2-Styrylchromones modulate prostaglandins production through the inhibition of COX-2

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INTRODUCTION

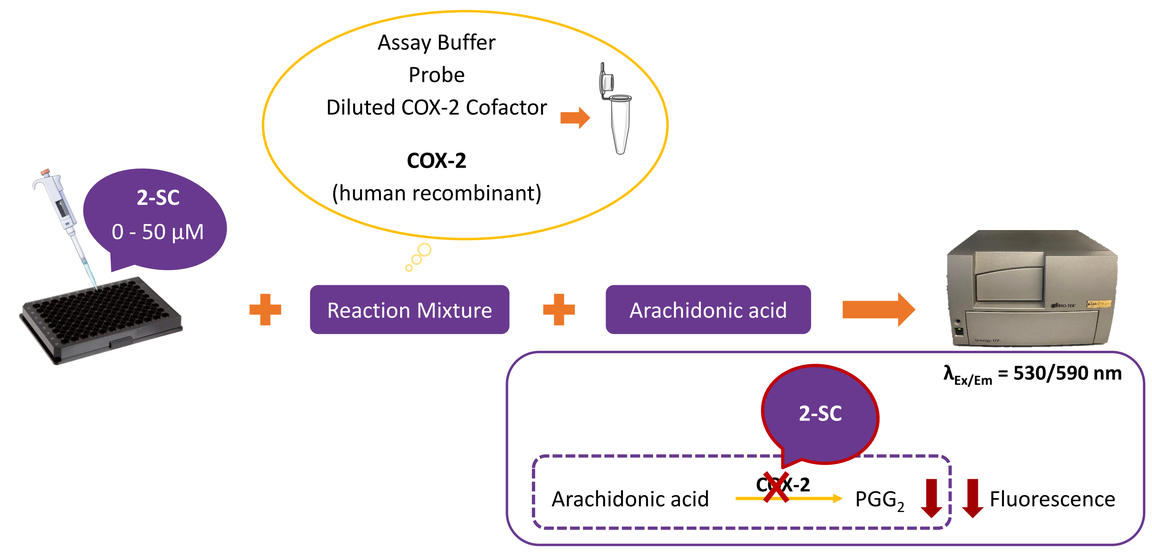
Cyclooxygenases (COX) are the enzymes responsible for the synthesis of prostanoids, namely prostaglandins (PG), through the conversion of arachidonic acid into PG. COX have two isoforms, COX-1 and COX-2, and the latter is the inducible one, which is triggered by inflammatory mediators, such as growth factors and cytokines. COX-2 plays an important role in the development and maintenance of the inflammatory state [1]. Therefore, the regulation of the inflammatory response and symptoms is influenced by the modulation of COX-2 activity.

2-Styrylchromones (2-SC) are heterocyclic compounds, with a styryl group attached to the C-2 of their chromone structure. Most of the know compounds in this group are of synthetic origin and have demonstrated several bioactive properties, including anti-inflammatory. Although their anti-inflammatory potential is recognized, their mechanisms of action still need to be deeply explored [2].

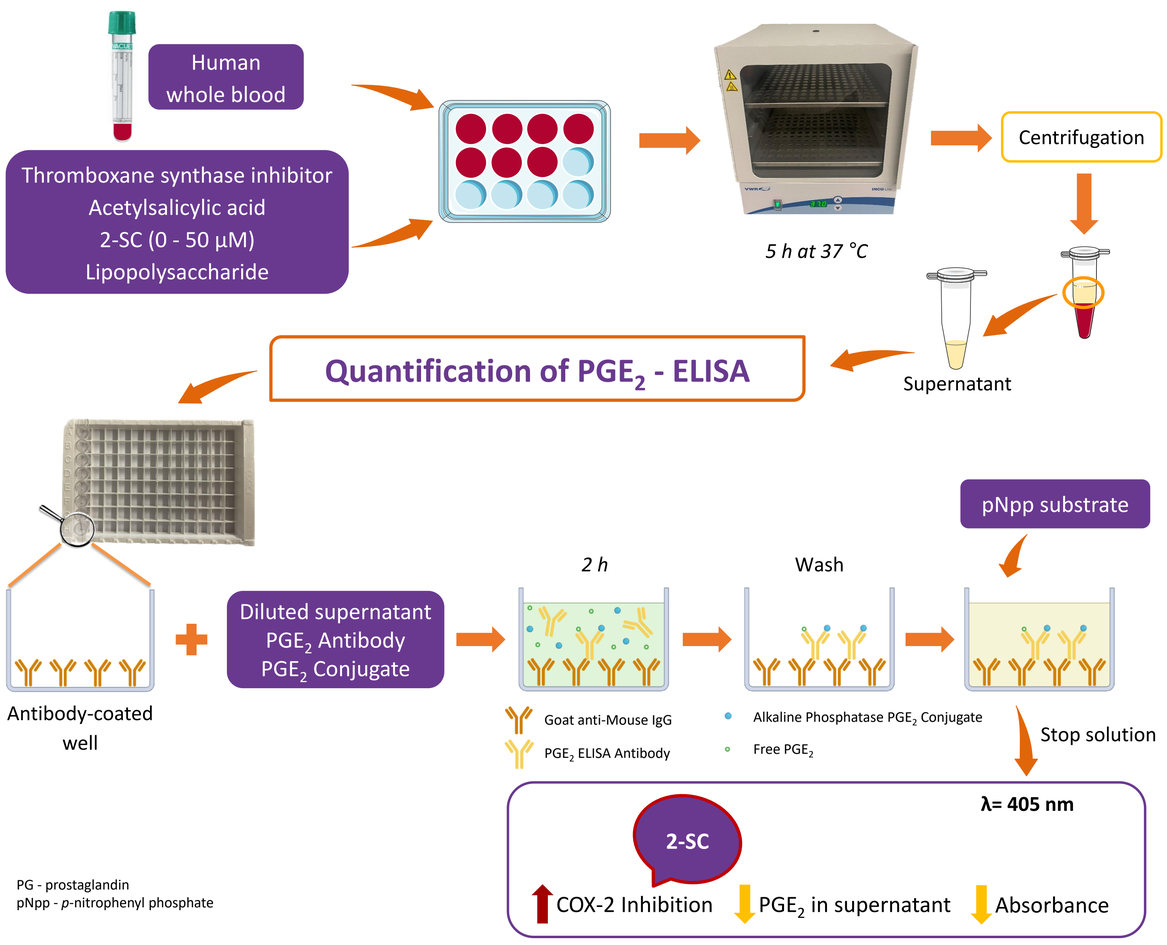
Aim: Evaluate the inhibitory activity of ten hydroxylated and methoxylated 2-SC (Figure 1) against COX-2 by fluorometric *in vitro* detection of PGG_2 and colorimetric *ex vivo* detection of PGE_2 production.

