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# A simple and reliable QSPR model for prediction of chromatography retention indices of volatile organic compounds in peppers†

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Worldwide, various types of pepper are used in food as an additive due to their unique pungency, aroma, taste, and color. This spice is valued for its pungency contributed by the alkaloid piperine and aroma attributed to volatile essential oils. The essential oils are composed of volatile organic compounds (VOCs) in different concentrations and ratios. In chromatography, the identification of compounds is done by comparing obtained peaks with a reference standard. However, there are cases where reference standards are either unavailable or the chemical information of VOCs is not documented in reference libraries. To overcome these limitations, theoretical methodologies are applied to estimate the retention indices (RIs) of new VOCs. The aim of the present work is to develop a reliable QSPR model for the RIs of 273 identified VOCs of different types of pepper. Experimental retention indices were measured using comprehensive two-dimensional gas chromatography coupled to quadrupole mass spectrometry (GC × GC/qMS) using a coupled BPX5 and BP20 column system. The inbuilt Monte Carlo algorithm of CORAL software is used to generate QSPR models using the hybrid optimal descriptor extracted from a combination of SMILES and HFG (hydrogen-filled graph). The whole dataset of 273 VOCs is used to make ten splits, each of which is further divided into four sets: active training, passive training, calibration, and validation. The balance of correlation method with four target functions *i.e.* TF0 (WIIC = WCII = 0), TF1 (WIIC = 0.5 & WCII = 0), TF2 (WIIC = 0 & WCII = 0.3) and TF3 (WIIC = 0.5 & WCII = 0.3) is used. The results of the statistical parameters of each target function are compared with each other. The simultaneous application of the index of ideality of correlation (IIC) and correlation intensity index (CII) improves the predictive potential of the model. The best model is judged on the basis of the numerical value of  $R^2$  of the validation set. The statistical result of the best model for the validation set of split 6 computed with TF3 (WIIC = 0.5 & WCII = 0.3) is  $R^2 = 0.9308$ , CCC = 0.9588, IIC = 0.7704, CII = 0.9549,  $Q^2 = 0.9281$  and RMSE = 0.544. The promoters of increase/decrease for RI are also extracted using the best model (split 6). Moreover, the proposed model was used for an external validation set.

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## 1. Introduction

Peppers are among the most ancient spices known to man and are extensively harvested all over the entire globe. Pepper fruits contain a high quantity of constituents advantageous to human health, such as antioxidants, minerals, vitamins (mainly A, C, and E), polyphenols and carotene. All types of pepper are eaten fresh or dried and are used in the food industry as additives (coloring and flavoring agents) because of their unique

pungency, color, flavor, and aroma.<sup>1–3</sup> The piperine alkaloid (as the (*E,E*)-isomer), which is responsible for pungency, and the volatile essential oils that provide flavour and aroma are primarily accountable for the quality of peppers as rated by humans.<sup>4,5</sup> However, other compounds have also been identified in peppers, such as terpenes, flavonoids, steroids, unsaturated fatty acids, and polysaccharides. Furthermore, the essential oil derived from the distillation of pepper contains various taste and flavouring components: *e.g.* oxygenated monoterpenoid compounds, monoterpene hydrocarbons and oxygenated compounds, sesquiterpene hydrocarbons and oxygenated compounds, oxygenated sesquiterpenes, and phenolic compounds. These compounds are designated as volatile organic compounds (VOCs).<sup>4,6,7</sup> The essential oils of peppers can also be employed as antioxidant, antiseptic, antibacterial, antimycotic, anti-epileptic, anti-inflammatory, diuretic, antipyretic, anthelmintic, and carminative agents.<sup>8,9</sup>

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Numerous reports have been published for the identification and characterization of diverse VOCs of peppers.<sup>10–13</sup> Gas chromatography (GC) and gas chromatography-mass spectrometry (GC-MS) techniques are generally employed for the quantitative determination of volatile compounds in peppers.<sup>14,15</sup> Other techniques such as proton-transfer-reaction time-of-flight mass spectrometry (PTR-ToF-MS), two-dimensional gas chromatography with flame ionization detection (GC × GC-FID), quadrupole mass spectrometry (GC × GC-qMS) and time-of-flight mass spectrometry (GC × GC/TOFMS) are also applied to identify VOCs.<sup>5,10,16</sup>

In chromatography, the chemical structure of compounds is identified by comparing obtained peaks with a reference standard. However, in some cases, reference standards may be unavailable or the chemical information about VOCs may not be registered in reference libraries. To reduce these limitations, theoretical techniques for estimating the retention index (RI) of new VOCs are employed. Hence, the quantitative structure–property/activity relationship (QSPR/QSAR) is employed to predict the retention index (RI).<sup>17</sup> QSPR/QSAR is a significant theoretical technique used to establish mathematical models that predict the properties/activities or endpoints of compounds, which have been newly designed or are undeveloped.<sup>18,19</sup>

A literature survey revealed that CORAL (CORrelation And Logic software available at <http://www.insilico.eu/coral>) software can be implemented for the development of predictive QSPR/QSAR models. CORAL is freeware software designed to calculate one-variable QSPR/QSAR models between an endpoint and descriptors using the Monte Carlo algorithm. In this software, the optimal descriptor of correlation weight (DCW) is calculated using the SMILES (Simplified Molecular-Input Line-Entry System) notation of the molecular structure.<sup>20–22</sup> According to a literature report, the index of ideality of correlation (IIC) and correlation intensity index (CII) are applied as new criteria for judging the predictive potential of the QSPR model. It is often mentioned in the literature that the numerical value of the coefficient of determination ( $R^2$ ) for the validation and calibration set is improved by the IIC, whereas the CII improves the numerical value of the coefficient of determination ( $R^2$ ) for all four sets: *i.e.* active training, passive training, calibration and validation.<sup>23–31</sup>

