Bioorganic & Medicinal Chemistry Letters 26 (2016) 910–913

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Amides of non-steroidal anti-inflammatory drugs with thiomorpholine can yield hypolipidemic agents with improved anti-inflammatory activity

Panagiotis Theodosis-Nobelos, Malamati Kourti, Antonios Gavalas, Eleni A. Rekka *

Department of Pharmaceutical Chemistry, School of Pharmacy, Aristotelian University of Thessaloniki, Thessaloniki 54124, Greece

ARTICLE INFO

Article history:
Received 5 November 2015
Revised 14 December 2015
Accepted 19 December 2015
Available online 19 December 2015

Keywords:
Non steroidal anti-inflammatory drugs
α-Lipoic acid
Thiomorpholine amides
Hypolipidemic activity
Inflammation

ABSTRACT

Novel amides of non steroidal anti-inflammatory drugs (NSAIDs), α-lipoic acid and indole-3-acetic acid with thiomorpholine were synthesised by a simple method and at high yields (60–92%). All the NSAID derivatives highly decreased lipidemic indices in the plasma of Triton treated hyperlipidemic rats. The most potent compound was the indomethacin derivative, which decreased total cholesterol, triglycerides and LDL cholesterol by 73%, 80% and 83%, respectively. They reduced acute inflammation equally or more than most parent acids. Hence, it could be concluded that amides of common NSAIDs with thiomorpholine acquire considerable hypolipidemic potency, while they preserve or augment their anti-inflammatory activity, thus addressing significant risk factors for atherogenesis.

© 2015 Elsevier Ltd. All rights reserved.

Lipid disorders and inflammation are implicated in many pathological conditions, such as neurodegenerative[1] and cardiovascular diseases,[2] metabolic syndrome,[3] cancer[4] and rheumatoid diseases.[5] Lipid control is considered to be essential for the prevention and treatment of most of these disorders.[6]

Low density lipoproteins (LDL), due to their large surface and high cholesterol content, are prone to oxidation, forming ox-LDL,[7] and to Schiff base formation,[8] leading to advanced glycation products.[9] Ox-LDL is recognised by scavenger receptors on macrophages at the subendothelium of the vessels, causing foam cell formation.[10] Foam cells and lipid accumulation, as well as platelet aggregation, lead to the final atherogenic plaque.[11] Hyperlipidemia also reduces nitric oxide production[12] and ox-LDL induces the promotion of endothelin-1,[13] attenuating vasoconstriction.

Dysregulation of cholesterol homeostasis in the brain is increasingly being linked to chronic neurodegenerative disorders, including Alzheimer's (AD), Huntington's (HD) and Parkinson's (PD) diseases.[14] It is noteworthy that high levels of plasma cholesterol correlate with increased risk of developing AD. Moreover, the E4 isoform of apolipoprotein E, a cholesterol-carrying protein, markedly increases the risk of developing AD.[14] Decreased level of cellular cholesterol increases α-secretase cleavage of amyloid precursor protein (APP), thereby decreasing the processing of APP into the toxic Aβ peptides that accumulate in amyloid plaques.[15] 27-Hydroxycholesterol (27OHC), depending on the blood–brain barrier dysfunction, may enter the brain.[16] This oxysterol antagonizes the preventive effect of 24OHC on β-amyloid generation.[17] There is a positive correlation between levels of cholesterol and 27OHC in the circulation.

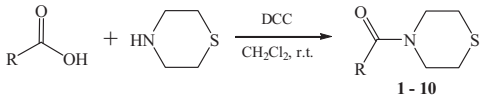
Inflammation is a response of the tissues to injury. It is a major factor for the propagation of several diseases and syndromes, whose negative effects could become obvious long after initiation of inflammation.[18,19] Tissue inflammation and lipid mediators coming, for example, from adipose tissue, are potentially involved in the pathogenesis of metabolic disorders such as obesity and atherosclerosis,[20] making this interrelation bidirectional.

In this investigation, we report the synthesis of amides of eight classic non steroidal anti-inflammatory drugs (NSAIDs) with thiomorpholine. Additionally, amides of indole-3-acetic acid, a part of the indomethacin structure, and of α-lipoic acid (5-(1,2-dithiolan-3-yl)pentanoic acid) were included. It has been reported that, in obese patients with impaired glucose tolerance and dyslipidemia, short-term treatment with α-lipoic acid decreased the levels of malondialdehyde, 8-iso-prostaglandin, TNF-α and IL-6.[21] Furthermore, α-lipoic acid has been found able to reduce inflammation and oxidative stress in the liver and kidney after sepsis in rats.[22]

It has been reported that amidation of NSAIDs, for example, ibuprofen and naproxen, with amino acids gave potent

* Corresponding author. Tel.: +30 2310997614; fax: +30 2310997852.
E-mail address: rekka@pharm.auth.gr (E.A. Rekka).

http://dx.doi.org/10.1016/j.bmcl.2015.12.063
0960-894X/© 2015 Elsevier Ltd. All rights reserved.



