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Selective synthesis of 5,6-dihydrophenanthridines, 5,6-dihydrobenzo[*c*][1,8]naphthyridines and their fully aromatized analogues via the Pictet–Spengler reaction mediated by peptide coupling agent propylphosphonic anhydride (T3P)

John Kallikat Augustine [a,*], Agnes Bombrun [b], Padma Alagarsamy [a], Anandh Jothi [a]

[a] *Syngene International Ltd, Biocon Park, Plot Nos. 2 & 3, Bommasandra IV Phase, Jigani Link Road, Bangalore 560 099, India*
[b] *Merck Serono SA, 9 Chemin des Mines, 1202 Geneva, Switzerland*

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ABSTRACT

A new method has been developed for the selective synthesis of 5,6-dihydrophenanthridines, 5,6-dihydrobenzo[*c*][1,8]naphthyridines and their fully aromatized analogues via the Pictet–Spengler reaction mediated by propylphosphonic anhydride (T3P). The method, which uses less toxic and readily available T3P, generally seems to be more flexible, efficient in the preparation of 5,6-dihydrophenanthridine derivatives and complementary to conventional routes in the preparation of fused pyridines.

Phenanthridines and their aza and benzo analogues are fused isoquinolines, found throughout the plant kingdom, possessing a broad range of biological properties.[1] Many phenanthridines exhibit antileukemic and antiviral activities.[2] They have been found in the metabolites of plant families and their ring system is present in many synthetic dye-stuffs.[3] Benzophenanthridine derivatives that possess significant topoisomerase I (TOP1)-targeting activity have been identified.[4] A recent study has shown that a class of 5,6-dihydrophenanthridine derivatives possess high affinity for bradykinin B1 receptors and selectivity over bradykinin B2 receptors, making them useful in the treatment or prevention of painful and inflammatory processes.[5] Besides naturally occurring phenanthridine alkaloids, there is a continuous demand for diversity of aromatic substitution to optimize the structure activity relationship (SAR) of novel phenanthridines as high-affinity ligands particularly in the field of medicinal chemistry. While traditional protocols for the preparation of phenanthridine derivatives relied extensively on Bischler–Napieralski cyclization methods,[6] strategies involving radical,[7] photochemical,[8] one-pot cascade,[9] iodine-induced,[10] benzyne-mediated,[11] microwave-assisted,[7b,12] transition-metal-catalysed[13] and the modified Pictet–Spengler syntheses[14] of the phenanthridine skeleton have been reported.

In an ongoing project we were interested in optimizing a common preparation of substituted ethyl-7,9-dimethoxy-5,6-dihydrophenanthridine-6-carboxylates and ethyl-7,9-dimethoxy-5,6-dihydrobenzo[*c*][1,8]naphthyridine-6-carboxylates (**3**, Scheme 1). However, methods directly leading to 5,6-dihydrophenanthridines and 5,6-dihydrobenzonaphthyridines are less common, and there remain many limitations such as multistep synthetic reactions, and limited functional group tolerance.[11a,15] The Pictet–Spengler strategy although quite robust in the C–N bond formation, leads directly to fully aromatized phenanthridines owing to in situ oxidation of dihydrophenanthridines.[12b,14] Therefore, the development of general and convenient processes using readily accessible reagents for the selective synthesis of 5,6-dihydrophenanthridine ring system is imperative. Accordingly we decided to optimize the Pictet–Spengler methodology (Scheme 1) involving *endo* cyclization on aryl amine substrates attached to sufficiently activated 3,5-dimethoxyphenyl ring (**1**) to produce the desired 5,6-dihydrophenanthridines (**3**).

Syntheses of substrates (**1a–h**, Table 2) suitable for cationic π-cyclization were carried out via the Suzuki coupling of 3,5-dimethoxybenzeneboronic acid with a variety of substituted

* Corresponding author. Tel.: +91 80 2808 3131; fax: +91 80 2808 3150.
E-mail addresses: john.kallikat@syngeneintl.com, john.kallikat@gmail.com (J.K. Augustine).

