Synthesis of 2-Substituted Trifluoromethylquinolines for the Evaluation of Leishmanicidal Activity

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The synthesis of 2-substituted-trifluoromethylquinolines from aniline, trifluoromethylanilines, 3-aminoquinoline and trifluoromethylquinaldines is reported. *In vitro* antileishmanial evaluation of 2-alkyl, 2-alkenyl and 2-epoxypropyl-trifluoromethylquinolines is presented.

Key words leishmaniasis; 2-propyltrifluoromethylquinoline; 2-epoxypropyltrifluoromethylquinoline; 2-(propen-1-yl)-trifluoromethylquinoline.

Leishmaniasis are a group of diseases with different clinical manifestations (cutaneous, mucocutaneous and visceral), which represent a severe public health problem in some tropical and subtropical areas. They are often disfiguring and sometimes fatal protozoan diseases affecting over 12 million people worldwide and, for which, there is still no effective vaccine.

Chemotherapy remains the most effective control measure for leishmaniasis. However, current drugs, like sodium stibogluconate (Pentostam®) or *N*-methylglucamine (Glucantime®), are expensive and variable in their efficacy. They also require protracted courses of parenteral administration and have toxic side effects,[1] which often result in the interruption of treatment. Furthermore, the increasing resistance to antimonial drugs in many parts of the world clearly indicates the need for a more effective and safer chemotherapeutic approach.

Based on ethnomedical information obtained from populations which use traditional remedies, new antileishmanial products like quinoline alkaloids have been discovered during the last decade.[2] Improving efficacy of chemotherapeutic treatment by introducing structural modifications within these new drugs constitutes a major goal.

Because the introduction of fluorine into molecules modifies the physiological activity of the resulting compounds, the development of fluorinated analogues has received increasing attention in recent years. We wish to present the methodology we used in the preparation of 2-propyltrifluoromethylquinolines **1** and the chemical transformations of trifluoromethylquinaldines **2** into 2-alkenyl and 2-epoxypropyltrifluoromethylquinolines *via* the corresponding aldehydes. Preliminary *in vitro* evaluation of these synthetic compounds will be presented.

Chemistry In a previous paper,[3] Song has described the synthesis of 6- and 7-fluorinated quinaldines by the Skraup reaction from the corresponding fluorinated anilines. We have revisited this reaction with poorly nucleophilic trifluoroanilines which were converted into 2-propyltrifluoromethylquinolines **1a**—**d**. The best yields were obtained by changing *p*-chloranil with air flow as the oxidant in refluxing butanol. The use of *m*-trifluoromethylaniline gave access to **1b** and **1d** in a 10/1 ratio (Chart 1).

In order to introduce a trifluoromethyl group on the pyridine ring of the quinoline skeleton, we have first studied the cyclization of the trifluoromethylenaminone **4** (Chart 1). Condensation of 1-pentynyllithium with 1,1-difluoroethyltrifluoroacetate in the presence of BF_3–Et_2O gave access to **3** which was transformed into **4** after a Michael reaction with aniline. Initial attempts at cyclization of **4** using a variety of Lewis acids ($AlCl_3$, BF_3–Et_2O or $TiCl_4$) failed, resulting in only the recovery of starting material. The use of trifluoroacetic or sulfuric acid leads to traces of quinoline **1e** in a mixture of tarry matters. The yield was finally substantially improved in polyphosphoric acid (24 h, reflux, 63%).

