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# Synthesis of 4-(trifluoromethyl)isoquinolines. Influence of trifluoromethyl group on the Pictet–Gams ring closure reaction

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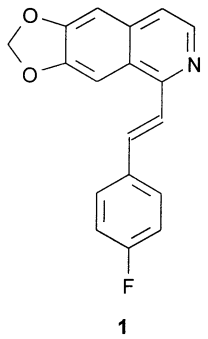
**Abstract**—Treatment of *N*-acyl-2-methoxy-2-(trifluoromethyl)arylethylamines under Pictet–Gams conditions afforded 4-methoxy-4-trifluoromethyl-3,4-dihydroisoquinolines which were aromatised by base catalysed methanol elimination. Earlier we described the synthesis of 2-oxazolines by conducting the Pictet–Gams sequence with *N*-acyl-2-hydroxy-2-(trifluoromethyl)arylethylamines. The operation of these two pathways is explained by the influence of the trifluoromethyl group. 

## 1. Introduction

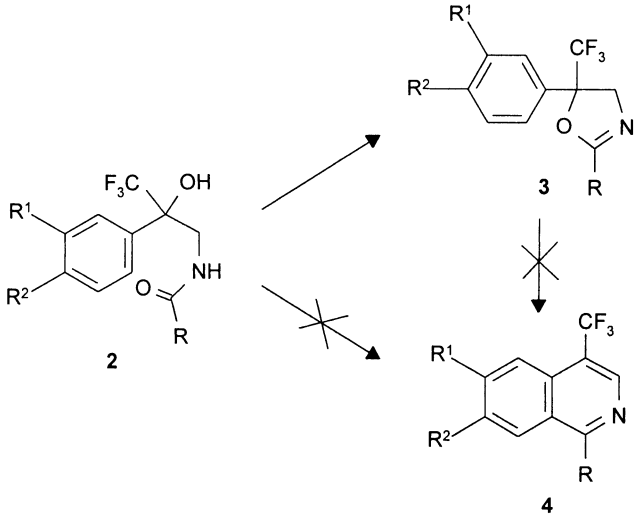
Derivatives of 1-styrylisoquinolines, in particular, 1-(4-fluorostyryl)-6,7-(methylenedioxy)isoquinoline (**1**) display remarkable anxiolytic activity without sedative side-effects.[1] Within the framework of our systematic structure–activity relationship studies we became interested in the synthesis of related 4-(trifluoromethyl)isoquinoline derivatives (Scheme 1).

In a recent publication[2] we disclosed that cyclisation of *N*-acyl-2-hydroxy-2-(trifluoromethyl)arylethylamines **2** under Pictet–Gams conditions (heating with phosphorus oxychloride in toluene for 4 h at 95°C) afforded 2-oxazolines **3** instead of the expected isoquinolines **4** (Scheme 2). The intermediacy of 2-oxazolines in Pictet–Gams cyclisation of *N*-acyl-2-hydroxyarylethylamines to isoquinolines has been demonstrated.[3,4] However, trifluoromethyl substituted 2-oxazolines **3** could not be converted to isoquinolines even under vigorous conditions (phosphorus pentoxide, boiling decaline).



**1**

**Scheme 1.**



**Scheme 2.** R: $CH_3$, styryl; $R^1$: alkoxy; $R^2$: H, alkoxy.

Nevertheless, we have accomplished the synthesis of 1-styryl-4-(trifluoromethyl)isoquinolines under Pictet–Gams conditions starting from *N*-acyl-2-methoxy-2-(trifluoromethyl)arylethylamines, which we report here.

## 2. Result and discussion

*N*-Acyl-2-methoxy-2-(trifluoromethyl)arylethylamines **8** and **9** were prepared as shown in Scheme 3. Compounds **6** were prepared conveniently from trifluoroacetophenones **5**[2] similarly to their unsubstituted analogue 'Mosher's nitrile'.[5]

*Keywords*: 4-(trifluoromethyl)isoquinoline; Pictet–Gams cyclisation; methanol elimination; destabilising effect of the trifluoromethyl group.

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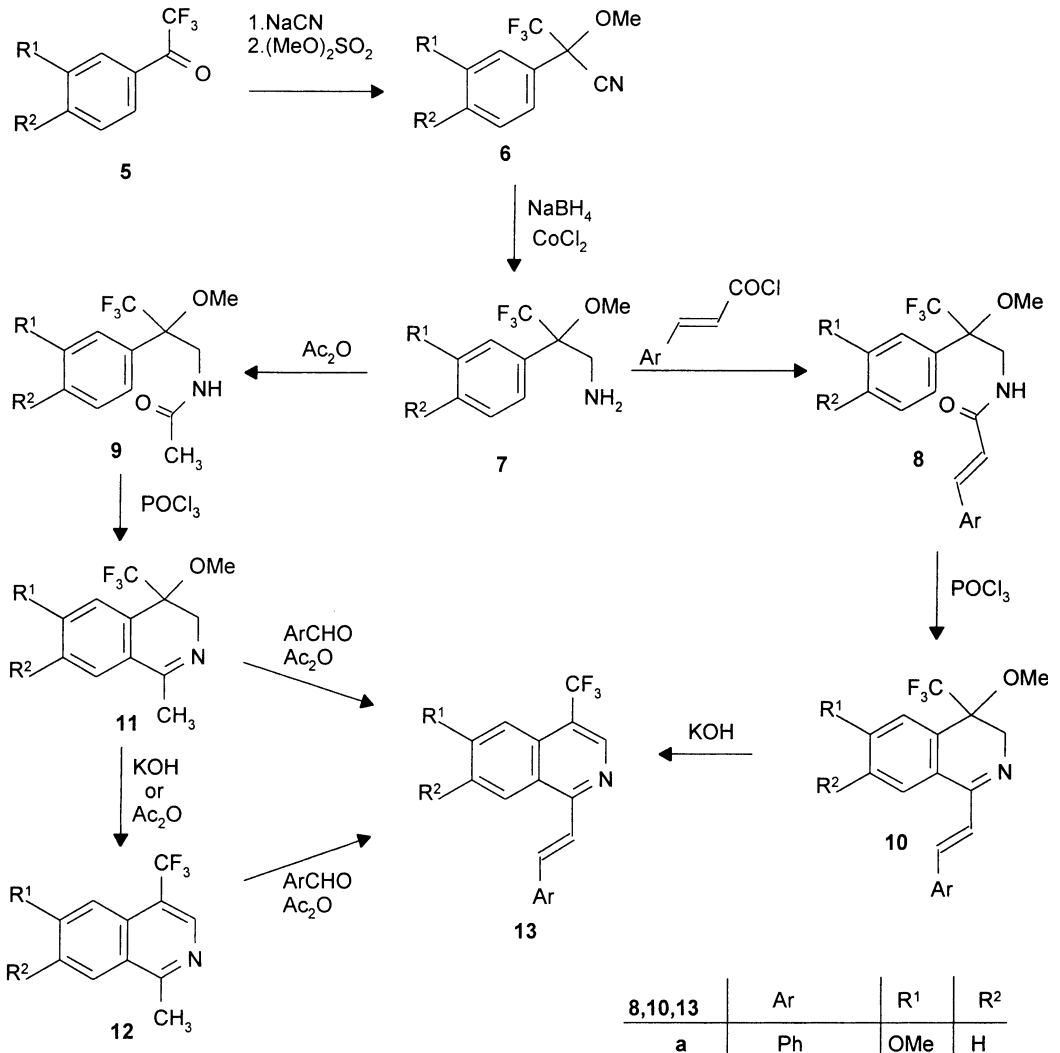



| 5-7 9,11,12 | R1 | R2 |
|---|---|---|
| a | OMe | H |
| b | O-CH2-O | |

| 8,10,13 | Ar | R1 | R2 |
|---|---|---|---|
| a | Ph | OMe | H |
| b | 4-F-C6H4 | OMe | H |
| c | 4-CF3-C6H4 | OMe | H |
| d | 4-NO2-C6H4 | OMe | H |
| e | 4-CF3-C6H4 | O-CH2-O | |

