Chemical Structure-Activity Relationship Visualization Using Structure-Activity Maps

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Abstract

This study shows an effective way to explore and visualize the structure-activity relationships (SARs) of flavonoids with antioxidant activity using structure- activity maps (SAMs). SAMs are graphical maps plotting molecular descriptors such as NAB or MSI against their biological activities. NAB (number of non-hydrogen atoms and bonds in a molecule) or MSI (molecular similarity index) is used to quantify the chemical structures. SAMs provide a very efficient method for representing and visualizing SAR information in a biochemical database. SAMs also provide a simple and effective way for ordering and grouping compounds. SAMs were examined for compounds grouped according to NAB to determine important activity trends utilizing structural orderings. SAMs were used to systematically identify the effects of chemical modification on the activities of compounds and to determine the site and type of modifications for improved activity.

1. Introduction

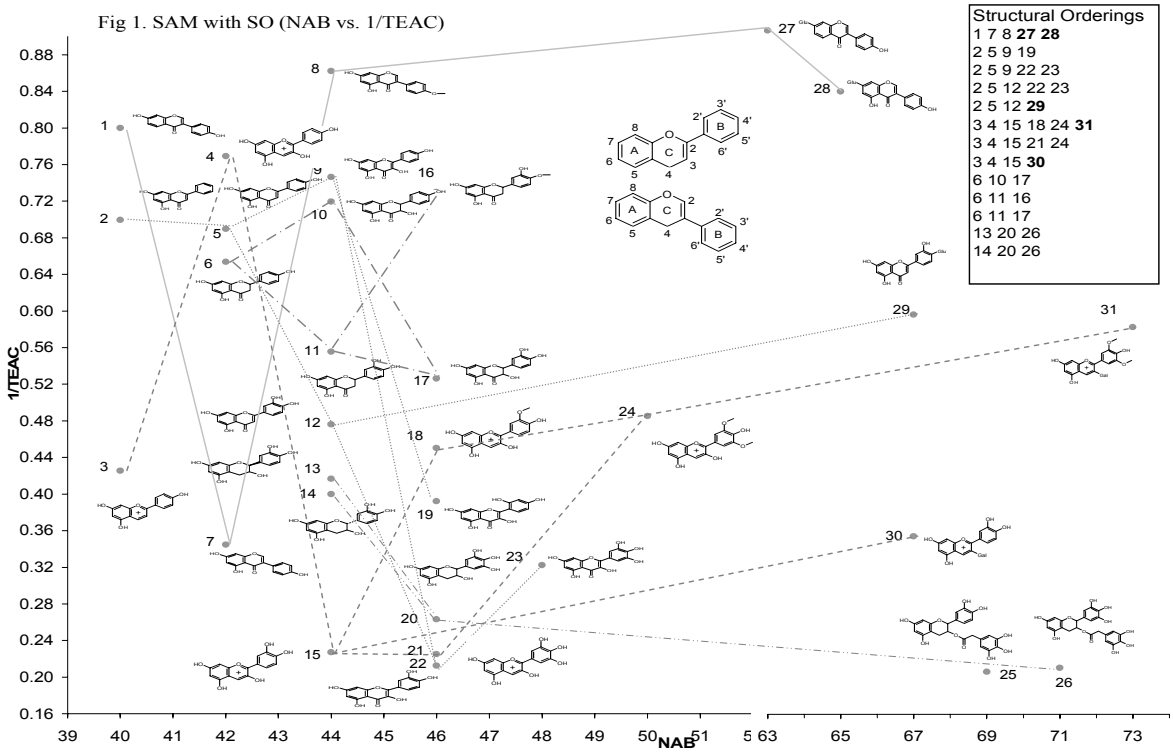
A primary focus of medicinal chemistry is to study the structures of biologically active materials and to relate these structures to their physical, chemical, and biological properties. In this paper, we describe an effective way to explore and visualize chemical structure-activity relationships of flavonoids with antioxidant activity using structure-activity maps (SAMs) and structural orderings (SOs).[1-2]

2. Methods

Biological Data. A database of antioxidant activities of flavonoids and isoflavonoids was compiled. 1/TEAC (Trolox equivalent antioxidant capacity) was used as the biological antioxidant activity measurement. [3-5]

Molecular Descriptors (NAB, MaCS, MSI, TD). NAB, a simple descriptor to quantify the chemical structure, is an integer value that denotes the number of non-hydrogen atoms and bonds in a molecule. NAB classifies compounds into topological isomer groups (topoisomers). MaCS(X,Y) (maximum common substructure) is defined as a substructure of molecules X and Y such that no other common substructure of X and Y has a greater value of NAB. MSI(X,Y) (molecular similarity index) describes the quantitative measure of the degree of similarity between the molecules X and Y. TD(X,Y), the topological distance between molecules X and Y, is defined as the dissimilarity between molecules. [1-2] A computer program TOPSIM[6] was used to calculate these descriptors.

Structure-activity maps (SAMs). SAMs are graphical representations plotting molecular descriptors such as NAB or MSI against their biological activities. SAMs generated for this study use NAB as structural quantitation and 1/TEAC for the antioxidant activity measurement. SAMs provide a very efficient way for representing and visualizing the structure-activity relationship information in a biochemical database. SAMs are examined for compounds grouped according to NAB. SAMs provide an effective way for comparing and contrasting the grouped topological isomers, and explore important trends in activity and sites of modification through structural orderings (SOs). A structural ordering is a set of compounds, L, if every triplet of the structures in L is collinear. Three compounds (X, Y, Z) are called collinear if the compound Y lies between the compounds X and Z such that: TD (X, Z) = TD (X, Y) + TD (Y, Z).



3. Results and Conclusions

Figure 1 describes a SAM (NAB-1/TEAC) of 31 flavonoids and isoflavonoids with antioxidant activity. These compounds were ordered and grouped according to NAB values. Thirteen structural orderings are indicated with lines. Based on the observation from the SOs in the SAM, we can easily identify the most active compounds are Compounds 7, 15, 19, 20, 21, 22 and 26. From the SO group {1,7,8,27,28}, we observed that the addition of a hydroxyl group at 5-position of A ring is vital to the antioxidant activity. Comparing the compounds in the SO group {2,5,12,22,23}, we found the important role of the hydroxyl group at 3-position in C ring of a flavonoid. The SO groups {3,4,25,18,24,31}, {3,4,15,21,24} and {3,4,15,30} showed the improve antioxidant activity for a flavonoid with the hydroxyl group at 3'-position in B ring.

In summary, using SAMs we can easily identify the important chemical structural features of flavonoids with antioxidant activity. SAMs with structural orderings can be used to systematically identify the effects of chemical modification on the activities of compounds and to determine the site and type of modification for improved activity.

References

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