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Heck-like coupling and Pictet–Spengler reaction for the synthesis of benzothieno[3,2-*c*]quinolines

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Abstract—A series of 6-arylbenzothieno[3,2-*c*]quinolines were synthesised in three steps from benzo[*b*]thiophene. After a selective Heck-type coupling of benzo[*b*]thiophene with different *o*-nitroaryl bromides to obtain 2-(*o*-nitroaryl)benzo[*b*]thiophenes, corresponding 2-(benzo-[*b*]thiophen-2-yl)anilines were involved in a Pictet–Spengler reaction to form the quinoline cycle.

1. Introduction

Synthesis of fused heterocyclic compounds is of considerable interest in organic synthesis because of their biological activities. Molecules such as quinolines and their derivatives represent an important heterocyclic family in medicinal chemistry. For example, indoloquinoline alkaloids, among which indolo[3,2-*c*]quinolines **1** (Fig. 1), have showed antiplasmodial activity.[1] These indolo[3,2-*c*]quinolines are also known as cytotoxic agents[2] and DNA intercalators.[3] All the synthetic methodologies required a last cyclisation step to yield indole[1c,2–4] or quinoline cycles.[1a,5]

Other heterocyclic analogues such as thieno,[6] benzofuro,[7] furo,[8] pyrazolo[9] and pyrrolo[3,2-*c*]quinolines[8a,10] are also described in the literature and some of them present interesting biological properties. Surprisingly, little interest has been given to the synthesis of benzothieno[3,2-*c*]quinolines **2** (Fig. 1).

Neidlein et al. described the synthesis of two benzothieno[3,2-*c*]quinolines by cyclocondensation of 2-bromobenzo[*b*]thiophene-3-carboxaldehyde with aniline and *p*-tolylamine with, respectively, 40 and 58% yield.[11] Based on a Suzuki coupling of 2-benzo[*b*]thiophen-2-ylboronic acid with *p*-bromo-*m*-nitroanisole followed by a Bischler–Napieralski reaction, Liu et al. synthesised benzothieno[3,2-*c*]quinoline as an intermediate of a rhodamine derivative.[5e] This methodology also allowed the preparation of other fused heterocycles such as thieno, furo and naphtho[3,2-*c*]quinolines.[12] Recently, we succeeded in the synthesis of 6-(methoxyphenyl)benzothieno[3,2-*c*]quinolines from benzo[*b*]thiophene. After a Heck-type coupling of benzo[*b*]thiophene, the corresponding 2-(*o*-nitroaryl)benzo[*b*]thiophenes were acylated at the 3-position. Finally, the use of Raney nickel allowed the reduction of nitro function followed by an intramolecular cyclisation affording the corresponding benzothieno[3,2-*c*]quinolines.[13]

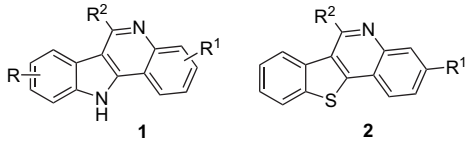

Figure 1.

We propose here an another strategy to access various benzothieno[3,2-*c*]quinolines **6–9** in three steps from benzo-[*b*]thiophene **3**. In our approach, a Heck-type coupling of benzo[*b*]thiophene **3** with different *o*-nitroaryl bromides gave 2-(*o*-nitroaryl)benzo[*b*]thiophenes **4**. The corresponding 2-(benzo[*b*]thiophen-2-yl)anilines **5** were then involved

Keywords: Fused-quinoline; Fused-benzo[*b*]thiophene; Heck reaction; Pictet–Spengler cyclisation.
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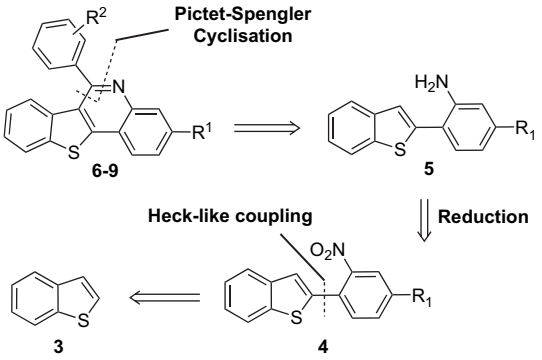
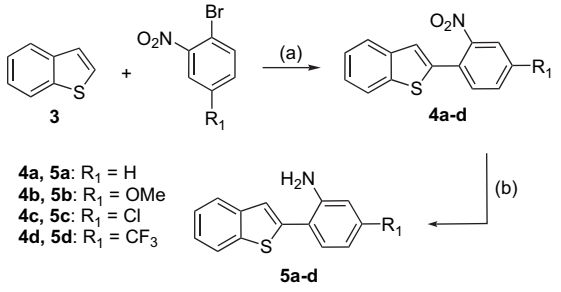
in a Pictet–Spengler cyclisation to form a C–C bond at the 3-position of benzo[*b*]thiophene moiety. According to Kundu's results about the synthesis of thiazolo and pyrazoloquinolines,[14] we expected to directly obtain 6-arylbenzothieno[3,2-*c*]quinolines **6–9** (Scheme 1).



Scheme 1. Synthetic approach to 6-arylbenzothieno[3,2-*c*]quinolines.

2. Result and discussion

We have recently reported a direct pallado-catalysed arylation at the position 2 of 3-substituted benzo[*b*]thiophenes.[15] Based on this work, benzo[*b*]thiophene **3** was first involved in a one-step Heck-type coupling with various *o*-nitroaryl bromides to selectively afford 2-(*o*-nitroaryl)benzo[*b*]thiophenes **4a–d** in 31–77% yield (Scheme 2).



Scheme 2. Reagents and conditions: (a) 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, 3 equiv K_2CO_3, DMF, 130 °C, (31–77%); (b) 1 mol % Pd/C (10%), H_2 10 bar, ethanol, rt (62–94%).

Couplings were carried out using a $(Pd(OAc)_2/PPh_3$:1:2) catalytic system, an excess of potassium carbonate as a base and a slight excess of the aryl bromide in DMF at 130 °C. Lower yields were obtained with 2-nitroaryl bromides bearing electron-withdrawing substituents (R^1=Cl, CF_3) (Table 1).

