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Evaluation of *in vitro* cytotoxic and hemolytic effects of a new series of hydroxy- and nitro-containing arylcoumarins

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pharmaceuticals MDPI

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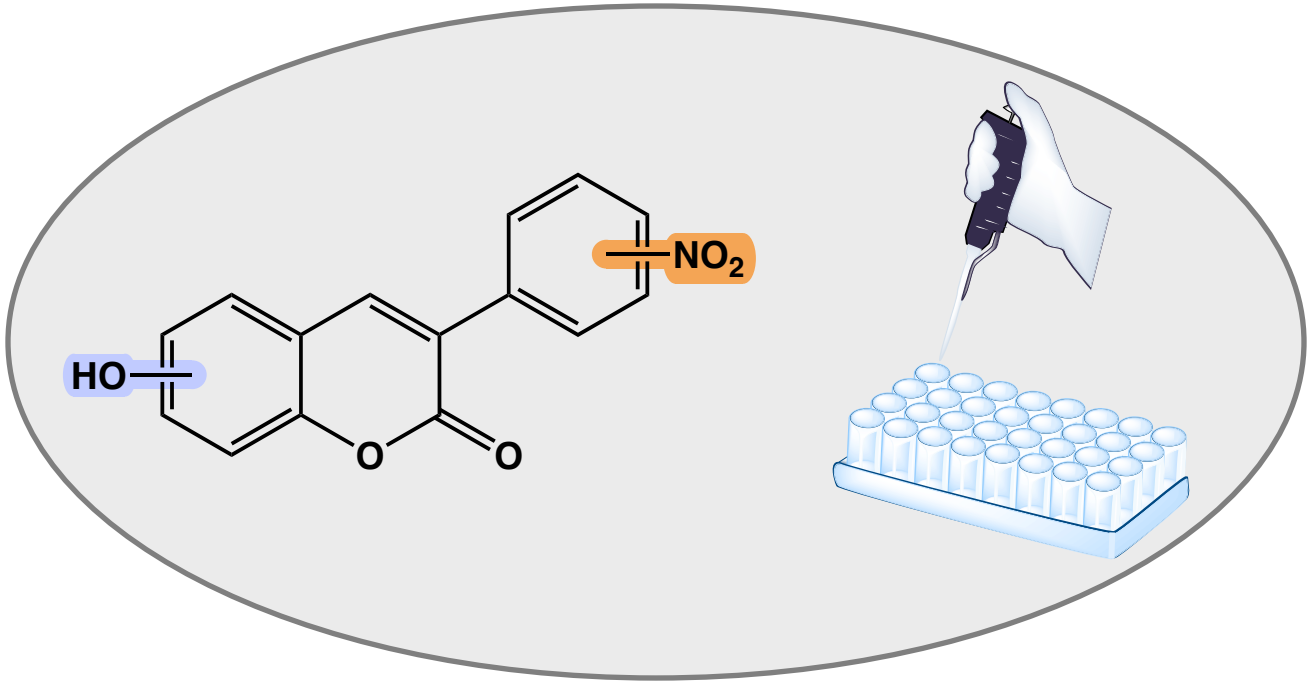
Evaluation of *in vitro* cytotoxic and hemolytic effects of a new series of hydroxy- and nitro-containing arylcoumarins



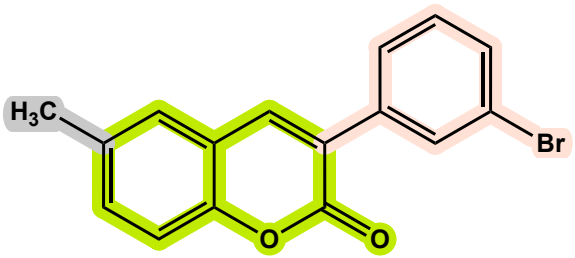
Abstract:

Coumarins are natural or synthetic compounds with diverse biological applications, from fluorescent probes to therapeutic agents. Our group has been studying the importance of this scaffold in the development of drugs targeting neurodegeneration. Based on the structure of acenocoumarol, an oral anticoagulant often prescribed to treat and prevent thromboembolism, nitro groups have been commonly introduced into coumarin-containing compounds. Therefore, assessing their safety for humans is essential. In the present work, twelve hydroxy- and nitro-substituted arylcoumarins were synthesized, and the cytotoxicity and hemolytic effects were studied. Human embryonic kidney cells (HEK-293, ATCC strain CRL1573) and human red blood cells (RBC) were used for the *in vitro* assays. Compounds were plated as a 2-fold dose-response from 32 to 0.25 µg/mL, with a maximum of 0.5% DMSO. CC_{50} (cytotoxicity) and HC_{10} (hemolytic activity) values are presented in this communication.

