



New phenstatin–fatty acid conjugates: Synthesis and evaluation



Jinhui Chen^a, David P. Brown^{a,*}, Yi-Jun Wang^b, Zhe-Sheng Chen^b

^a Department of Chemistry, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, USA

^b Department of Pharmaceutical Sciences, St. John's University, 8000 Utopia Parkway, Jamaica, NY 11439, USA

ARTICLE INFO

Article history:

Received 15 May 2013

Revised 10 July 2013

Accepted 16 July 2013

Available online 24 July 2013

Keywords:

Conjugates

Fatty acids

Microtubule-binding drugs

Cancer chemotherapy

Drug resistance reversal

ABSTRACT

New phenstatin–fatty acid conjugates have been synthesized and tested against the KB-3-1, H460, MCF-7 and HEK293 cell lines, with an increase in anti-proliferative activity being observed at the micro-molar level paralleling an increase in un-saturation in the fatty acid component.

© 2013 Elsevier Ltd. All rights reserved.

The quest for more potent and less toxic candidates in the treatment of various elusive forms of cancer remains unrelenting; and especially so, in light of the emergence of new multidrug resistance (MDR) mechanisms. It has been reported that this persistent MDR barrier is the most significant reason for treatment failures in excess of 90% of subjects with metastatic cancers.¹ Among the group of promising antineoplastic agents are new chemical entities which are hybrids of naturally occurring bioactive substances. These hybrids are often comprised of either the whole or partial structures of the natural product of interest. Indeed, reports indicate several cases of improved activity of the hybrids relative to the parent natural product.² Of direct relevance are the hybrids of recognized anti-cancer compounds and various unsaturated fatty acids, ranging from the monounsaturated systems (MUFAs) to different polyunsaturated systems (PUFAs).

The incorporation of unsaturated fatty acids provides a very promising alternative in addressing tumor-targeting delivery of drugs in an effort to improve the overall efficacy of these chemotherapeutic agents.³ PUFAs such as linoleic acid (LA) and docosahexaenoic acid (DHA) fulfill significant roles in cell growth and development.⁴

Furthermore, studies have shown that PUFAs are readily taken up by tumor cells, and that certain PUFA-drug conjugates exhibit tumor specific accumulation through *in vitro* and *in vivo* studies.⁵ For instance, Ojima et al. have synthesized conjugates of DHA or LNA (linolenic acid) with next generation taxoids that have demonstrated greatly improved efficacy.⁶

This study focuses on the effects of conjugating various fatty acids on the antiproliferative activity of the reported tubulin-binding compound phenstatin⁷ **1**. Presently, intense efforts have been devoted to the development of novel analogues of phenstatin and its derivatives, largely based on the fact that being a benzophenone derivative, its structure is not prone to the (*Z*)/(*E*) isomerization associated with combretastatin A-4 (CA-4), the cause of decreased efficacy. We have also examined hybrids of the new compound isopenstatin **2** (Fig. 1).

Phenstatin, like CA-4, binds to the colchicine site of endothelial tubulin, thus interfering with the equilibrium dynamics associated with the cell division process.⁸ Mitotic arrest typically follows leading to apoptosis and cell death.⁹

Herein we report the synthesis of some novel MUFA and PUFA-conjugates of phenstatin and isopenstatin.

