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# A Recalculation of Quantitative Structure Chromatographic Retention Time Relationships on Natural Phenols and Sterols Found in Olive Oil

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**Abstract**

A new approach to predict the chromatographic retention times for a group of natural phenols and sterols on olive oil is presented. A QSPR treatment from a initial set of *ca.* 450 molecular descriptors allows us to obtain the following empirical functions: a) a model relating the retention index of natural phenols in the olive oil with five molecular descriptors; b) two models which permit to calculate the retention index on two diferent columns (SE-54 and SE-52) for natural sterols (trimethyl-silyl ethers) from the olive oil with four quantum-chemical descriptors. In all cases, the correlations coefficients of the empirical functions are higher than 0.99, and the mean errors range between 0.01 and 0.37%. The new models found with the descriptors generated with the HYPERCHEM 4.0, AMPAC 6.7 and CODESSA 2.3 programs are the preferable for predictions because of their highest R value and lowest error percentage if compared with previously reported QSRR models.

**Keywords**. Olive Oil, Phenols, Sterols, Quantitative structure-activity relationships, Quantitative structure-retention time relationships, CODESSA.

**Abbreviations and notations**
CODESSA, comprehensive descriptors for structural and statistical analysis
GC, gas chromatography
HPLC, high-performance liquid chromatography
QSPR, quantitative structure property relationships
QSRR, quantitative structure-retention relationships
RT, retention time

## INTRODUCTION

Vegetable oils are mainly constituted by triacyl glycerols (95-98%) and complex mixtures of minor compounds (2-5%) of a wide range of chemical nature. The main groups of minor constituents present in vegetable oil are: fatty alcohols, wax esters, hydrocarbons, tocopherols and tocotrienols, phenolic compounds, volatiles, pigments, minor glyceridic compounds, phospholipids and triterpenic acids.

In the same species, content and composition of these components can vary due to agronomic and climatic conditions, fruit or seed quality, oil extraction system and refining procedures. Finally, during storage of the oil, the hydrolysis, sterification and oxidation also

originate changes in the minor constituents. Accordingly, the determination of the minor constituents is used for the analytical assessment of the quality, origin, extraction method, refining procedure and possible adulteration of the vegetable oils [1]. This is, however, a difficult task because these groups contain numerous species with a wide range of polarities, concentrations and chemical structures.

Phenolic compounds are a group of polar components in the olive oil, which contain one or more aromatic hydroxylated rings. Some of the most representative phenolic compounds in virgin olive oil include phenyl acids, phenyl alcohols, flavonoids, secoiridoids and lignans [2-5]. However, some other peaks in the HPLC chromatograms of phenolic compounds remain unidentified. These polyphenols enhance the resistence to autooxidation of the oil [6] and contribute to its pungent and bitter taste [7]. Both ortho- and nonorthodiphenols of olive oil have been shown to exert, *in vitro*, potent biological activities [8].

Sterols, which comprise a major portion of the unsaponifiable matter, are found in almost all fats and oils and they are also characteristic of the genuineness of vegetable oils. Sterol and alcohol profiles are used to characterize virgin olive oils and especially to detect the adulteration of olive oil with hazelnut oil [9]. Recently, it has also been proposed that these profiles could be used to classify virgin olive oils according to their fruit variety [10-11]. Four types of sterols may be found in olive oil: 4-desmethylsterols, 4-methylsterols, 4,4-dimethylsterols and triterpene dialcohols [12]. The standard method proposed by the EU legislation [13] for the determination of sterols, which also is the most frequently used, is based on the isolation of the unsaponifiable fraction, the sterols are transformed into trimethylsilyl ethers and are analyzed by capillary column GC.

The methodology of relating chemical structure with chromatographic retention parameters is known as QSRR [14] and has two main goals, the prediction of retention coefficients and the explanation of the chromatographic mechanisms [15]. In previous works, we studied the relationship between the chromatographic retention times of a group of phenols [16] and sterols [17] found in olive oil with an initial set of 62 molecular descriptors obtained by means of a program made by one of the authors. In order to improve the reported results, in the present paper three commercially available programs have been used, HYPERCHEM 4.0 [18], AMPAC 6.7 [19] and CODESSA 2.3 [20] using a set of more than 450 descriptors. The results obtained show a better correlation and a lower number of descriptors related to retention times in chromatographic column when compared with the previously reported ones.

