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Synthesis and Biological Activity of C-Glycosyl 3-Vinylchromones: Toward Novel Antioxidant Drugs

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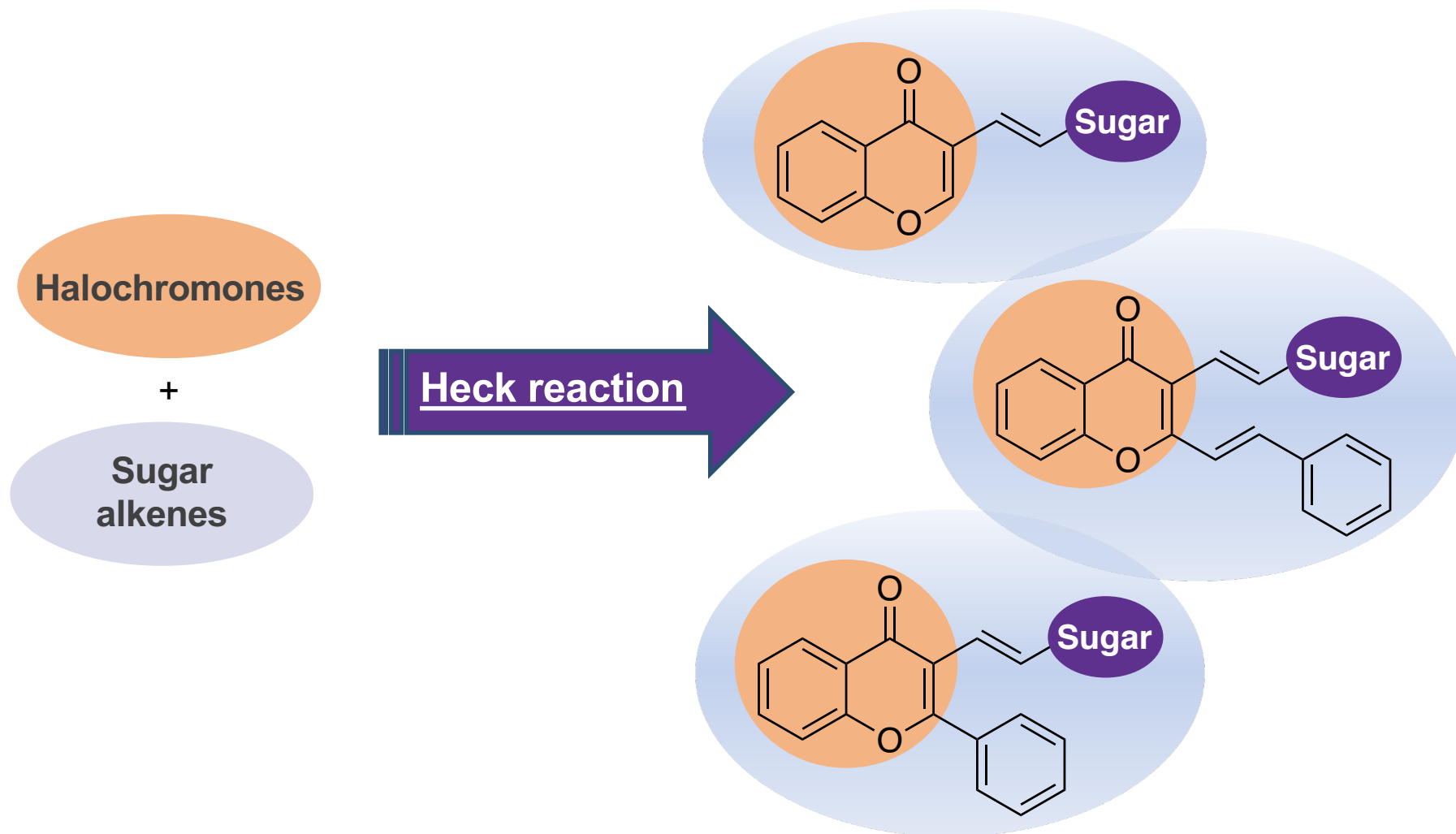
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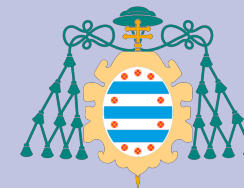
Universidad de Oviedo

Synthesis and Biological Activity of C-Glycosyl 3-Vinylchromones: Toward Novel Antioxidant Drugs





Abstract



4*H*-Chromen-4-ones (chromones) are a well-known class of oxygenated heterocyclic derivatives widely distributed in Nature. Due to their impressive pharmacological potential, chromones have attracted much attention. The extensive search for chromone derivatives resulted in the discovery of 3-(2-phenyl-vinyl)chromones, a small family of naturally occurring chromones characterized by a potent antioxidant activity.

