Bioorganic & Medicinal Chemistry Letters 20 (2010) 4555–4557

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Synthesis and activity of polyacetylene substituted 2-hydroxy acids, esters, and amides against microbes of clinical importance

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ARTICLE INFO

Article history:
Received 13 April 2010
Revised 2 June 2010
Accepted 3 June 2010
Available online 10 June 2010

Keywords:
Polyacetylene
2-Hydroxy acids
Microbes of clinical importance
Pseudomonas aeruginosa

ABSTRACT

A series of novel polyacetylene substituted 2-hydroxy acids and derivatives were prepared and characterized. Alkylation of butane-2,3-diacetal (BDA) protected glycolic acid with iodoalkyl substituted polyacetylene compounds gave the corresponding diacetal protected polyacetylene substituted 2-hydroxy acids. Diacetal deprotection through acid mediated hydrolysis, transesterification or aminolysis afforded the 2-hydroxy-polyacetylenic acid, ester or amide derivatives. Twenty one of these novel compounds were tested against 10 microbes of clinical importance and several of them showed good antimicrobial activity, in particular against *Pseudomonas aeruginosa*.

Polyacetylenic lipids and their derivatives have been isolated from a wide variety of species[1–3] and are known for an array of interesting properties.[4,5] Compounds containing three conjugated unsaturated moieties, such as yne–ene–yne, yne–yne–ene and yne–yne–yne polyacetylenics display a diverse range of biological effects including cytotoxicity, antifungal, antimicrobial, herbicidal and antibacterial activities.[6–9] Thus, such polyacetylenic compounds are of great interest to the pharmaceutical industry. A particularly important area of interest is the discovery and development of novel antimicrobial agents, since the number of effective antimicrobial agents is declining due to increased antimicrobial resistance. Moreover, advances in medicine have prolonged life, leading to an aging population with decreased immunity and increased susceptibility to hospital-acquired infections with multiresistant organisms, which are difficult to treat with antimicrobial agents. As a part of our ongoing studies into the chemistry and applications of polyacetylene containing molecules we recognised a hitherto unreported class of polyacetylene substituted 2-hydroxy acids and derivatives.[10] Herein, we describe an efficient synthesis of novel 2-hydroxy-polyacetylenic acid, ester and amide derivatives and their activity against ten species of *Candida* and bacteria.

Our synthetic protocols and products are summarized in Scheme 1 and Table 1. The polyacetylenic alcohols **1–11** were prepared according to the literature procedures.[9–16] The alcohols **1–11** were converted into the respective iodides **12–22** in good yield following the literature procedures.[17–19] We chose the iodo leaving group (instead of bromo or chloro leaving groups) for the subsequential alkylation based on our observations during the synthesis of 2-hydroxy-diyne acids where we were able to show good alkylation yield of glycolic acid butane-2,3-diacetal with iodo-diyne compounds.[16,17]

The alkylation[20–22] of glycolic acid BDA[23,24] was carried out with iodides **12–22** lithium bis(trimethylsilyl)amide (LHMDS) (1.05 equiv) in THF at −78 °C.[11,25] to afford products **23–33** in moderate yield. Diacetal deprotection was accomplished by acid mediated hydrolysis to give the 2-hydroxy-polyacetylenic acids **34–43** (Scheme 1) in quantitative yield and high purity.

Removal of the BDA protective group through transesterification was carried out with 3-phenyl propanol (80 °C), isopropanol (80 °C) and methanol (room temperature), giving the esters **44–47**, respectively, in excellent yield. Aminolysis reactions were carried out using each of benzylamine and 2-methyl-propanamine as reagent and solvent providing the desired products **48** and **49**, respectively, in good yield. The purity of all final products was greater than 95% by ^{1}H NMR. A similar approach has been used successfully for the synthesis of 2-hydroxy-diyne acids, amides and esters.[26,27]

Assay against *Candida* species—For the testing of antifungal activity of 21 selected compounds, five clinically important species of *Candida* (*Candida albicans* ATCC 90028, *Candida glabrata* ATCC 90030, *Candida krusei* ATCC 6258, *Candida tropicalis* ATCC 750,

