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Il Farmaco 60 (2005) 307–311
IL FARMACO
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Synthesis and antimalarial activity of sulfonamide chalcone derivatives

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Received 29 November 2004; received in revised form 20 January 2005; accepted 22 January 2005

Available online 16 March 2005

Abstract

A series of sulfonamide chalcone derivatives were synthesized and investigated for their abilities to inhibit β-hematin formation in vitro and their activity against cultured *Plasmodium falciparum* parasites. Inhibition of β-hematin formation was minimal in the aromatic ring of the chalcone moiety as it appeared for compounds 4b, 4d-f, and greatest with compounds 4g (IC_{50} 0.48 μM) and 4k (IC_{50} 0.50 μM) with a substitution of 3,4,5-trimethoxyl and 3-pyridinyl, respectively. In this study, the most active compound resulted 1[4'-N(2'',5''-dichlorophenyl) sulfonyl-amidephenyl]-3-(4-methylphenyl)-2-propen-1-one 4i, effective as antimalarial by the inhibition of cultured *P. falciparum* parasites (1 μM). These studies open up the novel possibility of development of sulfonamide derivatives as antimalarials that target β-hematin formation and the inhibition of the development of cultured *P. falciparum* parasites, which should help delay the rapid onset of resistance to drugs acting at only a single site. Results with these assays suggest that chalcones exert their antimalarial activity via multiple mechanisms.

Keywords: Antimalarial; Synthesis; Sulfonamide; Chalcone; β-hematin

1. Introduction

Malaria is one of the most important infectious disease problems of humans, particularly in tropical regions of the world, with over 275 million new cases annually and mortality reaching 2 million, especially among children in Africa [1]. Control of this debilitating disease has been severely compromised by the development in malaria parasites of resistance to nearly all antimalarial drugs used for prophylaxis and treatment, particularly in *Plasmodium falciparum*, the most virulent of the four species infecting humans. Thus, there is a compelling and urgent need for new antimalarials with modes of action different from those of existing ones in order to replace those that are becoming obsolete and to identify new drug targets [2]. Chloroquine has recently been shown to inhibit hemozoin formation within the parasite food vacuole [3]. This process is also thought to be the molecular target of other quinoline antimalarials [4]. Hemozoin was originally considered to be formed by the polymerization of heme [5], but it has now been demonstrated to be a crystalline cyclic dimer of ferriprotoporphyrin IX [6]. Thus, hemozoin synthesis, a process unique to the malaria parasite, offers a logical and valuable potential target for new antimalarial drug development. New drugs that attack the same vital target of chloroquine but that are not subject to the same resistance mechanism would be highly desirable. Varied biological activities have been attributed to sulfonamide compounds, including fungicidal, bactericidal and nematicidal activities [7]. Novel sulfonamide derivatives having CNS (Central Nervous System Disease) activity, processes for their preparation and their use as medicaments are disclosed [8]. In this study, a series of sulfonamide chalcones derivatives were investigated for their abilities to inhibit β-hematin formation in vitro and the inhibition of the development of cultured *P. falciparum* parasites.

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doi:10.1016/j.farmac.2005.01.005

