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Synthesis of Biologically Active Pyridoimidazole/Imidazobenzothiazole Annulated Polyheterocycles using Cyanuric Chloride in water

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Abstract: An efficient and mild protocol for rapid access to *N*-fused polyheterocycles *via* Pictet-Spengler type 6-*endo* cyclization using cyanuric chloride in aqueous reaction medium has been developed. The protocol is successfully applied to a wide range of aryl/heteroaryl aldehydes (**8a-o**), ketones (**10a-e**), 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 equiv.) as an additive at 80-90 ˚C to give polyheterocycles in good to excellent yield (66-92%). Moreover 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*.

Keywords: cyanuric chloride, heterocycles, imidazobenzothiazole, Pictet-Spengler reaction, pyridoimidazole, tetra-*n*-butylammonium bromide (TBAB)

Introduction

Reactions in aqueous media are gaining tremendous growth in last decades in the application of organic heterocycle synthesis to meet environmental considerations.[1] Water as universal solvent has great impact as it is environmentally acceptable, non-flammable and economic. Organic reactions in water have become exciting and/or essential research endeavors now. Indeed, industry prefers to use water as a solvent rather than conventional toxic organic solvents. However most of the inorganic reactions can be carried out using water as a solvent but when it comes to organic reactions, it is not preferred because of poor solubility of most organic compounds in water.[2] To overcome the solubility problem, micellar catalysis has found very helpful to utilise aqueous media for carrying out several organic transformations.[3]

In the community of small organic scaffolds, polyheterocycles are invaluable structural motifs with wide application in 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) **I** and **II** exhibit anticancer activity,[8] pyridino[1,2-*a*]imidazo[5,4-*b*]-indole **III** is a well known antihypertensive agent,[9] and dihydropyrano imidazopyridine **IV** is a potassium competitive acid blocker used for treatment of gastroesophageal reflux disease[10] (Figure 1). Moreover, the privileged benzothiazole motif has been recently functionalized by ring annulations with other pharmacophores to prepare pharmaceutically important scaffolds[11] such as arylimidazo-benzothiazole derivative YM-201627 (**V**) (Figure 1) for the treatment of solid tumours.[12] A recent discovery showed antiplasmodial activity of the racemic spirotetrahydro *ß*-carboline based spiroazepineindole (**VI**) (Figure 1).[13]

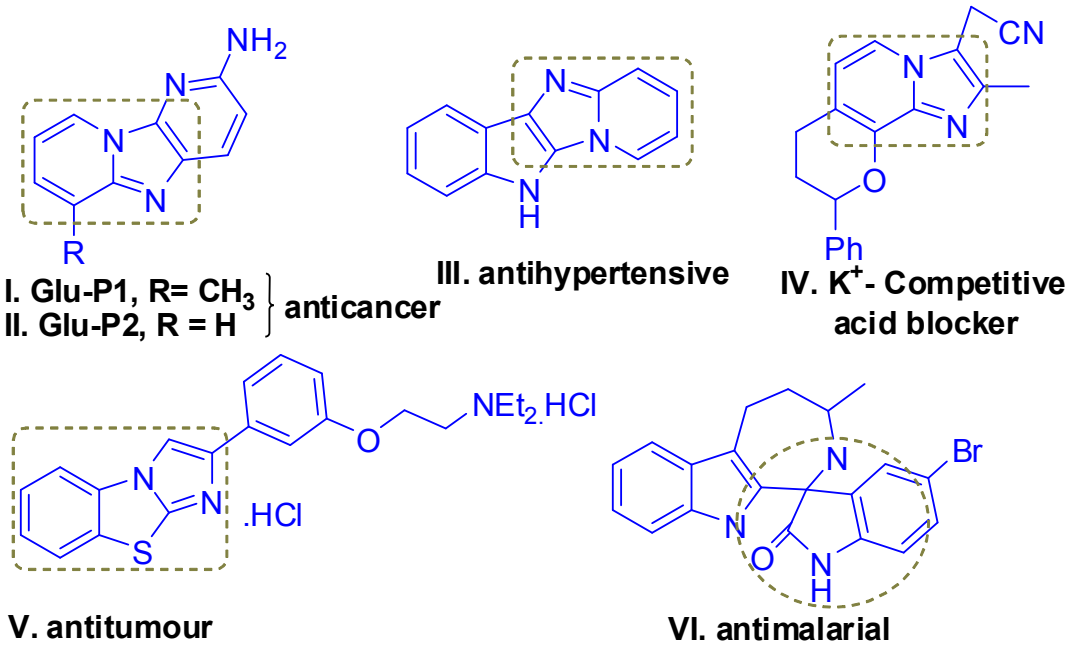


Figure 1. Several biologically active fused polyheterocycles.

Herein the present work we report privileged PIs and IBTs using Pictet-Spengler type cyclizations in aqueous medium to delivered biologically relevant polyheterocycles in moderate to good yield (Figure 2). The Pictet-Spengler reaction is one of the most powerful strategies for constructing C-C bond. Previously Pictet-Spengler reaction has been performed using strong brønsted acids like trifluoroacetic acid and methanesulphonic acid which tend to give diminished yields along with long reaction times, difficulties in work-up and/or the use of conventional solvents. [14-16] We chose cyanuric chloride as in our previous work[17,18] and reported litereture[19] we found it effective in several and/or similar transformations. Although there are some reports for Pictet-Spengler reaction using water as sole medium[20] but combination of water with cyanuric chloride has never been used in literature for similar transformation. Cyanuric chloride upon reaction with water provide HCl and cyanuric acid which could be useful in performing the

organic reactions under mild condition while at the same time produces metal free, non-volatile and essentially non toxic side product that encourage its application in medicinal chemistry.

