Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 14 (2004) 3635–3638

Biological evaluation of substituted quinolines

Xavier Franck,[a] Alain Fournet,[a,b] Eric Prina,[c] Renaud Mahieux,[d] Reynald Hocquemiller[a] and Bruno Figadère[a,*]

[a]*Laboratoire de Pharmacognosie (associé au CNRS-BioCIS), Faculté de Pharmacie, Université de Paris-Sud, rue J.B. Clément, 92296 Châtenay-Malabry, France*
[b]*Institut de Recherche pour le Développement (IRD), 213 rue Lafayette, 75480 Paris, France*
[c]*Unité d'Immunophysiologie et Parasitisme Intracellulaire, 25 rue du Dr. Roux, Institut Pasteur, 75724 Paris, France*
[d]*Unité d'Epidemiologie et Physiopathologie des Virus Oncogènes, 28 rue du Dr. Roux, Institut Pasteur, 75724 Paris, France*

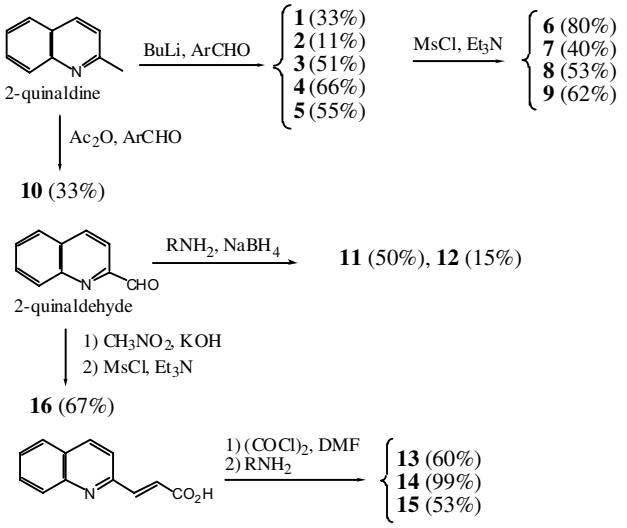
Received 24 March 2004; revised 11 May 2004; accepted 13 May 2004

Abstract—Several quinolines were synthesized and evaluated in vitro against several parasites (*Trypanosoma brucei*, *T. cruzi*, *Leishmania infantum*, *L. amazonensis*, *Plasmodium falciparum*). Then, they were evaluated in vitro (at 10 μM), against HTLV-1 transformed cells. A few of them displayed interesting activities, comparable to the reference drugs.

Parasitic diseases such as leishmaniases and trypanosomiases have significant impacts in developing countries, with infections spread over several hundred millions of people and are the cause of a mortality rate of several millions per year. Conventional chemotherapies are often inadequate, toxic or are becoming less effective due to emergence of numerous resistances.[1] There is, thus, an urgent need for new drugs for the chemotherapy of these diseases.

2-Alkylquinolines and 2-arylquinolines, isolated from plants[2] or prepared by total synthesis,[3a,b,c] have been investigated by us as new drug candidates. These low-molecular weight compounds exhibit pharmacological properties such as antiprotozoal activity (e.g. against *Leishmania* sp.,[4] *Plasmodium*,[5] *Trypanosoma* sp.[6]), and were found to inhibit the human immunodeficiency virus of type-1 (HIV-1) integrase,[7–9] as well as the proliferation of HTLV-1 transformed cell lines (HUT-102).[10] Imidazoquinolinamines such as imiquimod have also been found to be potent inducers of IFN-α and cytokines both in in vitro and in vivo experiments.[11] In this letter we report on the in vitro antiprotozoal activity of several 2-substituted quinolines and on the in vitro HTLV-1 activity of some of them.

Alcohols **1**–**5** were prepared by treating 2-quinaldine with *n*-butyllithium (1 equiv) followed by addition of the required aldehyde. Then compounds **6**–**9** were obtained by dehydration of the corresponding alcohols (by



Scheme 1. Synthesis of quinolines **1**–**16**.