Table 1. Results for arylation and reduction steps

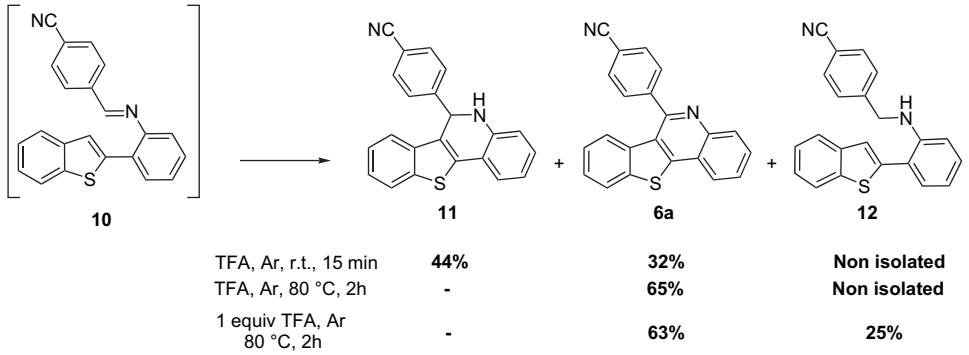
Bromide R^1	Isolated yield of **4**[a] (%)	Isolated yield of **5**[b] (%)
H	77	62
OMe	61	90
Cl	42	94
CF_3	31	85

[a] Performed with 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, 3 equiv of K_2CO_3 and 1.1 equiv of aryl bromide in DMF at 130 °C.
[b] Performed with 1 mol % Pd/C (10%) under 10 bar of H_2 in ethanol at rt.

2-(Benzo[*b*]thiophen-2-yl)anilines **5a–d** were obtained in good isolated yields by reduction of 2-(*o*-nitroaryl)benzo[*b*]thiophenes **4a–d** with Pd/C catalyst under 10 bar of hydrogen (Scheme 2, Table 1).

Anilines **5a–d** were then involved in a Pictet–Spengler reaction to afford 6-arylbenzothieno[3,2-*c*]quinolines **6–9**. Various benzaldehyde derivatives were condensed with anilines **5a–d** to give imine intermediates. Whatever the nature of anilines **5a–d** and benzaldehyde derivatives is, total conversions (followed by ^{1}H NMR) were obtained in refluxing toluene. As previously described for the synthesis of benz[*c*]benzothieno[2,3-*e*]azepines,[16] the Pictet–Spengler reaction was carried out using TFA according to Ohwada's conditions.[17]

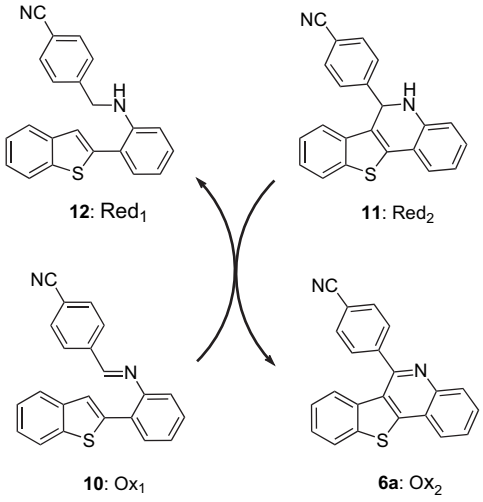
For the imine **10**, cyclisation in pure TFA under inert atmosphere afforded the desired benzothieno[3,2-*c*]quinoline **6a** in different yields depending on reaction conditions (Scheme 3). At room temperature in pure TFA, the dihydrobenzothieno[3,2-*c*]quinoline **11** (identified by ^{1}H, ^{13}C NMR) was isolated in 44% yield whereas the benzothieno[3,2-*c*]quinoline **6a** was isolated in a low yield of 32%. After 2 h of refluxing TFA, only the **6a** was isolated in a better yield of 65%. These results led us to predict an in situ oxidation of the dihydrobenzothieno[3,2-*c*]quinoline **11**. After optimisation, stoichiometric amount of TFA was sufficient to have total conversion of the imine after 2 h of stirring in toluene at 80 °C and a similar yield of 63% was so obtained. However, a catalytic amount of TFA was not sufficient probably due to protonation of the quinoline. Conditions using a stoichiometric amount of TFA at 80 °C in



Scheme 3. Synthesis of benzothieno[3,2-*c*]quinoline **6a**.

toluene were chosen. A by-product was also isolated in 25% yield and characterised as the amine **12** by ^{1}H and ^{13}C NMR.

This by-product **12** was certainly obtained from an oxydo-reduction reaction involving **10/12** and **6a/11** oxydo-reductive couples (Scheme 4). We assumed that the dihydrobenzothieno[3,2-*c*]quinoline **11** (Red_2) reduced the imine **10** (Ox_1) to afford the corresponding amine **12** (Red_1). At the same time, the dihydrobenzothieno[3,2-*c*]quinoline **11** (Red_2) might be oxidised by the imine **10** (Ox_1) to give the desired benzothieno[3,2-*c*]quinoline **6a** (Ox_2).



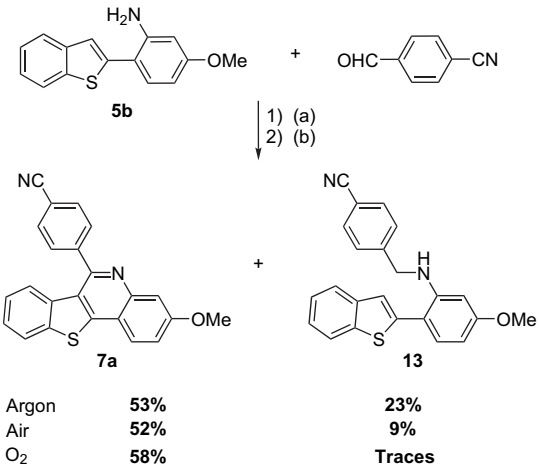
Scheme 4. Assumed oxydo-reduction reaction.

