Bioorganic & Medicinal Chemistry Letters 20 (2010) 942–944

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

Synthesis, antimalarial and antitubercular activity of acetylenic chalcones

Renate H. Hans [a], Eric M. Guantai [a], Carmen Lategan [b], Peter J. Smith [b], Baojie Wan [c], Scott G. Franzblau [c], Jiri Gut [d], Philip J. Rosenthal [d], Kelly Chibale [a,e,*]

[a] Department of Chemistry, University of Cape Town, Rondebosch 7701, South Africa
[b] Division of Pharmacology, University of Cape Town, Observatory 7925, South Africa
[c] Institute for Tuberculosis Research, College of Pharmacy, University of Illinois at Chicago, 833 South Wood Street, Chicago, IL 60612-723, USA
[d] Department of Medicine, San Francisco General Hospital, University of California at San Francisco, CA 94143, USA
[e] Institute of Infectious Disease and Molecular Medicine, University of Cape Town, Rondebosch 7701, South Africa

ARTICLE INFO

Article history:
Received 12 November 2009
Revised 14 December 2009
Accepted 15 December 2009
Available online 23 December 2009

Keywords:
Chalcones
Falcipain-2
P. falciparum
M. tuberculosis

ABSTRACT

A series of acetylenic chalcones were evaluated for antimalarial and antitubercular activity. The antimalarial data for this series suggests that growth inhibition of the W2 strain of *Plasmodium falciparum* can be imparted by the introduction of a methoxy group *ortho* to the acetylenic group. Most compounds were more active against non-replicating than replicating cultures of *Mycobacterium tuberculosis* $H_{37}Rv$, an unusual pattern with respect to existing anti-TB agents.

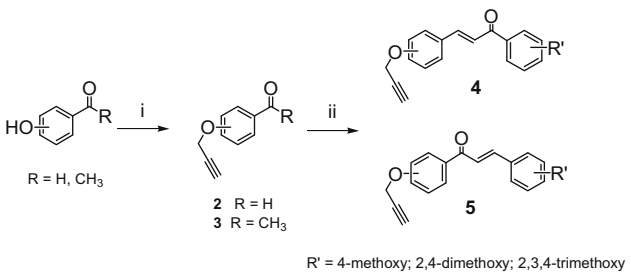
The greatest concern with infectious diseases, especially malaria and tuberculosis, is the alarming rate at which resistance against clinically used drugs develops. This imparts a degree of urgency for the discovery of affordable and effective alternative drugs. The appeal of working with chalcones (1,3-diarylprop-2-en-1-one) stems from their synthetic accessibility, the various ways the core structure can be diversified and their ability to confer drug-like properties to compound libraries modeled on them.[1] Consistent with its privileged status, a wide range of biological activities such as anti-inflammatory,[2] antileishmanial,[3] antibacterial,[4] antifungal,[5] antitumour,[6] antimalarial[7,8] and anti-TB activity[9] have been reported for chalcone derivatives. Regarding the antimalarial activity, it has been proposed that chalcones exert their mode of action by the inhibition of cysteine proteases.[10] Failure to correlate the antiplasmodial activity of some chalcones with cysteine protease inhibition led to the conclusion that other targets and/or pathways may be compromised.[8d] In fact, recent reports suggest that chalcones also play a role in the inhibition of new permeability pathways induced by the parasite in the erythrocyte membrane.[8g] Moreover, previous SAR studies revealed that the minimum requirements for antimalarial activity are the presence of the enone linker[8c] and for the double bond in this linker to have a *trans* (*E*)-configuration.[8e] These basic structural features were retained in the compounds synthesized in this study. Our drug design effort was further guided by a study which showed that alkoxylated chalcones are more important for antimalarial activity.[7a,8g]

Interestingly, the number and scope of SAR studies exploring the antimalarial effects of chalcones is in stark contrast to those investigating their antitubercular activity. One of the few studies on TB involved a 47-member chalcone library, which showed that halogenated chalcones display superior antitubercular activity.[9a] Another study explored the inhibitory effect of variously substituted chalcones on the protein tyrosine phosphatase (PtpA) of *Mycobacterium tuberculosis*.[9c] Incidentally, the latter study represents one of the few attempts at elucidating the mode of action of antitubercular chalcones.