Keywords: 3-Arylcoumarins; Cytotoxicity; Hemolytic effects

Introduction

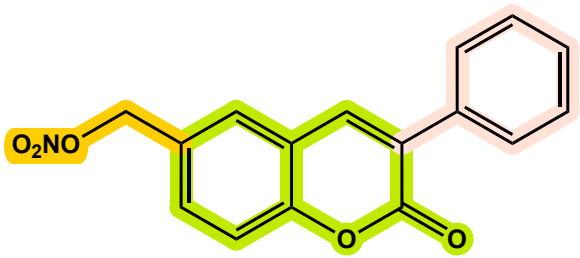
Arylcoumarins have been studied due to their interest in the development of different bioactive molecules. Our research group has been dedicated to finding the best substitution patterns to increase their potential as neuroprotective and cardioprotective agents, being useful in the treatment of age-related diseases.



IC_{50} *h*MAO-A > 100 μM

IC_{50} *h*MAO-B = 134 pM

Reversible inhibitor

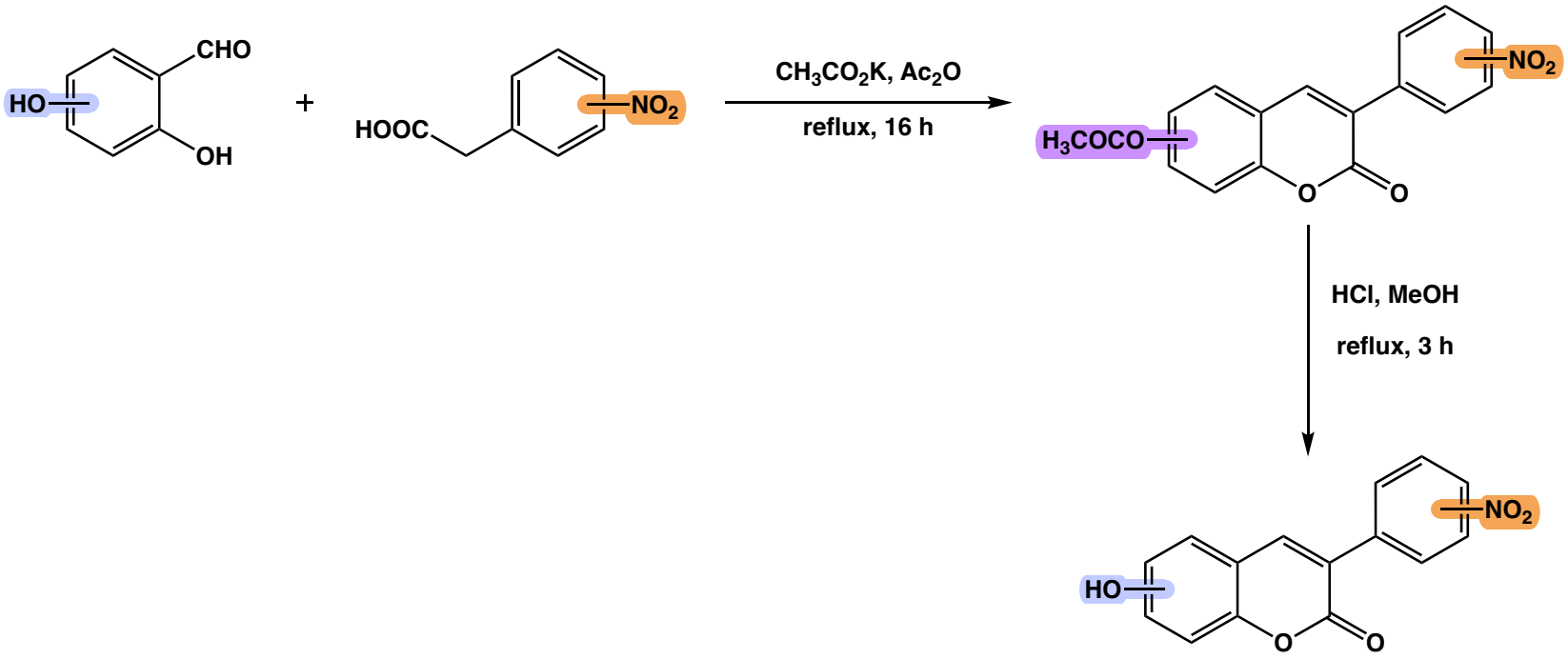


IC_{50} for the vasorelaxation induced in rat aorta rings pre-contracted with phenylephrine (1 μM) = 24.86 nM

