European Journal of Medicinal Chemistry 87 (2014) 197–202

Contents lists available at ScienceDirect

European Journal of Medicinal Chemistry

journal homepage: http://www.elsevier.com/locate/ejmech

Original article

Preparation and antimalarial activity of a novel class of carbohydrate-derived, fused thiochromans

Henok H. Kinfe [a, *], Paseka T. Moshapo [a], Felix L. Makolo [a], David W. Gammon [b], Martin Ehlers [c], Carsten Schmuck [c]

[a] Department of Chemistry, University of Johannesburg, Auckland Park 2006, South Africa
[b] Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa
[c] Institute of Organic Chemistry, University of Duisburg-Essen, Universitätstrasse 7, 45141 Essen, Germany

ARTICLE INFO

Article history:
Received 30 May 2014
Received in revised form
23 August 2014
Accepted 17 September 2014
Available online 19 September 2014

Keywords:
Antimalarial
Thiochromans
Chloroquine-sensitive
Chloroquine-resistant

ABSTRACT

A novel class of fused thiochroman derivatives has been prepared by an efficient and versatile synthetic procedure involving nucleophilic displacement of the side-chain iodo substituent in 2-deoxy-2-*C*-iodomethyl glucosides by thiophenolate ions, and subsequent intramolecular *C*-glycoside formation. A range of aromatic substituents is tolerated, and the subsequent facile selective oxidation of the sulfur to the sulfoxide or sulfone level expands the range and molecular diversity of the series of compounds. A selection of the sulfoxide and sulfone derivatives bearing lipophilic substituents on the aromatic portion were found to have antimalarial activities in the low micromolar range.

© 2014 Elsevier Masson SAS. All rights reserved.

1. Introduction

Thiochromans, 3,4-dihydro-2*H*-1-benzothiopyrans and their derivatives, continue to attract significant interest from organic and medicinal chemists due to their presence as key components in biologically active compounds that have shown anti-cancer [1,2], anti-HIV [3], anti-bacterial [4] and anti-fungal [5] activity, as well as being employed in the treatment of depression [6], schizophrenia, Parkinson's [7] and Alzheimer's diseases [8,9]. Moreover, the enhanced biological activity exhibited by thiochromans in comparison to their corresponding oxygen analogues [7,10] and the ease of derivatizing them into sulfoxides, sulfones, and Pummerer products, thus generating libraries of compounds for structure activity relationship studies, highlights their potential in medicinal chemistry programmes. However, despite their wide spectrum of biological and medicinal importance, the evaluation of thiochroman derivatives for their antimalarial activity has been overlooked. According to our literature survey, the last antimalarial activity study conducted on thiochroman derivatives was four decades ago. In 1978 Razdan et al. from the company *Arthur D. Little Inc*. reported that some derivatives of thiochromans were found to be active and were curative at dose levels of 160–360 mg/kg against *Plasmodium berghei* in mice [11]. Although these results were encouraging, there have been no further reports on any studies conducted to improve the efficacy and cytotoxicity (if any) of such thiochroman derivatives in relation to their antimalarial activity.

The reliability, effectiveness, limited host toxicity as well as low cost of chloroquine as an antimalarial drug in the past decades might have discouraged research and development of alternative antimalarials until the emergence of chloroquine-resistant malaria strains [12,13]. Currently, artemisinin-based combination therapy is World Health Organization's standard treatment against *Plasmodium falciparum*, the most lethal species that causes malaria in humans, in which the regimen uses a double or triple combination therapy with the aim of either delaying or preventing the development of drug resistance [14–16]. Although there are preventative and curative measures that have been adopted and with no clinical resistance having been reported against artemisinin, recent indications from South-East Asia are increasingly pointing towards tolerance which may eventually lead to resistance against this class of drugs [17–19]. Malaria accounts for over half-a-million deaths per annum worldwide and thus still constitutes a global health risk. Spitzmüller and Mestres have recently highlighted that while there is an urgent need to map the macromolecular drug target space in *P. falciparum*, there is also a need to expand the range of chemotypes with potential antimalarial activity [20]. Research in these

* Corresponding author.
E-mail address: hhkinfe@uj.ac.za (H.H. Kinfe).

http://dx.doi.org/10.1016/j.ejmech.2014.09.060
0223-5234/© 2014 Elsevier Masson SAS. All rights reserved.

directions will increase the chances of discovery and development of new antimalarial drugs with novel mechanisms of action [21].

Our interest in the stereoselective synthesis of carbohydrate based thiochroman derivatives and expansion of the range of antimalarial chemotypes, prompted us to prepare novel thiochroman derivatives and evaluate their antimalarial activities. Herein we report the *in vitro* antimalarial activity of thiochroman derivatives **3**–**9**, differing in their sulfur oxidation states, aromatic substituents, anomeric configurations and nature of protecting groups.

2. Results and discussion

2.1. Chemistry: preparation of thiochromans

Thiochroman derivatives (**3**–**4**) were synthesized starting with an α,β-anomeric mixture of 2-*C*-iodomethyl-glucosyl acetates **1** as outlined in Scheme 1 following our recently reported protocol [22,23]. Treatment of the anomeric mixture **1** with a range of aryl sodium thiolates that were each freshly prepared in DMF yielded sulfides (**2**) which then underwent Lewis acid catalysed Friedel–-Crafts alkylation to give the α-*C*-glycosides (**3**–**4**) as single isomers. Efforts to debenzylate thiochromans **3** using traditional hydrogenolysis using H_2 and catalytic Pd/C to obtain hydrophilic thiochroman derivatives were unsuccessful; however, acetylated thiochroman **3g** could be readily hydrolysed under basic conditions to afford the more hydrophilic derivative **4** (Scheme 1).