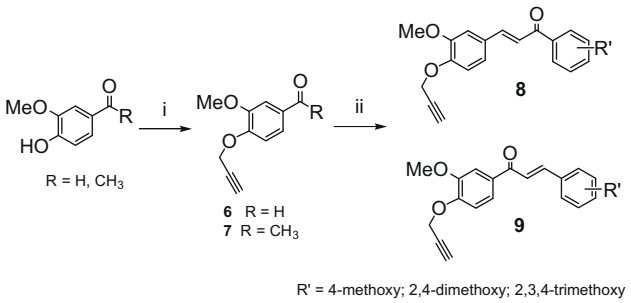
In the interest of developing a focused library from which meaningful SAR can be delineated, the substituent groups chosen were limited to the methoxy and acetylenic groups. While the former is based on previous SAR studies,[7a,8g] the latter not only serves as a site for further chemical diversification but is also of great interest in medicinal chemistry and the pharmaceutical industry. It moreover functions as a key pharmacophoric unit in acetylenic antibiotics[11] and its presence in anticancer[12] and antitubercular[13] agents is noteworthy. We envisaged that the combination of these functional groups would contribute towards increasing the lipophilicity of the target compounds relative to structurally similar phenolic compounds, that is, analogues which are devoid of the acetylenic group. Lipophilicity is an important requirement for antimalarial, but more so antimycobacterial agents because of the unusual lipid-rich cell wall of mycobacteria.

* Corresponding author. Tel.: +27 21 650 2553; fax: +27 21 689 7499.
E-mail address: Kelly.Chibale@uct.ac.za (K. Chibale).

0960-894X/$ - see front matter © 2009 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2009.12.062



Scheme 1. Reagents and conditions: (i) Propargyl bromide, K_2CO_3, DMF, rt, 16 h for **4** and 24 h for **5**; (ii) methoxylated acetophenone or benzaldehyde, 3 w/v % NaOH, MeOH, rt, 16 h.



Scheme 2. Reagents and conditions: (i) Propargyl bromide, K_2CO_3, DMF, rt, 12 h; (ii) methoxylated acetophenone (for **8**), methyoxylated benzaldehyde (for **9**), 2.5 M NaOH aq, MeOH, 70 °C, 3 h.

The two-step synthesis of compounds **4** and **5** is outlined in Scheme 1. As shown, commercially available hydroxyacetophenone or benzaldehyde was subjected to O-alkylation with 1.2 equiv of propargyl bromide in the presence of 1.5 equiv of K_2CO_3 in DMF. The intermediate acetylenes **2-3** were obtained in excellent to quantitative yields. The second step, also known as the Claisen–Schmidt condensation, provided access to **4** and **5**.[7a] Using commercially available vanillin and acetovanillone, compounds **8** and **9** were obtained under similar reaction conditions as shown in Scheme 2.

All synthesized chalcones were characterized with IR, ^{1}H- and ^{13}C NMR, low resolution mass spectroscopy and elemental analysis.

For antiplasmodial evaluation, the chalcones were screened for activity against chloroquine-sensitive (D10)[15] and chloroquine-resistant (W2)[14] strains of *Plasmodium falciparum*. Evaluation of in vitro activity against *M. tuberculosis* H_{37}Rv strain was conducted using the MABA assay in 7H12 medium.[16] The compounds that were found to be active in the latter were further tested in the LORA assay[17] for activity against slow growing or non-replicating *M. tuberculosis*. Results obtained are shown in Table 1.