In order to prevent the yield of the undesired amine and increase the yield of benzothieno[3,2-*c*]quinoline, we tried to introduce a more oxidative agent than the imine in the reaction mixture. When the amine **5b** was condensed with *p*-cyanobenzaldehyde under air atmosphere (Scheme 5), results showed a significant decrease of yield in the amine **13**. Under O_2 atmosphere, the amine **13** was only detected in traces and the desired quinoline **7a** was obtained in a better yield.

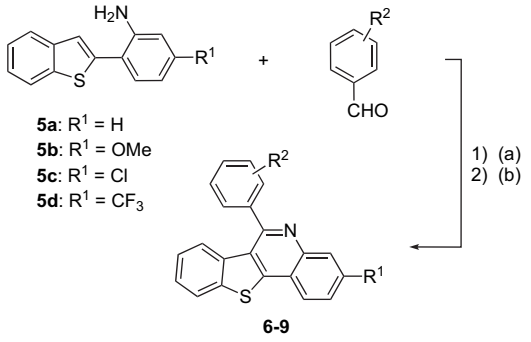
The synthesis of various 6-arylbenzothieno[3,2-*c*]quinolines **6–9** was then performed under these optimised conditions (Scheme 6).

Anilines **5a** and **5b** were first condensed with various benzaldehyde derivatives (Table 2). 6-Arylbenzothieno[3,2-*c*]quinolines **6** and **7** were obtained in 29–66% yield in short reaction times. Whatever the position of the electron-poor substituent R^2 on benzaldehyde derivative is, the cyclisation occurred, as well as with benzaldehyde (Table 2, entries 1–5, 7–10). However, the donating character of the chloro substituent seems to have an influence since isolated yields are lower (Table 2, entry 4). Comparing the position of R^2 electron-donating substituent clearly suggests that only *meta*-enriched benzaldehydes afforded benzothieno[3,2-*c*]quinolines (Table 2, entries 6, 11 and 12). With R^2=*p*-OMe (Table 2, entries 6 and 11), the cyclisation did not occur. This result could be explained by a higher electronic density on sp^2 carbon of imines derived from *para* and *ortho* enriched benzaldehydes.

Finally, the cyclisation was extended to anilines **5c** and **5d** with, respectively, a chloro and a trifluoromethyl R^1



Scheme 5. Reagents and conditions: (a) refluxing toluene; (b) 1 equiv TFA, toluene, 80 °C under precised atmospheres.



Scheme 6. Reagents and conditions: (a) refluxing toluene; (b) 1 equiv TFA, toluene, 80 °C, O_2.

substituent. With **5c** (R^1=Cl), cyclised compounds were obtained in short reaction times only with electron-poor benzaldehydes in 45–74% yield (Table 3, entries 1–3). With benzaldehyde, cyclisation did not occur even under other acidic conditions (APTS or TFSA) (Table 3, entry 4). We assume that an electron-withdrawing substituent R^1 affects the electronic density of the benzo[*b*]thiophene moiety.

3. Conclusion

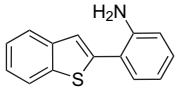
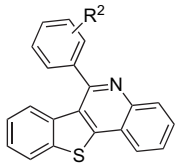
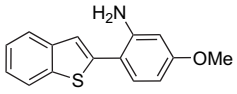
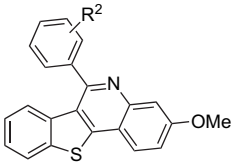
In summary, we have developed an efficient synthesis of various 6-arylbenzothieno[3,2-*c*]quinolines in three steps with good yields. The synthetic approach involves a Heck-type coupling of benzo[*b*]thiophene followed by a Pictet–Spengler cyclisation of the corresponding 2-(benzo[*b*]thiophen-2-yl)anilines with different benzaldehyde derivatives. This pathway could afford a large series of quinolines fused heterocycles with potential biological properties.

4. Experimental

4.1. General

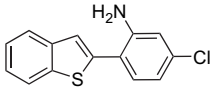
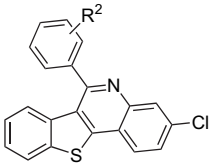
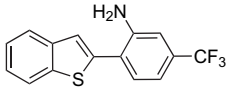
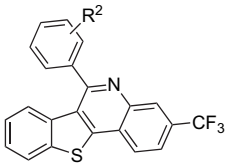
Reactants and solvents have been supplied by Acros, Aldrich, Alfa Aesar and Lancaster. TLCs were performed

Table 2. Pictet–Spengler cyclisation with anilines **5a** and **5b**

Entry	Aniline	Product	R^2		Time (h)	Isolated yield[a] (%)
1	 **5a**		*p*-CN	**6a**	2	66
2			*p*-CF_3	**6b**	6	58
3			*o*-NO_2	**6c**	2	64
4			*m*-Cl	**6d**	3	29
5			H	**6e**	1	66[b]
6			*p*-OMe	**6f**	24	—[b]
7	 **5b**		*p*-CN	**7a**	2	41
8			*p*-NO_2	**7b**	2	47
9			*p*-Cl	**7c**	5	39
10			H	**7d**	1.5	58
11			*p*-OMe	**7e**	4	—[b]
12			*m*-OMe	**7f**	24	49

[a] 1 M in refluxing toluene then 1 equiv TFA, 80 °C, O_2 in toluene for the time required.
[b] 1 M in refluxing toluene then 1 M in refluxing TFA.

Table 3. Pictet–Spengler cyclisation with anilines **5c** and **5d**

Entry	Aniline	Product	R^2		Time (h)	Isolated yield[a] (%)
1	 **5c**		*p*-CN	**8a**	0.5	45
2			*p*-CF_3	**8b**	3	58
3			*o*-NO_2	**8c**	2	74
4			H	**8d**	24	—[b,c,d]
5	 **5d**		*p*-NO_2	**9a**	2	49

[a] 1 M in refluxing toluene then 1 equiv TFA, 80 °C, O_2 in toluene for the time required.
[b] 1 M in refluxing toluene then 1 M in refluxing TFA.
[c] 1 M in refluxing toluene then 1 M in TFSA at 150 °C.
[d] 1 M in refluxing TFA then 0.1 M in DMF with 0.1 equiv APTS.

with Merck $60F_{254}$ silica gel plates. Flash chromatographies were performed with Merck Si 60 (40–63 μm). Mass spectra (EI) were recorded with a GC/MS Fisons Instrument MD 800. Mass spectra (ESI and HRMS) were, respectively, realised with ThermoFinnigan LCQ and a ThermoFinnigan MAT95XL by the 'Centre de masse de l'UCBL1'. NMR spectra were recorded on either a Brucker AMX 300 (^{1}H: 300 MHz; ^{13}C: 75 MHz) or a Brucker DPX 500, 500 MHz. Elemental analyses were made by the 'Service Central d'Analyses du CNRS' (Solaize, France). Melting points were measured on a Köfler bench.

