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Microwave-assisted traceless synthesis of hydantion-fused β-carboline scaffold

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Abstract—Multistep microwave-assisted reactions toward the synthesis of hydantoin-fused tricyclic tetrahydro-β-carbolines on the soluble polymer support have been developed. Polymer-bound tryptophan with various aldehydes has been subjected to Pictet–Spengler reaction to obtain tricyclic β-carboline conjugates. The terminal hydantoinyl moiety is constructed across polymer-bound β-carbolines by the reaction with various isocyanates under microwave irradiation to form urea intermediate. Simultaneous intramolecular cyclization of urea followed by cleavage of the polymer support leads to a traceless synthesis of tetracyclic scaffolds in high yield and high purity.

1. Introduction

With many new therapeutic targets emerging from chemical genomics research, combinatorial chemistry provides a quick access to the structural diverse collection to fuel chemical genetics.[1] Combinatorial chemistry is like modern organic synthesis, which designs target compounds containing diversity and facilitates the synthesis of a large number of compounds along the scaffolds in shorter time. Combinatorial synthesis is a powerful tool for drug discovery when it is combined with high throughput screening systems to search potential drug candidates. After Merrifield reported the solid-phase peptide synthesis, insoluble polymer-supported synthesis became an increasingly popular application in organic synthesis.[2] Solid-phase organic synthesis offers merits through the simple and rapid filtration process to separate side products and excess reagents. However, it suffers from various difficulties such as heterogeneous nature of reaction condition, reduced rate of reactions, solvation of the bound species and mass transport of reagents. Instead, it is easy to monitor reaction progress in solution-phase synthesis and it does not require any solid support/cleavage process but it has drawbacks such as difficult separation and purification. Combining the advantages of solid-phase and solution-phase chemistry, we focused on liquid phase strategy which enables standard solution-based chemistry to be utilized and product purification is just like that of solid-phase reactions. Furthermore, monitoring progress of reactions on the soluble support is significantly simplified by using conventional analytical methods. Nowadays microwave irradiation in chemical reaction enhancement has been widely applied in various synthetic fields, which features higher conversion and shorter reaction time. In order to quickly generate compounds of increasing molecular diversity, application of combinatorial chemistry and microwave technology has been a useful tool to accelerate the development of new drugs.[3,4]

The β-carboline skeletons are present in many indole alkaloids and appear in marine natural products.[5,6] Tricyclic tetrahydro-β-carbolines have a wide variety of pharmacological activities such as tumor cell anti-proliferative and anti-viral properties.[7] The tetrahydro-β-carboline-3-methylcarboxylates are shown to bind to benzodiazepine receptors.[8] In particular, HR22C16 which is the hydantoin-fused tetrahydro-β-carboline (Fig. 1) blocks cell division by Eg5 (or KSP) protein and leads to cell cycle arrest and apoptosis.[9] Among the natural products demethoxyfumitremorgine C and spirotryprostatin B isolated from fermentation broth of *Aspergillus fumigatus* BM939 inhibit the mammalian cell cycle in the G2/M phase.[10,11] Herein, we report a rapid microwave-assisted, traceless synthesis of tetrahydro-β-carbolinehydantoins with two points of structural diversity.

2. Results and discussion

The synthetic route to the tetrahydro-β-carbolinehydantoin library is described in Scheme 1. Polymer-bound Boc-L-tryptophan **3** was obtained by the reaction of soluble polymer support PEG-5000 **1** and Boc-L-tryptophan **2** in the presence of *N*,*N*′-dicyclohexylcarbodiimide (DCC) along with diaminopyridine (DMAP) as a catalyst. The coupling reaction is completed in dichloromethane under

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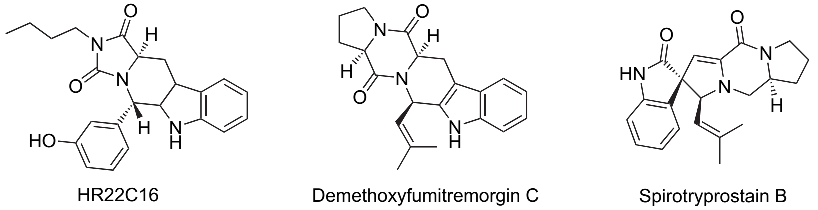


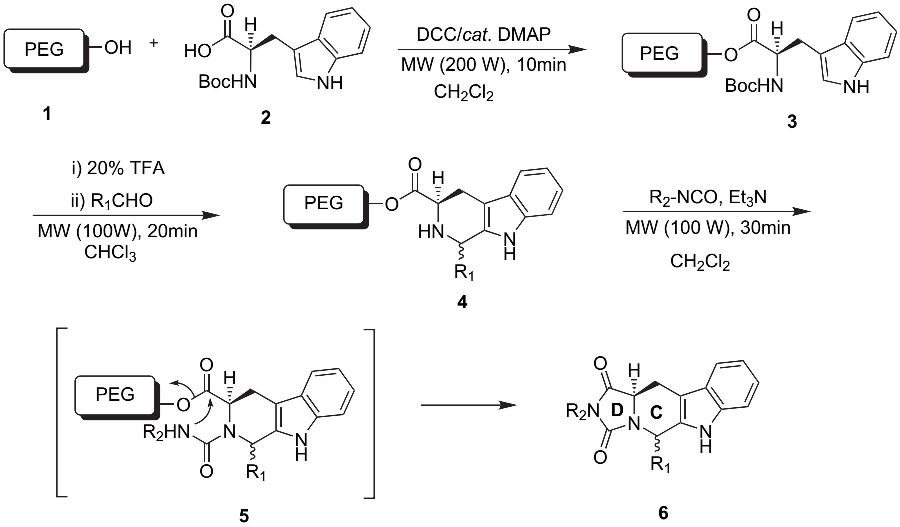
Figure 1. Biologically active tetrahydro-β-carboline derivatives.

microwave irradiation condition (200 W) in an open vessel system for 10 min to afford the polymer conjugated compound **3** in higher yield. The same esterification reaction performed under conventional refluxing method with the same stoichiometric equivalents of reagents required 24 h to reach completion. Merits of microwave irradiation compared to conventional method are shorter reaction time with higher conversion and high purity. After completion of the reaction, reaction mixtures are filtered off to remove undissolved dicyclohexyl urea (DCU) byproduct followed by slow addition of ether for precipitation. The precipitated polymer-bound Boc-L-tryptophan **3** was washed with ether subsequently to remove the excess reagents and side products. Compound **3** is deprotected with 20% trifluoroacetic acid (TFA) in microwave cavity for 20 min to give Boc-free tryptophan followed by in situ addition of various aldehydes. Deprotection of the Boc group was ensured by the disappearance of *tert*-butyloxyl group absorbance at 1.4 ppm in the crude ^{1}H NMR spectrum. The same reaction was completed in 24 h by conventional reflux heating. The Boc deprotection and Pictet–Spengler cyclization reaction are performed in one pot, which has the advantages of reducing the synthetic steps and introducing the first point of structural diversity. Polymer-bound β-carboline **4** is obtained after Pictet–Spengler reaction which indicates the formation of cis and trans diastereomers in various ratios through proton NMR analysis.