With regard to the antiplasmodial activity, it is of interest to note that the introduction of a methoxy group *ortho* to the acetylenic group imparts activity against the W2 strain, as can be concluded when comparing the activities of **4** and **5** with the low micromolar activities of **8** and **9**. Compound **8b** is the most active, with IC_{50}s of 3.4 μM against the D10 and 3.8 μM against the W2 strain, respectively. The chalcone series which lacks the *ortho* methoxy group showed activity against the chloroquine-sensitive (D10) strain, but no useful trends regarding the degree of methoxylation, position of attachment of the acetylenic group and the aromatic ring preference for substituents could be delineated. None of the chalcones in this series showed activity against the *P. falciparum* cysteine protease falcipain-2.

The limited series **8** and **9**, which displayed encouraging antiplasmodial activity, showed poor or a lack of antitubercular activity compared to series **4** and **5**. This may be advantageous if the

Table 1
In vitro antimalarial activities against *P. falciparum* D10 and W2 strains and in vitro antitubercular activities against replicating and non-replicating phenotypes of *M. tuberculosis* H_{37}Rv strain

Compd	Substitution	R′	Rec-FP-2[a] IC_{50} (μM)	W2 IC_{50} (μM)	D10 IC_{50} (μM)	MABA MIC (μM)	LORA MIC (μM)	C log P[b]
4a	*Ortho*	4-OMe	>100	>20	>100	47.5	50.7	4.36
4b	*Ortho*	2,4-diOMe	>100	>20	8.00	59.1	14.9	4.45
4c	*Ortho*	2,3,4-triOMe	>100	>20	50.57	61.9	28.6	3.74
4d	*Meta*	4-OMe	>100	>20	11.60	40.0	31.7	4.36
4e	*Meta*	2,4-diOMe	>100	>20	7.57	54.9	26.1	4.45
4f	*Meta*	2,3,4-triOMe	19.0	>20	>100	54.0	13.1	3.74
4g	*Para*	4-OMe	>100	>20	>100	>128	ND	4.36
4h	*Para*	2,4-diOMe	>100	>20	54.78	>128	ND	4.45
4i	*Para*	2,3,4-triOMe	>100	>20	13.34	>128	ND	3.74
5a	*Ortho*	4-OMe	>100	>20	>100	31.1	56.7	4.36
5b	*Ortho*	2,4-diOMe	>100	>20	18.86	53.7	62.8	4.45
5c	*Ortho*	2,3,4-triOMe	>100	>20	>100	98.7	46.1	3.74
5d	*Meta*	4-OMe	>100	>20	>100	51.2	>128	4.36
5e	*Meta*	2,4-diOMe	>100	>20	>100	>128	ND	4.45
5f	*Meta*	2,3,4-triOMe	>100	>20	33.03	58.7	29.7	3.74
5g	*Para*	4-OMe	>100	>20	16.52	>128	ND	4.36
5h	*Para*	2,4-diOMe	>100	>20	>100	31.0	108	4.45
5i	*Para*	2,3,4-triOMe	>100	>20	4.43	>128	ND	3.74
8a		4-OMe	ND	8.4	9.7	>128	ND	4.10
8b		2,4-diOMe	ND	3.8	3.4	>128	ND	4.13
8c		2,3,4-triOMe	ND	7.0	7.7	109	ND	3.38
9a		2,4-diOMe	ND	9.7	>20	>128	ND	4.13
9b		2,3,4-triOMe	ND	6.7	4.1	>128	ND	3.38
E64			0.047	ND				
Chloroquine				0.069	0.038			
Rifampin						0.05	2.4	
Isoniazid						0.37	>128	
Moxifloxacin						0.29	31.1	
PA824						0.16	3.3	

[a] Assay against recombinant falcipain-2 (Rec-FP-2) was performed as previously described.[14]
[b] Calculated using Chemdraw Ultra 9.0; ND = not determined

former were to be developed as antimalarials, as our results suggest specific anti-infective activity. Compounds **5a** and **5h** showed promising activity with MABA, with MICs of 31.0 μM and 31.1 μM, respectively. However, relative to the controls, the activities were rather poor. The MABA data also suggest that, with the exception of **4g** and **5g** which incidentally are both para substituted, the monomethoxylated derivatives **4a**, **4d**, 5a and **5d** showed good activity. Intriguingly, for most compounds, activity against non-replicating M. tuberculosis in the LORA was equivalent to or better than that observed against replicating cultures in the MABA. This is a rare observation as most compounds examined to date are much more active against replicating cultures. Furthermore, the LORA and MABA results collectively indicate that there is no correlation between the C log *P* or lipophilicity and antitubercular activity.