Naturally occurring chromones are usually glycosylated, which have a critical impact in their pharmacokinetics. Even though *O*-glycosyl chromones are more common, their *C*-glycosyl counterparts attracted much recent interest on account of their enhanced stability and bioactivity.

This study is aimed at the synthesis of a novel family of *C*-glycosyl 3-vinylchromones and the *in vitro* evaluation of their antioxidant activity.

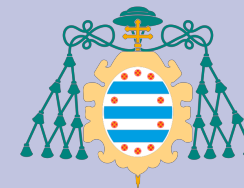
Keywords: Chromones; Antioxidants, *C*-Glycosyl chromones.



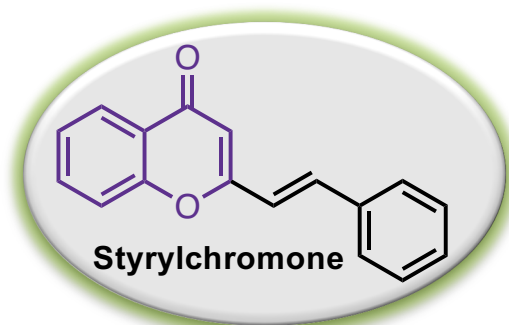
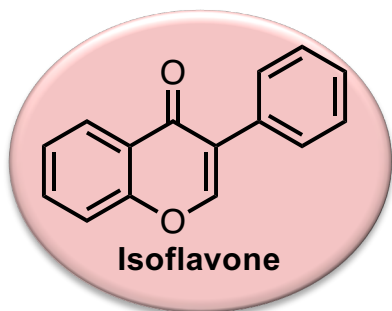
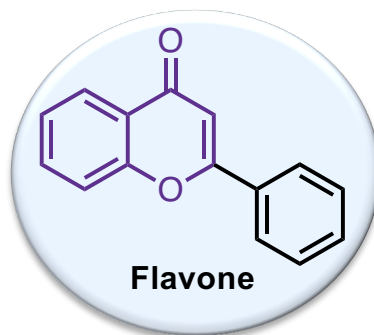
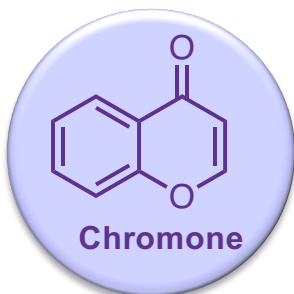


Introduction

The chromone structural unit



- **Chromone core** ubiquitous in natural products
- Huge **structural diversity**



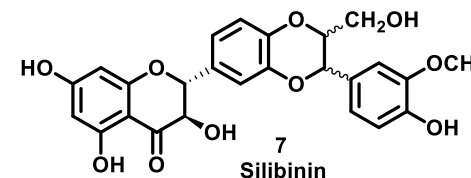
Interesting and broad biological activities:

- Antioxidant
- Anti-inflammatory
- Anticancer
- Antifungal
- Antiviral
- Antimalarial
- Hepatoprotective
- Cardioprotective
- Anti-allergic
- ...

Privileged structural motifs in drug design



Milk thistle
(*Silybum marianum*)



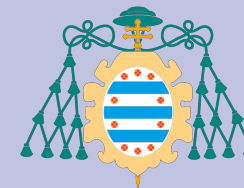
Impressive **antioxidant** and **hepatoprotective** activities





Introduction

C-glycosyl chromones

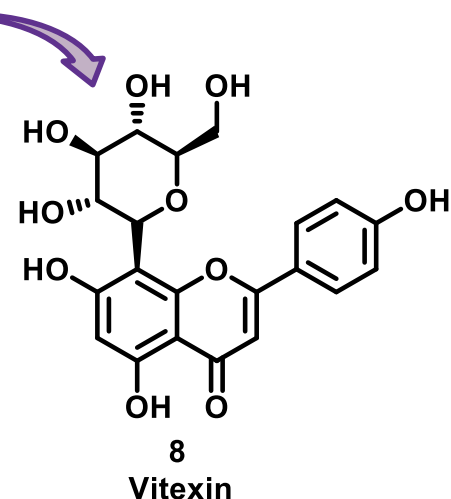


A pharmacological promising synergic effect...