Construction of D ring of hydantoin across the N-2/C-3 bond of the tetrahydro-β-carboline skeleton is achieved by the reaction of polymer-bound β-carboline **4** with several different isocyanates under microwave irradiation (100 W) for 30 min to give urea intermediate **5** which undergoes nucleophilic attack on the carbonyl carbon to give target compounds **6**. The same ring closure was completed within 18 h under classical refluxing conditions. The cyclization of hydantoin ring and subsequently traceless cleavage[12,13] of polymer support proceeded in one step under mild basic condition (Et_3N). The representative library of tetrahydro-β-carbolinehydantoin derivatives **6** and analytical data are shown in Table 1. The present investigation for the preparation of target compounds under liquid phase and MW approach affords 80% of compounds as trans isomers with high purity (Table 1).

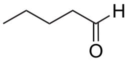
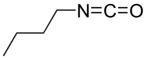
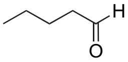
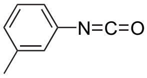
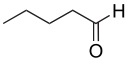
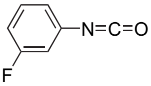
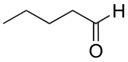
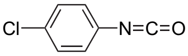
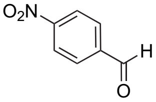
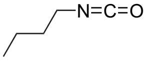
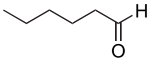
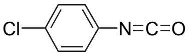
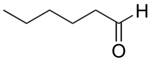
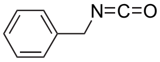
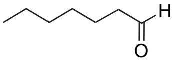
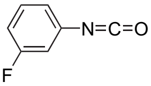
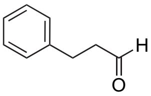
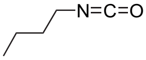
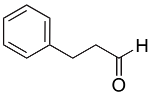
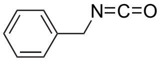
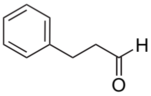
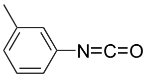
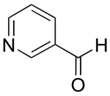
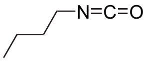
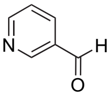
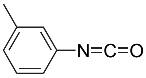
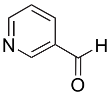
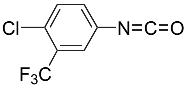
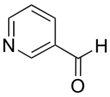
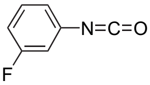
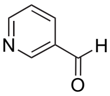
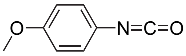
The cis/trans stereochemistry of tetrahydro-β-carbolinehydantoins **6** is confirmed by spectral and analytical data through the comparison with literature reported by Cook et al.[14,15] Single-crystal X-ray analysis of compound **6s** (Fig. 2) also confirms that the rings C and D are trans-fused and are non-planar, which shows that the hydrogens of C-2 and C-12 are *anti*-periplanar. Additionally, the NOE spectrum showed a correlation peak of the hydrogens in C-2 and C-12. Hence, the NOE experiments provide a clear indication regarding the spectrum of cis and trans isomers. Occurrence of a NOE effect at H_a or H_b proves cis configuration while irradiating the hydrogens in C-2 or C-12. Furthermore, the trans isomer structure was not observed any enhancement in H_a or H_b peak upon irradiation of hydrogens in C-2 or C-12.

In summary, we reported here a rapid, efficient, and convenient protocol for the synthesis of tetrahydro-β-carboline-hydantoin derivatives via Pictet–Spengler reaction using traceless linker approach. All the polymer-supported



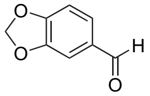
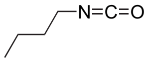
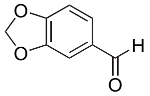
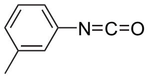
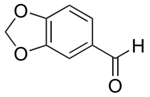
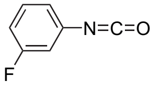
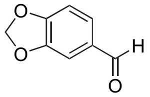
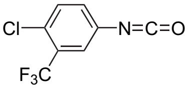
Scheme 1. Synthesis of tetrahydro-β-carbolinehydantoins **6** on soluble polymer support under microwave condition.

Table 1. Tetrahydro-β-carbolinehydantoins synthesized by multistep microwave irradiation on polymer support

Entry	R_1CHO	R_2NCO	Obsd mass	Yield % (trans/cis)
6a			353	90 (Trans only)
6b			387	85 (Trans only)
6c			391	84 (Trans only)
6d			407	93 (Trans only)
6e			418 (M+1)	80 (Trans only)
6f			422 (M+1)	83 (Trans only)
6g			402 (M+1)	79 (1.6:1)
6h			420 (M+1)	87 (Trans only)
6i			402 (M+1)	80 (1.5:1)
6j			436 (M+1)	91 (1.2:1)
6k			436 (M+1)	92 (Trans only)
6l			374	85 (1.2:1)
6m			408	92 (1.3:1)
6n			496	92 (Trans only)
6o			412	87 (Trans only)
6p			424	82 (Trans only)

(*continued*)

Table 1. (*continued*)

Entry	R_1CHO	R_2NCO	Obsd mass	Yield % (trans/cis)
6q			417	87 (1.2:1)
6r			451	89 (Trans only)
6s			455	92 (Trans only)
6t			539	94 (Trans only)