In summary the chalcones showed an interesting activity profile in the two disease models under study. Moreover it appears that the antimalarial and antimycobacterial activity of acetylenic chalcones herein reported can be tuned by the introduction of an *ortho* methoxy group. Expansion of the series **8** and **9** will provide further evidence. This study also showed that anti-TB chalcones are not limited to halogen substituted derivatives as previously reported.[9a]

Acknowledgments

We thank the African American Institute (R.H.H.), the National Research Foundation (E.G., K.C.), and the South African Research Chairs Initiative of the Department of Science and Technology (K.C.) for financial support.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.12.062.

References and notes

1. Nowakowska, Z. *Eur. J. Med. Chem.* **2007**, *42*, 125.
2. Herencia, F.; Ferrandiz, M. L.; Ubeda, A.; Domiguez, J. N.; Charris, J. E.; Lobo, G. M.; Alcaraz, M. J. *Bioorg. Med. Chem.* **1998**, *8*, 1169.
3. Nielsen, S. F.; Christensen, S. B.; Cruciani, G.; Kharazmi, A.; Lijefors, T. *J. Med. Chem.* **1998**, *41*, 4819.
4. (a) Nielsen, S. F.; Bosen, T.; Larsen, M.; Schonning, K.; Kromann, H. *Bioorg. Med. Chem.* **2004**, *12*, 3047; (b) Nielsen, S. F.; Larsen, M.; Bosen, T.; Schonning, K.; Kromann, H. *J. Med. Chem.* **2005**, *48*, 2667; (c) Liu, X. L.; Xu, Y. J.; Go, M. L. *Eur. J. Med. Chem.* **2008**, *43*, 1681; (d) Ansari, F. L.; Nazir, S.; Noureen, H.; Mirza, B. *Chem. Biodivers.* **2005**, *2*, 1656.
5. (a) Bhakuni, D. S.; Chaturvedi, J. *J. Nat. Prod.* **1984**, *47*, 585; (b) Tsuchiya, H.; Sato, M.; Akagiri, M.; Takagi, N.; Tanaka, T.; Iinuma, M. *Pharmazie* **1994**, *49*, 756.
6. (a) Go, M. L.; Wu, X.; Liu, X. L. *Curr. Med. Chem.* **2005**, *12*, 483; (b) Edwards, M. L.; Stemerick, D. M.; Sunkara, P. S. *J. Med. Chem.* **1990**, *33*, 1948; (c) Ducki, S.; Forrest, R.; Hadfield, J. A.; Kendall, A.; Lawrence, N. J.; Mcgown, A. T.; Rennison, D. *Bioorg. Med. Chem. Lett.* **1998**, *8*, 1051.
7. (a) Liu, M.; Wilairat, P.; Go, M.-L. *J. Med. Chem.* **2001**, *44*, 4443; (b) Mishra, N.; Arora, P.; Kumar, B.; Mishra, L. C.; Bhattacharya, A.; Awasthi, S. K.; Bhasin, V. K. *Eur. J. Med. Chem.* **2008**, *43*, 1530.