Comp. no.	RCOOH	Comp. no.	RCOOH
1	Ibuprofen	6	Flufenamic acid
2	Ketoprofen	7	Mefenamic acid
3	Naproxen	8	Indomethacin
4	Diclofenac	9	α-Lipoic acid
5	Tolfenamic acid	10	Indole-3-acetic acid

Figure 1. Synthesis of compounds. DCC: *N*,*N*′-dicyclohexylcarbodiimide; rt: room temperature.

Table 1
Effect of compounds **1**–**8** on Triton WR1339 (tyloxapol) induced hyperlipidemia

Compd	Plasma concentration (mg/dl) ± SEM (% reduction[a])		
	TC	TG	LDL-C
Saline	75.0 ± 5.0	170 ± 8.0	28.0 ± 2.1
Triton	315.3 ± 14.9	1466.0 ± 36.8	115.1 ± 5.9
Triton + **1**	125.2 ± 5.2 (60.3***)	524.9 ± 67.2 (64.2**)	48.8 ± 2.3 (57.6**)
Triton + **2**	160.1 ± 10.1 (49.0**)	835.5 ± 74.7 (43.0*)	40.4 ± 2.7 (64.9***)
Triton + **3**	133.1 ± 7.3 (57.8***)	568.6 ± 48.5 (61.3***)	21.4 ± 2.2 (81.4***)
Triton + **4**	175.9 ± 15.4 (44.1***)	786.0 ± 37.8 (46.4***)	33.5 ± 4.2 (70.8***)
Triton + **5**	107.7 ± 7.1 (65.9***)	293.2 ± 13.3 (80.0***)	33.9 ± 5.4 (70.5***)
Triton + **6**	148.4 ± 7.8 (52.8***)	672.9 ± 39.9 (54.1***)	41.2 ± 2.7 (64.2***)
Triton + **7**	62.3 ± 2.7 (80.5***)	291.5 ± 24.0 (81.5***)	33.0 ± 4.2 (71.3***)
Triton + **8**	85.1 ± 4.4 (73.0***)	295.4 ± 17.1 (79.5***)	19.4 ± 2.1 (83.0***)

Triton: 200 mg/kg, ip once; compounds: 150 μmol/kg, ip once.
Each group was composed of six to eight rats.
Significant difference from hyperlipidemic control: $^{*}P$ <0.05, $^{**}P$ <0.005, $^{***}P$ <0.001 (Student's *t* test).
[a] Compared to the Triton-treated hyperlipidemic control group; TC: total cholesterol; TG: triglycerides; LDL-C: LDL cholesterol.

anti-inflammatory and gastroprotective compounds.[23,24] Moreover, substituted morpholine and thiomorpholine derivatives have been found to acquire hypolipidemic activity.[25,26] Thus, the aim of this work was to investigate whether amides of some NSAIDs with thiomorpholine can yield molecules which would combine hypolipidemic and anti-inflammatory activity. Their potential lipoxygenase inhibitory and antioxidant activity were also examined, since lipoxygenase, as well as oxidative stress contribute to neurodegenerative and cardiovascular disorders.[27,28]

Compounds **1**–**10** were synthesised by direct amidation of the carboxylic group of the respective acids with thiomorpholine, using *N*,*N*′-dicyclohexyl-carbodiimide (DCC), at room temperature, with excellent yields (60–92%) (Fig. 1). Compound **9** is included in a patent[29] and it had been designed for its expected ability to enhance glutathione reductase activity.

The effect of derivatives **1**–**8** on plasma total cholesterol, triglyceride and LDL-cholesterol levels, 24 h post injection, was determined in rats with Triton-WR1339 induced hyperlipidemia, according to a protocol based on the literature,[30] with some modifications[31] (Table 1). The systemic administration of Triton-WR1339 to rats results in a biphasic elevation of plasma cholesterol and triglycerides. In phase I, plasma cholesterol levels

Download English Version:

https://daneshyari.com/en/article/1370084

Download Persian Version:

https://daneshyari.com/article/1370084

Daneshyari.com