To prepare the 2-propyl-3-trifluoromethylquinoline **1f**, we first synthesized the 2-propyl-3-iodoquinoline **5** by the use of a large excess of propyllithium on 3-aminoquinoline, followed by diazotisation and subsequent treatment with potassium iodide. Considerable attention has been devoted to finding methods for introducing the trifluoromethyl group onto aromatic halide compounds. For example, Kobayashi[4] prepared a trifluoromethylcopper species by the reaction of CF_3I with activated copper in DMF, Matsui[5] has developed a convenient trifluoromethylation of aromatic halides with sodium trifluoroacetate, and Fuchikami[6] used the (CF_3SiMe_3/KF/CuI) system for trifluoromethylation of halides. Best results

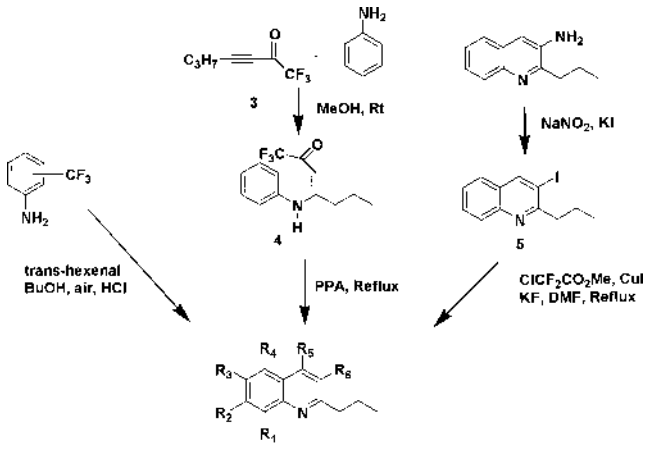

Chart 1

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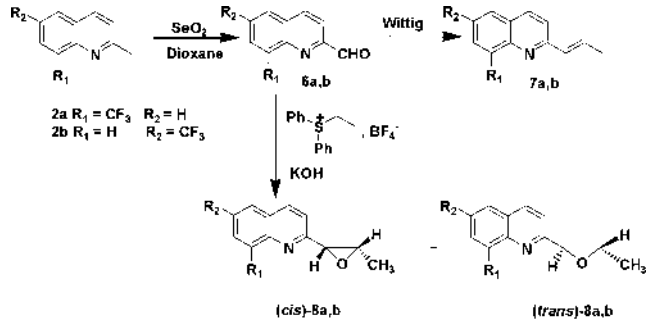

Chart 2

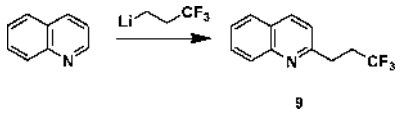

Chart 3

were obtained in the preparation of **1f** by using difluorocarbenes generated from methylchlorodifluoroacetate in the presence of KF and CuI in DMF[7] (Chart 1).

To prepare 2-propenyltrifluoromethylquinolines **7** and 2-epoxypropyl-trifluoromethylquinolines **8**, we first synthesised the quinaldines **2** as described for **1**. The transformation of quinaldines into 2-quinolinecarboxaldehydes **6** with SeO_2 in dioxane was not affected by the electron-withdrawing effect of the trifluoromethyl group.

Wittig olefination with ethyltriphenylphosphonium iodide afforded 2-propenyltrifluoromethylquinolines **7** as single *E* isomers in good yields. To prepare 2-epoxypropylpropyleneoxyde-trifluoromethylquinolines **8** as fluorinated analogues of the natural product isolated by Fournet,[2] we used the reaction of the sulfur ylide generated from ethyldiphenylsulfoniumtetrafluoroborate on 2-trifluoromethylquinolinecarboxaldehydes **6** as previously described by Brochet[8] and us.[9] Epoxides were then obtained in good yields as a separable mixture of *Z* and *E* isomers (1/1). The stereochemistry of these epoxides was determinated by studying their ^{1}H-NMR spectra : measure of $J_{H_2'-H_3'}$ (4.5 and 2 Hz for *Z* and *E* isomers respectively), NOE experiments and comparison with the ^{1}H-NMR spectra of the *E* antileishmanial natural epoxide.[9]

We have also synthesized the 2-(3,3,3-trifluoropropyl) quinoline **9** by the use of a Grignard reagent on *N*-quinolineoxide, but a more efficient way consisted in the preparation of the lithium salt of 3-bromo-1,1,1-trifluoromethylpropane that reacts with quinoline to give **9** in a 60 % yield (Chart 3).