The objective of this study is to construct a predictive QSPR model using the Monte Carlo technique of the CORAL software for the retention index property of 273 VOCs recognized in peppers. Ten random splits are made and each split is divided into four subsets. The IIC and CII statistical parameters are employed to predict a better model. The balance of correlation method with four target functions, *i.e.* TF0 ( $W_{\text{IIC}} = W_{\text{CII}} = 0$ ), TF1 ( $W_{\text{IIC}} = 0.5$  &  $W_{\text{CII}} = 0$ ), TF2 ( $W_{\text{IIC}} = 0$  &  $W_{\text{CII}} = 0.3$ ) and TF3 ( $W_{\text{IIC}} = 0.5$  &  $W_{\text{CII}} = 0.3$ ), is used to examine the robustness and accuracy of the constructed QSPR model.

## 2. Data and method

### 2.1. Data

The retention index (RI) data for 273 VOCs identified in 13 peppers were obtained from the literature by Rojas *et al.*<sup>32</sup>

Polydimethylsiloxane/divinylbenzene (PDMS/DVB) fiber was used for extraction of the VOCs. The peaks on the two-dimensional GC with a quadrupole mass spectrometric detection (GC × GC-qMS) chromatogram were identified by the column set comprising a non-polar molecule (5% phenyl polysilphenylenesiloxane) as the primary column and a polar molecule (polyethylene glycol) in the second column. Experimental retention indices were obtained using the van den Dool and Kratz equation and Adams' retention indices. Data preprocessing details were reported in the literature by Rojas *et al.*<sup>32</sup> The range of values for the retention index (RI) went from 930 to 1790. The IDs of the compound, SMILES codes, and corresponding experimental and predicted RI are provided in Table S1.† Ten splits were prepared and each split was further split randomly into four subsets: *i.e.* an active training set ( $\approx 26\%$ ), a passive training set ( $\approx 20\%$ ), a calibration set ( $\approx 20\%$ ), and a validation set ( $\approx 34\%$ ). The role of each set was fixed and is well explained in the literature.<sup>33–36</sup>

### 2.2. Method

The methodology for obtaining the results from the CORAL software can be summarized as a group by the following steps:

- (1) Data preparation involves converting the structure to SMILES and preparing the Total set file.
- (2) The process of data splitting in CORAL software is carried out using random splitting. This can be done using the classical scheme or balance of correlation. In the balance of correlation the data is divided into four sets: active training, passive training, calibration, and validation sets. However, if the amount of data is small, the classical scheme is used and the data set includes training, calibration, and validation sets.
- (3) The selection of descriptors is based on either SMILES or a graph, or a combination of both. The descriptors are chosen accordingly.
- (4) The target function selection involves computing correlation weights using the Monte Carlo method and maximizing one of the target functions: namely TF0, TF1, TF2, or TF3. The formulas of these target functions are described in the corresponding section.
- (5) Model building consists of two phases. In Phase 1, the preferable threshold and number of epochs are searched for using Monte Carlo optimization based on statistical results from the calibration set. In Phase II, the preferable model is constructed after optimization of the threshold and number of epochs.
- (6) External validation is performed on the test sets after model building.
- (7) Model interpretation is carried out in this step.
- (8) New molecules can be designed based on the model interpretation.

### 2.3. Hybrid optimal descriptor

As previously mentioned in the preceding section, in CORAL software three types of optimal descriptors can be calculated: *i.e.*, SMILES-based, graph-based, and hybrid descriptors

(obtained by combining SMILES and graph-based). The graph-based descriptor can be computed by using a hydrogen-filled graph (HFG), a hydrogen-suppressed molecular graph (HSG) or a graph of atomic orbitals (GAO).<sup>37–39</sup> A literature survey shows that QSPR models designed using the hybrid optimal descriptor provide robust models with higher statistical quality.<sup>40</sup> Here, the QSPR model for the prediction of RI is designed by utilizing a hybrid optimal descriptor based on the correlation weights of SMILES attributes and vertex degrees in the hydrogen-filled graph (HFG).

The hybrid optimal descriptor of the correlation weights (DCW) is computed using the following equation:

$$\text{DHybridCW}(T^*, N^*) = \text{DCW}_{\text{SMILES}}(T^*, N^*) + \text{DCW}_{\text{HFG}}(T^*, N^*) \quad (1)$$

The DCW of HFG and SMILES are calculated *via* mathematical eqn (2) and (3).

$$\text{DCW}_{\text{SMILES}}(T^*, N^*) = \sum \text{CW}(S_k) + \sum \text{CW}(SS_k) + \sum \text{CW}(SSS_k) + \text{CW}(\text{BOND}) + \text{CW}(\text{MFCs}) \quad (2)$$

$$\text{DCW}_{\text{HFG}}(T^*, N^*) = \sum \text{CW}(\text{EC0}_k) + \sum \text{CW}(\text{EC1}_k) + \sum \text{CW}(\text{pt2}_k) + \sum \text{CW}(\text{VS2}_k) + \sum \text{CW}(\text{nn}_k) + \sum \text{CW}(\text{C5}) + \sum \text{CW}(\text{C6}) \quad (3)$$

