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

Joël Dade, Olivier Provot, Henri Moskowitz, Joëlle Mayrargue and Eric Prina

Laboratoire de Chimie organique, Faculté de Pharmacie, UPRES-A CNRS 8076, Université de Paris-Sud, 5 rue J-B Clément, 92296 Châtenay-Malabry, France and Unité d’Immunophysiologie et Parasitisme Intracellulaire, Institut Pasteur, 25 rue du Dr Roux, 75724 Paris cedex 15, France. Received October 19, 2000; accepted December 22, 2000

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, 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. 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, Song has described the synthesis of 6- and 7-fluorinated quinaldine 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 ρ-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 trifluoromethyleniminone 4 (Chart 1). Condensation of 1-pentylnyllithium with 1,1-difluoroethyltrifluoroacetate in the presence of BF₃–Et₂O 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 (AlCl₃, BF₃–Et₂O or TiCl₄) 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-idoquinoline 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 prepared a trifluoromethylcopper species by the reaction of CF₃I with activated copper in DMF. Matsui has developed a convenient trifluoromethylation of aromatic halides with sodium trifluoroacetate, and Fuchikami used the (CF₃SiMe3/KF/Cul) system for trifluoromethylation of halides. Best results
were obtained in the preparation of **1f** by using difluorocarbene generated from methylchlorodifluoroacetate in the presence of KF and Cul in DMF.\(^7\) (Chart 1).

To prepare 2-propenyltrifluoromethylquinolines 7 and 2-epoxypropyltrifluoromethylquinolines 8, we first synthesised the quininaldes 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-epoxypropylpropylenoynoate-trifluoromethylquinolines 8 as fluorinated analogues of the natural product isolated by Fournet,\(^2\) we used the reaction of the sulfur ylide generated from ethyldiphenylsulfonium trifluoromethylquinoline dioxane was not affected by the electron-withdrawing effect of the trifluoromethyl group.

Epoxides were then obtained in good yields as a separable mixture of Z and E isomers (1:1). The stereochemistry of these epoxides was determined by studying their 1H-NMR spectra: measure of \(J_{HH} \cdot Hz\) (4.5 and 2 Hz for Z and E isomers respectively), NOE experiments and comparison with the 1H-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-quinolinoxide, 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 reproducible 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 \(\mu\)g/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 \(\mu\)g/ml. The 2-propylinoline was active at 12.5 \(\mu\)g/ml, whereas **1f** (the most efficient compound) was only active at 25 \(\mu\)g/ml. The 2-epoxypropyltrifluoromethylquinolines were poorly active around 100 \(\mu\)g/ml.

Preliminary works point out that natural quinolines, such as 2-propylquinoline, are transformed in liver cells into oxidized metabolites.\(^10\) Moreover, these metabolites 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-donor 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\(_3\), 1H- and 13C-NMR chemical shifts are reported in ppm, positive downfield relative to internal TMS. Spectra were recorded on Brucker 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 60F254 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-Propenyltrifluoromethylquinolines 1a—d** A mixture of trifluoromethylalanine (30 mmol), butanol (40 ml), HCl 12 \(\times\) (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 CHCl\(_3\). After drying, and the removal of the solvent, chromatographic purification on silica gel afforded the desired quinolines.

**2-Propyl-8-trifluoromethylquinoline 1a** 52%. \(^{19}\)H-NMR (CDCl\(_3\)) \(\delta\) 1.00 (3H, \(J=7.9\) 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), 8.15 (1H, d, \(J=7.9\) Hz), 8.35 (1H, d, \(J=8.4\) Hz). \(^{19}\)F-NMR (CDCl\(_3\)) \(\delta\) -60.31 (CF\(_3\), s). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 13.8, 22.1, 41.1, 122.3, 124.7, 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%. \(^{19}\)H-NMR (CDCl\(_3\)) \(\delta\) 1.00 (3H, \(J=7.3\) Hz), 1.90 (2H, m), 2.00 (2H, t, \(J=7.3\) Hz), 7.40 (1H, d, \(J=8.5\) Hz), 7.57 (1H, dd, \(J=1.4, 8.5\) 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\(_3\)) \(\delta\) -62.81 (CF\(_3\), s). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 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%. \(^{19}\)H-NMR (CDCl\(_3\)) \(\delta\) 0.95 (3H, \(J=7.3\) 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\(_3\)) \(\delta\) -62.42 (CF\(_3\), s). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 13.8, 22.9, 41.2, 122.5, 124.1 (q, \(J=270.4\) Hz), 124.8, 125.3, 125.5, 127.0, 130.0, 136.6, 148.8, 165.3.

**2-Propyl-5-trifluoromethylquinoline 1d** 6%. \(^{19}\)H-NMR (CDCl\(_3\)) \(\delta\) 1.00 (3H, \(J=7.5\) 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\(_3\)) \(\delta\) -59.44 (CF\(_3\), s). \(^{13}\)C-NMR (CDCl\(_3\)) \(\delta\) 13.8, 22.9, 41.0, 122.6, 124.1, 124.3 (q, \(J=274.1\) Hz), 126.1 (q, \(J=32\) Hz), 127.0, 127.5 132.4, 133.7, 148.1, 163.7.
2-Methyl-1,2,3-trifluoromethylquinolines 2a,b These compounds were prepared as described above by changing trans-butanal to trans-hexanal.