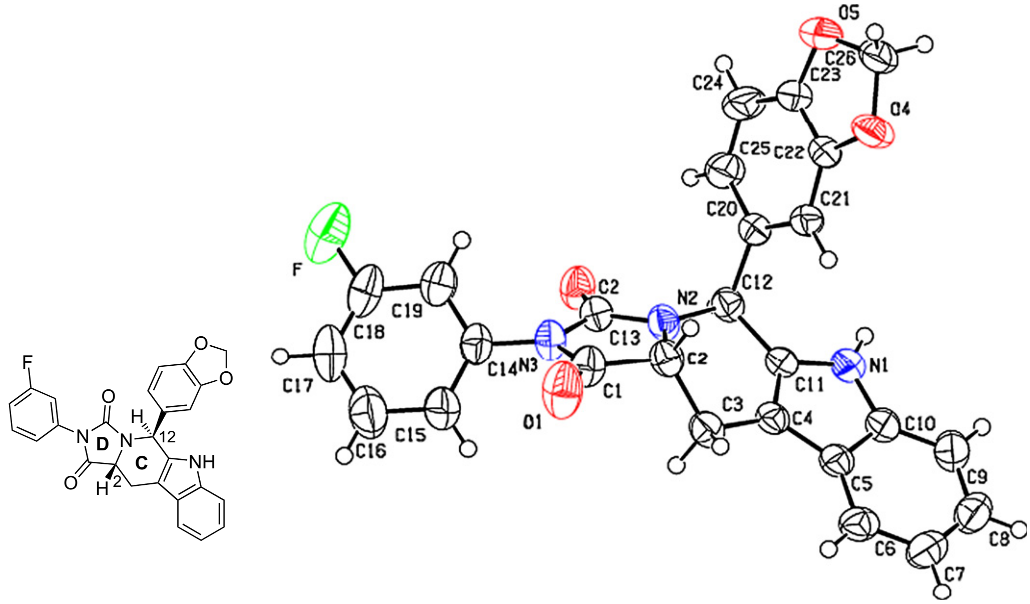


Figure 2. Single-crystal X-ray structural elucidation of compound **6s**.

reactions are carried out under microwave irradiation which can reduce the reaction time significantly from hours to minutes and gives the desired compounds in high yields. It should be noted that polymer-supported intermediates and the polymer itself are stable during the harsh MW irradiation. Synthesis and screening of focused combinatorial library based on pharmacophoric scaffolds may lead to the discovery of interesting biological profiles.

3. Experimental section

3.1. General procedure for the synthesis of tetracyclic tetrahydro-β-carbolines 6a–6t

The microwave-assisted polymer-bound reactions described here were performed in CEM Discover Microwave System at a frequency of 2450 Hz (0–300 W) in open vessel system. The soluble polymer support (PEG-OH, MW ~5000) **1** (1 g, 0.2 mmol) was esterified in 10 mL of dichloromethane with Boc-L-tryptophan **2** (0.146 g, 0.48 mmol) which was treated with DCC (2.6 equiv, 0.52 mmol) and 4-dimethylamino pyridine (DMAP) (0.002 g). The reaction mixtures were subjected to MW (200 W) irradiation for 10 min to obtain the polymer-bound Boc-L-tryptophan **3**. The dicyclohexyl urea (DCU) byproduct was filtered off and the reaction mixture was precipitated with ether. The precipitated polymer-bound Boc-L-tryptophan **3** was filtered through a fritted funnel and thoroughly washed with ether and dried. The deprotection of polymer-bound Boc-L-tryptophan **3** was performed with 10 mL of 20% trifluoroacetic acid to remove Boc followed by reaction with various aldehydes (3 equiv) in chloroform, and MW (100 W) irradiation for 20 min. After completion of the reaction, ether was added for precipitation to afford the polymer-bound secondary amine **4**. The precipitated solid **4** was washed three times with ether to remove the unreacted aldehyde and the solid was dried for the next step reaction.

The polymer-bound secondary amines **4** (1 g, 0.22 mmol) were reacted with various isocyanates (3 equiv, 0.66 mmol), triethylamine (1.40 mL, 1.33 mmol) in dichloromethane under microwave irradiation (100 W) for 20 min. When TLC showed complete release of the desired compound from the support, the reaction mixtures were then diluted with ether to precipitate the polymer and the residue again washed with ether. The combined filtrate was evaporated. The crude product was purified by silica gel column chromatography using 1:4 ratio of ethyl acetate/hexane as an eluent.

3.1.1. *trans*-2,10-Dibutyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6a). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.03 (s, 1H), 7.49 (d, 1H, *J*=7.8 Hz), 7.35 (d, 1H, *J*=7.8 Hz), 7.24–7.12 (m, 2H), 5.30–5.25 (dd, 1H, *J*=6.4, 4.5 Hz), 4.32–4.27 (dd, 1H, *J*=10.9, 5.7 Hz), 3.58 (td, 2H, *J*=7.1, 1.5 Hz), 3.44–3.37 (dd, 1H, *J*=15.2, 5.7 Hz), 2.83–2.73 (ddd, 1H, *J*=15.2, 10.9, 1.6 Hz), 2.04–1.98 (m, 1H), 1.83–1.73 (m, 1H), 1.69–1.61 (m, 4H), 1.41–1.33 (m, 4H), 0.97–0.88 (m, 6H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 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 (cm^{-1}, neat): 3344, 2958, 2929, 2857, 1705, 1620, 1454; $[\alpha]_D^{20}$ −44.1 (*c* 0.25, CH$_2$Cl$_2$); LRMS (EI) *m*/*z*: 353 (M$^+$). HRMS: calcd for $C_{21}H_{27}N_3O_2$: *m*/*z* 353.2103; found: 353.2109.

3.1.2. *trans*-10-Butyl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6b). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.29 (s, 1H), 7.51 (d, 1H, *J*=8.5 Hz), 7.41–7.14 (m, 7H), 5.34–5.31 (dd, 1H, *J*=6.9, 4.0 Hz), 4.51–4.45 (dd, 1H, *J*=10.8, 5.7 Hz), 3.52–3.45 (dd, 1H, *J*=15.2, 5.7 Hz), 2.97–2.82 (ddd, 1H, *J*=15.2, 10.8, 1.3 Hz), 2.40 (s, 3H), 2.09–1.77 (m, 1H), 1.90–1.76 (m, 1H), 1.58–1.40 (m, 4H), 0.92 (t, 3H, *J*=7.0 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 172.2, 154.7, 139.3, 136.4, 132.6, 131.4, 129.2, 129.0, 126.9, 126.3, 123.4, 122.5, 120.1, 118.2, 111.2, 105.8, 53.9, 49.0, 35.7, 27.8, 23.8, 22.8, 21.4, 14.0; IR (cm^{-1}, neat): 3411, 2958, 2929, 2875, 1735, 1648, 1440; $[\alpha]_D^{20}$ −42.6 (*c* 0.99, CH$_2$Cl$_2$); LRMS (EI) *m*/*z*: 387 (M$^+$). HRMS: calcd for $C_{24}H_{25}N_3O_2$: *m*/*z* 387.1947; found: 387.1945.

