

László Poszavác and Gyula Simig*

Chemical Research Division, EGIS Pharmaceuticals Ltd., P. O. Box 100, H-1475 Budapest, Hungary
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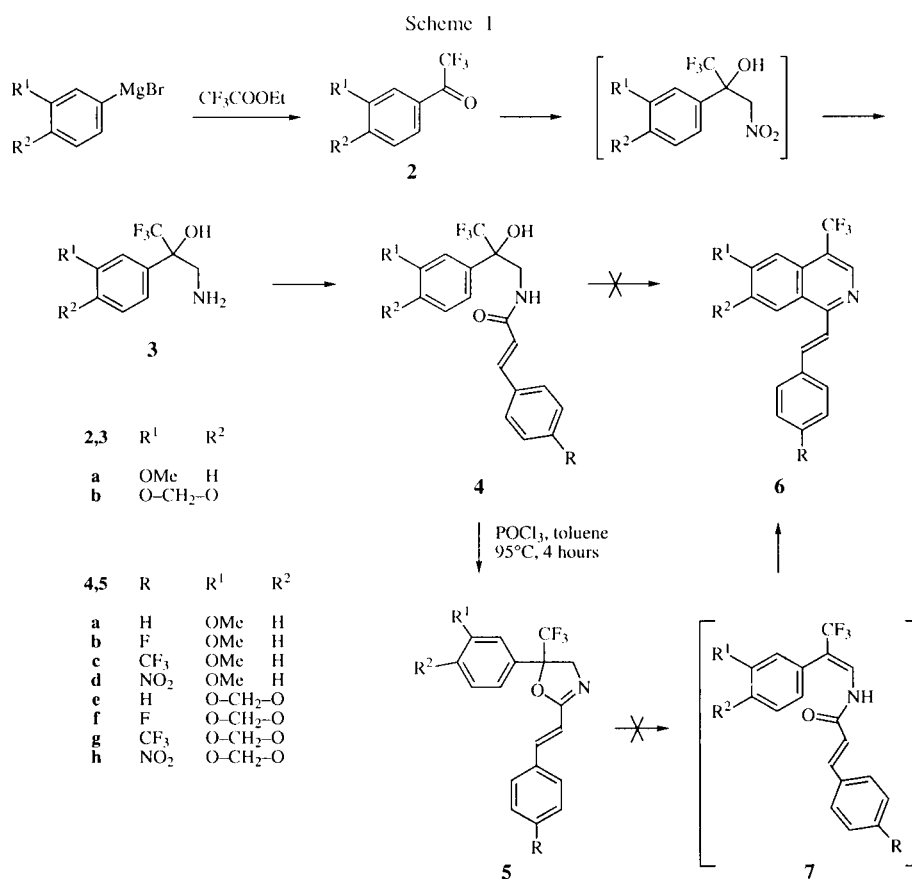
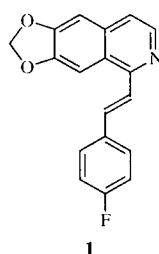
Cyclization of *N*-acyl-2-hydroxy-2-(trifluoromethyl)arylethylamines **4** under Pictet-Gams conditions afforded 2-oxazolines **5** instead of the expected isoquinolines **6**. The effect of the trifluoromethyl group on the result of the reaction is discussed.

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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.

We intended to carry out the synthesis of the target compounds using Pictet-Gams synthesis of isoquinolines. *N*-Acyl-2-hydroxy-2-(trifluoromethyl)arylethylamines required for the Pictet-Gams cyclization were obtained as outlined in Scheme 1. α,α,α -Trifluoroacetophenones **2** were prepared by treatment of ethyl trifluoroacetate with the corresponding arylmagnesium bromide. Potassium carbonate catalyzed addition of nitromethane to acetophenones **2** followed by catalytic hydrogenation of the nitro group gave 2-hydroxy-2-(trifluoromethyl)arylethylamines



3. *N*-Acylation of amines **3** with the corresponding cinnamoyl chlorides afforded amides **4**. Cyclization of amides **4** under Pictet-Gams conditions (phosphorus oxychloride, toluene, 95°C, 4 hours) led unexpectedly to the formation of 2-oxazolines **5** instead of isoquinolines **6**. Amides related to **4** without trifluoromethyl substituent are known to afford isoquinolines under similar conditions [2].

All the spectroscopic and analytical data prove the 2-oxazoline structure of the products. The most characteristic signal of the proton nuclear magnetic resonance spectrum is the AB quartet at 4-5 ppm which excludes the isoquinoline (**6**) structure and is assigned to the CH₂ moiety of the 2-oxazoline ring. Further support for the 2-oxazoline structure came from the single crystal X-ray analysis compound **5f**, as shown in Figure 1 [3]. The crystal structure determination confirmed the 2-oxazoline of structure of compound **5f**. The trifluoromethyl group is

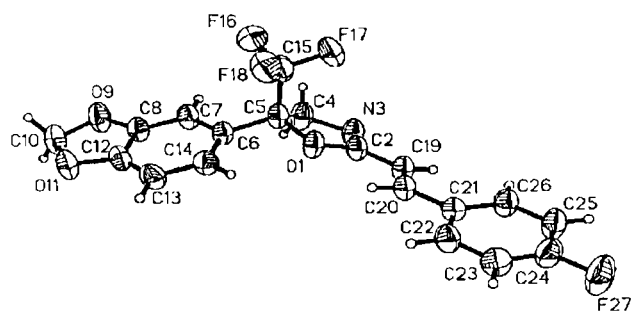


Figure 1. A perspective view of compound **5f** with 50% probability ellipsoids. The H atoms are shown as circles of a small arbitrary diameter.

linked axially. In Table 1 is a summary of crystal data, data collection parameters, and structure refinement statistics. Table 2 is a list of non-hydrogen atom positions and equivalent isotropic thermal parameters. Tables 3, 4, and 5 list the bond lengths, valence angles, and torsion angles, respectively.

