I008 | Arylidenebarbiturate Hybrids Targeting Inflammatory Disorders

Sotirios Katsamakas,[1] Anna Ntalli,[2] Christos Panagiotidis,[2] Dimitra Hadjipavlou-Litina[1]

1) Department of Pharmaceutical Chemistry, School of Pharmacy, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece
2) Department of Pharmacognosy-Pharmacology, School of Pharmacy, Faculty of Health Sciences, Aristotle University of Thessaloniki, Thessaloniki 54124, Greece

Cancer and Alzheimer's type senile dementia are two conditions absolutely unrelated to each other, but they share in common the presence of inflammation in both sites, arising beliefs that they are somehow linked to it. Thus, targeting lipid and polyunsaturated fatty acid metabolism, inflammation and carcinogenesis has been extensively examined in numerous molecular studies. Recent advances also show that such is the lysophosphatidylcholine (LPC) and lysophosphatidic acid (LPA), which are emerging as a novel class of inflammatory lipids, joining thromboxanes, leukotrienes and prostaglandins with which they share metabolic pathways and regulatory mechanisms.[1] Lipoxygenase (LOX) pathways play an important role in inflammatory sites, and reactive oxygen species (ROS) are produced during the inflammation process by phagocytic leukocytes that invade the tissue. These ROS are involved in the LOX-mediated conversion of arachidonic acid into proinflammatory intermediates. Autotaxin (ATX, ENPP2) is in turn an extracellular enzyme, which plays a central role in regulating LPC/LPA axis levels along with cyclooxygenases (COXs) and LOXs[2] intracellularly. LPA interacts with specific GPCRs and thereby stimulates mutations, cell proliferation, apoptosis, differentiation, and senescence.[3,4]

In a continuation of our previous studies on designing and synthesizing hybrid molecules bearing the barbiturate moiety, combined with substituted aryl aldehydes, we present 16 newly synthesized compounds that are subjected also to further optimization. Computer-aided drug design has been used[5] for the candidates' synthesis selection, which is partly based on published procedures. Preliminary antioxidant activity in vitro tests have been performed followed by inhibition of soybean LOX and ATX. The antiviral activity of selected compounds was tested using a recombinant herpes simplex virus carrying a reporter gene (β-galactosidase). None of the compounds exhibited significant antiviral effects. Further investigation is in progress concerning their multitarget profile.

Acknowledgments:

Sotirios Katsamakas is thankful to Novo Nordisk Hellas Ltd for financial support offering an EFMC-ISMC 2014 registration and to "The A. G. Leventis Foundation" for financial support. Dr. Hadjipavlou and S. Katsamakas are grateful to C-QSAR and Dr. A. Leo for free access to the C-QSAR program and to Dr Huib Ovaa, Division of Cell Biology, The Netherlands Cancer Institute, for the ATX experiments. Additionally, the authors would like to thank Openeye Scientific Software, Inc. for providing an academic license for their programs.

References:

[1] I. Sevastou, E. Kaffe, M.-A. Mouratis, V. Aidinis, *Biochim. Biophys. Acta, Mol. Cell Biol. Lipids* **2013**, *1831*, 42–60.
[2] E. Pontiki, D. Hadjipavlou-Litina, G. Geromichalos, A. Papageorgiou, *Chem. Biol. Drug Des.* **2009**, *74*, 266–275.
[3] M. Inoue, L. Ma, J. Aoki, H. Ueda, J. Neurchem. **2008**, *107*, 1556–1565.
[4] G.B. Mills, W.H. Moolenaar, Nat Rev Cancer **2003**, *3*, 582–591.
[5] S. Katsamakas, D. Hadjipavlou-Litina, *Lett. Drug Des. Discov.* **2013**, *10*, 11–18.

I009 | Synthetic Lignans Targeting Cardiovascular Diseases

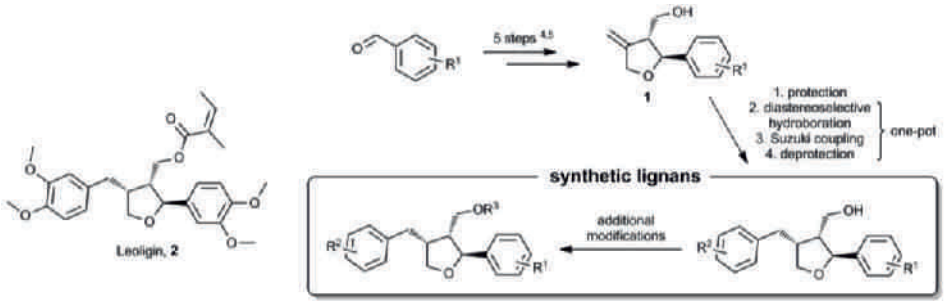
Thomas Linder,[1] Sophie Geyrhofer,[1] Atanas Atanasov,[2] Verena Dirsch,[2] Hermann Stuppner,[3] Michael Schnürch,[1] Marko D. Mihovilovic[1]

1) Institute of Applied Synthetic Chemistry, Vienna University of Technology, Getreidemarkt 9/163, 1060 Vienna, Austria
2) Department of Pharmacognosy, University of Vienna, Althanstrasse 14, 1090 Vienna, Austria
3) Institute of Pharmacy/Pharmacognosy, University of Innsbruck, Innrain 80/82, 6020 Innsbruck, Austria

Intimal hyperplasia is a condition mainly characterized by the infiltration of smooth muscle cells (SMCs) and their excessive proliferation at the inside of blood vessels. This inflammatory response is a key factor in the development of atherosclerosis, and hence thrombus formation, possibly with ensuing myocardial infarction or stroke. Compounded by damage to endothelial cells (ECs), this vessel-occluding over-response is frequently encountered in the wake of coronary artery bypass grafting (CABG) or percutaneous coronary intervention (PCI, stenting), leading to eventual restenosis.[1] A useful drug would therefore potently inhibit SMC proliferation and thus prevent intimal hyperplasia, but ideally not interfere with ECs.