Keywords: Protozoa; HTLV-1; Leishmaniases; Trypanozomiases.
* Corresponding author. Tel.: +33-01-46-83-55-92; fax:+33-01-46-83-53-99; e-mail: bruno.figadere@cep.u-psud.fr

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.05.026

Table 1

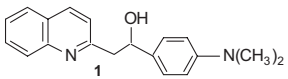
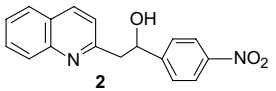
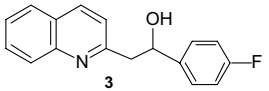
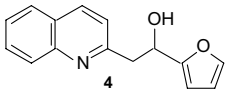
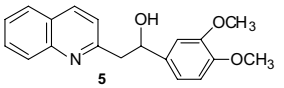
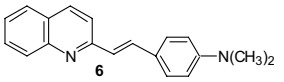
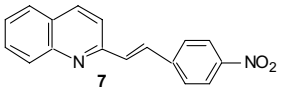
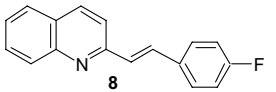
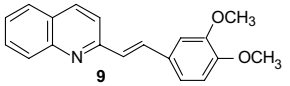
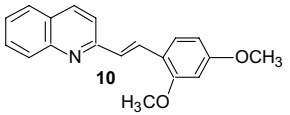
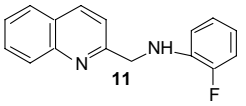
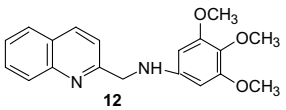
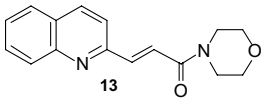
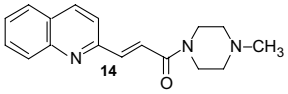
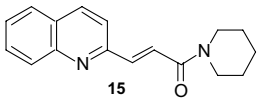
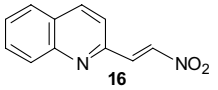
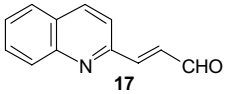
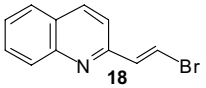
Compounds	*T. brucei*[a]	*T. cruzi*[b]	*L. infantum*[c]	*L. amazonensis*[d]	Cytox. macrophages	*P. falciparum*[e]		Cytox. MRC-5	HTLV-1[f](%) at 10 μM
						W2	Ghana		
	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	
 **1**	>32	>32	>32	>32	>32	>32	>32	>32	0
 **2**	>32	>32	>32	>32	>32	6	15	>32	10
 **3**	>32	>32	>32	>32	>32	1	4	>32	0
 **4**	>32	>32	>32	>32	>32	>32	>32	>32	0
 **5**	>32	>32	>32	>32	>32	>32	>32	>32	0
 **6**	6	17	>32	16	16	>32	>32	>32	26
 **7**	>32	28	>32	>32	>32	>32	>32	>32	0
 **8**	>32	22	>32	>32	>32	>32	>32	>32	26
 **9**	26	>32	22	>32	>32	>32	>32	>32	0
 **10**	18	>32	>32	>32	>32	30	>32	>32	0
 **11**	>32	>32	>32	>32	>32	>32	>32	>32	0

Table 1 (*continued*)

Compounds	*T. brucei*[a]	*T. cruzi*[b]	*L. infantum*[c]	*L. amazonensis*[d]	Cytox. macrophages	*P. falciparum*[e]		Cytox. MRC-5	HTLV-1[f](%) at 10 μM
						W2	Ghana		
	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	IC_{50} μM	
 **12**	>32	>32	>32	>32	>32	>32	>32	>32	0
 **13**	>32	13	18	>32	>32	16	12	>32	0
 **14**	>32	>32	>32	>32	>32	>32	>32	>32	0
 **15**	>32	17	16	18	>32	17	15	>32	0
 **16**	18	1	>8	>32	>32	14	16	22	76
 **17**	19	5	2	4	9	ND	31	16	34
 **18**	1	0.15	2	3	13	ND	>32	>32	ND
Suramin	0.09	ND	ND	ND	ND	ND	ND	ND	ND
Nifurtimox	ND	0.45	ND	ND	ND	ND	ND	ND	ND
Glucantime	ND	ND	7.15	ND	ND	ND	ND	ND	ND
Miltefosine	ND	ND	ND	3.12	12.5	ND	ND	ND	ND
Chloroquine	ND	ND	ND	ND	ND	0.11	0.018	ND	ND