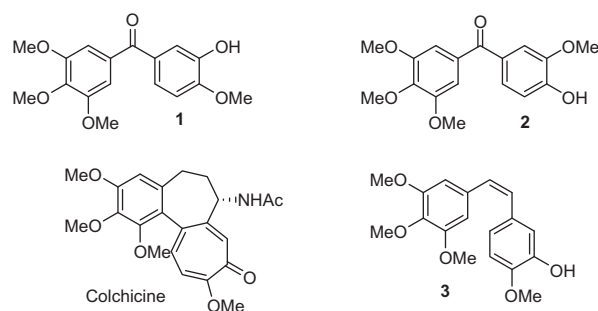
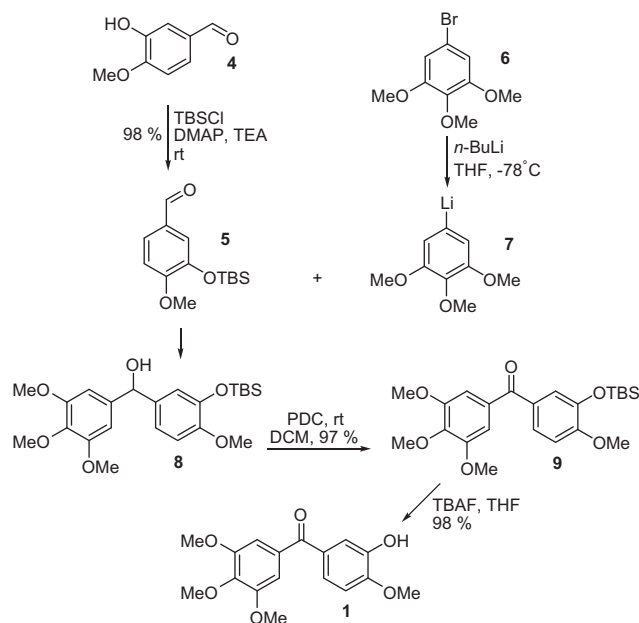


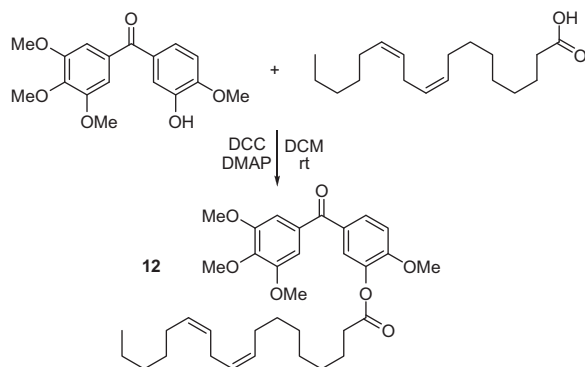
Figure 1. Structures of phenstatin, isopenstatin, CA-4 and colchicine.

* Corresponding author. Tel.: +1 718 990 5219; fax: +1 718 990 1876.

E-mail addresses: brownd@stjohns.edu, dvdpb@aol.com (D.P. Brown).



Scheme 1. Synthesis of phenstatin.



Scheme 2. Synthesis of phenstatin–linoleic acid conjugate.

Conjugates of oleic (OLA), linoleic (LA), and stearic acid (SA) have been prepared. Phenstatin was prepared in about 75% overall yield by the modified procedure outlined below.¹⁰ Thus aryl bromide **6** was lithiated and reacted with aldehyde **5** to afford the

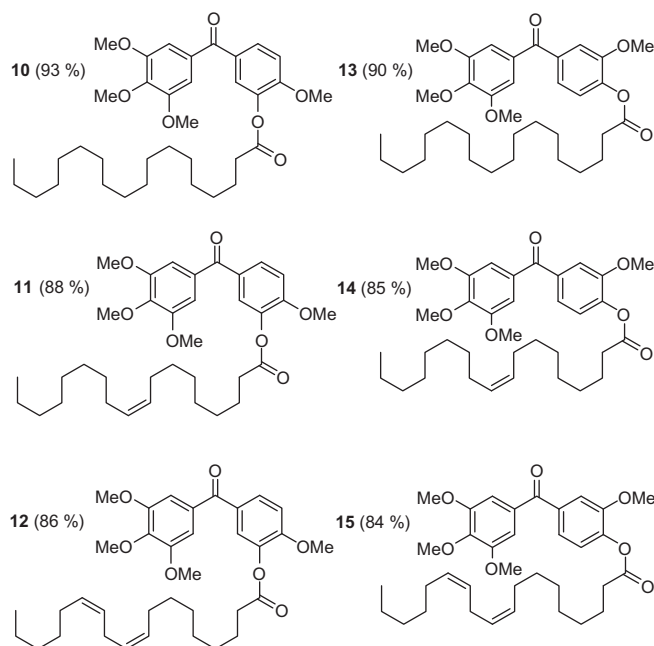


Figure 2. Fatty acid conjugates synthesized and isolated yields.