Antileishmanial Activity Various *in vitro* tests were used to assess the antileishmanial activity of 2-substituted trifluoromethylquinolines. These tests have been done at both the Pasteur Institute (Paris, France) and at the Swiss Tropical Institute (Basel, Switzerland). They were based upon the use of axenic amastigotes and peritoneal or bone marrow-derived mouse macrophages infected with amastigotes from different *Leishmania* species, including *L. donovani* (MHOM/ET/1967/L82), *L. infantum* (IPZ 229/1/89) and *L. amazonensis* (MPRO/BR/1972/M1841).

The reference drugs used were sodium stibogluconate, amphotericin B, allopurinol or allopurinol riboside and leucine-methyl ester (*L. amazonensis*). For all the tests, these products showed consistent and reproductible leishmanicidal activity proving the validity of our assays.

Unfortunately, the various molecular changes made on natural products did not further improve their activity. On the contrary, for all the compounds we have tested, *i.e.*, 2-alkyl, 2-alkenyl and 2-epoxypropyl-trifluoromethylquinolines, we have noted a decrease of antileishmanial activity compared to control drugs and natural products. For example, from a concentration of 1.5 μg/ml, the natural 2-prop-1-enylquinoline showed a leishmanicidal activity against *Leishmania amazonensis*; in contrast, trifluoromethylated analogues were only efficient at a concentration of 50 μg/ml. The 2-propylquinoline was active at 12.5 μg/ml, whereas **1f** (the most efficient compound **1**) was only active at 25 μg/ml. The 2-epoxypropyl-trifluoromethylquinolines were poorly active around 100 μg/ml.

Preliminary works point out that natural quinolines, such as 2-propylquinoline, are transformed in liver cells into oxidized metabolits.[10] Moreover, these metabolits should be the active drugs because the natural 2-propylquinoline is more efficient by oral administration than by parenteral route.[11] The introduction of a trifluoromethyl substituent must prevent or slow down this oxidizing mechanism which could explain the above antileishmanial results. Introduction of electro-donnor groups on 2-substituted-quinolines should give highly promising results.

Experimental

^{19}F-NMR chemical shifts are reported in ppm, negative upfield relative to internal $CFCl_3$, ^{1}H- and ^{13}C-NMR chemical shifts are reported in ppm, positive downfield relative to internal TMS. Spectra were recorded on Bruker AC 200P spectrometer (188, 200 and 50 MHz for ^{19}F, ^{1}H and ^{13}C, respectively). Analytical thin-layer chromatography was performed on Merck silica gel $60F_{254}$ glass precoated plates. All liquid chromatography separations were performed using Merck silica gel 60 (230—400 mesh ASTM). Elemental analyses[12] were performed by the Service de microanalyses, Centre d'Etudes Pharmaceutiques, Châtenay-Malabry, France, with a Perkin Elmer 2400 analyzer.

2-Propyltrifluoromethylquinolines 1a—d A mixture of trifluoromethylaniline (30 mmol), butanol (40 ml), HCl 12 N (10 ml) was heated under reflux and then *trans*-hexenal (150 mmol) was slowly added. The resulting solution was heated under reflux and under draught for 8 h. The cooled reaction mixture was made alkaline with KOH and extracted with CH_2Cl_2. After drying, and the removal of the solvent, chromatographic purification on silica gel afforded the desired quinolines.

2-Propyl-8-trifluoromethylquinoline **1a**: 52%. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.9 Hz), 1.90 (2H, m), 3.00 (2H, t, J=7.9 Hz), 7.35 (1H, d, J=8.4 Hz), 7.50 (1H, t, J=7.9 Hz), 7.85 (1H, d, J=7.9 Hz), 8.10 (1H, d, J=7.9 Hz), 8.35 (1H, d, J=8.4 Hz). ^{19}F-NMR ($CDCl_3$) δ: −60.31 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 13.8, 22.1, 41.1, 122.3, 124.1, 127.0, 127.2 (q, J=29 Hz), 127.5 (q, J=5.4 Hz), 129.7 (q, J=268 Hz), 131.9, 135.8, 144.6, 163.7.

