Multicomponent Synthesis of New Primaquine Thiazolidinone Derivatives

Patrícia D. Neuenfeldt,[a] Bruna B. Drawanz,[a] Anna Caroline C. Aguiar,[b,c] Flávio Figueiredo Jr.,[b] Antoniana U. Krettli,[b,c] Wilson Cunico*[a]

[a] Núcleo de Química Aplicada, Centro de Ciências Químicas, Farmacêuticas e de Alimentos, UFPel, Campus Universitário s/no, 96010-900, Pelotas, RS, Brazil
Fax +55(53)32757454; E-mail: wjcunico@yahoo.com.br

[b] Centro de Pesquisas René Rachou-Fiocruz, Laboratório de Malária, Av. Augusto de Lima 1715, 30190-002 Belo Horizonte, MG, Brazil

[c] Universidade Federal de Minas Gerais, Programa de Pós Graduação em Medicina Molecular, Faculdade de Medicina, Av. Alfredo Balena, 30130-100 Belo Horizonte, MG, Brazil

Received 3 September 2011; revised 26 September 2011

Abstract: Primaquine thiazolidinone derivatives, potentially useful as antimalarial agents, were synthesized in good yields by multicomponent reactions of primaquine diphosphate, mercaptoacetic acid, and an optionally substituted benzaldehyde or cyclohexanone for two to four hours. All the products were characterized by ^{1}H and ^{13}C NMR spectroscopy and by LC-MS.

Key words: heterocycles, multicomponent reactions, cyclocondensations, antimalarials

Malaria is one of the most devastating of human diseases and accounts for more than 800,000 human deaths each year, largely among children under five years of age. In Brazil, the disease is endemic in the Amazon region, causing over 500,000 cases annually.[1] Among the five species of parasites known to infect humans,[2] *Plasmodium vivax* is the most common and *P. falciparum* the most deadly. The disease is a consequence of invasion by the parasite, which replicates within red blood cells following an asymptomatic replicative stage inside hepatocytes. Because of the impact of malaria on human health, there is a pressing need to develop new antimalarial drug therapies.[3] The high rate of mutation of the parasites, which can lead to the development of drug resistance, means that effective drugs with known or new mechanisms of action are urgently needed.[4]

Primaquine (PQ), which was synthesized in 1946, is the most representative member of the family of 8-aminoquinolines that are effective against the liver stages of all malarial parasites. Because PQ is rather toxic, several new compounds have been prepared by modification of the terminal amino group of PQ.[5] Bulaquine (Figure 1) is a potent new antimalarial PQ analogue that is currently undergoing Phase II clinical trials. Unlike other PQ analogues, bulaquine has no free amino group and, as a result, causes less hemolysis than PQ in individuals who are deficient in glucose-6-phosphate hydrogenase.[6,7]

The heterocycle thiazolidinone is a five-membered ring that is widely used in medicinal chemistry.[8,9] Its derivatives show a diverse range of biological activities, for example, as antimicrobials,[10] anti-inflammatory agents,[11] tuberculostatic agents,[12] or anti-HIV agents.[13] We recently reported a synthesis of thiazolidinones by cyclocondensation of an aldehyde or ketone with mercaptoacetic acid and phenylhydrazine or 2,4-dinitrophenylhydrazine as the amino fragment.[14] Our research group has also been studying unconventional methods for the synthesis of thiazolidinones by using ultrasound irradiation to reduce reaction times.[15] Thiazolidinones have also been synthesized by means of microwave irradiation[16] or ionic liquid-phase catalysis.[17] Recently, Pratap and co-workers[18] described an efficient synthesis of such heterocycles by biocatalysis with *Saccharomyces cerevisiae* (baker's yeast).

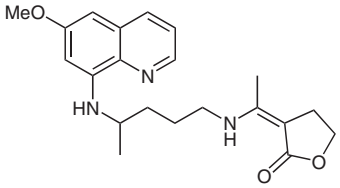
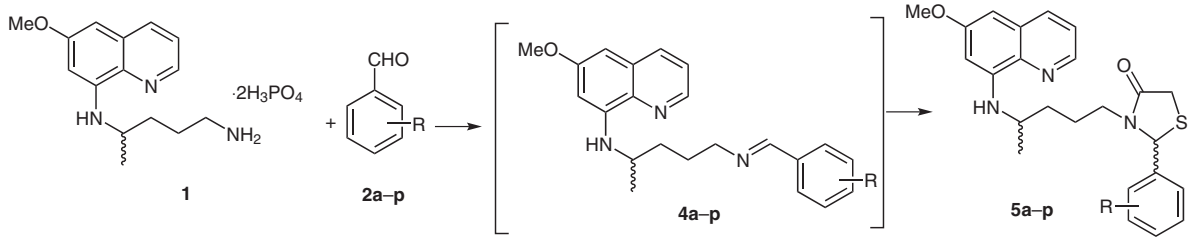


Figure 1 Structure of bulaquine

Solomon and co-workers[19] reported the use of thiazolidinone and thiazinanone chloroquine analogues as antimalarial agents that exhibit superior *in vitro* activity against *P. falciparum* compared with the standard drug chloroquine. In the present work, therefore, our aim was to explore primaquine as an amino precursor for the synthesis of thiazolidinone primaquine derivatives, potentially useful as antimalarial agents.