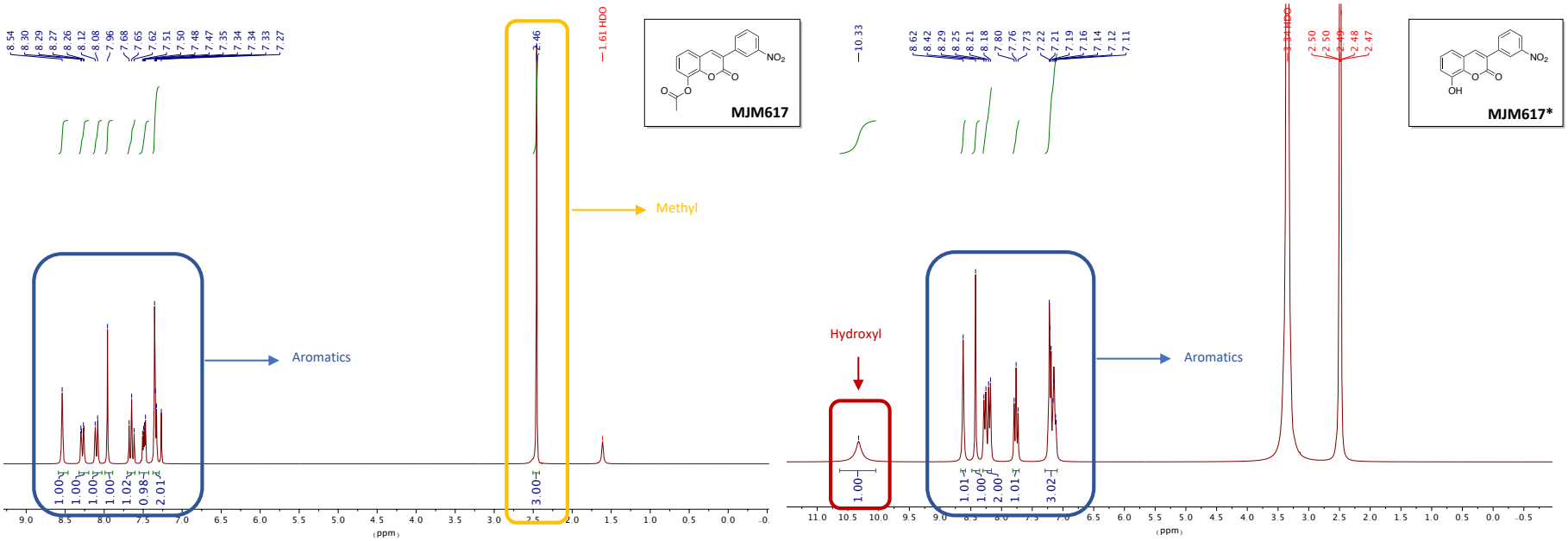
In addition to the biological activity that these molecules may present, important concerns about toxicity have been discussed over the years, especially related to the inclusion of nitro groups in the structures. Therefore, in the present work, we focused on the *in vitro* cytotoxic and hemolytic effects of a new series of hydroxy- and nitro-containing arylcoumarins.

Results and discussion

A new series of hydroxy- and nitro-containing arylcoumarins were synthesized following the conditions described in the Scheme. Perkin-Oglialoro was selected as the ideal method to synthesize the desired compounds since the final products are hydroxyl-containing 3-arylcoumarins.