In eqn (2), the structural attributes  $S_k$ ,  $SS_k$ , and  $SSS_k$  are single SMILES symbols (*e.g.*, Cl or S), two SMILES symbols and a combination of three SMILES symbols, respectively. The BOND code demonstrates the existence or absence of double (=), triple (#), or stereochemical bonds (@ or @@). Here, the molecular feature contributions (MFCs) are the total number of oxygen atoms (O), the number of double bonds (=), and the number of triple bonds (#). Therefore, in eqn (3), the attributes EC0 and EC1 are the number of neighbors of a vertex degree and Morgan's connectivity of first order;  $\text{pt2}_k$  is the number of paths of length 2; VS2 is the valence shells of radius 2 in the HFG; the nn symbol implies nearest neighbors; C5 and C6 are descriptors that represent the five- and six-membered rings in the molecular structure, respectively.  $T$  is the threshold to separate SMILES attributes into noise or active. The active SMILES are applied to construct the model. The noise SMILES are not involved in constructing the model.  $T^*$  and  $N^*$  are the optimum threshold and number of epochs of the Monte Carlo optimization method.  $T^*$  and  $N^*$  provide the maximum statistical quality for the calibration set. The numerical values for CWs are acquired from the Monte Carlo optimization and the optimal descriptor is computed with the optimal CWs. Then the calculated CWs are employed to design a predictive model of the RI according to the following equation:

$$\text{RI} = C_0 + C_1 \times \text{DCW}(T^*, N^*) \quad (4)$$

#### 2.4. The Monte Carlo optimization

Here to design robust QSPR models, four different kinds of target functions, TF0, TF1, TF2 and TF3, are used. Then, the

outcomes of the statistical results are compared with each other.

The mathematical equations for each target function can be demonstrated follows:

$$\text{TF}_0 = R_{\text{ATRn}} + R_{\text{PTRn}} - |R_{\text{ATRn}} - R_{\text{PTRn}}| \times \text{dr}_{\text{weight}} \quad (5)$$

$$\text{TF}_1 = \text{TF}_0 + \text{IIC}_{\text{CAL}} \times \text{weight for IIC} (\text{IIC}_{\text{weight}}) \quad (6)$$

$$\text{TF}_2 = \text{TF}_0 + \text{CII}_{\text{CAL}} \times \text{weight for CII} (\text{CII}_{\text{weight}}) \quad (7)$$

$$\text{TF}_3 = \text{TF}_0 + \text{IIC}_{\text{CAL}} \times \text{IIC}_{\text{weight}} + \text{CII}_{\text{CAL}} \times \text{CII}_{\text{weight}} \quad (8)$$

Here,  $R_{\text{ATRn}}$  and  $R_{\text{PTRn}}$  are the correlation coefficients between the observed and predicted RI for the active training and passive training sets, respectively. The numerical values for weights of index of ideality of correlation (IIC) and correlation intensity index (CII) are usually kept constant and here the numerical values of  $\text{dr}_{\text{weight}}$ ,  $\text{IIC}_{\text{weight}}$  and  $\text{CII}_{\text{weight}}$  were 0.1, 0.5 and 0.3, respectively.  $\text{IIC}_{\text{CAL}}$  and  $\text{CII}_{\text{CAL}}$  are computed for the calibration set using eqn (9).

$$\text{IIC}_{\text{CAL}} = R_{\text{CAL}} \times \frac{\min(-\text{MAE}_{\text{CAL}}, +\text{MAE}_{\text{CAL}})}{\max(-\text{MAE}_{\text{CAL}}, +\text{MAE}_{\text{CAL}})} \quad (9)$$

$R_{\text{CAL}}$  is the correlation coefficient between experimental values and calculated values of RI for the calibration set. The negative and positive mean absolute errors are indicated by  $-\text{MAE}$  and  $+\text{MAE}$ , which are computed as follows:

$$-\text{MAE}_{\text{CAL}} = -\frac{1}{N} \sum_{y=1}^{N^-} |\Delta_k| \quad (10)$$

$$\Delta_k < 0, \quad N^- \text{ is the number of } \Delta_k < 0$$

$$+\text{MAE}_{\text{CAL}} = +\frac{1}{N} \sum_{y=1}^{N^+} |\Delta_k| \quad (11)$$

$$\Delta_k \geq 0, \quad N^+ \text{ is the number of } \Delta_k \geq 0$$

$$\Delta_k = \text{observed}_k - \text{calculated}_k \quad (12)$$

The ' $k$ ' is the index (1, 2, ...,  $N$ ) and the  $\text{observed}_k$  and  $\text{calculated}_k$  are related to the endpoint.

$$\text{CII}_{\text{CAL}} = 1 - \sum \text{Protest}_k$$

$$\text{Protest}_k = \begin{cases} R_k^2 - R^2, & \text{if } R_k^2 - R^2 > 0 \\ 0 & \text{otherwise} \end{cases} \quad (13)$$

$R^2$  is the correlation coefficient for a set that contains  $n$  substances.  $R_k^2$  is the correlation coefficient for  $n - 1$  substances of a set after removing the  $k$ th substance. Hence, if  $(R_k^2 - R^2)$  is greater than zero, the  $k$ th substance is an "opponent" for the correlation between experimental and predicted values of the set. A small sum of "protests" means a more "intensive" correlation.

