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Synthesis of biologically active pyridoimidazole/imidazobenzothiazole annulated polyheterocycles using cyanuric chloride in water†

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An efficient and mild protocol for rapid access to N-fused polyheterocycles *via* Pictet–Spengler type 6-*endo* cyclization using cyanuric chloride in an aqueous reaction medium has been developed. The protocol was successfully applied to a wide range of compounds including aryl/heteroaryl aldehydes (**8a–o**), ketones (**10a–e**), an electron-rich metallocene aldehyde (**8e**) and indoline-2,3-diones (**12a–c**) using cyanuric chloride (15–20 mol%) with tetra-*n*-butylammonium bromide (TBAB) (2.0 eq.) as an additive at 80–90 °C to give a good to excellent yield (66–92%) of polyheterocycles. Some of the synthesized compounds were found to exhibit antiplasmodial activity against chloroquine-sensitive (CQ-S) 3D7 and chloroquine-resistant (CQ-R) K1 strains of *Plasmodium falciparum*.

Introduction

Research involving reactions in aqueous media, including syntheses of organic heterocycles in water, has been growing tremendously in the past few decades in order to satisfy environmental concerns.[1] Water as a universal solvent has great impact, as it is environmentally acceptable, non-flammable and economical. Organic reactions in water have become exciting and/or essential research endeavors. Indeed, industry prefers to use water as a solvent rather than conventional toxic organic solvents. Although most inorganic reactions can be carried out using water as a solvent, it is not the preferred solvent for organic reactions because of poor solubility of most organic compounds in water.[2] To overcome the solubility problem, micellar catalysis has been found to be very helpful to allow utilization of aqueous media for carrying out several organic transformations.[3]

As small organic scaffolds, polyheterocycles are invaluable structural motifs with many applications in the pharmaceutical[4] and material sciences.[5] The pyridoimidazole (PI) and imidazobenzothiazole (IBT) substructures are found in several drugs and biologically active molecules.[6,7] For example, the annulated dipyridoimidazoles (Glu-P1 and Glu-P2) (Fig. 1, panels I and II) exhibit anti-cancer activity,[8] pyridino[1,2-*a*]-imidazo[5,4-*b*]-indole (Fig. 1, panel III) is a well known antihypertensive agent,[9] and dihydropyrano imidazopyridine (Fig. 1, panel IV) is a potassium-competitive acid blocker used for treatment of gastroesophageal reflux disease.[10] Furthermore, the privileged benzothiazole motif has been recently functionalized by formation of rings (*i.e.*, annulations) with other pharmacophores to prepare pharmaceutically important scaffolds[11] such as the arylimidazo-benzothiazole derivative YM-201627 (Fig. 1, panel V) for the treatment of solid tumours.[12] Racemic spirotetrahydro β-carboline-based spiroazepineindole has also been recently shown to exhibit antiplasmodial activity (Fig. 1, panel VI).[13]

In the present work we report the use of privileged PI and IBT structures along with Pictet–Spengler-type cyclizations in

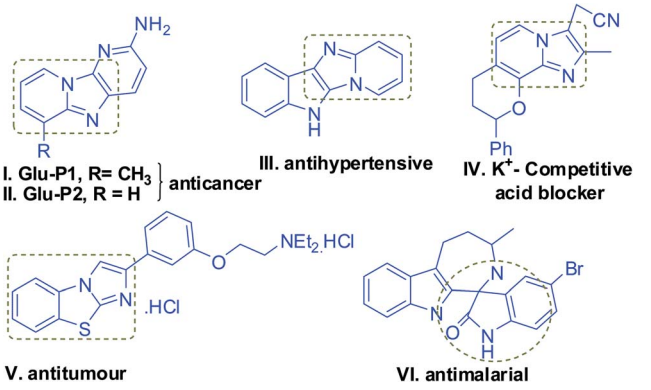

Fig. 1 Several biologically active fused polyheterocycles.

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aqueous medium to produce a moderate to good yield of biologically relevant polyheterocycles (Fig. 2). The Pictet–Spengler reaction is one of the most powerful strategies for constructing C–C bonds. Previously, the Pictet–Spengler reaction has been performed using strong Brønsted acids such as trifluoroacetic acid (TFA) and methanesulfonic acid, which tend to result in diminished yields, lead to long reaction times, create difficulties in work-up and/or require the use of conventional solvents.[14–16] We chose cyanuric chloride as in our previous work[17,18] and in research reported in the literature[19] it was found to be effective in several transformations. Although there are some reports of the Pictet–Spengler reaction using only water as the medium,[20] the use of the combination of water with cyanuric chloride for such transformations has not been reported in the literature. The reaction of cyanuric chloride with water produces HCl and cyanuric acid, which could be useful in carrying out the organic reactions under mild conditions while at the same time producing metal-free, non-volatile and essentially non-toxic side products that should encourage its application in medicinal chemistry.

Very recently, Sawant *et al.* developed a similar cyanuric chloride-promoted Pictet–Spengler cyclisation, but in dimethyl sulfoxide (DMSO) and with limited examples (Fig. 2).[21] In contrast, we present an extensive polyheterocyclic library with skeletal diversity using a relatively mild and "green" protocol by employing a range of oxo-substrates, such as aryl aldehydes, acetophenones and indoline-2,3-diones. Furthermore, for the first time we focus on using imidazo[1,2-*a*]benzothiazole as a substrate for such a transformation. It is worth mentioning that compounds bearing pyrido[1,2-*a*]imidazole annulations have been demonstrated to possess a variety of pharmacological properties.[9] Therefore, we speculated that this skeleton, upon fusion with aryl quinolone, may generate significant interest regarding its biological activity.[22]

Results and discussion

The modified Pictet–Spengler reaction is a two-step process, where an aryl amine and an oxo-substrate first react to give an imine as an intermediate followed by a 6-*endo* intramolecular cyclization to provide the cyclic product. In the present work the desired aryl amines **6** and **7** (see Scheme 1) were prepared in a mild two-step procedure from 2-amino azines **1** and **2**, respectively. Previously, however, synthon **6** was generally synthesized by bromination of 2-nitroacetophenone under harsh conditions.[16] Condensation with 1-(2,2-dibromovinyl)-2-nitrobenzene[23] (**3**) gives intermediates **4** and **5**,[24] which upon reduction with Fe powder/acetic acid provides the desired PI substrates **6** and **7** in good yields.

The Pictet–Spengler reaction between pyridoimidazole arylamine (**6**) and benzaldehyde (**8a**) was further explored to identify the optimal reaction conditions. Several Brønsted acids were evaluated as catalysts at various temperatures in organic and aqueous media (Table 1). Out of all Brønsted acids in different solvents (entries 1–5) screened, cyanuric chloride (20 mol%) in CH_3CN (entry 5) seemed promising, therefore, further refinement was limited to varying the solvents and temperature. Comparison of entries 5 and 7 suggests that increasing the polarity of an aprotic solvent may increase reaction yield, but upon replacing the aprotic solvent, DMSO, with the protic solvent, water, a slight drop in yield was observed (entry 8). Interestingly, further improvement of yield, ease of handling (without inert conditions) and reaction time was found upon using cyanuric chloride (15 mol%) as the reagent, water as the solvent, and a stoichiometric amount of TBAB as an additive (entry 9), which prompted us to further optimise the reaction conditions in aqueous media. Increasing the amount of cyanuric chloride to 20 mol% and of TBAB to 2 eq. was found to be beneficial in terms of reaction yield and time (entry 10). However, a further increase of TBAB to 3 eq. was not of significant benefit (entry 11). Replacing the TBAB with other additives

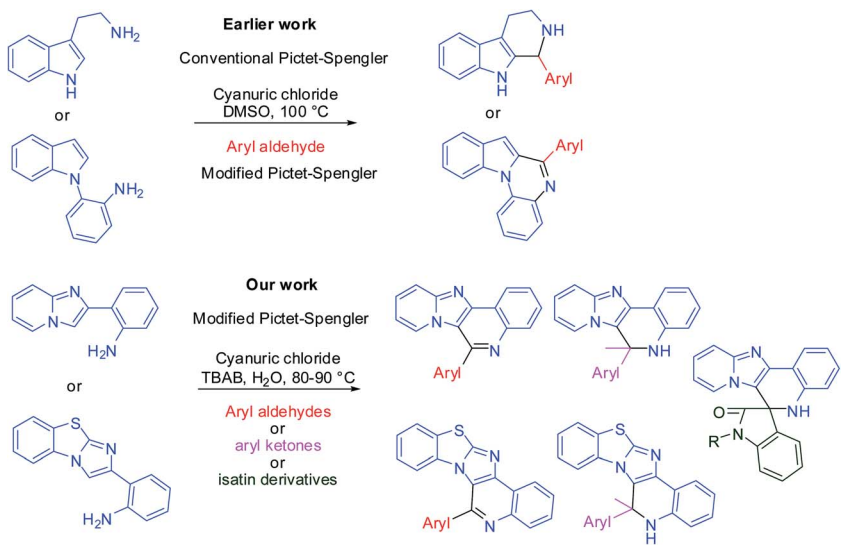
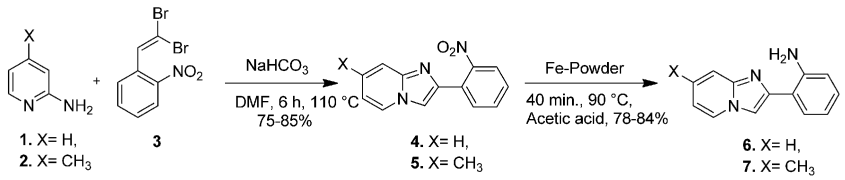


Fig. 2 Comparison of our Pictet–Spengler cyclisation strategy with previous work. TBAB = tetra-*n*-butylammonium bromide.