Very recently D. Sawant *et. al* developed a similar cyanuric chloride promoted Pictet-Spengler cyclisation, however in DMSO and with limited examples (Figure 2).[21] In contrast we presents a huge polyheterocyclic library with skeletal diversity using mild and greener protocol by employing a range of oxo-substrate like aryl aldehydes, acetophenones and indoline-2,3-diones. Moreover for the first time we dwell on imidazo[1,2-*a*]benzothiazole substrate for such 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 on fusion with aryl quinoline may generate significant interest in terms of biological activity.[22]

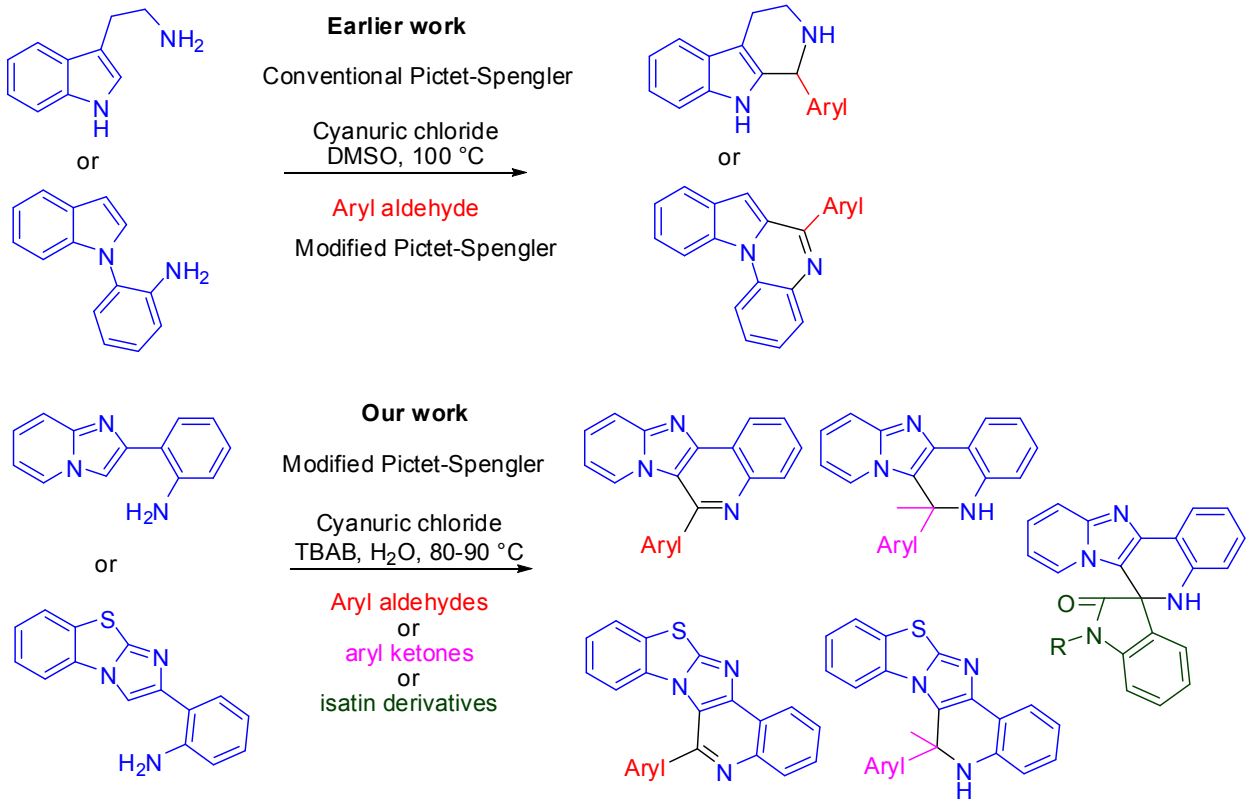


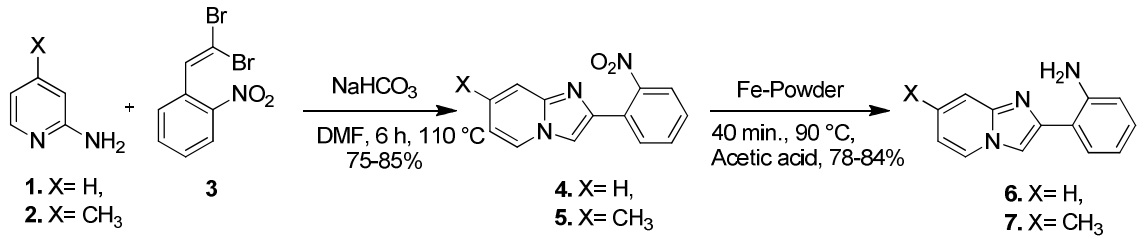
Figure 2: Comparison of our Pictet-Spengler cyclisation strategy with previous work. TBAB = tetra-*n*-butyl ammonium bromide

Results and Discussion.

The modified Pictet–Spengler reaction is a two-step process, where an aryl amine and an oxo-substrates first react to give an imine as an intermediate followed by a 6-*endo* intramolecular cyclization to provide the cyclic product. In the present manuscript the desired aryl amine **6** and **7** were prepared in a mild two-step procedure from 2-amino azine **1** and **2** respectively (Scheme 1). However previously synthon **6** is 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 IP substrates **6** and **7** in good yields.

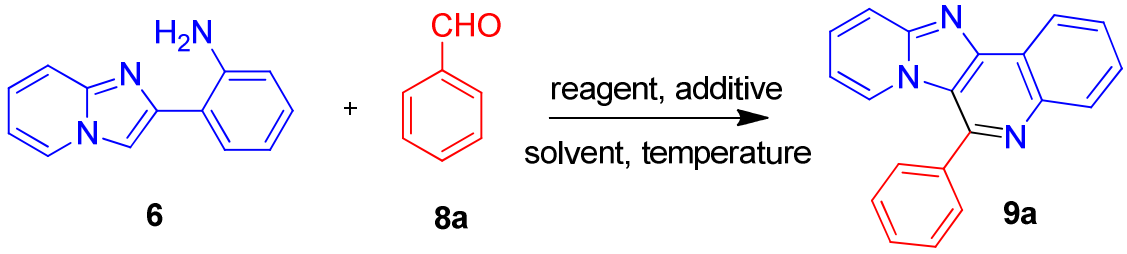
Scheme 1. Synthesis of proposed IP substrates for Pictet-Spengler type cyclization.