Biological activities of phenolic compounds together with the high **hydrophilic character** of the sugar unit and the **hydrolytic stability** of the C-glycosidic bond



Passiflora incarnata



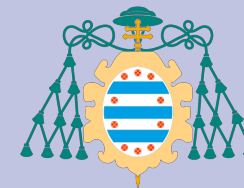
- **Enhanced stability** towards enzymatic and chemical hydrolysis
- **Improved activity** of the aglycones after their C-glycosylation



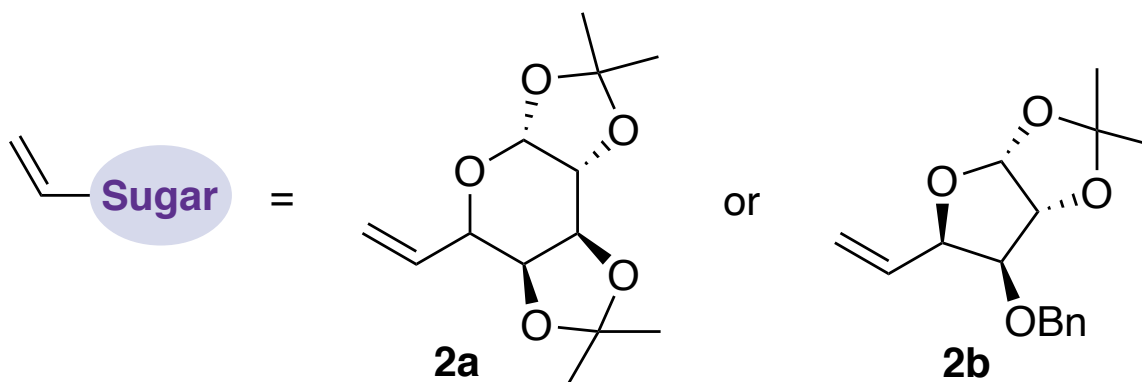
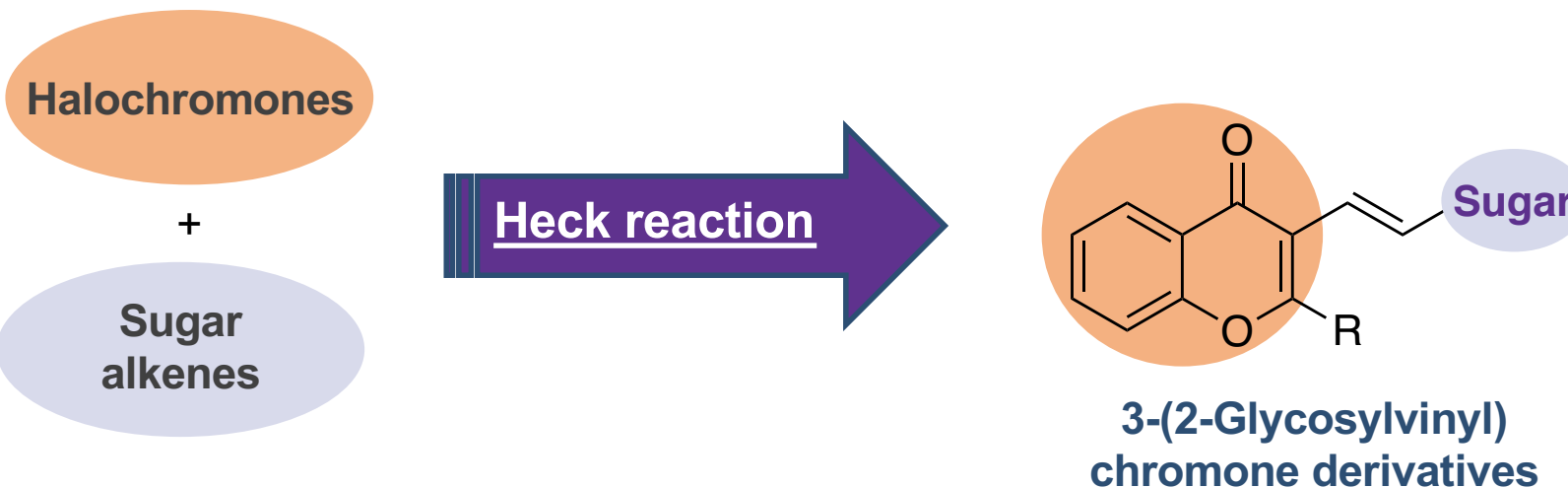