**Scheme 3.**

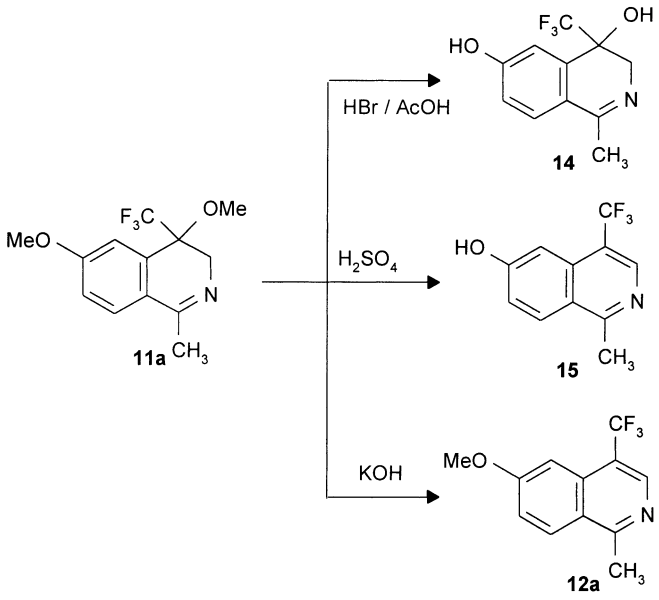
Amides **8** and **9** were obtained by reduction of nitriles **6** with sodium borohydride in the presence of cobalt chloride to amines **7** and subsequent acylation with the corresponding acid chlorides or acetic anhydride.

Treatment of *N*-acyl-2-methoxy-2-(trifluoromethyl)arylethylamines **8** and **9** under Pictet–Gams conditions (heating with phosphorus oxychloride in toluene or without solvent for 16 h at 90°C) afforded isoquinolines in good yields. Interestingly enough, the products were not type **4** aromatic derivatives as usual in Pictet–Gams cyclisations, but **10** and **11** 4-methoxy-4-trifluoromethyl-3,4-dihydroisoquinolines.

The non-occurrence of methanol elimination under Pictet–Gams conditions can be attributed to the presence of the trifluoromethyl group destabilising the cationic transition state of the acid catalysed elimination. 4,6-Dimethoxy-4-trifluoromethyl-3,4-dihydroisoquinoline (**11a**) was selected as a model compound to look for reaction conditions resulting in methanol elimination (Scheme 4). Reaction of **11a** with hydrogen bromide in glacial acetic acid afforded dihydroxy-3,4-dihydroisoquinoline **14** by hydrolysis of both methoxy groups. Treatment of **11a** with concentrated sulphuric acid under more vigorous acidic conditions gave aromatic isoquinoline **15**. However, aromatisation was accompanied with the undesirable hydrolysis of the 6-methoxy substituent.

After all, our target compounds **12** and **13** as well were obtained by base (potassium hydroxide) catalysed methanol elimination from 3,4-dihydroisoquinolines **10** and **11**, under conditions unusual for similar reactions in isoquinoline chemistry.

Condensation of 1-methylisoquinoline **12a** with benzaldehyde in acetic anhydride afforded **13a** in 60% yield.[6,7]




**Scheme 4.**

Interestingly, the reaction of **11a** with benzaldehyde under similar conditions also gave aromatic isoquinoline **13a**, i.e. the condensation reaction was accompanied by methanol elimination (Scheme 3).

The observed dissimilar reactivities can be explained by the different capability of *N*-acyl-2-hydroxy-2-(trifluoromethyl)arylethylamines (**2**) and their 2-methoxy counterparts (**8** and **9**) to form 2-oxazolines under Pictet–Gams conditions. Transformation of 2-oxazolines to isoquinolines formed in the cyclisation reaction of 2-hydroxy derivatives is hindered because of the destabilising effect of the trifluoromethyl group on the expected cationic intermediate of the reaction.[8] The formation of the isoquinolines in the case of 2-methoxy derivatives demonstrates that 2-oxazolines do not form in the course of this reaction at all.

## 3. Experimental

### 3.1. General

The melting points were determined on a Büchi 535 aparatus and were uncorrected. The IR spectra were recorded on an Aspect 2000 computer controlled Bruker IFS-113$v$ vacuum optic FT spectromer using KBr pellets or films of liquids. The $^1$H NMR and $^{13}$C NMR spectra were recorded on a Bruker WM 250 FT, or a Varian Gemini-200, or a Varian Unity Inova 400 spectrometer, in deuteriochloroform and dimethylsulfoxide-$d_6$ as solvents. Chemical shifts were reported as $\delta$ values (ppm) down field from internal tetramethylsilane. The EI MS were recorded on a Kratos MS25FRA mass spectrometer at 70 eV.

**3.1.1. Preparation of 3,3,3-trifluoro-2-methoxy-2-(3-methoxyphenyl)propionitrile (6a).** A mixture of α,α,α-trifluoro-3-methoxyacetophenone (**5a**, 61.25 g, 0.30 mol)[2] and potassium cyanide (32.56 g, 0.50 mol) was stirred for 30 min at ambient temperature in 1,2-dimethoxyethane. Dimethyl sulfate (38.0 ml, 50.45 g, 0.40 mol) was added and the mixture was stirred for 5 h at 60°C. After standing overnight the solid was filtered off. The filtrate was evaporated. The resulting oil was purified by distillation under reduced pressure (bp 80–82°C, 7 mmHg) to afford nitrile **6a** (60.0 g, 65%) as a colourless oil; IR (KBr) 2850, 2250, 1190 cm$^{-1}$; $^1$H NMR (250 MHz, $CDCl_3$): 7.41 (1H, t, $J$=8.0 Hz); 7.30–7.00 (3H, m); 3.83 (3H, s); 3.49 (3H, s). Anal. Calcd for $C_{11}H_{10}F_3NO_2$ (245.20): C, 53.88; H, 4.11; N, 5.71. Found: C, 53.50; H, 4.10; N, 5.51.

**3.1.2. Preparation of 3,3,3-trifluoro-2-methoxy-2-(3,4-methylenedioxyphenyl)propionitrile (6b).** A mixture of α,α,α-trifluoro-3,4-methylenedioxyacetophenone (**5b**, 32.72 g, 0.15 mol)[2] and sodium cyanide (14.70 g, 0.30 mol) was stirred for 15 min at ambient temperature in 1,2-dimethoxyethane. Anhydrous potassium carbonate (20.73 g, 0.15 mol) and dimethyl sulfate (42.7 ml, 56.76 g, 0.45 mol) was added and the mixture was stirred for 3 h at ambient temperature. After addition of aqueous ammonium hydroxide solution (25%, 42 ml) and water (330 ml) the mixture was extracted with ethyl acetate (2×160 ml). The organic layer was separated, washed with brine (2×160 ml), dried ($MgSO_4$) and evaporated. The residue was purified by distillation under reduced pressure (bp 78–88°C, 0.3 mmHg) to give nitrile **6b** (27.60 g, 71%) as a colourless oil; IR (KBr) 2909; 2248; 1492; 1254; 1189 cm$^{-1}$; $^1$H NMR (200 MHz, $CDCl_3$): 7.17 (1H, dd, $J$=8.1, 1.8 Hz); 7.05 (1H, d, $J$=1.8 Hz); 6.89 (1H, d, $J$=8.1 Hz); 6.05 (2H, s); 3.48 (3H, s). Anal. Calcd for $C_{11}H_8F_3NO_3$ (259.19): C, 50.98; H, 3.11; N5.40. Found: C, 50.75; H, 3.17; N, 5.45.

### 3.2. General procedure for the synthesis of amines 7

To a mixture of nitrile **6** (0.10 mol) and cobalt chloride hexahydrate (23.78 g, 0.10 mol) in methanol (250 ml) was added sodium borohydride (3.78 g, 0.10 mol) at 0°C. After standing overnight at room temperature the solvent was evaporated. Water (500 ml) and aqueous hydrochloric acid solution (2N) was added and the mixture was stirred for 1 h.

The pH was adjusted to 13 by adding aqueous sodium hydroxide (20%) solution and the mixture was extracted with dichloromethane (3×300 ml). After drying ($MgSO_4$) and evaporation the residual oil was distilled in vacuo.