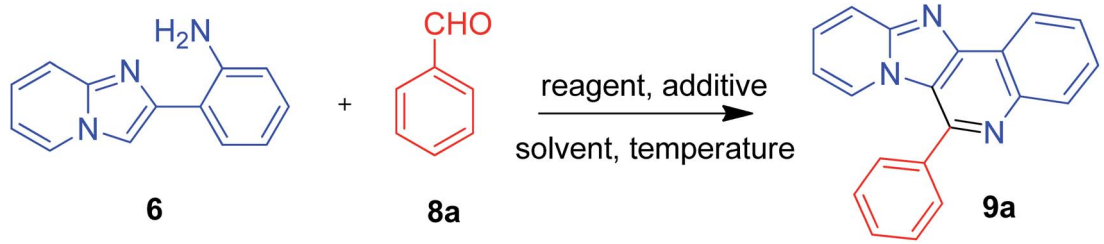
Scheme 1 Synthesis of proposed IP substrates for Pictet–Spengler type cyclization.

was found to decrease effectiveness (compare entries 10, 12 and 13). A slight increase in cyanuric chloride loading to 30 mol% was also not beneficial (entry 14). As predicted, the reaction did not work at all without cyanuric chloride (entry 15). Thus, a survey of different reaction conditions (compare entries 9, 10, 14) identified 20 mol% cyanuric chloride with 2.0 eq. TBAB to be the optimum conditions (entry 10). The use of *p*-toluenesulfonic acid (PTSA) in place of cyanuric chloride under otherwise optimized conditions provided the aromatic polycyclic product but the yield was poor (entry 16). To further validate our assumption that we had reached an optimized condition, we ran the same reaction with TBAB (2.0 eq.) in water but with cyanuric acid (20 mol%) in place of cyanuric chloride, which led to the polyheterocycles (**9a**) in a similar yield but with a prolonged reaction time (entry 17).

The optimized reaction condition (Table 1, entry 10) was applied to an array of aromatic/heteroaromatic (HetAr) aldehydes appended with various substituents (**8a–o**, Table 2). Neither steric nor electronic factors had a significant impact on the reaction time and/or yield (products **9a–s**). Furthermore, the organometallic and heteroaromatic aldehydes **8e** and **8n** also participated in a similar way, producing good yields of compounds **9e** and **9r**, respectively.

Interestingly, less reactive aromatic/HetAr ketone electrophiles also successfully participated in the Pictet–Spengler reaction (Table 3), with slightly improved reaction conditions [15 mol% cyanuric chloride with 2.0 eq. of TBAB at 80 °C in water (compare with Table 1, entry 10)] to produce the high yields (82–88%) of polyheterocycles **11a–f** shown in Table 3.

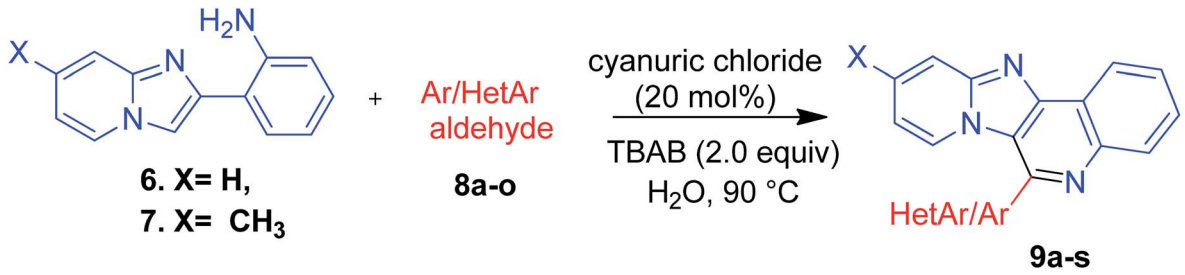
Table 1 Table for the optimisation of the reaction conditions for a Pictet–Spengler reaction[a]



Entry	Reagent (mol%)	Additive (eq.)	Solvent	Temp (°C)	Time (h)	Yield[b] (%)
1	TFA (500)	—	DCM	70	6	34
2	PTSA (20)	—	Toluene	120	5	46
3	CH_3COOH	—	Neat	90	5	54
4	CH_3SO_3H (100)	—	EtOH	90	5	45
5	Cyanuric chloride (20)	—	CH_3CN	85	3	56
6	Cyanuric chloride (20)	—	THF	75	3	52
7	Cyanuric chloride (20)	—	DMSO	90	2.0	68
8	Cyanuric chloride (15)	—	H_2O	90	3.0	62
9	Cyanuric chloride (15)	TBAB (1.0)	H_2O	90	2.0	73
10	Cyanuric chloride (20)	TBAB (2.0)	H_2O	90	1.5	82
11	Cyanuric chloride (20)	TBAB (3.0)	H_2O	90	1.5	83
12	Cyanuric chloride (20)	TMAI[c] (1.0)	H_2O	90	2.0	71
13	Cyanuric chloride (20)	Al_2O_3 (1.0)	H_2O	90	2.0	67
14	Cyanuric chloride (30)	TBAB (2.0)	H_2O	90	1.5	76
15	—[d]	TBAB (2.0)	H_2O	90	4	nr[e]
16	PTSA (20)	TBAB (2.0)	H_2O	90	3	46
17	Cyanuric acid (20)	TBAB (2.0)	H_2O	90	3.0	79

[a] Reaction conditions: substrate **6** (0.5 mmol), substrate **8a** (0.5 mmol), reagent (20 mol%), additive (2.0 eq.), solvent (0.64 M) at 90 °C for 1.5 h. [b] Isolated yield. [c] Tetramethylammonium iodide. [d] Reaction without cyanuric chloride. [e] No reaction. DCM: dichloromethane; THF: tetrahydrofuran.

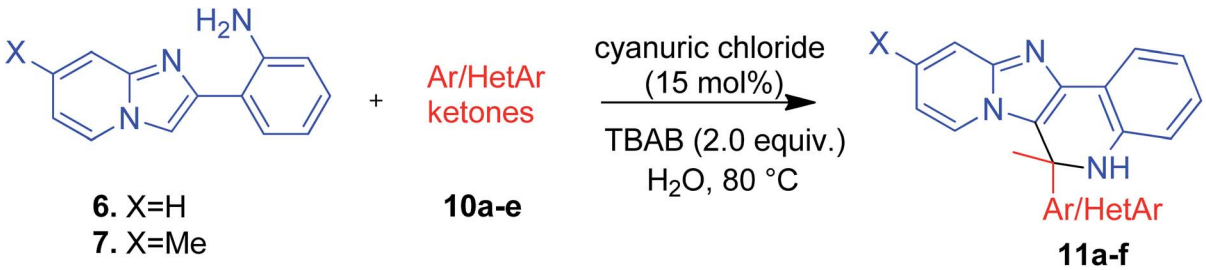
Table 2 Scope of the reaction with different aromatic and heteroaromatic aldehydes[a]



Entry	Ar/HetAr aldehyde	X	Yield[b] (%)
9a	Benzaldehyde (**8a**)	H	82
9b	4-Nitrobenzaldehyde (**8b**)	H	90
9c	4-Flourobenzaldehyde (**8c**)	H	82
9d	4-Methoxybenzaldehyde (**8d**)	H	77
9e	Ferrocene aldehyde (**8e**)	H	75
9f	Benzaldehyde (**8a**)	CH_3	82
9g	4-Nitrobenzaldehyde (**8b**)	CH_3	92
9h	2-Nitrobenzaldehyde (**8f**)	CH_3	77
9i	3-Nitrobenzaldehyde (**8g**)	CH_3	82
9j	4-Cyanobenzaldehyde (**8h**)	CH_3	86
9k	4-Isopropylbenzaldehyde (**8i**)	CH_3	83
9l	4-Bromobenzaldehyde (**8j**)	CH_3	86
9m	4-(*N*,*N*-Dimethylamino)benzaldehyde (**8k**)	CH_3	75
9n	4-Methoxybenzaldehyde (**8d**)	CH_3	78
9o	4-Hydroxybenzaldehyde (**8l**)	CH_3	72
9p	3,4,5-Trimethoxybenzaldehyde (**8m**)	CH_3	79
9q	4-Flourobenzaldehyde (**8c**)	CH_3	83
9r	Pyridine-4-aldehyde (**8n**)	CH_3	82
9s	1-Naphthaldehyde (**8o**)	CH_3	87

[a] Reaction conditions: **6** or **7** (0.5 mmol), Ar/HetAr aldehyde (**8a–o**) (0.5 mmol), cyanuric chloride (20 mol%), TBAB (2.0 eq.), H_2O (0.64 M) at 90 °C for 1.5 h. [b] Isolated yield.

Table 3 Reactions with different aromatic/HetAr ketones[a]



Entry	Ar/HetAr ketones	X	Yield[b] (%)
11a	Acetophenone (**10a**)	H	82
11b	1-(4-Nitrophenyl)ethanone (**10b**)	H	86
11c	1-(4-Methoxyphenyl)ethanone (**10c**)	H	82
11d	1-(4-Bromophenyl)ethanone (**10d**)	H	84
11e	Acetophenone (**10a**)	CH_3	88
11f	1-(Thiophen-2-yl)ethanone (**10e**)	H	83

[a] Reaction conditions: **6** or **7** (0.5 mmol), Ar/HetAr ketones (**10a–e**) (0.5 mmol), cyanuric chloride (15 mol%), TBAB (2.0 eq.), H_2O (0.64 M) at 80 °C for 1.5 h. [b] Isolated yield.

The spirooxindole core has great importance for medicinal chemistry and is found in several natural products such as spirotryprostatins A and B,[25a] horsfiline,[25b] rhynchophylline,[25c] and marcfortine A.[25d] Therefore, spirooxiindole-fused azapolycycles were prepared using our method, starting with indole-2,3-dione (**12a**) and its analogues (**12b,c**). Cyanuric chloride gave moderate to good yields (66–72%, Table 4) of the spirofused cyclic frameworks **13a–d**.

Preparation of tricyclic imidazobenzothiazoles **19** and **20** (Scheme 2), novel substrates for the Pictet–Spengler reaction, was analogous to the preparation of **6** and **7**, and carried out under the previously optimized reaction condition (Scheme 1). These substrates were successfully transformed into their respective polycyclic systems **21a–f** with good yields as shown in Table 5.