2-Propyl-7-trifluoromethylquinoline **1b**: 56%. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.3 Hz), 1.90 (m, 2H), 3.00 (2H, t, J=7.3 Hz), 7.40 (1H, d, J=8.5 Hz), 7.65 (1H, dd, J=8.5 Hz, J=1.4 Hz), 7.85 (1H, d, J=8.5 Hz), 8.10 (1H, d, J=8.5 Hz), 8.35 (1H, d, J=1.4 Hz). ^{19}F-NMR ($CDCl_3$) δ: −62.81 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 13.9, 22.9, 41.2, 121.3, 123.3, 124.8 (q, J=242 Hz), 126.8, 128.2, 128.6, 131.0, 135.8, 146.9, 164.5.

2-Propyl-6-trifluoromethylquinoline **1c**: 51%. ^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.3 Hz), 1.65 (2H, m), 2.45 (2H, t, J=7.3 Hz), 7.30 (1H, d, J=8.4 Hz), 7.75 (1H, d, J=8.9 Hz), 8.00 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −62.42 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 13.8, 22.9, 41.2, 122.5, 124.1 (q, J=270.4 Hz), 124.8, 125.3, 125.5, 127.5 , 130.0, 136.6, 148.8, 165.3.

2-Propyl-5-trifluoromethylquinoline **1d**: 6%. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.5 Hz), 1.85 (2H, m), 3.00 (2H, t, J=7.9 Hz), 7.40 (1H, d, J=8.8 Hz), 7.70 (1H, t, J=7.9 Hz), 7.85 (1H, d, J=7.9 Hz), 8.20 (1H, d, J=8.8 Hz), 8.40 (1H, d, J=7.9 Hz). ^{19}F-NMR ($CDCl_3$) δ: −59.44 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 13.8, 22.9, 41.0, 122.6, 124.1, 124.3 (q, J=274 Hz), 126.1 (q, J=32 Hz), 127.0, 127.5 132.4, 133.7, 148.1, 163.7.

2-Methyl-trifluoromethylquinolines 2a,b These compounds were prepared as described above by changing *trans*-butenal to *trans*-hexenal.

2-Methyl-8-trifluoromethylquinoline **2a**: 51%. ^{1}H-NMR ($CDCl_3$) δ: 2.85 (3H, s), 7.35 (1H, d, J=9 Hz), 7.50 (1H, t, J=8.0 Hz), 7.95 (1H, d, J=9 Hz), 8.05 2H, m). ^{19}F-NMR ($CDCl_3$) δ: −60.22 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 25.8, 122.7, 124.1, 124.3 (q, J=274 Hz), 126.5 (q, J=29 Hz), 126.8, 127.5 (q, J=5.3 Hz), 132.0, 135.9, 144.5, 160.2.

2-Methyl-6-trifluoromethylquinoline **2b**: 55%. ^{1}H-NMR ($CDCl_3$) δ: 2.77 (3H, s), 7.36 (1H, d, J=8.8 Hz), 7.80 (1H, dd, J=8.8 Hz, J=2.3 Hz), 8.10 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −62.42 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 25.5, 123.2, 125.0, 125.1 (q, J=278 Hz), 125.3, 125.5 (q, J=5.1 Hz), 128.1 (q, J=29 Hz), 129.8, 136.7, 148.9, 161.5

1,1,1-Trifluoromethylhept-3-yn-2-one 3 Butyllithium (1.6 M in hexane, 46 ml, 74 mmol) was added to pent-1-yne (4.59 g, 67 mmol) in THF (120 ml) at −78 °C and this mixture was stirred at this temperature for 30 min. 2,2-difluoroethyl trifluoroacetate (13.35 g, 75 mmol) in THF (100 ml) was added followed immediately by boron trifluoride-diethyl ether complex (11.3 g, 80 mmol). The mixture was stirred at −78 °C for 90 min. Saturated aqueous ammonium chloride (40 ml) was added and the solution was allowed to warm to ambient temperature. The THF was evaporated and the residue, taken up in dichloromethane, was washed with water and twice with brine and dried. The residue was then purified by silica gel column chromatography to give **3** (9.1 g , 85%).