The target compounds were prepared as outlined in Scheme 1. In our first attempt to obtain the primaquine thiazolidinone derivatives **5j**, a mixture of primaquine diphosphate (**1**; one equivalent), *N*,*N*-diisopropylethylamine (DIPEA; two equivalents), 4-nitrobenzaldehyde (**2j**; two equivalents), and an excess of mercaptoacetic acid (**3**) was heated at 110 °C for 16 h overnight, as reported in the literature (Scheme 1).[12] However, when this cyclocondensation reaction was carried out overnight, it produced large amounts of insoluble impurities and gave very low yields of products (< 20%). When the reaction was monitored every hour by thin-layer chromatography

SYNTHESIS 2011, No. 23, pp 3866–3870
Advanced online publication: 27.10.2011
DOI: 10.1055/s-0031-1289580; Art ID: M85911SS



Scheme 1 *Reagents and conditions*: DIPEA, $HSCH_2CO_2H$ (**3**), toluene, 110 °C, Dean–Stark distillation, 2–4 h.

(TLC) using hexane/ethyl acetate (3:1) as eluent, product **5j** was observed to be formed in three hours.

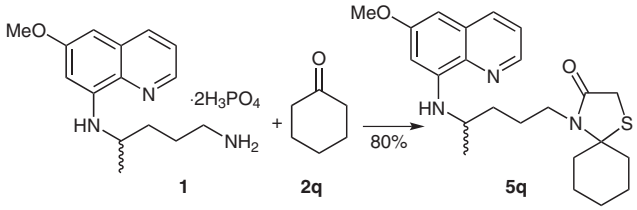
We therefore prepared the 3-[4-(6-methoxyquinolin-8-ylamino)pentyl]-2-aryl-1,3-thiazolidin-4-ones **5a**–**p** by a one-pot multicomponent reaction of primaquine diphosphate (**1**), DIPEA, benzaldehyde **2a**–**p**, and an excess of mercaptoacetic acid (**3**) in refluxing toluene for two to four hours while monitoring the reaction by TLC (Scheme 1). The desired heterocycles were obtained in moderate-to-good yields (37–89%) after purification of the crude product by column chromatography on silica gel (Table 1). Similar yields were obtained by adding the mercaptoacetic acid to a mixture of primaquine diphosphate, DIPEA, and the benzaldehyde that had previously been refluxed for one hour, and then refluxing the resultant mixture for an additional three hours or more. To our surprise, when 2-formylbenzonitrile was used as the aldehyde, the product **5** (R = 2-CN) was not obtained and, instead, a complex mixture of products was formed.

Table 1 Yields and LC-MS of Compounds **5a**–**p**

Product	R	Yield[a] (%)	Time (h)	LC-MS (*m/z*) (%)
5a	H	86	4	444.2 $[M + 23]^+$ (100)
5b	2-F	44	2	462.5 $[M + 23]^+$ (100)
5c	3-F	89	2	462.5 $[M + 23]^+$ (100)
5d	4-F	89	3	462.5 $[M + 23]^+$ (100)
5e	2-Cl	66	3	478.3 $[M + 23]^+$ (100)
5f	3-Cl	70	3	478.5 $[M + 23]^+$ (100)
5g	4-Cl	52	2	478.3 $[M + 23]^+$ (100)
5h	2-NO_2	59	3	489.5 $[M + 23]^+$ (100)
5i	3-NO_2	37	4	489.5 $[M + 23]^+$ (100)
5j	4-NO_2	52	3	489.5 $[M + 23]^+$ (100), 462.5 (40%)
5k	2-OMe	72	2	474.6 $[M + 23]^+$ (100)
5l	3-OMe	88	4	474.4 $[M + 23]^+$ (100)
5m	4-OMe	87	2	474.3 $[M + 23]^+$ (100)
5n	3-CN	41	3	469.3 $[M + 23]^+$ (100)
5o	4-CN	87	4	469.3 $[M + 23]^+$ (100)
5p	4-Me	89	3	458.5 $[M + 23]^+$ (100), 436.6 (83%)

[a] Yield of pure compound after chromatography.

To gain further insight into the nature of the reaction, we used the cyclohexanone **2q** as the carbonyl precursor in the one-pot reaction with primaquine (**1**) and mercaptoacetic acid (**3**) to give the spirothiazolidinone **5q** in a good yield (Scheme 2).



Scheme 2 *Reagents and conditions*: DIPEA, $HSCH_2CO_2H$ (**3**), toluene, 110 °C, Dean–Stark distillation, 3 h.

The analytical and spectral data (^1H and ^{13}C NMR) for all the compounds were in full agreement with the proposed structures (Figure 2). We used two-dimensional NMR techniques (HMBQ, HMQC and COSY) to help us assign the signals of the compounds correctly. As expected, the presence of two asymmetric carbons in the primaquine thiazolidinone derivatives **5a**–**p** resulted in the formation of a pair of diastereoisomers that were clearly observed in a 1:1 proportion in the NMR spectra. The H2 hydrogen (the CH of the thiazolidinone ring) appears as a singlet (or a doublet with a small coupling constant) at 5.38–5.97 ppm for each of the diastereoisomers. The appearances of the aromatic signals having the relative integrations expected for the quinoline ring or the benzaldehyde residue were as expected from the structures of the compounds. The ^1H NMR spectrum showed hydrogen signals for the methylene group of the thiazolidinone ring overlapping other aliphatic signals; the corresponding signals in the ^{13}C NMR could, however, be clearly observed at 31–33 ppm.

The racemic primaquine spirothiazolidinone derivative **5q** is characterized by an absence of hydrogen at the 2-position of the thiazolidine ring. Its ^{13}C NMR spectrum exhibited peaks at δ = 170.1, 73.2, and 33.2 ppm, corresponding to the C4 (C=O), C2 (quaternary), and C5 (CH_2) carbon atoms of the thiazolidinone ring, respectively.