Results and Discussion

Synthetic Strategy



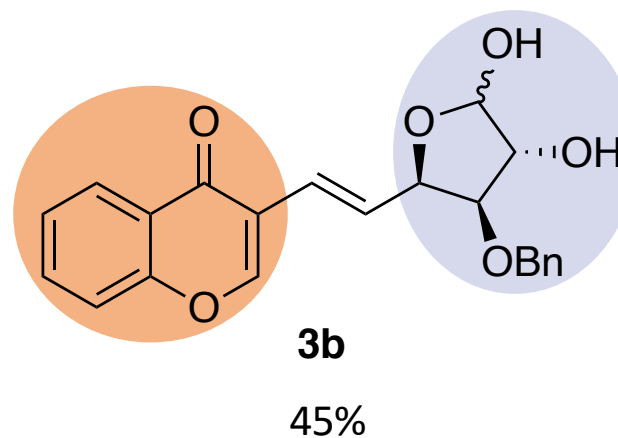
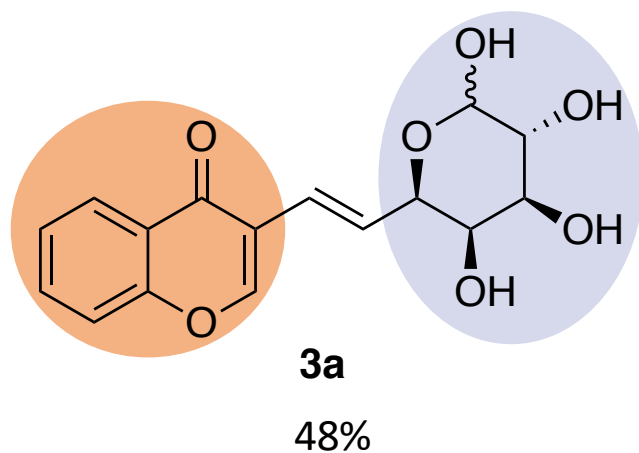
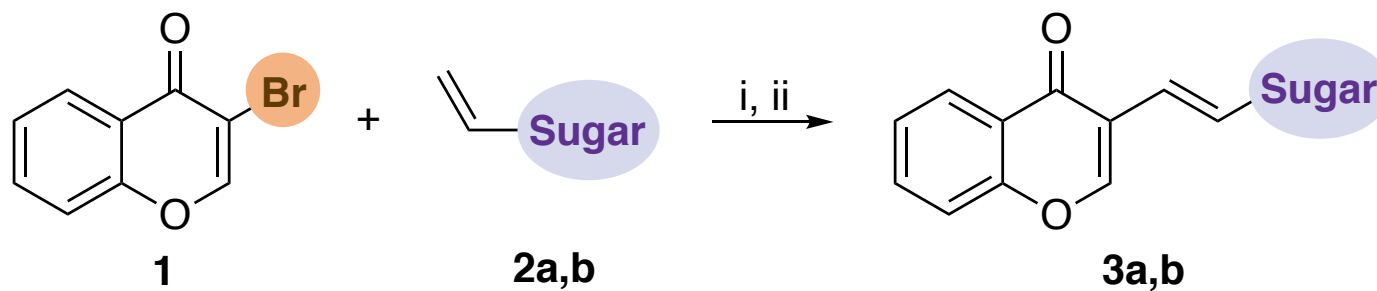
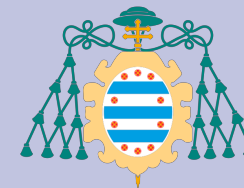
Palladium mediated C-C coupling strategy





