SYNTHESIS OF BENZOXAZINE DERIVATIVES WITH EXTENDED AROMATICITYAS MULTIFUNCTIONAL AGENTS

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Given the fact that most disorders such as cardiovascular, metabolic and inflammatory diseases are multifactorial in nature, multi-target drug design (MTD) seems to be a promising approach in order to aim amultiplicity of targets involved. In this study, a series of benzoxazines have been developed, based on structural modifications of a previouslydesigned and studied derivative by our research group[1]. The purpose is to simultaneously optimize the activity on several molecular biological mechanisms involved in multifactorial disorders.The 6 newly designed compounds were synthesized in good yields, characterized via ^{1}H and ^{13}C NMR spectroscopy and pharmacologically evaluatedin vitro and in vivofor their antioxidant, anti-inflammatory and anti-hyperlipidemic activity.

Most of the new derivatives exceeded the antioxidant activity of the parent molecule, in corresponding assays of scavenging the free radical DPPH and inhibiting lipid peroxidation, with the most active compound bearing an IC_{50} of 1uM against lipid peroxidation in vitro. In vivo studies confirm that plasma Total Antioxidant Capacity (TAC) is increased up to 79%, after treatment with this compound.

Inflammation is involved in many multifactorial diseases. Anti-inflammatory activity was studied via in vitro inhibition of the enzyme lipoxygenase (LOX). Results by derivatives studied so far, were really promising for further in vivo investigation.

Imbalance in cholesterol levels leads to hyperlipidemia which most likely results in CVD/atherosclerosis. According to an in vivo tyloxapol-induced hyperlipidemia protocol, the compounds are capable of restoring the plasma lipid levels back to normal with a significant decrease of Triglycerides by 50-81% and an HDL increase up to 117%.Given the promising hypolipidemic activity of the compounds and considering thatimbalance in cell cholesterol levels may lead to alterations in neuronal cell membranes, the derivatives were further evaluated for potential activity useful inneurodegenerative disorders. Assays include iron-chelation (ferrozine assay) with the new derivatives, bearing IC_{50} values 2 to 8-fold lower than the parent compound, as well as inhibition of acetylcholinesterase (AChE), in which they presented interesting activity, compared to thenon-active parent compound.

In conclusion, the combined antioxidant, anti-inflammatory and anti-hyperlipidemic properties, setthe derivativesas agents with potential against cardiovascular diseases, especially focusing on the field of atherosclerosis, while iron-chelation and AChE inhibitory activity may also contribute to the treatment of neurodegenerative disorders.

[1]Matralis, A. N., Katselou, M. G., Nikitakis, A., & Kourounakis, A. P. (2011). Novel benzoxazine and benzothiazine derivatives as multifunctional antihyperlipidemic agents. *Journal of Medicinal Chemistry*, *54*(15), 5583–5591.