The intermediacy of 2-oxazolines in Pictet-Gams cyclization has been demonstrated [4,5]. The primarily formed 2-oxazolines were converted to isoquinolines by heating with phosphorus pentoxide at the higher temperature of boiling decalin. It is commonly accepted [6] that this transformation proceeds *via* unsaturated amides (e.g. **7**). However, in our case attempts to convert 2-oxazolines **5** into isoquinolines **6** under the conditions mentioned above were unsuccessful. The unusual behaviour can be attributed to the presence of the trifluoromethyl group at the 5-position of the 2-oxazoline ring. Considering the tertiary alcohol structure of the substrates and the acidic reaction conditions, an E1-like mechanism can be expected to be involved in the transformation of 2-oxazolines **5** to unsaturated amides **7**. However, the electron-withdrawing effect of the trifluoromethyl group prevents the introductory

Table 1

Summary of Crystal Data and Experimental Conditions for **5f**

Formula	C ₁₉ H ₁₃ F ₄ NO ₃
Formula weight	379.30
Temperature	293(2) K
Wavelength	1.54180 Å
Crystal system	Triclinic
Space group	P-1
Unit cell dimensions	a = 9.594(1) Å b = 10.006(1) Å c = 10.786(2) Å α = 62.45(1) deg. β = 65.38(1) deg. γ = 85.99(1) deg.
Volume	824.8(2) Å ³
Molecules/unit cell	2
Density (calculated)	1.527 Mg/m ³
Absorption coefficient	1.162 mm ⁻¹
F (000)	388
Crystal size	0.50x0.30x0.30 mm
Theta range for data collection	5.04 to 75.70 deg.
Index ranges	0 ≤ h ≤ 12, -12 ≤ k ≤ 12, -12 ≤ l ≤ 13
Reflections collected	3767
Independent reflections	3433 [R(int) = 0.0115]
Refinement method	Full-matrix least-squares on F ²
Data / restraints / parameters	3433 / 0 / 245
Goodness-of-fit on F ²	1.108
Final R indices [I > 2σ(I)]	R1 = 0.0391, wR2 = 0.1155
R indices (all data)	R1 = 0.0419, wR2 = 0.1179
Extinction coefficient	0.0063(7)
Largest diff. peak and hole	0.225 and -0.192 e. Å ⁻³

Table 2

Atomic Coordinates (x10⁴) and Equivalent Isotropic Displacement Coefficients (Å² × 10³) for the Non-hydrogen Atoms of **5f**

Atom	x/a	y/b	z/c	U (eq)
O(1)	3752(1)	7423(1)	6511(1)	47(1)
C(2)	2383(2)	6460(2)	7651(2)	43(1)
N(3)	2465(2)	5060(1)	8393(2)	52(1)
C(4)	4103(2)	4886(2)	7739(2)	52(1)
C(5)	4976(2)	6541(2)	6668(2)	43(1)
C(6)	6259(2)	6886(2)	5095(2)	42(1)
C(7)	7357(2)	5889(2)	5016(2)	48(1)
C(8)	8579(2)	6312(2)	3593(2)	46(1)
O(9)	9814(1)	5555(2)	3234(1)	65(1)
C(10)	10757(2)	6466(2)	1619(2)	62(1)
O(11)	10077(1)	7791(2)	1046(1)	63(1)
C(12)	8730(2)	7639(2)	2289(2)	47(1)
C(13)	7666(2)	8615(2)	2333(2)	51(1)
C(14)	6416(2)	8214(2)	3777(2)	47(1)
C(15)	5595(2)	7057(2)	7501(2)	55(1)
F(16)	6729(1)	6304(2)	7775(1)	79(1)
F(17)	4492(1)	6823(2)	8884(1)	77(1)
F(18)	6163(1)	8539(1)	6687(1)	73(1)
C(19)	996(2)	7176(2)	7899(2)	45(1)
C(20)	1010(2)	8647(2)	7025(2)	43(1)
C(21)	-318(2)	9474(2)	7232(2)	41(1)
C(22)	-185(2)	10933(2)	6058(2)	48(1)
C(23)	-1395(2)	11772(2)	6201(2)	54(1)
C(24)	-2728(2)	11124(2)	7546(2)	56(1)
C(25)	-2920(2)	9690(2)	8746(2)	59(1)
C(26)	-1703(2)	8864(2)	8580(2)	50(1)
F(27)	-3920(1)	11951(2)	7721(2)	87(1)

Standard deviations in parentheses refer to the least significant digits.

Table 3

Bond Distances for **5f**. Standard deviations in parentheses refer to the least significant digits

Atom	Atom	Distance (Å)	Atom	Atom	Distance (Å)
O1	C2	1.379(2)	O11	C12	1.373(2)
O1	C5	1.438(2)	C12	C13	1.364(2)
C2	N3	1.269(2)	C13	C14	1.399(2)
C2	C19	1.449(2)	C15	F18	1.333(2)
N3	C4	1.467(2)	C15	F16	1.336(2)
C4	C5	1.548(2)	C15	F17	1.340(2)
C5	C6	1.513(2)	C19	C20	1.328(2)
C5	C15	1.531(2)	C20	C21	1.465(2)
C6	C14	1.383(2)	C21	C22	1.389(2)
C6	C7	1.403(2)	C21	C26	1.392(2)
C7	C8	1.370(2)	C22	C23	1.382(2)
C8	O9	1.375(2)	C23	C24	1.364(2)
C8	C12	1.375(2)	C24	F27	1.364(2)
O9	C10	1.421(2)	C24	C25	1.374(2)
C10	O11	1.421(2)	C25	C26	1.381(2)

Table 4

Valence Angles for **5f**. Standard deviations in parentheses refer to the least significant digits

Atom	Atom	Atom	Angle (°)	Atom	Atom	Atom	Angle (°)
C2	O1	C5	106.14 (10)	C13	C12	C8	121.91(14)
N3	C2	O1	117.29(13)	O11	C12	C8	109.67(14)
N3	C2	C19	126.83(13)	C12	C13	C14	116.83(14)
O1	C2	C19	115.86(12)	C6	C14	C13	121.66(14)
C2	N3	C4	106.93(12)	F18	C15	F16	107.1(2)
N3	C4	C5	104.39(12)	F18	C15	F17	106.5(2)
O1	C5	C6	111.09(12)	F16	C15	F17	106.30(14)
O1	C5	C15	104.60(12)	F18	C15	C5	112.31(14)
C6	C5	C15	109.57(13)	F16	C15	C5	112.07(14)
O1	C5	C4	102.86(11)	F17	C15	C5	112.17(14)
C6	C5	C4	116.81(13)	C20	C19	C2	122.73(14)
C15	C5	C4	111.08(14)	C19	C20	C21	126.36(14)
C14	C6	C7	120.43(13)	C22	C21	C26	118.59(14)
C14	C6	C5	120.72(13)	C22	C21	C20	119.13(13)
C7	C6	C5	118.67(13)	C26	C21	C20	122.26(13)
C8	C7	C6	116.90(14)	C23	C22	C21	121.53(14)
C7	C8	O9	127.63(14)	C24	C23	C22	117.6(2)
C7	C8	C12	122.26(14)	F27	C24	C23	118.4(2)
O9	C8	C12	110.09(13)	F27	C24	C25	118.3(2)
C8	O9	C10	105.57(13)	C23	C24	C25	123.3(2)
O11	C10	O9	108.76(13)	C24	C25	C26	118.3(2)
C12	O11	C10	105.88(12)	C25	C26	C21	120.6(2)
C13	C12	O11	128.4(2)				

step (the heterolysis of the carbon-oxygen bond) of the EI-like elimination reaction by destabilizing the incipient positive charge in the benzylic position. As a consequence, transformation of 2-oxazolines **5** to isoquinolines **6** cannot occur.

