STUDIES TOWARDS THE SYNTHESIS OF 2-BENZYL-2-HYDROXY-1-TETRALONES AND *IN SILICO* PREDICTION OF ADMETOX PROPERTIES AND CARDIOTOXICITY

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Introduction

Homo-isoflavanones are natural products mostly found in legumes acting as phytoalexins, they also display a wide variety of biological activities (Fig. 1).[1] The presence of a hydroxy group at Cα carbonyl increases activity, as shown in the cytotoxic activity against ovarian cancer A2780 and melanoma A2058 cell lines, when comparing structures **5** and **6** (Fig. 1).[2]

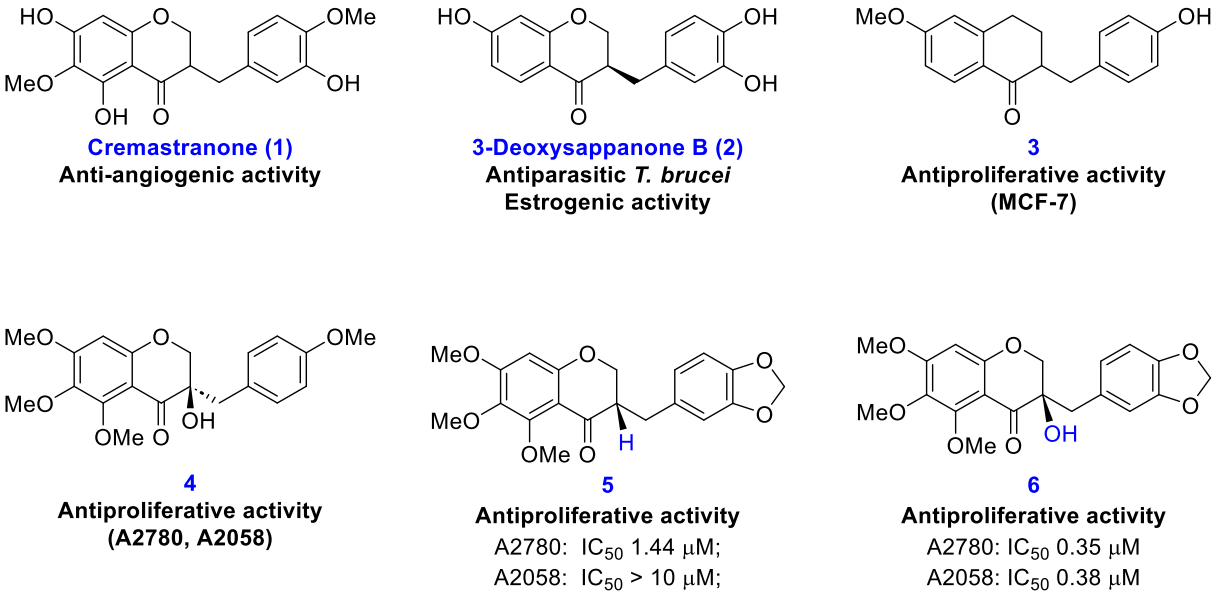


Figure 1

Limited pattern of substitution and difficulties associated with the isolation of homo-isoflavanones type **8** directed our attention to the synthetic analogues of these compounds, the 2-benzyl-2-hydroxy-tetralones **9**, isosteres with the substitution of the oxygen atom at the B-ring for a methylene (CH_2) group (Fig. 2). This O x CH_2 isosterism is a common approach in medicinal chemistry[3] and one example is also depicted in Figure 2, where the carba-aza-pterocarpan **11** shows a higher potency than aza-pterocarpan **10** in antiproliferative effect against HL-60, HCT-8 and MDA-MD435 cell lines.[4] No reports of the pharmacological evaluation of these carba-derivatives, 2-benzyl-2-hydroxy-tetralones **9**, were found.

