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Novel Anti-inflammatory Molecules with Reduced Gastrointestinal Toxicity Perspectives for further Applications

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INTRODUCTION

Inflammation implicates, both directly and indirectly, free radical processes and oxidative stress. The most important and common undesired effect of non steroidal anti-inflammatory drugs (NSAID), gastrointestinal toxicity, is due to their main biological action, the inhibition of cyclooxygenase-1 (1). In gastric lesions caused by NSAID oxidative stress is developed and an important part of their local toxicity is due to the acidic character of these drugs (1,2,3). Furthermore, inflammation (4) and oxidative stress (5) contribute to the pathogenesis of neurodegenerative diseases, such as Alzheimer's disease. Considering the above, we decided to synthesize a series of novel derivatives of NSAID, properly designed to acquire considerable anti-inflammatory activity, potent antioxidant action, to have their carboxylic group masked and, finally, to be able to cross the blood brain barrier. In this presentation, we report the activity of novel amide derivatives of known NSAID with cysteine ethyl ester, having the general structure: R-CONHCH($COOC_2H_5$)CH_2SH, where the corresponding RCOOH is a common NSAID.

METHODS AND RESULTS

Their antioxidant potential (inhibition of peroxidation of rat hepatic microsomal membrane lipids and interaction with the stable free radical DPPH), the in vivo anti-inflammatory activity (inhibition of rat paw edema model) (Figure 1), their gastrointestinal toxicity (Table 1) as well as the hypocholesterolemic-hypolipidemic action (effect on LDL levels) (Figure 1) are determined. Some physicochemical parameters (lipophilicity, solvation energy) are calculated.

All new compounds are proven to be potent antioxidant, anti-inflammatory and hypolipidemic-hypocholesterolemic agents. In all cases, they are equally active or even more effective than the parent NSAID. All new derivatives are found to possess considerably lower gastrointestinal toxicity than the starting drugs. In addition to their high anti-inflammatory action with greater safety margins, compared to the original NSAID, these compounds could be considered, as a result of their appropriate design, as good candidates for the treatment of neurodegenerative conditions. Therefore, we calculated their lipophilicity and energy of solvation, in order to get a substantial idea about their ability to cross the blood brain barrier, with satisfactory results.

CONCLUSIONS

The amide derivatives of NSAID we synthesized could be considered to be improved anti-inflammatory agents, as well as good lead compounds for the treatment of neurodegenerative conditions of Alzheimer's type.

REFERENCES

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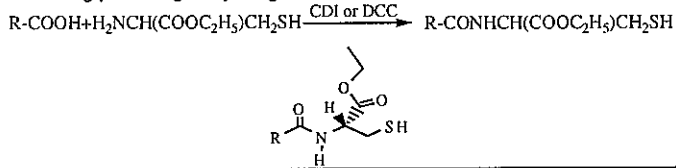
Table 1
Gastrointestinal toxicity of the novel amides of NSAID

Compound	*Mortality (%)* [a]	*Perforating ulcers (%)* [b]	*Body weight change* [c,d]	*Incidence of melena*	*Dose (μmoles/kg)*
Compound 1	0	0	3.4	-	84
Indomethacin	50	80	-13.0	+	84
Cysteine Et-ester	0	0	-1.9	-	84
Compound 2	0	0	3.1	-	240
Diclofenac	50	75	-13.5	+	240
Cysteine Et-ester	0	0	-2.0	-	240
Compound 3	0	0	7.5	-	760
Tolfenamic acid	50	50	-5.3	+	760
Cysteine Et-ester	0	0	-1.0	-	760
Compound 4	0	0	1.0	-	1600
Ibuprophen	50	88	-12.7	+	1600
Cysteine Et-ester	0	0	-1.6	-	1600
Compound 5	0	0	.3	-	200
Ketoprophen	50	83	-18.9	+	200
Cysteine Et-ester	0	0	-1.0	-	200

a: Dead per total x 100. *b*: Percent of animals with perforating ulcers. *c*: Standard deviation of body weight change is within 10% of the average value. *d*: In g per 100 g body weight.



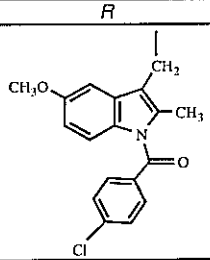
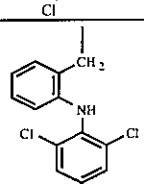
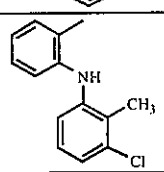
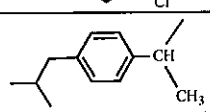
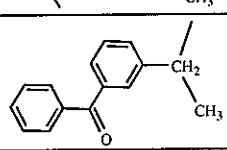
Comp.	*R*	*Starting NSAID*	*% Edema inhibition*	*% Decrease of LDL*
1			63	61
		Indomethacin	41	72
2			59	93
		Diclofenac	37	86
3			51	
		Tolfenamic acid	24	
4			61	69
		Ibuprophen	36	32
5			38	
		Ketoprophen	42	

Figure 1: Novel derivatives of NSAID: Synthesis, Structure, Inhibition of carageenan induced edema, Decrease of plasma LDL in hypercholesterolemic rat