**3.2.1. 3,3,3-Trifluoro-2-methoxy-2-(3-methoxyphenyl)-propylamine (7a).** This compound was obtained as a colourless oil (15.20 g, 61%), bp 103–104°C (4 mmHg); IR (KBr) 2800; 1174; 1119 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): 7.33 (1H, t, $J$=8.2 Hz); 7.05 (2H, m); 6.90 (1H, ddd, $J$=8.2, 2.5, 0.8 Hz); 3.82 (3H, s); 3.42 (3H, s); 3.36 (1H, d, $J$=14.6 Hz); 3.13 (1H, d, $J$=14.6 Hz); 1.20 (2H, bs); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): 159.7; 135.8; 129.4; 125.4 (q, $^1J_{CF}$=289.6 Hz); 119.2; 113.5; 82.2 (q, $^2J_{CF}$=24.8 Hz); 54.9; 52.5; 45.7. Anal. Calcd for $C_{11}H_{14}F_3NO_2$ (249.23): C, 53.01; H, 5.66; N, 5.62. Found: C, 52.70; H, 5.53; N, 5.78.

**3.2.2. 3,3,3-Trifluoro-2-methoxy-2-(3,4-methylenedioxyphenyl)propylamine (7b).** This compound was obtained as a colourless oil (17.9 g, 68%), bp 114–116°C (1.1 mmHg); IR (KBr) 2951; 1492; 1167 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 6.97 (1H, m); 6.93 (1H, ddd, $J$=8.2, 1.8, 0.4 Hz); 6.83 (1H, dd, $J$=8.2, 0.4 Hz); 5.97 (2H, s); 3.39 (3H, q, $J$=1.2 Hz); 3.36 (1H, d, $J$=14.6 Hz); 3.12 (1H, dq, $J$=14.6, 1.6 Hz); 1.28 (2H, bs); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 147.9; 147.7; 127.8; 125.3 (q, $^1J_{CF}$=289.5 Hz); 120.8 (q, $J$=1.5 Hz); 108.0; 107.7 (q, $J$=1.5 Hz); 101.2; 82.0 (q, $^2J_{CF}$=24.8 Hz); 52.3 (q, $J$=289.6 Hz); 45.3 (q, $^3J_{CF}$=1.1 Hz). Anal. Calcd for $C_{11}H_{12}F_3NO_3$ (263.22): C, 50.19; H, 4.60; N, 5.32. Found: C, 49.96; H, 4.58; N, 5.34.

### 3.3. General procedure for synthesis of amides 8

To a stirred mixture of amine **7** (50 mmol) in ether (20 ml) and sodium carbonate (5.3 g, 50 mmol) in water (50 ml) was added a solution of cinnamoyl chloride (50 mmol) in ether (50 ml) at 0°C. After stirring 2 h at room temperature, the resulting crystalline product was filtered and recrystallised from a mixture of 2-propanol and water.

**3.3.1. *N*-[2-Methoxy-2-(3-methoxyphenyl)-2-(trifluoromethyl)ethyl]cinnamic amide (8a).** This compound was obtained as colourless crystals (11.48 g; 61%), mp 72–73°C; IR (KBr) 1662; 1630; 1179 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): 7.63 (1H, d, $J$=15.6 Hz); 7.55–7.45 (2H, m); 7.40–7.30 (4H, m); 7.10–7.05 (2H, m); 6.99–6.90 (1H, m); 6.39 (1H, d, $J$=15.6 Hz); 5.89 (1H, bs); 4.27 (1H, dd, $J$=15.0, 5.4 Hz); 4.08 (1H, dd, $J$=15.0, 5.4 Hz); 3.83 (3H, s); 3.39 (3H, q, $J$=0.8 Hz); $^{13}C$ NMR (50,3 MHz, $CDCl_3$): 165.7; 159.8; 141.7; 135.0; 134.6; 129.8; 129.7; 128.8; 127.8; 124.9 (q, $^1J_{CF}$=288.4 Hz); 120.1; 119.5; 114.5; 113.6; 80.6 (q, $^2J_{CF}$=26.3 Hz); 55.3; 52.6; 40.9. Anal. Calcd for $C_{20}H_{20}F_3NO_3$ (379.38): C, 63.32; H, 5.31; N, 3.69. Found: C, 63.12; H, 5.27; N, 3.76.

**3.3.2. *N*-[2-Methoxy-2-(3-methoxyphenyl)-2-(trifluoromethyl)ethyl]-4-fluorocinnamic amide (8b).** This compound was obtained as colourless crystals (14.81 g; 75%), mp 100–101°C; IR (KBr) 3293; 1661; 1628; 1227; 1149 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 7.59 (1H, d, $J$=15.6 Hz); 7.51–7.44 (2H, m); 7.40–7.30 (1H, m); 7.10–7.00 (4H, m); 7.00–6.91 (1H, m); 6.31 (1H, d, $J$=15.6 Hz); 5.88 (1H, bs); 4.27 (1H, dd, $J$=14.9, 5.4 Hz); 4.06 (1H, ddd, $J$=14.9, 5.4, 1.3 Hz); 3.83 (3H, s); 3.39 (3H, s); $^{13}C$ NMR (62,9 MHz, $CDCl_3$): 163.5 (d, $^1J_{CF}$=249.2 Hz); 159.7; 140.4; 134.8; 130.7; 119.6 (d, $^3J_{CF}$=8.8 Hz); 129.3 (q, $^1J_{CF}$=289.1 Hz); 122.4; 119.6; 119.4; 117.8; 115.8 (d, $^2J_{CF}$=22.6 Hz); 114.3; 113.5; 80.5 (q, $^2J_{CF}$=27.2 Hz); 55.2; 52.5; 40.9. Anal. Calcd for $C_{20}H_{19}F_4NO_3$ (397.37): C, 60.45; H, 4.82; N, 3.52. Found: C, 60.31; H, 4.80; N, 3.55.

**3.3.3. *N*-[2-Methoxy-2-(3-methoxyphenyl)-2-(trifluoromethyl)ethyl]-4-(trifluoromethyl)cinnamic amide (8c).** This compound was obtained as colourless crystals (16.10 g; 72%), mp 85–86°C; IR (KBr) 3436; 1672; 1324; 1133 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): 7.64 (1H, d, $J$=15.6 Hz); 7.64–7.60 (4H, m); 7.35 (1H, t, $J$=8.2 Hz); 7.10–7.06 (2H, m); 6.97–6.92 (1H, m); 6.46 (1H, d, $J$=15.6 Hz); 5.92 (1H, bs); 4.27 (1H, dd, $J$=14.9, 5.4 Hz); 4.05 (1H, ddq, $J$=14.9, 5.4, 1.1 Hz); 3.83 (3H, s); 3.40 (3H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 165.0; 159.9; 140.1; 138.1; 134.9; 131.4 (q, $^2J_{CF}$=32.8 Hz); 129.8; 128.0; 126.5 (q, $^1J_{CF}$=278.9 Hz); 125.8 (q, $^3J_{CF}$=3.8 Hz); 124.8 (q, $^1J_{CF}$=288.0 Hz); 122.5; 119.5; 114.5; 113.6; 80.7 (q, $^2J_{CF}$=26.7 Hz); 55.4; 52.7; 41.2. Anal. Calcd for $C_{21}H_{19}F_6NO_3$ (447.38): C, 56.38; H, 4.28; N, 3.13. Found: C, 56.45; H, 4.32; N, 3.18.