3.1.3. *trans*-10-Butyl-2-(3-fluoro-phenyl)-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6c). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.16 (s, 1H), 7.53–7.41 (m, 2H), 7.35–7.33 (m, 3H), 7.25–7.08 (m, 3H), 5.39–5.35 (dd, 1H, *J*=7.4, 4.5 Hz), 4.52–4.46 (dd, 1H, *J*=10.8, 5.7 Hz), 3.54–3.47 (dd, 1H, *J*=15.3, 5.7 Hz), 2.99–2.90 (ddd, 1H, *J*=15.3, 10.8, 1.6 Hz), 2.08–1.88 (m, 2H), 1.72–1.62 (m, 2H), 1.62–1.60 (m, 2H), 1.00–0.799 (m, 3H); ^{13}C NMR (75 MHz, CDCl$_3$): δ 172.1, 164.7, 161.4, 154.3, 136.6, 133.2, 132.6, 130.5, 126.5, 122.9, 121.7, 118.4, 115.4, 113.8, 111.3, 105.9, 53.6, 48.8, 35.4, 27.5, 23.4, 22.4, 13.6; IR (cm^{-1}, neat): 3433, 2975, 2929, 2857, 1723, 1622, 1420; $[\alpha]_D^{20}$ −23.85 (*c* 0.7, CH$_2$Cl$_2$); LRMS (EI) *m*/*z*: 391 (M$^+$). HRMS: calcd for $C_{23}H_{22}FN_3O_2$: *m*/*z* 391.1679; found: 391.1692.

3.1.4. *trans*-10-Butyl-2-(4-chloro-phenyl)-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6d). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.01 (s, 1H), 7.53–7.14 (m, 8H), 5.36–5.30 (dd, 1H, *J*=7.4, 4.5 Hz), 4.50–4.44 (dd, 1H, *J*=10.2, 5.7 Hz), 3.52–3.45 (dd, 1H, *J*=15.1, 5.6 Hz), 2.98–2.89 (ddd, 1H, *J*=15.1, 10.2, 5.6 Hz), 2.13–2.01 (m, 1H), 1.91–1.79 (m, 1H), 1.59–1.29 (m, 4H), 0.90 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 171.7, 154.1, 136.3, 133.8, 132.4, 130.9, 130.2, 129.3, 128.8, 127.2, 126.3, 122.8, 120.2, 118.3, 111.1, 106.0, 53.8, 49.0, 35.7, 27.8, 23.8, 22.7, 14.1; IR (cm^{-1}, neat): 3344, 2958, 2929, 2857, 1705, 1620, 1454; $[\alpha]_D^{20}$ −15.6 (*c* 0.21, CH$_2$Cl$_2$); LRMS (EI) *m*/*z*: 407 (M$^+$). HRMS: calcd for $C_{23}H_{22}ClN_3O_2$: *m*/*z* 407.1401; found: 407.4108.

3.1.5. *trans*-2-Butyl-10-(4-nitro-phenyl)-3,4,9,10-tetrahydro-2,9,10-triaza-cyclopenta[*b*]fluorene-1,3-dione (6e). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.26 (s, 1H), 8.23 (d, 2H, *J*=8.5 Hz), 7.68 (d, 1H, *J*=7.6 Hz), 7.61 (d, 2H, *J*=8.5 Hz), 7.43 (d, 1H, *J*=7.6 Hz), 7.38–7.27 (m, 2H), 6.48 (s, 1H), 4.38–4.33 (dd, 1H, *J*=11.0, 5.4 Hz), 3.68–3.59 (m, 3H), 3.04–2.95 (dd, 1H, *J*=15.2, 11.0 Hz), 1.75–1.65 (m, 2H), 1.48–1.36 (m, 2H), 1.02 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 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 (cm^{-1}, neat): 3337, 2957, 2934, 2870, 1711, 1695, 1453, 1548, 1494; $[\alpha]_D^{20}$ −36.2 (*c* 0.51, CH$_2$Cl$_2$); LRMS (EI) *m*/*z*: 418 (M$^+$); HRMS: calcd for $C_{23}H_{22}N_4O_4$: *m*/*z* 418.1641; found: 418.1642.

3.1.6. *trans*-2-(4-Chloro-phenyl)-10-pentyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6f). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.04 (s, 1H), 7.56 (d, 1H, *J*=7.5 Hz), 7.48–7.42 (m, 4H), 7.39 (d, 1H, *J*=7.5 Hz), 7.27–7.16 (m, 3H), 5.15 (s, 1H), 4.39–4.33 (dd, 1H, *J*=11.4, 4.5 Hz), 3.47–3.45 (ddd, 1H, *J*=15.2, 4.5, 1.6 Hz), 3.10–3.00 (ddd, 1H, *J*=15.2, 11.4, 1.6 Hz), 1.27–1.06 (m, 4H), 0.92–0.85 (m, 2H), 0.78 (t, 3H, *J*=6.3 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 170.4, 153.6, 136.4, 133.9, 132.7, 130.1, 129.3, 127.4, 126.2, 122.7, 120.3, 118.3, 111.2, 108.1, 58.1, 52.9, 32.4, 31.6, 22.6, 22.5, 22.4, 14.0; IR (cm^{-1}, neat): 3300, 2932, 2912, 2823, 1725, 1611, 1422; $[\alpha]_D^{20}$ −67.5 (*c* 0.62, CH$_2$Cl$_2$); LRMS (FAB+) *m*/*z*: 422 (M$^+$+1). HRMS: calcd for $C_{24}H_{24}ClN_3O_2$: *m*/*z* 421.1557; found: 421.1514.

3.1.7. *trans*-2-Benzyl-10-pentyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6g). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.14 (s, 1H), 7.48–7.25 (m, 9H), 5.25 (dd, 1H, *J*=7.5, 4.2 Hz), 4.81–4.67 (dd, 2H, *J*=12.9, 7.4 Hz), 4.31 (dd, 1H, *J*=5.4, 5.7 Hz), 3.40–3.33 (dd, 1H, *J*=15.3, 5.7 Hz), 2.77–2.68 (ddd, 1H, *J*=15.3, 5.7, 1.2 Hz), 2.05–1.93 (m, 1H), 1.80–1.70 (m, 1H), 1.52–1.25 (m, 6H), 0.87 (t, 3H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, CDCl$_3$): δ 173.0, 155.3, 136.3, 136.2, 132.6, 128.8, 128.4, 128.0, 127.9, 122.6, 120.1, 118.2, 111.1, 105.9, 53.9, 48.7, 42.4, 36.1, 31.7, 25.4, 23.6, 22.5, 14.0; IR (cm^{-1}, neat): 3324, 2928, 2857, 1735, 1648, 1440; $[\alpha]_D^{20}$ −55.0 (*c* 0.28, CH$_2$Cl$_2$); LRMS (FAB+) *m*/*z*: 402 (M$^+$+1). HRMS: calcd for $C_{25}H_{27}N_3O_2$: *m*/*z* 401.2103; found: 401.2143.