In conclusion, seventeen new primaquine thiazolidinone derivatives were readily synthesized in moderate-to-good yields by a one-pot cyclocondensation reaction. The synthesized compounds are good starting points for develop-

ing new lead antimalarials, and a biological study is ongoing. There is an urgent need to identify new antimalarials to replace primaquine, and they would be especially useful if they were also active against the blood stages of the deadly *P. falciparum* parasite.

Unless otherwise indicated, all common reagents and solvents were used as obtained from commercial suppliers without further purification. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX 400 spectrometer (^{1}H at 400.14 MHz and ^{13}C at 100.61 MHz) or with a Bruker Avance 500 spectrometer (^{1}H at 500.13 MHz and ^{13}C at 125.75 MHz) in $CDCl_3$ or DMSO-d_6 containing TMS as an internal standard. The low-resolution LC-MS analyses were performed on a Micromass ZMD instrument using 1:1 $CHCl_3$–MeOH as the mobile phase at a flux of 0.3 mL/min. These analyses used electrospray ionization in the positive-ion mode, and the samples were introduced by the standard direct-insertion probe method.

Primaquine Thiazolidinone Analogues 5a–q: General Procedure

A soln of primaquine diphosphate (**1**; 2.275 g, 5 mmol), DIPEA (1.292 g, 1.74 mL, 10 mmol), benzaldehyde **2a–p** (0.435–0.466 g, 10 mmol) or cyclohexanone **2q** (0.490 g, 10 mmol), and $HSCH_2CO_2H$ (**3**; 1.380 g, 1.05 ml, 15 mmol) in toluene (50 mL) was refluxed with a Dean–Stark trap for 2–4 until the reagents were completely consumed (TLC). The organic layer was then washed with sat. aq $NaHCO_3$ (3 × 50 mL), dried ($MgSO_4$), and concentrated to give a crude product that was purified by column chromatography [silica gel 60 (0.2–0.5 mm), hexane–EtOAc (7:3)] to give an oil (R_f = 0.1). The generic structures and atom-numbering of compounds **5** are given in Figure 2.

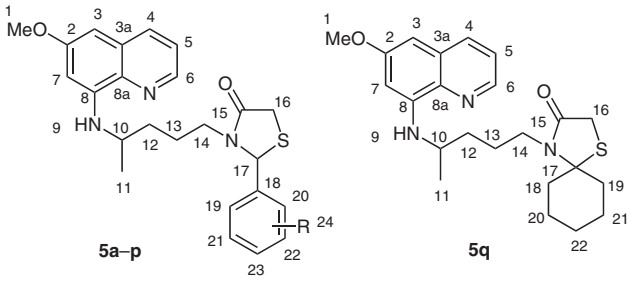


Figure 2 Primaquine thiazolidinone derivatives **5a–q**

3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-phenyl-1,3-thiazolidin-4-one (5a)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (2d, ^3J = 6.6 Hz, 6 H, H-11), 1.58 (m, 8 H, H-12 and H-13), 2.70 (m, 2 H, H-14b), 3.70 (m, 8 H, H-10, H-14a, and H-16), 3.89 (s, 6 H, H-1), 5.48 and 5.59 (2s, 2 H, H-17), 5.95 (s, 2 H, H-9), 6.23 (2d, ^4J = 2.2 Hz, ^4J = 2.5 Hz, 2 H, H-3), 6.34 (d, ^4J = 2.0 Hz, 2 H, H-7), 7.32 (m, 12 H, Ph and H-5), 7.92 (d, ^3J = 8.0 Hz, 2 H, H-4,), 8.53 (d, ^3J = 4.2, 2 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.4 and 20.6 (C11), 23.1 and 23.2 (C13), 32.8 and 32.9 (C16), 33.2 and 33.6 (C12), 42.6 and 42.7 (C14), 47.5 and 47.6 (C10), 55.2 (C1), 63.3 and 63.4 (C17), 91.6, 91.7, 96.7, 96.9, 121.9, 127.0, 128.9, 129.1, 129.8, 129.9, 134.7, 134.8, 153.3, 139.2, 139.3, 144.2, 144.3 (aryl), 159.4 and 159.5 (C2), 171.1 and 171.2 (C15).

2-(2-Fluorophenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5b)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (m, 6 H, H-11), 1.60 (m, 8 H, H-12 and H-13), 2.74 (m, 2 H, H-14b), 3.53 (m, 2 H, H-14a), 3.68 (dd, ^2J = 15.4 Hz, ^4J = 3.2 Hz, 2 H, H-16b), 3.79 (m, 2 H, H-10), 3.83 (ddd, ^2J = 15.1 Hz, ^4J = 5.0 Hz, ^4J = 1.5 Hz, 2 H, H-16a), 3.89 (s, 6 H, H-1), 5.85 and 5.90 (2d, ^4J = 1.7 Hz, 2 H, H-17), 5.95 (br s, 2 H, H-9), 6.23 (2d, ^4J = 2.3 Hz, 2 H, H-3), 6.35 (d, ^4J = 2.3 Hz, 2 H, H-7), 7.15 (m, 6 H, Ph), 7.23 (m, 2 H, Ph), 7.31 (ddd, ^3J = 8.0 Hz, ^3J = 4.3 Hz, ^5J = 1.0 Hz, 2 H, H-5), 7.92 (d, ^3J = 8.0 Hz, 2 H, H-4), 8.53 (m, 2 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 and 20.8 (C11), 23.7 (C13), 29.9 (C16), 33.7 and 33.9 (C12), 43.1 and 43.2 (C14), 47.7 and 47.9 (C10), 55.4 (C1), 57.1 and 57.2 (C17), 91.8, 91.9, 96.9, 97.0, 116.2, 116.4, 122.0, 124.8, 124.9, 127.0, 127.1, 128.1, 128.2, 130.1, 130.7, 130.8, 134.8, 134.9, 135.5, 144.4, 145.0, 145.1 (aryl), 159.6 (C2), 160.5 (d, $^1J_{C-F}$ = 250 Hz, C20), 171.5 (C15).

