.42 (s, 3H), 2.07–2.02 (m, 1H), 1.97–1.85 (m, 2H), 1.76–1.70 (m, 2H), 1.40–1.33 (m, 2H), 1.22–1.08 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.7, 155.6, 139.5, 136.7, 131.8, 131.7, 129.5, 129.3, 127.2, 126.6, 123.7, 122.9, 120.4, 118.5, 111.4, 106.9, 55.6, 54.1, 45.4, 31.1, 29.0, 26.4, 24.2, 21.7; IR ( $\text{cm}^{-1}$ , neat): 3349, 2925, 2851, 1711, 1591, 1415;  $[\alpha]_{\text{D}}^{20} = -2.3^\circ$  ( $c = 0.3$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 413 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_2$ :  $m/z$  413.2103; Found 413.2105.

**cis-10-Cyclohexyl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (5m').**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.14 (s, 1H), 7.59 (d,  $J = 7.3$  Hz, 1H), 7.41–7.37 (m, 2H), 7.29–7.18 (m, 5H), 4.99 (d,  $J = 2.5$  Hz, 1H), 4.29–4.24 (dd,  $J = 11.4, 3.9$  Hz, 1H), 3.55–3.49 (dd,  $J = 14.4, 3.9$  Hz, 1H), 3.27–3.19 (m, 1H), 2.97–2.88 (dd,  $J = 14.4, 11.6$  Hz, 1H), 2.42 (s, 3H), 1.97–1.80 (m, 2H), 1.66–1.56 (m, 4H), 1.40–1.23 (m, 4H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  170.9, 154.4, 139.5, 136.2, 132.0, 131.8, 129.4, 129.3, 127.2, 126.3, 123.7, 122.8, 120.5, 118.5, 111.5,

109.5, 59.2, 58.2, 39.7, 30.9, 27.1, 26.6, 26.1, 21.7; IR ( $\text{cm}^{-1}$ , neat): 3353, 2927, 2852, 1712, 1590, 1410;  $[\alpha]_{\text{D}}^{20} = -35.1^\circ$  ( $c = 0.2$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 413 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_2$ :  $m/z$  413.2103; Found 413.2103.

**trans-2-Butyl-10-cyclohexyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (5n).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.29 (s, 1H), 7.49 (d,  $J = 7.5$  Hz, 1H), 7.37–7.35 (m, 1H), 7.28–7.12 (m, 2H), 5.14 (s, 1H), 4.38–4.32 (dd,  $J = 10.6, 5.9$  Hz, 1H), 3.63–3.58 (m, 2H), 3.45–3.38 (dd,  $J = 15.3, 5.9$  Hz, 1H), 2.81–2.72 (m, 1H), 1.99 (m, 1H), 1.85 (m, 2H), 1.70–1.62 (m, 4H), 1.52–1.49 (m, 1H), 1.41–1.28 (m, 5H), 1.18–1.12 (m, 2H), 0.96 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  174.0, 156.7, 136.7, 131.9, 126.6, 122.8, 120.3, 118.5, 111.4, 106.8, 55.6, 53.8, 45.3, 39.0, 31.1, 28.9, 26.7, 26.4, 24.0, 20.3, 14.0; IR ( $\text{cm}^{-1}$ , neat): 3340, 2928, 2853, 1699, 1623, 1454;  $[\alpha]_{\text{D}}^{20} = -50.5^\circ$  ( $c = 0.8$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 379 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2$ :  $m/z$  379.2260; Found 379.2273.

**cis-2-Butyl-10-cyclohexyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (5n').**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.15 (s, 1H), 7.56 (d,  $J = 7.5$  Hz, 1H), 7.41–7.39 (m, 1H), 7.28–7.15 (d,  $J = 2.8$  Hz, 2H), 4.93 (d,  $J = 2.8$  Hz, 1H), 4.12–4.06 (dd,  $J = 11.5, 4.0$  Hz, 1H), 3.59 (t,  $J = 7.2$  Hz, 2H), 3.45–3.39 (dd,  $J = 14.4, 3.8$  Hz, 1H), 3.23–3.18 (m, 1H), 2.82–2.73 (ddd,  $J = 14.4, 11.8, 1.1$  Hz, 1H), 1.97–1.79 (m, 2H), 1.70–1.61 (m, 4H), 1.44–1.25 (m, 8H), 0.97 (t,  $J = 7.2$  Hz, 3H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.1, 155.5, 136.2, 132.1, 126.3, 122.7, 120.4, 118.4, 111.5, 109.5, 59.2, 58.0, 39.7, 38.8, 30.6, 27.1, 26.6, 26.3, 22.7, 20.3, 14.0; IR ( $\text{cm}^{-1}$ , neat): 3354, 2931, 2853, 1702, 1622, 1452;  $[\alpha]_{\text{D}}^{20} = -42.8^\circ$  ( $c = 0.3$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 379 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{23}\text{H}_{29}\text{N}_3\text{O}_2$ :  $m/z$  379.2260; Found 379.2273.

**trans-10-Cyclohexyl-2-(3-fluoro-phenyl)-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[b]fluorene-1,3-dione (5o).**  $^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  8.52 (s, 1H), 7.53–7.08 (m, 7H), 6.79–6.74 (m, 1H), 5.20 (d,  $J = 3.5$  Hz, 1H), 4.58–4.52 (dd,  $J = 10.8, 6.0$  Hz, 1H), 3.52–3.44 (dd,  $J = 15.4, 6.0$  Hz, 1H), 2.94–2.85 (dd,  $J = 14.2, 10.8$  Hz, 1H), 2.03–1.04 (m, 11H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  172.5, 164.6, 161.3, 155.1, 140.0, 136.8, 133.4, 133.3, 130.6, 130.4, 126.5, 122.9, 120.3, 118.5, 115.7, 115.4, 114.1, 113.8, 111.5, 110.5, 110.2, 106.4, 55.6, 54.3, 45.2, 31.2, 28.9, 26.4, 23.8; IR ( $\text{cm}^{-1}$ , neat): 3345, 2929, 2852, 1713, 1608, 1494, 1420;  $[\alpha]_{\text{D}}^{20} = +7.2^\circ$  ( $c = 1.5$ ;  $\text{CH}_2\text{Cl}_2$ ); MS (EI)  $m/z$ : 417 ( $\text{M}^+$ ); Hrms calcd for  $\text{C}_{25}\text{H}_{24}\text{FN}_3\text{O}_2$ :  $m/z$  417.1853; Found 417.1854.

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**Supporting Information Available.** Representative  $^1\text{H}$  NMR and  $^{13}\text{C}$  NMR spectrum of compounds 5a–5o and the schematic representation of F-SPE concept are enclosed herewith. 1D NOE experiment of 5m and 5m' are included. This material is available free of charge via the internet at <http://pubs.acs.org>.

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