4.2. General procedure for the preparation of compounds (4)

In a 1 M stirred solution of benzo[*b*]thiophene **3** in anhydrous DMF were successively added PPh_3 (10 mol %), K_2CO_3 (3 equiv) and aryl bromide (1.1 equiv). The mixture was heated at 100 °C for 5 min and $Pd(OAc)_2$ (5 mol %) was added. The mixture was then heated at 130 °C for 15 h. After cooling to room temperature, the mixture was filtered over Celite (rinsed with CH_2Cl_2). The resulting organic layer was successively washed with water and brine, dried over $MgSO_4$, filtered and the solvents were removed under reduced pressure. The crude product was purified by flash chromatography.

4.2.1. 2-(*o*-Nitrophenyl)benzo[*b*]thiophene (4a). Yellow solid obtained in 77% yield after flash chromatography (heptane/CH_2Cl_2=9:1) of the crude product; mp 92–94 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.28 (s, 1H), 7.38–7.50 (m, 3H), 7.55–7.64 (m, 2H), 7.80–7.89 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.1 (CH), 123.8 (CH), 123.9 (CH), 124.1 (CH), 124.7 (CH), 124.9 (CH), 128.4 (C), 129.2 (CH), 132.1 (CH), 132.4 (CH), 137.5 (C), 139.8 (C), 140.3 (C), 149.4 (C); Anal. Calcd for $C_{14}H_9NO_2S$: C, 65.87; H, 3.55; N, 5.49; S, 12.56. Found: C, 65.98; H, 3.45; N, 5.54; S, 12.65; MS (EI$^+$): *m*/*z* 255 ($M^{+\bullet}$).

4.2.2. 2-(*p*-Methoxy-*o*-nitrophenyl)benzo[*b*]thiophene (4b). Orange solid obtained in 61% yield after flash chromatography (heptane/CH_2Cl_2=7:3) of the crude product; mp 112–114 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.89 (s, 3H), 7.13 (dd, 1H, *J* 2.7, 8.5 Hz), 7.24 (s, 1H), 7.33–7.38 (m,

3H), 7.52 (d, 1H, *J* 8.7 Hz), 7.75–7.85 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 56.1 (CH_3), 109.3 (CH), 118.3 (CH), 120.7 (C), 122.2 (CH), 123.4 (CH), 124.0 (CH), 124.7 (2CH), 133.5 (CH), 137.8 (C), 140.0 (C), 140.3 (C), 150.1 (C), 160.0 (C); Anal. Calcd for $C_{15}H_{11}NO_3S$: C, 63.14; H, 3.89; N, 4.91; S, 11.24. Found: C, 62.98; H, 3.90; N, 4.92; S, 11.89; MS (EI^+): *m*/*z* 285 ($M^{+\bullet}$).

4.2.3. 2-(*p*-Chloro-*o*-nitrophenyl)benzo[*b*]thiophene (4c). Orange solid obtained in 42% yield after flash chromatography (heptane/CH_2Cl_2=8:2) of the crude product; mp 110–112 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.30 (s, 1H), 7.40 (m, 2H), 7.56 (m, 2H), 7.77–7.86 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.2 (CH), 124.2 (2CH), 124.3 (CH), 124.9 (CH), 125.2 (CH), 127.1 (C), 132.3 (CH), 133.5 (CH), 135.0 (C), 136.2 (C), 139.8 (C), 140.5 (C), 149.6 (C); Anal. Calcd for $C_{14}H_8ClNO_2S$: C, 58.04; H, 2.78; N, 4.83; Cl, 12.24. Found: C, 57.68; H, 2.91; N, 4.78; Cl, 12.51; MS (EI^+): *m*/*z* 289 ($M^{+\bullet}$).

4.2.4. 2-(*p*-Trifluoromethyl-*o*-nitrophenyl)benzo[*b*]thiophene (4d). Orange solid obtained in 31% yield after flash chromatography (heptane/CH_2Cl_2=5:5) of the crude product; mp 68–70 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.37–7.42 (m, 3H), 7.78–7.86 (m, 4H), 7.08 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.7 (C), 121.5 (CH), 122.3 (CH), 124.5 (CH), 125.0 (CH), 125.1 (CH), 125.6 (CH), 128.7 (CH), 132.3 (C), 133.4 (C), 135.7 (C), 139.8 (C), 140.7 (C), 149.4 (C), 150.6 (C); ^{19}F NMR (188 MHz, $CDCl_3$): δ −63.3 (s, 3F); MS (EI^+): *m*/*z* 323 ($M^{+\bullet}$).

4.3. General procedure for the preparation of compounds 5

To a 0.2 M solution of the 2-(*o*-nitroaryl)benzo[*b*]thiophene **4** derivative in ethanol was added Pd/C (10%) (1 mol %). The reaction mixture was stirred overnight at room temperature under 10 bar of hydrogen. The reaction mixture was then filtered over Celite (rinsed with CH_2Cl_2). The resulting organic layer was dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude product was purified by flash chromatography.

4.3.1. 2-(Benzo[*b*]thiophen-2-yl)aniline (5a). White solid obtained in 62% yield after flash chromatography (heptane/CH_2Cl_2=6:4) of the crude product; mp 116–118 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.11 (br s, 2H), 6.80–6.87 (m, 2H), 7.20 (ddd, 1H, *J* 1.4, 7.7 Hz), 7.32–7.42 (m, 3H), 7.43 (s, 1H), 7.80 (dd, 1H, *J* 1.6, 6.9 Hz), 7.86 (d, 1H, *J* 7.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 116.1 (CH), 118.7 (CH), 119.9 (C), 122.2 (CH), 122.6 (CH), 123.6 (CH), 124.3 (CH), 124.6 (CH), 129.6 (CH), 131.2 (CH), 139.9 (C), 140.5 (C), 141.7 (C), 144.3 (C); Anal. Calcd for $C_{14}H_{11}NS$: C, 74.63; H, 4.92; N, 6.22; S, 14.23. Found: C, 74.44; H, 4.98; N, 6.23; S, 14.35; MS (EI^+): *m*/*z* 225 ($M^{+\bullet}$).