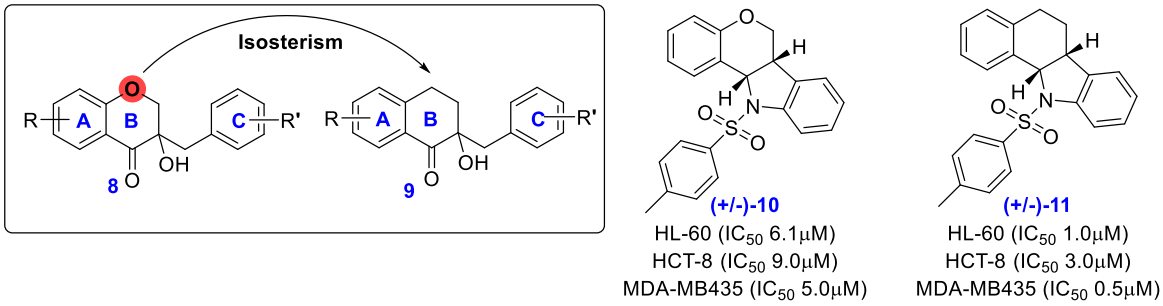
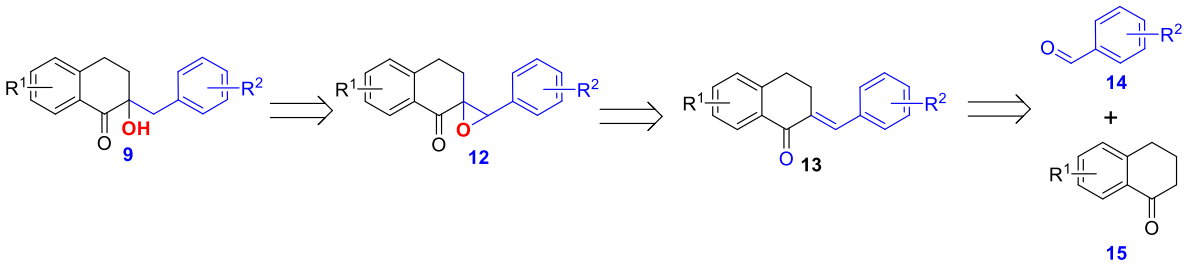


Figure 2

We decided to investigate the synthesis and evaluate *in silico* the ADMETOX properties and cardiotoxicity of 2-benzyl-2-hydroxy-1-tetralones **9**, as potentially bioisosteres of homo-isoflavanones.

Material and Methods

→ Synthetic strategy: The retrosynthetic approach towards the 2-benzyl-2-hydroxy-1-tetralones **9** is shown in Scheme 1. Compounds **9** can be obtained through the reduction of the epoxide **12**, by catalytic hydrogenation in the presence of Lyndlar's catalyst.[5] Compound **12** can be prepared by epoxidation of the benzilidene-1-tetralones **13**,[5,6] that can be synthesized through the aldol condensation/elimination reaction[7] between benzaldehydes **14** and 1-tetralones **15**, both commercially available.



Scheme 1

→ *In silico* ADMETOX and cardiotoxicity evaluation - These studies will be performed by using the following tools

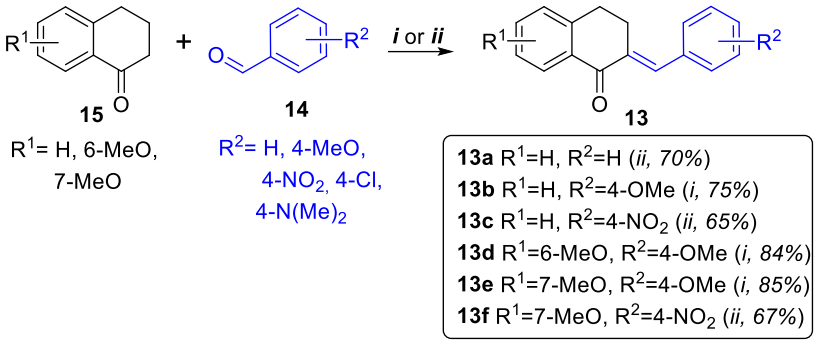
SwissADME (http://www.swissadme.ch/) – determination of pharmacokinectics properties, ADMET parameters and possible enzyme interactions (P-glycoprotein, Cytochromes P450);