3.1.8. *cis*-2-Benzyl-10-pentyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6g′). ^{1}H NMR (300 MHz, CDCl$_3$): δ 8.05 (s, 1H), 7.52 (d, 1H, *J*=7.5 Hz), 7.44 (d, 1H, *J*=7.5 Hz), 7.37–7.14 (m, 7H), 5.05 (s, 1H), 4.74–4.67 (dd, 2H, *J*=11.9, 7.4 Hz), 4.20–4.15 (dd, 1H, *J*=5.7, 4.5 Hz), 3.41–3.35 (dd, 1H, *J*=7.5, 4.2 Hz), 3.11–2.99 (m, 1H), 2.84–2.75 (ddd, 1H, *J*=7.3, 5.9, 0.9 Hz), 1.90–1.79 (m, 1H), 1.27–1.06 (m, 4H), 0.92–0.85 (m, 2H), 0.77 (t, 3H, *J*=6.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.5, 154.8, 136.4, 136.3, 132.9, 128.7, 128.5, 127.9, 126.3, 122.5, 120.1, 118.2, 111.1, 108.2, 58.2, 52.5, 42.2, 32.3, 31.6, 29.7, 22.5, 22.2, 14.0; IR (cm^{-1}, neat): 3320, 2931, 2850, 1705, 1620, 1454; $[\alpha]_{\mathrm{D}}^{20}$ −80.5 (*c* 0.38, CH_2Cl_2); LRMS (FAB+) *m*/*z*: 402 (M^++1). HRMS: calcd for $C_{25}H_{27}N_3O_2$: *m*/*z* 401.2103; found: 401.2127.

3.1.9. *trans*-2-(3-Fluoro-phenyl)-10-hexyl-1-thioxo-1,2,3a,4,9,10-hexahydro-2,9,10a-triaza-cyclopenta[*b*]-fluoren-3-one (6h). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.06 (s, 1H), 7.53–7.06 (m, 8H), 5.37–5.30 (dd, 1H, *J*=6.5, 4.5 Hz), 4.50–4.45 (dd, 1H, *J*=11.1, 5.7 Hz), 3.53–3.45 (dd, 1H, *J*=15.3, 5.7 Hz), 2.98–2.89 (ddd, 1H, *J*=15.3, 10.8, 1.5 Hz), 2.12–2.00 (m, 1H), 1.92–1.79 (m, 1H), 1.61–1.26 (m, 8H), 0.87 (t, 3H, *J*=6.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 164.3, 161.0, 153.9, 136.4, 133.1, 133.0, 132.4, 130.2, 130.1, 126.3, 122.7, 121.5, 121.5, 120.2, 118.3, 115.2, 114.9, 113.6, 113.3, 111.1, 106.0, 53.8, 49.0, 36.0, 31.7, 29.3, 25.7, 23.8, 22.6, 14.0; IR (cm^{-1}, neat): 3410, 2975, 2931, 1730, 1642, 1490; $[\alpha]_{\mathrm{D}}^{20}$ −9.8 (*c* 0.21, CH_2Cl_2); LRMS (FAB+) *m*/*z*: 420 (M^++1). HRMS: calcd for $C_{25}H_{26}FN_3O_2$: *m*/*z* 419.2009; found: 419.2014.

3.1.10. *trans*-2-Butyl-3a-methyl-10-phenethyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6i). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.07 (s, 1H), 7.48 (d, 1H, *J*=7.8 Hz), 7.33–7.12 (m, 8H), 5.35–5.31 (dd, 1H, *J*=7.2, 3.6 Hz), 4.24–4.18 (dd, 1H, *J*=10.8, 5.7 Hz), 3.59 (t, 2H, *J*=7.5 Hz), 3.41–3.34 (dd, 1H, *J*=15.5, 5.7 Hz), 2.89–2.71 (m, 3H), 2.30–2.26 (m, 1H), 2.18–2.05 (m, 1H), 1.71–1.61 (m, 2H), 1.43–1.27 (m, 2H), 0.96 (t, 3H, *J*=7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.2, 155.8, 140.9, 140.9, 136.4, 128.6, 128.3, 126.3, 122.7, 120.1, 118.3, 111.1, 106.2, 53.6, 48.3, 38.7, 37.5, 31.9, 30.3, 23.6, 20.0, 13.7; IR (cm^{-1}, neat): 3420, 2980, 2877, 1740, 1638, 1450; $[\alpha]_{\mathrm{D}}^{20}$ −63.5 (*c* 0.27, CH_2Cl_2); LRMS (FAB+) *m*/*z*: 402 (M^++1). HRMS: calcd for $C_{25}H_{27}O_3N_2$: *m*/*z* 401.2103; found: 401.2143.

3.1.11. *cis*-2-Butyl-10-phenethyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6i′). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.19 (s, 1H), 7.56 (d, 1H, *J*=7.5 Hz), 7.38 (d, 1H, *J*=7.5 Hz), 7.33–7.06 (m, 7H), 5.11 (s, 1H), 4.18–4.12 (dd, 1H, *J*=10.8, 5.7 Hz), 3.60 (t, 2H, *J*=7.5 Hz), 3.43–3.41 (dd, 1H, *J*=15.5, 5.7 Hz), 2.87–2.72 (ddd, 1H, *J*=15.5, 5.7, 1.2 Hz), 2.59–2.48 (td, 1H, *J*=9.9, 3.2 Hz), 2.19–2.10 (m, 1H), 1.79–1.61 (m, 2H), 1.43–1.25 (m, 4H), 0.971 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.9, 155.3, 141.4, 136.6, 132.5, 128.5, 128.4, 126.3, 126.0, 122.6, 120.2, 118.3, 111.3, 108.4, 57.0, 52.3, 38.5, 34.4, 30.3, 29.2, 22.5, 20.1, 13.7; IR (cm^{-1}, neat): 3422, 2981, 2873, 1735, 1637, 1430; $[\alpha]_{\mathrm{D}}^{20}$ −21.5 (*c* 0.98, CH_2Cl_2); LRMS (FAB+) *m*/*z*: 402 (M^++1). HRMS: calcd for $C_{25}H_{27}O_3N_2$: *m*/*z* 401.2103; found: 401.2127.