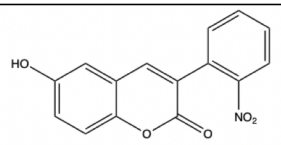
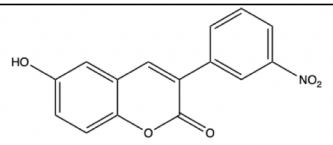
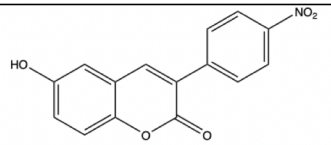
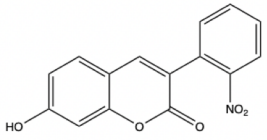
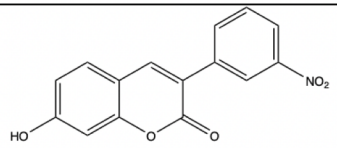
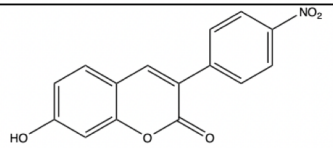
Results and discussion



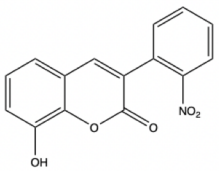
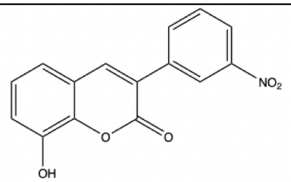
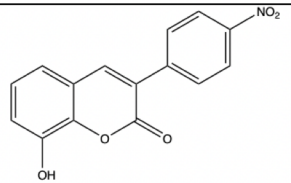
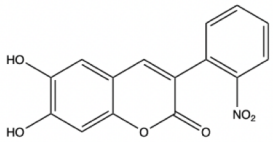
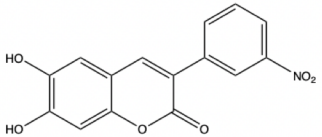
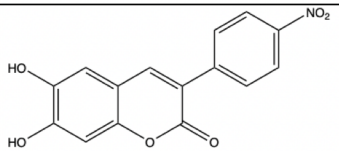
Example of ^{1}H NMR spectra of a hydroxyl derivative (**MJM617***) and its acetoxy precursor (**MJM617**).

Results and discussion

CC_{50} (cytotoxicity) and HC_{10} (hemolytic activity) values for each compound, obtained for human embryonic kidney cells (HEK-293, strain ATCC CRL1573) and human red blood cells (RBC) are presented in the Table.

 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM610*** CC_{50} > 32 µg/mL HC_{10} > 32 µg/mL	 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM611*** CC_{50} > 32 µg/mL HC_{10} > 32 µg/mL	 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM612*** CC_{50} > 32 µg/mL HC_{10} > 32 µg/mL
 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM613*** CC_{50} > 32 µg/mL HC_{10} > 32 µg/mL	 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM614*** CC_{50} > 32 µg/mL HC_{10} > 32 µg/mL	 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM615*** CC_{50} > 32 µg/mL HC_{10} > 32 µg/mL

Results and discussion

 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM616*** $CC_{50} > 32$ µg/mL $HC_{10} > 32$ µg/mL	 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM617*** $CC_{50} > 32$ µg/mL $HC_{10} > 32$ µg/mL	 Chemical Formula: $C_{15}H_9NO_5$ Molecular Weight: 283,24 **MJM618*** $CC_{50} > 32$ µg/mL $HC_{10} > 32$ µg/mL
 Chemical Formula: $C_{15}H_9NO_6$ Molecular Weight: 299,24 **MJM619*** $CC_{50} > 32$ µg/mL $HC_{10} > 32$ µg/mL	 Chemical Formula: $C_{15}H_9NO_6$ Molecular Weight: 299,24 **MJM620*** $CC_{50} > 32$ µg/mL $HC_{10} = 28.38$ µg/mL	 Chemical Formula: $C_{15}H_9NO_6$ Molecular Weight: 299,24 **MJM621*** $CC_{50} > 32$ µg/mL $HC_{10} > 32$ µg/mL

All compounds studied were non-cytotoxic for HEK-293 cells, at the highest concentration tested (32 µg/mL). Only 6,7-dihydroxy-3-(3-nitrophenyl)coumarin (**MJM620***) presented RBC HC_{10} below 32 µg/mL.

Conclusions

Under the experimental conditions used in the present study, it can be concluded that synthetic 3-arylcoumarins, up to the maximum tested concentration of 32 µg/mL, do not present cytotoxic effects for human cells. However, analyzing the data related to hemolytic effects, a decrease in cell viability was observed for the compound **MJM620***, presenting an HC_{10} of 28.38 µg/mL. The data described in this report highlight the need to expand studies to address the complete biosafety of this molecule. Furthermore, this information encourages further pharmacological studies based on this scaffold and its substitution patterns.

Acknowledgments

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