2-Methyl-8-trifluoromethylquinoline 2a: 51%. 1H-NMR (CDCl3): 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). 19F-NMR (CDCl3): δ = −60.22 (CF3, s). 13C-NMR (CDCl3): δ = 25.8, 122.7, 124.1, 124.3 (q, J = 7.4 Hz), 126.5 (q, J = 29 Hz), 126.8, 127.5 (q, J = 5.3 Hz), 132.5, 135.9, 144.5, 160.2.

2-Methyl-6-trifluoromethylquinoline 2b: 55%. 1H-NMR (CDCl3): 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). 19F-NMR (CDCl3): δ = −62.42 (CF3, s). 13C-NMR (CDCl3): 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 Butyl lithium (1.65 mL in hexane, 46, 74 mmol) was added to penta-1,4-ylene (45.9 g, 67 mmol) in THF (120 mL) at −78 °C. THF was refluxed at room temperature for 24 h. A solution of carbonyl trichloroacetate (13.35 g, 75 mmol) in THF (100 mL) was added following 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 (1.9 g, 85%).

2-Methylquinoline 4 (1H-NMR (CDCl3): δ 3.90 (3H, s), 7.40(2H, m), 7.90 (1H, d, J = 8 Hz)). 19F-NMR (CDCl3): δ = −62.65 (CF3, s).

2-Propyl-1,2,3-trifluoromethylquinoline 1e (2g, 7.8 mmol) and polyphosphoric acid (10 mL) were stirred under reflux for 24 h. The cooled reaction mixture was washed with KOH (1s, 40 mL) and extracted with dichloromethane. After drying, and the removal of the solvent, chromatographic purification on silica gel afforded 1e (1.17 g, 67%).

2-Methylquinoline 4 (1H-NMR (CDCl3): δ 3.90 (3H, s), 7.40(2H, m), 7.90 (1H, d, J = 8 Hz)). 19F-NMR (CDCl3): δ = −61.81 (CF3, s). 13C-NMR (CDCl3): δ = 13.7, 22.8, 41.1, 118.2, 121.3, 123.6 (q, J = 273 Hz), 123.7, 127.2, 129.8 (2, J = 30.5 Hz), 148.7, 162.2.

Iodo-2-propylquinoline 5 tert-Butyl lithium (1.5 mL in pentane, 35.5 mmol) was slowly added at −78 °C to a stirred solution of iodopropene (5.1 g, 330 mmol) in ether (10 mL). The mixture was stirred for 1 h and was then treated with sodium iodide (8.05 g, 50 mmol) and 3-aminoquinoline (1.44 g, 10 mmol) in ether (10 mL) at −78 °C for 1 h. The reaction mixture was then cooled at −78 °C and quinoline (0.4 g, 3.1 mmol) in ether (5 mL) was added. The solution was treated with sodium hydroxide (1N) and extracted with dichloromethane, then dried. After evaporation, the residue was purified by silica gel column chromatography to give 5 (1.02 g, 57%).

2-Trifluoromethylquinoline 6 (1H-NMR (CDCl3): δ 2.85 (3H, s), 7.05 (1H, d, J = 8 Hz), 7.35 (1H, m), 7.55 (1H, m), 7.90 (1H, d, J = 8.4 Hz), 8.45 (1H, s). 13C-NMR (CDCl3): 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-1,2,3-trifluoromethylquinoline 1f Under argon, 0.80 g (2.69 mmol) of 1, 2.17 g (8.08 mmol) methyl 2-chloro-2,2-difluoroacetate, 0.84 g (4.40 mmol) of Cul 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%).

2-Trifluoromethylquinoline 6 (1H-NMR (CDCl3): δ 2.85 (3H, s), 7.05 (1H, d, J = 8 Hz), 7.35 (1H, m), 7.55 (1H, m), 7.90 (1H, d, J = 8.4 Hz), 8.45 (1H, s). 13C-NMR (CDCl3): 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-Trifluoromethylquinoline 6 (1H-NMR (CDCl3): δ 2.85 (3H, s), 7.05 (1H, d, J = 8 Hz), 7.35 (1H, m), 7.55 (1H, m), 7.90 (1H, d, J = 8.4 Hz), 8.45 (1H, s). 13C-NMR (CDCl3): 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-Trifluoromethylquinoline 6 (1H-NMR (CDCl3): δ 2.85 (3H, s), 7.05 (1H, d, J = 8 Hz), 7.35 (1H, m), 7.55 (1H, m), 7.90 (1H, d, J = 8.4 Hz), 8.45 (1H, s). 13C-NMR (CDCl3): 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.
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

12) Satisfactory microanalyses obtained: C ±0.35, H ±0.11