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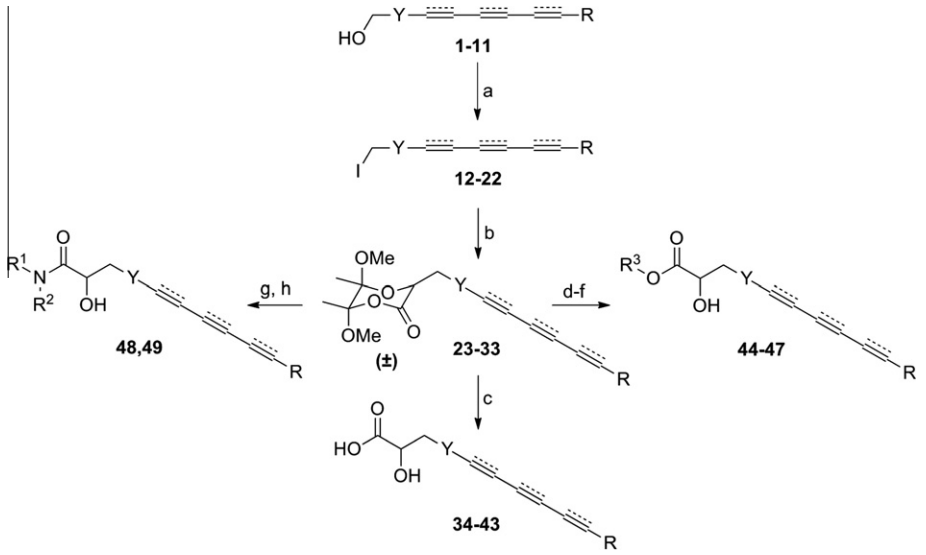
doi:10.1016/j.bmcl.2010.06.020



Scheme 1. Synthesis of polyacetylene substituted 2-hydroxy acids and derivatives. Reagents and conditions: (a) PPh_3, imidazole, I_2, CH_2Cl_2, 1 h, −10 °C; (b) LHMDS, (±) glycolic acid BDA, AcOH, 3 h, −78–20 °C; (c) CF_3COOH/H_2O, 20 °C; (d) HCl, 3-phenylpropanol, 80 °C; (e) HCl, *i*-PrOH, reflux; (f) HCl, MeOH, 20 °C; (g) benzylamine, 20 °C, then TFA/H_2O; (h) 2-methyl-propanamine, 20 °C, then TFA/H_2O.

Table 1

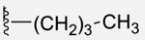
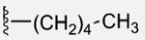
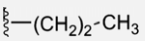
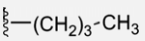
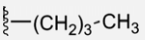
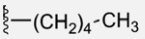
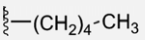
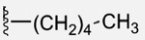
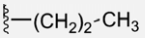
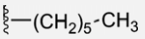
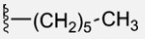
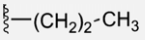
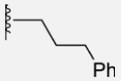
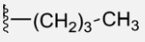
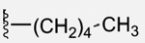
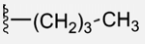
Product	Y		R	R^1	R^2	R^3
1, **12**, **23**, **34**		yne–ene(*cis*)–yne				
2, **13**, **24**, **35**		yne–ene(*cis*)–yne				
3, **14**, **25**, **36**		yne–ene(*cis*)–yne				
4, **15**, **26,37**		yne–ene(*cis*)–yne				
5, **16**, **27**, **38**		ene(*cis*)–yne–yne				
6, **17**, **28**, **39**		ene(*trans*)–yne–yne				
7, **18**, **29**, **40**		ene(*trans*)–yne–yne				
8, **19**, **30**, **41**		yne–yne–ene(*cis*)				
9, **20**, **31**, **42**		yne–yne–yne				
10, **21**, **32**, **43**		yne–yne–yne				
11, **22**, **33**		yne–yne–ene(*cis*)				
44		yne–yne–ene(*cis*)				
45		yne–ene(*cis*)–yne				
46		ene(*trans*)–yne–yne				
47		ene(*trans*)–yne–yne				
48		ene(*trans*)–yne–yne				
49		yne–yne–ene(*cis*)				