Further the Pictet-Spengler reaction between pyridoimidazole arylamine **6** and benzaldehyde (**8a**) was explored to identify optimal reaction conditions. Several Brønsted acids were evaluated as catalysts at variable temperature in organic and aqueous medium as well (Table 1). Out of all screened Brønsted acids in different solvents (Entry 1-5), cyanuric chloride (20 mol%) in CH_3CN (entry 5) seems promising, and so further variations were limited to solvents and temperature. From the closer observation it can be concluded that polarity of aprotic solvents directly affect reaction yields positively (compare entry 5-7). However on shifting towards aprotic to protic solvent (water), a slight drop in yield was observed (entry 8). Interestingly sustainable improvement with respect to yield, ease of handling (without inert condition) and reaction time was found upon keeping the reaction with cyanuric chloride (15 mol%) in water as solvent using TBAB as an additive in stoichiometric amount (entry 9), which prompted us to further optimise reaction conditions in aqueous medium. Increasing amount of cyanuric chloride (20 mol%) and TBAB (2 equiv.) was found beneficial in terms of reaction yield and time again (entry 10). However further increase (by 3 equiv.) and decrease (1 equiv.) in TBAB loading was not useful (entry 11 and 12). Replacing the TBAB with other additive were found less effective

(compare entries 10, 12 and 13). A slight increase in cyanuric chloride loading by 30 mol% was again not profitable (entry 14). As predicted the reaction did not work at all without cyanuric chloride (entry 15). Hence a survey of different reaction conditions (compare entries 9, 10, 14) identified 20 mol% cyanuric chloride with TBAB (2.0 equiv.) to be the optimum condition (entry 10). The use of *p*-toluenesulfonic acid in place of cyanuric chloride under otherwise optimized conditions provided the aromatic polycyclic product but in poor yield (entry 16). Further to validate our assumption, we run the same reaction with cyanuric acid (20 mol %) in place of cyanuric chloride with TBAB (2.0 equiv.) in water, which led the polyheterocycles (**9a**) in similar yield but with prolong reaction time (entry 17).

Table 1. Table for optimisation of reaction condition for Pictet-Spengler reaction[a]



6 **8a** **9a**

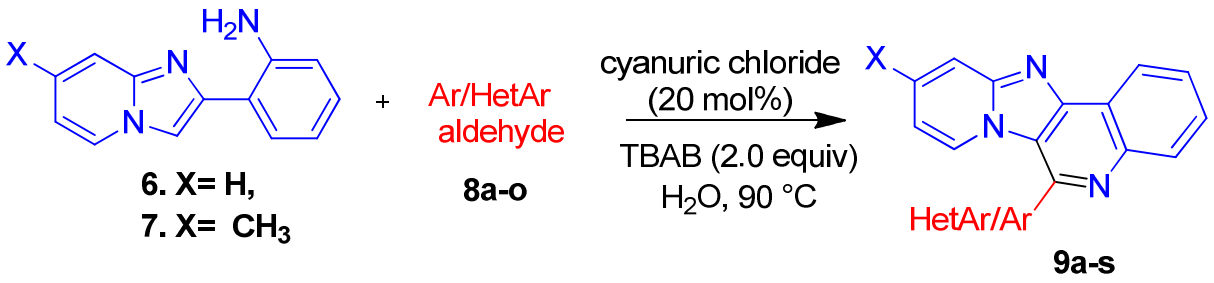
entry	reagent (mol%)	additive (equiv.)	solvent	Temp (˚C)	time (h)	yield (%)[b]
1	TFA (500)	-	DCM	70	6	34
2	PTSA (20)	-	toluene	120	5	46
3	CH_3COOH	-	neat	90	5	54
4	CH_3SO_3H (100)	-	EtOH	90	5	45
5	cyanuric chloride (20)	-	CH_3CN	85	3	56
6	cyanuric chloride (20)	-	THF	75	3	52
7	cyanuric chloride (20)	-	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 equiv.), solvent (0.64 M) at 90 °C for 1.5 h. [b] Isolated yield. [c] tetra methyl ammonium iodide. [d] reaction without cyanuric chloride. [e] no reaction.

The optimized reaction condition (Table 1, entry 10) was applied to an array of aromatic/heteroaromatic 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)**. Further the organometallic and heteroaromatic aldehydes **8e** and **8n** also participated in a similar way, providing compounds **9e** and **9r** respectively in good yields.

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



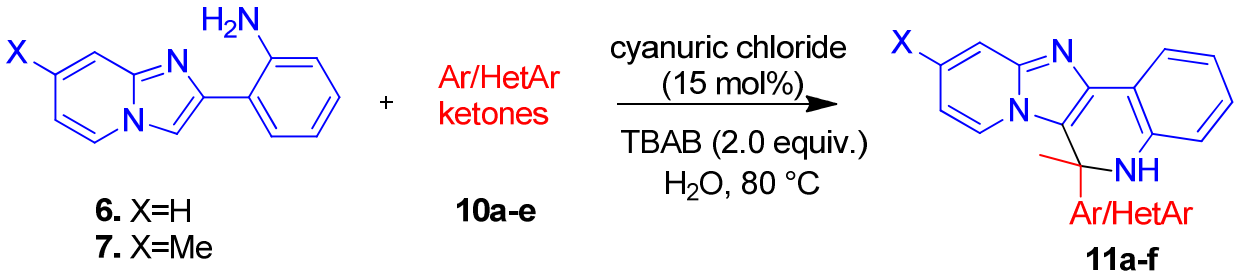
entry	Ar/HetAr aldehyde	X	Yield (%)[b]
9a	benzaldehyde (**8a**)	H	82

9b	4-nitro benzaldehyde (**8b**)	H	90
9c	4-flouro benzaldehyde (**8c**)	H	82
9d	4-methoxy benzaldehyde (**8d**)	H	77
9e	Ferrocene aldehyde (**8e**)	H	75
9f	Benzaldehyde (**8a**)	CH_3	82
9g	4-nitro benzaldehyde (**8b**)	CH_3	92
9h	2-nitro benzaldehyde (**8f**)	CH_3	77
9i	3-nitro benzaldehyde (**8g**)	CH_3	82
9j	4-cyano benzaldehyde (**8h**)	CH_3	86
9k	4-isopropyl benzaldehyde (**8i**)	CH_3	83
9l	4-bromo benzaldehyde (**8j**)	CH_3	86
9m	4-(*N*,*N*-dimethylamino)benzaldehyde (**8k**)	CH_3	75
9n	4-methoxy benzaldehyde (**8d**)	CH_3	78
9o	4-hydroxy benzaldehyde (**8l**)	CH_3	72
9p	3,4,5-trimethoxy benzaldehyde (**8m**)	CH_3	79
9q	4-flouro benzaldehyde (**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 equiv.), H_2O (0.64 M) at 90 °C for 1.5 h. [b] isolated yield.