# MATERIALS AND METHODS

Experimental liquid chromatographic RT of the 16 natural phenols and the experimental gas chromatographic retention time of the trimethylsilyl ethers of the sterols from the olive oil and the corresponding experimental details used in this work have been taken from bibliography [13, 21, 22]. In Table 1, the used phenolic compounds together with the experimental and calculated RT values are given. In the same way, the studied sterols together with the experimental and calculated RT values for their trimethylsilyl ethers in two different chromatographic columns (SE 54 and SE 52) are listed in Table 2.

The procedure used in the present study comprised two fundamental stages: (i) molecular descriptors generation and (ii) statistical analysis.

**Table 1.** Values of experimental and calculated retention times (min) for the studied phenolic compounds from the proposed model.

| Compound | RT(exp) | RT(calc) | Δ(%)[a] |
|---|---|---|---|
| Caffeic acid | 14,47 | 15,16 | -4,58 |
| Ferulic acid | 23,15 | 23,70 | -2,33 |
| Gallic acid | 4,20 | 4,65 | -9,65 |
| p-Cumaric acid | 19,50 | 19,95 | -2,24 |
| p-Hydroxyphenylacetic acid | 11,00 | 10,95 | 0,43 |
| Protocatechic acid | 7,30 | 6,93 | 5,32 |
| Sinapic acid | 27,02 | 26,47 | 2,08 |
| Syringic acid | 15,00 | 14,76 | 1,62 |
| Vanillic acid | 13,70 | 14,22 | -3,64 |
| Veratric acid | 22,05 | 22,04 | 0,03 |
| Salicylic acid | 18,25 | 17,68 | 3,22 |
| p-Hydroxybenzoic acid | 9,88 | 10,02 | -1,39 |
| p-Hydroxybenzaldehyde | 12,25 | 12,16 | 0,72 |
| 4-Hydroxybenzylalcohol | 5,80 | 5,57 | 4,15 |
| Vanillin | 15,42 | 14,49 | 6,42 |
| Syringaldehyde | 16,35 | 16,58 | -1,39 |

[(a)] $\Delta(\%)=[(RT_{exp}-RT_{calc})/RT_{calc}]x100$

**Table 2.** Values of experimental and calculated retention times (min) for the sterol-trimethylsilylethers from the proposed models.

