NOVEL SUBSTITUTED BENZOXAZINE DERIVATIVES WITH POTENT ANTIHYPERLIPIDEMIC/ANTIOXIDANT ACTIVITY AS ATHEROSCLEROSIS AGENTS

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Cardiovascular disorders, including atherosclerosis, are related to conditions such as dyslipidemia, inflammation and chronic oxidative stress. Their multifactorial nature consequently requires their treatment with the co-administration of two or more drugs, each of which mayaddressadifferent molecular target. Alternatively, multi-targetdrugs are an established by now approach for the treatment of such diseases.

The present research work aims at the design and development of multi-functional molecules with anti-inflammatory, antioxidant and anti-hyperlipidemic activity. For this purpose, based on the successful scaffold of 2-biphenyl-1,4-benzoxazine, which was previously designed and studied by our research group[1], we considered and explored further benzoxazine substitutions.

The 5 newly designed derivativeswere synthesized in good yields, characterized via ^{1}H-NMR and^{13}C-NMR spectroscopy and studied for their *in vitro*/*in vivo* antioxidant, anti-inflammatory and anti-dyslipidemic activity.

The antioxidant activity of the new compounds was investigated *in vitro* via their interaction with the free stable radical DPPH and through the protection offered against lipid peroxidation of mouse liver microsomal membranes. In both assays, almost all compounds successfully maintained or even exceeded the activity of the corresponding reference compound. The *in vitro* anti-inflammatory activity was evaluated by the ability to inhibit the enzyme lipoxygenase (LOX); all molecules demonstrated significant activity, with IC_{50} values ranging from 99 to 157 μM.

The synthesized derivatives were studied for their antidyslipidemic and antioxidant activity *in vivo*, via acute induction of hyperlipidemia induced by tyloxapol administration in mice. Their effect on Total Cholesterol (TC), HDL, LDL, LDL/HDL ratio, triglyceride (TG) plasma levels as well as plasma Total Antioxidant Capacity (TAC) and uric acid levels, was investigated. Almost all tested derivatives proved a remarkable ability to reduce the examined lipid parameters in the plasma of hyperlipidemic mice, while contributing to the *in vivo* antioxidant profile. Finally, the new molecules showed a significant reduction (36-54%) in an *in vivo* carrageenan-induced paw edema protocol.

In conclusion, the results of the *in vitro* and *in vivo* pharmacological evaluation of this new class of molecules confirm their multifunctional action as they exhibited at least two of the designed/desired activities, justifying potential interest for their further study as useful tools against multifactorial diseases, such as atherosclerosis.

[1]Matralis, A., Kourounakis, A. et al. *J. Med. Chem.*2011*,* 54(15), 5583–5591.