Thus, our study has demonstrated that the cyclization of *N*-acyl-2-hydroxy-2-(trifluoromethyl)arylethylamines under Pictet-Gams conditions leads to 2-oxazolines due to the presence of the trifluoromethyl group. Further experiments for the synthesis of type **6** isoquinolines are underway in our laboratory.

Table 5

Torsion Angles for **5f**.

Atom	Atom	Atom	Atom	Angle(°)
C5	O1	C2	N3	-9.15(0.19)
C5	O1	C2	C19	169.28(0.14)
O1	C2	N3	C4	-1.16(0.21)
C19	C2	N3	C4	-179.40(0.16)
C2	N3	C4	C5	10.15(0.19)
C2	O1	C5	C6	139.92(0.13)
C2	O1	C5	C15	-101.96(0.13)
C2	O1	C5	C4	14.19(0.15)
N3	C4	C5	O1	-14.84(0.17)
N3	C4	C5	C6	-136.77(0.14)
N3	C4	C5	C15	96.57(0.16)
O1	C5	C6	C14	19.65(0.20)
C15	C5	C6	C14	-95.43(0.17)
C4	C5	C6	C14	137.18(0.16)
O1	C5	C6	C7	-165.13(0.14)
C15	C5	C6	C7	79.79(0.18)
C4	C5	C6	C7	-47.61(0.20)
C14	C6	C7	C8	0.97(0.24)
C5	C6	C7	C8	-174.26(0.15)
C6	C7	C8	O9	177.94(0.16)
C6	C7	C8	C12	-0.67(0.25)
C7	C8	O9	C10	-179.46(0.18)
C12	C8	O9	C10	-0.71(0.20)
C8	O9	C10	O11	1.69(0.20)
O9	C10	O11	C12	-2.03(0.20)
C10	O11	C12	C13	179.96(0.18)
C10	O11	C12	C8	1.60(0.19)
C7	C8	C12	C13	-0.23(0.27)
O9	C8	C12	C13	-179.06(0.15)
C7	C8	C12	O11	178.26(0.15)
O9	C8	C12	O11	-0.58(0.20)
O11	C12	C13	C14	-177.37(0.16)
C8	C12	C13	C14	0.81(0.26)
C7	C6	C14	C13	-0.40(0.25)
C5	C6	C14	C13	174.73(0.15)
C12	C13	C14	C6	-0.49(0.25)
O1	C5	C15	F18	-61.07(0.16)
C6	C5	C15	F18	58.08(0.17)
C4	C5	C15	F18	-171.37(0.13)
O1	C5	C15	F16	178.34(0.12)
C6	C5	C15	F16	-62.50(0.17)
C4	C5	C15	F16	68.05(0.17)
O1	C5	C15	F17	58.85(0.17)
C6	C5	C15	F17	178.01(0.13)
C4	C5	C15	F17	-51.44(0.18)
N3	C2	C19	C20	-177.40(0.17)
O1	C2	C19	C20	4.34(0.24)
C2	C19	C20	C21	-177.34(0.15)
C19	C20	C21	C22	-168.00(0.16)
C19	C20	C21	C26	13.43(0.25)
C26	C21	C22	C23	-0.53(0.25)
C20	C21	C22	C23	-179.16(0.15)
C21	C22	C23	C24	0.56(0.27)
C22	C23	C24	F27	178.41(0.16)
C22	C23	C24	C25	-0.16(0.30)
F27	C24	C25	C26	-178.81(0.17)
C23	C24	C25	C26	-0.24(0.31)
C24	C25	C26	C21	0.27(0.29)
C22	C21	C26	C25	0.11(0.26)
C20	C21	C26	C25	178.69(0.16)

EXPERIMENTAL

Melting points were determined on a Büchi 535 apparatus and were not corrected. The IR spectra were recorded on an Aspect 2000 computer-controlled Bruker IFS-113v vacuum optic FT spectrometer, using potassium bromide pellets of solids or films of liquids. The ^1H and ^{13}C NMR spectra were taken on a Bruker WM 250 FT, or a Varian Gemini-200, or a Varian Unity Inova 400 spectrometer, in deuteriochloroform and dimethyl- d_6 sulfoxide as the solvents. Chemical shifts were reported as δ values (ppm) down field from internal tetramethylsilane.

Synthesis of α,α,α -Trifluoro-4-methoxyacetophenone (**2a**).

To a solution of ethyl trifluoroacetate (35.5 g, 0.25 mol) in tetrahydrofuran (100 ml) was added a solution of 4-methoxyphenylmagnesium bromide [prepared from magnesium (6.3 g, 0.26 mol) and (4-methoxy)bromobenzene (46.8 g, 0.25 mol) in tetrahydrofuran (200 ml)] at -70°C and stirred for 1 hour. It was allowed to reach 0°C and aqueous 2 M hydrochloric acid (100 ml) was added. The organic layer was separated, dried on magnesium sulfate and evaporated. The residual oil was distilled *in vacuo* to give **2a** (39.8 g, 78%) as colourless oil, bp $83\text{--}85^\circ\text{C}$ (12 mm Hg). ^1H NMR (deuteriochloroform, δ , ppm): 7.70–7.20 (4H, m), 3.88 (3H, s). (The preparation of this compound is described in the literature starting from trifluoroacetic acid [7] or *N*-(trifluoroacetyl)pyridine [8].)

Synthesis of α,α,α -Trifluoro-3,4-methylenedioxyacetophenone (**2b**).