3.1.12. *trans*-2-Benzyl-10-phenethyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6j). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.13 (s, 1H), 7.47–7.43 (m, 2H), 7.37–7.04 (m, 12H), 5.33–5.29 (dd, 1H, *J*=7.9, 3.6 Hz), 4.80–4.67 (dd, 2H, *J*=12.2, 7.2 Hz), 4.25–4.20 (dd, 1H, *J*=10.8, 5.7 Hz), 3.38–3.31 (dd, 1H, *J*=15.3, 5.7 Hz), 2.84–2.65 (m, 2H), 2.36–2.24 (m, 1H), 2.14–2.02 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.9, 155.5, 140.9, 136.4, 136.1, 132.2, 128.8, 128.7, 128.6, 128.5, 128.3, 128.0, 126.2, 122.6, 120.1, 118.3, 111.2, 105.9, 53.8, 48.5, 42.4, 37.3, 31.9, 23.5; IR (cm^{-1}, neat): 3406, 2981, 2873, 1746, 1603, 1454; $[\alpha]_{\mathrm{D}}^{20}$ −54.7 (*c* 2.41, CH_2Cl_2); LRMS (FAB+) *m*/*z*: 436 (M^++1). HRMS: calcd for $C_{28}H_{25}N_3O_2$: *m*/*z* 435.1947; found: 435.1911.

3.1.13. *cis*-2-Benzyl-10-phenethyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6j′). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.12 (s, 1H), 7.55 (d, 1H, *J*=7.2 Hz), 7.48 (d, 1H, *J*=7.3 Hz), 7.37–7.03 (m, 12H), 5.06 (s, 1H), 4.80–4.69 (dd, 2H, *J*=10.1, 7.2 Hz), 4.18–4.12 (dd, 1H, *J*=10.1, 5.8 Hz), 3.43–3.34 (m, 2H), 2.88–2.79 (ddd, 1H, *J*=14.7, 5.8, 0.9 Hz), 2.55–2.45 (m, 1H), 2.17–2.08 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 154.9, 141.3, 136.5, 136.2, 132.4, 129.0, 128.8, 128.6, 128.4, 128.0, 126.3, 126.0, 122.6, 120.2, 118.3, 111.3, 108.4, 58.1, 52.4, 42.3, 34.3, 29.1, 22.5; IR (cm^{-1}, neat): 3396, 2976, 2867, 1726, 1613, 1424; $[\alpha]_{\mathrm{D}}^{20}$ −54.7 (*c* 2.41, CH_2Cl_2); LRMS (FAB+) *m*/*z*: 436 (M^++1). HRMS: calcd for $C_{28}H_{25}N_3O_2$: *m*/*z* 435.1947; found: 435.1930.

3.1.14. *trans*-10-Phenethyl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6k). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.18(s, 1H), 7.50 (d, 1H, *J*=7.8 Hz), 7.41–7.14 (m, 12H), 5.43–5.40 (dd, 1H, *J*=10.8, 5.7 Hz), 4.38–4.35 (dd, 1H, *J*=15.4, 5.7 Hz), 3.48–3.45 (dd, 1H, *J*=15.4, 5.7 Hz), 2.95–2.75 (m, 3H), 2.40 (s, 3H), 2.24–2.11 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 154.7, 140.9, 139.3, 136.4, 132.2, 131.4, 129.3, 129.0, 128.6, 128.3, 126.9, 126.3, 123.4, 122.7, 120.1, 118.2, 111.2, 111.2, 106.0, 53.6, 48.7, 37.2, 31.9, 23.8, 21.4; IR (cm^{-1}, neat): 3417, 2959, 2909, 1738, 1652, 1498; $[\alpha]_{\mathrm{D}}^{20}$ −33.9 (*c* 1.04, CH_2Cl_2); LRMS (FAB+) *m*/*z*: 436 (M^++1). HRMS: calcd for $C_{28}H_{25}N_3O_2$: *m*/*z* 435.1947; found: 435.1869.

3.1.15. *trans*-2-Butyl-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6l). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.93 (s, 1H), 8.65 (s, 1H), 8.55 (d, 1H, *J*=4.6 Hz), 7.73 (d, 1H, *J*=7.8 Hz), 7.56 (d, 1H, *J*=7.4 Hz), 7.41–7.37 (dd, 1H, *J*=7.8, 4.8 Hz), 7.29 (d, 1H, *J*=8.0 Hz), 7.12–7.00 (m, 2H), 6.29 (s, 1H), 4.71–4.66 (dd, 1H, *J*=10.7, 5.5 Hz), 3.54–3.43 (m, 3H), 2.85–2.76 (dd, *J*=12.5, 11.3 Hz, 1H), 1.55–1.42 (m, 2H), 1.30–1.18 (m, 2H), 0.86 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 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 (cm^{-1}, neat): 3347, 2932, 2850, 1707, 1599, 1422; $[\alpha]_{\mathrm{D}}^{20}$ −158.5 (*c* 0.31, CH_2Cl_2); LRMS (EI) *m*/*z*: 374 (M^+); HRMS: calcd for $C_{22}H_{22}N_4O_2$: *m*/*z* 374.1743; found: 374.1740.

3.1.16. *cis*-2-Butyl-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6l′). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.8 (s, 1H), 8.63 (d, 1H, *J*=1.9 Hz), 8.46–8.44 (dd, 1H, *J*=4.7, 1.5 Hz), 7.56–7.61 (dd, 1H, *J*=6.1, 1.6 Hz), 7.56 (d, 1H, *J*=7.3 Hz), 7.30–7.18 (m, 2H), 7.12–6.97 (m, 2H), 5.95 (s, 1H), 4.59–4.54 (dd, 1H, *J*=11.3, 4.3 Hz), 3.40–3.30 (m, 3H), 2.21–2.11 (dd, 1H, *J*=15.1, 11.1 Hz), 1.49–1.42 (m, 2H), 1.30–1.18 (m, 2H), 0.86 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 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 (cm^{-1}, neat): 3345, 2929, 2864, 1711, 1588, 1424; $[\alpha]_D^{20}$ −44.6 (*c* 0.32, CH_2Cl_2); LRMS (EI) *m/z*: 374 (M$^+$); HRMS: calcd for $C_{22}H_{22}N_4O_2$: *m/z* 374.1743; found: 374.1746.

3.1.17. *trans*-10-Pyridin-3-yl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6m). ^{1}H NMR (300 MHz, CD_3OD): δ 8.66 (d, 1H, *J*=1.8 Hz), 8.54–8.52 (dt, 1H, *J*=4.8, 1.4 Hz), 7.83–7.79 (dt, 1H, *J*=7.9, 1.6 Hz), 7.58 (d, 1H, *J*=7.3 Hz), 7.48–7.44 (dd, 1H, *J*=7.8, 4.9 Hz), 7.37–7.27 (m, 4H), 7.23–7.07 (m, 4H), 6.45 (s, 1H), 4.70–4.65 (dd, 1H, *J*=11.0, 5.5 Hz), 3.57–3.50 (dd, 1H, *J*=15.0, 5.5 Hz), 3.07–2.97 (dd, 1H, *J*=15.0, 11.0 Hz), 2.37 (s, 3H); ^{13}C NMR (75 MHz, CD_3OD): δ 172.6, 154.6, 149.1, 139.2, 137.7, 137.0, 136.5, 131.94, 129.6, 129.4, 129.0, 128.8, 127.4, 126.3, 124.6, 123.9, 122.4, 119.5, 118.2, 111.3, 107.6, 53.8, 50.5, 23.0, 20.2; IR (cm^{-1}, neat): 3326, 2957, 2930, 2871, 1702, 1602, 1453; $[\alpha]_D^{20}$ −19.6 (*c* 0.23, CH_2Cl_2); LRMS (EI) *m/z*: 408 (M$^+$); HRMS: calcd for $C_{25}H_{20}N_4O_2$: *m/z* 408.1586; found: 408.1593.