In addition, substrate **19** was condensed with different electron-deficient or electron-rich aromatic ketones and **10a–c** with cyanuric chloride to obtain their corresponding polyheterocycles **22a–c** (Table 6).

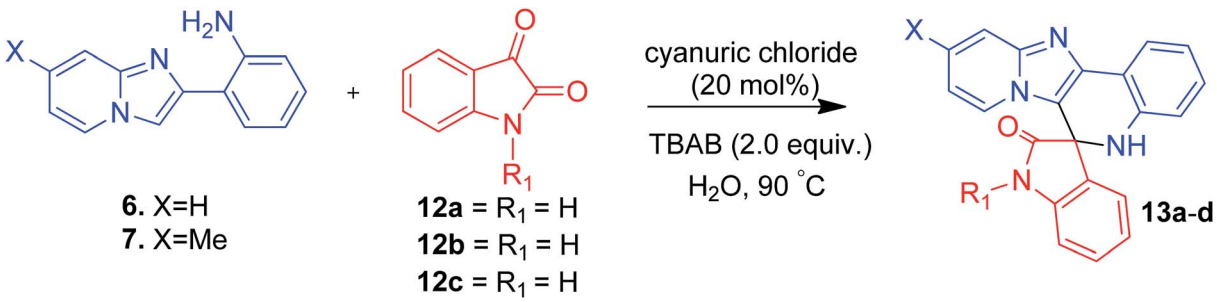
A plausible mechanism for the formation of the polyheterocycles is proposed in Fig. 3. The rate-determining step of the Pictet–Spengler reaction is the conversion of the imine intermediate to the cyclised product by a 6-*endo* intramolecular electrophilic reaction. From research in the literature, we envisage that cyanuric chloride under aqueous conditions releases hydrochloric acid and cyanuric acid.[18,26] The generated HCl as well as cyanuric acid (**23a**) (entry 17, Table 1) may activate the imine **23b**, converting it to the quaternized imine salt **23c** to facilitate 6-*endo* intramolecular cyclisation to provide **23d**. When this intermediate **23d** is an acetophenone (**11a**) or indole-2,3-dione (**13a**), its deprotonation would afford the polycylic product, but when the intermediate is an aromatic aldehyde, its deprotonation and aerial oxidation would lead to the aromatised polyheterocycle (**9a**).

Biological activity

Bioevaluation methods

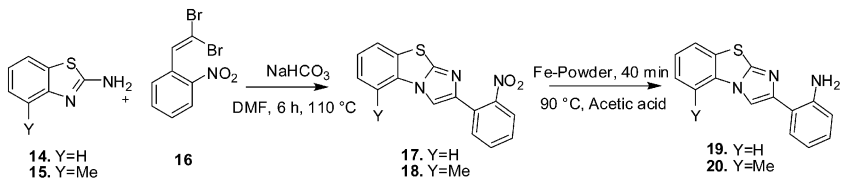
In vitro assay for evaluation of antimalarial activity. The compounds were evaluated for antimalarial activity against both chloroquininesensitive 3D7 (CQ-S) and chloroquinine-resistant K1 (CQ-R) strains of *Plasmodium falciparum* using malaria SYBR Green I nucleic acid staining dye-based fluorescence assay as described by Singh *et al.*[27] The stock solution (5 mg mL^{-1}) was prepared in DMSO and test dilutions were prepared in culture medium (RPMI-1640-FBS). Chloroquine was used as a reference drug. The compounds were tested in 96-well plates (in duplicate wells). A parasitized cell suspension (1.0%) containing 0.8% parasitemia was used. The plates were incubated at 37 °C in a CO_2 incubator in an atmosphere of 5% CO_2

Table 4 Synthesis of spiro-oxyindoles **13a–d** *via* the Pictet–Spengler reaction[a]



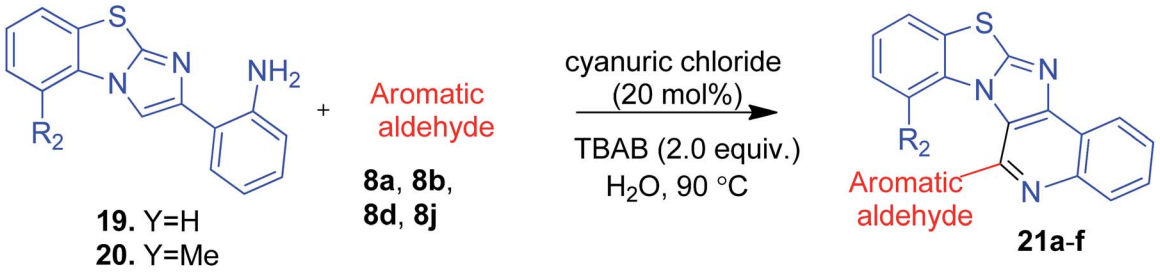
Entry	Indoline-2,3-dione and analogues	X	R_1	Yield[b] (%)
13a	Indoline-2,3-dione (**12a**)	H	H	66
13b	1-Ethylindoline-2,3-dione (**12b**)	H	Et	69
13c	1-Methylindoline-2,3-dione (**12c**)	CH_3	Me	72
13d	1-Ethylindoline-2,3-dione (**12b**)	CH_3	Et	68

[a] Reaction conditions: **6** or **7** (0.5 mmol), indole-2,3-dione and its analogues (**12a–c**) (0.5 mmol), cyanuric chloride (20 mol%), TBAB (2.0 eq.), H_2O (0.64 M) at 90 °C for 3.0 h. [b] Isolated yield.



Scheme 2 Synthesis of the proposed tricyclic substrate (**19**, **20**) for Pictet–Spengler cyclisation.

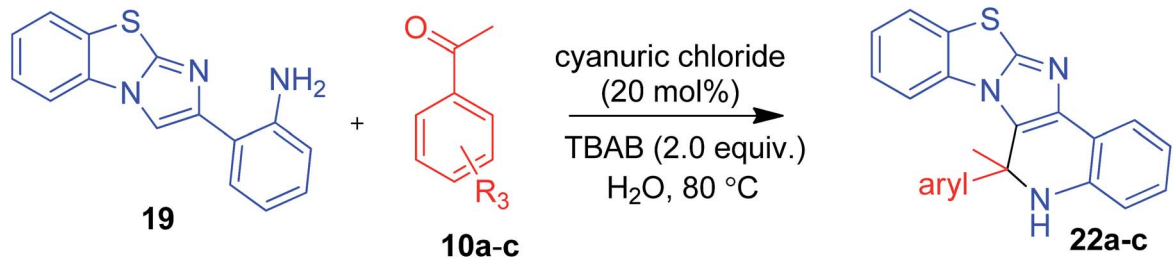
Table 5 Synthesis of IBT polyheterocycles (**21a–f**) *via* the Pictet–Spengler reaction[a]



Entry	Aryl aldehyde	Y	Yield[b] (%)
21a	Benzaldehyde (**8a**)	H	76
21b	4-Nitrobenzaldehyde (**8b**)	H	83
21c	4-Methoxybenzaldehyde (**8d**)	H	78
21d	4-Nitrobenzaldehyde (**8b**)	CH_3	78
21e	4-Methoxybenzaldehyde (**8d**)	CH_3	76
21f	4-Bromobenzaldehyde (**8j**)	CH_3	78

[a] Reaction conditions: **19** or **20** (0.5 mmol), aryl aldehyde (**8a-b** or **8d** or **8j**) (0.5 mmol), cyanuric chloride (20 mol%), TBAB (2.0 eq.), H_2O (0.64 M) at 90 °C for 2.0 h. [b] Isolated yield.

Table 6 Synthesis of IBT polyheterocycles (**22a–c**) using acetophenones[a]



Entry	Acetophenones	Yield[b] (%)
22a	Acetophenone (**10a**)	76
22b	1-(4-Nitrophenyl)ethanone (**10b**)	78
22c	1-(4-Methoxyphenyl)ethanone (**10c**)	74

[a] Reaction conditions: **19** (0.5 mmol), Ar ketone (**10a–c**) (0.5 mmol), cyanuric chloride (20 mol%), TBAB (2.0 eq.), H_2O (0.64 M) at 80 °C for 2.0 h. [b] Isolated yield.

and air mixture. After 72 h, 100 mL of lysis buffer containing 2× concentration of SYBR Green-I (Invitrogen) was added to each well and incubated for 1 h at 37 °C. Relative fluorescence units (RFU) of the wells were measured at 485 ± 20 nm excitation and 530 ± 20 nm emission using the fluorescence plate reader (FLUOstar, BMG LabTech). Data were transferred into a graphic programme (EXCEL) and the concentration values corresponding to 50% growth inhibition of the parasite (IC_{50}) were obtained by Logit regression analysis using a pre-programmed Excel spreadsheet.

In vitro assay for evaluation of cytotoxic activity. Cytotoxicity of the compounds was evaluated using a Vero cell line (C 1008; Monkey kidney fibroblast) following the method described by Sashidhara *et al.*[28] The cells were incubated with compound dilutions for 72 h and 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was used as the reagent for the detection of cytotoxicity. The 50% cytotoxic concentration (CC_{50}) was determined using non-linear regression analysis using a pre-programmed Excel spreadsheet. The Selectivity Index was calculated as SI equals CC_{50}/IC_{50}.