Results and Discussion

Synthesis of Glycosylvinyl Chromones



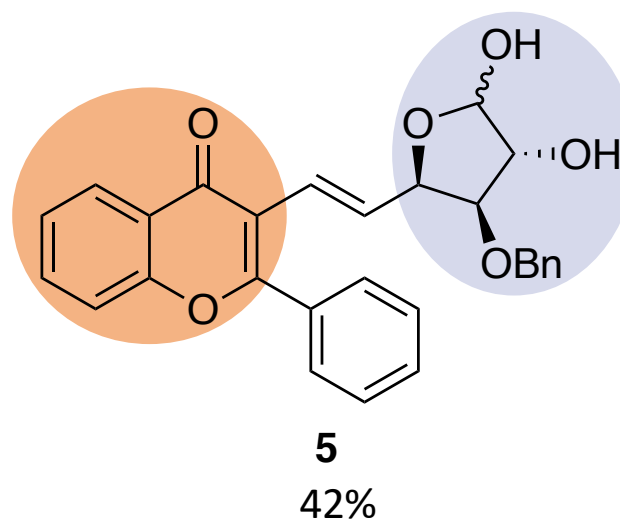
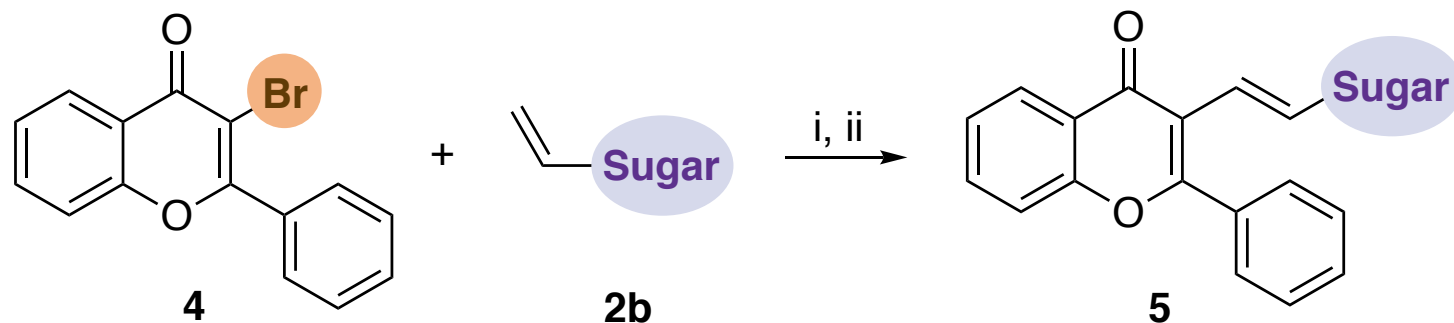
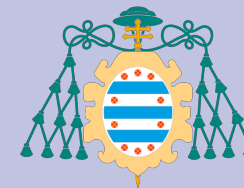
(i) K_2CO_3 , TBAB, $Pd(OAc)_2$, DMF, 100 °C, 12 h. (ii) TFA/ H_2O (1:1), r.t., 12 h.





Results and Discussion

Synthesis of Glycosylvinyl Flavones