Interestingly less reactive aromatic/heteroaromatic ketone electrophiles also successfully participated in the Pictet-Spengler reaction (Table 3), with slightly improved reaction conditions [15 mol% cyanuric chloride with 2.0 equiv. of TBAB at 80 ˚C in water (compare with Table 1, entry 10)] to provide products **11a-f** in promising yields (82-88%).

Table 3. Substrate scope with different Aromatic/Heteroaromatic ketones[a]



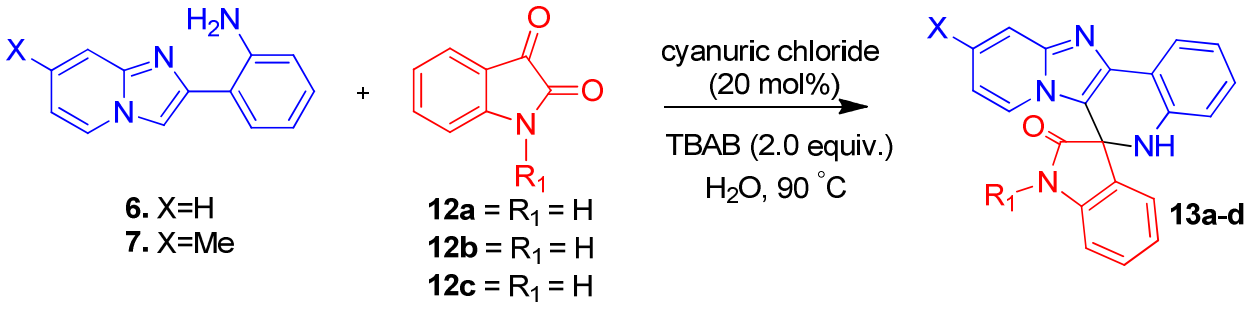
entry	Ar/HetAr ketones	X	Yield (%)[b]
11a	acetophenone (**10a**)	H	82
11b	1-(4-nitrophenyl)ethanone (**10b**)	H	86

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 equiv.), H_2O (0.64 M) at 80 °C for 1.5 h. [b] isolated yield.

From the medicinal chemistry view point, the spiro-oxindole core has great importance and is found in several natural products such as Spirotryprostatins A and B,[25a] Horsfiline,[25b] Rhynchophylline,[25c] and Marcfortine A.[25d] Therefore, spiro-oxiindole fused azapolycycles were prepared using our method, starting with indole-2,3-dione (**12a**) and analogues (**12b**, **12c**). Cyanuric chloride gave the spirofused cyclic frameworks **13a-d** in moderate to good yields (66-72%, Table 4).

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



6. X=H
7. X=Me

12a = R_1 = H
12b = R_1 = H
12c = R_1 = H

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 analogues (**12a-c**) (0.5 mmol), cyanuric chloride (20 mol%), TBAB (2.0 equiv.), H_2O (0.64 M) at 90 °C for 3.0 h. [b] isolated yield.

Tricyclic imidazobenzothiazoles **19** and **20**, novel substrates for the PS reaction, were analogously prepared as **6** and **7** (Scheme 2), and elaborated under the previously optimized reaction condition (scheme 1). These substrates were successfully transformed into respective polycyclic systems **21a-f** in promising yields as shown in Table 5.

Scheme 2. Synthesis of proposed tricyclic substrate (**19**, **20**) for Pictet-Spengler cylisation

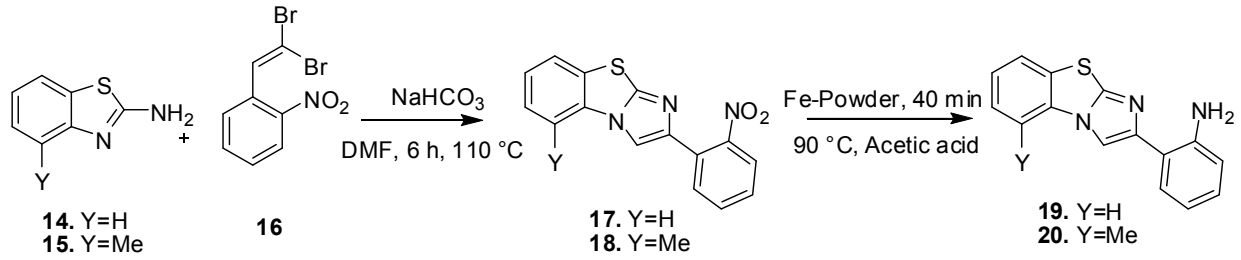
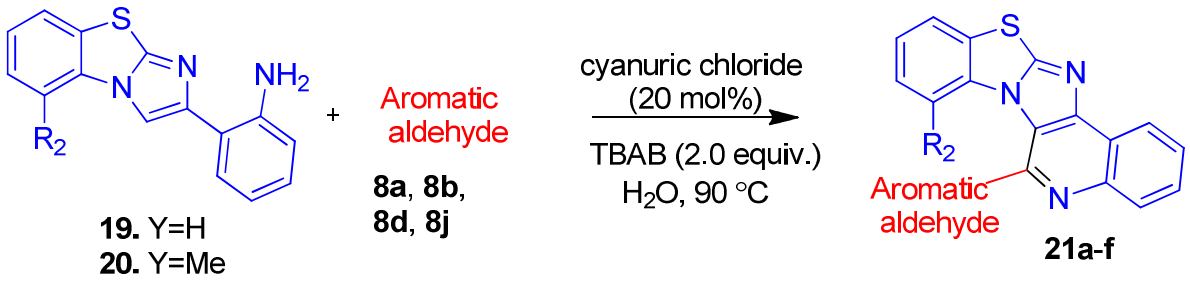