In the preceding manner, trifluoroacetate (35.5 g, 0.25 mol) and 3,4-methylenedioxyphenylmagnesium bromide [prepared from magnesium (6.1 g, 0.25 mol) and (3,4-methylenedioxy)bromobenzene (50.3 g, 0.25 mol)] gave **2b** (34.1 g, 63%) as colourless oil, bp $84\text{--}85^\circ\text{C}$ (2.8 mm Hg); IR (potassium bromide): ν 1702 cm^{-1} ; ^1H NMR (deuteriochloroform, δ , ppm): 7.68 (1H, dd, $J = 8.3, 1.2$ Hz), 7.45 (1H, d, $J = 1.2$ Hz), 6.90 (1H, d, $J = 8.3$ Hz), 6.10 (2H, s).

Anal. Calcd. for $\text{C}_9\text{H}_5\text{F}_3\text{O}_3$ (218.13): C, 49.56; H, 2.31. Found: C, 49.43; H, 2.20.

Synthesis of 2-Hydroxy-2-trifluoromethyl-(4-methoxyphenyl)ethylamine (**3a**)

A suspension of **2a** (10.2 g, 50 mmol), nitromethane (25 ml) and potassium carbonate (6.9 g, 50 mmol) was stirred at room temperature for 2 hours. An aqueous acetic acid (50 ml:3 ml) solution was added to the reaction mixture at 0°C and the layers were separated. The aqueous layer was extracted with dichloromethane (2 x 30 ml). The organic layers were combined, dried on magnesium sulfate and evaporated. The solution of the residue in methanol (100 ml) was hydrogenated in the presence of palladium on activated charcoal under 7×10^5 Pascal hydrogen for 8 hours at room temperature. After removal of the catalyst by filtration and evaporation of the solvent, the residue was distilled *in vacuo* to afford **3a** (9.2 g, 78%) as colourless oil, bp $120\text{--}121^\circ\text{C}$ (1.6 mm Hg); ^1H NMR (deuteriochloroform, δ , ppm): 7.29 (1H, t, $J = 7.9$ Hz), 7.18 (1H, s), 7.10 (1H, dd, $J = 7.9, 0.8$ Hz), 6.88 (1H, m), 3.81 (3H, s), 3.46 (1H, d, $J = 13.3$ Hz), 3.02 (1H, dd, $J = 13.3, 0.9$ Hz), 2.87 (3H, bs).

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{F}_3\text{NO}_2$ (235.21): C, 51.07; H, 5.14; N, 5.96. Found: C, 51.12; H, 5.09; N, 5.98.

To a mixture of **3a** (7.1 g, 30 mmol) in hexane was added hydrogen chloride (36 mmol) in ethanol (5.8 ml). The crystalline

product was filtered to afford **3a** hydrochloride (6.9 g, 85%), mp $159\text{--}160^\circ\text{C}$, ^1H NMR (dimethyl- d_6 sulfoxide, δ , ppm): 8.17 (3H, bs), 7.59 (1H, bs), 7.39 (1H, t, $J = 8.1$ Hz), 7.20 (2H, m), 7.02 (1H, dd, $J = 8.1, 2.1$ Hz), 3.79 (3H, s), 3.65 (1H, d, $J = 13.6$ Hz), 3.48 (1H, d, $J = 13.6$ Hz); ^{13}C NMR (dimethyl- d_6 sulfoxide, δ , ppm): 159.3, 135.8, 129.7, 124.8 (q, $^1J_{\text{CF}} = 287.0$ Hz), 119.1, 114.6, 113.2, 74.6 (q, $^2J_{\text{CF}} = 27.3$ Hz); 55.3, 42.4.

Anal. Calcd. for $\text{C}_{10}\text{H}_{13}\text{ClF}_3\text{NO}_2$ (271.67): C, 44.21; H, 4.82; Cl, 13.05; N, 5.16. Found: C, 44.01; H, 4.86; Cl, 12.96; N, 5.21.

Synthesis of 2-Hydroxy-2-trifluoromethyl-(3,4-methylenedioxyphenyl)-ethylamine hydrochloride (**3b** • HCl)

The amine **3b** obtained from **2b** (10.9 g, 50 mmol) in the preceding manner could not be purified by distillation, **3b** hydrochloride (10.6 g, 74%) was prepared in analytically pure form as described above, mp $203\text{--}204^\circ\text{C}$. ^1H NMR (dimethyl- d_6 sulfoxide, δ , ppm): 8.16 (3H, bs), 7.20 (1H, s), 7.15 (1H, d, $J = 8.2$ Hz), 6.99 (1H, d, $J = 8.2$ Hz), 6.08 (2H, s), 3.65 (1H, d, $J = 13.5$ Hz), 3.44 (1H, d, $J = 13.5$ Hz), 2.35 (1H, bs); ^{13}C NMR (dimethyl- d_6 sulfoxide, δ , ppm): 148.0, 147.6, 127.7, 124.8 (q, $^1J_{\text{CF}} = 287.0$ Hz), 121.1, 108.2, 107.6, 101.5, 74.5 (q, $^2J_{\text{CF}} = 28.2$ Hz), 42.4.

Anal. Calcd. for $\text{C}_{10}\text{H}_{11}\text{ClF}_3\text{NO}_3$ (285.65): C, 42.05; H, 3.88; Cl, 12.41; N, 4.90. Found: C, 41.80; H, 3.92; Cl, 12.29; N, 4.96.

General Procedure for the Synthesis of Amides **4**.

To a stirred mixture of amine **3** (50 mmol) in ether (20 ml) and sodium carbonate (5.3 g, 50 mmol) in water (50 ml) was added a solution of substituted cinnamoyl chloride (50 mmol) in ether (50 ml) at 0°C . After stirring 2 hours at room temperature, the resulting crystalline precipitate was filtered and recrystallized from a mixture of 2-propanol and water.

N-Cinnamoyl-2-hydroxy-2-trifluoromethyl-(4-methoxyphenyl)-ethylamine (**4a**).