4.3.2. 2-(Benzo[*b*]thiophen-2-yl)-5-methoxyaniline (5b). Orange solid obtained in 90% yield after flash chromatography (heptane/CH_2Cl_2=7:3) of the crude product; mp 108–110 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 3.82 (s, 3H), 4.14 (br s, 2H), 6.35 (d, 1H, *J* 2.4 Hz), 6.42 (dd, 1H, *J* 2.4, 8.5 Hz), 7.28–7.41 (m, 4H), 7.77 (d, 1H, *J* 8.5 Hz), 7.84 (d, 1H, *J* 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.4 (CH_3), 101.2 (CH), 104.7 (CH), 113.0 (C), 121.9 (CH), 122.2 (CH), 123.4 (CH), 124.1 (CH), 124.5 (CH), 132.3 (CH), 139.7 (C), 140.6 (C), 141.8 (C), 145.6 (C), 161.0 (C); Anal. Calcd for $C_{15}H_{13}NOS$: C, 70.56; H, 5.13; N, 5.49; S, 12.56. Found: C, 70.57; H, 5.14; N, 5.43; S, 12.60; MS (EI^+): *m*/*z* 255 ($M^{+\bullet}$).

4.3.3. 2-(Benzo[*b*]thiophen-2-yl)-5-chloroaniline (5c). White solid obtained in 94% yield after flash chromatography (heptane/CH_2Cl_2=85:15) of the crude product; mp 124–126 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.18 (br s, 2H), 6.77–6.81(m, 2H), 7.26 (m, 1H), 7.32–7.41 (m, 3H), 7.79 (d, 1H, *J* 8.5 Hz), 7.85 (d, 1H, *J* 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 115.6 (CH), 118.3 (C), 118.7 (CH), 122.3 (CH), 122.8 (CH), 123.6 (CH), 124.6 (CH), 124.7 (CH), 132.2 (CH), 135.2 (C), 139.9 (C), 140.3 (C), 140.4 (C), 145.4 (C); Anal. Calcd for $C_{14}H_{10}ClNS$: C, 64.74; H, 3.88; Cl, 13.65; N, 3.59; S, 12.34. Found: C, 64.94; H, 3.82; Cl, 13.53; N, 5.44; S, 12.26; MS (EI^+): *m*/*z* 259 ($M^{+\bullet}$).

4.3.4. 2-(Benzo[*b*]thiophen-2-yl)-5-(trifluoromethyl)aniline (5d). Pale yellow solid obtained in 85% after flash chromatography (heptane/CH_2Cl_2=8:2) of the crude product; mp 130–132 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.29 (br s, 2H), 7.03 (s, 1H), 7.06 (d, 1H, *J* 8.7 Hz), 7.35–7.45 (m, 3H), 7.47 (s, 1H), 7.82 (dd, 1H, *J* 2.3, 6.6 Hz), 7.88 (dd, 1H, *J* 1.6, 6.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.5 (q, CH, *J* 3.9 Hz), 115.0 (q, CH, *J* 3.7 Hz), 122.3 (CH), 123.4 (CH), 123.8 (CH), 124.8 (2CH), 131.4 (C), 131.6 (CH), 131.7 (C), 131.8 (C), 139.9 (C), 140.0 (C), 140.3 (C), 144.7 (C); ^{19}F NMR (188 MHz, $CDCl_3$): δ −63.4 (s, 3F); Anal. Calcd for $C_{15}H_{10}F_3NS$: C, 61.42; H, 3.44; F, 19.43; N, 4.78; S, 10.93. Found: C, 61.07; H, 3.56; F, 19.55; N, 4.82; S, 11.00; MS (EI^+): *m*/*z* 293 ($M^{+\bullet}$).

4.4. General procedure for the preparation of compounds (6–9)

To a 1 M stirred solution of the 2-(benzo[*b*]thiophen-2-yl)-aniline **5a–d** in anhydrous toluene was added the benzaldehyde derivative (1.05 equiv) and the mixture was refluxed until completion. The reaction mixture was cooled to 80 °C under oxygen atmosphere. TFA (1 equiv) was added and the mixture was stirred at 80 °C under oxygen atmosphere for the time required. The reaction mixture was then quenched with a saturated Na_2CO_3 aqueous solution and extracted with CH_2Cl_2. The resulting organic layer was washed with brine, dried over $MgSO_4$, filtered and solvents were removed under reduced pressure. The crude product was purified by flash chromatography.

4.4.1. 6-(*p*-Cyanophenyl)benzothieno[3,2-*c*]quinoline (6a). White solid obtained in 65% yield after flash chromatography (heptane/CH_2Cl_2=9:1) of the crude product; mp 204–206 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, 1H, *J* 8.3 Hz), 7.25 (m, 1H), 7.45 (m, 1H), 7.64 (m, 1H), 7.74–7.80 (m, 3H), 7.88–7.96 (m, 3H), 8.11 (dd, 1H, *J* 0.9, 8.1 Hz), 8.23 (dd, 1H, *J* 0.5, 8.4 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 112.9 (C), 118.7 (C), 123.1 (CH), 123.5 (C), 123.9 (CH), 124.2 (CH), 125.0 (CH), 126.3 (C), 126.7 (CH), 127.5 (CH), 129.8 (2CH), 130.0 (CH), 130.2 (C), 132.7 (2CH), 134.6 (C), 139.0 (C), 144.1 (C), 145.3 (C), 148.0 (C), 151.1 (C); Anal. Calcd for $C_{22}H_{12}N_2S$: C,

78.55; H, 3.60; N, 8.33; S, 9.53. Found: C, 78.52; H, 3.60; N, 8.26; S, 9.61; MS (ESI^+): *m/z* 337 (MH^+).