alcohol **8**. Mild oxidation with pyridinium dichromate followed by desilylation afforded phenstatin **1** (Scheme 1). Isofenstatin was similarly prepared from vanillin.

Conjugation of the fatty acids with phenstatin and isophenstatin to the hybrids of Figure 2, was accomplished at room temperature in DCM mediated by DCC and DMAP, Scheme 2.

IC₅₀ values for compounds **10–15** (Fig. 2) in addition to values for phenstatin **1**, isophenstatin **2** and colchicine tested against the human epidermoid carcinoma cell line (KB-3-1), lung cancer cell line (H460), breast adenocarcinoma cell line (MCF-7), and human embryonic kidney cell line (HEK293) are summarized in Table 1.

Conjugates **12** and **15** (hybrids of linoleic acid) exhibited the greatest inhibitory effects against all four cell lines, while the conjugates of stearic acid (**10** and **13**) showed the least. For conjugate **12** average IC₅₀ values of 0.163, 0.176, 0.181 and 0.210 μM against KB-3-1, H460, MCF-7 and HEK293 cells respectively were observed. Compound **15** gave average IC₅₀ values of 0.547, 0.867, 0.745 and 0.903 μM, respectively, against the tested cell lines.

The data further reflects a consistent increase in anti-proliferative activity of the conjugate with increasing unsaturation in the fatty

Table 1
Summary of cytotoxicity data

Compounds	IC ₅₀ ± SD ^a (μmol/L)			
	KB-3-1	H460	MCF-7	HEK293
Phenstatin + stearic acid 10	2.777 ± 0.071	4.699 ± 0.736	3.353 ± 0.080	2.637 ± 0.356
Phenstatin + oleic acid 11	0.786 ± 0.011	0.909 ± 0.030	0.943 ± 0.029	0.950 ± 0.004
Phenstatin + linoleic acid 12	0.163 ± 0.032	0.176 ± 0.037	0.181 ± 0.062	0.210 ± 0.001
Iso-phenstatin + stearic acid 13	16.932 ± 1.389	17.598 ± 6.940	26.914 ± 1.871	15.605 ± 0.649
Iso-phenstatin + oleic acid 14	1.721 ± 0.288	2.195 ± 0.136	2.173 ± 0.464	2.363 ± 0.227
Iso-phenstatin + linoleic acid 15	0.547 ± 0.148	0.867 ± 0.012	0.745 ± 0.052	0.903 ± 0.039
Phenstatin 1	0.015 ± 0.004	0.020 ± 0.001	0.019 ± 0.004	0.023 ± 0.002
Iso-phenstatin 2	0.146 ± 0.046	0.188 ± 0.004	0.199 ± 0.064	0.196 ± 0.008
Colchicine	0.018 ± 0.001	0.022 ± 0.002	0.019 ± 0.001	0.009 ± 0.001

The cytotoxic effect of phenstatin–PUFA hybrids on KB-3-1 (human epidermoid carcinoma cell line), H460 (lung cancer cell line), MCF-7 (breast adenocarcinoma cell line) and HEK293 (human embryonic kidney cell line).

Values in table are representative of at least three independent experiments performed in triplicate.

^a IC₅₀: concentration that inhibited cell survival by 50% (means ± SD).

Download English Version:

<https://daneshyari.com/en/article/10595092>

Download Persian Version:

<https://daneshyari.com/article/10595092>

[Daneshyari.com](https://daneshyari.com)