This compound was obtained as colourless crystals (16.4 g, 90%), mp $137\text{--}138^\circ\text{C}$; IR (potassium bromide): ν 1605 cm^{-1} ; ^1H NMR (deuteriochloroform, δ , ppm): 7.63 (1H, d, $J = 15.6$ Hz), 7.50–7.25 (7H, m), 7.16 (1H, d, $J = 8.1$ Hz), 6.90 (1H, ddd, $J = 8.1, 2.6, 0.7$ Hz), 6.29 (1H, d, $J = 15.6$ Hz), 6.01 (2H, bs), 4.27 (1H, dd, $J = 14.8, 6.2$ Hz), 3.85 (1H, dd, $J = 14.8, 6.2$ Hz), 3.82 (3H, s); ^{13}C NMR (dimethyl- d_6 sulfoxide, δ , ppm): 166.6, 159.1, 139.8, 137.9, 134.8, 129.7, 129.2, 129.0, 127.8, 125.4 (q, $^1J_{\text{CF}} = 287.3$ Hz), 121.5, 119.2, 113.8, 113.2, 76.8 (q, $^2J_{\text{CF}} = 26.7$ Hz), 55.2, 43.3.

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{F}_3\text{NO}_3$ (365.36): C, 62.46; H, 4.97; N, 3.83. Found: C, 62.25; H, 4.99; N, 3.81.

N-(4-Fluorocinnamoyl)-2-hydroxy-2-trifluoromethyl-(4-methoxyphenyl)-ethylamine (**4b**).

This compound was obtained as colourless crystals (13.3 g, 69%), mp $135\text{--}136^\circ\text{C}$; IR (potassium bromide): ν 1614 cm^{-1} ; ^1H NMR (deuteriochloroform, δ , ppm): 7.55 (1H, d, $J = 15.6$ Hz), 7.42–7.35 (2H, m), 7.31 (1H, t, $J = 8.1$ Hz), 7.26–7.24 (1H, m), 7.18–7.14 (1H, m), 7.01 (2H, t, $J = 8.6$ Hz), 6.89 (1H, ddd, $J = 8.1, 2.6, 0.9$ Hz), 6.21 (1H, d, $J = 15.6$ Hz), 6.19 (1H, bs), 6.11 (1H, s), 4.24 (1H, dd, $J = 14.7, 6.2$ Hz), 3.88 (1H, dd, $J = 14.7, 6.2$ Hz), 3.79 (3H, s); ^{13}C NMR (dimethyl- d_6 sulfoxide, δ , ppm): 169.2, 163.9 (d, $^1J_{\text{CF}} = 251.4$ Hz), 159.8, 142.2, 137.7, 130.4 (d, $^4J_{\text{CF}} = 3.4$ Hz), 129.9 (d, $^3J_{\text{CF}} = 8.4$ Hz), 129.5, 125.0 (q, $^1J_{\text{CF}} = 286.1$ Hz), 118.7, 118.2, 116.1 (d, $^2J_{\text{CF}} = 21.7$ Hz), 114.1, 112.9, 77.6 (q, $^2J_{\text{CF}} = 27.5$ Hz), 55.3, 46.2.

Anal. Calcd. for $C_{19}H_{17}F_4NO_3$ (383.35): C, 59.53; H, 4.47; N, 3.65. Found: C, 59.31; H, 4.46; N, 3.61.

N-[(4-Trifluoromethyl)cinnamoyl]-2-hydroxy-2-trifluoromethyl-(4-methoxyphenyl)ethylamine (**4c**).

This compound was obtained as colourless crystals (17.5 g, 81%), mp 150-151°C; ir (potassium bromide): ν 1605 cm^{-1} ; 1H nmr (deuteriochloroform, δ , ppm): 7.61 (1H, d, $J = 15.6$ Hz), 7.59 (2H, d, $J = 8.4$ Hz), 7.51 (2H, d, $J = 8.4$ Hz), 7.32 (1H, t, $J = 8.1$ Hz), 7.25-7.22 (1H, m), 7.17-7.13 (1H, m), 6.91 (1H, ddd, $J = 8.1, 2.6, 0.9$ Hz), 6.35 (1H, d, $J = 15.6$ Hz), 6.06 (1H, t, $J = 6.5$ Hz), 5.66 (1H, s), 4.25 (1H, dd, $J = 14.7, 6.5$ Hz), 3.89 (1H, dd, $J = 14.7, 6.5$ Hz), 3.81 (3H, s); ^{13}C nmr (dimethyl- d_6 sulfoxide, δ , ppm): 166.0, 159.1, 138.9 (q, $^4J_{CF} = 1.5$ Hz), 138.0, 137.8, 129.5 (q, $^2J_{CF} = 32.0$ Hz), 129.2, 128.3, 125.9 (q, $^3J_{CF} = 3.8$ Hz), 125.4 (q, $^1J_{CF} = 287.3$ Hz), 124.4, 124.2 (q, $^1J_{CF} = 272.0$ Hz), 119.1, 113.8, 113.2, 76.7 (q, $^2J_{CF} = 26.3$ Hz), 55.2, 43.3.

Anal. Calcd. for $C_{20}H_{17}F_6NO_3$ (433.35): C, 55.43; H, 3.95; N, 3.23. Found: C, 55.23; H, 3.93; N, 3.20.

N-(4-Nitrocinnamoyl)-2-hydroxy-2-trifluoromethyl-(4-methoxyphenyl)-ethylamine (**4d**).

This compound was obtained as yellow crystals (15.5 g, 75%), mp 133-134°C; ir (potassium bromide): ν 1614 cm^{-1} ; 1H nmr (deuteriochloroform, δ , ppm): 8.20 (2H, d, $J = 8.8$ Hz), 7.93 (1H, t, $J = 5.9$ Hz), 7.62 (1H, d, $J = 8.8$ Hz), 7.60 (1H, d, $J = 15.8$ Hz), 7.31 (1H, t, $J = 8.1$ Hz), 7.25-7.23 (1H, m), 7.22-7.18 (1H, m), 6.89 (1H, ddd, $J = 8.1, 2.6, 0.8$ Hz), 6.71 (1H, bs), 6.63 (1H, d, $J = 15.8$ Hz), 4.04 (2H, m); ^{13}C nmr (deuteriochloroform, δ , ppm): 168.1, 159.8, 148.4, 140.4, 140.3, 137.4, 129.6, 128.6, 124.9 (q, $^1J_{CF} = 286.5$ Hz), 124.1, 122.8, 118.6, 114.0, 113.0, 78.0 (q, $^2J_{CF} = 27.8$ Hz), 55.3, 46.0.

Anal. Calcd. for $C_{19}H_{17}F_3N_2O_5$ (410.35): C, 55.61; H, 4.18; N, 6.83. Found: C, 55.44; H, 4.20; N, 6.65.