To assess their potential biological activities, subsets of the synthesized compounds were evaluated for their *in vitro* antimalarial activity against CQ-S 3D7 and CQ-R K1 strains of *P. falciparum* and their cytotoxicity toward the VERO cell line (Table 7). Compounds **9j**, **9l**, **9m**, **9p**, **11a**, **11b**, **11d**, **11f** and **13a**

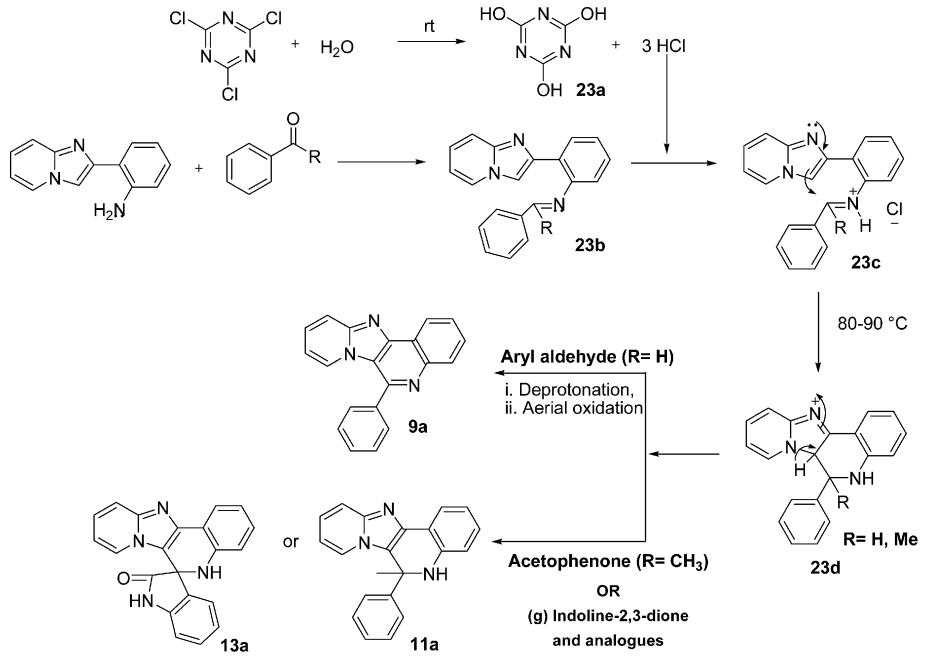


Fig. 3 Proposed mechanism for synthesis of different polyheterocycles.

Table 7 *In vitro* antimalarial activity of compounds against 3D7 and K1 strains of *P. falciparum* and their cytotoxicity against the VERO cell line

	IC_{50}[a] (μM)		
Comp. no.	CQ-S (3D7)	CQ-R (K1)	CC_{50}[b] (μM)
9a	3.40	ND[c]	34.54
9b	4.62	ND	66.63
9c	>5.0	ND	104.92
9d	1.24	ND	24.23
9e	2.05	ND	21.94
9f	3.04	ND	37.10
9j	2.83	0.53	43.36
9l	0.99	1.02	31.92
9m	0.75	0.56	25.57
9n	1.07	ND	33.98
9p	0.56	0.67	13.01
9q	1.71	ND	28.47
11a	0.20	0.50	50.17
11b	0.48	0.27	42.16
11d	0.22	0.50	32.28
11f	0.84	0.96	20.92
13a	1.04	1.87	73.02
13b	1.12	ND	80.76
CQ[d]	0.005	0.15	125

[a] IC_{50} (μM): concentration corresponding to 50% growth inhibition of the parasite. [b] CC_{50} (μM): concentration corresponding to 50% toxicity. [c] ND: not done. [d] Biological activity of the standard drug chloroquine.

exhibited low micromolar antiplasmodial activity against both strains, which were comparable to chloroquine for the CQ-resistant organism and were much less active than chloroquine for the CQ-sensitive parasite.

Conclusion

In summary, we have developed a mild protocol for the synthesis of annulated polyheterocycles through Pictet–Spengler type 6-*endo* cyclisation reactions under aqueous conditions. The process is applicable to a variety of aryl/HetAr/metallocene aldehydes, ketones, and indoline-2,3-diones. High yields, mild reaction conditions, operational simplicity and minimum environmental pollution are the key features of our methodology that make it useful for the construction of pharmaceutically important heterocycles, demonstrated by the observation of moderate anti-plasmodial activity *in vitro*.

Experimental section

General

Melting points are uncorrected and were determined in capillary tubes on a precision melting point apparatus containing silicon oil. Infrared (IR) spectra were recorded on an FTIR spectrophotometer Shimadzu 8201 PC and are reported in terms of frequency of absorption (cm^{-1}). ^{1}H-NMR and ^{13}C-NMR spectra were recorded either on a Bruker DPX-200, a Bruker Advance DRX-300 FT or a Bruker Advance DRX-400 FT spectrometer. Nuclear magnetic resonance (NMR) spectra were recorded on 300 MHz and 400 MHz spectrometers for ^{1}H-NMR and 50, 75, 100 MHz for ^{13}C-NMR in deuterated chloroform ($CDCl_3$) or deuterated dimethylsulfoxide (DMSO-d_6) with trimethylsilane (TMS) as the internal reference wherever mentioned. Chemical shifts (δ) are reported in parts per million (ppm) for ^{1}H-NMR and ^{13}C-NMR spectra. Coupling constants, J, are reported in hertz (Hz). Multiplicities are reported as follows: singlet (s), broad (br), doublet (d), triplet (t), quartet (q), and

multiplet (m). The high-resolution mass spectroscopy (HRMS) spectra were recorded as electrospray ionization (ESI)-HRMS on an Agilent 6520 Q-TOF, LC-MS/MS mass spectrometer. The progress of the reaction was routinely monitored by thin-layer chromatography (TLC) on pre-coated silica gel plates. Column chromatography was performed over silica gel. All the solvents and chemicals were used as procured from the suppliers.

1-(2,2-Dibromovinyl)-2-nitrobenzene (7). To a chilled solution of triphenylphosphine (3.934 g, 15.0 mol) in DCM (40 mL), carbon tetrabromide (CBr_4) (9.948 g, 30 mol) was added in fractions for 15 minutes. To this solution, 2-nitrobenzaldehyde (2.266 g, 15.0 mmol) in DCM (10 mL) was added dropwise (through a dropping funnel) for 15 minutes at 0 °C and the reaction was allowed to run for 4 h at ambient temperature. After completion (monitored by TLC), the reaction mixture was poured into hexane and the precipitated triphenylphosphine oxide was filtered using sintering. This filtrate was concentrated under reduced pressure followed by column chromatography using 60–120 mesh silica gel with $CHCl_3$ as eluent, to obtain the intermediate **7** as a yellow solid (3.90 g, yield 85%).[23]

General procedure 1

Synthesis of intermediates 4, 5, 17 and 18. To a stirred solution of different 2-amino pyridines (**1** or **2**) (10.0 mmol) or 2-amino benzothiazoles (**14** or **15**) (10.0 mmol) in dimethylformamide (DMF; 8 mL), $NaHCO_3$ (40.0 mmol) was added followed by addition of 1-(2,2-dibromovinyl)-2-nitrobenzene (**7**) (10.0 mmol), and the reaction was allowed to run for 6 h at 120 °C. After completion (monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (40 mL × 4), the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure followed by column chromatography using 60–120 mesh silica gel with 20% ethyl acetate–hexane as eluent to obtain the solid products (**4**, **5**, **17** and **18**) with yields of 75–85%.[24]

General procedure 2

Synthesis of intermediates 6, 7, 19 and 20. To a solution of intermediates **4** or **5** or **17** or **18** (10.0 mmol) in acetic acid (10 mL), Fe powder (50.0 mmol) was added. The reaction mixture was heated at 90 °C for 40 minutes. After completion of the reaction (indicated by a change in colour of the reaction mixture from brown to yellow and monitored by TLC), the reaction mixture was filtered through a celite pad followed by neutralisation with 10% sodium bicarbonate solution and extracted with ethyl acetate (40 mL × 3). The combined organic layer was dried over Na_2SO_4, concentrated under reduced pressure and the crude product was purified by column chromatography using 60–120 mesh silica gel with ethyl acetate–hexane (30%) as eluent to get the intermediates **6**, **7**, **19**, and **20** as brown solids (yield 78–84%).

2-(3-Methyl-imidazo[2,1-b]-benzothiazol-6-yl)-phenylamine (7). The title compound was obtained according to general procedure **2** as a brown solid. Yield: 2.17 g, 78%; mp: 140–143 °C; IR (KBr): ν 761, 1215, 1388, 1614, 3020, 3432 cm^{-1}, ^{1}H-NMR ($CDCl_3$, 300 MHz): 7.87 (s, 1H), 7.51–7.47 (m, 3H), 7.26 (s, 1H), 7.13 (t, $J = 7.2$ Hz, 1H), 6.77 (d, $J = 7.6$ Hz, 2H), 2.47 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 147.7, 146.5, 145.2, 135.0, 130.2, 130.1, 128.5, 127.6, 127.2, 124.4, 117.6, 116.9, 112.4, 107.3, 21.4 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{16}H_{14}N_3S$: 280.0908, actual: 280.0917.

General procedure 3

Synthesis of 6-phenyl-5,6*b*,11-triaza-benzo[*a*]fluorenes (9a–s). To a solution of Pictet–Spengler substrate (**6** or **7**) (0.96 mmol) in water (1.5 mL), each one of the desired aromatic aldehydes (**8a–o**) (1 eq.) was added followed by addition of tetra-*n*-butylammonium bromide (2.0 eq.). The reaction mixture was stirred for 15 minutes followed by addition of cyanuric chloride (0.19 mmol, 20 mol%) at 90 °C. The reaction was allowed to run for 1.5 h. After completion (monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the crude product was purified by column chromatography using 60–120 mesh silica gel with 3% MeOH–$CHCl_3$ as eluent to obtain good to excellent yields of the Pictet–Spengler products **9a–s**.

*6-Phenyl-5,6b,11-triaza-benzo[a]fluorene (**9a**).* The title compound was obtained according to general procedure **3** using substrate **6** as an off-white solid. Yield: 0.23 g, 82%; mp: 214–217 °C; IR (KBr): ν 1386, 1489, 3023 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.81 (d, $J = 7.9$ Hz, 1H), 8.32 (d, $J = 8.2$ Hz, 1H), 8.05 (d, $J = 6.9$ Hz, 1H), 7.95 (d, $J = 9.1$, 1H), 7.82 (t, $J = 7.1$, 1H), 7.73 (br, 3H), 7.66–7.61 (m, 3H), 7.54 (t, $J = 7.5$, 1H), 6.80 (t, $J = 6.8$, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 149.6, 148.2, 147.2, 145.0, 138.2, 129.9, 129.6, 129.5, 129.3, 128.9, 128.7, 127.1, 126.5, 122.6, 121.4, 120.3, 117.9, 112.0 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{20}H_{14}N_3$: 296.1183, actual: 296.1178.