## 2.5. Applicability domain

In QSPR/QSAR models, the applicability domain (AD) is used to specify whether the designed model interpolates (correct predictions) or extrapolates (incorrect predictions). In the CORAL software, the distribution of SMILES attributes in the active training, passive training, and calibration sets is used to calculate the AD. Therefore, the AD for the model acquired as a result of Monte Carlo optimization varies depending on the distribution of the datasets in the training and calibration sets. In the QSPR/QSAR models designed by CORAL software, the statistical defects of SMILES are employed to define the AD. The “statistical defect,”  $d(A)$  is computed according to the following mathematical equation:

$$\text{Defect}_{A_k} = \frac{|P_{\text{ATR}}(A_k) - P_{\text{PTR}}(A_k)|}{N_{\text{ATR}}(A_k) + N_{\text{PTR}}(A_k)} + \frac{|P_{\text{ATR}}(A_k) - P_{\text{CAL}}(A_k)|}{N_{\text{ATR}}(A_k) + N_{\text{CAL}}(A_k)} + \frac{|P_{\text{PTR}}(A_k) - P_{\text{CAL}}(A_k)|}{N_{\text{PTR}}(A_k) + N_{\text{CAL}}(A_k)} \quad \text{If } A_k = 0 \quad (14)$$

$$\text{Defect}_{A_k} \quad \text{If } A_k = 0$$

$P_{\text{ATR}(A_k)}$ ,  $P_{\text{PTR}(A_k)}$  and  $P_{\text{CAL}(A_k)}$  are the probability of attributes in the active training set, passive training set, and calibration set, respectively;  $N_{\text{ATR}(A_k)}$ ,  $N_{\text{PTR}(A_k)}$ , and  $N_{\text{CAL}(A_k)}$  are frequencies of attributes in the active training, passive training and calibration sets, respectively.

The SMILES-statistical defect ( $D$ ) can be calculated as the sum of statistical defects of all attributes:

$$\text{Defect}_{\text{Molecule}} = \sum_{k=1}^{\text{NA}} \text{Defect}_{A_k} \quad (15)$$

NA is the number of active SMILES attributes for the given compounds.

In CORAL, a SMILES is an outlier if:

$$\text{Defect}_{\text{molecule}} > 2 \times \overline{\text{Defect}_{\text{ATR}}} \quad (16)$$

$\overline{\text{Defect}_{\text{ATR}}}$   $D$  is an average of statistical defects for the dataset of the active training set.

## 3. Results and discussion

### 3.1. QSPR modelling for RI

Based on ten initial QSPR models, three compounds (compounds 49, 205, and 265) were identified as outliers. Therefore, these compounds were excluded from the data set before further processing. Herein, to achieve consistent statistical performance, ten different QSPR models were built for each type of target function (TF<sub>0</sub>, TF<sub>1</sub>, TF<sub>2</sub>, and TF<sub>3</sub>) employing hybrid optimal descriptors. The summary of statistical results for all QSPR models is summarized in Table S2.† The numerical value of  $R^2$  calculated with TF<sub>3</sub> for the validation set of all splits is higher than the  $R^2$  calculated with the other target functions (TF<sub>0</sub>, TF<sub>1</sub> and TF<sub>2</sub>); thus the TF<sub>3</sub> calculated with eqn (8) was

selected as the best target function. A comparison of the determination coefficients of the validation set for all splits computed *via* four target functions is represented in Fig. 1.

The QSPR models for the ten splits formulated with TF<sub>3</sub> for prediction of the RI of the VOCs are given below:

Split 1

$$\text{RI} = 73.8025(\pm 7.0844) + 24.5924(\pm 0.1499) \times \text{DCW}(1,15) \quad (17)$$

Split 2

$$\text{RI} = 121.5622(\pm 6.8196) + 26.4093(\pm 0.1507) \times \text{DCW}(1,15) \quad (18)$$

Split 3

$$\text{RI} = 315.0484(\pm 6.5146) + 20.0374(\pm 0.1270) \times \text{DCW}(1,15) \quad (19)$$

Split 4

$$\text{RI} = 133.8434(\pm 9.0780) + 16.6644(\pm 0.1272) \times \text{DCW}(1,15) \quad (20)$$

Split 5

$$\text{RI} = 120.8001(\pm 5.6911) + 22.7349(\pm 0.1122) \times \text{DCW}(1,15) \quad (21)$$

Split 6

$$\text{RI} = 265.7739(\pm 6.3219) + 23.9520(\pm 0.1477) \times \text{DCW}(1,15) \quad (22)$$

Split 7

$$\text{RI} = 107.8894(\pm 7.4311) + 23.2382(\pm 0.1417) \times \text{DCW}(1,15) \quad (23)$$

Split 8

$$\text{RI} = 40.7742(\pm 6.0698) + 25.9964(\pm 0.1255) \times \text{DCW}(1,20) \quad (24)$$

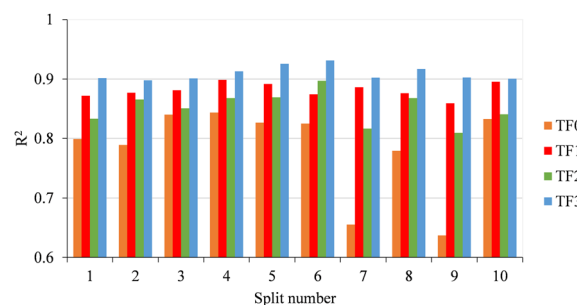


Fig. 1 Comparison of determination coefficients computed with TF<sub>0</sub>, TF<sub>1</sub>, TF<sub>2</sub> and TF<sub>3</sub> of all ten splits.