METHODS

2-SC's inhibition of isolated human recombinant COX-2 activity [3]

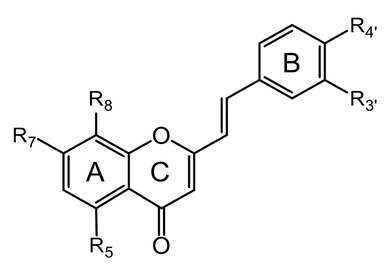


2-SC's inhibition of PGE_2 production in human whole blood [4]



PG - prostaglandin
pNpp - *p*-nitrophenyl phosphate

STUDIED 2-SC



1 $R_5 = R_7 = R_8 = R_{3'} = H$; $R_{4'} = OH$
2 $R_5 = R_8 = H$; $R_7 = R_{3'} = R_{4'} = OH$
3 $R_5 = R_7 = R_{3'} = R_{4'} = OH$; $R_8 = H$
4 $R_5 = R_8 = H$; $R_7 = OCH_3$; $R_{3'} = R_{4'} = OH$
5 $R_5 = R_7 = OCH_3$; $R_8 = H$; $R_{3'} = R_{4'} = OH$
6 $R_5 = H$; $R_7 = R_8 = R_{3'} = R_{4'} = OH$
7 $R_5 = H$; $R_7 = R_8 = OCH_3$; $R_{3'} = R_{4'} = OH$
8 $R_5 = R_7 = R_8 = R_{3'} = H$; $R_{4'} = OCH_3$
9 $R_5 = H$; $R_7 = R_8 = R_{3'} = R_{4'} = OCH_3$
10 $R_5 = H$; $R_7 = R_8 = OH$; $R_{3'} = R_{4'} = OCH_3$

Figure 1 Chemical structures of the tested 2-SC and the respective substituents.

RESULTS

Table 1 Inhibition of isolated human recombinant COX-2 activity and inhibition of PGE_2 production in human whole blood, via COX-2, by the tested 2-SC and the positive control, celecoxib. The most active 2-SC tested are highlighted in **bold**.

2-SC	Inhibitory activity (% ± SEM)* or IC_{50} (µM, mean ± SEM)	
	Inhibition of human recombinant COX-2	Inhibition of PGE_2 production, via COX-2
1	51 ± 4 % $^{50\ \mu M}$	57 ± 5 % $^{50\ \mu M}$
2	1.5 ± 0.2	NA $^{50\ \mu M}$
3	1.7 ± 0.2	47 ± 6 % $^{50\ \mu M}$
4	2.0 ± 0.3	NA $^{25\ \mu M}$
5	1.8 ± 0.1	NA $^{25\ \mu M}$
6	**0.36 ± 0.07**	NA $^{50\ \mu M}$
7	0.9 ± 0.1	NA $^{50\ \mu M}$
8	NA $^{50\ \mu M}$	**18 ± 1**
9	NA $^{50\ \mu M}$	NA $^{25\ \mu M}$
10	1.9 ± 0.3	NA $^{50\ \mu M}$
Positive control **Celecoxib**	0.23 ± 0.04	0.98 ± 0.04

* The percentage of inhibition is expressed for the highest tested concentration (in superscript) that could be tested under the assay conditions to avoid interferences with the methodology (n≥3). SEM - standard error of the mean. NA - No activity found, up to the highest tested concentration (in superscript).

CONCLUSIONS

The 2-SC **6** was the most active in the inhibition of isolated human recombinant COX-2.

The 2-SC **8** was the most active in the inhibition of PGE_2 production.

The presence of OH groups, namely at C-8 on A-ring, seems to be essential for the direct inhibition of COX-2.

The presence of a OCH_3 at C-4' on B-ring seems to be important for the inhibition of PGE_2 production, in human whole blood.

References

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Acknowledgements

This work received financial support from PT national funds (FCT/MCTES, Fundação para a Ciência e Tecnologia and Ministério da Ciência, Tecnologia e Ensino Superior) through the projects UIDB/50006/2020 and UIDP/50006/2020, and from the European Union (FEDER funds through COMPETE2020 POCI-01-0145-FEDER-029253-Project PTDC/MED-QUI/29253/2017). ML thanks FCT/MCTES and ESF (European Social Fund) through NORTE 2020 (Programa Operacional Região Norte) for her PhD grant ref. 2021.06746.BD). MF acknowledges her contract under the CEEC Individual (2020.04126.CEECIND/CP1596/CT0006) and thanks LAQV/REQUIMTE for her contract under the reference LA/P/0008/2020.