

SYNTHESIS OF 4-ALKYLAMINO-6-CHLOROQUINOLINES AS POTENTIAL TRYPANOCIDAL AGENTS

Ricardo A. Tapia,^{a,*} Yolanda Prieto,^a Jaime A. Valderrama,^a Alain Fournet,^b Antonieta Rojas de Arias^c, Héctor Nakayama^c and Susana Torres^c

a. Facultad de Química, Pontificia Universidad Católica de Chile, Correo 22, Santiago, Chile.

b. Institut de Recherche pour le Développement (IRD), 213 Rue La Fayette, 75480 Paris Cedex, France.

c. Instituto de Investigaciones en Ciencias de la Salud (IICS), Río de la Plata y Lagrenza, Casilla 2511, Asunción, Paraguay.

Abstract: A simple synthesis of 4-alkylamino-6-chloroquinolines **5-9** from 5,8-dimethoxy-6-chloro-4(1H)quinolone **3**, is described. Thermolysis of arylaminomethylene Meldrum's acid derivative **2** is the key step on the preparation of compound **3**. These compounds were tested *in vitro* against trypomastigote forms of *Trypanosoma cruzi*. Some derivatives were found to have a significant activity.

Introduction

Chagas' disease is a zoonosis caused by protozoan *Trypanosoma cruzi* and it is a serious health problem in tropical and subtropical countries of Latin America. It has been estimated that 16-18 million people are currently infected with *Trypanosoma cruzi*, and mortality indexes range from 8 to 12%.¹ Currently available drugs, nifurtimox and benznidazole, have toxic effects and are mutagenic.² The requirement for more effective drugs, with less or no side effect has stimulated the search for new compounds.

We described recently some 4-alkylamino-6-nitroquinolines with low trypanocidal activity.³ In the search for more active trypanocidal agents we describe herein the synthesis of 4-alkylamino-6-chloroquinolines.

Results and Discussion

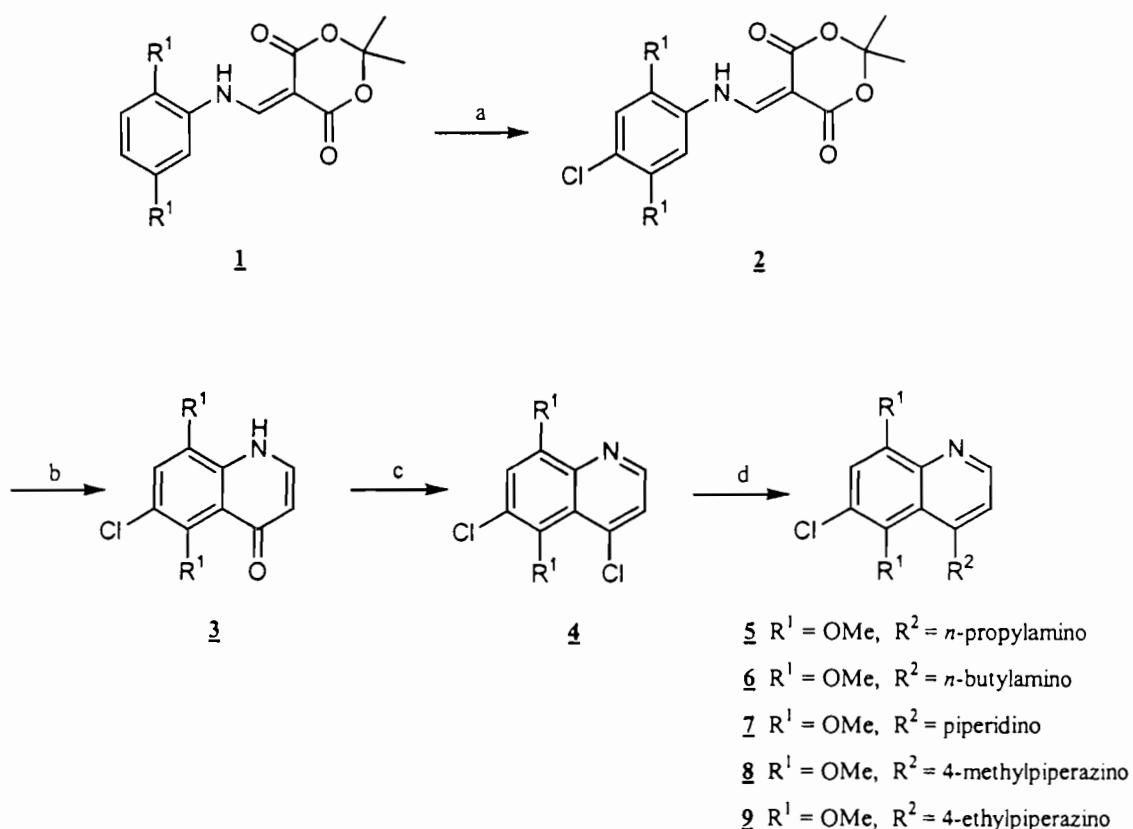
Previously we reported a convenient method for the preparation of 4(1H)-quinolones by thermolysis of arylaminomethylene Meldrum's acid derivatives, easily obtained by reaction of arylamines and methoxymethylene Meldrum's.⁴ In the present study we use this procedure to obtain the required 4(1H)-quinolone **3** as intermediate for the synthesis of 4-alkylamino-6-chloroquinolines (Scheme 1).