## Split 9

$$RI = 25.2594(\pm 6.5441) + 25.5860(\pm 0.1587) \times DCW(1,15) \quad (25)$$

## Split 10

$$RI = 110.5639(\pm 6.0444) + 21.8635(\pm 0.1077) \times DCW(1,15) \quad (26)$$

### 3.2. Model validation

In this study, the RI of the VOCs was predicted using QSPR models based on Monte Carlo optimization employing four target functions  $TF_0$  ( $W_{IIC} = W_{CII} = 0$ ),  $TF_1$  ( $W_{IIC} = 0.5$  &  $W_{CII} = 0$ ),  $TF_2$  ( $W_{IIC} = 0$  &  $W_{CII} = 0.3$ ) and  $TF_3$  ( $W_{IIC} = 0.5$  &  $W_{CII} = 0.3$ ), and each target function was checked with ten random splits. The balance of correlation method was applied to generate QSPR models. The statistical results presented in Table S2† indicate that all designed QSPR models are within the standard range in terms of statistical criteria and have robust predictability. It can also be seen from Table S2† that simultaneously adding the weight IIC and CII to the target function increases its ability to predict RI as well as improving the statistical results. The numerical value of  $R^2$  for the validation set of split 6 ( $R^2 = 0.9308$ , eqn (22)) was found to be higher than the numerical value of  $R^2$  for the other models created with  $TF_3$ , so it was identified as the best model. Fig. 2 displays the plot between observed and calculated data of the RI for the QSPR models computed with  $TF_3$ . A good correlation between observed RI and calculated RI, as well as a uniform distribution of RI for active training, passive training, calibration and validation sets can be seen in Fig. 2. Finally, the validation metrics for each model are calculated using three strategies: (i) internal validation or cross-validation with the training set data; (ii) external validation with the test set data; and (iii) Y-scrambling or data randomization. If  $CR^2_p > 0.5$  for the created model in a Y-randomization test, the model is free of chance correlation. For all constructed QSPR models the numerical value of  $CR^2_p$  was more than 0.5, indicating the robustness of the developed models.

### 3.3. Interpretation of the QSPR model

In the QSPR model developed by the CORAL software, mechanistic interpretation is defined as the description of structural attributes acquired from SMILES or hydrogen-filled graphs which are responsible for the increase or decrease of an endpoint. If the numerical value of correlation weights of these structural attributes is negative in three or more runs of the optimization, then these structural features are defined as a promoter of endpoint decrease. On the other hand, if the numerical value of correlation weights of these structural attributes is positive in three or more runs of the optimization, then these structural features are defined as a promoter of endpoint increase. However the structural attribute is undefined if the correlation weight of the structural descriptors has both positive and negative numerical values.

The promoters for endpoint RI increase or decrease were computed from the best model (split 6) and are displayed in Table 1. Morgan extended connectivity of zero-order for hydrogen atom as 1 (ec0-h...1...), Morgan extended connectivity of first-order for hydrogen atom as 4 (ec1-h...4...), Morgan extended connectivity of first-order for carbon atom as 7 (ec1-c...7...), Morgan extended connectivity of zero-order for carbon atom as 3 (ec0-c...3...), Morgan extended connectivity of first-order for carbon atom as 4 (ec1-c...10...), the number of paths of length 2 which started from a hydrogen atom is equal to 3 (pt2-h...3...), the number of paths of length 2 which started from a carbon atom is equal to 5 (pt2-c...5...), the number of paths of length 2 which started from a hydrogen atom is equal to 2 (pt2-h...2...), two sp<sup>3</sup> hybridized carbon joined by branching (c...c...), the presence of two consecutive aliphatic carbons (c...c...) *etc.* were some significant promoters of endpoint increase. The nearest neighbours code for carbon equal to 413 (nnc-c...413), the nearest neighbours code for carbon equal to 440 (nnc-c...440), a combination of the carbon atom, oxygen and branching (c...o...), and 28 as a sum of vertex degrees which take place at a topological distance of 2 relatively to carbon vertex (*vs.* 2-c...28) *etc.* were some significant promoters of endpoint decrease.

### 3.4. A comparison of various QSPR models based on RI

A survey of the literature indicates that Rojas *et al.* (2019) reported only one QSPR model for retention index: the QSPR model for 273 VOCs of pepper.<sup>32</sup> The molecular descriptors and molecular fingerprints were calculated using Dragon and PaDEL-Descriptor software. To create balanced subsets, the dataset was divided into training, validation, and test sets of molecules using the Balanced Subsets Method (BSM). Afterward, the Wootton, Sergeant, and Phan-Tan-Luu (WSP) unsupervised variable reduction method was employed to reduce the presence of multicollinearity, redundancy, and noise among the initial pool of 4336 molecular descriptors and fingerprints. By implementing this method, a reduced pool consisting of 1664 descriptors was subjected to supervised selection through replacement method (RM) variable subset selection in order to establish a four-descriptor model. The efficacy of the model was assessed by evaluating the coefficient of determination and the root-mean-square deviation in fitting. Specifically, the values obtained for  $R^2$  and RMSD for training were 0.879 and 72.1, respectively. Similarly,  $R^2$  and RMSD were found to be 0.832 and 91.7 in the validation set, while  $R^2$  and RMSD were 0.915 and 55.4 in the test set. The minimal discrepancies observed among these parameters across the three sets indicate the stability and predictability of the QSPR model.

