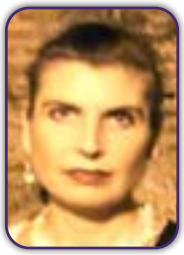
Medicinal Chemistry



Novel competitive and uncompetitive quercetin derivatives as LOX inhibitors

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Abstract

Introduction: Although, inflammation is a process involved in the natural defence of the organism, anti-inflammatory treatment is needed in many cases to inhibit unregulated, life threatening or chronic inflammatory response. Arachidonic acid derivatives, prostaglandins(PG), produced via the cyclooxygenase(COX) pathway and leukotrienes(LT), produced by the 5-lipoxygenase(5-LOX) pathway are involved in inflammation. Lipoxins(LX), produced by the sequential action of 5-LOX and 15- or 12-LOX, exhibit both pro- and anti-inflammatory action. Particularly in asthma, a limited amount of lipoxins seems to be mandatory for the anticipation of inflammation.

Most anti-inflammatory drugs are mainly COX inhibitors. Although, leukotrienes are important mediators of inflammation, only one LOX inhibitor has been approved till now for the treatment of asthma. Research for finding novel effective and safe LOX inhibitors continuous.

In the present study, twelve quercetin derivatives were synthesised and evaluated in vitro for LOX inhibitory action. The contribution of substituents to the mode of binding to human 5-LOX was investigated using docking analysis.

Methods: Docking analysis was performed using human 5-LOX 3V99. Soybean 1-LOX, broadly used in drug development, was used for in vitro activity evaluation.

Results: All compounds exhibited activity with IC50 values between 4μM and 18μM. Competitive inhibitors with increased inhibition at low substrate concentrations and uncompetitive inhibitors with increased inhibition at high substrate concentrations were among the active compounds. Docking analysis was in accordance with the in vitro results. Compound 1 bearing N-isobutyl, 6-MeO, 2-quinolinone substituent showed the best action exhibiting competitive inhibition, while compound 6 bearing a tricyclic 1H-pyrrolo[3,2,1-ij]quinolin-4(2H)-one moiety was the best uncompetitive inhibitor(IC50 =7μM).

Conclusions: The best inhibitor exhibited improved activity compared to quercetin, while five of the compounds exhibited IC50 values lower or equal to 7μM. The presence of compounds with uncompetitive inhibitory action may be of interest for the development of novel inhibitors targeting to balanced inhibition.

Biography

Phaedra Eleftheriou has completed her PhD in Chemistry at the area of Biochemistry at the Aristotle University of Thessaloniki, Greece (1998). She now works as a Professor of Clinical Chemistry & Biochemistry at the International Hellenic University. Enzyme Inhibitors with Applications in Diagnosis and Therapy: COX-1/2, LOX inhibitors (anti-inflammatory agents), Phosphatase Inhibitors: SHP-2 (JMML), PTP1B, LAR, DPP4 (Diabetes II), Squalene synthase inhibitors (dyslipidemia), HIV-1 RT and Integrase inhibitors are among her research interests. She has 53 relevant publications and 1060 citations. Her H-index is 16 (i-10index 24)..

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