*6-(4-Nitro-phenyl)-5,6b,11-triaza-benzo[a]fluorene (**9b**).* The title compound was obtained according to general procedure **6** as a pale-yellow solid. Yield: 0.29 g, 90%; mp: >250 °C; IR (KBr): ν 1384, 1600, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.83 (d, $J = 7.2$ Hz, 1H), 8.53 (d, $J = 8.4$ Hz, 2H), 8.30 (d, $J = 7.8$ Hz, 1H), 8.04–7.96 (m, 4H), 7.86–7.75 (m, 2H), 7.61 (t, $J = 7.8$, 1H), 6.89 (t, $J = 6.9$, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 149.9, 148.7, 147.8, 145.5, 145.0, 144.7, 139.4, 130.4, 130.3, 129.8, 129.4, 127.4, 126.8, 124.6, 122.9, 118.5, 112.7 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{20}H_{13}N_4O_2$: 341.1039, actual: 341.1032.

*6-(4-Flouro-phenyl)-5,6b,11-triaza-benzo[a]fluorene (**9c**).* The title compound was obtained according to general procedure **6** as a brown solid. Yield: 0.24 g, 82%; mp: 209–212 °C; IR (KBr): ν 1384, 1612, 3021 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.81 (d, $J = 8.1$ Hz, 1H), 8.30 (d, $J = 7.4$ Hz, 1H), 8.07 (d, $J = 5.7$, 1H), 7.96 (d, $J = 8.1$, 1H), 7.80–7.74 (m, 4H), 7.57 (t, $J = 7.5$, 1H), 7.37 (t, $J = 7.8$, 2H), 6.84 (t, $J = 5.1$, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 161.1, 149.7, 147.3, 147.0, 144.9, 134.4, 130.8, 130.7, 130.0, 129.5, 129.0, 126.9, 126.7, 122.6, 121.3, 118.0, 116.6, 116.2, 112.1 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{20}H_{13}FN_3$: 314.1094, actual: 314.1116.

*6-(4-Methoxy-phenyl)-5,6b,11-triaza-benzo[a]fluorene (**9d**).* The title compound was obtained according to general procedure **3** as an off-white solid. Yield: 0.24 g, 77%; mp: 224–227 °C; IR (KBr): ν 1384, 1610, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.82 (d, J = 7.5 Hz, 1H), 8.32 (d, J = 7.9 Hz, 1H), 8.20 (d, J = 6.7, 1H), 7.97 (d, J = 9.0, 1H),7.81–7.68 (m, 4H), 7.58 (t, J = 7.8, 1H), 7.19 (d, J = 8.0, 2H), 6.85 (t, J = 6.7, 1H), 3.97 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 160.8, 149.7, 148.2, 147.4, 145.2, 130.7, 130.2, 130.0, 129.6, 128.9, 127.3, 126.5, 122.7, 121.4, 120.6, 118.1, 114.8, 112.0 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{21}N_2O_4$: 365.1501, actual: 365.1501.

*6-(Ferrocenyl)-5,6b,11-triaza-benzo[a]fluorene (**9e**).* The title compound was obtained according to general procedure **3** as a black solid. Yield: 0.28 g, 75%; mp: 216–219 °C; IR (KBr): ν 1384, 1640, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.75 (d, J = 7.8 Hz, 1H), 8.50 (d, J = 6.6 Hz, 1H), 8.31 (d, J = 8.2 Hz, 1H), 7.88 (d, J = 8.9 Hz, 1H), 7.81 (t, J = 7.4 Hz, 1H), 7.71 (t, J = 7.4 Hz, 1H), 7.51 (t, J = 7.0 Hz, 1H), 6.81 (t, J = 6.6 Hz, 1H), 4.73 (s, 2H), 4.51 (s, 2H), 4.47 (s, 5H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 149.2, 146.3, 145.2, 139.2, 129.5, 129.4, 128.5, 127.8, 126.1, 122.5, 122.0, 121.3, 117.7, 111.3, 87.2, 70.6, 70.3, 68.7, ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{24}H_{18}FeN_3$: 404.0850, actual: 404.0844.

*6-(Phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9f**).* The title compound was obtained according to general procedure **3** as an orange solid. Yield: 0.24 g, 82%; mp: 217–220 °C; IR (KBr): ν 1384, 1485, 1652, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.78 (d, J = 6.4 Hz, 1H), 8.29 (d, J = 6.2 Hz, 1H), 7.90 (d, J = 5.7, 1H), 7.78–7.62 (m, 8H), 6.61 (d, J = 5.8, 1H), 2.47 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 150.3, 148.0, 147.7, 145.1, 141.7, 138.5, 129.6, 129.4, 128.9, 126.4, 126.3, 122.8, 121.6, 120.4, 116.3, 114.8, 21.8 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{16}N_3$: 310.1344, actual: 310.1339.

*6-(4-Nitro-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9g**).* The title compound was obtained according to general procedure **3** as a yellow solid. Yield: 0.31 g, 92%; mp: >250 °C; IR (KBr): ν 1384, 1653, 2924 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.79 (d, J = 7.8 Hz, 1H), 8.52 (d, J = 8.4 Hz, 2H), 8.27 (d, J = 8.2, 1H), 7.98 (d, J = 8.4, 2H), 7.88 (d, J = 7.0, 1H), 7.83 (t, J = 7.2, 1H), 7.76 (t, J = 7.5, 1H), 7.69 (s, 1H), 6.68 (d, J = 7.0, 1H), 2.50 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): compound is too insoluble to record a carbon NMR spectrum; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{15}N_4O_2$: 355.1195, actual: 355.1193.

*6-(2-Nitro-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9h**).* The title compound was obtained according to general procedure **3** as a yellow solid. Yield: 0.26 g, 77%; mp: >250 °C; IR (KBr): ν 1389, 1648, 3021 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 8.80 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 7.90 (t, J = 7.4 Hz, 1H), 7.83–7.66 (m, 5H), 7.53 (d, J = 7.0, 1H), 6.62 (d, J = 6.9, 1H), 2.48 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 150.4, 148.2, 147.1, 144.7, 144.2, 143.3, 134.7, 132.9, 131.8, 131.3, 129.5, 129.0, 127.4, 125.5, 125.3, 122.8, 121.6, 120.8, 116.2, 21.9 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{15}N_4O_2$: 355.1195, actual: 355.1236.

*6-(3-Nitro-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9i**).* The title compound was obtained according to general procedure **3** as a yellow solid. Yield: 0.28 g, 82%; mp: >250 °C; IR (KBr): ν 1389, 1648, 3021 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.80 (d, J = 7.8 Hz, 1H), 8.67 (s, 1H), 8.50 (d, J = 7.9 Hz, 1H), 8.28 (d, J = 8.1, 1H), 8.14 (d, J = 7.1, 1H), 7.90–7.72 (m, 5H), 6.69 (d, J = 7.0, 1H), 2.51 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 150.4, 148.7, 147.9, 145.0, 144.8, 142.4, 140.1, 135.1, 130.4, 129.5, 129.3, 127.1, 125.6, 124.5, 124.3, 122.9, 121.5, 119.9, 116.6, 115.5, 21.9 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{15}N_4O_2$: 355.1195, actual: 355.1237.

*6-(4-Cyano-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9j**).* The title compound was obtained according to general procedure **3** as a beige solid. Yield: 0.27 g, 86%; mp: >250 °C; IR (KBr): ν 1384, 1650, 2265, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.78 (d, J = 7.4 Hz, 1H), 8.26 (d, J = 7.8 Hz, 1H), 7.96–7.67 (m, 8H), 6.67 (d, J = 6.4, 1H), 2.49 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 150.5, 148.1, 145.5, 145.1, 143.0, 142.2, 133.1, 130.0, 129.7, 129.2, 127.1, 125.8, 122.8, 121.7, 120.0, 118.5, 116.7, 115.3, 113.6, 21.9 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{22}H_{15}N_4$: 335.1297, actual: 335.1294.

*6-(4-Isopropyl-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9k**).* The title compound was obtained according to general procedure **3** as a beige solid. Yield: 0.28 g, 83%; mp: 237–240 °C; IR (KBr): ν 1386, 1655, 3019 cm^{-1}, ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.75 (d, J = 7.2 Hz, 1H), 8.28 (d, J = 8.0 Hz, 1H), 8.00 (d, J = 6.9 Hz, 1H), 7.77–7.62 (m, 5H), 7.48 (d, J = 7.7, 2H), 6.60 (d, J = 6.60, 1H), 3.10–3.01 (m, 1H), 2.45 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 153.2, 150.6, 150.3, 148.2, 147.7, 145.3, 141.7, 136.0, 129.7, 128.9, 128.8, 127.4, 126.5, 126.4, 122.8, 121.6, 120.5, 116.3, 114.8, 31.8, 24.1, 21.9 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{24}H_{22}N_3$: 352.1814, actual: 352.1839.

*6-(4-Bromo-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9l**).* The title compound was obtained according to general procedure **3** as a white solid. Yield: 0.32 g, 86%; mp: 218–221 °C; IR (KBr): ν 1384, 1651, 3023 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.80 (d, J = 7.5 Hz, 1H), 8.30 (d, J = 7.6 Hz, 1H), 7.99 (d, J = 7.0 Hz, 1H), 7.82–7.63 (m, 7H), 6.70 (d, J = 7.2, 1H), 2.52 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 150.5, 150.1, 148.1, 147.6, 145.1, 141.5, 135.8, 129.5, 128.7, 127.3, 126.3, 126.2, 122.6, 121.4, 120.4, 116.1, 114.6, 21.7 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{15}BrN_3$: 388.0449, actual: 388.0468.