Oxidation of thiochromans **3(a–f)** in the presence of cerium ammonium nitrate, wet silica gel and catalytic amounts of potassium bromide formed a diastereomeric 2:1 mixture of sulfoxides without over-oxidation to sulfones. The diastereomers were separated by column chromatography to afford **5(a–f)** and **6(a–f)**. Efforts to identify the stereochemistry of each sulfoxide by growing crystals of the respective compounds with a view to obtain single crystal X-ray diffraction were unsuccessful and the configurations are tentatively assigned. The chemical structure of the sulfoxides was confirmed by a combination of common techniques such as IR, NMR and HRMS (Scheme 2) [24].

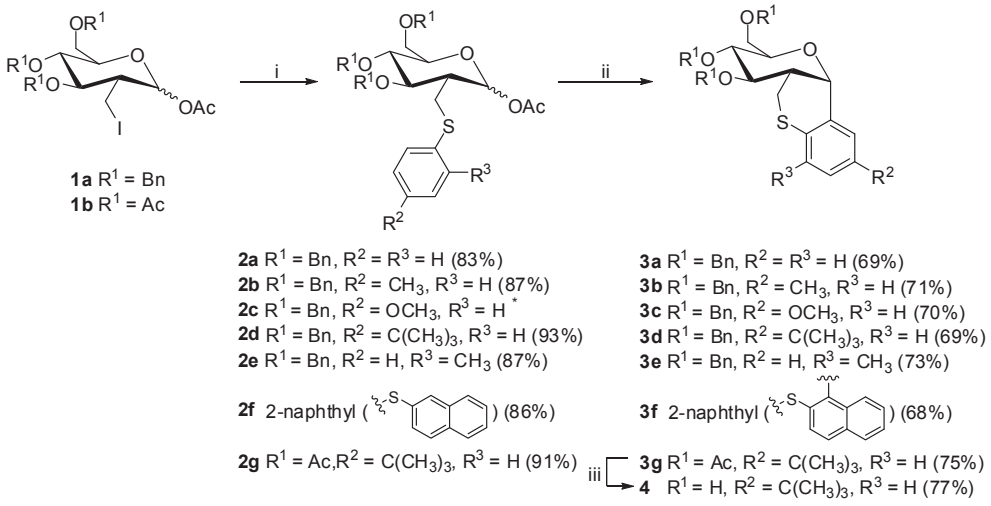
Oxidation of sulfides **3** with excess OXONE® produced sulfones **7**. The acetylated thiochroman **7g** was further hydrolysed to afford the triol **8**. Portions of **7(a–e)** were then epimerized upon treatment with NaH to provide the β-C-glycosides **9(a–e)** in excellent yields following our recently reported protocol (Scheme 3) [25].

2.2. Antimalarial activity of synthetic thiochromans

After the successful synthesis of the thiochroman derivatives, these were evaluated for their activity against the chloroquine-sensitive 3D7 and chloroquine-resistant FCR3 strains of the malaria parasite, *P. falciparum*, by measuring parasite survival using a parasite lactate dehydrogenase (pLDH) assay. Compounds that exhibited parasite survival rates of 0–15% at a single concentration of 10 μM were screened further for dose–response to determine the IC_{50} values and the results are summarized in Table 1 (refer to the supporting information for detailed data).

The structural parameters explored for SAR correlation were oxidation state of the sulfur (sulfide, sulfoxide and sulfone), nature and position of the substituent on the aromatic ring of the thiochroman motif, stereochemistry of the sulfoxide group, anomeric configuration of the sugar moiety (and consequent geometry of the ring fusion), nature of protecting group and hydrophilicity.

The lack of high potency and activity of thiochromans **3a–f** and thiochroman derivatives **5a**, **6a**, and **7a**, in comparison to the other analogues, indicates the requirement for sulfur in higher oxidation states and the presence of a substituent on the aromatic ring of the thiochroman moiety to impart activity/potency. In agreement with the literature report, the sulfone functional group imparted higher antimalarial activity than the corresponding sulfides (compare **3a–f** vs **7b–f** and the epimerized sulfones in Table 1) [26]. With regard to the sulfoxides, there is only one instance of significant difference in the activity of the diastereomeric sulfoxides, *viz*. the case of **5b** and **6b**, with **5b** essentially inactive against strain 3D7,



[a]Reagents and conditions: i) 60% NaH, Aryl thiol, DMF, rt, 5 min; ii) $BF_3{\cdot}Et_2O$, DCM, 0 °C, 5 min; iii) K_2CO_3, MeOH, rt, 3 h. *Sulfide **2c** was unstable on standing and thus it was immediately cyclized without purification.

Scheme 1. Diastereoselective synthesis of thiochroman derivatives **3-4**[a].

Download English Version:

https://daneshyari.com/en/article/7800469

Download Persian Version:

https://daneshyari.com/article/7800469

Daneshyari.com