2-(3-Fluorophenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5c)

^{1}H NMR (500 MHz, DMSO-d_6): δ = 1.16 (d, ^3J = 6.4 Hz, 6 H, H-11), 1.40 (m, 8 H, H-12 and H-13), 2.62 (m, 2 H, H-14b), 3.53 (m, 4 H, H-10 and H-14a), 3.64 (2d, ^2J = 15.6 Hz, 2 H, H-16b), 3.81 (s, 6 H, H-1), 3.88 (2dd, ^2J = 15.6 Hz, ^4J = 4.9 Hz, 2 H, H-16a), 5.76 and 5.83 (2s, 2 H, H-17), 6.06 (t, ^3J = 9.8 Hz, 2 H, H-9), 6.20 (s, 2 H, H-3), 6.47 (d, ^4J = 1.9 Hz, 2 H, H-7), 7.14 (m, 6 H, Ph), 7.35 (m, 2 H, Ph), 7.42 (dd, ^3J = 7.8 Hz, ^3J = 3.9 Hz, 2 H, H-5), 8.07 (d, ^3J = 8.2 Hz, 2 H, H-4), 8.53 (d, ^3J = 4.0 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, DMSO-d_6): δ = 9.9 and 20.1 (C11), 22.9 and 23.1 (C13), 31.8 (C16), 32.6 and 32.9 (C12), 42.2 (C14), 46.8 (C10), 55.0 (C1), 61.1 and 61.2 (C17), 91.7, 91.8, 96.1, 96.3, 113.5, 113.7, 115.5, 115.6, 122.1, 122.8, 129.6, 130.8, 130.9, 134.5, 134.8, 143.4, 143.5, 144.3, 144.5, 144.6 (aryl), 159.0 (C2), 162.3 (d, $^1J_{C-F}$ = 243.7 Hz, C22), 170.7 (C15).

2-(4-Fluorophenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5d)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (2d, ^3J = 5.8 Hz, 6 H, H-11), 1.50 (m, 8 H, H-12 and H-13), 2.65 (m, 2 H, H-14b), 3.60 (m, 2 H, H-14a), 3.78 (m, 6 H, H-10 and H-16), 3.89 (s, 6 H, H-1), 5.45 and 5.56 (2s, 2 H, H-17), 5.93 (br s, 2 H, H-9), 6.22 (2d, ^4J = 2.9 Hz, ^4J = 1.9 Hz, 2 H, H-3), 6.35 (d, ^4J = 1.9 Hz, 2 H, H-7), 6.93 (m, 4 H, Ph), 7.16 (m, 4 H, Ph), 7.33 (m, 2 H, H-5), 7.93 (m, 2 H, H-4), 8.54 (m, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6 and 20.8 (C11), 23.2 (C13), 33.0 and 33.2 (C16), 33.6 (C12), 42.8 (C14), 47.4 and 47.7 (C10), 55.9 (C1), 62.8 (C17), 91.8, 91.9, 96.8, 97.0, 115.8, 116.2, 116.3, 121.9, 128.9, 129.1, 130.0, 134.8, 134.9, 135.4, 144.3, 144.9, 145.0 (aryl), 159.5 (C2), 165.4 (C23), 171.0 and 171.1 (C15).

2-(2-Chlorophenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5e)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.30 (2d, ^3J = 5.8 Hz, 6 H, H-11), 1.65 (m, 8 H, H-12 and H-13), 2.70 (m, 2 H, H-14b), 3.63 (m, 2 H, H-14a), 3.65 (2d, ^2J = 15.6 Hz, 2 H, H-16b), 3.74 (dd, ^2J = 16.6 Hz, ^4J = 5.8 Hz, 2 H, H-16a), 3.83 (m, 2 H, H-10), 3.89 (s, 6 H, H-1), 5.97 (d, ^3J = 8.0 Hz, 2 H, H-9), 6.02 and 6.06 (2s, 2 H, H-17), 6.23 (2d, ^4J = 1.9 Hz, 2 H, H-3), 6.35 (d, ^4J = 1.9 Hz, 2 H, H-7), 7.20 (m, 6 H, Ph), 7.31 (m, 2 H, Ph), 7.33 (m, 2 H, H-5), 7.92 (dd, ^3J = 7.8 Hz, ^4J = 1.9 Hz, 2 H, H-4), 8.53 (m, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.5 and 20.6 (C11), 23.5 (C13), 32.3 (C16), 33.5 and 33.7 (C12), 43.0 and 43.1 (C14), 47.5 and 47.7 (C10), 55.2 (C1), 59.6 (C17), 91.7, 96.6, 96.7, 121.8, 127.5, 129.7, 129.9, 130.2, 132.8, 134.7, 135.3, 144.2, 144.8, 144.9 (aryl), 159.4 (C2), 171.7 (C15).