*6-(4-N,N-Dimethylamino-phenyl)-9-methyl-5,6b,11-triaza-benzo-[a]fluorene (**9m**).* The title compound was obtained according to general procedure **3** as a yellow solid. Yield: 0.25 g, 75%; mp: 235–238 °C; IR (KBr): ν 1384, 1610, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.77 (d, J = 7.6 Hz, 1H), 8.30–8.23 (m, 2H), 7.79–7.61 (m, 5H), 6.95 (d, J = 8.2 Hz, 2H), 6.66 (d, J = 6.3 Hz, 1H), 3.11 (s, 6H), 2.50 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 151.3, 150.1, 148.7, 147.6, 145.3, 141.4, 131.0, 129.9, 128.9, 128.6, 126.6, 125.9, 122.6, 121.3, 120.7, 116.1, 114.5, 112.5, 40.5, 21.8 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{23}H_{21}N_4$: 353.1766, actual: 353.1760.

*6-(4-Methoxy-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9n**).* The title compound was obtained according to general procedure 3 as a brown solid. Yield: 0.25 g, 78%; mp: >250 °C; IR (KBr): ν 1215, 1390, 1507, 1609, 3020 cm^{-1}; ^{1}H-NMR (CDCl3, 300 MHz): δ 8.64 (d, J = 7.5 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H),

7.75–7.64 (m, 4H), 7.46 (s, 1H), 7.12 (d, J = 8.5, 2H), 6.87 (d, J = 8.5, 1H), 6.06 (d, J = 8.5, 1H), 3.94 (s, 3H), 2.38 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 160.9, 157.6, 150.5, 146.5, 144.2, 134.9, 133.1, 131.2, 131.0, 129.2, 128.3, 127.1, 126.5, 124.2, 123.9, 122.1, 120.8, 116.2, 114.4, 55.7, 21.0 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{22}H_{18}N_3O$: 340.1540, actual: 340.1543.

*4-(9-Methyl-5,6b,11-triaza-benzo[a]fluoren-6-yl)-phenol (**9o**).* The title compound was obtained according to general procedure **3** as a white solid. Yield: 0.22 g, 72%; mp: >250 °C; IR (KBr): ν 1384, 1650, 3019, 3416 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 10.78 (s, 1H), 9.44 (d, J = 9.0 Hz, 1H), 8.94 (d, J = 6.0 Hz, 2H), 8.59–8.51 (m, 3H), 8.42 (d, J = 9.0, 2H), 7.85 (d, J = 6.0, 2H), 7.77 (d, J = 9.0, 1H), 3.31 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): compound is too insoluble to record a carbon NMR spectrum; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{16}N_3O$: 326.1293, actual: 326.1329.

*6-(3,4,5-Trimethoxy-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]-fluorene (**9p**).* The title compound was obtained according to general procedure **3** as a beige solid. Yield: 0.30 g, 79%; mp: 212–214 °C; IR (KBr): ν 1215, 1325, 1385, 1464, 1586, 1651, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.78 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 7.5 Hz, 1H), 7.99 (d, J = 6.8 Hz, 1H), 7.78–7.68 (m, 3H), 6.91 (s, 2H), 6.67 (d, J = 6.6, 1H), 3.96 (s, 3H), 3.90 (s, 6H), 2.50 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 154.2, 153.4, 150.3, 147.7, 145.0, 141.8, 139.1, 133.9, 129.6, 128.8, 126.5, 122.7, 121.6, 120.2, 116.3, 114.8, 105.8, 61.2, 56.5, 21.9 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{24}H_{22}N_3O_3$: 400.1661, actual: 400.1652.

*6-(4-Flouro-phenyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9q**).* The title compound was obtained according to general procedure **3** as a beige solid. Yield: 0.26 g, 83%; mp: 175–177 °C; IR (KBr) 1504, 1653, 3026 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.79 (d, J = 7.8 Hz, 1H), 8.30 (d, J = 8.0 Hz, 1H), 7.94 (d, J = 6.9 Hz, 1H), 7.83–7.71 (m, 5H), 7.38 (t, J = 8.4, 2H), 6.67 (d, J = 6.3, 1H), 2.51 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 150.3, 147.6, 146.8, 145.0, 142.0, 136.3, 134.5, 130.9, 130.8, 144.7, 141.9, 129.5, 128.9, 126.8, 125.7, 123.5, 122.6, 121.5, 119.6, 116.2, 115.0, 21.7 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{15}FN_3$: 328.1250, actual: 328.1244.

*6-(4-Pyridyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9r**).* The title compound was obtained according to general procedure **3** as a brown solid. Yield: 0.24 g, 82%; mp: 217–219 °C; IR (KBr): ν 1384, 1653, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.91 (d, J = 5.2 Hz, 2H), 8.74 (d, J = 7.8 Hz, 1H), 8.24 (d, J = 8.1 Hz, 1H), 7.89 (d, J = 7.0 Hz, 1H), 7.80–7.68 (m, 4H), 7.61 (s, 1H), 6.61 (d, J = 7.0, 1H), 2.45 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 150.7, 150.1, 147.7, 146.2, 144.8, 144.7, 141.9, 129.5, 128.9, 126.8, 125.7, 123.5, 122.6, 121.5, 119.6, 116.2, 115.0, 21.7 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{20}H_{15}N_4$: 311.1297, actual: 311.1266.

*6-(1-Naphthyl)-9-methyl-5,6b,11-triaza-benzo[a]fluorene (**9s**).* The title compound was obtained according to general procedure **3** as a beige solid. Yield: 0.30 g, 87%; mp: 239–241 °C; IR (KBr): ν 1387, 1504, 1653, 3026 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.85 (d, J = 7.0 Hz, 1H), 8.35 (d, J = 7.8 Hz, 1H), 8.12 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.84–7.69 (m, 4H), 7.64 (s, 1H), 7.55 (t, J = 7.1, 1H), 7.43 (d, J = 8.1, 1H), 7.34 (t, J = 7.2, 1H), 7.11 (d, J = 6.9, 1H), 6.37 (d, J = 6.6, 1H), 2.40 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 150.2, 146.6, 145.2, 141.7, 135.3, 133.7, 131.3, 129.8, 129.6, 128.8, 128.6, 127.3, 127.0, 126.6, 125.9, 124.8, 122.7, 121.7, 116.1, 114.8, 21.7 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{25}H_{18}N_3$: 360.1501, actual: 360.1492.

General procedure 4

Synthesis of 5,6-dihydro-5,6*b*,11-triaza-benzo[*a*]fluorene (11a–f). To a solution of Pictet–Spengler substrate (**6** or **7**) (0.96 mmol) in water (1.5 mL), each one of the desired acetophenones (**10a–e**) (1.0 eq.) was added followed by addition of TBAB (2.0 eq.). The reaction mixture was stirred for 15 minutes followed by addition of cyanuric chloride (0.14 mmol, 15 mol%) at 80 °C. The reaction was allowed to run for 1.5 h. After completion (monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using 60–120 mesh silica gel with 1% MeOH–$CHCl_3$ as eluent to obtain a good to excellent yield of the Pictet–Spengler products **11a–f**.

*6-Methyl-6-(phenyl)-5,6-dihydro-5,6b,11-triaza-benzo[a]fluorene (**11a**).* The title compound was obtained according to general procedure **4** as a gray solid. Yield: 0.24 g, 82%; mp: 245–247 °C; IR (KBr): ν 1384, 1620, 3019, 3412 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.96 (d, J = 7.1 Hz, 1H), 7.65–7.59 (m, 3H), 7.37 (br, 3H), 7.20 (d, J = 6.4, 1H), 7.08 (br, 2H), 6.82 (t, J = 7.1, 1H), 6.52 (d, J = 5.9, 2H), 4.25 (s, 1H), 2.04 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 145.8, 143.9, 141.7, 139.2, 137.4, 129.1, 128.9, 128.2, 126.9, 124.4, 123.3, 123.0, 120.3, 118.0, 116.9, 115.0, 114.1, 113.0, 112.4, 58.8, 25.7 ppm; HRMS (EI) calculated for $[M + H]^+$: $C_{21}H_{18}N_3$: 312.1501, actual: 312.1507.

*6-Methyl-6-(4-nitro-phenyl)-5,6-dihydro-5,6b,11-triaza-benzo[a]-fluorene (**11b**).* The title compound was obtained according to general procedure **4** as a gray solid. Yield: 0.29 g, 86%; mp: >250 °C; IR (KBr): ν 1384, 1622, 3019, 3409 cm^{-1}; ^{1}HNMR ($CDCl_3$, 300 MHz): δ 8.23 (d, J = 9.0 Hz, 2H), 7.97 (d, J = 7.2 Hz, 1H), 7.78 (d, J = 8.2, 2H), 7.68 (d, J = 9.2, 1H), 7.24 (d, J = 7.2, 1H), 7.16–7.09 (m, 2H), 6.89 (t, J = 7.2, 1H), 6.61 (t, J = 8.2, 2H), 4.27 (s, 1H), 2.16 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$ + deuterated methanol (CD_3OD), 50 MHz): δ 157.4, 151.7, 150.9, 147.6, 142.9, 133.9, 132.5, 129.4, 129.1, 128.9, 127.2, 124.2, 121.9, 121.7, 119.9, 117.9, 117.6, 63.3, 30.9 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{17}N_4O_2$: 357.1352, actual: 357.1360.

*6-Methyl-6-(4-methoxy-phenyl)-5,6-dihydro-5,6b,11-triaza-benzo-[a]fluorene (**11c**).* The title compound was obtained according to general procedure **4** as a gray solid. Yield: 0.26 g, 82%; mp: 248–251 °C; IR (KBr): ν 1217, 1384, 1622, 3019, 3409 cm^{-1}, ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.96 (d, J = 7.0 Hz, 1H), 7.68 (d, J = 8.1 Hz, 1H), 7.54 (d, J = 7.0, 2H), 7.21 (d, J = 6.4, 1H), 7.09 (d, J = 7.0, 2H), 6.90 (d, J = 7.0, 2H), 6.82 (t, J = 7.0, 1H), 6.54 (t, J = 6.5, 2H), 4.15 (s, 1H), 3.79 (s, 3H), 2.00 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$ + CD_3OD, 50 MHz): δ 163.6, 149.8, 147.7, 143.6, 141.6, 141.4, 136.1, 133.9, 132.7, 129.6, 128.7, 127.8, 127.0, 125.4, 121.2, 120.9, 119.1, 118.6, 117.8, 117.5, 62.6, 59.9, 27.2 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{22}H_{20}N_3O$: 342.1606, actual: 342.1617.