Reaction of arylaminomethylene Meldrum's acid **1** with N-chlorosuccinimide (NCS) in dichloromethane for five hours at 40 °C gave compound **2** in 88% yield. It is interesting to note that the reaction of arylamines with NCS is an electrophilic aromatic substitution.⁵ Thermal cyclization of **2** in boiling diphenylether gave quinolone **3** in 86% yield. Treatment of quinolone **3** with phosphorus oxychloride yielded 4,6-dichloroquinoline **4** (98%). Nucleophilic displacement of the chlorine atom to obtain 4-alkylaminoquinolines from 4-chloroquinolines is known to

proceed straightforward.⁶⁻⁸ Thus reaction of 4,6-dichloroquinoline **4** with some primary and secondary amines gave 4-alkylaminoquinolines **5-9** in 31-73% yields.

The *in vitro* activity against trypomastigote forms of *Trypanosoma cruzi* for compounds **5-11** were determined in albino mice seven days after infection with *T. Cruzi*. Blood was obtained by cardiac puncture using 3.8% sodium citrate anticoagulant in a 7:3 blood/anticoagulant ratio. The parasitaemia in infected mice ranged from 1×10^5 to 5×10^5 parasites per millilitre. The compounds were dissolved in cold DMSO to give a final concentration of 250 μ g/ml. Aliquots (10 μ l) of the solution of each compound were mixed in microlitre plates with 100 μ l infected blood containing different parasite concentrations (1×10^5 and 1×10^6 parasites per ml). Infected blood and infected blood containing gentian violet, 250 μ g/ml were used as controls. The plates were shaken for 10 min at room temperature and kept at 4 °C for 24 hours. Each solution was examined microscopically at 400x, placing a 5 μ l sample on a slide and covering with a 22x22 mm coverglass for parasite counting.⁹

All the quinolines tested inhibit the growth of the parasites, and compounds **5** and **6** being the more actives. (Table 1)



Reagents and conditions: a) NCS, CH_2Cl_2 , reflux 5 hours; b) Ph_2O , 240-250 °C 15 min; c) POCl_3 , reflux 45 min; d) Alkylamine, reflux 2 hours.

Scheme 1

Table 1. In vitro activity of compounds **5-11** against bloodstream forms of *T. Cruzi*.

Compound	Lysis at 250 µg/mL (%)
4	37
5	100
6	100
7	73
8	68
9	31
Gentian Violet	100

Experimental

Melting points were determined on a Kofler apparatus and are not corrected. IR spectra were obtained on a Bruker Model Vector 22 spectrophotometer. ¹H and ¹³C spectra were recorded on a Bruker AM-200 spectrometer, using tetramethylsilane as internal reference. Column chromatography were performed on Merck silica gel 60 (70-230 mesh). Elemental analyses were carried out on a FISONS EA 1108 CHNS-O analyzer.