2-(3-Chlorophenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5f)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (2d, ^3J = 5.8 Hz, 6 H, H-11), 1.60 (m, 8 H, H-12 and H-13), 2.68 (m, 2 H, H-14b), 3.63 (m, 4 H, H-10 and H-14a), 3.74 (m, 2 H, H-16b), 3.83 (m, 2 H, H-16a), 3.89

(s, 6 H, H-1), 5.39 and 5.53 (2s, 2 H, H-17), 5.94 (br s, 2 H, H-9), 6.25 (2d, ^4J = 2.9 Hz, ^4J = 1.9 Hz, 2 H, H-3), 6.35 (d, ^4J = 2.9 Hz, 2 H, H-7), 7.03 (m, 2 H, Ph), 7.20 (m, 6 H, Ph), 7.32 (dd, ^3J = 7.8 Hz, ^3J = 3.9 Hz, 2 H, H-5), 7.93 (d, ^3J = 7.8 Hz, 2 H, H-4), 8.52 (d, ^3J = 3.9 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.4 and 20.6 (C11), 23.5 (C13), 32.5 (C16), 33.5 and 33.8 (C12), 42.9 (C14), 47.6 and 47.7 (C10), 55.4 (C1), 59.1 (C17), 91.9, 96.0, 96.1, 121.2, 127.6, 129.7, 129.8, 130.1, 132.3, 134.8, 135.3, 144.0, 144.7, 144.9 (aryl), 159.2 (C2), 171.3 (C15).

2-(4-Chlorophenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5g)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.15 (2d, ^3J = 5.8 Hz, 6 H, H-11), 1.48 (m, 8 H, H-12 and H-13), 2.69 (m, 2 H, H-14b), 3.73 (m, 8 H, H-16, H-10, and H-14a), 3.87 (s, 6 H, H-1), 5.44 and 5.55 (2s, 2 H, H-16), 5.93 (br s, 2 H, H-9), 6.23 and 6.26 (2d, ^4J = 1.9 Hz, 2 H, H-3), 6.33 (d, ^4J = 1.9 Hz, 2 H, H-7), 7.30 (m, 4 H, Ph), 7.44 (m, 2 H, Ph), 7.61 (m, 2 H, Ph), 7.91 (m, 2 H, H-5), 8.05 (d, ^3J = 8.0 Hz, 2 H, H-4), 8.53 (d, ^3J = 4 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6 and 20.8 (C11), 23.1 (C13), 32.9 and 33.0 (C16), 33.6 (C12), 42.5 (C14), 47.7 (C10), 55.3 (C1), 62.7 (C17), 91.8, 91.9, 95.8, 96.8, 97.0, 121.9, 128.4, 128.2, 129.3, 134.8, 137.7, 144.4, 145.0 (aryl), 159.5 (C2), 171.0 (C15).

3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-(2-nitrophenyl)-1,3-thiazolidin-4-one (5h)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (2d, ^3J = 5.8 Hz, 6 H, H-11), 1.66 (m, 8 H, H-12 and H-13), 2.62 (m, 2 H, H-14b), 3.58 (m, 2 H, H-14a), 3.59 (d, ^2J = 15.6 Hz, 2 H, H-17b), 3.68 (d, ^2J = 15.6 Hz, 2 H, H-17a), 3.82 (m, 2 H, H-10), 3.83 (s, 6 H, H-1), 6.08 (br s, 2 H, H-9), 6.21 (m, 4 H, H-3 and H-17), 6.47 (d, ^4J = 1.9 Hz, 2 H, H-7), 7.33 (m, 6 H, Ph), 7.42 (m, 2 H, Ph), 7.63 (m, 2 H, H-5), 7.91 (d, ^3J = 7.8 Hz, 2 H, H-4), 8.04 (2d, ^3J = 6.8 Hz, 2 H, Ph), 8.51 (m, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7 (C11), 23.6 (C13), 31.8 (C16), 33.6 and 33.9 (C12), 43.5 (C14), 47.4 and 47.9 (C10), 55.2 (C1), 58.6 (C17), 91.8, 91.9, 96.7, 96.8, 121.9, 125.9, 126.2, 129.2, 129.3, 129.9, 134.4, 134.7, 134.8, 135.3, 136.6, 144.4, 144.9 (aryl), 159.4 (C2), 172.3 (C15).

3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-(3-nitrophenyl)-1,3-thiazolidin-4-one (5i)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (2d, ^3J = 6.8 Hz, 6 H, H-11), 1.60 (m, 8 H, H-12 and H-13), 2.71 (m, 2 H, H-14b), 3.57 (m, 4 H, H-10 and H-14a), 3.74 (m, 2 H, H-16b), 3.80 (m, 2 H, H-16a), 3.89 (2s, 6 H, H-1), 5.50 and 5.65 (s, 1 H, H-17), 5.89 (br s, 2 H, H-9), 6.18 and 6.21 (2d, ^4J = 1.9 Hz, 2 H, H-3), 6.34 (2d, ^4J = 2.9 Hz, 2 H, H-7), 7.32 (m, 2 H, Ph), 7.43 (m, 4 H, Ph), 7.94 (m, 2 H, H-5), 8.02 (m, 2 H, Ph), 8.05 (m, ^3J = 8.8 Hz, 2 H, H-4), 8.53 (s, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7 and 20.9 (C11), 23.0 and 23.2 (C13), 32.9 (C16), 33.7 (C12), 42.8 and 43.1 (C14), 47.3 and 47.6 (C10), 55.2 and 55.3 (C1), 62.4 (C17), 91.8, 91.9, 96.7, 97.0, 122.0, 123.9, 124.0, 130.0, 130.1, 132.6, 132.7, 134.9, 135.9, 141.9, 144.4 (aryl), 159.4 (C2), 171.1 and 171.2 (C15).

