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SCIENCE DIRECT
Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 16 (2006) 815–820

Synthesis and antiprotozoal activity of some new synthetic substituted quinoxalines

Xu Hui,[†] Julie Desrivot, Christian Bories, Philippe M. Loiseau, Xavier Franck, Reynald Hocquemiller and Bruno Figadère[*]

Address Laboratoire de Pharmacognosie et Groupe Chimiothérapie Antiparasitaire (associé au CNRS-BioCIS) Faculté de Pharmacie, Université de Paris-Sud, rue J.B. Clément, 92296 Châtenay-Malabry, France

Received 10 October 2005; revised 7 November 2005; accepted 7 November 2005
Available online 23 November 2005

Abstract—A series of 29 new quinoxalines was synthesized and evaluated in vitro against several parasites (*Leishmania donovani*, *Trypanosoma brucei brucei*, and *Trichomonas vaginalis*). Several of them displayed interesting activities, and particularly four quinoxaline amides showed in vitro antileishmanial properties (IC_{50} less than 20 μM).

Several hundred millions of people, in developing countries, faced infection diseases, due to parasites, such as leishmaniases and trypanosomiasis that have significant health and economical impacts because of a high mortality rate per year. There is, thus, an urgent need for new drugs for the chemotherapy of these diseases, since conventional treatments are often inadequate, toxic or are becoming less effective due to emergence of numerous resistances.[1]

In our search for new bioactive compounds, we have found that 2-alkylquinolines and 2-arylquinolines, isolated from plants[2] or prepared by total synthesis,[3a–c] can be new drug candidates, and exhibit antiprotozoal activity (e.g., against *Leishmania* sp.,[4] *Plasmodium*,[5] *Trypanosoma* sp.,[6] and *Trichomonas vaginalis*[7]), and were found to inhibit the human immunodeficiency virus of type-1 (HIV-1) integrase,[8–10] as well as the proliferation of HTLV-1 transformed cell lines (HUT-102).[11] In this letter, in continuation of the search for new antiparasitic compounds, we report on the in vitro antiprotozoal activity of several synthetic substituted quinoxalines.

Up to now, only a few quinoxaline derivatives have been prepared and evaluated against protozoa,[12] whereas quinoxaline derivatives are important components of several pharmacologically active compounds.[13] In this paper, we carried out new pharmacomodulations including substituents having antiprotozoal properties such as quinoline, and *p*-nitrophenyl moieties or substituents modifying the hydrophobicity of the compounds, such as alkyl chains (C6 to C15) and various aromatic rings. Thus, new quinoxaline amides and amines **1**–**29** were prepared by treating 2-amino-4-nitroaniline with several 1,2-dioxoalkanes (1 equiv.)[14] followed by nitro-reduction and either amide formation (compounds **1**–**8**) or reductive amination (for compounds **14**–**18**) (Scheme 1). For the bromo derivatives, bromination of the intermediate 7-aminoquinoxaline was performed prior to amide formation (compounds **9**–**13**, Scheme 1). Whereas quinoxalines **19**–**29** were obtained by condensation of 2-amino-4-aminobenzoic acid with several 1,2-dioxoalkanes (1 equiv) followed by amide formation (compounds **19**–**29**, Scheme 2). All the 29 synthesized compounds gave satisfactory spectral data (^1H and ^{13}C NMR data, MS and UV spectroscopic data). Then compounds **1**–**29** were evaluated against several parasites (*Leishmania donovani*, *Trypanosoma brucei brucei*, and *T. vaginalis*).

Antiprotozoal activities of the synthesized quinoxalines **1**–**29** are presented in Table 1. Against the promastigote forms of *L. donovani*[15] compounds **5**, **6**, **7**, and **27** were the most active ones (with IC_{50}: 12.5, 8.2, 18.5, and 18.4 μM, respectively) being slightly less potent than the reference drug, miltefosine (IC_{50}: 7.3 μM). Interestingly, compounds **26**, **27**, and **28** in which the amide

Keywords: Quinoxalines; Amides; Amines; Synthesis; Bioassays.
* Corresponding author. Tel.: +33 01 46 83 55 92; fax: +33 01 46 83 53 99; e-mail: bruno.figadere@cep.u-psud.fr
† Present address: College of Life Science, Northwest Sci-Tec University of Agriculture and Forestry, China.