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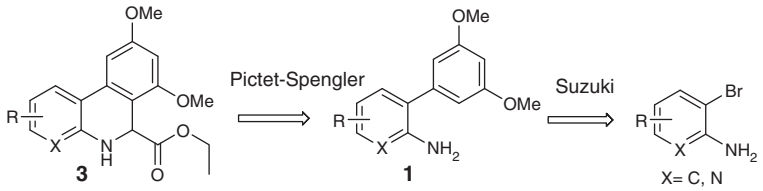
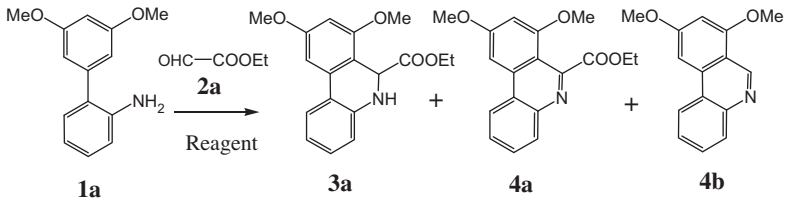


Scheme 1. Synthetic approach to 5,6-dihydrophenanthridines-6-carboxylates.

Table 1
Screening optimum conditions for cyclization



Entry [a]	Reagent (1.0 equiv)	Time (h)	Temp (°C)	Yield %		
				3a	**4a**	**4b**
1[b]	*p*-TsOH	6	25	—	9	—
2[b]	*p*-TsOH	5	100	—	24	17
3[c]	AcOH	8	60	—	19	—
4[d]	CF_3COOH	8	25	—	61	12
5[d]	$MeSO_3H$	6	25	—	19	17
6[d]	CF_3SO_3H	5	0	—	66	7
7[e]	T3P	8	25	92	—	—
8[e,f]	T3P	10	50	78	—	—
9[g,e]	T3P	10	65	—	92	—

[a] All the reactions were performed under nitrogen atmosphere except entry 9.
[b] Reaction was performed in toluene.
[c] Reaction was performed in ethanol.
[d] Reaction was performed in 1,2-dichloromethane.
[e] Reaction was performed in EtOAc.
[f] 0.5 equiv of T3P were used.
[g] Reaction was performed under oxygen atmosphere.

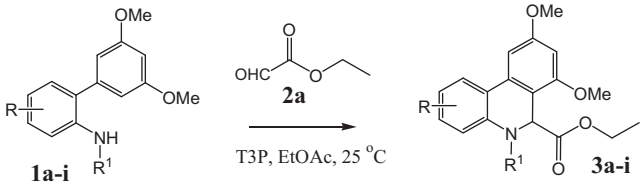
2-haloaryl amines as shown in Scheme 1.[16] To access the 5,6-dihydrophenanthridine-6-carboxylate (**3a**), substrate **1a** was treated with a fairly sensitive aldehyde **2a** (1.0 equiv, 50% soln in toluene) under traditional Pictet–Spengler conditions in the presence of *p*-TsOH in toluene at room temperature under nitrogen atmosphere (Table 1, entry 1). After 6 h of reaction, however, the fully aromatized product (**4a**) was isolated in 9% yield and there was no trace of **3a** in the reaction mass. Heating the reaction mixture for 5 h at 100 °C gave a mixture of **4a** and the decarboxylated product **4b** (Table 1, entry 2). The reaction was then screened at temperatures between 0 and 60 °C against other traditional acids such as AcOH (Table 1, entry 3), CF_3COOH (Table 1, entry 4), methanesulfonic acid (Table 1, entry 5) and triflic acid (Table 1, entry 6). To our surprise, all these protocols failed to produce the dihydrophenanthridine **3a**, but directly gave **4a** and/or **4b**.

At this point we decided to screen propylphosphonic anhydride (T3P), a popular coupling reagent generally used for amide synthesis[17] but has found handy in many other transformations in the recent years.[18] It was pleasing to note that the required product **3a** was exclusively isolated in 92% yield after 8 h of reaction at room temperature in the presence of T3P (1.0 equiv, 50% soln in EtOAc) in EtOAc under nitrogen atmosphere (Table 1, entry 7). The above conditions were most suitable for the transformation as an incomplete reaction was observed even after 10 h of heating at 50 °C in the presence of 0.5 equiv of T3P (Table 1, entry 8). Further, it is noteworthy that the exclusive synthesis of **4a** could be achieved by performing the reaction under oxygen atmosphere (Table 1, entry 9).[19] Likewise, the formation of **4a** or **4b** was not observed under any of the reaction conditions involving T3P.