2. Experimental

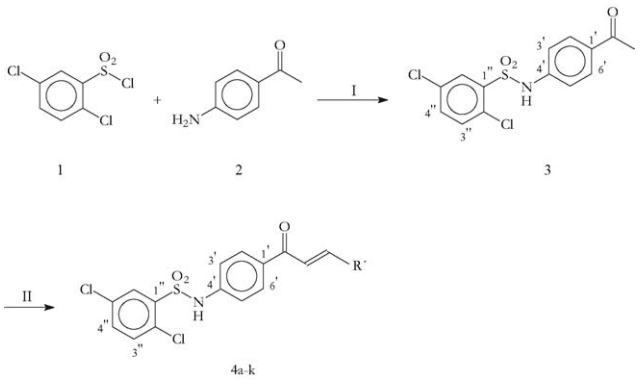
2.1. Chemistry

Melting points were determined in a Thomas micro hot stage apparatus and are uncorrected. Infrared spectra were determined as KBr pellets on a Shimadzu model 470 spectrophotometer and are expressed in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on a JEOL GSX (270 MHz) spectrometer; chemical shifts are expressed in δ (ppm) relative to tetramethylsilane are given. All the exchangeable protons were confirmed by addition of D_2O. Mass spectral data were obtained with a Varian CP3800 model coupled with Saturn 2000/Gas Chromatograph ionization energy 70 eV, using CIMS (Chemical Ionization Mass Spectrometry). Elemental analyses were performed by Atlantic Microlab; Norcross, GA, USA, results were within ± 0.4% of predicted values for all compounds. All solvents were dried and distilled under nitrogen atmosphere. Analytical TLC was carried out on precoated plates (silica gel 60, F_{254}) and visualized with UV light. The progress of the reactions was monitored by TLC with ethyl acetate: hexane (1:1 v/v) as eluant.

We report a facile synthesis of several sulfonamide compounds containing a chalcone moiety starting from commercial and available materials (Scheme 1). The starting materials 4-aminoacetophenone and 2, 5-dichlorobenzene sulfonyl chloride **1** were reacted at room temperature to yield the corresponding sulfonamide **3**, which was used in one-step Claisen-Schmidt condensations with substituted aromatic aldehydes to obtain sulfonamide chalcone derivatives 4a–k. The formation of the α,β unsaturated ketones almost always yielded the trans alkene (E-form) as judged by ^1H NMR spectroscopy, which have been fully characterized by analytical and spectral data.

2.1.1. Synthesis of 4'-N [(2'', 5''-dichlorophenyl) sulfonyl-amide] acetophenone 3

The compound **3** was prepared according to a previously described procedure with some modifications [9]. A mixture of 4-aminoacetophenone **2** (1 mmol) and recently distillated 2, 5-dichlorobenzene sulfonyl chloride (1 mmol) was dissolved in 5 ml of chloroform. The solution was stirred at room temperature for 3–6 h. The resulting precipitate was washed with acetone and then filtered off; the crude material obtained was recrystallized in acetonitrile to give brown crystals. mp: 232–233 °C. Yield: 57%. IR 3216 (NH); 1667 (CO); 1584 (Ar); 1337, 1270 (SO_2).^1H NMR: (DMSO-d_6) 2.49 (s, 3H, MeCO); 7.21 (d, 2H, $H_{3'}$ and $H_{5'}$, J = 8.91 Hz); 7.69 (d, 1H, $H_{3''}$, J = 8.41 Hz); 7.77 (dd, 1H, $H_{4''}$, $J_{4''\text{-}3''}$ = 8.41 Hz; $J_{4''\text{-}6''}$ = 2.47 Hz); 7.86 (d, 2H, $H_{2'}$ and $H_{6'}$, J = 8.91 Hz); 8.10 (d, 1H, $H_{6''}$, J = 2.47 Hz); 11.38 (s, 1H, NH).



Scheme 1. Synthesis of sulfonamide chalcone derivatives.

2.1.2. General procedure for E-2[4'-N (2'',5''-dichlorophenyl) sulfonylamide] chalcones derivatives 4a–k

Mixture of 4'-*N*[(2'',5''-dichlorophenyl)sulfonylamide]acetophenone (1 mmol), substituted aldehydes (1 mmol) and 2.5 mmol of pulverized sodium hydroxide dissolved in dry methanol (5 ml). The reaction mixture was stirred at room temperature for 8–12 h, the resulting precipitates were filtered off and recrystallized in ethanol, yields 25–89%.