| Compound | SE54 column | | | SE52 colum | | |
|---|---|---|---|---|---|---|
| | RT(exp) | RT(calc) | Δ(%)[a] | RT(exp) | RT(calc) | Δ(%)[a] |
| Cholesterol, Δ-5-cholesten-3β-ol | 0,67 | 0,68 | -1,73 | 0,63 | 0,65 | -2,42 |
| Cholestanol, 5α-cholestan-3β-ol | 0,68 | 0,69 | -0,96 | 0,64 | 0,65 | -1,64 |
| Brassicasterol, (24S)-24-methyl-Δ-5, 22-cholesten-3β-ol | 0,73 | 0,73 | -0,11 | 0,71 | 0,70 | 1,44 |
| 24-methylene-cholesterol, 24-methylene Δ-5, 24-cholesten-3β-ol | 0,82 | 0,80 | 2,90 | 0,80 | 0,77 | 3,33 |
| Campesterol, (24R)-24-methyl-Δ-5-cholesten-3β-ol | 0,83 | 0,84 | -0,62 | 0,81 | 0,82 | -0,84 |
| Campestanol, (24R)-24-methyl-cholestan-3β-ol | 0,85 | 0,85 | -0,51 | 0,82 | 0,84 | -2,09 |
| Stigmasterol, (24R)-24-methyl-Δ-5, 22-cholestadien-3β-ol | 0,88 | 0,91 | -3,26 | 0,87 | 0,90 | -3,60 |
| Δ-7-campesterol, (24R)-24-methyl-Δ-7-cholestern-3β-ol | 0,93 | 0,90 | 3,40 | 0,92 | 0,89 | 3,81 |
| Δ-5, 23-stigmastadienol, (24R, S)-24-ethyl-Δ-5, 23-cholestadien-3β-ol | 0,95 | 0,95 | -0,27 | 0,95 | 0,94 | 0,56 |
| Chlerosterol, (24S)-24-ethyl-Δ-5, 25-cholestadien-3β-ol | 0,96 | 1,00 | -3,65 | 0,96 | 1,00 | -3,56 |
| β-sitosterol, (24R)-24-ethyl-Δ-5 cholesten-3β-ol | 1,00 | 0,98 | 1,97 | 1,00 | 0,98 | 2,08 |
| Sitostanol, (24R)-24-ethyl-cholestan-3β-ol | 1,02 | 1,01 | 1,27 | 1,02 | 1,01 | 1,15 |
| Δ-5-avenasterol, (24Z)-24-ethylidene-5-cholesten-3β-ol | 1,03 | 1,02 | 1,47 | 1,03 | 1,01 | 1,69 |
| Δ5, 24-stigmastadienol, (24R, S)-24-ethyl-Δ-5, 24-cholestadien-3β-ol | 1,08 | 1,06 | 2,24 | 1,08 | 1,05 | 2,67 |
| Δ-7-stigmastenol, (24R, S)-24-ethyl-Δ-7-cholesten-3β-ol | 1,12 | 1,14 | -1,90 | 1,12 | 1,14 | -1,97 |
| Δ-7-avenasterol, (24Z)-24-ethylidene-Δ-7-cholesten-3β-ol | 1,16 | 1,17 | -0,46 | 1,16 | 1,17 | -0,93 |

[(a)] $\Delta(\%)=[(RT_{exp}-RT_{calc})/RT_{calc}]x100$

## Molecular Descriptors Generation

The molecular structures of the phenols and sterol-trimethylsilylethers were drawn and optimized using the HYPERCHEM 4.0 and the generated geometries were refined using the semiempirical AM1 parameterization [23] together with the eigenvector following geometry optimization procedure inside the AMPAC 6.7 software until a rms of 0.001 $kcal\cdot Å^{-1}\cdot mol^{-1}$. The available data-exportation from HYPERCHEM 4.0 (*.HIN files) and AMPAC 6.7 (*.OUT files) to CODESSA 2.3 allowed us to account for a large set (>450) of molecular descriptors (constitutional,

topological, geometrical, electrostatic, quantum-chemical and thermodynamic) for each of the compounds in this study. The QSPR analysis was carried out using the CODESSA 2.3 program [24,25], including the constitutional, topological [26-28], electrostatic [29-32], geometrical [33,34] and quantum-chemical molecular descriptors [35,36].

## Statistical analysis

An initial set of 458 molecular descriptors was used to explain the behaviour of the dependent variable liquid or gas chromatographic RT. At first, those descriptors whose distribution is not normal according to asymmetry and excess were rejected. Then, in the resulting set (*ca.* 36 descriptors), a stepwise regression was carried out to select the best independent variables subset, following as criterion the minimum value for the Mallow´s C*p*. For this purpose, the multicolinearity effect inside each set was eliminated. From this, we considered the following independent variables, whose definitions are given in Table 3.

**Table 3.** Molecular descriptors employed for the proposed QSRR models.

| Molecular descriptor | References |
|---|---|
| <u>Geometrical</u> | [29,30] |
| YZ shadow / YZ rectangle | |
| <u>Topological</u> | [22-24] |
| Bonding information content (order 0) | |
| <u>Electrostatic</u> | [25-28] |
| HASA-1/TMSA | |
| <u>Quantum-Chemical</u> | [31,32] |
| Max 1-electron react. Index for a C atom | |
| Min atomic orbital electronic population | |
| RPCG Relative positive charge (QMPOS/QTPLUS) | |
| Min Total interaction for a C-C bond | |
| ESP-RNCG Relative negative charge (QMNEG/QTMINUS) | |
| ESP-FHASA Fractional HASA (HASA/TMSA) | |

Then, with the 9R program in the BMDP statistical package, the best subset of regression was selected. If the set of descriptors is studied simultaneously and the variables that show

multicolinearity are removed, the best regression equation of the phenolic compounds is given in Table 4. Data and statistics for the sterolic derivatives in each column are given in Table 5.