**3.3.4. *N*-[2-Methoxy-2-(3-methoxyphenyl)-2-(trifluoromethyl)ethyl]-4-nitrocinnamic amide (8d).** This compound was obtained as colourless crystals (13.50 g; 64%), mp 80–81°C; IR (KBr) 1659; 1515; 1345; 1168; 1120 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 8.23 (2H, d, $J$=8.8 Hz); 7.67 (1H, d, $J$=15.6 Hz); 7.65 (2H, d, $J$=8.8 Hz); 7.37 (1H, t, $J$=8.2 Hz); 7.15–7.03 (2H, m); 7.00–6.90 (1H, m); 6.55 (1H, d, $J$=15.6 Hz); 6.02 (1H, t, $J$=5.2 Hz); 4.30 (1H, dd, $J$=15.0, 5.5 Hz); 4.04 (1H, ddq, $J$=15.0, 5.5, 1.6 Hz); 3.84 (3H, s); 3.40 (3H, s); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): 164.7; 159.9; 148.3; 140.9; 139.2; 134.8; 129.9; 128.5; 124.9 (q, $^1J_{CF}$=288.8 Hz); 124.3; 124.2; 119.5; 114.5; 113.6; 80.7 (q, $^2J_{CF}$=26.3 Hz); 55.3; 52.7; 41.3. Anal. Calcd for $C_{20}H_{19}F_3N_2O_5$ (424.38): C, 56.61; H, 4.51; N, 6.60. Found: C, 56.36; H, 4.52; N, 6.60.

**3.3.5. *N*-[2-Methoxy-2-(3,4-methylenedioxyphenyl)-2-(trifluoromethyl)ethyl]-4-(trifluoromethyl)cinnamic amide (8e).** This compound was obtained as colourless crystals (19.61 g; 85%), mp 104–106°C; IR (KBr) 3310; 1665; 1630; 1326; 1170; 1125 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 7.66 (1H, d, $J$=15.4 Hz); 7.61 (4H, m); 7.05–6.95 (2H, m); 6.85 (1H, d, $J$=7.7 Hz); 6.48 (1H, d, $J$=15.4 Hz); 6.01 (2H, s); 5.96 (1H, bs); 4.24 (1H, dd, $J$=14.9, 5.1 Hz); 4.04 (1H, dd, $J$=14.9, 5.1 Hz); 3.36 (3H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 165.1; 148.4; 148.2; 140.1; 138.0 (q, $^4J_{CF}$=1.5 Hz); 131.3 (q, $^2J_{CF}$=32.4 Hz); 128.0; 126.8; 125.7 (q, $^3J_{CF}$=3.8 Hz); 124.8 (q, $^1J_{CF}$=288.0 Hz); 123.8 (q, $^1J_{CF}$=274.3 Hz); 122.5; 121.2; 108.3; 107.9; 101.5; 80.4 (q, $^2J_{CF}$=26.7 Hz); 52.4; 41.0. Anal. Calcd for $C_{21}H_{17}F_6NO_4$ (461.36): C, 54.67; H, 3.71; N, 3.04. Found: C, 54.46; H, 3.70; N, 3.05.

### 3.4. General procedure for synthesis of acetamides 9

To a solution of amine **7** (50 mmol) in ethyl acetate (90 ml) was added acetic anhydride (4.9 ml, 5.31 g, 52 mmol) at 0°C. After stirring for 2 h at room temperature, water

(90 ml) was added and the layers were separated. The aqueous layer was extracted with ethyl acetate (2×60 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was recrystallised from a mixture of 2-propanol and water.

**3.4.1. *N*-[2-Methoxy-2-(3-methoxyphenyl)-2-(trifluoromethyl)ethyl]acetamide (9a).** This compound was obtained as colourless crystals (14.50 g; 98%), mp 74–75°C; IR (KBr) 3330; 1613; 1119 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 7.34 (1H, t, $J$=8.3 Hz); 7.03 (2H, m); 6.93 (1H, s); 5.79 (1H, s); 4.13 (1H, dd, $J$=14.8, 5.4 Hz); 3.90 (1H, ddd, $J$=14.8, 5.4, 1.4 Hz); 3.83 (3H, s); 3.35 (3H, q, $J$=0.9 Hz); 1.99 (3H, s); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): 170.1; 159.9; 135.0; 129.8; 124.9 (q, $^1J_{CF}$=288.8 Hz); 119.6; 114.5; 113.9; 80.7 (q, $^2J_{CF}$=26.3 Hz); 55.4; 52.7; 41.0; 23.2. Anal. Calcd for $C_{13}H_{16}F_3NO_3$ (291.27): C, 53.61; H, 5.54; N, 4.81. Found: C, 53.48; H, 5.50; N, 4.75.

**3.4.2. *N*-[2-Methoxy-2-(3,4-methylenedioxyphenyl)-2-(trifluoromethyl)ethyl]acetamide (9b).** This compound was obtained as colourless crystals (7.48 g; 98%), mp 119–120°C; IR (KBr) 3340; 1679; 1171; 1111 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): 6.97 (1H, s); 6.93 (1H, d, $J$=8.2 Hz); 6.83 (1H, d, $J$=8.2 Hz); 6.00 (1H, d, $J$=1.4 Hz); 5.99 (1H, d, $J$=1.4 Hz); 5.86 (1H, bs); 4.09 (1H, dd, $J$=14.8, 5.3 Hz); 3.89 (1H, ddq, $J$=14.8, 5.3, 1.2 Hz); 3.33 (3H, s); 1.99 (3H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 170.0; 148.2; 148.1; 126.8; 124.7 (q, $^1J_{CF}$= 288.0 Hz); 121.1; 108.2; 107.8; 101.4; 80.3 (q, $^2J_{CF}$= 26.6 Hz); 52.2; 40.7; 23.1. Anal. Calcd for $C_{13}H_{14}F_3NO_4$ (305.25): C, 51.15; H, 4.62; N, 4.59. Found: C, 51.38; H, 4.67; N, 4.69.

### 3.5. General procedure for synthesis of 1-styryl- and 1-methyl-4-methoxy-4-trifluoromethyl-3,4-dihydroisoquinolines (10,11)

A mixture of amide **8** or **9** (10 mmol) and phosphorus oxychloride (4.5 ml, 7.67 g, 50 mmol) was heated for 16 h at 90°C. The mixture was poured into ice-water (40 ml) and the pH adjusted to 11 by addition of aqueous ammonium hydroxide solution (28%). The aqueous layer was extracted with ethyl acetate (3×30 ml). The combined organic layers were dried ($MgSO_4$) and evaporated. The residue was recrystallised from hexane (**10b**–**e**) or acetonitrile (**11a**,**b**) to afford the title compounds. Hydrochloride salts were obtained by addition of an equivalent amount of hydrochloric acid in ethanolic solution (25.3 g/100 ml) to a solution of the bases in isopropyl ether (~5 ml/mmol). The hydrochloride salts were recrystallised from ethanol.

**3.5.1. 4,6-Dimethoxy-1-styryl-4-trifluoromethyl-3,4-dihydroisoquinoline hydrochloride (10a·HCl).** This compound was obtained as pale yellow crystals (53%), mp 188–189°C; IR (KBr) 3435; 1508; 1477 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$ and $CDCl_3$): 8.49 (1H, d, $J$=8.9 Hz); 8.22 (1H, m); 7.88 (2H, dd, $J$=7.6, 1.8 Hz); 7.73 (1H, d, $J$=16.1 Hz); 7.53 (3H, m); 7.35 (1H, dd, $J$=8.9, 2.6 Hz); 7.29 (1H, d, $J$=2.6 Hz); 6.60 (1H, bs); 4.42 (1H, d, $J$=16.0 Hz); 4.26 (1H, d, $J$=16.0 Hz); 4.04 (3H, s); 3.42 (3H, s); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$ and $CDCl_3$): 166.9; 166.6; 149.6; 135.7; 134.2; 133.7; 132.3; 129.8; 129.3; 124.4 (q, $^1J_{CF}$=287.5 Hz); 119.0; 115.9; 115.8; 114.7; 75.0 (q, $^2J_{CF}$=28.5 Hz); 55.8; 53.3; 42.2. Anal. Calcd for $C_{20}H_{19}ClF_3NO_2$ (397.82): C, 60.38; H, 4.81; Cl, 8.91; N, 3.54. Found: C, 60.24; H, 4.84; Cl, 8.92; N, 3.49.