Pred-hERG 5.0 (http://predherg.labmol.com.br/)- Evaluation of the possible cardiotoxicity through hERG receptor;

Cyto-Safe (http://cytosafe.labmol.com.br/)- Prediction system of cytotoxicity of novel drug candidates.

Results and Discussion

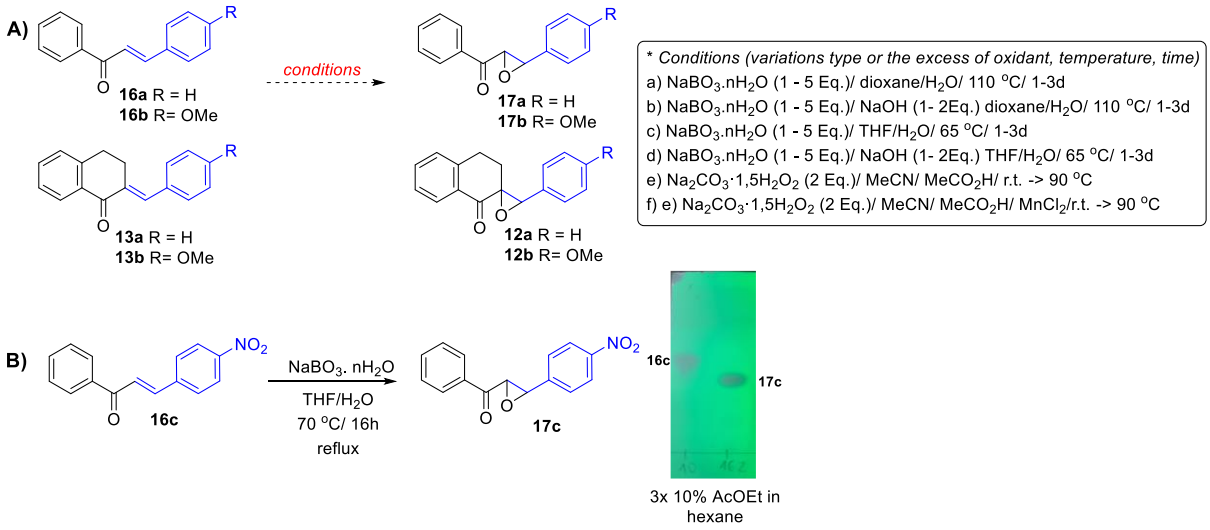
The synthesis started with the formation of benzylidene-tetralones **13** through the condensation of 1-tetralones (**15**) and benzaldehydes (**14**). Benzilidene-1-tetralones **13** were obtained in good yields (65-85%), either under acidic or basic conditions.



Conditions: i- HCl, MeOH, reflux, 16h; *ii-* NaOH, MeOH, r.t, 16h;

Scheme 2

The epoxidation reaction was also studied with chalcones, as a model reaction to compare with the benzilidenes-1-tetralones **13**. The initial tests were performed with Sodium perborate (SPB) or sodium percarbonate (SPC), as cheap and stable oxidants. Neither the benzilidenes (**13a,b**) or the chalcones (**16a,b**) derived from benzaldehyde or *p*-anisaldehyde reacted under these conditions (Scheme 3 - A). In contrast, **16c**, a chalcone derived from 4-nitrobenzaldehyde reacted with SPB and gave origin to the corresponding epoxide (~60 yield) (Scheme 3 - B). This can be related with the possible mechanism of the reaction as the OMe group acts deactivating the double bond towards a conjugate addition reaction with peroxide anion whereas the NO_2 group acts activating.