Table 2
Antifungal activities of selected compounds

Products	IC_{50} range for *Candida* species (μM)				
	C. albicans	*C. glabrata*	*C. tropicalis*	*C. krusei*	*C. parapsilosis*
25					
26					
28					
30					
32					
34					500–1000
35					500–1000
36					
37					
38					
39	500–1000	~500	500–1000	500–1000	~250
40	500–1000	500–1000	500–1000	500–1000	~2
41		500–1000		~1000	2–4
42		500–1000	500–1000	500–1000	2–4
43	500–1000	500–1000	500–1000	500–1000	125–250
44		1000–2000			~30
45					
46					
47	~1000	~500	~1000		
48					
49					

Blanks spaces indicate no inhibition.

Table 3
Inhibition of bacterial growth

Products	*S. aureus* ATCC 25923	*P. aeruginosa* ATCC 27853	*E. coli* ATCC 25922	*S. pyogenes* ATCC 19615	*MRSA* clinical isolate
25	+	+++	++	+++	+
26	+	+++	++	+++	+
28	+	+++	++	+++	+
30	++	+++	++	+++	+
32	++	+++	+++	+++	+
34	+++	+++	+++	+++	+
35	+++	+++	+++	+++	+++
36	+++	+++	++	+++	+++
37	+++	+++	++	+++	+++
38	+	+++	–	–	–
39	++	+++	–	+	–
40	–	+++	+	++	+++
41	+++	+++	+++	+++	+++
42	+++	+++	+++	++	+++
43	+++	+++	+++	+++	+++
44	++	+++	+	+++	+++
45	+	+++	++	+++	+
46	+	+++	++	+++	++
47	+	+++	++	+++	+++
48	+	+++	++	+++	++
49	++	+++	++	+++	+++

Reduction in optical density (OD_{595}) compared with control without compound: +++ >75%, ++ 50%, – 75%, + between 25% and 50%.

and *Candida parapsilosis*) were chosen. The results are summarized in Table 2. Carboxylic acids **39**, **40**, and **43** inhibited all species. Of the other compounds carboxylic acids **34**, **35**, **41**, and **42** and methyl ester **44** and **47** inhibited specific species. The latter does not set any precedent, since these yeasts are known to have different susceptibilities to some existing antifungals such as fluconazole.[28] Like *C. albicans*, *C. glabrata* and *C. krusei*, *C. parapsilosis* displayed much higher sensitivity to carboxylic acids **39**–**43**, and methyl esters **44** and **47**. Larger esters or amides were inactive.

Assay against bacterial species—Four reference strains and a clinical isolate of methicillin-resistant *Staphylococcus aureus* were used in this study. All compounds, except **38**, **39**, and **40**, showed activity against all five bacterial species tested. The strong activity of all compounds against *P. aeruginosa* is very significant, since this species is resistant to most currently available antimicrobial agents (Table 3).

We have described a convenient and high yielding methodology to prepare polyacetylene substituted 2-hydroxy acids, esters and amides **31–45** through the hydrolysis, transesterification or aminolysis of diacetal protected polyacetylenic substituted 2-hydroxy acids **21–30**. Twenty one of these novel compounds were tested against 10 microbes of clinical importance and in particular most of the compounds showed strong activity against *P. aeruginosa*. Additionally carboxylic acids **39–43**, and methyl esters **44** and **47** showed activity against *C. parapsilosis*. This is a significant result, since this *P. aeruginosa* is resistant to most currently available antimicrobial agents. Future work will focus upon the biological activity of other 2-hydroxy polyacetylene variants and the determination of structure–activity relationships.

Acknowledgments

We thank the GRDC (Grains Research and Development Corporation), Australia for financial support and Drs. Kathleen Turner and Craig Francis for critical comments on the manuscript.

Supplementary data

Supplementary data (full experimental details and characterization data for all new compounds) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.020.

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