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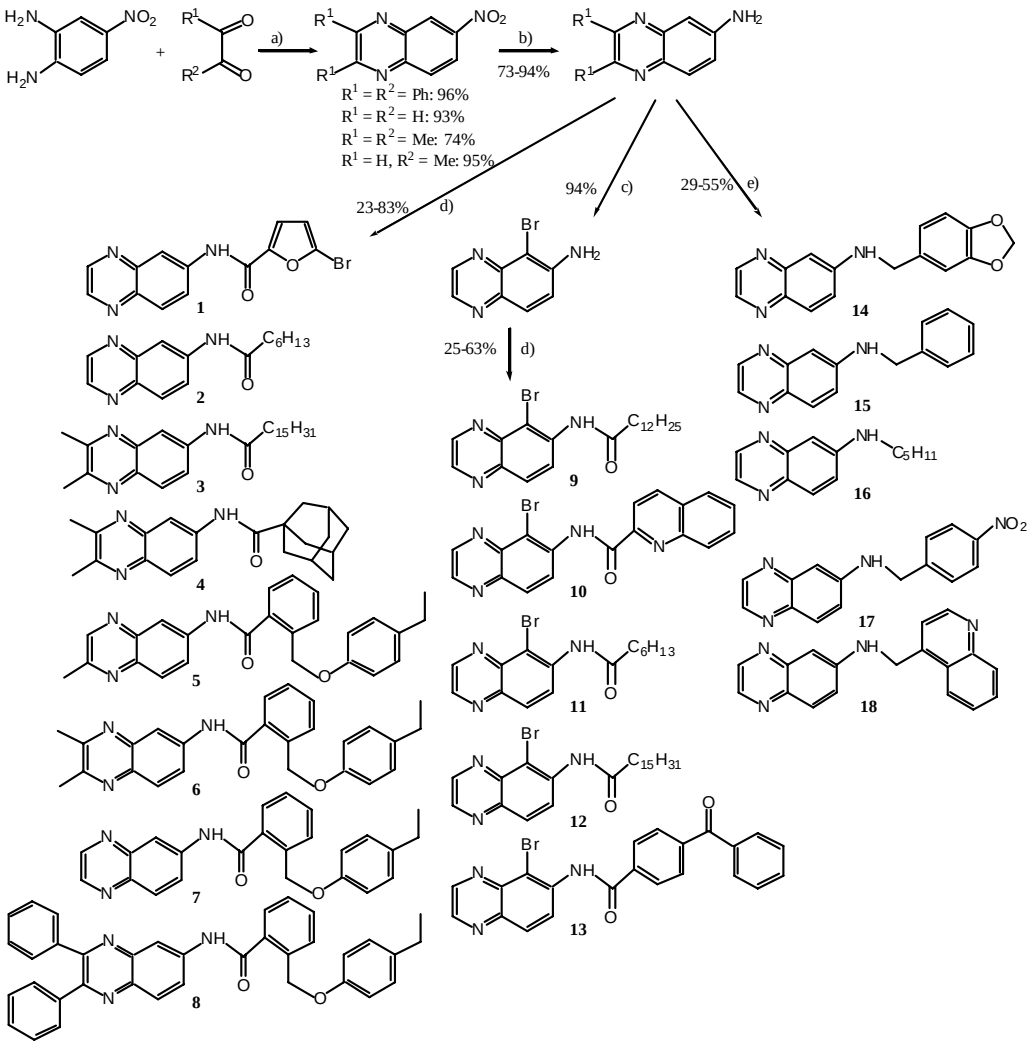
doi:10.1016/j.bmcl.2005.11.025



Scheme 1. Reagents and condition: Synthesis of quinoxalines **1**–**18**: (a) HOAc or EtOH reflux; (b) $SnCl_2$, EtOH; (c) Br_2, HOAc; (d) EDC, HOBt, Et_3N or oxalyl chloride then Et_3N, RCO_2H, RNH_2; (e) $NaBH_3CN$, HOAc, RCHO.

bond has been inverted showed different activities (IC_{50}: >300, 18.4, >300 μM, respectively). However, the amide group position did not seem to be essential for antileishmanial properties since compound **27** had similar activity as compound **7**. The sole other quinoxaline amide showing some activity is compound **2** (IC_{50}: 116.9 μM) possessing a simple aliphatic side chain. Then aminoquinoxalines **14**, **15**, **16**, and **18** showed moderate activity (IC_{50}: 79.5, 92.4, 46.3, and 34.0 μM, respectively), but to a lesser extent that the previous compounds. All other tested quinoxalines did not show any activity against *L. donovani*. The tests against the trypomastigote forms of *T. b. brucei* were performed as described.[16] The same compounds **27**, **5**, **6**, and **7** showed again activity, expressed as minimum active concentration (MAC: 200, 200, 200, and 150 μM, respectively), but were by far less active than melarsoprol, the reference drug (MAC: 0.1 μM). Although the quinoxaline amide derivative **24** showed also a slight activity (MAC: 200 μM), all other quinoxalines did not show any particular activity (MAC >300 μM). Against *T. vaginalis*,[17] the aminoquinoxalines **15**, **16**, **17** and the amide **7** showed an activity (IC_{50}: 264, 243, 191, and 126 μM, respectively), being still less potent than the reference drug, metronidazole (IC_{50}: 5.8 μM), whereas the other compounds showed no activity.

Concerning the specificity of action, compounds **2**, **14**, and **18** specifically act on *L. donovani* promastigotes, compound **24** on *T. b. brucei* trypomastigotes, and compound **17** on *T. vaginalis*, suggesting the possibility of action on target specific to each parasite. However, compounds **7** act in the same way against the three Protozoa, suggesting that this compound could affect target(s) common to the three parasites. The difference in these activities could also be the result of compound uptake that is different in these parasites.

In conclusion, this study showed that among the 29 quinoxalines tested in these assays, four of them were found to exhibit interesting antileishmanial activity against *L. donovani* (IC_{50} less than 20 μM), five of them against *T. b. brucei*, and four of them against *T. vaginalis*. No clear-cut structure–activity relationship emerged in this series although, none of the brominated quinoxalines displayed any activity, neither any