Leoligin (**2**), a furan-type lignan isolated from the roots of *Leontopodium alpinum*,[2] had previously been shown to inhibit intimal hyperplasia in in vitro human saphenous vein organ cultures as well as in vivo mouse models.[3] Our aims were to prepare a library of analog compounds of this natural product via a suitable intermediate **1**[4,5] using a modular synthetic route (see Scheme) and study their inhibition profiles. With such synthetic analogs, we were able to increase the SMC inhibitory activity up to 15-fold compared to leoligin itself. Additionally, our most active analogs did not show inhibition activity on ECs, unlike the natural hit compound or other compounds which are currently used clinically, e.g. in drug-eluting stents. We therefore conclude that the synthetic lignans we prepared are both

useful probes to investigate the causative factors of graft disease and stent-related complications, as well as potential treatments for intimal hyperplasia and its detrimental consequences on the cardiovascular system.



References:

[1] G. T. Lau, H. C. Lowe, L. Kritharides, *Semin. Vasc. Med.* **2004**, *4*, 153–159.
[2] M. J. Dobner, E. P. Ellmerer, S. Schwaiger, O. Batsugkh, S. Narantuya, M. Stuetz, H. Stuppner, *Helv. Chim. Acta* **2003**, *86*, 284–285.
[3] U. Reisinger, S. Schwaiger, I. Zeller, B. Messner, R. Stigler, D. Wiedemann, T. Mayr, C. Seger, T. Schachner, V. M. Dirsch, A. M. Vollmar, J. O. Bonatti, H. Stuppner, G. Laufer, D. Bernhard, *Cardiovasc. Res.* **2009**, *82*, 542–549.
[4] P. K. Mandal, G. Maiti, S. C. Roy, *J. Org. Chem.* **1998**, *63*, 2829–2834.
[5] J. Stambasky, A. V. Malkov, P. Kocovsky, *J. Org. Chem*. **2008**, *73*, 9148–9150.

I010 | Amino Acid Linkage of Non-steroidal Anti-inflammatory Drugs and Bioactive Alcohols Resulting in Potent Anti-inflammatory Agents

Panagiotis Theodosis-Nompelos, Paraskevi Tziona, Antonis Gavalas, Eleni Rekka, Panos Kourounakis

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

Inflammatory diseases are among the prevalent causes of disability in western countries, and non-steroidal anti-inflammatory drugs (NSAIDs) are still the most commonly used medications. However, NSAIDs cause several serious adverse effects, the most important being gastric injury and renal damage. In addition, the involvement of oxygen free radicals and lipid peroxidation in the development of the NSAID-induced mucosal damage has been proposed as an important event. Attempts to develop better tolerated treatments have been associated with gastroprotective agents that partly counteract the damaging effects of prostaglandin synthesis inhibition. However, a combination therapy introduces problems of pharmacokinetics, toxicity, and compliance of patients.

In this investigation, we report the synthesis and study of known NSAIDs derivatives, aiming to reduce the undesired effects and retain or reinforce the anti-inflammatory action. The anti-inflammatory molecules are amidated with an amino acid (alanine, proline, cysteine), since the use of natural amino acids as a linker was considered advantageous in terms of potentially low toxicity of the derivatives. Then, the carboxylic group of the compounds is esterified with cinnamyl alcohol or trimethoxybenzyl alcohol, based on the reported anti-inflammatory activity of these compounds. Indol-3-acetic acid derivatives are also prepared. The anti-inflammatory activity of the derivatives is assessed from their ability to inhibit the paw edema induced by carrageenan in rats. The compounds were administered i.p. at a dose of 150 μmol/kg and demonstrated significant inhibition of edema. The effect of the synthesized compounds on lipoxygenase activity is examined monitoring the conversion of linoleic acid to 13-hydroperoxylinoleic acid, producing a conjugated diene that absorbs at 234 nm. The free radical scavenging ability of the molecules is determined from the extent of their interaction with the stable free radical DPPH, as well as the inhibition of rat hepatic microsomal membrane lipid peroxidation, induced by ferrous-ascorbate and assessed as thiobarbituric acid reacting product, at 535 nm. The potential for further development of this type of compounds is discussed.

I011 | Novel Anti-inflammatory Agents by Conjugation of Antioxidant Compounds with Cysteamine and Cysteine

Panagiotis Theodosis-Nompelos, Antonis Gavalas, Eleni Rekka, Panos Kourounakis

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

The production of various reactive oxidant species in excess of endogenous anti-oxidant defense mechanisms promotes the development of oxidative stress, with significant biological consequences. Evidence has emerged that oxidative stress plays a crucial role in the development and perpetuation of inflammation, and thus contributes to the pathophysiology of a number of debilitating illnesses. Oxidants affect most stages of the inflammatory response. Reversely, it is cleared that antioxidants are potentially able to suppress, at least in part, the immune reaction and to enhance the normal cellular protective responses to tissue damage.