IN SILICO STUDY OF NEW STRUCTURAL ALERTS OF AGENTS CLASTOGENIC

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SUMMARY

Natural polyphenols and their derivatives from diet have been reported by their pro-oxidant and clastogenic activities. In an aim of elucidating structural alerts for this genotoxicity endpoint, a QSTR study was conducted under the TOPS-MODE approach. It was possible to establish structural alerts from the DNA oxidative damage as an endpoint of clastogenicity at optimum leaders with high probability of being clastogenic. Some important fragments to obviate this activity were also identified. The results constitute a reference system for designing new food or pharmaceutical matrices as an alternative to the experimental toxicology.

KEYWORDS: structural alerts; pro-oxidant activity; clastogenicity; flavonoids; TOPS-MODE approach.

INTRODUCTION

Combinatorial chemistry applied to computational toxicology allows to explore a broad universe of molecular structures from materials that nature has selected on the basis of evolution. In this context, the use of computational approaches (*in silico*) allow a thorough exploration of the structural diversity that can be created from structural patterns (1). Estrada *et al.* (2004) raised the possibility of combining approaches QSAR (Quantitative Structure-Activity Relationship) and generating structures as a way for the discovery of new chemical entities of interest (2). In this project, it is shown how the use of the approach TOPS-MODE (Topological Sub-Structural Molecular Design) and substructural analysis lead to the identification of critical structural alerts for clastogenic activity of a series of compounds derived from the basic skeleton of flavonoids, and maximum alerts clastogenicity.

METHODS

Dataset was created including polyphenolic compounds with reported pro-oxidant activity and a series of design derivatives. It was taken into account the decodification of the clastogenic structure-activity relationship for the selection of the structural alerts of maximal clastogenicity described by Yordi *et al.* (2012). The alerts correspond to previous QSAR studies, centred in flavonoids reported as pro-oxidants *in vitro*, presented in food plants(3). The selected precursors present and hydrocarbonated scaffold: C6-C3-C6. They are flavonoids from the subclasses: flavonols, flavanones and isoflavones. In figure 1 it is shown the prediction using TOPS-MODE approach and applied methodology.