3.1.18. *cis*-10-Pyridin-3-yl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6m′). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.71 (d, 1H, *J*=1.5 Hz), 8.46 (d, 1H, *J*=3.7 Hz), 7.75 (d, 1H, *J*=7.8 Hz), 7.60 (d, 1H, *J*=7.4 Hz), 7.37–7.24 (m, 4H), 7.20–7.13 (m, 3H), 7.10–7.00 (m, 2H), 6.03 (s, 1H), 4.76–4.71 (dd, 1H, *J*=11.0, 4.3 Hz), 3.43–3.50 (dd, 1H, *J*=11.0, 4.3 Hz), 3.35–3.21 (dd, 1H, *J*=15.0, 11.0 Hz), 2.32 (s, 3H); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.5, 154.3, 149.9, 149.5, 139.0, 137.6, 137.0, 135.7, 134.5, 132.6, 129.3, 129.2, 127.9, 126.7, 124.6, 124.3, 122.5, 119.8, 119.2, 112.2, 106.5, 58.3, 54.4, 22.5, 21.6; IR (cm^{-1}, neat): 3322, 2957, 2932, 2861, 1712, 1610, 1450; $[\alpha]_D^{20}$ −9.3 (*c* 0.23, CH_2Cl_2); LRMS (EI) *m/z*: 408 (M$^+$); HRMS: calcd for $C_{25}H_{20}N_4O_2$: *m/z* 408.1586; found: 408.1583.

3.1.19. *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 (6n). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.98 (s, 1H), 8.70 (d, 1H, *J*=1.6 Hz), 8.57–8.55 (dd, 1H, *J*=4.6, 1.2 Hz), 8.02 (d, 1H, *J*=2.2 Hz), 7.87 (d, 1H, *J*=8.6 Hz), 7.81–7.77 (dt, 2H, *J*=8.6, 2.2 Hz), 7.59 (d, 1H, *J*=7.6 Hz), 7.44–7.40 (dd, 1H, *J*=7.7, 4.7 Hz), 7.32 (d, 1H, *J*=7.8 Hz), 7.15–7.02 (m, 2H), 6.38 (s, 1H), 4.87–4.82 (dd, 1H, *J*=10.7, 5.6 Hz), 3.49–3.43 (dd, 1H, *J*=15.0, 5.5 Hz), 3.14–3.10 (dd, 1H, *J*=13.9, 12.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 172.1, 153.8, 150.2, 150.0, 137.6, 136.4, 136.2, 133.0, 132.2, 131.0, 130.5, 127.8, 127.4, 126.9, 126.8, 126.6, 124.8, 122.7, 119.8, 119.2, 112.2, 107.3, 54.2, 50.7, 23.0; IR (cm^{-1}, neat): 3342, 2922, 2852, 1720, 1602, 1484, 1429, 748; $[\alpha]_D^{20}$ −163.4 (*c* 0.39, CH_2Cl_2); LRMS (EI) *m/z*: 496 (M$^+$); HRMS: calcd for $C_{25}H_{16}ClF_3N_4O_2$: *m/z* 496.0914; found: 496.0913.

3.1.20. *trans*-2-(3-Fluoro-phenyl)-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6o). ^{1}H NMR (300 MHz, DMSO-d_6): δ 11.02 (s, 1H), 8.75 (s, 1H), 8.58 (d, 1H, *J*=4.3 Hz), 7.80 (d, 1H, *J*=7.9 Hz), 7.61 (d, 1H, *J*=7.6 Hz), 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, 1H, *J*=10.7, 5.5 Hz), 3.50–3.44 (dd, 1H, *J*=15.1, 5.5 Hz), 3.12–3.04 (dd, 1H, *J*=13.1, 11.3 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 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 (cm^{-1}, neat): 3352, 2935, 2853, 1715, 1610, 1412, 1257; $[\alpha]_D^{20}$ −36.0 (*c* 0.58, CH_2Cl_2); LRMS (EI) *m/z*: 412 (M$^+$); HRMS: calcd for $C_{24}H_{17}FN_4O_2$: *m/z* 412.1336; found: 412.1333.

3.1.21. *trans*-2-(3-Fluoro-phenyl)-10-pyridin-3-yl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6p). ^{1}H NMR (300 MHz, DMSO-d_6): δ 9.76 (s, 1H), 8.54 (d, 1H, *J*=1.4 Hz), 8.38–8.36 (dd, 1H, *J*=4.7, 1.4 Hz), 7.59 (d, 1H, *J*=8.1 Hz), 7.42–7.18 (m, 6H), 7.01–6.89 (m, 3H), 6.36 (s, 1H), 4.44–4.38 (dd, 1H, *J*=10.9, 5.4 Hz), 3.78 (s, 3H), 3.59–3.52 (dd, 1H, *J*=15.3, 5.5 Hz), 3.03–2.94 (ddd, 1H, *J*=13.9, 11.1, 1.2 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.6, 160.4, 154.3, 149.8, 149.6, 137.5, 136.5, 135.7, 132.6, 130.2, 129.4, 126.3, 124.5, 123.3, 120.4, 118.8, 118.6, 114.6, 112.2, 111.9, 108.3, 60.8, 55.8, 53.6, 50.4, 23.7, 21.4, 14.6; IR (cm^{-1}, neat): 3338, 2936, 2836, 1716, 1605, 1421; $[\alpha]_D^{20}$ −126.1 (*c* 0.37, CH_2Cl_2); LRMS (EI) *m/z*: 424 (M$^+$); HRMS calcd for $C_{25}H_{20}N_4O_3$: *m/z* 424.1535; found: 424.1532.

3.1.22. *trans*-10-Benzo[1,3]dioxol-4-yl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6q). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.43 (s, 1H), 7.57 (d, 1H, *J*=7.2 Hz), 7.31 (d, 1H, *J*=7.2 Hz), 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, 1H, *J*=10.9, 5.4 Hz), 3.57–3.42 (m, 3H), 2.89–2.80 (ddd, 1H, *J*=15.2, 11.0, 1.7 Hz), 1.67–1.57 (m, 2H), 1.40–1.30 (m, 2H), 0.92 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 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 (cm^{-1}, neat): 3327, 2958, 2932, 2872, 1703, 1622, 1449; $[\alpha]_D^{20}$ −36.3 (*c* 0.33, CH_2Cl_2); LRMS (EI) *m/z*: 417 (M$^+$); HRMS: calcd for $C_{24}H_{23}N_3O_4$: *m/z* 417.1689; found: 417.1695.