Table 5. Synthesis of IBT polyheterocycles (**21a-f**) *via* Pictet-Spengler reaction[a]

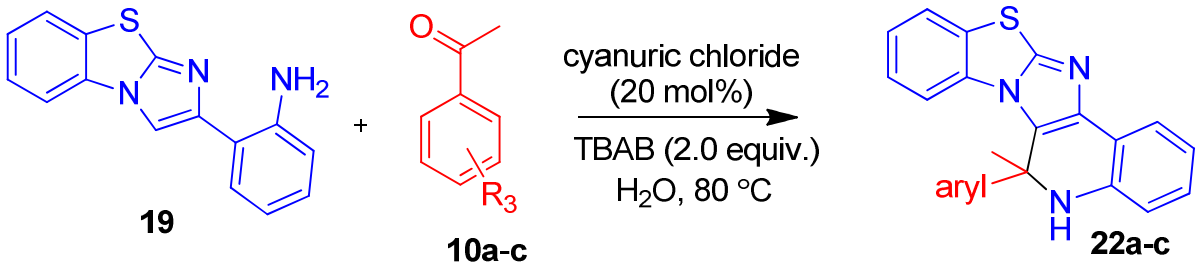


entry	Aryl aldehyde	Y	Yield (%)[b]
21a	benzaldehyde (**8a**)	H	76
21b	4-nitro benzaldehyde (**8b**)	H	83
21c	4-methoxy benzaldehyde (**8d**)	H	78
21d	4-nitro benzaldehyde (**8b**)	CH_3	78
21e	4-methoxy benzaldehyde (**8d**)	CH_3	76
21f	4-bromo benzaldehyde (**8j**)	CH_3	78

[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 equiv.), H_2O (0.64 M) at 90 °C for 2.0 h. [b] isolated yield.

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

Table 6. Synthesis of IBT polyheterocycle (**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 equiv.), H_2O (0.64 M) at 80 °C for 2.0 h. [b] isolated yield.

A plausible mechanism for the formation of polyheterocycle is proposed in Figure 3. The rate determining step of Pictet-Spengler reaction is the conversion of imine intermediate to cyclised product by a 6-*endo* intramolecular electrophilic reaction. On the basis of literature, we envisaged that cyanuric chloride under aqueous condition released hydrochloric acid and cyanuric acid.[18, 26] We believe that generated HCl as well as cyanuric acid (**23a**) (entry 17, table 1) activates the formed imine **23b** to give quarternized imine salt **23c** to facilitate 6-*endo* intramolecular cyclisation to provide **23d**. This intermediate **23d** upon deprotonation afford the

polycylic product in the case of acetophenone (**11a**), and indole-2,3-dione (**13a**) however in the case of aromatic aldehyde aerial oxidation leads to aromatised polyheterocycle **(9a)**.

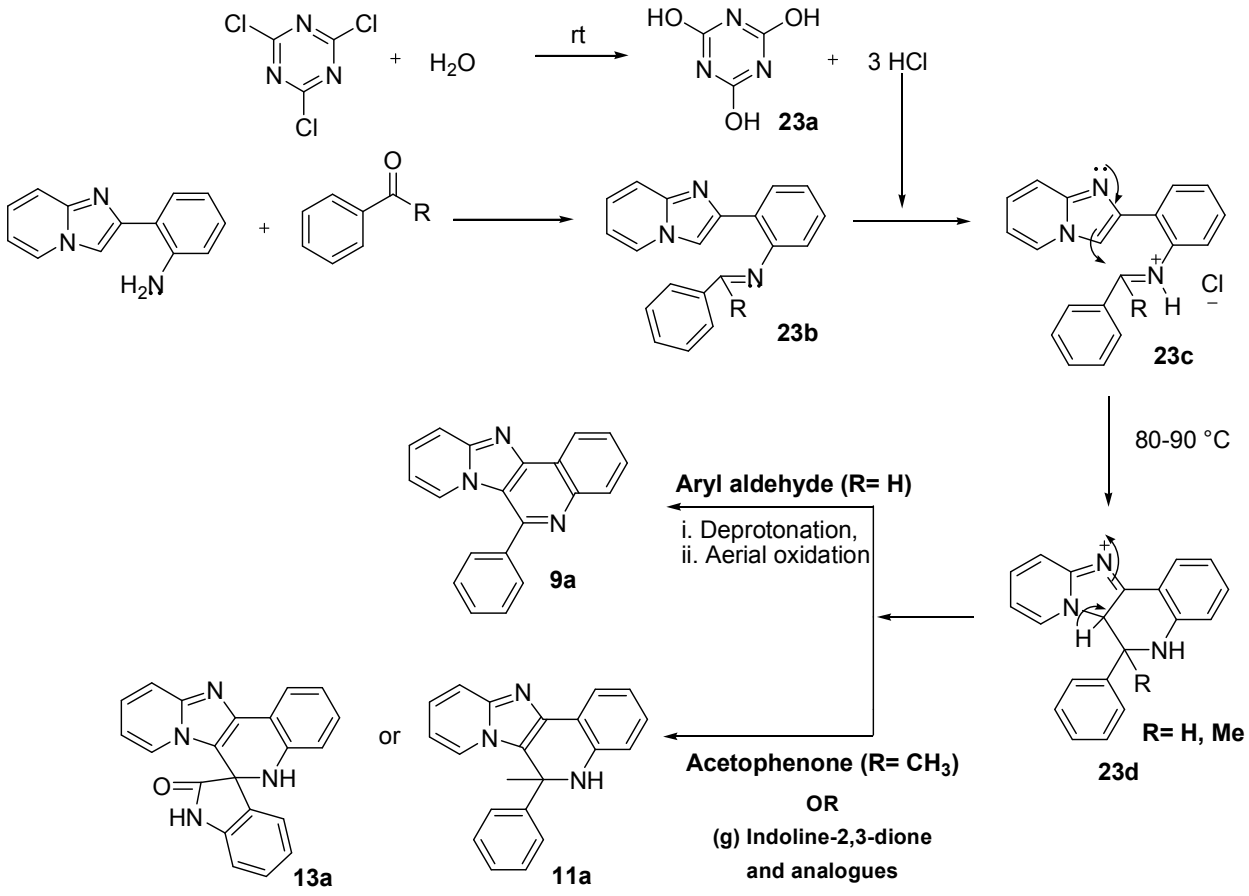


Figure 3. Proposed mechanism for synthesis of different ployheterocycles.