(i) K_2CO_3 , TBAB, $Pd(OAc)_2$, DMF, 100 °C, 12 h. (ii) TFA/ H_2O (1:1), r.t., 12 h.



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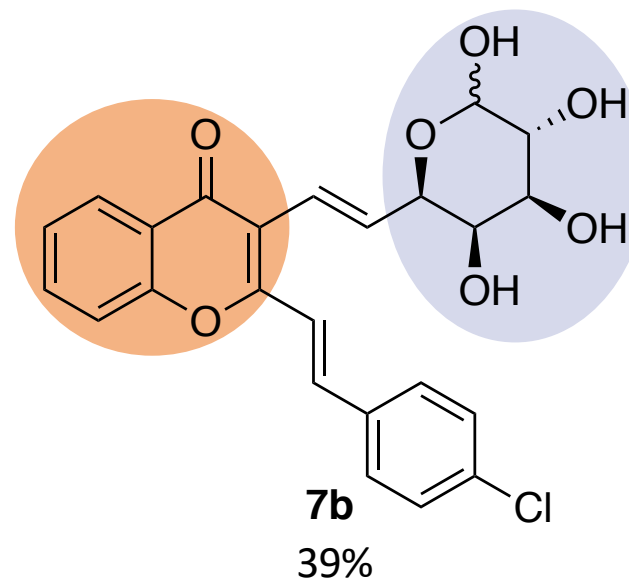
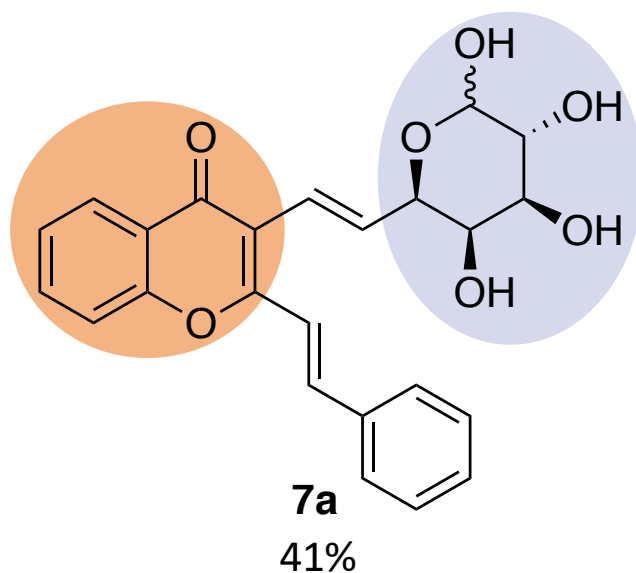
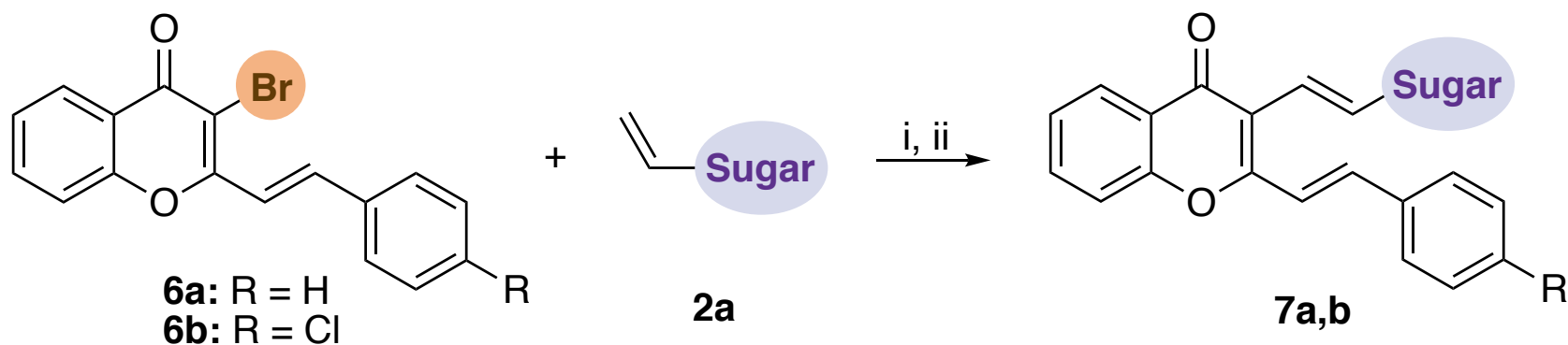
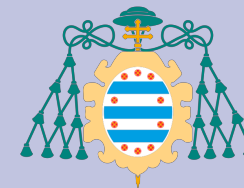