4.4.2. 6-(*p*-Trifluoromethylphenyl)benzothieno[3,2-*c*]-quinoline (6b). White solid obtained in 58% yield after flash chromatography (heptane/CH_2Cl_2=6:4) of the crude product; mp 218–220 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.30 (m, 2H), 7.45 (ddd, 1H, *J* 2.5, 5.7, 8.2 Hz), 7.69 (ddd, 1H, *J* 1.2, 7.0, 8.1 Hz), 7.77–7.90 (m, 5H), 7.98 (d, 1H, *J* 8.1 Hz), 8.18 (dd, 1H, *J* 0.9, 8.1 Hz), 8.27 (d, 1H, *J* 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.5 (C), 123.1 (CH), 123.7 (C), 124.0 (CH), 124.5 (CH), 125.1 (CH), 126.1 (q, 2CH, *J* 3.8 Hz), 126.8 (CH), 127.5 (CH), 129.5 (2CH), 130.0 (CH), 130.3 (CH), 131.0 (C), 131.5 (C), 135.0 (C), 139.1 (C), 144.3 (C), 144.5 (C), 148.0 (C), 155.0 (C); ^{19}F NMR (188 MHz, $CDCl_3$): δ −62.9 (s, 3F); Anal. Calcd for $C_{22}H_{12}F_3NS$: C, 69.65; H, 3.19; F, 15.02; N, 3.69; S, 8.45. Found: C, 69.84; H, 3.38; F, 14.57; N, 3.60; S, 8.60; MS (ESI^+): *m/z* 380 (MH^+).

4.4.3. 6-(*o*-Nitrophenyl)benzothieno[3,2-*c*]quinoline (6c). Beige solid obtained in 64% yield after flash chromatography (heptane/CH_2Cl_2=5:5) of the crude product; mp 214–216 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.91 (d, 1H, *J* 8.1 Hz), 7.19 (ddd, 1H, *J* 0.9, 7.2, 8.2 Hz), 7.41 (ddd, 1H, *J* 0.9, 7.2, 8.2 Hz), 7.61–7.69 (m, 2H), 7.74–7.87 (m, 3H), 7.94 (d, 1H, *J* 8.1 Hz), 8.17 (dd, 1H, *J* 0.9, 8.1 Hz), 8.21 (d, 1H, *J* 8.2 Hz), 8.38 (dd, 1H, *J* 1.2, 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.1 (CH), 123.2 (CH), 123.7 (C), 124.1 (CH), 125.2 (CH), 125.3 (CH), 126.7 (CH), 127.1 (C), 127.5 (CH), 129.9 (CH), 130.1 (2CH), 131.6 (CH), 134.4 (CH), 134.8 (C), 136.2 (C), 139.1 (C), 144.2 (C), 147.5 (C), 147.9 (C), 152.8 (C); Anal. Calcd for $C_{21}H_{12}N_2O_2S$: C, 70.77; H, 3.39; N, 7.86; S, 9.00. Found: C, 70.91; H, 3.61; N, 7.83; S, 8.67; MS (ESI^+): *m/z* 357 (MH^+).

4.4.4. 6-(*m*-Chlorophenyl)benzothieno[3,2-*c*]quinoline (6d). White solid obtained in 29% yield after flash chromatography (CH_2Cl_2/heptane=6:4) of the crude product; mp 162–164 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.26–7.28 (m, 2H), 7.45 (ddd, 1H, *J* 2.6, 5.6, 8.1 Hz), 7.53–7.61 (m, 3H), 7.65–7.71 (m, 2H), 7.80 (ddd, 1H, *J* 1.4, 7.0, 8.3 Hz), 7.97 (d, 1H, *J* 8.1 Hz), 8.17 (dd, 1H, *J* 0.9, 8.1 Hz), 8.28 (d, 1H, *J* 8.3 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.0 (CH), 123.7 (C), 124.0 (CH), 124.7 (2CH), 125.1 (CH), 126.7 (CH), 126.9 (C), 127.1 (CH), 127.4 (CH), 129.1 (CH), 129.3 (CH), 129.9 (CH), 130.3 (CH), 135.0 (C), 135.1 (C), 139.1 (C), 144.3 (C), 150.3 (C), 155.0 (C), 162.4 (C); Anal. Calcd for $C_{21}H_{12}ClNS$: C, 72.93; H, 3.50; Cl, 10.25; N, 4.05; S, 9.27. Found: C, 72.34; H, 3.63; Cl, 10.60; N, 3.92; S, 9.50; MS (ESI^+): *m/z* 346 (MH^+).

4.4.5. 6-Phenylbenzothieno[3,2-*c*]quinoline (6e). Yellow solid obtained in 66% yield after flash chromatography (CH_2Cl_2/heptane=6:4) of the crude product; mp 148–150 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.21–7.25 (m, 2H), 7.45 (ddd, 1H, *J* 2.3, 5.9, 8.1 Hz), 7.59–7.70 (m, 6H), 7.78 (ddd, 1H, *J* 1.4, 7.1, 8.4 Hz), 7.95 (d, 1H, *J* 8.1 Hz), 8.16 (dd, 1H, *J* 0.9, 8.1 Hz), 8.30 (d, 1H, *J* 8.5 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.9 (CH), 123.6 (C), 123.9 (CH), 124.9 (2CH), 126.5 (CH), 127.1 (CH), 127.2 (C), 128.7 (2CH), 129.0 (2CH), 129.1 (CH), 129.7 (CH), 130.3 (CH), 135.5 (C), 139.0 (C), 141.0 (C), 144.4 (C), 147.5 (C), 156.7 (C); Anal. Calcd for $C_{21}H_{13}NS$: C, 81.00; H, 4.21; N, 4.50. Found: C, 81.08; H, 4.62; N, 40.50; MS (ESI^+): *m/z* 312 (MH^+).