Biological activity.

Bioevaluation methods: *In vitro* assay for evaluation of antimalarial activity: The compounds were evaluated for antimalarial activity against both 3D7 (CQ-S) and K1 (CQ-R)

strains of *P. falciparum* using Malaria SYBER Green I nucleic acid staining dye based fluorescence (MSF) assay as mentioned by Singh et al.[27] The stock (5 mg/ml) solution was prepared in DMSO and test dilutions were prepared in culture medium (RPMI-1640-FBS). The Chloroquine was used as reference drug. The compounds were tested in 96 well plates (in duplicate wells). 1.0% parasitized cell suspension containing 0.8% parasitemia was used. The plates were incubated at 37 ˚C in CO_2 incubator in an atmosphere of 5% CO_2 and air mixture and 72 h later 100 mL of lysis buffer containing 2 x concentration of SYBER Green-I (Invitrogen) was added to each well and incubated for 1 h at 37 ˚C. The plates were examined at 485 ± 20 nm of excitation and 530 ± 20 nm of emission for relative fluorescence units (RFUs) per well using the fluorescence plate reader (FLUO star, BMG lab technologies). Data was transferred into a graphic programme (EXCEL) and IC_{50} values were obtained by Logit regression analysis using a pre-programmed Excel spreadsheet.

1.2. *In vitro* assay for evaluation of cytotoxic activity: Cytotoxicity of the compounds was carried out using Vero cell line (C1008; Monkey kidney fibroblast) following the method as mentioned by Sashidhara et al.[28] The cells were incubated with compound dilutions for 72 h and MTT was used as reagent for the detection of cytotoxicity. 50% cytotoxic concentration (CC_{50}) was determined using nonlinear regression analysis using pre-programmed Excel spreadsheet. Selectivity Index was calculated as SI equals CC_{50}/IC_{50}.

To assess their potential biological activity, subsets of the synthesized compounds were evaluated for their *in vitro* antimalarial activity against chloroquine sensitive (CQ-S) 3D7 and chloroquine resistant (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** exhibited low-

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

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

comp. no.	IC_{50} (in µM)[a]		CC_{50} (in µM)[b]
	CQ-S (3D7)	CQ-R (K1)	
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 standard drug Chloroquine

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 condition. The process is applicable to a range of aryl/heteroaryl/metallocene aldehydes, ketones, and indoline-2,3-diones. High yields, mild reaction conditions, operational simplicity and minimum environmental pollution are the key feature of our methodology that makes it useful for the construction of pharmaceutically important heterocycles, demonstrated by the observation of moderate anti-plasmodial activity *in vitro*.

Experimental Section:

2. General: Melting points are uncorrected and were determined in capillary tubes on a precision melting point apparatus containing silicon oil. 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 or Bruker Advance DRX-300 FT or Bruker Advance DRX-400 FT spectrometers. 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 $CDCl_3$ or DMSO-d_6 with TMS as internal reference wherever mentioned. Chemical shifts (δ) are reported in parts per million (ppm) for ^{1}H 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 HRMS spectra were recorded as ESI-HRMS on

Agilent 6520 Q-TOF, LC-MS/MS mass spectrometer. The reaction progress was routinely monitored by thin-layer chromatography (TLC) on precoated silica gel plates. Column chromatography was performed over silica gel. All the solvents and chemicals were used as procured from the suppliers.

3.1. ***1-(2,2-Dibromovinyl)-2-nitrobenzene*** **(7).** To a chilled solution of triphenylphosphine (3.934 g, 15.0 mol) in DCM (40 mL) carbontetrabromide (CBr_4) (9.948 g, 30 mol) was added in fraction for 15 minutes. To this solution, 2-nitrobenzaldehyde (2.266 g, 15.0 mmol) in DCM (10 mL) was added dropwise (through dropping funnel) for 15 minutes at 0 ˚C and reaction was allowed to run for 4 h at ambient temperature. After completion (monitored by TLC), the reaction mixture was poured into hexane and precipitated triphenyl phosphine oxide was filtered using sintered. This filtrate was concentrated under reduced pressure followed by column chromatography using 60-120 mesh silica gel with $CHCl_3$ as eluent to get the intermediate **7** as a yellow solid 3.90 g (yield 85%).[23]

3.2. General procedure 1: Synthesis of intermediate 4, 5, 17 and 18; To a stirred solution of different 2-amino pyridine (**1** or **2**) (10.0 mmol) or 2-amino benzothiazole **(14** or **15)** (10.0 mmol) in 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), reaction mixture was poured into water and extracted with ethyl acetate (40 mL x 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 get the solid product **(4, 5, 17** and **18)** in 75-85% yield.[24]

3.3. General procedure 2: Synthesis of intermediate 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 colour change of reaction mixture from brown to yellow and monitored by TLC), reaction mixture was filtered through 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): υ 761, 1215, 1388, 1614, 3020, 3432 cm^{-1}, ^1H 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 (EI) calcd for $[M+H]^+$: $C_{16}H_{14}N_3S$: 280.0908, found: 280.0917.