After successfully establishing the optimal conditions for **3a**, substrates **1b**–**h** were subjected to T3P mediated Pictet–Spengler reaction with ethyl glyoxalate (**2a**) to give ethyl-7,9-dimethoxy-5,6-dihydrophenanthridine-6-carboxylates (Table 2, entries 2–6) and ethyl-7,9-dimethoxy-5,6-dihydrobenzo[*c*][1,8]naphthyridine-6-carboxylates (Table 2, entries 7 and 8) in moderate to good yields. Besides functional group tolerance, as shown in Table 2, the method was equally effective for N-substituted substrate **1i** giving **3i** in excellent yield (Table 2, entry 9). In all cases, the crude products obtained after workup were purified over silica column chromatography.

The extent of the reaction was further explored by performing the reaction between a heterocyclic substrate **1h** with diverse aldehydes and ketones (**2b**–**q**) in the presence T3P and the results are summarized in Table 3. As observed from Table 3, various aliphatic aldehydes (Table 3, entries 1–3), aromatic/heteroaromatic aldehydes (Table 3, entries 4–10) and ketones (Table 3, entries 11–16) reacted smoothly with **1h** in EtOAc at 65 °C and produced a range of dihydrobenzonaphthyridine derivatives. Contrary to the optimized conditions for ethyl glyoxalate (**2a**), heating for 6–10 h was essential to drive the reaction to completion for all carbonyl compounds listed in Table 3. It is notable that the cyclic ketones underwent smooth reaction and gave the respective spiro-phenanthridine derivatives in excellent yields (Table 3, entries 13–15). Also, the reaction conditions were sufficiently mild to tolerate an

Table 2
T3P mediated 5,6-dihydrophenanthridine synthesis



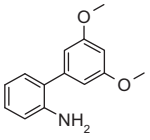
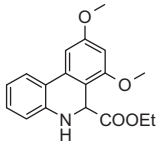
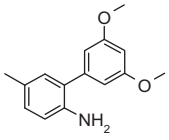
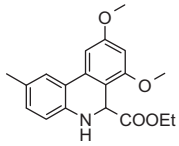
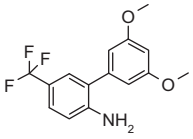
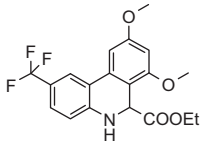
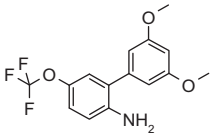
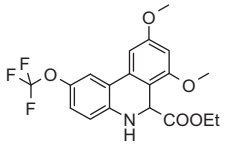
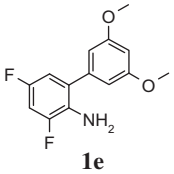
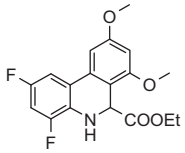
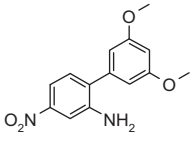
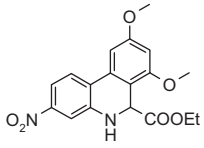
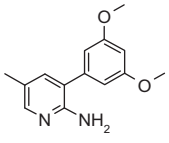
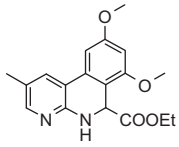
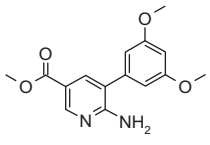
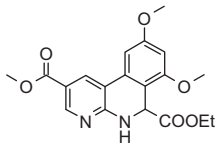
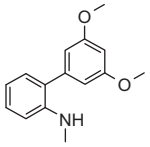
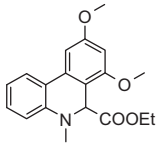
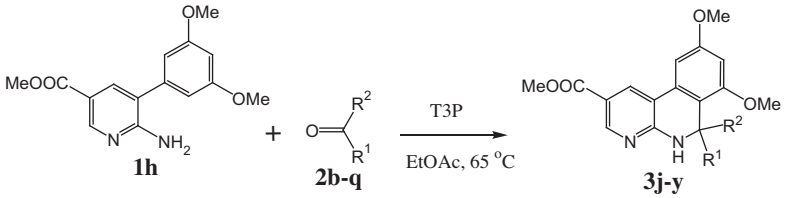
Entry	Substrate	Product	Yield[a] (%)
1	 **1a**	 **3a**	92
2	 **1b**	 **3b**	93
3	 **1c**	 **3c**	87
4	 **1d**	 **3d**	89
5	 **1e**	 **3e**	93
6	 **1f**	 **3f**	86
7	 **1g**	 **3g**	82