5-[(2,5-dimethoxyphenylamino)methylidene]-2,2-dimethyl-4,6-dioxo-1,3-dioxane **2**.

To a solution of 5-[(2,5-dimethoxyphenylamino)methylidene]-2,2-dimethyl-4,6-dioxo-1,3-dioxane **1** (1.0 g, 3.27 mmol) in dichloromethane (135 ml) was added N-chlorosuccinimide (0.52 g, 3.90 mmol) and the mixture was heated at 40 °C for five hours. The solvent was removed and the residue was purified by column chromatography on silica gel (dichloromethane-ethyl acetate 1:1) to give compound **2** (0.97 g, 88%), mp 154-155 °C. ¹H-NMR (CDCl₃) δ: 1.75 (6H, s, 2xCH₃), 3.92 (6H, s, OCH₃), 6.89 (1H, s, H-3), 7.02 (1H, s, H-6), 8.61 (1H, d, J=14.5 Hz, =CH), 11.54 (1H, d, J=14.5 Hz, NH); ¹³C-NMR (CDCl₃) δ: 27.1, 56.8, 57.1, 87.8, 100.4, 105.2, 114.3, 120.2, 126.1, 143.4, 149.9, 150.6, 163.8, 165.2. IR (KBr) cm⁻¹: 3440, 1725, 1680, 1630. *Anal.* Calcd for C₁₅H₁₆ClNO₆: C, 52.72; H, 4.72; N, 4.10. Found: C, 52.74; H, 4.70; N, 4.23.

6-Chloro-5,8-dimethoxy-4(1H)quinolone **3**.

A mixture of **2** (0.60 g, 1.76 mmol) and phenyl ether (30 g) was heated at 240-250 °C for 15 min. After cooling at room temperature the reaction mixture was diluted with petroleum ether (150 ml) and filtered to give compound **3** (0.36 g, 86%). mp 233-234 °C. ¹H-NMR (DMSO-*d*₆) δ: 3.73 (3H, s, OCH₃), 3.92 (3H, s, OCH₃), 6.01 (1H, d, J=7.2, H-3), 7.31 (1H, s, H-7), 7.67 (1H, m, H-2), 11.27 (1H, br s, NH); ¹³C-NMR (DMSO-*d*₆) δ: 56.7, 61.0, 111.7, 112.2, 120.0, 120.8, 131.8, 137.5, 144.7, 147.3, 175.5. IR (KBr) cm⁻¹: 3420, 1570. *Anal.* Calcd for C₁₁H₁₀ClNO₃: C, 55.13; H, 4.21; N, 5.84. Found: C, 54.97; H, 4.10; N, 5.93.

4,6-Dichloro-5,8-dimethoxyquinoline **4**

Freshly distilled POCl₃ (3.0 ml) was slowly added to compound **5** (300 mg, 1.25 mmol) and the resulting solution was heated under reflux for 45 min. After cooling, the mixture was poured into ice-water, treated with charcoal and filtered. The filtrate was neutralized with sodium bicarbonate and extracted with dichloromethane (3x75 ml). The combined organic layers were washed with brine, dried over MgSO₄, filtered and concentrated to give compound **4** (320 mg, 98%); mp 104-105 °C. ¹H-NMR (CDCl₃) δ: 3.79 (3H, s, OCH₃), 3.95 (3H, s, OCH₃), 6.91 (1H, s, H-7), 7.41 (1H, d, J=4.7 Hz, H-3), 8.60 (1H, d, J=4.7 Hz, H-2); ¹³C-NMR (CDCl₃) δ: 56.4, 61.9, 110.1, 122.4, 125.1, 126.8, 139.6, 141.2, 144.2, 148.4, 152.3. IR (KBr) cm⁻¹: 1595, 1575, 1340, 1235. *Anal.* Calcd for C₁₁H₉Cl₂NO₂: C, 51.19; H, 3.51; N, 5.43. Found: C, 51.28; H, 3.37; N, 5.56.