^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.3 Hz), 1.65 (2H, m), 2.45 (2H, t, J=7.3 Hz). ^{19}F-NMR ($CDCl_3$) δ: −78.51 (CF_3, s).

1,1,1-Trifluoromethyl-4-phenylaminohept-3-en-2-one 4 Aniline (5.3 g, 56.9 mmol) and **3** (9.34 g, 57 mmol) were stirred in methanol (50 ml) for 24 h at ambient temperature. After evaporation of the solvent, the residue was purified by silica gel column chromatography to give **4** (11.23 g, 77%).

^{1}H-NMR ($CDCl_3$) δ: 0.80 (3H, t, J=7.3 Hz), 1.20 (1H, bs), 1.50 (2H, m), 2.25 (2H, t, J=7.3 Hz), 5.50 (1H, s), 7.00—7.40 (5H, m). ^{19}F-NMR ($CDCl_3$) δ: −62.65 (CF_3, s).

2-Propyl-4-trifluoromethylquinoline 1e **4** (2 g, 7.8 mmol) and polyphosphoric acid (10 ml) were stirred under reflux for 24 h. The cooled reaction mixture was basified with KOH (1 N, 40 ml) and extracted with dichloromethane. After drying, and the removal of the solvent, chromatographic purification on silica gel afforded **1e** (1.17 g, 63%).

^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.3 Hz), 1.85 (2H, m), 2.95 (2H, t, J=7.3 Hz), 7.50 (2H, m), 7.70 (1H, m), 8.10 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −61.81 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 13.7, 22.8, 41.1, 118.2, 121.3, 123.6 (q, J=273 Hz), 123.7, 127.2, 129.8 (2), 134.2 (q, J=30.5 Hz), 148.7, 162.2.

3-Iodo-2-propylquinoline 5 *tert*-Butyllithium (1.5 M in pentane, 35.5 ml) was slowly added at −78 °C to a stirred solution of iodopropane (5.1 g, 30 mmol) in ether. The mixture was stirred 30 min at this temperature and allowed to warm to 0 °C for 1 h. The solution was then cooled at −78 °C and 3-aminoquinoline (1.44 g, 10 mmol) in ether (10 ml) was slowly added. After stirring 24 h at ambient temperature, the solution was quenched by the addition of saturated aqueous NH_4Cl. After extraction ($CHCl_3$), the solution was dried and concentrated. The crude product was subjected to chromatography to give 3-amino-2-propylquinoline (1.16 g, 60%). This latest compound (1.12 g) was dissolved in acetic acid (18 ml) at 0 °C and sodium nitrite (1.48 g, 21.5 mmol) in H_2O (10 ml) then potassium iodide (3.57 g, 21.5 mmol) in H_2O (15 ml) were added to the mixture. After 2 h, the solution was treated with NaOH (1 N, 30 ml) and extracted with dichloromethane, then dried. After evaporation, the residue was purified by silica gel column chromatography to give **5** (1.02 g, 57%).

^{1}H-NMR ($CDCl_3$) δ: 1.00 (3H, t, J=7.4 Hz), 1.75 (2H, m), 3.00 (2H, t, J=7.4 Hz), 7.35 (1H, m), 7.55 (2H, m), 7.90 (1H, d, J=8.4 Hz), 8.45 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 22.4, 43.6, 93.4, 126.2, 126.4, 128.2, 128.8, 129.8, 146.2, 147.0, 162.0.