3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-(4-nitrophenyl)-1,3-thiazolidin-4-one (5j)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (m, 6 H, H-11), 1.60 (m, 8 H, H-12 and H-13), 2.65 (m, 2 H, H-14b), 3.57 (m, 4 H, H-10 and H-14a), 3.68 (m, 2 H, H-16b), 3.82 (m, 2 H, H-16a), 3.87 and 3.90 (2s, 6 H, H-1), 5.50 and 5.62 (2d, ^4J = 1.2 Hz, 2 H, H-17), 6.11 and 6.22 (2d, ^4J = 2.5 Hz, 2 H, H-3), 6.34 (2d, ^4J = 2.5 Hz, 2 H, H-7), 7.32 (m, 4 H, Ph), 7.35 (m, 2 H, H-5), 7.97 (m, 2 H, Ph), 8.08 (d, ^3J = 8.8 Hz, 2 H, H-4), 8.55 (2dd, ^3J = 4.2 Hz, ^4J = 1.5 Hz, 2 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9 and 21.0 (C11), 22.9 and 23.3 (C13), 32.9 and 33.0 (C16), 33.1 and 33.4 (C12), 42.6 and 43.2 (C14), 47.0 and 47.8 (C10), 55.4 (C1), 62.3 and 62.4 (C17), 92.0, 92.1, 96.9, 97.1, 122.1, 124.3, 124.4, 127.7, 127.8, 128.6, 130.1, 130.2, 133.5, 134.1, 134.2, 135.4, 144.5, 144.9, 146.6, 146.8, 148.1, 148.2 (aryl), 159.5 (C2), 171.2 and 171.3 (C15).

2-(2-Methoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5k)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.26 (2d, ^3J = 6.8 Hz, 6 H, H-11), 1.80 (m, 8 H, H-12 and H-13), 2.71 (m, 2 H, H-14b), 3.60 (m, 4 H, H-10 and H-14a), 3.74 (m, 4 H, H-16), 3.76 and 3.81 (2s, 6 H, H-24), 3.88 (s, 6 H, H-1), 5.96 (m, 4 H, H-9 and H-17), 6.24 (m, 2 H, H-3), 6.33 (s, 2 H, H-7), 6.87 (m, 4 H, Ph), 7.06 (2d, ^3J = 6.8 Hz, 2 H, Ph), 7.25 (m, 2 H, Ph), 7.30 (dd, ^3J = 7.8, ^3J = 3.9, 2H, H-5), 7.92 (d, ^3J = 8.8 Hz, 2 H, H-4), 8.52 (2d, ^3J = 3.9 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6 (C11), 23.6 and 23.8 (C13), 32.8 (C16), 33.8 (C12), 43.0 and 43.1 (C14), 47.7 and 47.9 (C10), 55.2 (C24), 55.5 (C1), 57.8 and 57.9 (C17), 91.7, 96.7, 96.8, 111.0, 120.9, 121.9, 126.7, 127.6, 129.8, 129.9, 134.8, 135.4, 144.3, 145.0 (aryl), 156.9 and 159.5 (C2), 171.9 (C15).

2-(3-Methoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5l)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.26 (2d, ^3J = 6.3 Hz, 6 H, H-11), 1.75 (m, 8 H, H-12 and H-13), 2.75 (m, 2 H, H-14b), 3.58 (m, 4 H, H-10 and H-14a), 3.68 (m, 2 H, H-16b), 3.74 and 3.78 (2s, 6 H, H-24), 3.80 (m, 2 H, H-16a), 3.90 (s, 6 H, H-1), 5.47 and 5.58 (2d, J = 1.7 Hz, 2 H, H-17), 5.96 (d, ^3J = 8.8 Hz, 2 H, H-9), 6.24 and 6.26 (2d, J = 2.2 Hz, 2 H, H-3), 6.35 (2d, ^4J = 2.2 Hz, 2 H, H-7), 6.76 (m, 4 H, Ph), 6.82 (m, 2 H, Ph), 7.20 (m, 2 H, Ph), 7.31 (dd, ^3J = 8.3 Hz, ^3J = 4.2 Hz, 2 H, H-5), 7.93 (dd, ^3J = 8.3 Hz, ^4J = 1.5 Hz, 2 H, H-4), 8.55 (m, 2 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6 and 20.8 (C11), 23.4 and 23.6 (C13), 33.1 (C16), 33.4 and 33.9 (C12), 42.9 and 43.0 (C14), 47.8 and 47.9 (C10), 55.4 (C24), 55.1 (C1), 63.4 and 63.5 (C17), 91.9, 92.0, 96.9, 97.1, 112.3, 112.4, 114.8, 114.9, 119.3, 122.0, 130.1, 130.2, 130.3, 134.9, 135.5, 135.5, 141.2, 144.5, 145.1 (aryl), 159.6 and 160.3 (C2), 171.4 (C15).

2-(4-Methoxyphenyl)-3-{4-[(6-methoxyquinolin-8-yl)amino]pentyl}-1,3-thiazolidin-4-one (5m)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.16 (d, ^3J = 6.3 Hz, 6 H, H-11), 1.45 (m, 8 H, H-12 and H-13), 2.58 (m, 2 H, H-14b) 3.50 (m, 4 H, H-10 and H-14a), 3.65 (m, 2 H, H-16b), 3.71 and 3.72 (2s, 6 H, H-24) 3.78 (m, 2 H, H-16a), 3.82 (s, 6 H, H-1), 5.67 and 5.75 (2s, 2 H, H-17) 6.08 (t, ^3J = 9.3 Hz, 2 H, H-9), 6.20 (d, ^4J = 2.5 Hz, 2 H, H-3), 6.47 (d, ^4J = 2.0 Hz, 2 H, H-7), 6.86 (2d, ^3J = 8.5 Hz, ^3J = 8.3 Hz, 4 H, Ph), 7.23 (2d, ^3J = 8.5 Hz, ^3J = 8.3 Hz, 4 H, Ph), 7.43 (dd, ^3J = 8.3 Hz, ^3J = 4.3 Hz, 2 H, H-5), 8.07 (d, ^3J = 8.0 Hz, 2 H, H-4), 8.53 (2d, ^3J = 3.8 Hz, 2 H, H-6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 19.9 and 20.0 (C11), 22.8 and 22.9 (C13), 32.0 (C16), 32.6 and 32.8 (C12), 41.8 and 41.9 (C14), 46.8 (C10), 54.9 and 55.1 (C1), 61.6 and 61.7 (C17), 91.6, 91.7, 96.0, 96.2, 114.0, 114.1, 122.0, 128.4, 128.5, 129.5, 131.5, 134.5, 134.7, 144.2, 144.4, 144.6 (aryl), 158.9 and 159.4 (C2), 170.3 and 170.4 (C15).

