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

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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

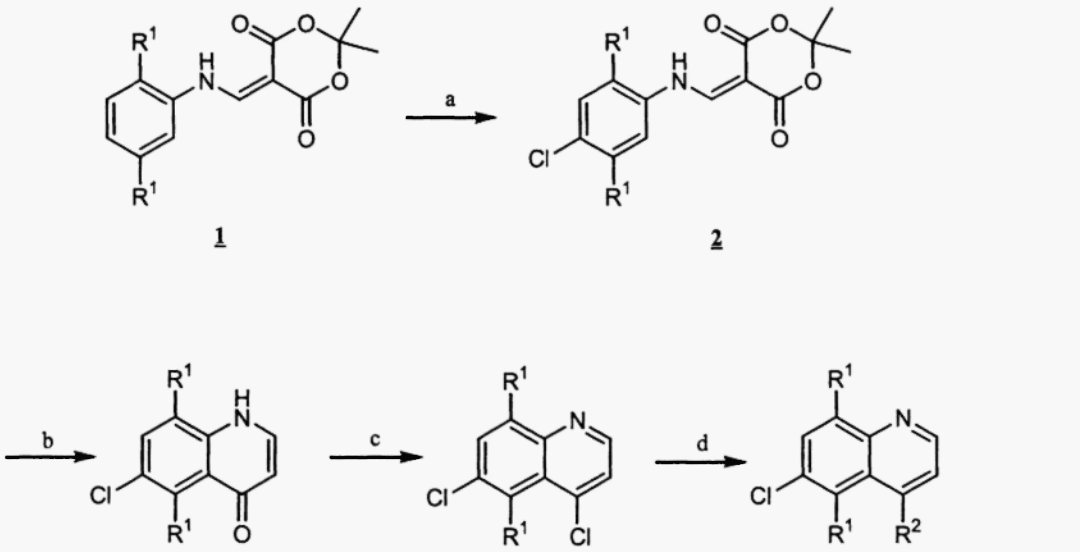
Previously we reported a convenient method for the preparation of 4(1H)-quinolones by thermolysis of arylaminomethylene Meldrum's acid derivatives, easily obtained by reaction of arylamines and methoxymethylene Meldrum's .[4] In the present study we use this procedure to obtain the required 4(1H)-quinolone **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 $1x10^5$ to $5x10^5$ parasites per millilitre. The compounds were disolved in cold DMSO to give a final concentration of 250 μg/ml. Aliquots (10 μl) of the solution of each compound were mixed in microlitre plates with 100 μl infected blood containing different parasite concentrations ($1x10^5$ and $1x10^6$ parasites per ml). Infected blood and infected blood containing gentian violet, 250 μg/ml were used as controls. The plates were shaken for 10 min at room temperature and keep at 4 °C for 24 hours. Each solution was examined microscopically at 400x, placing a 5 μl 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)



1 **2** **3** **4**

5 R^1 = OMe, R^2 = *n*-propylamino
6 R^1 = OMe, R^2 = *n*-butylamino
7 R^1 = OMe, R^2 = piperidino
8 R^1 = OMe, R^2 = 4-methylpiperazino
9 R^1 = OMe, R^2 = 4-ethylpiperazino

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. ^{1}H and ^{13}C 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. ^{1}H-NMR ($CDCl_3$) δ: 1.75 (6H, s, 2xCH_3), 3.92 (6H, s, OCH_3), 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); ^{13}C-NMR ($CDCl_3$) 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 $C_{15}H_{16}ClNO_6$: 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. ^{1}H-NMR (DMSO-d_6) δ: 3.73 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 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); ^{13}C-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 $C_{11}H_{10}ClNO_3$: 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 $POCl_3$ (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 $MgSO_4$, filtered and concentrated to give compound **4** (320 mg, 98%); mp 104-105 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.79 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 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); ^{13}C-NMR ($CDCl_3$) 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 $C_{11}H_9Cl_2NO_2$: 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. ^{1}H-NMR ($CDCl_3$) δ: 1.08 (3H, t, *J*=7.3 Hz, CH_3), 1.77 (2H, sext, *J*=7.3 Hz, H-2'), 3.1-3.3 (2H, m, H-1'), 3.87 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 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); ^{13}C-NMR ($CDCl_3$) 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 $C_{14}H_{17}ClN_2O_2$: 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. ^{1}H-NMR ($CDCl_3$) δ: 0.99 (3H, t, *J*=7.2 Hz, CH_3), 1.4-1.6 (2H, m, CH_2), 1.7-1.8 (2H, m, CH_2), 3.2-3.3 (2H, m, CH_2), 3.86 (3H, s, OCH_3), 3.99 (3H, s, OCH_3), 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); ^{13}C-NMR ($CDCl_3$) 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 $C_{15}H_{19}ClN_2O_2$: 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. ^{1}H-NMR ($CDCl_3$) δ: 1.2-1.8 (6H, m, 3xCH_2), 2.6-2.8 (2H, m, CH_2), 3.4-3.7 (2H, m, CH_2), 3.69 (3H, s, OCH_3), 4.07 (s, 3H, OCH_3), 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), ^{13}C-NMR ($CDCl_3$) 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 $C_{16}H_{19}ClN_2O_2$: 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. ^{1}H-NMR ($CDCl_3$) δ: 2.40 (s, 3H, CH_3), 2.5-3.6 (m, 4H, 4xCH_2), 3.73 (s, 3H, OCH_3), 4.04 (s, 3H, OCH_3), 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), ^{13}C-NMR ($CDCl_3$) 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 $C_{16}H_{20}ClN_3O_2$: 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. ^{1}H-NMR ($CDCl_3$) δ: 1.14 (t, 3H, *J*= 7.2 Hz, CH_3), 2.5-2.6 (m, 4H, 2xCH_2), 2.7-3.2 (m, 4H, 2xCH_2), 3.4-3.5 (m, 2H, CH_2), 3.71 (s, 3H, OCH_3), 4.03 (s, 3H, OCH_3), 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), ^{13}C-NMR ($CDCl_3$) 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 $C_{17}H_{22}ClN_3O_2$: C, 60.8; H, 6.60; N, 12.51. Found: C, 60.72; H, 6.66; N, 12.25.

Acknowledgements

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