Table 2 displays a comparison of the statistical results of the present QSPR model with the reported QSPR model. The previously reported model was implemented with only one split, but in the present QSPR models, 10 splits were used to design 40 QSRR models employing four target functions ( $TF_0$ ,  $TF_1$ ,  $TF_2$  and  $TF_3$ ). Two significant criteria, the index of ideality

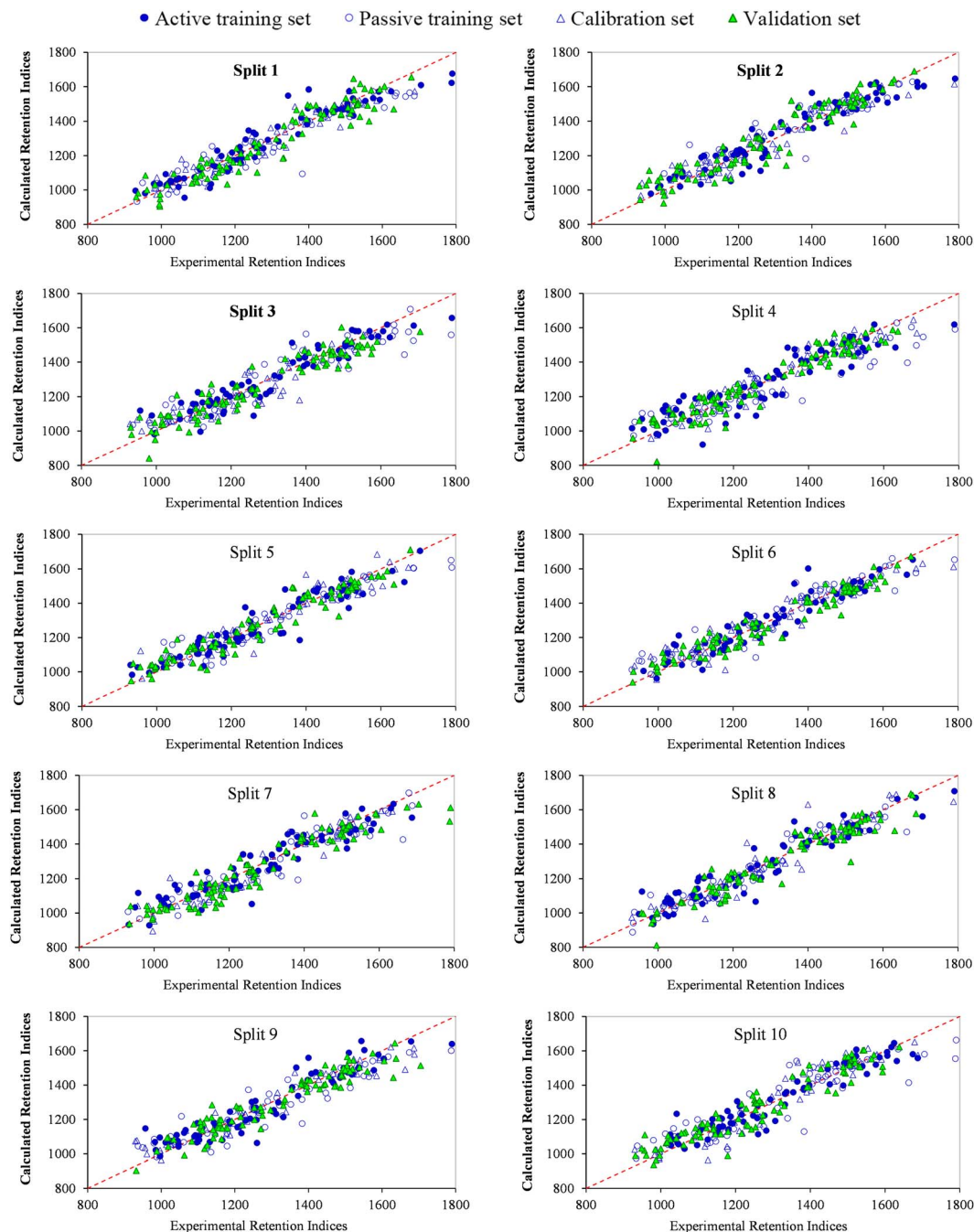


Fig. 2 Experimental versus predicted retention indices of split 1 to 10 for VOCs detected in peppers by the Monte Carlo method based on target function TF3.

correlation (IIC) and correlation intensity index (CII), are also addressed in this work, which were not studied in earlier work. In the present QSPR models, only one descriptor, DCW, was used to construct the QSPR models but in the previously reported model, four descriptors were applied. The numerical value of the determination coefficient ( $R_{\text{val}}^2$ ) of the QSPR model generated with TF3 for split 6 is 0.9308, which is much better

than the value for the reported model. Thus, the presented QSPR models are more robust and predictable.