**Table 4.** Regression model for the phenolics compounds (see fig. 1 and 4).

| Variable | Regression coefficient | Standard error | Contrib. to R-SQ |
|---|---|---|---|
| HASA-1/TMSA | -61.200 | 3.564 | 60.282 |
| Bonding information content (order 0) | 0.837 | 0.137 | 39.830 |
| Min atomic orbital electronic population | -143.73 | 9.407 | 18.136 |
| Max-1 electron react. Index for a C atom | -550.694 | 38.333 | 37.641 |
| YZ Shadow / YZ Rectangle | 32.550 | 5.627 | 6.666 |
| Intercept | 112.945 | 9.589 | |

n=16; Mallows= $C_P$=6.00; mean absolute error=0.378; R=0.9972; $R^2$=0.9945; F(5,10)=366.51.

For explanation of variables see Table 3.

**Table 5.** Regression models for the sterol-derived compounds (see fig. 2, 3 and 5).

| Variable | RT(SE54 column)[a] | | | RT(SE52 column)[b] | | |
|---|---|---|---|---|---|---|
| | Regression coefficient | Std. error | Contrib. to R-SQ | Regression coefficient | Std. error | Contrib. to R-SQ |
| RPCG Relative positive charge (QMPOS/QTPLUS) | -34.028 | 1.957 | 58.168 | -37.774 | 2.199 | 60.227 |
| Min total interaction for a C-C bond | -1.371 | 0.131 | 38.001 | -1.472 | 0.148 | 36.714 |
| ESP-RNCG Relative negative charge (QMNEG/QTMINUS) | 8.452 | 2.152 | 7.783 | 9.220 | 2.417 | 8.072 |
| ESP-FHASA Fractional HASA (HASA/TMSA) | 44.313 | 5.914 | 26.593 | 45.713 | 6.644 | 24.774 |
| Intercept | 25.906 | 1.785 | | 28.022 | 2.005 | |

[a]n=16; Mallows' $C_P$=5.00; mean absolute error=0.0155; R=0.998; $R^2$=0.998; F(4,11)=158.40.

[b]n=16; Mallows' $C_P$=5.00; mean absolute error=0.0190; R=0.9908; $R^2$=0.981; F(4,11)=148.66

For explanation of variables see Table 3.

## RESULTS AND DISCUSSION

In previous reports [16,17], we described the regression models to explain the behaviour of the dependent variable RT using a initial set of 62 molecular descriptors. These models were significant and showed $R^2$ values between 0.96 and 0.99, with 5 or 7 independent variables. In the

present report, using 458 molecular descriptors generated by the software HYPERCHEM 4.0 and AMPAC 6.7 and the CODESSA 2.3, three new models have been found to explain the behaviour of the dependent variable RT. In the three model all coefficients are significant above the 99.9% level.

Plots of experimental vs. expected values, for each regression equation are depicted in figures 1 to 3. Residuals vs. experimental RT values, have been ploted in figure 4 and 5. The residuals are normally distributed and independent, there is no autocorrelation between them. In the same way, the Mahalanobis distance shows that extremely high values do not exist at a confidence level of 95%. If we consider leverage values about the influence of a sample value, there are no sample values greater than three times of an average data point for RT in the three studied models.

The largest studentized residuals in absolute value among cases is 2.085 for the phenolic compounds model regression equation. In the trimethylsilyl ethers models regression equation, these values are 2.681 and 2.610 for SE 54 and SE 52 models, respectively.

## CONCLUSIONS

The use of the software HYPERCHEM 4.0 and AMPAC 6.7, which generate more than 400 molecular descriptors, has allowed to establish new numerical models to relate the chromatographic RT for a number of polyphenols and sterols found in the olive oil. The new models need for their right use a lower number of variables and, in addition, give higher accuracy levels than models previously reported by us, using a dramatically smaller set of molecular descriptors (*ca.* 60). However, the lack of reproducibility of the chromatographic columns may be the major problem in applying the results reported here; obviously, these models are valid only with the same experimental conditions in which the RT values, from which the statistical models have been calculated, have been measured. Finally, the prediction of RT for new related compounds will also depend on the degree of similarity between the query molecules and those in the data set.