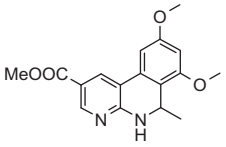
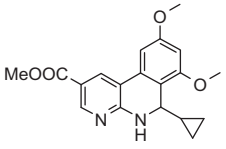
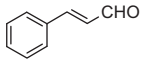
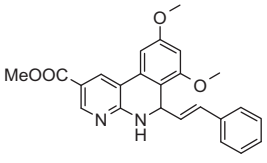
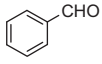
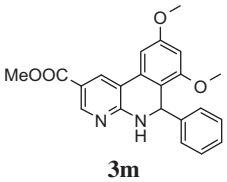
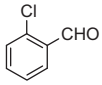
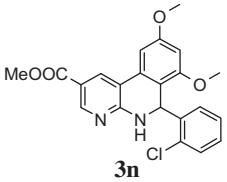
Table 2 (*continued*)

Entry	Substrate	Product	Yield[a] (%)
8	 **1h**	 **3h**	84
9	 **1i**	 **3i**	96

[a] Isolated yields.

Table 3
5,6-Dihydrobenzo[*c*][1,8]naphthyridine synthesis



Entry	Aldehyde/ketone	Product	Yield[a] (%)
1	 **2b**	 **3j**	88
2	 **2c**	 **3k**	85
3	 **2d**	 **3l**	91
4	 **2e**	 **3m**	95
5	 **2f**	 **3n**	94

(*continued on next page*)

Table 3 (*continued*)

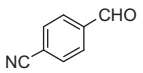
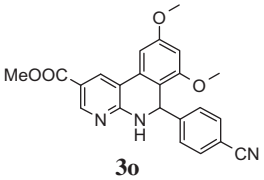
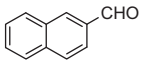
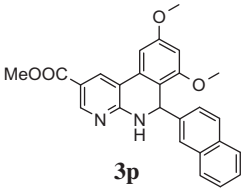
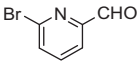
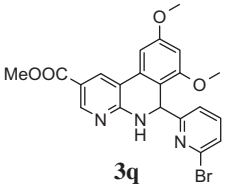
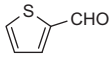
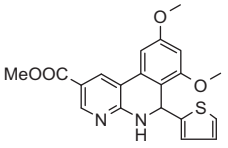
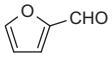
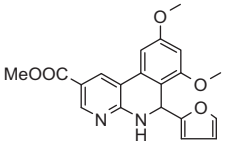
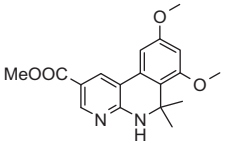
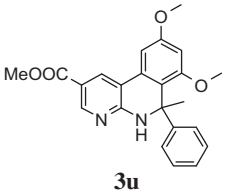
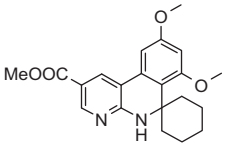
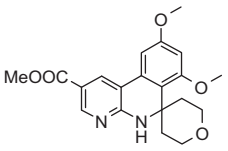
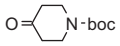
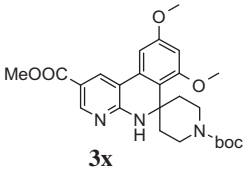
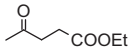
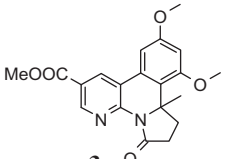
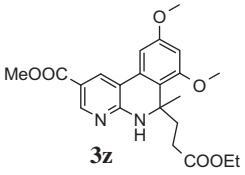
Entry	Aldehyde/ketone	Product	Yield[a] (%)
6	 **2g**	 **3o**	97
7	 **2h**	 **3p**	96
8	 **2i**	 **3q**	87
9	 **2j**	 **3r**	95
10	 **2k**	 **3s**	93
11	 **2l**	 **3t**	85
12	 **2m**	 **3u**	90
13	 **2n**	 **3v**	92
14	 **2o**	 **3w**	94