Scheme 3

This can also be considered by comparing the LUMO energies of the chalcones and benzilidenes-1-tetralones (Figure 3). These energies were calculated by using Spartan '14 software. Compounds with lower LUMO energies are more reactive towards conjugated additions.[8] Although nitro-benzylidene-1-tetralone **13c** is more reactive (lower LUMO energy)

than the *p*-metoxi benzylidene-1-tetralone (**13b**), under the same conditions with SPB no reaction was observed.

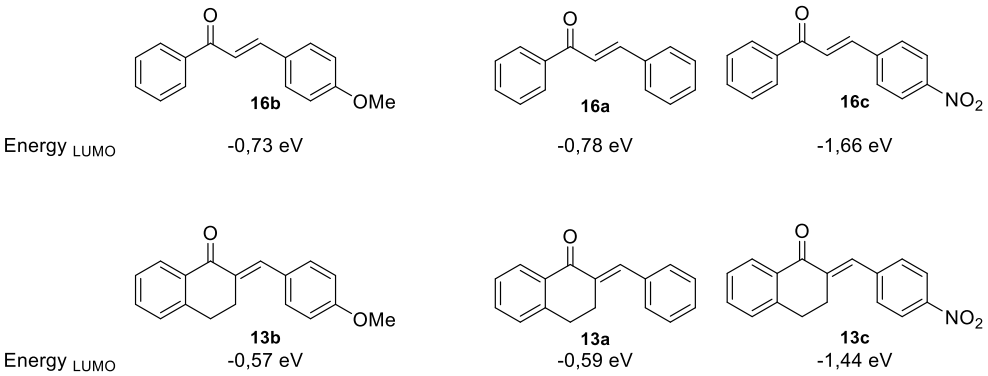


Figure 3

We decided to study the H_2O_2 as the epoxidation agent and under basic conditions (H_2O_2 35%, NaOH aq. (pH = 12), dioxane, 65ºC, 5h), *p*-metoxi chalcone **16b** was converted into the corresponding epoxide (71% yield), but the benzylidene **13b** still did not react. Other benzilidenes and other reaction conditions are under evaluation.

Eleven structures, 2-benzyl-2-hydroxy-tetralones **9**, along with the corresponding non-hydroxy derivatives (2-benzyl-1-tetralones, **18**) were analysed in SwissADME, PRED-HERG and Cyto-Safe. All the compounds showed a similar profile in biodisponibility radar (Lipophilicity, size, polarity, insolubility, number of insaturations, molecular flexibility - Fig. 4A) and druglikeness were favorable concerning Lipinski's rule of five. In the case of cardiotoxicity associated with hERG blockage, only compounds with 4-Cl (Fig. 4C), 4-NO_2 and 4-$N(Me)_2$, in the C-ring showed to be potentially cardiotoxic, the others were considered non-toxic (for example Fig 4B). None of the compounds screened on Cyto-safe analysis indicate cytotoxicity. The possible interactions (P-gp, CYP450) are shown in Table 1.