8. (a) Chen, M.; Theander, T. G.; Christensen, B. S.; Hviid, L.; Zhai, L.; Kharazmi, A. *Antimicrob. Agents Chemother.* **1994**, *38*, 1470; (b) Domínguez, J. N.; León, C.; Rodrigues, J.; Gamboa de Domínguez, N.; Gut, J.; Rosenthal, P. J. *J. Med. Chem.* **2005**, *48*, 3654; (c) Li, R.; Kenyon, G. L.; Cohen, F. E.; Chen, X.; Gong, B.; Domínguez, J. N.; Davidson, E.; Kurzban, R. E.; Miller, R. E.; Nuzum, E. O.; Rosenthal, P. J.; McKerrow, J. H. *J. Med. Chem.* **1995**, *38*, 5031; (d) Domínguez, J. N.; Charris, J. E.; Lobo, G.; Gamboa de Domínguez, N.; Moreno, M. M.; Riggione, F.; Sanchez, E.; Olson, J.; Rosenthal, P. J. *Eur. J. Med. Chem.* **2001**, *36*, 555; (e) Larsen, M.; Kromannn, H.; Kharazmi, A.; Nielsen, S. F. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4858; (f) Li, R.; Chen, X.; Gong, B.; Selzer, P. M.; Li, Z.; Davidson, E.; Kurzban, G.; Miller, R. E.; Nuzum, E. O.; McKerrow, J. H.; Fletterick, R. J.; Gilmor, S. A.; Craik, C. S.; Kuntz, I. D.; Cohen, F. E.; Kenyon, G. L. *Bioorg. Med. Chem.* **1996**, *4*, 142; (g) Go, M. L.; Liu, M.; Wilairat, P.; Rosenthal, P. J.; Saliba, K. J. *Antimicrob. Agents Chemother.* **2004**, *48*, 3241.
9. (a) Lin, Y.-M.; Flavin, M. T.; Zhou, L.-M.; Nie, W.; Chen, F.-C. *Bioorg. Med. Chem.* **2002**, *10*, 2795; (b) Friis-Moller, A.; Chen, M.; Fuursted, K.; Christensen, S. B.; Kharazmi, A. *Planta Med.* **2002**, *68*, 416; (c) Chiaradia, L. D.; Mascarello, A.; Purificação, M.; Vernal, J.; Cordeiro, M. N. S.; Zenteno, M. E.; Villarino, A.; Nunes, R. J.; Yunes, R. A.; Terenzi, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6227.
10. Ring, C. S.; Sun, E.; McKerrow, J. H.; Lee, G. K.; Rosenthal, P. J.; Kuntz, I. D.; Cohen, F. E. *Proc. Natl. Acad. Sci.* **1993**, *90*, 3583.
11. Maretina, I. A.; Trofimov, B. A. *Russ. Chem. Rev.* **2006**, *75*, 825.
12. Siddiq, A.; Dembitsky, V. *Anti-cancer Agents Med. Chem.* **2008**, *8*, 132.
13. Deng, S.; Wang, Y.; Inui, T.; Chen, S.-N.; Farnsworth, N. R.; Cho, S.; Franzblau, S. G.; Pauli, G. F. *Phytother. Res.* **2008**, *22*, 878.
14. Greenbaum, D. C.; Mackey, Z.; Hansell, E.; Doyle, P.; Gut, J.; Caffrey, C. R.; Lehman, J.; Rosenthal, P. J.; McKerrow, J. H.; Chibale, K. *J. Med. Chem.* **2004**, *47*, 3212.
15. (a) Trager, W.; Jensen, J. B. *Science* **1976**, *193*, 673; (b) Makler, M. T.; Ries, J. M.; Williams, J. A.; Bancroft, J. E.; Piper, R. C.; Gibbins, B. L.; Hinrichs, D. *J. Am. Soc. Trop. Med. Hyg.* **1993**, *48*, 739.
16. (a) Collins, L.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **1997**, *41*, 1004; (b) Falzari, K.; Zhu, Z.; Pan, D.; Liu, H.; Hongmanee, P.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **2005**, *49*, 1447.
17. Cho, S. H.; Warit, S.; Wan, B.; Hwang, C. H.; Pauli, G. F.; Franzblau, S. G. *Antimicrob. Agents Chemother.* **2007**, *51*, 1380.