3-(3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-4-oxo-1,3-thiazolidin-2-yl)benzonitrile (5n)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.27 (2d, ^3J = 6.4 Hz, 6 H, H-11), 1.60 (m, 8 H, H-12 and H-13), 2.67 (m, 2 H, H-14b) 3.57 (m, 4 H, H-10 and H-14a), 3.72 (m, 2 H, H-16b), 3.79 (m, 2 H, H-16a), 3.91 (s, 6 H, H-1), 5.38 and 5.57 (2s, 2 H, H-17) 5.93 (br s, 2 H, H-9), 6.21 and 6.26 (2d, ^4J = 2.9 Hz, 2 H, H-3), 6.37 (d, ^4J = 1.9 Hz, 2 H,

H-7), 7.36 (m, 8 H, Ph), 7.51 (dd, ^3J = 8.0 Hz, ^3J = 4.0 Hz, 2 H, H-5), 7.96 (d, ^3J = 8.1 Hz, 2 H, H-4), 8.56 (m, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.6 and 20.9 (C11), 22.8 and 23.3 (C13), 32.6 (C16), 32.8 and 33.7 (C12), 42.7 and 42.9 (C14), 47.4 and 47.5 (C10), 55.3 (C1), 62.3 and 62.4 (C17), 91.9, 92.0, 96.8, 97.1, 113.3, 118.0, 122.0, 122.1, 129.9, 130.0, 130.4, 130.5, 131.1, 131.2, 132.6, 134.9, 135.3, 141.3, 141.4, 144.4, 144.5, 144.8, 145.0 (aryl and C24), 159.5 (C2), 171.1 and 171.2 (C15).

4-(3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-4-oxo-1,3-thiazolidin-2-yl)benzonitrile (5o)

^{1}H NMR (500 MHz, $CDCl_3$): δ = 1.25 (2d, ^3J = 6.4 Hz, 6 H, H-11), 1.58 (m, 8 H, H-12 and H-13), 2.64 (m, 2 H, H-14b) 3.66 (m, 4 H, H-10 and H-14a), 3.73 (m, 2 H, H-16b), 3.83 (m, 2 H, H-16a), 3.91 (s, 6 H, H-1), 5.46 and 5.58 (2s, 2 H, H-17) 5.92 (br s, 2 H, H-9), 6.16 and 6.25 (2s, 2 H, H-3), 6.38 (d, ^4J = 2.9 Hz, 2 H, H-7), 7.21 (m, 4 H, Ph), 7.37 (m, 4 H, Ph), 7.54 (dd, ^3J = 8.0 Hz, ^3J = 4.0 Hz, 2 H, H-5), 7.98 (d, ^3J = 7.8 Hz, 2 H, H-4), 8.55 (d, ^3J = 4.0 Hz, 2 H, H-6).

^{13}C NMR (125 MHz, $CDCl_3$): δ = 20.7 and 20.9 (C11), 22.9 and 23.2 (C13), 32.8 and 32.9 (C16), 33.1 and 33.4 (C12), 42.6 and 43.1 (C14), 47.0 and 47.7 (C10), 55.3 (C1), 62.5 (C17), 91.9, 96.8, 97.0, 112.8, 112.9, 118.2, 122.0, 127.5, 130.0, 132.7, 132.9, 134.9, 135.3, 144.4, 144.6, 144.8, 144.9 (aryl and C24), 159.5 (C2), 171.1 and 171.2 (C15).

3-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-2-(4-methylphenyl)-1,3-thiazolidin-4-one (5p)

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.25 (2d, ^3J = 6.3 Hz, 6 H, H-11), 1.55 (m, 8 H, H-12 and H-13), 2.30 and 2.32 (2s, 6 H, H-24), 2.68 (m, 2 H, H-14b), 3.57 (m, 2 H, H-14a), 3.65 (m, 2 H, H-10), 3.66 (2d, ^2J = 15.4 Hz, 2 H, H-16b), 3.78 (2dd, ^2J = 15.4 Hz, ^4J = 1.7 Hz, 2 H, H-16a), 3.89 (s, 6 H, H-1), 5.46 and 5.57 (2d, ^4J = 1.7 Hz, J = 1.5 Hz, 2 H, H-17), 5.94 (d, ^3J = 8.3 Hz, 2 H, H-9), 6.21 and 6.24 (2d, ^4J = 2.2 Hz, 2 H, H-3), 6.34 (d, ^4J = 2.5 Hz, 1 H, H-7), 7.18 (m, 8 H, Ph), 7.32 (ddd, ^3J = 8.3 Hz, ^3J = 4.0 Hz, ^4J = 1.2 Hz, 2 H, H-5), 7.93 (dt, ^3J = 8.3 Hz, ^4J = 1.7 Hz, 2 H, H-4), 8.54 (2dd, ^3J = 4.0 Hz, ^4J = 1.7 Hz, 2 H, H-6).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.7 and 20.8 (C11), 21.3 (C24), 23.3 and 23.4 (C13), 33.2 (C16), 33.4 and 33.8 (C12), 42.7 and 42.8 (C14), 47.7 and 47.9 (C10), 55.4 (C1), 63.4 and 63.5 (C17), 91.9, 96.9, 97.1, 122.0, 127.1, 129.8, 129.9, 130.1, 134.9, 135.0, 135.5, 136.4, 139.3, 144.5, 145.0, 145.1 (aryl), 159.6 (C2), 171.3 and 171.4 (C15).

