QSAR model: prediction of the clastogenic potential of 3-arylcoumarins

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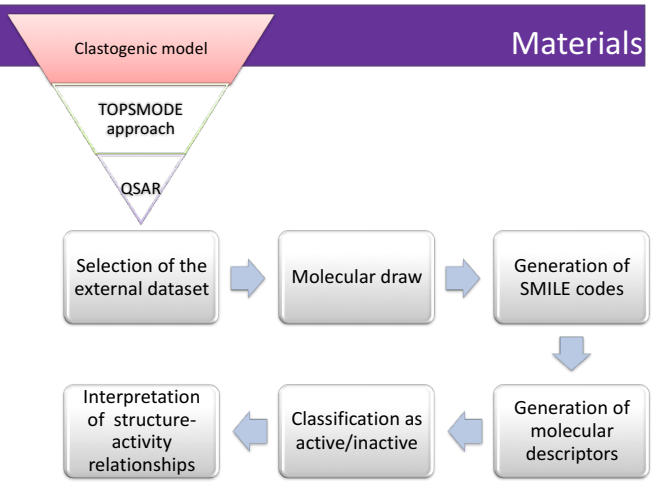
Abstract. Drug discovery is a challenging task for researchers due to the complexity of biomolecules involved in pathologic processes. Design and development of efficient drugs is still urgent for several diseases. Cheminformatics tools are useful to better understand the interaction between new chemical entities and their targets. We studied a selected series of 3-arylcoumarins with antioxidant potential, and how their chemical features can contribute for the clastogenic activity. A virtual screening, based on the TOPSMODE approach, using a clastogenic model, was performed. The results suggest that the presence and position of hydroxyl groups in the scaffold is important for the activity. This communication is focused on cheminformatics, and its applications in drug effectiveness and safety.
Keywords. 3-Arylcoumarins; Clastogenicity; TOPSMODE; Cheminformatics.

Introduction

The possibilities of studying new chemical coumarinic structures as potential drugs is a field of great interest because of the synthetic versatility of the scaffold. The antioxidant activity has been extensively studied in the last years, and has been reported for natural and synthetic coumarins. Recently, our research group has experimentally studied the antioxidant activity of several synthetic coumarins. This activity is of great interest in the treatment of chronic diseases.
Specially 3-arylcoumarins, have been studied. Part of this series of coumarins, and some new ones, form the basis of new research that has been based on previous results related to the safety of natural coumarins in food sources and the use of computational toxicology. To increase the safety of these molecules as potential drugs, the present work aims to predict clastogenic

Materials



Results

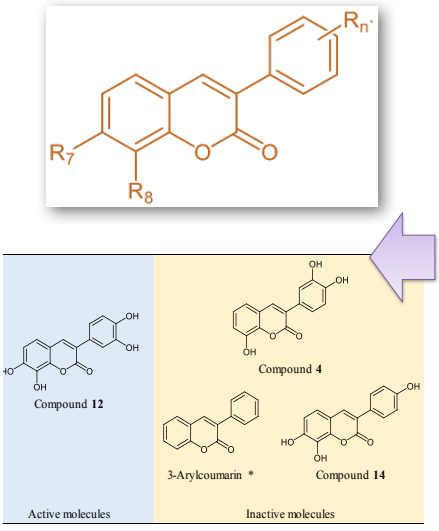
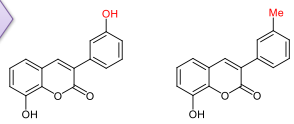


Figure 2. Example of *in silico* 3-arylcoumarins predicted as active/inactive. * prediction of this coumarin was previously published.

Table 1. External Dataset and prediction

Compound	R_7	R_8	R_2	R_3	R_4	R_5	Prob.*	Class
1	H	OH	H	H	H	H	75.7	G1:-1
2	H	OH	H	H	OH	H	67.1	G1:-1
3	H	OH	H	OH	H	H	67.0	G1:-1
4	H	OH	H	OH	OH	H	52.7	G1:-1
5	H	OH	OH	H	H	H	64.4	G1:-1
6	H	OH	H	H	Me	H	79.4	G1:-1
7	OH	H	H	H	Me	H	82.1	G1:-1
8	OH	OH	H	H	H	H	62.6	G1:-1
9	OH	H	H	OH	H	H	70.5	G1:-1
10	OH	OH	H	H	H	OH	52.4	G1:-1
11	OH	OH	OH	H	H	H	50.6	G2:1
12	OH	OH	H	H	OH	OH	62.7	G2:1
13	OH	H	H	H	H	Br	74.1	G1:-1
14	OH	OH	H	H	OH	H	52.2	G1:-1
15	OH	H	OH	H	H	H	68.1	G1:-1
16	OH	H	H	H	H	H	70.6	G1:-1

Figure 3. 3-Arylcoumarins with high *in vitro* antioxidant activity (predicted as non clastogenic *in silico*).



Compound **2** Compound **6**

These compounds presented high antioxidant activity in ORAC-FL studies, are significant for the future work of the research group. These compounds could become future antioxidants for several uses

This structural fragment must be considered in the design of new derivatives, since the clastogenic model used in previous studies carried out with natural coumarins recognizes the methyl substituents as an important chemical feature for the compounds to be non-clastogenic

Conclusions

The preliminary interpretation of the relationship between structure and clastogenicity, considering this external dataset, suggests the importance of hydroxyl groups in the coumarin ring at 7 and/or 8 positions. In general, a tendency to be clastogenic was observed for polyhydroxylated coumarins (specially positions 7 and 8, together with a catechol group in the 3-phenyl group. Future work of SAR is required, for which it is necessary to expand the dataset and the experimental studies that allow to validate these predictions.

References

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