*6-Methyl-6-(4-bromo-phenyl)-5,6-dihydro-5,6b,11-triaza-benzo-[a]fluorene (**11d**).* The title compound was obtained according to

general procedure **4** as a brown solid. Yield: 0.31 g, 84%; mp: >250 °C; IR (KBr): ν 1384, 1650, 3019, 3412 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.03 (d, J = 6.7 Hz, 1H), 7.87 (d, J = 8.6 Hz, 1H), 7.50 (br, 3H), 7.28 (br, 3H), 7.13 (t, J = 6.7, 1H), 6.84 (t, J = 7.7, 1H), 6.75 (t, J = 6.7, 1H), 6.60 (d, J = 8.6, 1H), 4.50 (s, 1H), 2.07 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): compound is insoluble and a carbon NMR spectrum could not be recorded; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{17}BrN_3$: 390.0606, actual: 390.0608.

*6-Methyl-6-(phenyl)-5,6-dihydro-9-methyl-5,6b,11-triaza-benzo-[a]fluorene (**11e**).* The title compound was obtained according to general procedure **4** as a brown solid. Yield: 0.27 g, 88%; mp: 210–213 °C; IR (KBr): ν 1384, 1651, 3019, 3411 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.93 (d, J = 7.7 Hz, 1H), 7.60 (d, J = 7.7 Hz, 2H), 7.37–7.28 (m, 4H), 7.07 (d, J = 7.1, 2H), 6.81 (t, J = 7.1, 1H), 6.51 (d, J = 8.2, 1H), 6.34 (d, J = 6.6, 1H), 4.24 (s, 1H), 2.29 (s, 3H), 2.03 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 146.4, 144.2, 141.6, 137.3, 135.3, 128.8, 128.1, 126.9, 122.8, 122.5, 119.8, 117.9, 115.5, 114.8, 112.9, 58.8, 25.8, 21.2 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{22}H_{20}N_3$: 326.1657, actual: 326.1672.

*6-Methyl-6-(2-thiophenyl)-5,6-dihydro-5,6b,11-triaza-benzo[a]-fluorene (**11f**).* The title compound was obtained according to general procedure **4** as a yellow solid. Yield: 0.25 g, 83%; mp: 187–189 °C; IR (KBr): ν 1384, 1653, 3019, 3408 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.98 (d, J = 7.2 Hz, 1H), 7.68 (d, J = 8.8 Hz, 1H), 7.44 (d, J = 6.4 Hz, 1H), 7.35 (d, J = 4.6 Hz, 1H), 7.17–7.08 (m, 3H), 7.02 (br, 1H), 6.88 (t, J = 7.2, 1H), 6.60 (d, J = 7.5, 2H), 4.43 (s, 1H), 2.09 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 150.1, 146.2, 141.2, 137.4, 129.0, 127.3, 126.5, 124.8, 124.4, 123.3, 122.9, 119.8, 118.5, 117.1, 115.6, 113.3, 112.4, 59.9, 27.4 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{19}H_{16}N_3S$: 318.1065, actual: 318.1080.

General procedure 5

Synthesis of spirooxyindoles (13a–d). To a solution of Pictet–Spengler substrate (**6** or **7**) (0.96 mmol) in water (1.5 mL), indoline-2,3-dione or N-substituted indoline-2,3-dione (1.0 eq.) was added followed by addition of TBAB (2.0 eq.). The reaction mixture was stirred for 15 minutes followed by addition of cyanuric chloride (0.19 mmol, 20 mol%) at 90 °C. The reaction was allowed to run for 3.0 h. The progress of the reaction was monitored by TLC. After completion, the reaction mixture was poured into water and was extracted with ethyl acetate (20 mL × 5). The combined organic layers were washed with saturated brine solution and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using 60–120 mesh silica gel with 3% MeOH–$CHCl_3$ as eluent to obtain a good yield of the Pictet–Spengler product **(13a–d)**.

*6-Spiro-indol-2(1H)-one-5,6-dihydro-5,6b,11-triaza-benzo[a]-fluorine (**13a**).* The title compound was obtained according to general procedure **5** as a yellow solid. Yield: 0.21 g, 66%; mp: 244–246 °C; IR (KBr): ν 1384, 1639, 1724, 3019, 3417 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 10.50 (s, 1H), 7.83 (s, 1H), 7.71 (d, J = 7.4 Hz, 1H), 7.50 (d, J = 9.0 Hz, 1H), 7.29–7.21 (m, 2H), 7.10 (t, J = 7.5, 1H), 6.98 (br, 4H), 6.65 (t, J = 7.5, 1H), 6.58 (t, J = 6.8, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 180.4, 151.2, 147.9, 146.3, 144.8, 143.8, 135.3, 134.8, 133.7, 130.7, 129.4, 127.9, 127.7, 127.1, 121.9, 119.5, 119.3, 118.5, 118.0, 117.7, 115.6, 68.2 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{21}H_{15}N_4O$: 339.1246, actual: 339.1247.

*6-Spiro-indol-2(N-ethyl)-one-5,6-dihydro-5,6b,11-triaza-benzo-[a]fluorine (**13b**).* The title compound was obtained according to general procedure **5** as a yellow solid. Yield: 0.24 g, 69%; mp: 228–230 °C; IR (KBr): ν 1384, 1611, 1721, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.95 (d, J = 7.3 Hz, 1H), 7.62 (d, J = 9.0 Hz, 1H), 7.43–7.38 (m, 2H), 7.12–7.00 (m, 4H), 6.88 (m, 2H), 6.61 (d, J = 7.8 Hz, 1H), 6.52 (t, J = 6.7 Hz, 1H), 4.55 (s, 1H), 3.94–3.73 (m, 2H), 1.37 (t, J = 7.1, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 50 MHz): δ 173.5, 146.8, 141.5, 141.4, 140.4, 130.8, 129.0, 126.2, 124.3, 123.9, 123.0, 122.5, 118.8, 117.5, 115.5, 113.2, 113.0, 112.6, 109.0, 63.3, 35.1, 12.7 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{23}H_{19}N_4O$: 367.1559, actual: 367.1552.

*6-Spiro-indol-2(N-methyl)-one-5,6-dihydro-9-methyl-5,6b,11-tri-aza-benzo[a]fluorine (**13c**).* The title compound was obtained according to general procedure **5** as a yellow solid. Yield: 0.25 g, 72%; mp: >250 °C; IR (KBr): ν 1385, 1617, 1719, 3020 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.92 (d, J = 7.3 Hz, 1H), 7.42–7.35 (m, 3H), 7.07 (br, 2H), 6.99 (d, J = 7.7 Hz, 1H), 6.87 (t, J = 7.3, 1H), 6.69 (d, J = 6.8 Hz, 1H), 6.60 (d, J = 6.9 Hz, 1H), 6.35 (d, J = 6.9 Hz, 1H), 4.68 (s, 1H), 3.26 (s, 3H), 2.29 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 174.2, 147.1, 142.6, 141.3, 139.9, 136.0, 131.0, 129.1, 129.0, 126.0, 124.2, 123.2, 121.9, 119.1, 115.9, 115.6, 113.3, 112.4, 109.0, 63.4, 26.6, 21.3 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{23}H_{19}N_4O$: 367.1559, actual: 367.1550.

*6-Spiro-indol-2(N-ethyl)-one-5,6-dihydro-9-methyl-5,6b,11-tri-aza-benzo[a]fluorine (**13d**).* The title compound was obtained according to general procedure **5** as a yellow solid. Yield: 0.24 g, 68%; mp: 232–234 °C; IR (KBr): ν 1386, 1622, 1718, 3020 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.91 (d, J = 7.3 Hz, 1H), 7.41–7.35 (m, 3H), 7.07–6.98 (m, 3H), 6.86 (t, J = 7.3 Hz, 1H), 6.74 (d, J = 6.7 Hz, 1H), 6.60 (d, J = 7.8 Hz, 1H), 6.34 (d, J = 6.4 Hz, 1H), 4.65 (s, 1H), 3.90–3.72 (m, 2H), 2.28 (s, 3H), 1.35 (t, J = 6.9 Hz, 1H), ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 173.6, 147.3, 141.4, 140.1, 135.4, 130.7, 129.4, 128.8, 126.1, 123.8, 123.0, 121.7, 118.7, 116.0, 115.7, 115.2, 113.2, 112.5, 109.0, 63.4, 35.0, 21.2, 12.7 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{24}H_{21}N_4O$: 381.1715, actual: 381.1719.

General procedure 6

Synthesis of 6-(phenyl)-(11-*S*)-5,6*b*,12-triaza-benzo[*a*]fluorenes (21a–f). To a solution of Pictet–Spengler substrate (**19** or **20**) (0.96 mmol) in water (1.5 mL), each one of the desired aromatic aldehydes (1.0 eq.) was added followed by addition of TBAB (2.0 eq.). The reaction mixture was stirred for 15 minutes followed by addition of cyanuric chloride (0.15 mmol, 20 mol%) at 90 °C. The reaction was allowed to run for 2.0 h. After completion (monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine solution, dried over anhydrous Na_2SO_4, concentrated under reduced pressure and the crude product was purified by column

chromatography using 60–120 mesh silica gel using 30% ethyl acetate–hexane as eluent to obtain a good yield of the Pictet–Spengler products (**21a–f**).