Preparation of 4-alkylaminoquinolines. General Procedure

A mixture of dichloroquinoline **4** (100 mg, 0.37 mmol) and the amine (1.0 ml) was heated to reflux for 2 h. The reaction mixture was concentrated under vacuum and the residue was purified by column chromatography on silica gel (dichloromethane-ethyl acetate 19:1)

4-N-Propylamino-5,8-dimethoxy-6-chloroquinoline 5 (80 mg, 73%), mp 104-105 °C. ¹H-NMR (CDCl₃) δ: 1.08 (3H, t, J=7.3 Hz, CH₃), 1.77 (2H, sext, J=7.3 Hz, H-2'), 3.1-3.3 (2H, m, H-1'), 3.87 (3H, s, OCH₃), 3.99 (3H, s, OCH₃), 6.38 (1H, d, J=5.4 Hz, H-3), 6.89 (1H, s, H-7), 7.52 (1H, s, NH), 8.45 (1H, d, J=5.4 Hz, H-2); ¹³C-NMR (CDCl₃) δ: 11.8, 22.1, 44.8, 56.2, 61.6, 100.2, 108.8, 114.1, 121.2, 140.9, 145.6, 150.1, 151.2, 152.6. IR (KBr) cm⁻¹: 3440, 1595, 1575, 1495, 1340, 1235. *Anal.* Calcd for C₁₄H₁₇ClN₂O₂: C, 59.89; H, 6.10; N, 9.98. Found: C, 59.70; H, 6.25; N, 9.92.

4-N-Butylamino-5,8-dimethoxy-6-chloroquinoline 6 (76 mg, 66%), mp 108-109 °C. ¹H-NMR (CDCl₃) δ: 0.99 (3H, t, J=7.2 Hz, CH₃), 1.4-1.6 (2H, m, CH₂), 1.7-1.8 (2H, m, CH₂), 3.2-3.3 (2H, m, CH₂), 3.86 (3H, s, OCH₃), 3.99 (3H, s, OCH₃), 6.37 (1H, d, J=5.4 Hz, H-3), 6.88 (1H, s, H-7), 7.48 (1H, br. s, NH), 8.45 (1H, d, J=5.4 Hz, H-2); ¹³C-NMR (CDCl₃) δ: 13.8, 20.4, 30.8, 42.7, 56.2, 61.6, 100.2, 108.7, 114.1, 121.2, 140.9, 145.5, 150.1, 151.2, 152.6. IR (KBr) 3400, 1585, 1470, 1335, cm⁻¹. *Anal.* Calcd for C₁₅H₁₉ClN₂O₂: C, 61.12; H, 6.50; N, 9.50. Found: C, 60.94; H, 6.51; N, 9.31.

4-N-piperidin-5,8-dimethoxy-6-chloroquinoline 7 (87 mg, 73%), mp 174-175 °C. ¹H-NMR (CDCl₃) δ: 1.2-1.8 (6H, m, 3xCH₂), 2.6-2.8 (2H, m, CH₂), 3.4-3.7 (2H, m, CH₂), 3.69 (3H, s, OCH₃), 4.07 (s, 3H, OCH₃), 6.94 (d, 1H, J= 5.3 Hz, H-3), 7.27 (s, 1H, H-7); 8.70 (d, 1H, J=5.3 Hz, H-2), ¹³C-NMR (CDCl₃) δ: 24.3, 26.0, 54.2, 56.2, 64.1, 101.9, 110.3, 117.8, 140.1, 144.3, 145.0, 151.6, 152.3, 158.5. IR (KBr) cm⁻¹: 1590, 1580, 1510. *Anal.* Calcd for C₁₆H₁₉ClN₂O₂: C, 62.64; H, 6.24; N, 9.13. Found: C, 62.81; H, 6.31; N, 8.78