**3.5.2. 1-(4-Fluorostyryl)-4,6-dimethoxy-4-trifluoromethyl-3,4-dihydroisoquinoline (10b).** This compound was obtained as colourless crystals (67%), mp 92–93°C; IR (KBr) 2959; 1646; 1510; 118 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): 7.70 (1H, d, $J$=8.6 Hz); 7.53 (2H, m); 7.42 (1H, d, $J$=15.9 Hz); 7.24 (1H, d, $J$=2.6 Hz); 7.14 (1H, d, $J$=15.9 Hz); 7.10–7.02 (3H, m); 4.26 (1H, d, $J$=17.2 Hz); 4.17 (1H, d, $J$=17.2 Hz); 3.90 (3H, s); 3.32 (3H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 163.1 (d, $^1J_{CF}$=249.1 Hz); 161.8; 161.6; 135.5; 132.6; 132.4; 129.0 (d, $^3J_{CF}$=8.4 Hz); 128.1; 125.2 (q, $^1J_{CF}$=286.1 Hz); 123.6 (d, $^4J_{CF}$=2.3 Hz); 123.0; 115.8 (d, $^2J_{CF}$=22.1 Hz); 114.8; 112.8; 75.1 (q, $^2J_{CF}$=27.5 Hz); 55.6; 52.6; 49.4. Anal. Calcd for $C_{20}H_{17}F_4NO_2$ (379.35): C, 63.32; H, 4.52; N, 3.69. Found: C, 63.05; H, 4.48; N, 3.61.

Hydrochloride (**10b·HCl**): mp 213–214°C; IR (KBr) 2541; 1599; 1241 $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$ and $CDCl_3$): $\delta$: 8.51 (1H, d, $J$=8.8 Hz); 8.16 (1H, d, $J$=15.8 Hz); 8.05–7.96 (2H, m); 7.77 (1H, d, $J$=15.8 Hz); 7.50–7.30 (3H, m); 7.25 (1H, s); 4.49 (1H, d, $J$=16.1 Hz); 4.25 (1H, d, $J$=16.1 Hz); 4.02 (3H, s); 3.39 (3H, s). Anal. Calcd for $C_{20}H_{18}ClF_4NO_2$ (415.81): C, 57.77; H, 4.36; Cl, 8.53; N, 3.37. Found: C, 57.54; H, 4.31; Cl, 8.57; N, 3.40.

**3.5.3. 4,6-Dimethoxy-4-trifluoromethyl-1-[4-(trifluoromethyl)styryl]-3,4-dihydroisoquinoline (10c).** This compound was obtained as beige crystals (72%), mp 87–88°C; IR (KBr) 1608; 1325; 1166 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): 7.69 (1H, d, $J$=8.7 Hz); 7.67–7.61 (4H,m); 7.48 (1H, d, $J$=15.9 Hz); 7.30 (1H, d, $J$=15.9 Hz); 7.25 (1H, d, $J$=2.4 Hz); 7.04 (1H, dd, $J$=8.7, 2.4 Hz); 4.28 (1H, d, $J$=17.5 Hz); 4.18 (1H, d, $J$=17.5 Hz); 3.91 (3H, s); 3.33 (3H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 161.9; 161.4; 139.7; 135.1; 132.5; 130.5 (q, $^2J_{CF}$=32.4 Hz); 128.0; 127.5; 126.3; 125.4 (q, $^1J_{CF}$=293.8 Hz); 125.8 (q, $^3J_{CF}$=3.8 Hz); 124.0 (q, $^1J_{CF}$=272.0 Hz); 122.8; 114.9; 112.9; 75.1 (q, $^2J_{CF}$=27.8 Hz); 55.6; 52.6; 49.6. Anal. Calcd for $C_{21}H_{17}F_6NO_2$ (429.36): C, 58.75; H, 3.99; N, 3.26. Found: C, 58.58; H, 3.95; N, 3.30.

Hydrochloride (**10c·HCl**): mp 234–235°C; IR (KBr) 1599; 1423; 1252 $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$): $\delta$: 8.56 (1H, d, $J$=8.9 Hz); 8.31 (1H, d, $J$=16.1 Hz); 8.13 (2H, d, $J$=8.2 Hz); 7.94 (1H, d, $J$=16.1 Hz); 7.90 (2H, d, $J$=8.2 Hz); 7.43 (1H, dd, $J$=8.9, 2.4 Hz); 7.26 (1H, bs); 4.54 (1H, d, $J$=16.5 Hz); 4.27 (1H, d, $J$=16.5 Hz); 4.03 (3H, s); 3.40 (3H, s). Anal. Calcd for $C_{21}H_{18}ClF_6NO_2$ (465.82): C, 54.15; H, 3.89; Cl, 7.61; N, 3.01. Found: C, 53.94; H, 3.86; Cl, 7.57; N, 2.99.

**3.5.4. 4,6-Dimethoxy-1-(4-nitrostyryl)-4-trifluoromethyl-3,4-dihydroisoquinoline (10d).** This compound was obtained as colourless crystals (63%), mp 146–147°C; IR (KBr) 1612; 1514; 1313; 1178 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 8.24 (2H, dd, $J$=8.8, 1.9 Hz); 7.75–7.65 (3H, m); 7.53 (1H, d, $J$=15.9 Hz); 7.37 (1H, d, $J$=15.9 Hz); 7.25

(1H, d, $J$=2.6 Hz); 7.06 (1H, dd, $J$=8.3, 2.6 Hz); 4.32 (1H, d, $J$=17.6 Hz); 4.18 (1H, d, $J$=17.6 Hz); 3.92 (3H, s); 3.34 (3H, s). Anal. Calcd for $C_{20}H_{17}F_3N_2O_4$ (406.36): C, 59.11; H, 4.22; N, 6.89. Found: C, 58.87; H, 4.24; N, 6.83.

Hydrochloride (**10d·HCl**): mp 245–246°C; IR (KBr) 1599; 1345; 1250; 1181 $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$ and $CDCl_3$): $\delta$: 8.48 (1H, d, $J$=8.8 Hz); 8.36 (1H, d, $J$=8.8 Hz); 8.24–8.06 (4H, m); 7.97 (1H, d, $J$=16.1 Hz); 7.40 (1H, dd, $J$=8.8, 2.2 Hz); 7.25 (1H, s); 4.51 (1H, d, $J$=16.5 Hz); 4.02 (1H, d, $J$=16.5 Hz); 4.02 (3H, s); 3.38 (3H, s). Anal. Calcd for $C_{20}H_{18}ClF_3N_2O_4$ (442.82): C, 54.25; H, 4.10; Cl, 8.01; N, 6.33 Found: C, 54.14; H, 4.08; Cl, 8.07; N, 6.23.

**3.5.5. 4-Methoxy-6,7-methylenedioxy-4-trifluoromethyl-1-[4-(trifluoromethyl)styryl]-3,4-dihydroisoquinoline (10e).** This compound was obtained as beige crystals (55%), mp 87–88°C; IR (KBr) 1579; 1389; 1167 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): 7.70–7.60 (4H, m); 7.46 (1H, d, $J$=15.9 Hz); 7.24 (1H, d, $J$=15.9 Hz); 7.19 (1H, s); 7.18 (1H, s); 6.15 (1H, d, $J$=1.3 Hz); 6.09 (1H, d, $J$=1.3 Hz); 4.26 (1H, d, $J$=17.7 Hz); 4.16 (1H, d, $J$=17.7 Hz); 3.30 (3H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 161.0; 150.1; 148.9; 139.5; 135.4; 130.6 (q, $^2J_{CF}$=32.4 Hz); 127.5; 126.2; 125.7 (q, $^3J_{CF}$=5.4 Hz); 125.6; 125.3 (q, $^1J_{CF}$= 287.3 Hz); 124.5; 124.0 (q, $^1J_{CF}$=272.0 Hz); 107.6; 106.4; 102.1; 75.2 (q, $^2J_{CF}$=27.5 Hz); 52.4; 49.6. Anal. Calcd for $C_{21}H_{15}F_6NO_3$ (443.35): C, 56.89; H, 3.41; N, 3.16. Found: C, 56.71; H, 3.39; N, 3.22.