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Results and Discussion

Synthesis of Glycosylvinyl Styrylchromones



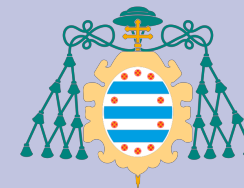
(i) K_2CO_3 , TBAB, $Pd(OAc)_2$, DMF, 100 °C, 12 h. (ii) TFA/ H_2O (1:1), r.t., 12 h.





Results and Discussion

Synthetic Strategy

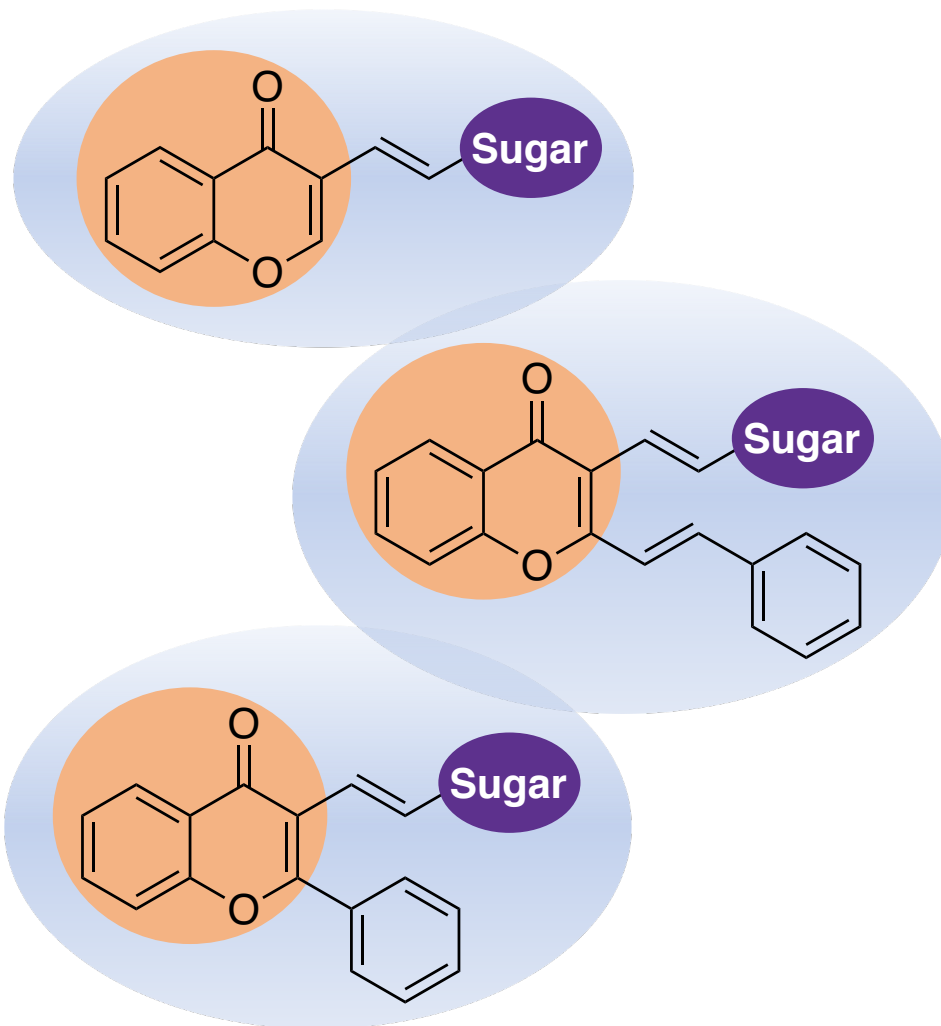


Wide scope
Heck protocol!

New conjugates of chemical and
biological interest containing
unsaturated linking groups

By using the same methodology...

- ✓ 3-(2-Glycosylvinyl)chromones
- ✓ 3-(2-Glycosylvinyl)flavones
- ✓ 3-(2-Glycosylvinyl)-2-styrylchromones



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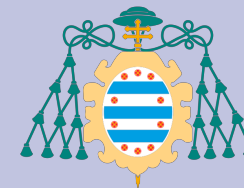


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Results and Discussion

Antioxidant activity



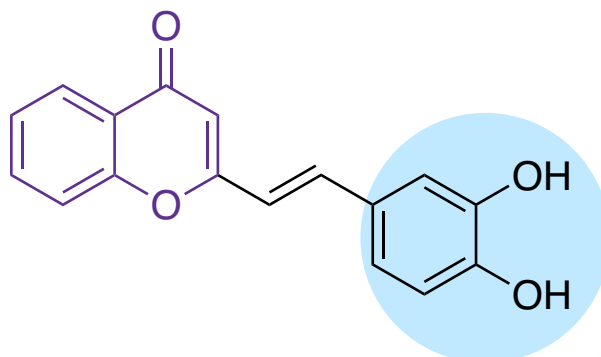
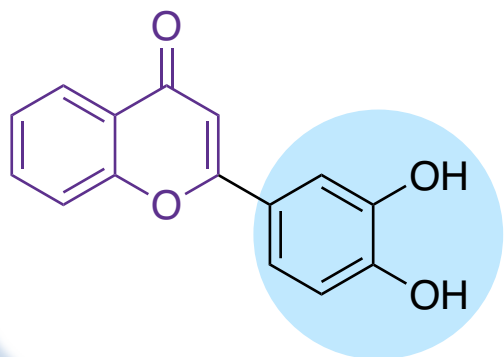
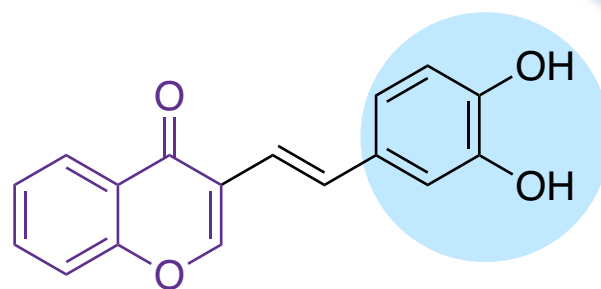
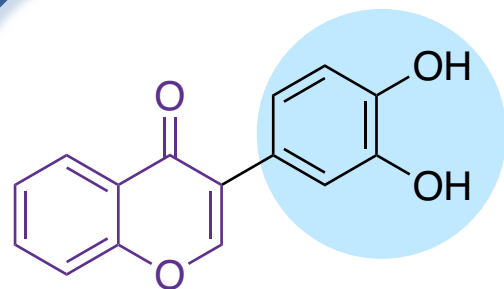
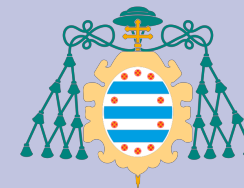
Structure	EC ₅₀ (μM)	Structure	EC ₅₀ (μM)
 Chr	16.9 ± 1.5	 5	>200
 3a	>200	 7a	>200
 3b	>200	 7b	>200