2-Propyl-3-trifluoromethylquinoline 1f Under argon, 0.80 g (2.69 mmol) of **5**, 1.27 g (8.08 mmol) of methyl 2-chloro-2,2-difluoroacetate, 0.84 g (4.40 mmol) of CuI and 0.255 g (4.39 mmol) of KF were stirred in DMF at 120 °C for 8 h. The resulting solution was poured into water, extracted with dichloromethane and dried. After evaporation, the residue was purified by silica gel column chromatography to give **1f** (0.37 g, 57%).

^{1}H-NMR ($CDCl_3$) δ: 0.95 (3H, t, J=7.5 Hz), 1.80 (2H, m), 2.95 (2H, t, J=7.5 Hz), 7.40 (1H, t, J=7.8 Hz), 7.70 (2H, m), 8.00 (1H, d, J=7.8 Hz), 8.30 (1H, s). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 22.9, 37.9, 122.7 (q, J=28 Hz), 124.1 (q, J=273 Hz), 124.8, 126.9, 128.2, 128.8, 131.5, 134.9 (q, J=6 Hz), 148.7, 159.2. ^{19}F-NMR ($CDCl_3$) δ: −60.79 (CF_3, s).

Trifluoromethyl-2-quinolinecarboxaldehydes 6 500 mg (2.3 mmol) of trifluoromethylquinaldine **2** and SeO_2 (0.38 g, 3.45 mmol) were stirred in dioxane (10 ml) under reflux for 4 h. After cooling and filtration, the solution was concentrated and the residue was purified on silica gel to give **6**.

8-Trifluoromethyl-2-quinolinecarboxaldehyde **6a**: 81%. ^{1}H-NMR ($CDCl_3$) δ: 7.75 (1H, m), 8.10 (3H, m), 8.40 (1H, d), 10.20 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −60.28 (CF_3, s).

6-Trifluoromethyl-2-quinolinecarboxaldehyde **6b**: 75%. ^{1}H-NMR ($CDCl_3$) δ: 8.00 (1H, d, J=8.6 Hz), 8.10 (1H, d, J=8.6 Hz), 8.25 (1H, s), 8.40 (2H, t, J=8.6 Hz), 10.20 (1H, s). ^{19}F-NMR ($CDCl_3$) δ: −62.93 (CF_3, s).

(*E*)-2-(Propen-1-yl)-trifluoromethylquinolines 7 To a 0 °C cooled solution of ethyltriphenylphosphonium iodide (5.8 g, 13.86 mmol) in THF (20 ml) was added PhLi (1.8 M in cyclohexan/ether, 7.7 ml). The red ylide solution was stirred at 0 °C for 10 min then quinolinecarboxaldehydes **6** (1.5 g, 6.6 mmol) in THF (10 ml) were slowly added *via* syringe. The resulting mixture was allowed to warm to 20 °C and stirred further for 24 h. The solution was poured into water, extracted with dichloromethane and dried. After evaporation of the solvent, the residue was purified by column chromatography.

(*E*)-2-(Propen-1-yl)-8-trifluoromethylquinoline **7a**: 53%. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, dd, J=6.7 Hz, J=1.6 Hz), 6.60 (1H, qd, J=1.6 Hz, J=13.2 Hz), 6.90 (1H, qd, J=6.7 Hz, J=13.2 Hz), 7.30 (2H, m), 7.75 (1H, d, J=8.2 Hz), 7.90 (2H, m). ^{19}F-NMR ($CDCl_3$) δ: −60.91 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 18.5, 119.9, 124.1, 124.3 (q, J=273.9 Hz), 127.0, 127.3 (q, J=29 Hz), 127.8 (q, J=5.3 Hz), 131.8, 131.9, 134.1, 136.1, 144.6, 156.7.