Hydrochloride (**10e·HCl**): mp 248–250°C; IR (KBr) 1623; 1514; 1394; 1325; 1171; 1126 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): $\delta$: 8.15–8.05 (4H, m); 7.90–7.80 (3H, m); 7.32 (1H, m); 6.37 (1H, d, $J$=0.9 Hz); 6.34 (1H, d, $J$=0.9 Hz); 4.45 (1H, d, $J$=17.0 Hz); 4.24 (1H, d, $J$=17.0 Hz); 3.60 (1H, bs); 3.35 (3H, s). Anal. Calcd for $C_{21}H_{16}ClF_6NO_3$ (479.81): C, 52.57; H, 3.36; Cl, 7.39; N, 2.92. Found: C, 52.61; H, 3.38; Cl, 7.38; N, 2.94.

**3.5.6. 4,6-Dimethoxy-1-methyl-4-trifluoromethyl-3,4-dihydroisoquinoline (11a).** This compound was obtained as colourless crystals (81%), mp 203–204°C; IR (KBr) 1609; 1247; 1178 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): 7.56 (1H, d, $J$=8.7 Hz); 7.19 (1H, dd, $J$=2.6, 0.8 Hz); 7.00 (1H, dd, $J$=8.7, 2.6 Hz); 4.12 (1H, dq, $J$=17.5, 1.5 Hz); 4.02 (1H, dq, $J$=17.5, 1.5 Hz); 3.88 (3H, s); 3.27 (3H, s); 2.39 (3H, t, $J$=1.7 Hz); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): 162.7; 161.5; 131.2; 127.8; 125.1 (q, $^1J_{CF}$=287.2 Hz); 123.2; 114.7; 112.4; 74.9 (q, $^2J_{CF}$=27.9 Hz); 55.3; 52.1; 48.9; 23.0. Anal. Calcd for $C_{13}H_{14}F_3NO_2$ (273.25): C, 57.14; H, 5.16; N, 5.13. Found: C, 57.27; H, 5.26; N, 5.11.

Hydrochloride (**11a·HCl**): mp 209–210°C; IR (KBr) 2496; 1608; 1254; 1178 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$ and $CDCl_3$): $\delta$: 8.25 (1H, d, $J$=8.8 Hz); 7.40 (1H, dd, $J$=8.8, 2.5 Hz); 7.19 (1H, d, $J$=2.5 Hz); 4.44 (1H, d, $J$=16.5 Hz); 4.18 (1H, d, $J$=16.5 Hz); 3.99 (3H, s); 3.35 (3H, s); 2.89 (3H, s). Anal. Calcd for $C_{13}H_{15}ClF_3NO_2$ (309.72): C, 50.42; H, 4.88; Cl, 11.45; N, 4.52. Found: C, 50.25; H, 4.85; Cl, 11.46; N, 4.48.

**3.5.7. 4-Methoxy-1-methyl-6,7-methylenedioxy-4-trifluoromethyl-3,4-dihydroisoquinoline (11b).** This compound was obtained as colourless crystals (1.08 g; 75%), mp 203–204°C; IR (KBr) 1606; 1286; 1173 $cm^{-1}$; $^1H$ NMR (400 MHz, $CDCl_3$): 7.13 (1H, q, $J$=0.9 Hz); 7.07 (1H, s); 6.08 (1H, d, $J$=0.9 Hz); 6.06 (1H, d, $J$=1.3 Hz); 4.01 (1H, ddd, $J$=16.8, 3.0, 1.5 Hz); 4.00 (1H, dd, $J$=16.8, 1.5 Hz); 3.24 (3H, s); 2.37 (3H, t, $J$=1.7 Hz); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 162.4; 149.8; 148.9; 125.2 (q, $^1J_{CF}$=287.3 Hz); 125.1; 124.5; 107.3 (q, $^3J_{CF}$=1.9 Hz); 106.4; 102.0; 75.2 (q, $^2J_{CF}$=27.6 Hz); 52.1; 49.1; 23.6. Anal. Calcd for $C_{13}H_{12}F_3NO_3$ (287.24): C, 54.36; H, 4.21; N, 4.88. Found: C, 54.19; H, 4.27; N, 4.79.

Hydrochloride (**11b·HCl**): mp 209–210°C; IR (KBr) 2523; 1501; 1182; 1120 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$ and $CDCl_3$): $\delta$: 7.81 (1H, s); 7.29 (1H, s); 6.36 (1H, d, $J$=0.8 Hz); 6.33 (1H, d, $J$=0.8 Hz); 4.40 (1H, d, $J$=16.6 Hz); 4.14 (1H, dd, $J$=16.6, 0.8 Hz); 3.31 (3H, s); 2.84 (3H, d, $J$=0.6 Hz). Anal. Calcd for $C_{13}H_{13}ClF_3NO_3$ (323.70): C, 48.24; H, 4.05; Cl, 10.95; N, 4.33. Found: C, 48.54; H, 4.02; Cl, 10.94; N, 4.36.

### 3.6. General procedure for synthesis of 1-methyl-4-(trifluoromethyl)isoquinolines (12)

A mixture of 3,4-dihydroisoquinolines **11** (10 mmol) and potassium hydroxide (0.84 g, 15 mmol) in 2-propanol (20 ml) was stirred for 2 h at 50°C. The solvent was evaporated and the residue was triturated with water (10 ml). The crystalline precipitate was filtered and recrystallised from petroleum ether (bp 80–100°C).

**3.6.1. 6-Methoxy-1-methyl-4-(trifluoromethyl)isoquinoline (12a).** This compound was obtained as colourless crystals (2.05 g; 85%), mp 95–96°C; IR (KBr) 1624; 1256; 1165; 1126 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): 8.64 (1H, d, $J$=0.7 Hz); 8.10 (1H, d, $J$=9.0 Hz); 7.35–7.20 (2H, m); 3.98 (3H, s); 2.96 (3H, s); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): 162.7; 161.5; 140.8 (q, $^3J_{CF}$=6.7 Hz); 133.7; 128.0; 124.7 (q, $^1J_{CF}$=272.4 Hz); 122.6; 120.2; 118.0 (q, $^2J_{CF}$=28.9 Hz); 102.1; 55.4; 22.8. Anal. Calcd for $C_{12}H_{10}F_3NO$ (241.21): C, 59.75; H, 4.18; N, 5.81. Found: C, 59.57; H, 4.13; N, 5.76.

**3.6.2. 1-Methyl-6,7-methylenedioxy-4-(trifluoromethyl)-isoquinoline (12b).** This compound was obtained as colourless crystals (2.30 g; 90%), mp 139–141°C; IR (KBr) 1477; 1167; 1112 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 8.58 (1H, s); 7.44 (1H, s); 7.40 (1H, q, $J$=1.8 Hz); 6.17 (2H, s); 2.91 (3H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 161.1; 151.8; 148.6; 139.3 (q, $^3J_{CF}$=6.5 Hz); 130.1; 124.7 (q, $^1J_{CF}$= 273.1 Hz); 124.6; 118.6 (q, $^2J_{CF}$=30.5 Hz); 102.2; 100.6; 23.3. Anal. Calcd for $C_{12}H_8F_3NO_2$ (255.196): C, 56.48; H, 3.16; N, 5.49. Found: C, 56.33; H, 3.14; N, 5.45.

### 3.7. General procedure for synthesis of 1-styryl-4-(trifluoromethyl)isoquinolines (13)

*Method A* (starting from compounds **10**): A mixture of 4-methoxy-1-styryl-4-trifluoromethyl-3,4-dihydroisoquinoline hydrochlorides (**10·HCl**, 3 mmol) and potassium hydroxide (0.42 g, 7.5 mmol) in methanol (10 ml) was stirred for 2 h at ambient temperature. The solvent was evaporated and the residue was triturated with water (10 ml), filtered, washed

with ice-cold ethanol (2×4 ml) and recrystallised from chloroform.

*Method B* (starting from compounds **11**): A mixture of 4-methoxy-1-methyl-4-trifluoromethyl-3,4-dihydroisoquinoline (**11**, 10 mmol), an aromatic aldehyde (11 mmol, see Scheme 3) and acetic anhydride (1.33 g, 13 mmol) was heated for 16 h at 100°C. After cooling the crystalline precipitate was filtered washed with ice-cold ethanol (2×4 ml) and recrystallised from chloroform.