### 3.5. External validation of the proposed models

An external dataset of 115 VOCs reported by Rojas *et al.*<sup>32</sup> was used to predict the RI of molecules outside the dataset for

Table 1 The list of the promoters RI increase and decrease from splits 6 calculated with TF3

No.	Structural attributes	CWs Probe 1	CWs Probe 2	CWs Probe 3	NSs	NSc	NSv	Defect [SAk]	Description
<b>The promoters of RI increase</b>									
1	EC0-H...1...	0.0509	0.16064	0.34295	68	58	54	0	Morgan extended connectivity of zero-order for hydrogen atom as 1
2	EC1-H...4...	0.18025	0.22099	0.18401	68	57	54	0	Morgan extended connectivity of first-order for hydrogen atom as 4
3	PT2-H...3...	0.16527	0.2584	0.3257	68	57	54	0	The number of paths of length 2 which started from a hydrogen atom is equal to 3
4	C...C.....	0.44726	0.01345	0.30905	65	55	50	0.0003	The presence of two consecutive aliphatic carbons
5	EC1-C...7...	0.31326	0.46929	0.21017	63	56	50	0	Morgan extended connectivity of first-order for carbon atom as 7
6	VS2-H...6...	0.10836	0.05545	0.26739	63	56	50	0	6 as a sum of vertex degrees which take place at a topological distance of 2 relatively to hydrogen vertex
7	EC0-C...3...	0.56731	0.20537	0.33853	62	47	46	0.0006	Morgan extended connectivity of zero-order for carbon atom as 3
8	EC1-C...10	0.22378	0.25831	0.04221	61	52	47	0.0002	Morgan extended connectivity of first-order for carbon atom as 4
9	NNC-C...422	0.20503	0.01758	0.05181	60	53	48	0.0001	The nearest neighbours codes for carbon equal to 422
10	C...(...C...	0.29947	0.13954	0.33177	59	49	49	0.0004	Two sp3 hybridized carbon joined by branching
11	=.....	0.15273	0.45098	0.39027	56	43	44	0.0001	Presence of double covalent bond
12	1.....	0.26393	0.42999	0.64276	53	46	42	0	Presence of at least one ring
13	NNC-C...321	0.44352	0.72343	0.10398	53	39	38	0.0008	The nearest neighbours codes for carbon equal to 321
14	PT2-H...2...	0.06983	0.57052	0.40344	53	42	38	0.0008	The number of paths of length 2 which started from a hydrogen atom is equal to 2
15	PT2-C...5...	0.21029	0.22211	0.19676	52	42	39	0.0005	The number of paths of length 2 which started from a carbon atom is equal to 5
<b>The promoters of RI decrease</b>									
1	NNC-C...413	-0.08801	-0.07644	-0.57505	67	57	52	0.0002	The nearest neighbours codes for carbon equal to 413
2	C...1...(...	-0.30101	-0.02505	-0.28091	26	27	20	0.0003	Combination of aliphatic carbon, one ring and branching
3	NNC-C...440	-0.3105	-0.03567	-0.80092	26	27	20	0.0003	The nearest neighbours codes for carbon equal to 440
4	C...O...(...	-0.39833	-1.30355	-0.7525	8	1	4	0.0036	Combination of the carbon atom, oxygen and branching
5	O...(...(...	-0.15072	-1.42791	-2.29626	5	1	5	0.0019	Oxygen atom with two branching
6	VS2-C...28	-0.05713	-0.5657	-0.85747	5	8	4	0.0001	28 as a sum of vertex degrees which take place at a topological distance of 2 relatively to carbon vertex
7	3...C...1...	-1.16603	-0.21466	-2.69557	1	6	1	0.0019	

Table 2 Comparison of present QSPR models with the previously reported study

No.	Set	n	Descriptor generator	Regression method	R <sup>2</sup> train	RMSD	IIC	CII	Ref.
1	Training	92	Dragon and PaDEL	MLR	0.879	72.1	—	—	32
	Validation	91			0.832	91.7	—	—	
	Test	90			0.915	55.4	—	—	
2	ActivTRN	68	CORAL package	LR	0.885	62.7	0.658	0.928	Present work
	PassTRN	58			0.900	70.8	0.677	0.943	
	Calib	54			0.904	51.6	0.951	0.944	
	Valid	90			0.931	54.4	0.770	0.955	

modeling. The RI properties of these compounds were predicted by ten models based on TF3 and average values were compared with external predictions by Rojas *et al.* Table 3 shows the average predicted RI of ten models, the prediction by Rojas *et al.*<sup>32</sup> for the BPX5 and BP20 column coupled system, and experimental retention indices from the literature.

Fig. 3 shows a plot of the RI of the external set predicted by CORAL software *versus* the RI predicted by Rojas *et al.*<sup>32</sup> There is good agreement between the external predictions by the two methods.

**Table 3** External set of common VOCs detected in peppers: name, CAS registry number, predicted retention indices based on the average prediction of models 1 to 10, and prediction by Rojas *et al.*<sup>32</sup> for the BPX5 and BP20 column coupled system, experimental retention indices from the literature, and source