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### Supplementary Material

The following tables and files are available: (a) Tables with compounds and values of doubly normal distributed descriptors used in the regresssion analysis for each one (POLIFE.XLS and STEROL.XLS); in these tables, the compounds are named as POLIFE?? and STEROL??, where ?? are the number of each compound in the Tables 1 or 2 in the manuscript. (b) Tables with the values of the finally used descriptors for each of the studied phenols and sterol-trimethylsilyl ethers and the corresponding correlation matrices (IEJMD_UJA_SUP.DOC). (c) Files with molecular (POLIFE??.HIN and STEROL??.HIN) and quantum-chemistry data (POLIFE??.OUT and STEROL??.OUT) for the parametrized compounds.

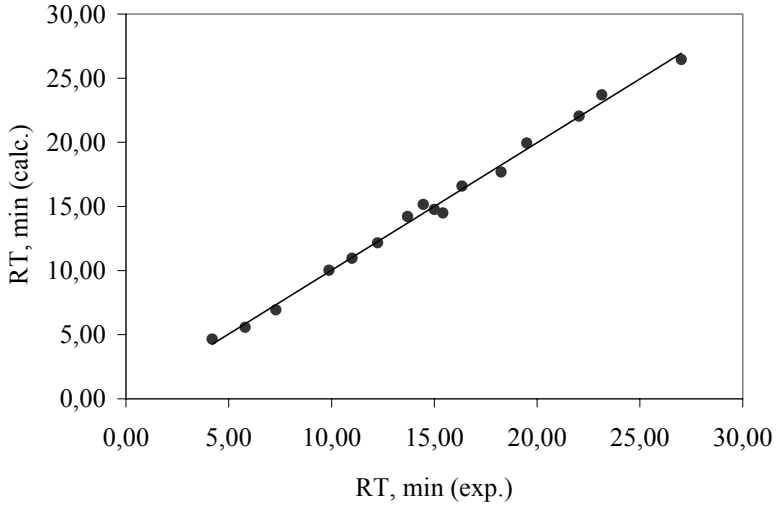


Figure 1. Plot of experimental vs. expected values of RT for natural phenols model (see Table 1).

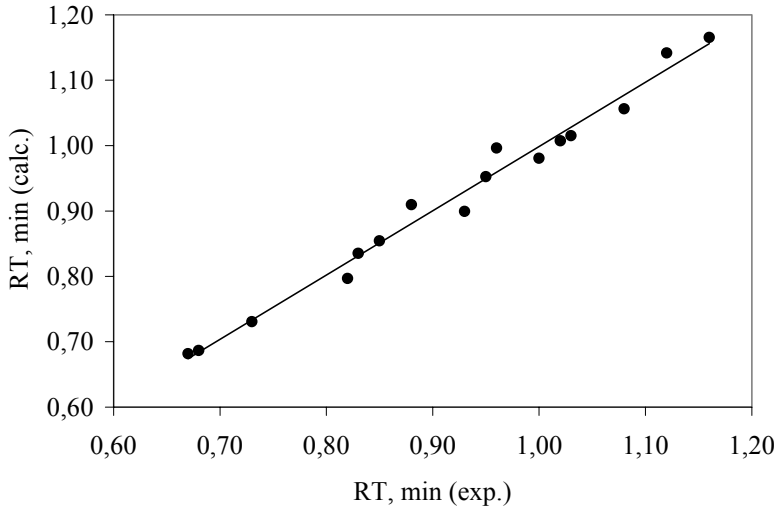


Figure 2. Plot of experimental vs. expected values of RT(SE54) for natural sterols (trimethylsilylethers) model (see Table 2).