4-{4-[(6-Methoxyquinolin-8-yl)amino]pentyl}-1-thia-4-azaspiro[4.5]decan-3-one (5q)

^{1}H NMR (400 MHz, DMSO-d_6): δ = 1.21 (d, ^3J = 6.4 Hz, 3 H, H-11), 1.58 (m, 14 H, cyclohexane, H-12 and H-13), 3.41 (m, 5 H, H-10, H-14 and H-16), 3.82 (s, 3 H, H-1), 6.10 (s, 1 H, H-9), 6.29 (d, ^4J = 2.3 Hz, 1 H, H-3), 6.46 (d, ^4J = 2.3 Hz, 1 H, H-7), 7.40 (dd, ^3J = 8.1 Hz, ^3J = 4.4 Hz, 1 H, H-5), 8.05 (d, ^3J = 8.2 Hz, 1 H, H-4), 8.53 (d, ^3J = 4.0 Hz, 1 H, H-6).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 20.3 (C11), 23.0 (C20 and C21), 23.5 (C22), 25.8 (C13), 30.2 (C12), 33.2 (C16), 37.2 (C18 and C19), 41.2 (C14), 46.8 (C10), 54.8 (C1), 73.2 (C17), 91.7, 95.9, 121.9, 129.4, 134.4, 134.6, 144.1, 144.6 (aryl), 158.9 (C2), 170.1 (C15).

Acknowledgment

The authors thank CNPq (Projects 575746/2008-4 and 305314/2009-2) for their financial support of the research. We also thank UFPel and CAPES.

References

(1) *Dados Epidemiológicos de Malária, Por Estado. Amazônia Legal, Janeiro a Maio de 2009 e 2010*; Ministério da Saúde: Brasilia. Available on: http://portal.saude.gov.br/portal/arquivos/pdf/avaliacao_malaria_jan_maio_19_07_2010.pdf. (Accessed: Aug. 24, 2011).
(2) Cox-Singh, J.; Hiu, J.; Lucas, S. B.; Divis, P. C.; Zulkarnaen, M.; Chandran, P.; Wong, K. T.; Adem, P.; Zaki, S. R.; Singh, B.; Krishna, S. *Malar. J.* **2010**, *9*, 10.
(3) Krettli, A. U. *Expert Opin. Drug Discovery* **2009**, *4*, 95.
(4) Baird, J. K. *Clin. Microbiol. Rev.* **2009**, *22*, 508.
(5) Vale, N.; Moreira, R.; Gomes, P. *Eur. J. Med. Chem.* **2009**, *44*, 937.
(6) Valecha, N.; Adak, T.; Bagga, A. T.; Asthana, O. P.; Srivastava, P.; Joshi, H.; Sharma, V. P. *Curr. Sci.* **2011**, *80*, 561.
(7) Puri, S. K.; Dutta, G. P. *Exp. Parasitol.* **2005**, *111*, 8.
(8) Cunico, W.; Gomes, C. R. B.; Vellasco, W. T. Jr. *Mini-Rev. Org. Chem.* **2008**, *5*, 336.
(9) Liesen, A. P.; de Aquino, T. M.; Góes, A. J. S.; de Lima, J. G.; de Faria, A. R.; Alves, A. J. *Quim. Nova* **2008**, *31*, 369.
(10) Shah, T. J.; Desai, V. A. *ARKIVOC* **2007**, *(xiv)*, 218.
(11) Sharma, A.; Kumar, V.; Jain, S.; Sharma, P. C. *J. Enzyme Inhib. Med. Chem.* **2011**, *26*, 546.
(12) Gomes, C. R. B.; Moreth, M.; Facchinetti, V.; de Souza, M. V. N.; Vellasco, W. T. Jr.; Lourenço, M. C. S.; Cunico, W. *Lett. Drug Des. Discovery* **2010**, *7*, 353.
(13) (a) Rawal, R. K.; Tripathi, R.; Katti, S. B.; Pannecouque, C.; De Clercq, E. *Eur. J. Med. Chem.* **2008**, *43*, 2800. (b) Ravichandran, V.; Prashantha Kumar, B. R.; Sankar, S.; Agrawal, R. K. *Eur. J. Med. Chem.* **2009**, *44*, 1180.
(14) Neuenfeldt, P. D.; Drawanz, B. B.; Siqueira, G. M.; Gomes, C. R. B.; Wardell, S. M. S. V.; Flores, A. F. C.; Cunico, W. *Tetrahedron Lett.* **2010**, *51*, 3106.
(15) Neuenfeldt, P. D.; Duval, A. R.; Drawanz, B. B.; Rosales, P. F.; Gomes, C. R. B.; Pereira, C. M. P.; Cunico, W. *Ultrason. Sonochem.* **2011**, *18*, 65.
(16) Bolognese, A.; Correale, G.; Manfra, M.; Lavecchia, A.; Novellino, E.; Barone, V. *Org. Biomol. Chem.* **2004**, *2*, 2809.
(17) Fraga-Dubreuil, J.; Bazureau, J. P. *Tetrahedron* **2003**, *59*, 6121.
(18) Pratap, U. R.; Jawale, D. V.; Bhosle, M. R.; Mane, R. A. *Tetrahedron Lett.* **2011**, *52*, 1689.
(19) Solomon, V. R.; Haq, W.; Srivastava, K.; Puri, S. K.; Katti, S. B. *J. Med. Chem.* **2007**, *50*, 394.