*Method C* (starting from compounds **12**): A mixture of 1-methyl-4-(trifluoromethyl)isoquinoline (**12**, 10 mmol), an aromatic aldehyde (11 mmol, see Scheme 3) and acetic anhydride (1.33 g, 13 mmol) was heated for 16 h at 100°C. After cooling the crystalline precipitate was filtered and washed with ice-cold ethanol (2×4 ml) and recrystallised from chloroform.

Hydrochloride salts were obtained by addition of an equivalent amount of hydrochloric acid in ethanolic solution (25.3 g/100 ml) to a solution of the bases in isopropyl ether (~5 ml/mmol). The hydrochloride salts were recrystallised from ethanol.

Compounds **13** were prepared by all the three methods, the yields are indicated accordingly.

**3.7.1. 6-Methoxy-1-styryl-4-(trifluoromethyl)isoquinoline (13a).** This compound was obtained as light yellow crystals (95, 65, 60%), mp 202–203°C; IR (KBr) 1619; 1411; 1318; 1221; 1100 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 8.79 (1H, s); 8.36 (1H, d, $J$=9.5 Hz); 8.07 (1H, d, $J$=15.8 Hz); 7.92 (1H, d, $J$=15.8 Hz); 7.75–7.65 (2H, m); 7.45–7.30 (5H, m); 3.99 (3H, s); $^{13}C$ NMR (50.3 MHz, $CDCl_3$): 161.7; 157.8; 141.1 (q, $^3J_{CF}$=6.5 Hz); 138.7; 136.4; 135.0; 129.3; 128.9; 127.7; 127.1; 124.8 (q, $^1J_{CF}$=273.1 Hz); 121.8; 120.5; 117.8 (q, $^2J_{CF}$=30.1 Hz); 102.1; 55.6; MS: 329 (37%); 328 (100%); 314 (7%); 310 (3%); 298 (8%); 286 (10%); 285 (37%); 252 (7%). Anal. Calcd for $C_{19}H_{14}F_3NO$ (329.32): C, 69.20; H, 4.28; N, 4.25. Found: C, 69.02; H, 4.25; N, 4.20.

Hydrochloride (**10e·HCl**): mp 189–190°C; IR (KBr) 1618; 1240 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$): 8.92 (1H, d, $J$=9.4 Hz); 8.76 (1H, s); 8.28 (1H, d, $J$=15.7 Hz); 8.15 (1H, d, $J$=15.7 Hz); 7.93–7.89 (2H, m); 7.58 (1H, d, $J$=9.4 Hz); 7.50–7.40 (3H, m); 7.32 (1H, s); 4.00 (3H, s). Anal. Calcd for $C_{19}H_{15}ClF_3NO$ (365.78): C, 62.39; H, 4.13; Cl, 9.69; N, 3.83. Found: C, 62.21; H, 4.17; Cl, 9.60; N, 3.86.

**3.7.2. 1-(4-Fluorostyryl)-6-methoxy-4-(trifluoromethyl)-isoquinoline (13b).** This compound was obtained as light yellow crystals (93, 64, 63%), mp 187–188°C; IR (KBr) 1618; 1510; 1321; 1275; 1130 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): 8.77 (1H, s); 8.31 (1H, d, $J$=9.1 Hz); 8.01 (1H, d, $J$=15.5 Hz); 7.81 (1H, d, $J$=15.5 Hz); 7.70–7.63 (2H, m); 7.35–7.29 (2H, m); 7.11 (2H, t, $J$=8.7 Hz); 3.98 (3H, s); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): 165.2; 161.5; 159.5 (d, $^1J_{CF}$= 221.5 Hz); 141.3 (q, $^3J_{CF}$=6.6 Hz); 136.9; 134.8; 132.6; 129.3; 129.2; 126.8; 124.8 (q, $^1J_{CF}$=273.6 Hz); 121.8; 120.3; 117.7 (q, $^2J_{CF}$=29.3 Hz); 115.8 (d, $^2J_{CF}$=21.0 Hz); 102.1; 55.4; MS: 347 (34%); 346 (100%); 332 (10%); 328 (4%); 316 (9%); 304 (10%); 303 (34%); 252 (8%). Anal. Calcd for $C_{19}H_{13}F_4NO$ (347.32): C, 65.71; H, 3.77; N, 4.03. Found: C, 65.84; H, 3.79; N, 4.08.

Hydrochloride (**13b·HCl**): mp 189–190°C; IR (KBr) 3437; 1615; 1228; 1162 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$): 8.95 (1H, d, $J$=9.5 Hz); 8.77 (1H, s); 8.29 (1H, d, $J$= 15.6 Hz); 8.18 (1H, d, $J$=15.6 Hz); 8.04 (1H, d, $J$= 5.6 Hz); 8.00 (1H, d, $J$=5.6 Hz); 7.56 (1H, dd, $J$=9.5 Hz; $J$=2.4 Hz); 7.33 (2H, t, $J$=8.8 Hz); 7.29 (1H, s); 4.02 (3H, s). Anal. Calcd for $C_{19}H_{14}ClF_4NO$ (383.77): C, 59.46; H, 3.68; Cl, 9.24; N, 3.65. Found: C, 59.19; H, 3.72; Cl, 9.10; N, 3.58.

**3.7.3. 6-Methoxy-4-(trifluoromethyl)-1-[(4-trifluoromethyl)styryl]isoquinoline (13c).** This compound was obtained as light yellow crystals (90, 62, 70%), mp 160–161°C; IR (KBr) 1620; 1409; 1324; 1121 $cm^{-1}$; $^1H$ NMR (250 MHz, $CDCl_3$): 8.80 (1H, s); 8.34 (1H, d, $J$=9.7 Hz); 8.08 (1H, d, $J$=15.6 Hz); 7.98 (1H, d, $J$=15.6 Hz); 7.78 (2H, d, $J$=8.3 Hz); 7.68 (2H, d, $J$=8.3 Hz); 7.37 (1H, s); 7.35 (1H, dd, $J$=9.7, 2.5 Hz); 4.00 (3H, s); $^{13}C$ NMR (62.9 MHz, $CDCl_3$): 161.7; 157.2; 141.4 (q, $^3J_{CF}$=6.5 Hz); 139.8; 136.5; 135.0; 130.1 (q, $^2J_{CF}$=32.5 Hz); 127.8; 126.8; 125.8 (q, $^3J_{CF}$=4.6 Hz); 124.8 (q, $^1J_{CF}$=271.8 Hz); 124.5; 124.2 (q, $^1J_{CF}$=271.0 Hz); 122.6; 120.8; 118.5 (q, $^2J_{CF}$=27.8 Hz); 102.1; 55.6; MS: 397 (57%); 396 (100%); 382 (11%); 378 (9%); 366 (12%); 354 (10%); 353 (36%); 328 (6%); 285 (11%); 252 (16%); 69 (8%). Anal. Calcd for $C_{20}H_{13}F_6NO$ (397.32): C, 60.46; H, 3.30; N, 3.53. Found: C, 60.70; H, 3.27; N, 3.63.

Hydrochloride (**13c·HCl**): mp 189–190°C; IR (KBr) 3433; 1613; 1319; 1132 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$): 8.92 (1H, d, $J$=9.5 Hz); 8.83 (1H, s); 8.47 (1H, d, $J$=15.5 Hz); 8.20–8.13 (3H, s); 7.81 (2H, d, $J$=8.2 Hz); 7.54 (1H, dd, $J$=9.5, 2.4 Hz); 7.29 (1H, s); 4.00 (3H, s). Anal. Calcd for $C_{20}H_{14}ClF_6NO$ (433.78): C, 55.38; H, 3.25; Cl, 8.17; N, 3.23. Found: C, 55.62; H, 3.37; Cl, 8.29; N, 3.19.