ND—not determined.
[a] *Trypanosoma brucei* strain S427.
[b] *T. cruzi* strain Tulahuen CL2.
[c] *Leishmania infantum* strain MHOM-ET-67/L82.
[d] *L. amazonensis* strain MHOM/ET/L82/LV9.
[e] *P. falciparum* sensitive strain W2 and resistant strain Ghana.
[f] HTLV-1 infected HUT-102 cells.

treatment with mesyl chloride and triethyl amine), whereas compound **10**[12] was directly produced by the treatment of quinaldine and 2,4-dimethoxybenzaldehyde under reflux of acetic anhydride. Compounds **11** and **12** were obtained by reductive amination of 2-quinaldehyde with the corresponding amines. Amides **13**–**15** were obtained by coupling reaction of the unsaturated carboxylic acid chloride with the corresponding amines. Compound **16**[13] was obtained by nitroaldol condensation of 2-quinaldehyde with nitromethane, followed by mesyl chloride and triethyl amine treatment. Compounds **17** and **18** were prepared by published methods[3a,b,c] (Scheme 1). All the synthesized compounds gave satisfactory spectral data.

Anti-protozoal, anti-retroviral and cytotoxicity activities of the synthesized quinolines **1**–**18** are presented in a single Table 1. The tests against the amastigote forms of *T. brucei* and *T. cruzi*, were performed as described.[9] Compounds **6**, **16**, **17** showed the best activity, but were still less active than suramin and nifurtimox, whereas **18** (*T. cruzi*: $IC_{50} = 0.15\,\mu M$) was more active than the reference drug, nifurtimox (*T. cruzi*: $IC_{50} = 0.45\,\mu M$). Against the amastigote forms of *L. infantum*[9] the same compounds **17** and **18** were more active than the reference drug, glucantime ($IC_{50} = 2\,\mu M$, with glucantime $IC_{50} = 7.15\,\mu M$), whereas **16** was as active as the reference drug ($IC_{50} = 8\,\mu M$) and amides **13** and **15** showed some interesting activity ($IC_{50} = 18$ and $16\,\mu M$, respectively). Again, compounds **17** and **18** were as active as miltefosine, the oral reference drug ($IC_{50} = 3\,\mu M$), against the amastigote forms of *L. amazonensis*. Against *P. falciparum* resistant W2 strain, compound **3** showed a surprising activity ($IC_{50} = 1\,\mu M$, chloroquine: $IC_{50} = 0.11\,\mu M$), whereas the corresponding dehydrated compound **8** showed no activity. Against *P. falciparum* sensitive Ghana strain, the same compound **3** showed the best activity ($IC_{50} = 4\,\mu M$) but by far less active than chloroquine ($IC_{50} = 0.018\,\mu M$). Then, the synthesized compounds were tested against HTLV-1 transformed cells, as already reported.[10] The most active compound was **16**, showing 76% inhibition of the cells proliferation at $10\,\mu M$. Compounds **6**, **8**, **17** showed a weaker activity (26%, 26%, 34%, respectively) at $10\,\mu M$. It is interesting to note that the tested compounds did not show any cytotoxicity against normal cells, such as macrophages, except for compounds **17** and **18**.

In conclusion, this study showed that among the quinolines tested in these assays, a new 2-substituted quinoline, compound **16**, was found to exhibit promising antiprotozoal activity (against *T. cruzi*). A fluorinated product, compound **3**, showed an interesting activity against *P. falciparum*. Against HTLV-1 transformed cells, again compound **16** showed a significant inhibition activity. Further studies are now under way to evaluate their in vivo activity.