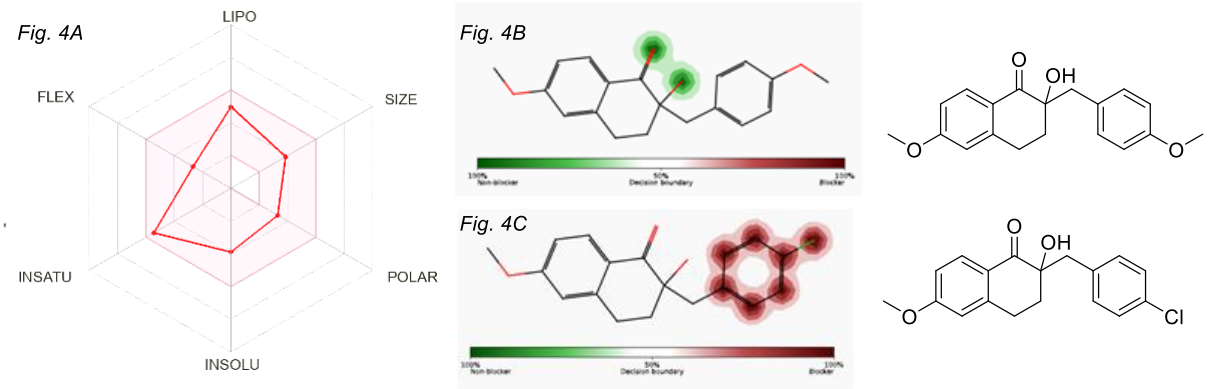


Figure 4

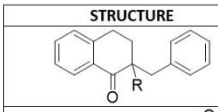
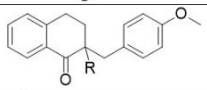
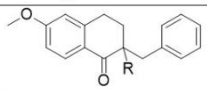
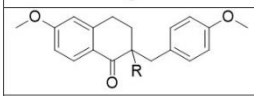
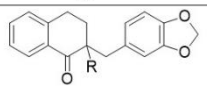
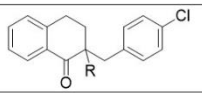
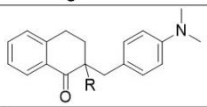
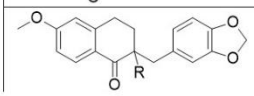
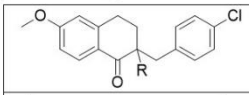
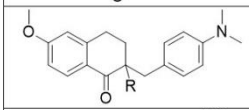
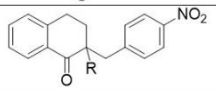
STRUCTURE	R	gp-P	CYP1A2	CYPC19	CYP2C9	CYP2D6	CYP3A4	hERG
	H (18a)	No	No	No	No	Yes	No	(+)50%
	OH (9a)	No	No	No	No	Yes	No	(-)60%
	H (18b)	No	No	Yes	Yes	Yes	No	(+)60%
	OH (9b)	No	No	No	No	Yes	No	(-)50%
	H (18c)	No	No	Yes	Yes	Yes	No	(-)50%
	OH (9c)	No	No	No	No	Yes	No	(-)50%
	H (18d)	No	No	Yes	Yes	Yes	Yes	(-)50%
	OH (9d)	No	No	Yes	No	Yes	Yes	(-)50%
	H (18e)	Yes	Yes	Yes	Yes	Yes	Yes	(+)60%
	OH (9e)	Yes	Yes	Yes	Yes	Yes	Yes	(-)50%
	H (18f)	No	Yes	No	Yes	Yes	No	(+)70%
	OH (9f)	No	Yes	No	No	Yes	No	(+)60%
	H (18g)	No	Yes	Yes	Yes	Yes	No	(+)50%
	OH (9g)	No	Yes	No	No	Yes	No	(+)50%
	H (18h)	No	Yes	Yes	Yes	Yes	Yes	(-)50%
	OH (9h)	Yes	Yes	Yes	Yes	Yes	Yes	(-)60%
	H (18i)	No	Yes	Yes	Yes	Yes	No	(+)70%
	OH (9i)	No	Yes	Yes	Yes	Yes	Yes	(+)50%
	H (18j)	No	No	Yes	Yes	Yes	Yes	(+)50%
	OH (9j)	No	No	Yes	No	Yes	Yes	(-)50%
	H (18k)	No	Yes	Yes	Yes	No	Yes	(+)60%
	OH (9k)	No	Yes	Yes	Yes	Yes	Yes	(-)50%

Table 1

Conclusion

Epoxidation reaction of benzilidene-1-tetralones needs to be optimized, specially for the derivatives with metoxi groups. *In silico* studies showed promising results for the designed compound as drug candidates. Further and more detailed studies are under development.

Acknowledgements

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