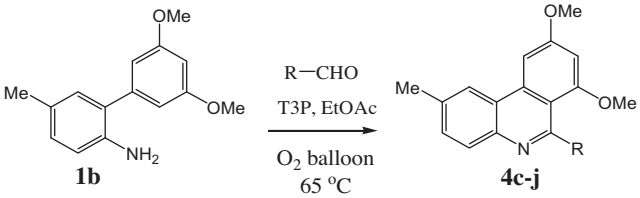
Table 3 (*continued*)

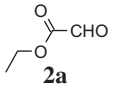
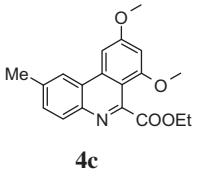
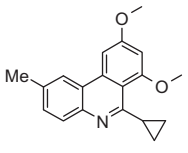
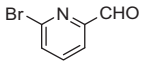
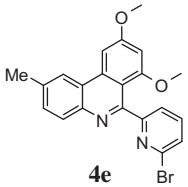
Entry	Aldehyde/ketone	Product	Yield[a] (%)
15	 **2p**	 **3x**	88
16[b]	 **2q**	 **3y**	43
		 **3z**	51

[a] Isolated yields.
[b] Reaction took 23 h for completion and gave a mixture of **3y** and **3z**.

acid sensitive group (Table 3, entry 15) that can serve as handle for further extension of the phenanthridine products. Ethyl levulinate (**2q**), under the reaction conditions, gave a mixture of dihydrobenzo[c]pyrrolo[1,2-a][1,8]naphthyridin-11-one (**3y**) and the Pictet–Spengler product (**3z**) in 43% and 51% yields respectively.

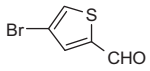
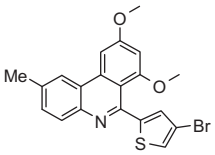
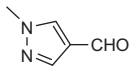
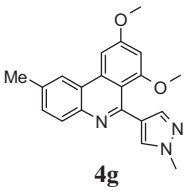
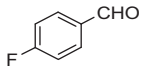
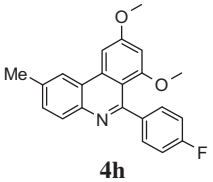
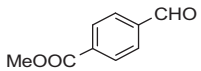
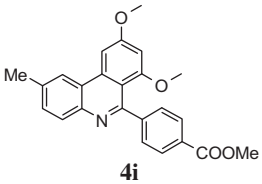
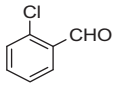
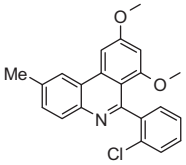
Table 4
T3P mediated phenanthridine synthesis



Entry	Aldehyde	Product	Yield[a] (%)
1	 **2a**	 **4c**	87
2	 **2c**	 **4d**	91
3	 **2i**	 **4e**	88

(*continued on next page*)

Table 4 (*continued*)

Entry	Aldehyde	Product	Yield[a] (%)
4	 **2r**	 **4f**	94
5	 **2s**	 **4g**	83
6	 **2t**	 **4h**	95
7	 **2u**	 **4i**	93
8	 **2f**	 **4j**	91

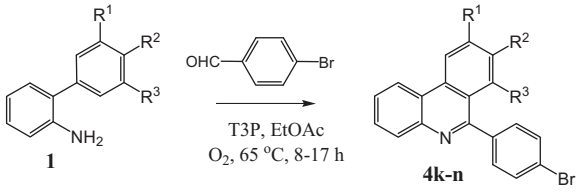
[a] Isolated yields.

Protocols allowing for efficient aromatization of the heterocycle were then explored. The optimized conditions (Table 1, entry 9) for obtaining fully aromatized heterocycle were generalized by reacting substrate **1b** with a variety of aldehydes in the presence T3P (1.0 equiv) at 65 °C under oxygen atmosphere and the results are depicted in Table 4. As summarized in Table 4, various aliphatic, aromatic and heterocyclic aldehydes reacted smoothly with **1b** to produce a range of phenanthridine derivatives (Table 4, entries 1–8), albeit, 10–12 h of heating was necessary for optimal conversion.