3.1.23. *cis*-10-Benzo[1,3]dioxol-4-yl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6q′). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.53 (s, 1H), 7.73 (s, 1H), 7.59–7.57 (dd, 1H, *J*=5.7, 2.4 Hz), 7.24–7.14 (m, 3H), 6.91–6.88 (dd, 1H, *J*=7.9, 1.6 Hz), 6.79 (d, 1H, *J*=7.9 Hz), 6.62 (d, 1H, *J*=1.6 Hz), 5.94–5.90 (dd, 1H, *J*=9.3, 1.3 Hz), 5.73 (s, 1H), 4.39–4.34 (dd, 1H, *J*=11.3, 4.5 Hz), 3.57–3.40 (m, 3H), 3.08–2.98 (ddd, 1H, *J*=15.0, 11.4, 1.9 Hz), 1.66–1.53 (m, 2H), 1.39–1.25 (m, 2H), 0.92 (t, 3H, *J*=7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 155.2, 148.6, 148.2, 137.1, 133.9, 132.9, 126.6, 123.2, 121.9, 120.5, 118.9, 111.6, 108.6, 107.9, 107.3, 101.7, 58.3, 56.9, 38.9, 30.5, 22.8, 20.4, 14.0; IR (cm^{-1}, neat): 3327, 2958, 2932, 2872, 1703, 1622, 1449; $[\alpha]_D^{20}$ −26.4 (*c* 0.36, CH_2Cl_2); LRMS (EI) *m/z*: 417 (M$^+$); HRMS: calcd for $C_{24}H_{23}N_3O_4$: *m/z* 417.1689; found: 417.1693.

3.1.24. *trans*-10-Benzo[1,3]dioxol-4-yl-2-*m*-tolyl-3a,4,9,10-tetrahydro-2,9,10a-triaza-cyclopenta[*b*]fluorene-1,3-dione (6r). ^{1}H NMR (300 MHz, $CDCl_3$): δ 8.05 (s, 1H), 7.60 (d, 1H, J=6.9 Hz), 7.38–7.19 (m, 7H), 6.98–6.77 (m, 3H), 6.32 (s, 1H), 5.94 (s, 2H), 4.49–4.43 (dd, 1H, J=10.9, 5.5 Hz), 3.62–3.55 (dd, 1H, J=15.3, 5.5 Hz), 3.08–2.99 (ddd, 1H, J=15.2, 11.0, 1.6 Hz), 2.39 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.0, 154.2, 148.7, 148.5, 139.5, 137.0, 133.1, 131.6, 130.7, 129.5, 129.3, 127.1, 126.5, 123.6, 123.3, 122.5, 120.6, 118.8, 111.6, 109.1, 109.0, 108.4, 101.8, 53.4, 52.3, 23.9, 21.7; IR (cm^{-1}, neat): 3344, 2919, 2852, 1716, 1600, 1492, 1420; $[\alpha]_D^{20}$ −78.4 (*c* 0.21, CH_2Cl_2); LRMS (EI) *m*/*z*: 451 (M^+); HRMS: calcd for $C_{27}H_{21}N_3O_4$: *m*/*z* 451.1532; found: 451.1535.

3.1.25. *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 (6s). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H), 7.62 (d, 1H, J=7.5 Hz), 7.52–7.47 (dd, 1H, J=8.2, 6.0 Hz), 7.42–7.35 (m, 3H), 7.19–7.08 (m, 3H), 6.92–6.81 (m, 3H), 6.33 (s, 1H), 5.99 (s, 2H), 4.75–4.69 (dd, 1H, J=10.8, 5.6 Hz), 3.54–3.47 (dd, 1H, J=15.1, 5.6 Hz), 3.11–3.02 (ddd, 1H, J=15.0, 10.9, 1.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.6, 164.2, 161.0, 153.5, 148.4, 148.1, 137.6, 134.5, 134.3, 131.5, 130.3, 126.7, 122.4, 119.7, 118.6, 114.5, 113.7, 111.7, 108.9, 108.4, 107.5, 101.7, 53.4, 52.3, 28.6, 23.3; IR (cm^{-1}, neat): 3344, 2919, 2852, 1716, 1600, 1492, 1420; $[\alpha]_D^{20}$ −64.8 (*c* 0.23, CH_2Cl_2); LRMS (EI) *m*/*z*: 455 (M^+); HRMS: calcd for $C_{26}H_{18}FN_3O_4$: *m*/*z* 455.1281; found: 455.1278.

3.1.26. *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 (6t). ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.0 (s, 1H), 7.62 (d, 1H, J=7.5 Hz), 7.52–7.47 (dd, 1H, J=8.2, 6.0 Hz), 7.42–7.35 (m, 3H), 7.19–7.08 (m, 3H), 6.92–6.81 (m, 3H), 6.33 (s, 1H), 5.99 (s, 2H), 4.75–4.69 (dd, 1H, J=10.8, 5.6 Hz), 3.54–3.47 (dd, 1H, J=15.1, 5.6 Hz), 3.11–3.02 (ddd, 1H, J=15.1, 10.8, 1.7 Hz); ^{13}C NMR (75 MHz, DMSO-d_6): δ 171.6, 164.2, 161.0, 153.5, 148.4, 148.1, 137.6, 134.5, 134.3, 131.5, 130.3, 126.7, 122.4, 119.7, 118.6, 114.5, 113.7, 111.7, 108.9, 108.4, 107.5, 101.7, 53.4, 52.3, 28.6, 23.3; IR (cm^{-1}, neat): 3345, 2924, 2850, 1721, 1605, 1486, 1429, 745; $[\alpha]_D^{20}$ −46.2 (*c* 0.38, CH_2Cl_2); LRMS (EI) *m*/*z*: 539 (M^+); HRMS: calcd for $C_{27}H_{17}ClN_3O_4F_3$: *m*/*z* 539.0860; found: 539.0861.

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Supplementary data

Representative ^{1}H NMR and ^{13}C NMR spectra of compounds **6a**–**6t** are enclosed herewith. 1D NOE experimental data of **6u** and **6u′** are also included. This information is available free of charge via the internet at <http://www.sciencedirect.com>. Supplementary data associated with this article can be found in the online version, at doi:10.1016/j.tet.2007.09.054.

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