4-(4-Methylpiperazin-1-yl)-5,8-dimethoxy-6-chloroquinoline 8 (85 mg, 68%) mp 176-177 °C. ¹H-NMR (CDCl₃) δ: 2.40 (s, 3H, CH₃), 2.5-3.6 (m, 4H, 4xCH₂), 3.73 (s, 3H, OCH₃), 4.04 (s, 3H, OCH₃), 6.91 (d, 1H, J= 5.1 Hz, H-3), 7.0 (s, 1H, H-7); 8.67 (d, 1H, J=5.1 Hz, H-2), ¹³C-NMR (CDCl₃) δ: 46.1, 52.7, 55.1, 56.3, 62.2, 109.1, 110.0, 118.9, 124.6, 142.0, 144.3, 149.5, 152.6, 155.9. IR (KBr) cm⁻¹: 1590, 1580, 1510. *Anal.* Calcd for C₁₆H₂₀ClN₃O₂: C, 59.72; H, 6.26; N, 13.06. Found: C, 59.71; H, 6.32; N, 12.96.

4-(4-Ethylpiperazin-1-yl)-5,8-dimethoxy-6-chloroquinoline 9 (40 mg, 31%) mp 134-135 °C. ¹H-NMR (CDCl₃) δ: 1.14 (t, 3H, J= 7.2 Hz, CH₃), 2.5-2.6 (m, 4H, 2xCH₂), 2.7-3.2 (m, 4H, 2xCH₂), 3.4-3.5 (m, 2H, CH₂), 3.71 (s, 3H, OCH₃), 4.03 (s, 3H, OCH₃), 6.89 (d, 1H, J= 5.1 Hz, H-3), 6.99 (s, 1H, H-7); 8.65 (d, 1H, J=5.1 Hz, H-2), ¹³C-NMR (CDCl₃) δ: 12.0, 52.5, 52.8, 52.9, 56.3, 62.2, 109.0, 109.9, 118.9, 124.6, 142.1, 144.3, 149.6, 152.6, 155.9. IR (KBr) cm⁻¹: 1580, 1570, 1510, 1463. *Anal.* Calcd for C₁₇H₂₂ClN₃O₂: C, 60.8; H, 6.60; N, 12.51. Found: C, 60.72; H, 6.66; N, 12.25.

Acknowledgements

The authors acknowledge FONDECYT, Research Grant 2990104 for the support of this work.

References

- (1) WORLD HEALTH ORGANIZATION. *Tropical Disease Research, 12th Programme Report of the UNDP/World Bank/WHO, Special Programme for Research and Training in Tropical Disease*, Geneva. (1995).
- (2) J. A. Castro and E. G. Díaz de Torranzo, *Biomed. Envir. Sci.*, **1**, 19 (1988).
- (3) R. A. Tapia, Y. Prieto, G. Zamora, A. Morello and Y. Repetto, *Heterocycl. Commun.*, **6**, 539 (2000).
- (4) R. Cassis, R. Tapia and J. A. Valderrama, *Synth. Commun.*, **15**, 125 (1985).
- (5) L. A. Paquette and W. C. Farley, *J. Org. Chem.*, **32**, 2725 (1967).
- (6) L. Skrzypek, *Heterocycles*, **48**, 71 (1998).
- (7) D. De, L. D. Byers and D. J. Krogstad, *J. Heterocycl. Chem.*, **34**, 315 (1997)
- (8) A. R. Surrey and H. F. Hammer, *J. Am. Chem. Soc.*, **68**, 113 (1946).
- (9) A. Rojas de Arias, A. Inchausti, A. Ascurría, N. Fleitas, E. Rodriguez and A. Fournet, *Phytother. Res.*, **8**, 141 (1994).

Received on May 15, 2002

Tapia R.A., Prieto Y., Valderrama J.A., Fournet Alain, Rojas de Arias A., Nakayama H., Torres S. (2002).

Synthesis of 4-alkylamino-6-chloroquinolines as potential trypanocidal agents.

Heterocyclic Communications, 8 (4), 339-342.