4.4.6. 6-(*p*-Cyanophenyl)-3-methoxybenzothieno[3,2-*c*]quinoline (7a). Beige solid obtained in 41% yield after flash chromatography (CH_2Cl_2/heptane=8:2) of the crude product then recrystallisation in methanol; mp 240–242 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.94 (s, 3H), 7.12 (d, 1H, *J* 8.3 Hz), 7.23 (m, 1H), 7.29 (dd, 1H, *J* 1.9, 8.9 Hz), 7.40 (m, 1H), 7.54 (d, 1H, *J* 1.9 Hz), 7.78 (d, 2H, *J* 7.9 Hz), 7.87–7.92 (m, 3H), 7.99 (d, 1H, *J* 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8 (CH_3), 108.6 (CH), 112.9 (C), 118.4 (C), 118.8 (C), 120.4 (CH), 123.1 (CH), 123.9 (CH), 125.1 (2CH), 125.8 (C), 126.5 (CH), 129.9 (2CH), 132.8 (2CH), 134.8 (C), 138.6 (C), 145.5 (C), 146.1 (C), 148.3 (C), 154.5 (C), 161.3 (C); Anal. Calcd for $C_{23}H_{14}N_2OS$: C, 75.39; H, 3.85; N, 7.64. Found: C, 75.22; H, 3.98; N, 7.68; MS (ESI^+): *m/z* 367 (MH^+).

4.4.7. 3-Methoxy-6-(*p*-nitrophenyl)benzothieno[3,2-*c*]-quinoline (7b). Yellow solid obtained in 47% yield after flash chromatography (CH_2Cl_2/heptane=9:1) of the crude product then recrystallisation in isopropanol; mp 176–178 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.98 (s, 3H), 7.15–7.27 (m, 2H), 7.34 (dd, 1H, *J* 2.5, 9.1 Hz), 7.43 (m, 1H), 7.59 (d, 1H, *J* 2.5 Hz), 7.88 (d, 2H, *J* 8.7 Hz), 7.95 (d, 1H, *J* 8.9 Hz), 8.05 (d, 1H, *J* 8.9 Hz), 8.47 (d, 2H, *J* 8.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8 (CH_3), 108.5 (CH), 118.4 (C), 120.6 (CH), 123.2 (CH), 123.8 (CH), 123.9 (CH), 124.0 (C), 124.3 (2CH), 125.1 (CH), 126.6 (CH), 129.7 (C), 130.2 (2CH), 134.7 (C), 138.6 (C), 146.0 (C), 147.3 (C), 148.3 (C), 154.1 (C), 161.4 (C); Anal. Calcd for $C_{22}H_{14}N_2O_3S$: C, 68.38; H, 3.65; N, 7.25. Found: C, 68.31; H, 3.85; N, 7.12; MS (ESI^+): *m/z* 387 (MH^+).

4.4.8. 3-Methoxy-6-(*p*-chlorophenyl)benzothieno[3,2-*c*]-quinoline (7c). White solid obtained in 39% after flash chromatography (heptane/CH_2Cl_2=6:4) of the crude product; mp 206–208 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.23–7.31 (m, 3H), 7.41 (ddd, 1H, *J* 1.8, 6.3, 8.0 Hz), 7.57–7.64 (m, 5H), 7.91 (d, 1H, *J* 7.9 Hz), 8.00 (d, 1H, *J* 8.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.8 (CH_3), 108.6 (CH), 118.3 (CH), 120.0 (C), 122.9 (CH), 124.3 (CH), 125.0 (2CH), 125.5 (C), 126.3 (CH), 129.3 (2CH), 130.2 (2CH), 135.2 (C), 135.3 (C), 138.6 (C), 139.5 (C), 146.1 (C), 148.0 (C), 155.6 (C), 161.2 (C); Anal. Calcd for $C_{22}H_{14}ClNOS \cdot 1/2H_2O$: C, 65.59; H, 4.25; Cl, 8.80; N, 3.48; S, 7.96. Found: C, 65.57; H, 3.99; Cl, 9.32; N, 3.45; S, 8.22; MS (ESI^+): *m/z* 376 (MH^+).

4.4.9. 3-Methoxy-6-phenylbenzothieno[3,2-*c*]quinoline (7d). White solid obtained in 58% yield after flash chromatography (heptane/CH_2Cl_2=6:4) of the crude product; mp 178–180 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.96 (s, 3H), 7.18–7.20 (m, 2H), 7.27 (dd, 1H, *J* 2.5, 8.9 Hz), 7.38 (m, 1H), 7.58–7.69 (m, 6H), 7.90 (d, 1H, *J* 8.1 Hz), 7.99 (d, 1H, *J* 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.7 (CH_3), 108.6 (CH), 118.2 (C), 119.7 (CH), 122.7 (CH), 124.5 (CH), 124.7 (CH), 124.9 (CH), 125.7 (C), 126.1 (CH), 128.7 (2CH), 129.0 (3CH), 135.5 (C), 138.5 (C), 141.0 (C), 146.1 (C), 147.6 (C), 156.9 (C), 161.0 (C); Anal. Calcd

for $C_{22}H_{15}NOS$: C, 77.39; H, 4.43; N, 4.10. Found: C, 77.26; H, 4.73; N, 3.92; MS (ESI^+): *m/z* 342 (MH^+).

4.4.10. 3-Methoxy-6-(*m*-methoxyphenyl)benzothieno-[3,2-*c*]quinoline (7e). Beige solid obtained in 49% yield after flash chromatography (CH_2Cl_2/heptane=9:1) of the crude product; mp 150–152 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 3.88 (s, 3H), 3.96 (s, 3H), 7.16 (ddd, 1H, *J* 1.0, 2.6, 8.3 Hz), 7.19–7.30 (m, 5H), 7.39 (ddd, 1H, *J* 1.6, 6.6, 8.1 Hz), 7.52 (dd, 1H, *J* 7.9 Hz), 7.64 (d, 1H, *J* 2.4 Hz), 7.89 (d, 1H, *J* 7.9 Hz), 7.99 (d, 1H, *J* 9.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 55.5 (CH_3), 55.7 (CH_3), 108.6 (CH), 113.5 (CH), 115.3 (CH), 118.2 (C), 119.7 (CH), 121.0 (CH), 122.7 (CH), 124.6 (CH), 124.8 (CH), 124.9 (CH), 125.6 (C), 126.1 (CH), 130.1 (CH), 135.4 (C), 138.5 (C), 142.2 (C), 146.0 (C), 147.6 (C), 156.6 (C), 160.1 (C), 161.0 (C); Anal. Calcd for $C_{23}H_{17}NO_2S$: C, 74.37; H, 4.61; N, 3.77; S, 8.63. Found: C, 74.01; H, 4.77; N, 3.66; S, 8.94; MS (ESI^+): *m/z* 372 (MH^+).