Acknowledgements

CNRS is acknowledged for financial support, and thanks are due to G. Epane, B. Vidovic, M. dos Santos for their technical helps. We wish to thank particularly Dr. J. R. L. Pink of Special Programme for Research and Training in Tropical Diseases (TDR) and Programme Drug Discovery (DDR). Association pour la Recherche contre le Cancer (ARC) is acknowledged for a financial support to R.M.

References and notes

1. Antoine, J. C.; Jouanne, C.; Ryter, A. *Parasitology* **1989**, *99*, 1547–1552.
2. (a) Fournet, A.; Hocquemiller, R.; Roblot, F.; Cavé, A.; Richomme, P.; Bruneton, J. *J. Nat. Prod.* **1993**, *56*, 1547–1552; (b) Fournet, A.; Vagneur, B.; Richomme, P.; Bruneton, J. *Can. J. Chem.* **1989**, *67*, 2116–2118.
3. (a) Fakhfakh, M. A. **2001**, Ph.D. Thesis. University of Pari-Sud, Châtenay-Malabry, France; (b) Fakhfakh, M. A.; Franck, X.; Fournet, A.; Hocquemiller, R.; Figadère, B. *Tetrahedron Lett.* **2001**, *42*, 3847–3850; (c) Fakhfakh, M. A.; Franck, X.; Hocquemiller, R.; Figadère, B. *J. Organomet. Chem.* **2001**, *624*, 131–135; (d) Fakhfakh, M. A.; Franck, X.; Fournet, A.; Hocquemiller, R.; Figadère, B. *Synth. Commun.* **2002**, *32*, 2863–2875; (e) Seck, M.; Franck, X.; Hocquemiller, R.; Figadère, B.; Peyrat, J. F.; Provot, O.; Brion, J. D.; Alami, M. *Tetrahedron Lett.* **2004**, *45*, 1881–1884.
4. Fournet, A.; Ferreira, M. E.; Torres de Ortiz, S.; Fuentes, S.; Nakayama, H.; Rojas de Arias, A.; Schinini, A.; Hocquemiller, R. *Antimicrob. Agents Chemother.* **1996**, *40*, 2447–2451.
5. Gantier, J. C.; Fournet, A.; Munos, M. H.; Hocquemiller, R. *Planta Med.* **1996**, *62*, 285–286.
6. Nakayama, H.; Ferreira, M. E.; Rojas de Arias, A.; de Bilbao, N. V.; Schinini, A.; Fournet, A. *Phytother. Res.* **2001**, *15*, 630–632.
7. Mekouar, K.; Mouscadet, J. F.; Desmaële, D.; Subra, F.; Leh, H.; Savouré, D.; Auclair, C.; d'Angelo, J. *J. Med. Chem.* **1998**, *41*, 2846–2857.
8. Zouhiri, F.; Mouscadet, J. F.; Mekouar, K.; Desmaële, D.; Savouré, D.; Leh, H.; Subra, F.; Le Bret, M.; Auclair, C.; d'Angelo, J. *J. Med. Chem.* **2000**, *43*, 1533–1540.
9. Fakhfakh, M. A.; Prina, E.; Mouscadet, J. F.; Fournet, A.; Franck, X.; Hocquemiller, R.; Figadère, B. *Bioorg. Med. Chem.* **2003**, *11*, 5013–5023.
10. Fournet, A.; Mahieux, R.; Fakhfakh, M. A.; Franck, X.; Hocquemiller, R.; Figadère, B. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 891–894.
11. Buates, S.; Matlashewski, G. *J. Infect. Dis.* **1999**, *179*, 1485–1494.
12. Bahner, C. T.; Rives, L. M.; McGaha, S. W.; Rutledge, D.; Ford, D.; Gooch, E.; Westberry, D.; Ziegler, D. *Arzneimittelforschung* **1981**, *31*, 404–406.
13. Shoeb, H. A.; Korkor, M. I.; Tammam, G. H. *Pharmazie* **1978**, *33*, 581–583.