N-Cinnamoyl-2-hydroxy-2-trifluoromethyl-(3,4-methylenedioxyphenyl)-ethylamine (**4e**).

This compound was obtained as colourless crystals (16.1g, 85%), mp 174-175°C; ir (potassium bromide): ν 1614 cm^{-1} ; 1H nmr (deuteriochloroform, δ , ppm): 7.64 (1H, d, $J = 15.6$ Hz), 7.46-7.40 (2H, m), 7.40-7.33 (3H, m), 7.13 (1H, s), 7.09 (1H, d, $J = 8.2$ Hz), 6.82 (1H, d, $J = 8.2$ Hz), 6.31 (1H, d, $J = 15.6$ Hz), 5.97 (2H, s), 5.96 (2H, bs), 4.23 (1H, dd, $J = 14.7, 6.4$ Hz), 3.81 (1H, dd, $J = 14.7, 6.4$ Hz); ^{13}C nmr (dimethyl- d_6 sulfoxide, δ , ppm): 166.6, 147.4, 147.2, 139.8, 134.7, 129.9, 129.6, 128.9, 127.7, 125.3 (q, $^1J_{CF} = 292.4$ Hz), 121.3, 120.8, 107.8, 107.5, 101.3, 76.6 (q, $^2J_{CF} = 27.2$ Hz), 43.3.

Anal. Calcd. for $C_{19}H_{16}F_3NO_4$ (379.34): C, 60.16; H, 4.25; N, 3.69. Found: C, 60.21; H, 4.20; N, 3.67.

N-(4-Fluorocinnamoyl)-2-hydroxy-2-trifluoromethyl-(3,4-methylenedioxy-phenyl)ethylamine (**4f**).

This compound was obtained as colourless crystals (15.4 g, 77%), mp 175-176°C; ir (potassium bromide): ν 1620 cm^{-1} ; 1H nmr (deuteriochloroform, δ , ppm): 8.14 (1H, t, $J = 5.5$ Hz), 7.65-7.59 (2H, m), 7.46 (1H, d, $J = 15.8$ Hz), 7.24 (2H, t, $J = 8.8$ Hz), 7.14-7.10 (3H, m), 6.95 (1H, d, $J = 8.0$ Hz), 6.71 (1H, d, $J = 15.8$ Hz), 6.05 (2H, s), 4.12 (1H, dd, $J = 14.2, 6.6$ Hz), 3.87 (1H, dd, $J = 14.2, 4.7$ Hz); ^{13}C nmr (dimethyl- d_6 sulfoxide, δ , ppm): 166.6, 162.9 (d, $^1J_{CF} = 247.0$ Hz), 147.4 (d, $^3J_{CF} = 9.0$ Hz), 138.6, 131.4, 129.9, 125.4 (q, $^1J_{CF} = 287.4$ Hz), 121.3, 120.9, 116.0 (d, $^2J_{CF} = 21.8$ Hz), 107.9, 107.6, 101.4, 76.7 (q, $^2J_{CF} = 27.0$ Hz), 43.3.

Anal. Calcd. for $C_{19}H_{15}F_4NO_4$ (397.33): C, 57.44; H, 3.81; N, 3.53. Found: C, 57.55; H, 3.83; N, 3.60.

N-[(4-Trifluoromethyl)cinnamoyl]-2-hydroxy-2-trifluoromethyl-(3,4-methylenedioxyphenyl)ethylamine (**4g**).

This compound was obtained as colourless crystals (17.8 g, 80%), mp 203-204°C; ir (potassium bromide): ν 1617 cm^{-1} ; 1H nmr (deuteriochloroform, δ , ppm): 7.68 (1H, d, $J = 15.6$ Hz), 7.62 (2H, d, $J = 8.3$ Hz), 7.57 (2H, d, $J = 8.3$ Hz), 7.13 (1H, s), 7.09 (1H, d, $J = 8.3$ Hz), 6.84 (1H, d, $J = 8.3$ Hz), 6.38 (1H, d, $J = 15.6$ Hz), 5.99 (2H, s), 5.90 (1H, bs), 5.80 (1H, bs), 4.24 (1H, dd, $J = 14.7, 6.6$ Hz), 3.83 (1H, dd, $J = 14.7, 6.6$ Hz); ^{13}C nmr (dimethyl- d_6 sulfoxide, δ , ppm): 166.0, 147.3, 138.9 (q, $^4J_{CF} = 1.1$ Hz), 138.0, 129.5 (q, $^2J_{CF} = 32.0$ Hz), 128.3, 125.8 (q, $^3J_{CF} = 3.8$ Hz), 125.3 (q, $^1J_{CF} = 287.3$ Hz), 124.3, 124.1 (q, $^1J_{CF} = 272.0$ Hz), 120.8, 107.8, 107.6, 101.3, 76.6 (q, $^2J_{CF} = 26.7$ Hz), 43.3.

Anal. Calcd. for $C_{20}H_{15}F_6NO_4$ (447.33): C, 53.70; H, 3.38; N, 3.13. Found: C, 53.53; H, 3.48; N, 3.26.

N-(4-Nitrocinnamoyl)-2-hydroxy-2-trifluoromethyl-(3,4-methylenedioxy-phenyl)ethylamine (**4h**).

This compound was obtained as yellow crystals (14.6 g, 69%), mp 204-205°C; ir (potassium bromide): ν 1617 cm^{-1} ; 1H nmr (deuteriochloroform, δ , ppm): 8.20 (2H, d, $J = 8.8$ Hz), 7.95 (1H, t, $J = 5.9$ Hz), 7.62 (2H, d, $J = 8.8$ Hz), 7.59 (1H, d, $J = 8.1$ Hz), 7.13 (2H, m), 6.81 (1H, d, $J = 8.1$ Hz), 6.72 (1H, bs), 6.63 (1H, d, $J = 15.8$ Hz), 5.97 (2H, s), 4.00 (2H, d, $J = 5.9$ Hz); ^{13}C nmr (deuteriochloroform, δ , ppm): 165.7, 147.7, 147.5, 147.3, 141.5, 137.3, 129.9, 128.79, 126.0, 125.4 (q, $^1J_{CF} = 287.6$ Hz), 124.2, 120.8, 107.9, 107.6, 101.4, 76.5 (q, $^2J_{CF} = 26.7$ Hz), 43.3.

Anal. Calcd. for $C_{19}H_{15}F_3N_2O_6$ (424.34): C, 53.78; H, 3.56; N, 6.60. Found: C, 54.02; H, 3.57; N, 6.50.