4.4.11. 3-Chloro-6-(*p*-cyanophenyl)benzothieno[3,2-*c*]-quinoline (8a). White solid obtained in 45% yield after flash chromatography (CH_2Cl_2) of the crude product; mp 220–222 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, 1H, *J* 8.1 Hz), 7.26 (m, 1H), 7.48 (m, 1H), 7.58 (dd, 1H, *J* 1.9, 8.7 Hz), 7.79 (d, 2H, *J* 8.2 Hz), 7.91 (d, 2H, *J* 8.2 Hz), 7.96 (d, 1H, *J* 7.8 Hz), 8.04 (d, 1H, *J* 8.7 Hz), 8.20 (d, 1H, *J* 1.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.2 (C), 118.7 (C), 122.0 (C), 123.2 (CH), 124.1 (CH), 125.1 (CH), 125.3 (CH), 126.6 (C), 127.1 (CH), 128.4 (CH), 129.3 (CH), 129.8 (2CH), 132.8 (2CH), 134.4 (C), 135.7 (C), 139.9 (C), 144.6 (C), 144.9 (C), 147.9 (C), 155.2 (C); Anal. Calcd for $C_{22}H_{11}ClN_2S$: C, 71.25; H, 2.99; Cl, 9.56; N, 7.55; S, 8.65. Found: C, 70.73; H, 3.30; Cl, 9.86; N, 7.58; S, 8.53; MS (ESI^+): *m/z* 371 (MH^+).

4.4.12. 3-Chloro-6-(*p*-trifluoromethylphenyl)benzothieno-[3,2-*c*]quinoline (8b). Pale pink solid obtained in 58% yield after flash chromatography (heptane/AcOEt=95:5) of the crude product; mp 180–182 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.22–7.30 (m, 2H), 7.47 (m, 1H), 7.61 (dd, 1H, *J* 1.8, 8.7 Hz), 7.81 (d, 2H, *J* 8.1 Hz), 7.88 (d, 2H, *J* 8.1 Hz), 7.97 (d, 1H, *J* 8.1 Hz), 8.09 (d, 1H, *J* 8.7 Hz), 8.24 (d, 1H, *J* 1.8 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.1 (C), 123.1 (CH), 124.5 (CH), 125.2 (CH), 125.3 (CH), 126.1 (q, 2CH, *J* 3.8 Hz), 127.0 (CH), 128.3 (CH), 129.4 (3CH), 131.2 (C), 134.7 (C), 135.7 (C), 139.0 (C), 144.1 (C), 144.8 (C), 147.8 (C), 156.0 (C), 162.5 (C), 171.3 (C); ^{19}F NMR (188 MHz, $CDCl_3$): δ −63.0 (s, 3F); HRMS (ESI^+) *m/z* calcd for $C_{22}H_{11}F_3NS$: 414.0331; found: 414.0334.

4.4.13. 3-Chloro-6-(*o*-nitrophenyl)benzothieno[3,2-*c*]-quinoline (8c). Yellow solid obtained in 74% yield after flash chromatography (heptane/CH_2Cl_2=5:5) of the crude product; mp 178–180 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 6.90 (d, 1H, *J* 8.3 Hz), 7.20 (ddd, 1H, *J* 0.9, 7.7 Hz), 7.43 (m, 1H), 7.60–7.64 (m, 2H), 7.81 (ddd, 1H, *J* 1.7, 7.8 Hz), 7.89 (ddd, 1H, *J* 1.4, 7.4 Hz), 7.95 (d, 1H, *J* 8.1 Hz), 8.10 (d, 1H, *J* 8.7 Hz), 8.21 (d, 1H, *J* 1.9 Hz), 8.40 (dd, 1H, *J* 1.2, 8.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$): δ 122.2 (C), 123.2 (2CH), 125.3 (2CH), 125.5 (CH), 126.9 (CH), 127.2 (C), 128.3 (CH), 129.2 (CH), 130.3 (CH), 131.4 (CH), 134.4 (CH), 134.6 (C), 135.6 (C), 135.9 (C), 139.1 (C), 144.7 (C), 147.4 (C), 147.8 (C), 153.9 (C); Anal. Calcd for $C_{21}H_{11}ClN_2O_2S$: C, 64.53; H, 2.84; Cl, 9.07; N, 7.17; S, 8.20. Found: C, 64.67; H, 2.90; Cl, 8.85; N, 7.08; S, 8.30; MS (EI^+): *m/z* 391 ($M^{+\bullet}$).

4.4.14. 3-Trifluoromethyl-6-(*p*-nitrophenyl)benzo-thieno[3,2-*c*]quinoline (9a). Yellow solid obtained in 49% yield after flash chromatography (CH_2Cl_2/heptane=6:4) of the crude product; mp 224–226 °C; ^1H NMR (300 MHz, $CDCl_3$): δ 7.28–7.33 (m, 2H), 7.51 (ddd, 1H, *J* 2.2, 6.0, 8.1 Hz), 7.84–7.91 (m, 3H), 8.01 (d, 1H, *J* 8.1 Hz), 8.27 (d, 1H, *J* 8.5 Hz), 8.48 (d, 2H, *J* 8.7 Hz), 8.56 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 123.4 (CH), 123.5 (q, CH, *J* 3.3 Hz), 124.4 (2CH), 124.6 (CH), 125.2 (CH), 125.4 (C), 125.6 (CH), 127.6 (CH), 127.9 (C), 128.2 (q, CH, *J* 3.8 Hz), 130.2 (2CH), 131.6 (C), 132.0 (C), 134.3 (C), 139.5 (C), 143.3 (C), 146.6 (C), 147.8 (C), 148.6 (C), 155.4 (C); ^{19}F NMR (188 MHz, $CDCl_3$): δ −63.0 (s, 3F); Anal. Calcd for $C_{22}H_{11}F_3N_2O_2S$: C, 62.26; H, 2.61; F, 13.43; N, 6.60; S, 7.56. Found: C, 62.58; H, 2.82; F, 12.95; N, 6.55; S, 7.56; MS (ESI^+) *m/z* 425 (MH^+).

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