3.4. General procedure 3: Synthesis of *6-phenyl-5,6b,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), desired aromatic aldehydes (**8a-o**) (1 equiv) was added followed by addition of tetra-*n*-butyl ammonium bromide (2.0 equiv). Stired the reaction mixture for 15 minute followed by addition of cyanuric chloride (0.19 mmol, 20 mol%) at 90 ˚C. The reaction was allowed to run for 1.5 hour. 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 get the Pictet-Spengler products **9a-s** in good to excellent yield.

6-Phenyl-5,6b,11-triaza-benzo[a]fluorene **(9a).** The title compound was obtained according to general procedure **3** using substrate **6** as a off-white solid; mp 214-217 °C; Yield 0.23 g, 82%; IR (KBr): υ 1386, 1489, 3023 cm^{-1}; ^1H 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 (EI) calcd for $[M+H]^+$: $C_{20}H_{14}N_3$: 296.1183, found: 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; mp >250 °C; Yield 0.29 g, 90%; IR (KBr): υ 1384, 1600, 3019 cm^{-1};^1H 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 (EI) calcd for $[M+H]^+$: $C_{20}H_{13}N_4O_2$: 341.1039, found: 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; mp 209-212 °C; Yield 0.24 g, 82%; IR (KBr): υ 1384, 1612, 3021 cm^{-1}, ^1H 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 (EI) calcd for $[M+H]^+$: $C_{20}H_{13}FN_3$: 314.1094, found: 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 a off-white solid; mp 224-227 °C; Yield 0.24 g, 77%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{21}H_{21}N_2O_4$: 365.1501, found: 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; mp 216-219 °C; Yield 0.28 g, 75%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{24}H_{18}FeN_3$: 404.0850, found: 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 a orange solid; mp 217-220 °C; Yield 0.24 g, 82%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{21}H_{16}N_3$: 310.1344, found: 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; mp >250 °C; Yield 0.31 g, 92%; IR (KBr): υ 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 insoluble to record a carbon NMR spectrum; HRMS (EI) calcd for $[M+H]^+$: $C_{21}H_{15}N_4O_2$: 355.1195, found: 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; mp >250 °C; Yield 0.26 g, 77%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{21}H_{15}N_4O_2$: 355.1195, found: 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; mp >250 °C; Yield 0.28 g, 82%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{21}H_{15}N_4O_2$: 355.1195, found: 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; mp >250 °C; Yield 0.27 g, 86%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{22}H_{15}N_4$: 335.1297, found: 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; mp 237-240 °C; Yield 0.28 g, 83%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{24}H_{22}N_3$: 352.1814, found: 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; mp 218-221 °C; Yield 0.32 g, 86%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{21}H_{15}BrN_3$: 388.0449, found: 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; mp 235-238 °C; Yield 0.25 g, 75%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{23}H_{21}N_4$: 353.1766, found: 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; mp >250 °C; Yield 0.25 g, 78%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: C22H18N3O: 340.1540, found: 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; mp >250 °C; Yield 0.22 g, 72%; IR (KBr): υ 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 insoluble to record a carbon NMR spectrum; HRMS (EI) calcd for $[M+H]^+$: $C_{21}H_{16}N_3O$: 326.1293, found: 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; mp 212-214 °C; Yield 0.30 g, 79%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{24}H_{22}N_3O_3$: 400.1661, found: 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; mp 175-177 °C; Yield 0.26 g, 83%; 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 (EI) calcd for $[M+H]^+$: $C_{21}H_{15}FN_3$: 328.1250, found: 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; mp 217-219 °C; Yield 0.24 g, 82%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{20}H_{15}N_4$: 311.1297, found: 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; mp 239-241 °C; Yield 0.30 g, 87%; IR (KBr) 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 (EI) calcd for $[M+H]^+$: $C_{25}H_{18}N_3$: 360.1501, found: 360.1492.

3.5. General procedure 4: Synthesis of *5,6-Dihydro-5,6b,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), desired acetophenones (**10a-e)** (1.0 equiv) was added followed by addition of tetra-*n*-butyl ammonium bromide (2.0 equiv). Stired the reaction mixture for 15 minute followed by addition of cyanuric chloride (0.14 mmol, 15 mol %) at 80 ˚C. The reaction was allowed to run for 1.5 hour. After completion (monitored by TLC), the reaction mixture was poured into water and extracted with ethyl acetate (20 mL x 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 get the Pictet-Spengler product **11a-f** in good to excellent yield.

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; mp 245-247 °C; Yield 0.24 g, 82%; IR (KBr): υ 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) calcd for $[M+H]^+$: $C_{21}H_{18}N_3$: 312.1501, found: 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; mp >250 °C; Yield 0.29 g, 86%; IR (KBr): υ 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 ($CDCl_3$ + 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 (EI) calcd for $[M+H]^+$: $C_{21}H_{17}N_4O_2$: 357.1352, found: 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; mp 248-251 °C; Yield 0.26 g, 82%; IR (KBr): υ 1217, 1384, 1622, 3019, 3409 cm^{-1}, ^{1}HNMR ($CDCl_3$, 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 (EI) calcd for $[M+H]^+$: $C_{22}H_{20}N_3O$: 342.1606, found: 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; mp >250 °C; Yield 0.31 g, 84%; IR (KBr): υ 1384, 1650, 3019, 3412 cm^{-1};^{1}HNMR ($CDCl_3$, 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;) ppm; ^{13}C NMR ($CDCl_3$, 50 MHz): compound is insoluble to record a carbon NMR spectrum; HRMS (EI) calcd for $[M+H]^+$: $C_{21}H_{17}BrN_3$: 390.0606, found: 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; mp 210-213 °C; Yield 0.27 g, 88%; IR (KBr): υ 1384, 1651, 3019, 3411 cm^{-1};^{1}HNMR ($CDCl_3$, 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 (EI) calcd for $[M+H]^+$: $C_{22}H_{20}N_3$: 326.1657, found: 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; mp 187-189 °C; Yield 0.25 g, 83%; IR (KBr): υ 1384, 1653, 3019, 3408 cm^{-1};^{1}HNMR ($CDCl_3$, 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): δ150.1, 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 (EI) calcd for $[M+H]^+$: $C_{19}H_{16}N_3S$: 318.1065, found:318.1080.

