Peptides 99 (2018) 179–188

Contents lists available at ScienceDirect

Peptides

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

Research paper

Glutathione salts of O,O-diorganyl dithiophosphoric acids: Synthesis and study as redox modulating and antiproliferative compounds

Rezeda A. Akhmadishina[a], Elena V. Kuznetsova[a], Gulnaz R. Sadrieva[a], Leysan R. Sabirzyanova[a], Ilyas S. Nizamov[b,*], Gulnaz R. Akhmedova[b], Ilnar D. Nizamov[b], Timur I. Abdullin[a,*]

[a] Institute of Fundamental Medicine and Biology, Kazan (Volga Region) Federal University, 420008 Kazan, 18 Kremlyovskaya St., Russia
[b] Alexander Butlerov Institute of Chemistry, Kazan (Volga Region) Federal University, 420008 Kazan, 18 Kremlyovskaya St., Russia

ARTICLE INFO

Keywords:
Peptides
Glutathione
Ammonium dithiophosphates
Monoterpenes
Antiradical activity
Antiproliferative activity

ABSTRACT

Reactions of glutathione (GSH) with O,O-diorganyl dithiophosphoric acids (DTPA) were studied to develop bioactive derivatives of GSH. Effective coupling reaction of GSH with DTPA was proposed to produce the ammonium dithiophosphates (GSH–DTPA) between the NH_2 group in γ-glutamyl residue of GSH and the SH group in DTPA. A series of the GSH–DTPA salts based on O-alkyl or O-monoterpenyl substituted DTPA were synthesized. Enhanced radical scavenging activity of the GSH–DTPA over GSH was established with the use of DPPH assay and improved fluorescent assay which utilizes Co/H_2O_2 Fenton-like reaction. Similarly to GSH, the dithiophosphates induced both pro- and antioxidant effects in vitro attributed to different cellular availability of the compounds. Whereas extracellularly applied GSH greatly stimulated proliferation of cancer cells (PC-3, vinblastine-resistant MCF-7 cells), the GSH–DTPA exhibited antiproliferative activity, which was pronounced for the O-menthyl and O-isopinocampheolyl substituted compounds **3d** and **3e** ($IC_{50} \geq 1$ μM). Our results show that the GSH–DTPA are promising redox modulating and antiproliferative compounds. The approach proposed can be extended to modification and improvement of bioactivity of various natural and synthetic peptides.

1. Introduction

L-γ-Glutamyl-L-cysteinyl-glycine (glutathione, GSH) is the prevailing antioxidant oligopeptide in mammals, which plays a crucial role in non-specific and enzyme-assisted defense of living cells from oxygen radicals, detoxification of xenobiotics, maintenance and regulation of the redox homeostasis in cells [1–4].

The association of GSH deficiency with a variety of human metabolic, degenerative, aging-related diseases [4] and viral infection [3] is well established. At the same time, elevated GSH level is often involved in tumor resistance and progression [5]. GSH, its analogues and metabolizing enzymes attract considerable interest in biomedical and pharmacological research. Most enzymes of the GSH metabolism, e.g. catalyzing biosynthesis of GSH (γ-glutamyl transferase), nucleophilic addition reactions of the thiol group (glutathione-*S*-transferase), methylglyoxal detoxification (glyoxalase) and redox reactions (glutathione reductase, glutathione peroxidase) are established pharmacotherapeutic targets [1,6].

A number of synthetic approaches to developing enzyme effectors based on the tripeptide GSH have been proposed to date. Main strategies for generation of the bioactive analogues and derivatives of GSH, summarized by Lucente et al. [1], include replacement of one or more amino acids in the tripeptide backbone with artificial analogues (*D*-, N-methyl-, α-methyl-glutamic acid, α-methyl-L-cysteine, β-alanine) as well as modification of the SH group of cysteine in order to produce both reversible and irreversible inhibitors of GSH-metabolizing enzymes (see [1] and references within). Some other approaches in GSH chemistry proposed are aimed at the GSH derivatives with increased biological stability, e.g. resistance to blood γ-glutamyl transpeptidase, by means of esterification of the carboxyl functions [6] and cyclization of the GSH molecule [1].

Burg and Mulder summarized the state of the art in developing derivatives and analogues of GSH with antiproliferative activity and studying their capacity to overcome cancer drug resistance associated with GSH-dependent enzymes [6]. These enzymes are glutathione *S*-transferases catalyzing GSH conjugation to harmful electrophilic compounds, including carcinogens and anticancer drugs, DNA-dependent protein kinase (PI 3-kinase family) involved in repairing double-strand breaks in DNA as well as glyoxalase system (glyoxalases I and II) participating in elimination of cytotoxic α-oxoaldehydes [6]. Some examples of effective inhibitors of these enzymes include *S*-alkyl derivatives of γ-glutamyl-2-aminoadipic acid analogue, GSH derivatives

* Corresponding authors.
E-mail addresses: isnizamov@mail.ru (I.S. Nizamov), tabdulli@gmail.com (T.I. Abdullin).

http://dx.doi.org/10.1016/j.peptides.2017.10.002
Received 28 June 2017; Received in revised form 16 September 2017; Accepted 5 October 2017
Available online 06 October 2017
0196-9781/