Next, in an attempt to probe the electronic requirements of T3P mediated phenanthridine synthesis, substrates with varied electron densities (Table 5, entries 1–4) were reacted with 4-bromobenzaldehyde in the presence of T3P at 65 °C under oxygen atmosphere. While substrates **1a** and **1j** gave the respective phenanthridines in excellent yields within 8 h of reaction (Table 5, entries 1 and 2), 17 h of heating was required for **1k** to produce **4m** regioselectively in 87% yield. However, substrate **1l** failed to produce the desired phenanthridine (**4n**) even after prolonged heating. These results reveal that the reaction is limited to electron rich substrates.

A likely involvement of T3P during the initiation of reaction between amine (**1**) and carbonyl partner (**2**) enhances the rate of formation of Schiff's base.[18k] The 'open' hydrated T3P produced during the process activates the imine towards cyclization leading to dihydrophenanthridines **3** (see, Supplementary data Scheme 2). When the carbonyl partner is an aldehyde, prolonged heating in the presence of oxygen leads to fully aromatized phenanthridines **4**.

Table 5
Screening electronic parameters of the amine



Entry	Substrate	R^1	R^2	R^3	Product	Yield (%)
1	**1a**	OMe	H	OMe	**4k**	95
2	**1j**	OMe	OMe	OMe	**4l**	96
3	**1k**	OMe	H	H	**4m**	87[a]
4	**1l**	H	H	H	**4n**	0[b]

[a] Exclusive formation of **4m** was observed.
[b] Reaction did not proceed beyond imine formation.

In conclusion, a new method has been developed for the selective synthesis of 5,6-dihydrophenanthridines, 5,6-dihydrobenzo

[*c*][1,8]naphthyridines[20,21] and their fully aromatized analogues[22] via the T3P mediated Pictet–Spengler reaction. The method, which uses less toxic and readily available T3P, generally seems to be more flexible, efficient in the preparation of 5,6-dihydrophenanthridine derivatives and complementary to conventional routes in the preparation of fused pyridines.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.034.