3.6. 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 equiv) was added followed by addition of tetra-*n*-butyl ammonium bromide (2.0 equiv). Stired the reaction mixture for 15 minute followed by addition of cyanuric chloride (0.19 mmol, 20 mol%) at 90 ˚C. The reaction was allowed to run for 3.0 hour. 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 get the Pictet-Spengler product **(13a-d)** in good yield.

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; mp 244-246 °C; Yield 0.21 g, 66%; IR (KBr): υ 1384, 1639, 1724, 3019, 3417 cm^{-1};^{1}HNMR ($CDCl_3$, 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 (EI) calcd for $[M+H]^+$: $C_{21}H_{15}N_4O$: 339.1246, found: 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; mp 228-230 °C; Yield 0.24 g, 69%; IR (KBr): υ 1384, 1611, 1721, 3019 cm^{-1};^{1}HNMR ($CDCl_3$, 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 (EI) calcd for $[M+H]^+$: $C_{23}H_{19}N_4O$: 367.1559, found: 367.1552.

6-Spiro-indol-2(N-methyl)-one-5,6-dihydro-9-methyl-5,6b,11-triaza-benzo[a]fluorine **(13c):** The title compound was obtained according to general procedure **5** as a yellow solid; mp >250 °C; Yield 0.25 g, 72%; IR (KBr): υ 1385, 1617, 1719, 3020 cm^{-1};^{1}HNMR ($CDCl_3$, 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 (EI) calcd for $[M+H]^+$: $C_{23}H_{19}N_4O$: 367.1559, found: 367.1550.

6-Spiro-indol-2(N-ethyl)-one-5,6-dihydro-9-methyl-5,6b,11-triaza-benzo[a]fluorine **(13d):** The title compound was obtained according to general procedure **5** as a yellow solid; mp 232-234 °C; Yield 0.24 g, 68%; IR (KBr): υ 1386, 1622, 1718, 3020 cm^{-1}; ^{1}HNMR ($CDCl_3$, 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 (EI) calcd for $[M+H]^+$: $C_{24}H_{21}N_4O$: 381.1715, found: 381.1719.

3.7. General procedure 6: Synthesis of *6-(Phenyl)-(11-S)-5,6b,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), desired aromatic aldehydes (1.0 equiv) was added followed by addition of tetra-*n*-butyl ammonium bromide (2.0 equiv). Stired the reaction mixture for 15 minute followed by addition of cyanuric chloride (0.15 mmol, 20 mol %) at 90 ˚C. The reaction was allowed to run for 2.0 hour. 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 30% ethyl acetate: hexane as eluent to get the Pictet-Spengler products **(21a-f)** in promising yield.

***6-(Phenyl)-(11-S)-5,6b,12-triaza-benzo[a]fluorine* (21a):** The title compound was obtained according to general procedure **6** as a orange solid; mp 175-177 °C; Yield 0.19 g, 76%; IR (KBr): υ 1384, 1653, 3019 cm^{-1}; ^1H 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 (EI) calcd for $[M+H]^+$: $C_{22}H_{14}N_3S$: 352.0908, found: 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; mp 175-177 °C; Yield 0.24 g, 83%; IR (KBr): υ 1348, 1521, 1654, 3019 cm^{-1};^1H 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 (EI) calcd for $[M+H]^+$: $C_{22}H_{13}N_4O_2S$: 397.0759, found: 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; mp 173-175 °C; Yield 0.22 g, 78%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{23}H_{16}N_3OS$: 382.1014, found: 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 a orange solid; mp >250 °C; Yield 0.24 g, 79%; IR (KBr): υ 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 (EI) calcd for $[M+H]^+$: $C_{23}H_{15}N_4O_2S$: 411.0916, found: 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; mp >250 °C; Yield

0.23 g, 79%; IR (KBr): υ 1387, 1647, 3022 cm^{-1}; ^1H 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 (EI) calcd for $[M+H]^+$: $C_{24}H_{18}N_3OS$: 396.1171, found: 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; mp >250 °C; Yield 0.25 g, 78%; IR (KBr): υ 1384, 1645, 3019 cm^{-1}; ^1H 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 (EI) calcd for $[M+H]^+$: $C_{23}H_{15}BrN_3S$: 444.0170, found: 444.0236.

3.8. General procedure 7: Synthesis of *6-(Phenyl)-5,6-dihydro-(11-S)-5,6b,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), acetophenones (**10a-c)** (1.0 equiv) was added followed by addition of tetra-*n*-butyl ammonium bromide (2.0 equiv). Stired the reaction mixture for 15 minute followed by addition of cyanuric chloride (0.15 mmol, 20 mol %) at 80 ˚C. The reaction was allowed to run for 2.0 hour. 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 the Pictet-Spengler product **22a-c** in promising yield.

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; mp 236-238 °C; Yield 0.20 g, 76%; IR (KBr): υ 1384, 1653, 3021, 3407 cm^{-1}; ^1H 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 (EI) calcd for $[M+H]^+$: $C_{23}H_{18}N_3S$: 368.1221, found: 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; mp >250 °C; Yield 0.24 g, 78%; IR (KBr): υ 1384, 1653, 3019, 3409 cm^{-1}; ^1H 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 (EI) calcd for $[M+H]^+$: $C_{23}H_{17}N_4O_2S$: 413.1072, found: 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; mp 246-247 °C; Yield 0.22 g, 74%; IR (KBr): υ 1384, 1653, 3019, 3407 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 7.78 (d, *J* = 7.7 Hz, 1H), 7.58 (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 (EI) calcd for $[M+H]^+$: $C_{24}H_{20}N_3OS$: 398.1327, found: 398.1380.

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Synthesis of Biologically Active Pyridoimidazole/Imidazobenzothiazole Annulated Polyheterocycles using Cyanuric Chloride in water

An efficient and mild protocol for rapid access to *N*-fused polyheterocycles *via* Pictet-Spengler type 6-*endo* cyclization by cyanuric chloride in aqueous medium has been developed.