Results and Discussion

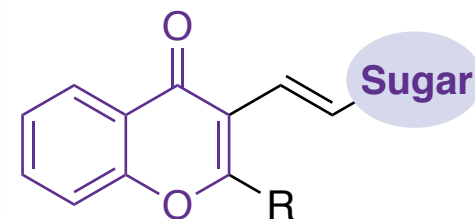
SAR for the antioxidant activity



Strong antioxidant activity

Chromone unit ✓

Catechol unit ✓



R = H, Ar, CH=CHAr

No antioxidant activity

Chromone unit ✓

Catechol unit ✗

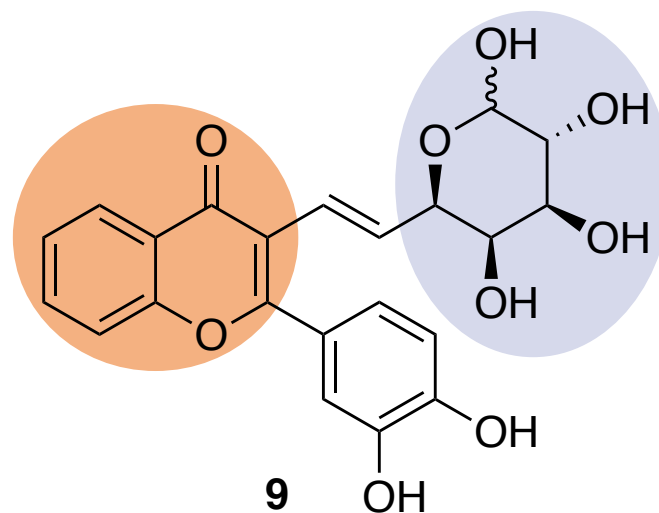
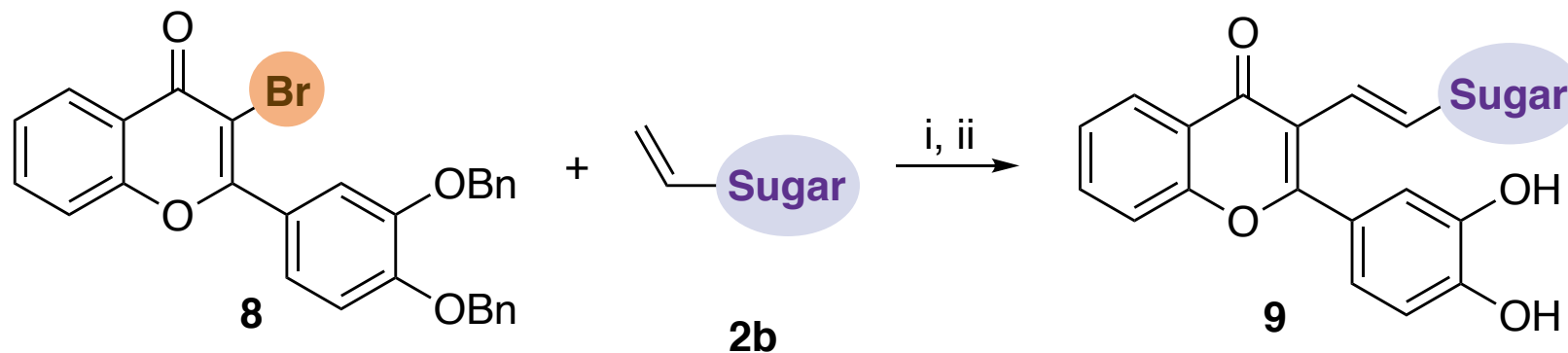




Results and Discussion



Synthesis of a glycosylvinyl chromones with a catechol unit



(i) K_2CO_3 , TBAB, $Pd(OAc)_2$, DMF, 100 °C, 12 h. (ii) HCl/TFA, r.t., 12 h.



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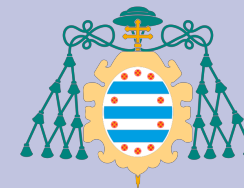
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Conclusions

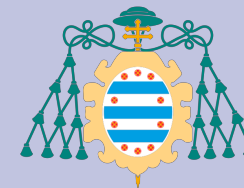


- The **Heck cross-coupling reaction** of halochromones with alkene sugars proved to be a **straightforward synthetic C-glycosylation** route;
- The methodology is **wide in scope** as **3-(2-glycosylvinyl)flavones, chromones and 2-styryl-chromones** were successfully synthesized;
- The **antioxidant activity** of the C-glycosyl conjugates was evaluated;
- Surprisingly, the obtained new conjugates were **inactive**;
- On the study of the structure-activity relationship, we hypothesized that the lack of activity was related to the lack of a **catechol unit**;
- A catechol-containing **3-(2-glycosylvinyl)flavone** was then synthesized;
- The next step would be the evaluation of the **antioxidant potential** of the obtained conjugates and the study of their structure-activity relationship.





Acknowledgements



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