(*E*)-2-(propen-1-yl)-6-trifluoromethylquinoline **7b**: 67%. ^{1}H-NMR ($CDCl_3$) δ: 1.90 (3H, dd, J=6.5 Hz, 1.3 Hz), 6.60 (1H, qd, J=1.3 Hz, J=15.6 Hz), 6.80 (1H, qd, J=6.5 Hz, J=15.6 Hz), 7.40 (1H, d, J=8.7 Hz), 7.70 (1H, dd, J=2.1 Hz, J=8.7 Hz), 8.00 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −62.30 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 18.6, 121.4, 124.0 (q, J=273 Hz), 125.2 (q, J=5.6 Hz), 125.4 (q, J=5.0 Hz), 126.9 (q, J=29 Hz), 127.9, 130.2, 131.9, 134.4, 136.7, 149.1, 158.4.

2-Epoxypropyltrifluoromethylquinolines 8 Ethyldiphenylsulfonium tetrafluoroborate[13] (673 mg, 2.23 mmol) in CH_3CN (10 ml), KOH (125 mg, 2.20 mmol) and water (31 mg, 1.74 mmol) were stirred for 20 min at ambient temperature. Quinolinecarboxaldehyde **6** (400 mg, 1.86 mmol) in CH_3CN (10 ml) was then added to the resulting solution and stirred for 20 h at room temperature. The reaction was quenched by the addition of water (50 ml), and after phase separation, the aqueous layer was extracted several times with dichloromethane. After evaporation of the solvent, the residue was purified by column chromatography to give **8**.

cis-2-(2-Methyloxirane)-8-trifluoromethylquinoline **8a**: 40%. ^{1}H-NMR ($CDCl_3$) δ: 1.50 (3H, d, J=5.2 Hz), 3.20 (1H, qd, J=2.1 Hz, J=5.2 Hz), 3.90 (1H, d, J=2.1 Hz), 7.25 (1H, d, J=8.7 Hz), 7.50 (1H, t, J=8.0 Hz), 7.90 (1H, d, J=8.0 Hz), 7.95 (1H, d, J=8.0 Hz), 8.10 (1H, d, J=8.7 Hz). ^{19}F-NMR ($CDCl_3$) δ: −60.30 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 17.8, 58.4, 60.4, 117.5, 122.0 (q, J=29 Hz), 124.1 (q, J=275.5 Hz), 125.0, 128.0 (q, J=5.9 Hz), 132.1 (2), 136.9, 147.1, 159.1.

trans-2-(2-Methyloxirane)-8-trifluoromethylquinoline **8a**: 40%. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=5.6 Hz), 3.40 (1H, m), 4.25 (1H, d, J=4.5 Hz), 7.40 (2H, m), 7.90 (1H, d, J=8.3 Hz), 7.95 (1H, d, J=7.6 Hz), 8.10 (1H, d, J=8.3 Hz). ^{19}F-NMR ($CDCl_3$) δ: −60.27 (CF^3, s). ^{13}C-NMR ($CDCl_3$) δ: 12.8, 55.5, 58.7, 119.9, 124.1 (q, J= 273 Hz), 124.9, 127.2 (q, J=29 Hz), 127.8, 128.1 (q, J=5.5 Hz), 132.1, 136.0, 144.2, 157.7.

cis-2-(2-Methyloxirane)-6-trifluoromethylquinoline **8b**: 38%. ^{1}H-NMR ($CDCl_3$) δ: 1.55 (3H, d, J=5.0 Hz), 3.25 (1H, qd, J=2.0 Hz, J=5.0 Hz), 4.00 (1H, d, J=2.0 Hz), 7.40 (1H, d, J=8.8 Hz), 7.80 (1H, dd, J=2.1 Hz, J=8.8 Hz), 8.20 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −62.50 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 17.8, 58.4, 60.1, 117.9, 124.0 (q, J=277 Hz), 125.5,126.7, 128.3 (q, J=29 Hz), 130.1, 137.7, 148.5, 160.5.

trans-2-(2-Methyloxirane)-6-trifluoromethylquinoline **8b**: 40%. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, d, J=5.3 Hz), 3.40 (1H, qd, J=4.4 Hz, J=5.3 Hz), 4.25 (1H, d, J=4.4 Hz), 7.40 (1H, d, J=8.5 Hz), 7.80 (1H, dd, J=8.7 Hz, J=2.0 Hz), 8.10 (3H, m). ^{19}F-NMR ($CDCl_3$) δ: −62.62 (CF_3, s). ^{13}C-NMR ($CDCl_3$) δ: 12.8, 55.3, 58.3, 120.3, 124.0 (q, J=272 Hz), 125.5 (2), 126.4, 128.3 (q, J=28.5 Hz), 130.1, 136.8, 148.5, 159.1.