General Procedure for the Synthesis of Oxazolines 5.

A mixture of amide **4** (10 mmol), phosphorus oxychloride (1 ml, 1.8 g, 20 mmol) and toluene (15 ml) was heated with stirring for 4 hours at 95°C. After cooling to room temperature the mixture was poured into a stirred ice-cold solution of 28% ammonium hydroxide. The layers were separated, the aqueous layer was extracted with ethyl acetate (2 x 20 ml). The combined organic layers were dried on magnesium sulfate and evaporated. Recrystallization of the residue from 2-propanol gave oxazolines **5**.

5-(3-Methoxyphenyl)-2-styryl-5-trifluoromethyl-2-oxazoline (**5a**).

This compound was obtained as colourless crystals (2.4 g, 68%), mp 78-79°C; ir (potassium bromide): ν 1666 cm^{-1} ; 1H nmr (deuteriochloroform, δ , ppm): 7.60-7.52 (3H, m), 7.44-7.33 (4H, m), 7.11-7.08 (2H, m), 6.97-6.92 (1H, m), 6.67 (1H, d, $J = 16.3$ Hz), 4.68 (1H, d, $J = 15.7$ Hz), 4.29 (1H, d, $J = 15.7$ Hz), 3.84 (3H, s); ^{13}C nmr (deuteriochloroform, δ , ppm): 162.7, 159.7, 141.7, 137.2, 134.7, 130.0, 129.9, 128.9, 128.0, 124.3 (q, $^1J_{CF} = 283.8$ Hz), 118.3, 114.2, 113.6, 112.6, 85.8 (q, $^2J_{CF} = 30.4$ Hz), 63.6, 55.4.

Anal. Calcd. for $C_{19}H_{16}F_3NO_2$ (347.34): C, 65.70; H, 4.64; N, 4.03. Found: C, 65.45; H, 4.62; N, 3.96.

2-(4-Fluorostyryl)-5-(3-methoxyphenyl)-5-trifluoromethyl-2-oxazoline (**5b**).

This compound was obtained as colourless crystals (3.1 g, 85%), mp 134-135°C; ir (potassium bromide): ν 1663 cm^{-1} ; 1H nmr (deuteriochloroform, δ , ppm): 7.57-7.50 (3H, m), 7.37 (1H, t, $J = 8.3$ Hz)

7.14-7.06 (4H, m), 6.98-6.93 (1H, m), 6.59 (1H, d, J = 16.4 Hz), 4.67 (1H, d, J = 15.8 Hz), 4.29 (1H, d, J = 15.8 Hz), 3.84 (3H, s); ^{13}C nmr (deuteriochloroform, δ , ppm): 163.7 (d, $^1\text{J}_{\text{CF}} = 251.0$ Hz), 162.3, 159.7, 140.0, 137.1, 131.1 (d, $^4\text{J}_{\text{CF}} = 3.4$ Hz), 129.8, 129.5 (d, $^3\text{J}_{\text{CF}} = 8.4$ Hz), 124.3 (q, $^1\text{J}_{\text{CF}} = 283.7$ Hz), 118.2, 116.0 (d, $^2\text{J}_{\text{CF}} = 22.1$ Hz), 114.1, 113.6, 112.6, 85.7 (q, $^2\text{J}_{\text{CF}} = 30.5$ Hz), 63.9, 55.3.

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{F}_4\text{NO}_2$ (365.33): C, 62.47; H, 4.14; N, 3.83. Found: C, 62.19; H, 4.12; N, 3.88.

5-(3-Methoxyphenyl)-5-trifluoromethyl-2-[4-(trifluoromethyl)-styryl]-2-oxazoline (**5c**).

This compound was obtained as colourless crystals (3.6 g, 87%), mp 161-162°C; ir (potassium bromide): ν 1665 cm^{-1} ; ^1H nmr (deuteriochloroform, δ , ppm): 7.70-7.63 (4H, m), 7.59 (1H, d, J = 16.4 Hz), 7.41-7.35 (1H, m), 7.13-7.07 (2H, m), 7.00-6.94 (1H, m), 6.75 (1H, d, J = 16.4 Hz), 4.70 (1H, d, J = 16.0 Hz), 4.32 (1H, d, J = 16.0 Hz), 3.84 (3H, s); ^{13}C nmr (deuteriochloroform, δ , ppm): 162.0, 159.8, 139.6, 138.2, 137.1, 131.5 (q, $^2\text{J}_{\text{CF}} = 32.8$ Hz), 129.9, 127.8, 125.9 (q, $^3\text{J}_{\text{CF}} = 3.8$ Hz), 124.3 (q, $^1\text{J}_{\text{CF}} = 283.4$ Hz), 123.9 (q, $^1\text{J}_{\text{CF}} = 272.4$ Hz), 118.2, 116.3, 114.1, 112.7, 85.9 (q, $^2\text{J}_{\text{CF}} = 30.5$ Hz), 63.9, 55.4.

Anal. Calcd. for $\text{C}_{20}\text{H}_{15}\text{F}_6\text{NO}_2$ (415.34): C, 57.84; H, 3.64; N, 3.37. Found: C, 57.67; H, 3.68; N, 3.31.

5-(3-Methoxyphenyl)-2-(4-nitrostyryl)-5-trifluoromethyl-2-oxazoline (**5d**).

This compound was obtained as yellow crystals (2.8 g, 72%), mp 154-155°C; ir (potassium bromide): ν 1663 cm^{-1} ; ^1H nmr (deuteriochloroform, δ , ppm): 8.27 (2H, d, J = 6.8 Hz), 7.70 (2H, d, J = 6.8 Hz), 7.60 (1H, d, J = 16.4 Hz), 7.45-7.30 (1H, m), 7.12-7.05 (2H, m), 7.00-6.92 (1H, m), 6.80 (1H, d, J = 16.4 Hz), 4.71 (1H, d, J = 16.3 Hz), 4.32 (1H, d, J = 16.3 Hz), 3.85 (3H, s); ^{13}C nmr (deuteriochloroform, δ , ppm): 161.9, 159.8, 148.4, 140.8, 139.0, 136.8, 130.0, 128.3, 124.2, 124.1 (q, $^1\text{J}_{\text{CF}} = 284.2$ Hz), 118.2, 117.8, 114.2, 112.7, 86.1 (q, $^2\text{J}_{\text{CF}} = 30.1$ Hz), 63.7, 55.4.