**3.7.4. 6-Methoxy-1-(4-nitrostyryl)-4-(trifluoromethyl)-isoquinoline (13d).** This compound was obtained as light yellow crystals (92, 74, 73%) mp 223–224°C; IR (KBr) 1619; 1327; 1106 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): 8.92 (1H, d, $J$=9.3 Hz); 8.87 (1H, s); 8.56 (1H, d, $J$=15.3 Hz); 8.29 (2H, d, $J$=8.7 Hz); 8.21 (2H, d, $J$=8.7 Hz); 8.18 (1H, d, $J$=15.3 Hz); 7.55 (1H, d, $J$=9.3 Hz); 7.30 (1H, s); 4.00 (3H, s).; $^{13}C$ NMR (50.3 MHz, $CDCl_3$): 161.9; 157.4; 147.5; 142.8; 135.7; 134.2; 129.3; 128.7; 127.0; 126.2 (q, $^1J_{CF}$= 274.3 Hz); 124.1; 121.8; 120.7; 116.4 (q, $^2J_{CF}$=32.7 Hz); 101.7; 55.9.; MS: 374 (100%); 373 (99%); 359 (12%); 355 (7%); 344 (12%); 343 (28%); 328 (27%); 327 (68%); 326 (15%); 313 (15%); 285 (29%); 284 (23%); 283 (16%); 252 (26%); 216 (12%); 215 (19%). Anal. Calcd for $C_{19}H_{13}F_3N_2O_3$ (374.32): C, 60.97; H, 3.50; N, 7.48. Found: C, 60.78; H, 3.46; N, 7.46.

Hydrochloride (**13d·HCl**): mp > 250°C; IR (KBr) 2440; 1646; 1345; 1262 $cm^{-1}$; $^1H$ NMR (200 MHz, DMSO-$d_6$): 8.96 (1H, d, $J$=9.5 Hz); 8.86 (1H, s); 8.57 (1H, d, $J$=15.4 Hz); 8.36–8.14 (5H, m); 7.57 (1H, dd, $J$=9.5,

2.2 Hz); 7.30 (1H, s); 3.85 (3H, s). Anal. Calcd for $C_{19}H_{14}ClF_3N_2O_3$ (410.78): C, 55.56; H, 3.44; Cl, 8.63; N, 6.82. Found: C, 55.87; H, 3.29; Cl, 8.56; N, 6.84.

**3.7.5. 6,7-Methylenedioxy-4-(trifluoromethyl)-1-[(4-trifluoromethyl)styryl]isoquinoline (13e).** This compound was obtained as light yellow crystals (92, 64, 68%), mp 180–182°C; IR (KBr) 1615; 1478; 1324; 1104 $cm^{-1}$; $^1H$ NMR (200 MHz, $CDCl_3$): 8.72 (1H, s); 8.04 (1H, d, $J$=15.4 Hz); 7.84 (1H, d, $J$=15.4 Hz); 7.76 (2H, s); 7.69 (2H, s); 7.66 (1H, s); 7.43 (1H, q, $J$=1.8 Hz); 6.20 (2H, s); $^{13}C$ NMR (100.6 MHz, $CDCl_3$): 155.8; 152.0; 149.0; 139.8 (q, $^4J_{CF}$=1.5 Hz); 136.7; 136.2; 131.5; 130.6 (q, $^2J_{CF}$=32.8 Hz); 127.7; 125.8 (q, $^3J_{CF}$=3.8 Hz); 124.6; 124.6 (q, $^1J_{CF}$=273.1 Hz); 124.0 (q, $^1J_{CF}$=272.0 Hz); 124.0; 102.4; 101.1; 100.5 (q, $^3J_{CF}$=2.7 Hz); MS: 411 (37%); 410 (100%); 392 (10%); 382 (13%); 382 (2%); 380 (2%); 353 (11%); 352 (7%); 284 (7%); 283 (7%); 266 (28%); 240 (3%); 171 (16%). Anal. Calcd for $C_{20}H_{11}F_6NO_2$ (411.30): C, 58.40; H, 2.70; N, 3.41. Found: C, 58.22; H, 2.73; N, 3.35.

Hydrochloride (**13e·HCl**): mp 259–260°C; IR (KBr) 1630; 1482; 1320; 1180; 1134 $cm^{-1}$; $^1H$ NMR (400 MHz, DMSO-$d_6$): 8.73 (1H, s); 8.41 (1H, s); 8.38 (1H, d, $J$=15.4 Hz); 8.16 (2H, d, $J$=8.2 Hz); 8.11 (1H, d, $J$=15.4 Hz); 7.80 (2H, d, $J$=8.2 Hz); 7.34 (1H, q, $J$=1.4 Hz); 6.36 (2H, s). Anal. Calcd for $C_{20}H_{12}ClF_6NO_2$ (447.77): C, 53.65; H, 2.70; Cl, 7.92; N, 3.13. Found: C, 53.82; H, 2.63; Cl, 7.87; N, 3.16.

**3.7.6. 4,6-Dihydroxy-1-methyl-4-trifluoromethyl-3,4-dihydroisoquinoline hydrochloride (14·HCl).** A mixture of 4,6-dimethoxy-1-methyl-4-trifluoromethyl-3,4-dihydroisoquinoline (**11a**, 1.37 g, 5 mmol) and a solution (w/w 30%) of hydrobromic acid in glacial acetic acid (20 ml) was refluxed for 6 h. After cooling to room temperature the pH of the mixture was adjusted to 11 by addition of aqueous ammonium hydroxide solution (28%). It was extracted with ethyl acetate (3×40 ml). The combined organic layer were dried ($MgSO_4$) and evaporated. The residue was dissolved in ether (20 ml) and an equivalent amount of hydrochloric acid solution in 2-propanol (25.3 g/100 ml) was added. The crystalline product was filtered to give **14** hydrochloride (0.81 g, 57%) as colourless crystals, mp 242–243°C; IR (KBr) 1612; 1567; 1300; 1240 $cm^{-1}$; $^1H$ NMR (400 MHz, $D_2O$): 8.01 (1H, d, $J$=8.9 Hz); 7.27 (1H, d, $J$=2.4 Hz); 7.08 (1H, dd, $J$=8.9, 2.4 Hz); 4.29 (1H, d, $J$=15.9 Hz); 3.97 (1H, d, $J$=15.9 Hz); 2.75 (3H, s); $^{13}C$ NMR (100.6 MHz, DMSO-$d_6$): 174.3; 166.1; 137.3; 134.5; 117.4; 116.8; 114.2; 69.2 (q, $^2J_{CF}$=29.0 Hz); 45.7; 19.4. Anal. Calcd for $C_{11}H_{11}ClF_3NO_2$ (281.66): C, 46.91; H, 3.94; Cl, 12.59; N, 4.97. Found: C, 46.65; H, 3.90; Cl, 12.64; N, 4.94.

**3.7.7. 6-Hydroxy-1-methyl-4-(trifluoromethyl)isoquinoline (15).** A mixture of dihydroisoquinoline (**11a**, 1.37 g, 5 mmol) and concentrated sulphuric acid (6 ml) was heated with stirring for 6 h at 110°C. After cooling to room temperature the pH of the mixture was adjusted to 11 by addition of aqueous ammonium hydroxide solution (28%). The mixture was extracted with ethyl acetate (3×40 ml). The combined organic layer were dried ($MgSO_4$) and evaporated. The residue was purified by column chromatography (eluent: toluene/ethyl acetate=95:5) to give **15** (0.72 g, 63%), mp 243–244°C; IR (KBr) 1609; 1515; 1248; 1126 $cm^{-1}$; $^1H$ NMR (250 MHz, DMSO-$d_6$): 10.85 (1H, bs); 8.58 (1H, s); 8.26 (1H, d, $J$=9.0 Hz); 7.32 (1H, dd, $J$=9.0, 2.2 Hz); 7.28 (1H, t, $J$=2.0 Hz); 2.89 (3H, s); $^{13}C$ NMR (62.9 MHz, DMSO-$d_6$ and $CDCl_3$): 163.3; 160.5; 140.4 (q, $^3J_{CF}$=6.7 Hz); 132.9; 129.5; 124.9 (q, $^1J_{CF}$= 273.5 Hz); 121.3; 120.4; 116.0 (q, $^2J_{CF}$=29.3 Hz); 104.4; 22.7. Anal. Calcd for $C_{11}H_8F_3NO$ (227.19): C, 58.16; H, 3.55; N, 6.17. Found: C, 57.92; H, 3.65; N, 6.09.

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