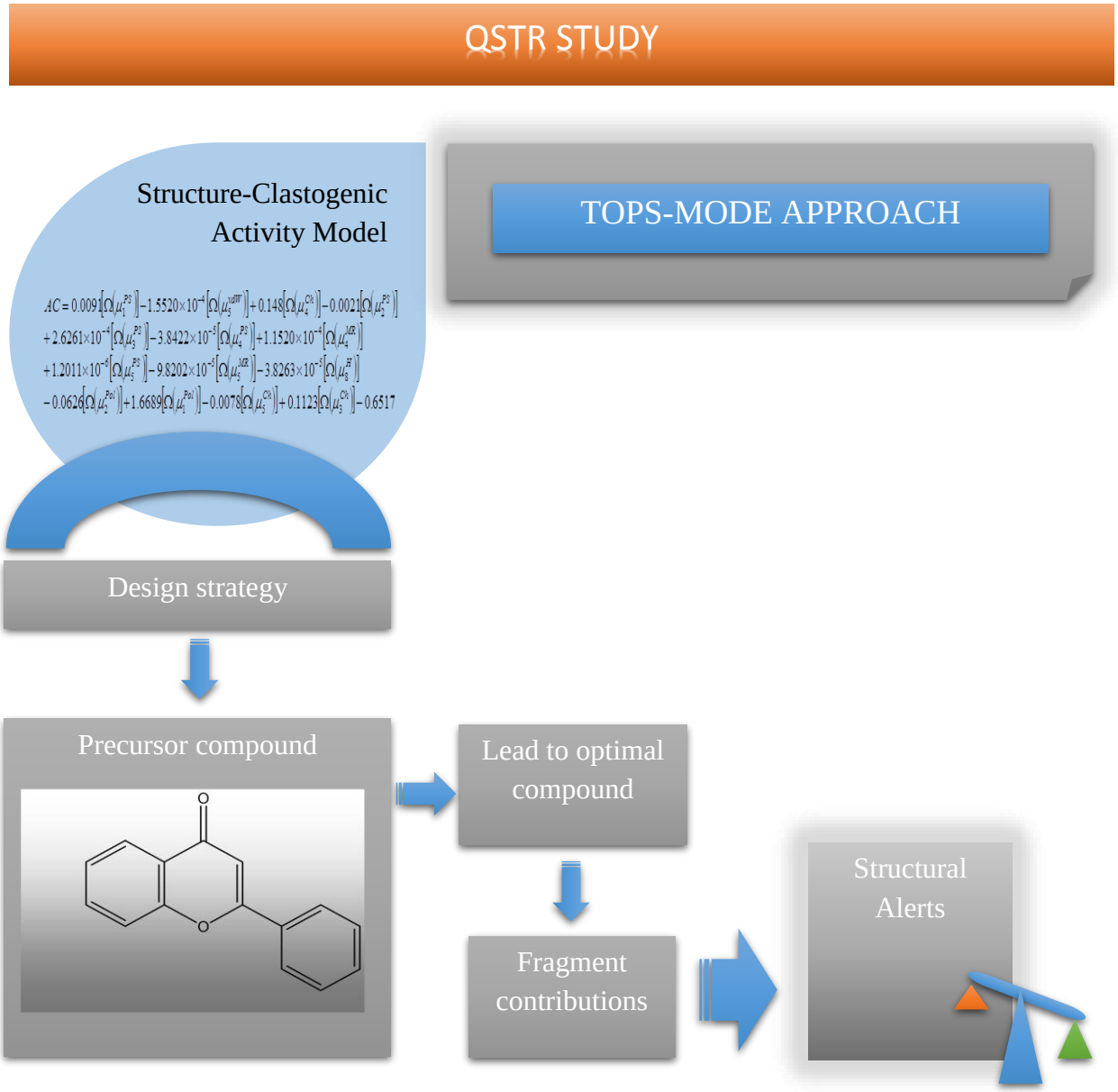

Fig. 1. Scheme of the applied methodology.

RESULTS AND DISCUSSION

In Figure 2 are represented the chemical criteria used for the design of lead and optimal compounds. The design strategy was based on: i) generate transformations into precursors centred in the molecular formation, until the inclusion of a furan ring; ii) submit the lead compounds to a methylation process. In Table 1 it is shown the dataset and structure

compounds used. The prediction and fragment contributions are represented in the table 2 and figure 3, respectively.

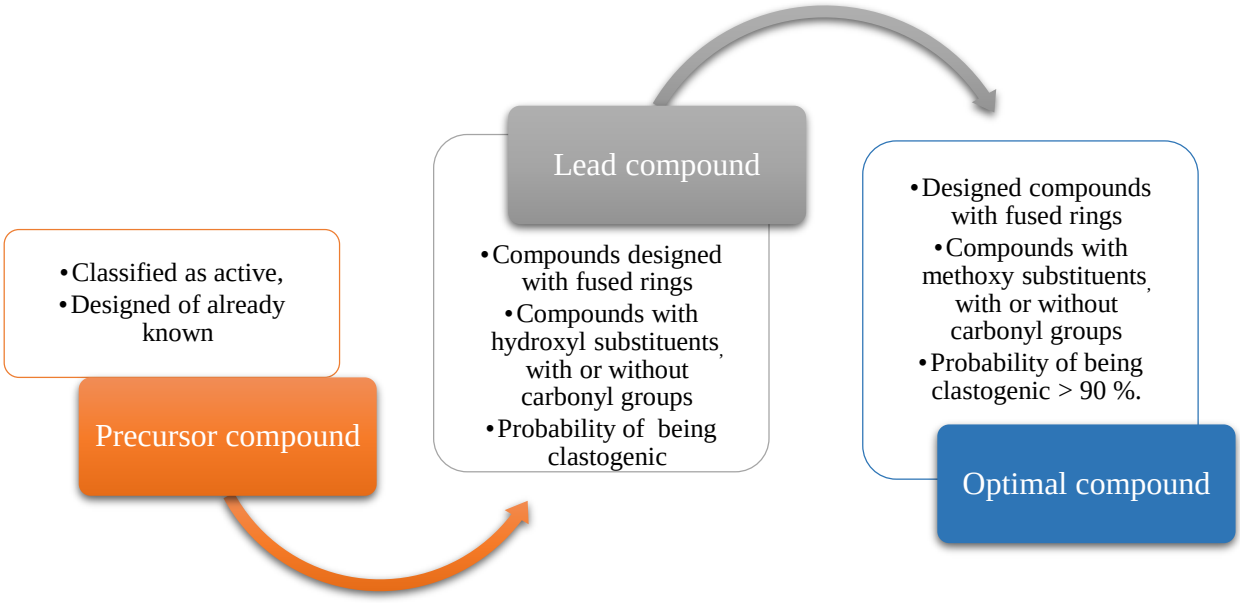

Fig. 2. Selection criteria and characteristics of which level of designed compound (precursor compound, lead compound or optimal compound).

Table 1. Structure of the compounds present in the dataset.