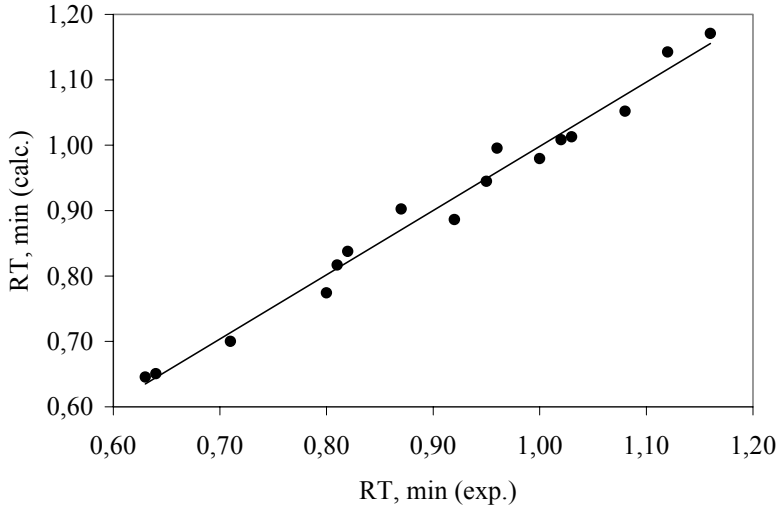


Figure 3. Plot of experimental vs. expected values of RT(SE52) for natural sterols (trimethylsilylethers) model (see Table 2).

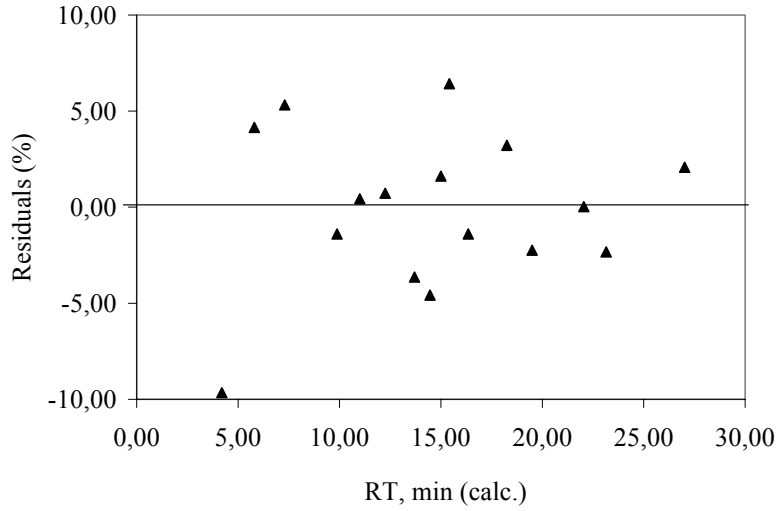


Figure 4. Plot of residuals vs. experimental values of RT for the natural phenols proposed model.

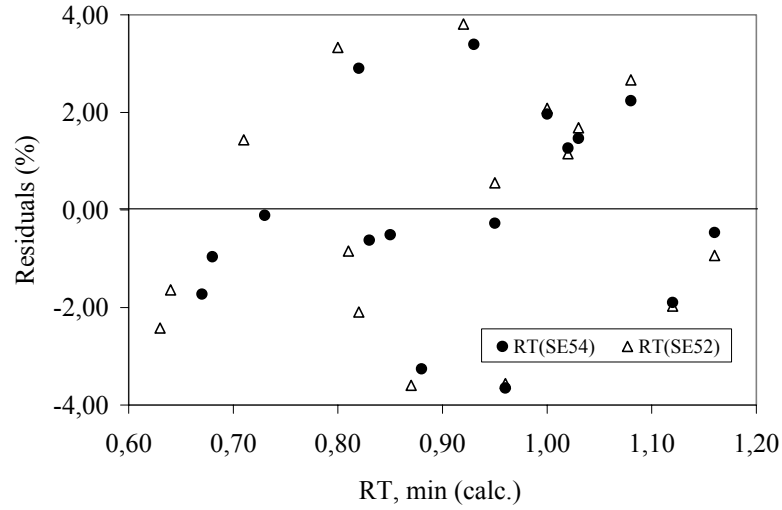


Figure 5. Plot of residuals vs. experimental values of RT for the natural sterols (trimethylsilylethers) proposed models.

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