Anal. Calcd. for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_4$ (392.34): C, 58.17; H, 3.85; N, 7.14. Found: C, 57.95; H, 3.83; N, 7.07.

5-(3,4-Methylenedioxyphenyl)-2-styryl-5-trifluoromethyl-2-oxazoline (**5e**).

This compound was obtained as colourless crystals (2.7 g, 75%), mp 120-121°C; ir (potassium bromide): ν 1660 cm^{-1} ; ^1H nmr (deuteriochloroform, δ , ppm): 7.60-7.52 (3H, m), 7.45-7.36 (3H, m), 7.03-6.96 (2H, m), 6.86 (1H, d, J = 8.1 Hz), 6.66 (1H, d, J = 16.2 Hz), 6.00 (2H, m), 4.64 (1H, d, J = 15.7 Hz), 4.26 (1H, d, J = 15.7 Hz); ^{13}C nmr (deuteriochloroform, δ , ppm): 162.3, 148.4, 148.0, 141.2, 134.7, 129.9, 129.4, 128.9, 127.6, 124.3 (q, $^1\text{J}_{\text{CF}} = 284.1$ Hz), 119.9, 113.8, 108.3, 106.9, 101.5, 85.5 (q, $^2\text{J}_{\text{CF}} = 30.6$ Hz), 64.0.

Anal. Calcd. for $\text{C}_{19}\text{H}_{14}\text{F}_3\text{NO}_3$ (361.32): C, 63.16; H, 3.91; N, 3.88. Found: C, 62.90; H, 3.88; N, 3.80.

2-(4-Fluorostyryl)-5-(3,4-methylenedioxyphenyl)-5-trifluoromethyl-2-oxazoline (**5f**).

This compound was obtained as colourless crystals (3.0 g, 79%), mp 165-166°C; ir (potassium bromide): ν 1664 cm^{-1} ; ^1H nmr (deuteriochloroform, δ , ppm): 7.56-7.48 (3H, m), 7.10 (2H, t, J = 8.7 Hz), 7.03-6.96 (2H, m), 6.86 (1H, d, J = 8.2 Hz), 6.59 (1H, d, J = 16.3 Hz), 6.00 (2H, m), 4.64 (1H, d, J = 15.9 Hz), 4.26 (1H, d, J = 15.9 Hz); ^{13}C nmr (deuteriochloroform, δ , ppm): 163.6 (d, $^1\text{J}_{\text{CF}} = 250.9$ Hz), 162.2, 148.4, 148.0, 140.0, 132.0 (d,

$^4\text{J}_{\text{CF}} = 2.8$ Hz), 129.4 (d, $^3\text{J}_{\text{CF}} = 8.5$ Hz), 129.3, 124.3 (q, $^1\text{J}_{\text{CF}} = 283.9$ Hz), 119.9, 116.0 (d, $^2\text{J}_{\text{CF}} = 21.3$ Hz), 113.5 (d, $^4\text{J}_{\text{CF}} = 2.8$ Hz), 108.3, 106.9, 101.5, 85.5 (q, $^2\text{J}_{\text{CF}} = 30.6$ Hz), 64.0.

Anal. Calcd. for $\text{C}_{19}\text{H}_{13}\text{F}_4\text{NO}_3$ (379.31): C, 60.16; H, 3.45; N, 3.69. Found: C, 59.98; H, 3.46; N, 3.75.

5-(3,4-Methylenedioxyphenyl)-5-trifluoromethyl-2-[4-(trifluoromethyl)styryl]-2-oxazoline (**5g**).

This compound was obtained as colourless crystals (3.7 g, 85%), mp 149-150°C; ir (potassium bromide): ν 1666 cm^{-1} ; ^1H nmr (deuteriochloroform, δ , ppm): 7.69-7.62 (4H, m), 7.56 (1H, d, J = 16.3 Hz), 7.02-6.96 (2H, m), 6.86 (1H, d, J = 8.1 Hz), 6.73 (1H, d, J = 16.3 Hz), 6.01 (2H, m), 4.66 (1H, d, J = 15.9 Hz), 4.28 (1H, d, J = 15.9 Hz); ^{13}C nmr (deuteriochloroform, δ , ppm): 161.8, 148.5, 148.0, 139.4, 138.1, 131.4 (q, $^2\text{J}_{\text{CF}} = 32.7$ Hz), 129.1, 127.8, 125.8 (q, $^3\text{J}_{\text{CF}} = 3.6$ Hz), 124.2 (q, $^1\text{J}_{\text{CF}} = 283.6$ Hz), 123.8 (q, $^1\text{J}_{\text{CF}} = 271.3$ Hz), 119.9, 116.3, 108.4, 106.8, 101.5, 85.7 (q, $^2\text{J}_{\text{CF}} = 30.5$ Hz), 64.1.

Anal. Calcd. for $\text{C}_{20}\text{H}_{13}\text{F}_6\text{NO}_3$ (429.32): C, 55.95; H, 3.05; N, 3.26. Found: C, 55.79; H, 3.08; N, 3.30.

5-(3,4-Methylenedioxyphenyl)-2-(4-nitrostyryl)-5-trifluoromethyl-2-oxazoline (**5h**).

This compound was obtained as yellow crystals (3.0 g, 74%), mp 211-212°C; ir (potassium bromide): ν 1664 cm^{-1} ; ^1H nmr (deuteriochloroform, δ , ppm): 7.69-7.62 (4H, m), 7.56 (1H, d, J = 16.3 Hz), 7.02-6.96 (2H, m), 6.86 (1H, d, J = 8.1 Hz), 6.73 (1H, d, J = 16.3 Hz), 6.01 (2H, m), 4.66 (1H, d, J = 15.9 Hz), 4.28 (1H, d, J = 15.9 Hz); ^{13}C nmr (deuteriochloroform, δ , ppm): 161.6, 148.6, 148.4, 148.1, 140.9, 138.6, 128.9, 128.3, 124.2, 124.2 (q, $^1\text{J}_{\text{CF}} = 283.6$ Hz), 119.9, 118.0, 108.4, 106.8, 101.6, 86.0 (q, $^2\text{J}_{\text{CF}} = 30.9$ Hz), 64.0.

Anal. Calcd. for $\text{C}_{19}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_5$ (406.32): C, 56.17; H, 3.22; N, 6.89. Found: C, 56.11; H, 3.20; N, 6.92.

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