2.1.3. 1[4'-N(2'',5''-dichlorophenyl)sulfonylamidephenyl]-3-(2,4-dimethoxyphenyl)-2-propen-1-one 4a

Mp: 210–212 °C. Yield: 89%. IR 3424 (NH); 1638 (CO); 1555 (Ar); 1338, 1290 (SO_2). ^1H-NMR: (DMSO-d_6) 3.83 (s, 3H, OMe); 3.88 (s, 3H, OMe); 6.63 (s, 1H, H_3); 7.24 (d, 2H, H_5; H_6, J = 8.64 Hz); 7.67 (d, 1H, H_α, J = 15.82 Hz); 7.69 (d, 2H, $H_{3'}$ and $H_{5'}$, J = 8.64 Hz); 7.77 (dd, 1H, $H_{4''}$, $J_{4''\text{-}3''}$ = 8.40 Hz; $J_{4''\text{-}6''}$ = 2.70 Hz); 7.87 (d, 1H, $H_{3''}$, J = 8.40 Hz); 7.93 (d, 1H, H_β, J = 15.82 Hz); 8.01 (d, 2H, $H_{2'}$ and $H_{6'}$, J = 8.64 Hz); 8.11 (d, 1H, $H_{6''}$, J = 2.70 Hz), 11.37 (s, 1H, NH); CIMS(m/z): 493 [M+1]; Anal. Calculated: C, 56.11%; H, 3.89%; N, 2.84%. Found: C, 56.82% H, 4.19%; N, 2.43%.

2.1.4. 1[4'-N(2'',5''-dichlorophenyl)sulfonylamidephenyl]-3(4-fluorophenyl)-2-propen-1-one 4b

Mp: 205–206 °C. Yield: 51%. IR 3424 (NH); 1638 (CO); 1555 (C=C Ar); 1338, 1290 (SO_2). ^1H NMR: (DMSO-d_6) 7.00 (d, 2H, H_3 and H_5, J = 8.91 Hz); 7.24 (d, 2H, H_2 and H_6, J = 8.91 Hz); 7.68–7.83 (m, 6H, $H_{3''}$; $H_{4''}$; $H_{3'}$ and $H_{5'}$; H_α, H_β); 8.06 (d, 2H, $H_{2'}$ and $H_{6'}$, J = 8.64 Hz); 8.13 (d, 1H, $H_{6''}$, J = 2.24 Hz); 11.43 (s, 1H, NH); CIMS(m/z): 451 [M+1]; Anal. Calculated: C, 56.01%; H, 3.13%; N, 3.11%. Found: C, 55.99%; H, 3.57%; N, 3.88%.

2.1.5. 1[4'-N(2'',5''-dichlorophenyl)sulfonylamidephenyl]-3(3,4-methylendioxi-phenyl)-2-propen-1-one 4c

Mp: 254–256°°C. Yield: 58%. cm^{-1} 3504 (NH); 1651 (CO); 1542 (Ar); 1306, 1245 (SO_2). ^1H NMR: (DMSO-d_6) 6.08 (s, 2H, $-OCH_2O-$); 6.82 (d, 1H, H_5, J = 8.91 Hz); 6.95 (d, 1H, H_6, J = 8.91 Hz); 7.24 (d, 2H, $H_{3'}$ and $H_{5'}$, J = 8.64 Hz); 7.45–7.59 (m, 2H, $H_{3''}$; $H_{4''}$); 7.68 (d, 1H, H_α, J = 15.34 Hz); 7.73 (d, 1H, H_β, J = 15.34 Hz); 7.83 (d, 2H, $H_{2'}$ and $H_{6'}$, J = 8.64 Hz); 7.93 (br s, 1H, $H_{6''}$); ^{13}C NMR: δ 102.03 ($-OCH_2O-$); 107.31 (C_5); 109.00 (C_2); 120.37 ($C_{3'\text{-}5'}$); 121.06 (C_α); 125.70 ($C_{4''}$); 127.10 ($C_{2''}$); 129.84