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19. Although aromatization was observed while allowing the reaction mixture open to air for longer hours, maintaining a balloon of oxygen allowed a clean and more rapid reaction.
20. Representative procedure for the T3P mediated synthesis of Ethyl-5,6-dihydrophenanthridine-6-carboxylates (**3a–i**): To a mixture of 3′,5′-dimethoxy-5-(trifluoromethoxy)biphenyl-2-amine (**1d**) (1.0 g, 0.003 mol) and ethyl glyoxalate (**2a**) (0.65 g, 0.003 mol, 50% soln in toluene) in EtOAc (10 mL) was added T3P (2.02 g, 0.003 mol, 50% soln in EtOAc). The resulting reaction mixture was stirred at room temperature for 8 h under nitrogen atmosphere. When the reaction was completed as confirmed by TLC, the mixture was diluted with water and extracted with ethyl acetate (2 × 25 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (1 × 20 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was passed through a small plug of silica to afford ethyl-7,9-dimethoxy-2-(trifluoromethoxy)-5,6-dihydrophenanthridine-6-carboxylate (**3d**) as pale yellow solid: Yield 1.12 g (89%); mp 107.2–109 °C; IR (KBr): 3351, 1716, 1606, 1131 cm^{-1}; MS (ESI-APCI, positive mode) 398 $[M+H]^+$; ^1H NMR (DMSO-d_6, 400 MHz): δ_H = 7.70 (d, *J* = 2.2 Hz, 1H), 7.04-7.01 (dd, *J* = 8.7, 1.4 Hz, 1H), 6.94-6.91 (m, 2H), 6.80 (d, *J* = 8.7 Hz, 1H), 6.55 (d, *J* = 2.2 Hz, 1H), 5.16 (d, *J* = 1.2 Hz, 1H), 3.98-3.89 (q, 2H), 3.84 (s, 3H), 3.79 (s, 3H), 1.03 (t, 3H); ^{13}C NMR (DMSO-d_6, 400 MHz): δ_C = 171.6, 160.4, 156.8, 143.6, 139.9, 131.7, 121.9, 120.0, 117.0, 115.4, 111.4, 99.0, 98.4, 60.3, 55.8, 55.5, 51.0, 13.9.
21. Representative procedure for the T3P mediated synthesis of 5,6-dihydrobenzonaphthyridines (**3j-z**): To a mixture of methyl-6-amino-5-(3,5-dimethoxyphenyl)nicotinate (**1h**) (1.0 g, 0.003 mol) and tetrahydropyran-4-one (**2o**) (0.35 g, 0.003 mol) in EtOAc (10 mL) was added T3P (2.22 g, 0.003 mol, 50% soln in EtOAc). The resulting reaction mixture was stirred at 65 °C for 7 h under nitrogen atmosphere. When the reaction was completed as confirmed by TLC, the mixture was diluted with water and extracted with ethyl acetate (2 × 25 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (1 × 20 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was passed through a small plug of silica to afford 1.2 g (94%) of methyl-7,9-dimethoxy-2′,3′,5′6′-tetrahydro-5*H*-spiro[benzo[*c*][1,8]naphthyridine-6,4′-pyran]-2-carboxylate (**3w**) as white solid: mp 215.1–216.7 °C; IR (KBr): 3381, 1701, 1609, 1237 cm^{-1}; MS (ESI-APCI, positive mode) 371 $[M+H]^+$; ^1H NMR (DMSO-d_6, 400 MHz): δ_H = 8.49 (s, 1H), 8.30 (s, 1H), 7.86 (s, 1H), 6.98 (d, *J* = 1.4 Hz, 1H), 6.62 (d, *J* = 1.2 Hz, 1H), 3.99–3.93 (m, 2H), 3.85 (s, 3H), 3.83 (s, 3H), 3.80 (s, 3H), 3.66-3.62 (m, 2H), 2.82–2.74 (m, 2H), 1.52-1.49 (m, 2H); ^{13}C NMR (DMSO-d_6, 400 MHz): δ_C = 165.5, 159.7, 157.7, 156.1, 150.6, 130.5, 130.1, 118.5, 114.4, 111.6, 100.4, 98.8, 61.4, 55.7, 55.3, 54.3, 51.5, 36.2.
22. Representative procedure for the T3P mediated synthesis of phenanthridines (**4c–m**): To a mixture of 3′,5′-dimethoxy-5-methylbiphenyl-2-amine (**1b**) (1.0 g, 0.004 mol) and 4-bromo thiophene-2-carboxaldehyde (**2r**) (0.78 g, 0.004 mol) in EtOAc (10 mL) was added T3P (2.6 g, 0.004 mol, 50% soln in EtOAc). The resulting reaction mixture was stirred at 65 °C for 11 h under oxygen balloon. When the reaction was completed as confirmed by LCMS, the mixture was diluted with water and extracted with ethyl acetate (2 × 25 mL). The combined organic phase was washed with saturated $NaHCO_3$ solution (1 × 20 mL) and brine. The organic phase was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure. The crude product was recrystallized with acetonitrile to afford 1.59 g (94%) of 6-(4-bromothiophen-2-yl)-7,9-dimethoxy-2-methylphenanthridine (**4f**) as white solid: mp 139.4–141 °C; IR (KBr): 2361, 2336, 1607, 1345, 1197 cm^{-1}; MS (ESI-APCI, positive mode) 416 $[M+2]^+$; ^1H NMR ($CDCl_3$, 400 MHz): δ_H = 8.19 (s, 1H), 8.03 (d, *J* = 8.3 Hz, 1H), 7.55–7.53 (m, 2H), 7.28 (t, *J* = 1.4 Hz, 1H), 7.13 (d, *J* = 1.4 Hz, 1H), 6.63 (d, *J* = 2.2 Hz, 1H), 4.05 (s, 3H), 3.73 (s, 3H), 2.62 (s, 3H); ^{13}C NMR ($CDCl_3$, 400 MHz): δ_C = 162.2, 158.9, 149.2, 141.8, 137.1, 136.8, 131.0, 129.7, 129.5, 122.9, 122.3, 121.8, 112.0, 108.4, 99.4, 94.9, 55.6, 55.4, 22.0.