2-3,3,3-(Trifluoropropyl)-quinoline 9 *tert*-Butyllithium (1.5 M in pentane, 7.5 ml) was slowly added at −78 °C to a stirred solution of 3-bromo-1,1,1-trifluoropropane (1 g, 5.65 mmol) in ether (5 ml). The solution was then stirred 30 min at −78 °C and allowed to warm to 0 °C for 1 h. The solution was cooled at −78 °C and quinoline (0.4 g, 3.1 mmol) in ether (5 ml) was slowly added to the mixture. After stirring at ambient temperature for 24 h, the solution was quenched (NH_4Cl), extracted ($CHCl_3$) and dried, then purified by silica gel column chromatography to give **9** (0.42 g, 60%).

^{1}H-NMR ($CDCl_3$) δ: 2.75 (2H, m), 3.25 (2H, m), 7.30 (1H, d, J=8.5 Hz), 7.50 (1H, t, J=8.5 Hz), 7.75 (2H, m), 8.05 (1H, d, J=8.5 Hz), 8.10 (1H, d, J=8.5 Hz). ^{19}F-NMR ($CDCl_3$) δ: −66.64 (CF_3, t). ^{13}C-NMR ($CDCl_3$) δ:

25.5 (q, J=3 Hz), 31.4 (q, J=29.6 Hz), 119.4, 122.5, 125.6, 126.8 (q, J=275 Hz), 128.3 (2), 129.5, 130.7, 141.6, 145.5.

References and Notes

1) Croft S. L., *Trends Pharmacol. Sci*., **9**, 376 (1988).
2) Fournet A., Barrios A., Munoz V., Hoquemiller R., Robelot F., Bruneton J., *International Patent* PCT/FR92/00903; Fournet A., Hocquemiller R., Roblot F., Cavé A., Richomme P., Bruneton J., *J. Nat. Prod*., **56**, 1547 (1993).
3) Song Z., Mertzman M., Hughes D. L., *J. Heterocyclic Chem.*, **30**, 17 (1993).
4) Kobayashi Y., Kumadaki I., *Tetrahedron Lett*., **47**, 4095 (1969); Kobayashi Y., Kumadaki I., Sato S., Hara N., Chikami E., *Chem. Pharm. Bull*., **18**, 2334 (1970).
5) Matsui K., Tobita E., Ando M., Kondo K., *Chem. Lett*., **1981**, 1719.
6) Urata H., Fuchikami T., *Tetrahedron Lett*., **32**, 91 (1991).
7) Su D. B., Duan J. X., Chen Q. Y., *Tetrahedron Lett*., **32**, 7689 (1991).
8) Brochet C., Syssa J. L., Mouloungui Z., Delmas M., Gaset A., *Synthetic Commun*., **21**, 1735 (1991).
9) Munos M. H., Mayrargue J., Fournet A., Gantier J. C., Hocquemiller R., Moskowitz H., *Chem. Pharm. Bull*., **42**, 1914 (1994).
10) Iglarz M., Baune B., Gantier J. C., Hocquemiller R., Farinotti R., *J. Chromatogr*. *B*, 714, **335**, 1998.
11) Munos M. H., *Thèse de l'Université de Paris-Sud*, N° 497, 1997.
12) Satisfactory microanalyses obtained : C±0.35, H±0.11
13) Mischitz M., Mirtl C., Saf R., Faber K., *Tetrahedron*: *Asymmetry*, **7**, 2041 (1996).