Design Group	Subclass	Precursor	3	5	7	2'	3'	4'	6'
I	Flavonol	Designed (FOL 3)*	OH	OH	OH	OH	H	OH	OH
	Flavanon	Designed (FAN 3)*	OH H	OH	OH	OH	H	OH	OH
II	Flavonol	Datiscetin**	OH	OH	OH	OH	H	H	H
		Morin**	OH	OH	OH	OH	H	OH	H
III	Isoflavone	Designed (iFON 5)	OH	OH	OH	OH	H	OH	OH
IV	Flavanon	Designed (FAN 6)*	OH H	OH	OH	OH	OH	OH	H

Table 2. *In silico* clastogenic activity prediction of the design compounds.

Precursor	% Prob[a]	Lead	% Prob	Methoxyl lead	% Prob
FOL 3	77.8	FOL Lead	86.0	FOL Lead Me*	99.9
FAN 3	80.4	FAN Lead	92.3	FAN Lead Me*	99.9
Datiscetin	56.1	FOL Lead 2	68.8	FOL Lead 2 Me	96.0
Morin	66.5	FOL Lead 3	77.5	FOL Lead 3 Me*	99.2
iFON 5	75.0	iFON Lead	78.7	iFON Lead Me*	99.8
FAN 6	83.7	FAN Lead 2	93.6	FAN Lead 2 Me*	99.9

[a] from (3), *Optimal compounds.

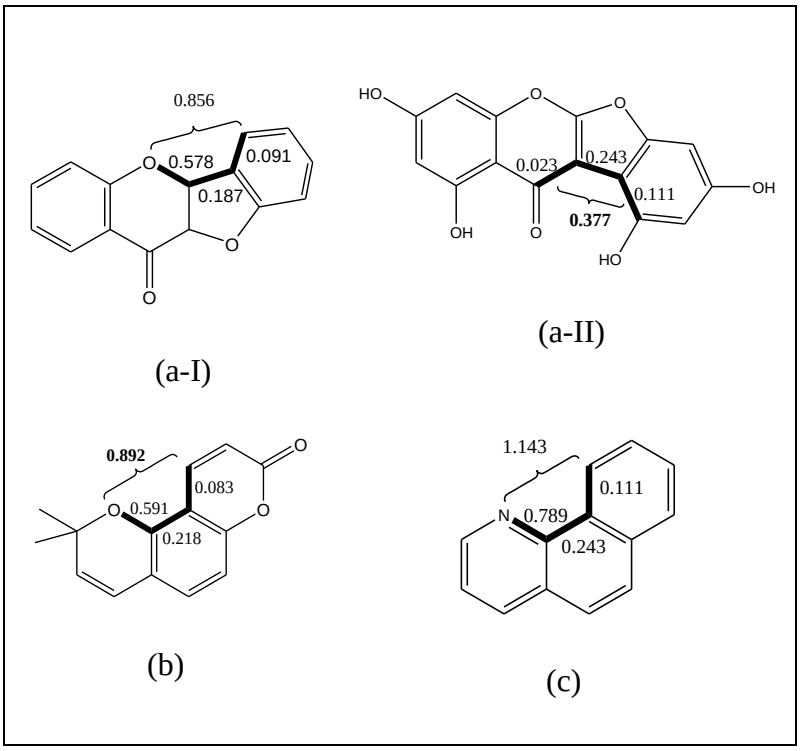

Fig. 3. Example fragment positive contributions of bay region of (A) tetracyclic fused ring system designed, a-I (0.856), a-II (0.377) compared as (B) Benzo(h)quinoline (BHQ) (0.892), Saeki et al. (2003) Estrada et al. (2006) and (C) Pyranocoumarins (angular type) (1.143) (4).

CONCLUSIONS

The phenybenzolpyran skeleton of flavonoids has been a precursor of a series of structural alerts for maximum clastogenicity. This toxicological alert could be of interest in making decisions involving an assessment of the risk/benefit of molecular entities. An *in silico* design strategy is based on structural alerts to the clastogenicity that may have reported pro-oxidant molecules presented in this article. Transformation of hydroxyl to methoxy groups in the same positions, are an active element of great importance. This should be in conjunction with the formation of a fourth ring that provides the formation of a bay region, area of influence to the activity. This topological-statistical model can be used in predicting clastogenic and non-clastogenic substances, and the design can be used to characterize new chemical entities. This theoretical study also allows the identification of local fragments that contribute to the activity. Methoxy groups proved to be the functional elements that mostly influence the achievement of the optimal results. It can also be a benchmark of importance in the design of compounds targeting functional foods or dietary supplements.

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