*6-(Phenyl)-(11-S)-5,6b,12-triaza-benzo[a]fluorine (**21a**).* The title compound was obtained according to general procedure **6** as an orange solid. Yield: 0.19 g, 76%; mp: 175–177 °C; IR (KBr): ν 1384, 1653, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.67 (d, J = 7.8 Hz, 1H), 8.29 (d, J = 8.1 Hz, 1H), 7.78–7.59 (m, 8H), 7.25 (s, 1H), 7.01 (t, J = 7.9, 1H), 5.96 (d, J = 8.4, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.0, 150.8, 146.9, 144.4, 140.8, 133.4, 129.8, 129.7, 129.5, 129.3, 129.2, 128.6, 126.9, 126.3, 124.9, 124.0, 122.2, 121.0, 116.5 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{22}H_{14}N_3S$: 352.0908, actual: 352.0926.

*6-(4-Nitro-phenyl)-(11-S)-5,6b,12-triaza-benzo[a]fluorene (**21b**).* The title compound was obtained according to general procedure **6** as a brown solid. Yield: 0.24 g, 83%; mp: 175–177 °C; IR (KBr): ν 1348, 1521, 1654, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.68 (d, J = 7.6 Hz, 1H), 8.48 (d, J = 8.1 Hz, 2H), 8.26 (d, J = 7.8 Hz, 1H), 7.98 (d, J = 8.1 Hz, 2H), 7.81–7.71 (m, 3H), 7.33 (t, J = 7.4, 1H), 7.09 (t, J = 8.5, 1H), 6.15 (d, J = 8.6 Hz, 1H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.5, 151.4, 148.6, 146.8, 144.5, 139.1, 133.0, 131.1, 129.6, 129.0, 127.6, 129.3, 125.3, 124.5, 124.2, 123.4, 122.3, 121.1, 119.8, 115.8 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{22}H_{13}N_4O_2S$: 397.0759, actual: 397.0805.

*6-(4-Methoxy-phenyl)-(11-S)-5,6b,12-triaza-benzo[a]fluorene (**21c**).* The title compound was obtained according to general procedure **6** as a brown solid. Yield: 0.22 g, 78%; mp: 173–175 °C; IR (KBr): ν 1348, 1521, 1654, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.63 (d, J = 7.2 Hz, 1H), 8.26 (d, J = 7.6 Hz, 1H), 7.73–7.66 (br, 5H), 7.25 (s, 1H), 7.11–6.85 (m, 3H), 6.20 (d, J = 8.2, 1H), 3.93 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 161.0, 148.9, 148.3, 146.7, 141.7, 132.0, 131.9, 131.1, 130.8, 130.5, 128.2, 127.5, 126.4, 125.5, 124.5, 123.7, 114.5, 113.1, 110.1, 55.8 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{23}H_{16}N_3OS$: 382.1014, actual: 382.1063.

*6-(4-Nitro-phenyl)-7-methyl-(11-S)-5,6b,12-triaza-benzo[a]fluorene (**21d**).* The title compound was obtained according to general procedure **6** as an orange solid. Yield: 0.24 g, 79%; mp: >250 °C; IR (KBr): ν 1384, 1653, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.66 (d, J = 7.7 Hz, 1H), 8.47 (d, J = 8.4 Hz, 2H), 8.25 (d, J = 7.9 Hz, 1H), 7.97 (d, J = 8.4 Hz, 2H), 7.79–7.69 (m, 2H), 7.51 (s, 1H), 6.87 (d, J = 8.3, 1H), 5.98 (d, J = 8.5, 1H), 2.40 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 158.3, 151.0, 148.6, 146.7, 144.3, 143.8, 135.6, 131.0, 130.8, 129.4, 128.8, 127.4, 127.2, 124.5, 124.1, 123.3, 122.2, 121.0, 115.3, 21.1 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{23}H_{15}N_4O_2S$: 411.0916, actual: 411.0919.

*6-(4-Methoxy-phenyl)-7-methyl-(11-S)-5,6b,12-triaza-benzo[a]fluorene (**21e**).* The title compound was obtained according to general procedure **6** as a brown solid. Yield: 0.23 g, 79%; mp: >250 °C; IR (KBr): ν 1387, 1647, 3022 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.64 (d, J = 7.5 Hz, 1H), 8.26 (d, J = 8.1 Hz, 1H), 7.75–7.60 (m, 4H), 7.46 (s, 1H), 7.11 (d, J = 8.5, 2H), 6.87 (d, J = 8.5, 1H), 6.05 (d, J = 8.5, 1H), 3.94 (s, 3H), 2.37 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 160.9, 157.7, 150.5, 146.5, 144.2, 134.9, 133.1, 131.2, 131.1, 129.2, 128.3, 127.1, 126.5, 124.2, 123.9, 122.1, 120.8, 116.2, 114.4, 55.7, 21.0 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{24}H_{18}N_3OS$: 396.1171, actual: 396.1171.

*6-(4-Bromo-phenyl)-7-methyl-(11-S)-5,6b,12-triaza-benzo[a]fluorene (**21f**).* The title compound was obtained according to general procedure **6** as a beige solid. Yield: 0.25 g, 78%; mp: >250 °C; IR (KBr): ν 1384, 1645, 3019 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 8.65 (d, J = 7.8 Hz, 1H), 8.25 (d, J = 8.0 Hz, 1H), 7.75–7.66 (m, 4H), 7.63 (d, J = 7.7, 2H), 7.49 (s, 1H), 6.92 (d, J = 8.4, 1H), 6.01 (d, J = 8.4, 1H), 2.40 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 100 MHz): δ 158.1, 150.9, 148.0, 145.4, 144.4, 139.6, 135.4, 132.3, 131.6, 131.2, 129.5, 128.7, 127.3, 127.0, 124.3, 124.1, 124.0, 122.2, 121.0, 115.9, 21.3 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{23}H_{15}BrN_3S$: 444.0170, actual: 444.0236.

General procedure 7

Synthesis of 6-(phenyl)-5,6-dihydro-(11-*S*)-5,6*b*,12-triaza-benzo[*a*]fluorines (22a–c). To a solution of Pictet–Spengler substrate (**19** or **20**) (0.96 mmol) in water (1.5 mL), each one of the acetophenones (**10a–c**) (1.0 eq.) was added followed by addition of TBAB (2.0 eq.). The reaction mixture was stirred for 15 minutes followed by addition of cyanuric chloride (0.15 mmol, 20 mol%) at 80 °C. The reaction was allowed to run for 2.0 h. After completion of the reaction (monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (20 mL × 3). The combined organic layers were washed with brine solution and dried over anhydrous Na_2SO_4. The crude product was purified by column chromatography using 60–120 mesh silica gel with 30% ethyl acetate–hexane as eluent to get a good yield of the Pictet–Spengler product **22a–c**.

*6-Methyl-6-(phenyl)-5,6-dihydro-(11-S)-5,6b,12-triaza-benzo[a]-fluorine (**22a**).* The title compound was obtained according to general procedure **7** as a brown solid. Yield: 0.20 g, 76%; mp: 236–238 °C; IR (KBr): ν 1384, 1653, 3021, 3407 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.80 (d, J = 7.4 Hz, 1H), 7.63 (t, J = 7.8 Hz, 3H), 7.41–7.31 (m, 3H), 7.16 (t, J = 7.1, 1H), 7.04–6.94 (m, 2H), 6.80 (d, J = 7.3, 1H), 6.47 (d, J = 8.0, 2H), 4.08 (s, 1H), 2.10 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 149.7, 145.9, 140.2, 140.0, 132.3, 130.3, 130.1, 130.0, 129.3, 128.4, 128.2, 128.0, 126.9, 125.8, 124.1, 122.0, 118.0, 114.3, 112.5, 59.9, 32.1 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{23}H_{18}N_3S$: 368.1221, actual: 368.1269.

*6-Methyl-6-(4-nitro-phenyl)-5,6-dihydro-(11-S)-5,6b,12-triaza-benzo[a]fluorine (**22b**).* The title compound was obtained according to general procedure **7** as a brown solid. Yield: 0.24 g, 78%; mp: >250 °C; IR (KBr): ν 1384, 1653, 3019, 3409 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 300 MHz): 8.26 (d, J = 7.9 Hz, 2H), 7.81–7.76 (m, 3H), 7.65 (d, J = 8.1 Hz, 1H), 7.20 (d, J = 7.5, 1H), 7.07 (t, J = 6.3, 2H), 6.84 (t, J = 7.3, 1H), 6.50 (t, J = 6.7, 2H), 4.04 (s, 1H), 2.22 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 152.2, 151.7, 147.3, 140.4, 139.6, 131.9, 130.1, 128.5, 127.7, 126.1, 125.9, 124.5, 122.3, 122.1, 121.0, 118.9, 118.4, 113.6, 112.5, 59.6, 32.0 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{23}H_{17}N_4O_2S$: 413.1072, actual: 413.1128.

*6-Methyl-6-(4-methoxy-phenyl)-5,6-dihydro-(11-S)-5,6b,12-triaza-benzo[a]fluorine (**22c**).* The title compound was obtained according to general procedure **7** as a brown solid. Yield: 0.22 g, 74%; mp: 246–247 °C; IR (KBr): ν 1384, 1653, 3019, 3407 cm^{-1}; ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, J =

8.3 Hz, 1H), 7.52 (d, $J = 8.9$ Hz, 1H), 7.15 (t, $J = 7.2$, 1H), 7.02 (t, $J = 7.7$, 2H), 6.89 (d, $J = 8.3$, 1H), 6.77 (t, $J = 7.8$, 1H), 6.54 (d, $J = 8.3$, 1H), 6.44 (d, $J = 8.4$, 1H), 3.77 (s, 3H), 2.06 (s, 3H) ppm; ^{13}C-NMR ($CDCl_3$, 75 MHz): δ 159.4, 149.6, 140.1, 138.3, 132.3, 130.3, 130.1, 130.0, 129.8, 128.1, 128.0, 125.9, 124.1, 121.9, 117.8, 115.8, 114.5, 112.4, 59.4, 55.4, 32.0 ppm; HRMS (ESI) calculated for $[M + H]^+$: $C_{24}H_{20}N_3OS$: 398.1327, actual: 398.1380.

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