No.	Name	CAS number	R <sub>i</sub> <sup>predicted</sup> (this study)		R <sub>i</sub> <sup>predicted</sup> (Rojas <i>et al.</i> )		Experimental R <sub>i</sub> <sup>literature</sup>									
			number	study	number	<i>et al.</i>	DB-5 column	HP-5MS stationary phase	HP-5 column	DB-Wax stationary phase	BPX5 column	RTX-Wax stationary phase	HP-20M column	DB-5MS stationary phase	BP20 column	Ref.
1	Myrcenol	543-39-5	1164.719	1159.6	NA	NA <sup>a</sup>	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
2	( <i>E,F</i> )- $\alpha$ -Farnesene	502-61-4	1483.631	1496.2	1508	NA	1508	NA	NA	NA	NA	NA	NA	NA	NA	15, 42 and 43
3	$\alpha$ -Farnesene	487-11-6	1501.785	1565	1540	NA	1540	NA	NA	NA	NA	NA	NA	NA	NA	41 and 44
	Elemicin				1554	NA	1554	NA	NA	NA	NA	NA	NA	NA	NA	43 and 45
					1556	NA	1556	NA	NA	NA	NA	NA	NA	NA	NA	
4	Myristicin	607-91-0	1391.435	1546.5	1520	NA	1520	NA	NA	NA	NA	NA	NA	NA	NA	43
5	Apiole	523-80-8	1541.468	1721.7	1679	NA	1679	NA	NA	NA	NA	NA	NA	NA	NA	43
					1680	NA	1680	NA	NA	NA	NA	NA	NA	NA	NA	
					1685	NA	1685	NA	NA	NA	NA	NA	NA	NA	NA	
6	Dillapiole	484-31-1	1565.236	1709.1	1622	1622	1622	1622	NA	NA	NA	NA	NA	NA	NA	14,43
					1644	NA	1644	NA	NA	NA	NA	NA	NA	NA	NA	
7	Eugenol acetate	93-28-7	1568.772	1577.7	1524	NA	1524	NA	NA	NA	NA	NA	NA	NA	NA	45
8	Carvone oxide	18 383-49-8	1239.442	1367.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41, 42 and 46-49
	<i>trans</i> -Carvone oxide	33 204-74-9	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
9	$\alpha$ -Bulnesene	3691-11-0	1484.066	1508.7	1493	1505	1505	1505	NA	NA	NA	NA	NA	NA	NA	41
					1503	NA	1503	NA	NA	NA	NA	NA	NA	NA	NA	
					1505	NA	1505	NA	NA	NA	NA	NA	NA	NA	NA	
10	$\delta$ -Guaiene	619-01-2	1164.505	1184.8	1192	NA	1192	NA	NA	1195	1195	1195	1941	NA	NA	42 and 43
	Dihydrocarveol				1195	NA	1195	NA	NA	NA	NA	NA	NA	NA	NA	41, 42, 44 and 46-49
	<i>p</i> -Menth-8-en-2-ol				NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	42
	<i>trans-p</i> -Menth-8-en-2-ol				NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	47-49
	Neo-dihydrocarveol	18 675-34-8	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
					NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	
11	<i>cis</i> - $\beta$ -Terpineol	138-87-4	1196.492	1181	1159	NA	1159	NA	NA	NA	NA	NA	NA	NA	NA	41
12	$\beta$ -Bisabolol	15 352-77-9	1647.933	1604.1	NA	NA	NA	1668	NA	NA	NA	2021	NA	NA	NA	41 and 42
13	$\alpha$ -Bisabolol	515-69-5	1644.237	1594.9	1683	NA	1683	NA	NA	NA	NA	NA	NA	NA	NA	14 and 44
					1701	NA	1701	NA	NA	NA	NA	NA	NA	NA	NA	
14	Squalene	111-02-4	2742.641	2726	2790	NA	2790	NA	NA	NA	NA	NA	NA	NA	NA	6
15	$\delta$ -Terpinyl acetate	93 836-50-1	1382.135	1356	1313	NA	1313	NA	NA	NA	NA	NA	NA	NA	NA	41
16	1,4-Cincole	470-67-7	1139.433	1117.1	1016	1016	1016	1016	1171	NA	NA	NA	NA	NA	NA	41
17	Cadina,1,4-dien-3-ol		1608.026	1636.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
18	<i>trans</i> -Piperitone oxide	4713-38-6	1194.878	1303.8	1258	NA	1258	NA	NA	NA	NA	NA	NA	NA	NA	50
19	3-Buten-2-ol	598-32-3	642.9435	758.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41



Table 3 (Contd.)

No.	Name	CAS number	RI <sub>predicted</sub>		Experimental RI <sub>literature</sub>										Ref.	
			(this study)	(Rojas <i>et al.</i> )	DB-5 column	HP-5MS stationary phase	HP-5 column	DB-Wax stationary phase	BPX5 column	RTX-Wax stationary phase	HP-20M column	DB-5MS stationary phase	BP20 column			
20	Vomifolol	23 526-45-6	1573.99	1735.6	NA	1796	NA	NA	3167	1814	NA	NA	NA	NA	NA	41
21	Neryl isovalerate	3915-83-1	1578.39	1593	NA	NA	NA	NA	3175	NA	NA	NA	NA	1872	NA	43
22	Retrofractamide B	54 794-74-0	2393.783	2624	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
23	Guineensine	55 038-30-7	2568.907	2783.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
24	Caryophyllene alcohol Caryophyllenol	472-97-9	1586.876	1548.9	1568	1560 1564	NA	NA	NA	NA	NA	NA	NA	NA	NA	42
25	Clovene	469-92-1	1440.777	1460	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41, 44 and 46-49
26	Piperitol	491-04-3	1170.929	1143.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	42
27	Humulene oxide II	19 888-34-7	1609.486	1589.6	1606	1607	1607	1607	1607	1607	1607	1607	1607	1607	1607	43
28	$\alpha$ -Cedrene	469-61-4	1447.516	1451.9	1409	1409	1409	1409	1409	1409	1409	1409	1409	1409	1409	43
29	Hedycaryl	21 657-90-9	1627.43	1612.5	1530	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	44
30	Germaecene D-4-ol	198 991-79-6	1594.602	1606.5	1511	1567	1574	1574	1574	1574	1574	1574	1574	1574	1574	43
31	$\alpha$ -Eudesmol	473-16-5	1592.197	1595.8	1652	NA	NA	NA	NA	NA	NA	NA	NA	2230	NA	41 and 43
32	Furanodiene	19 912-61-9	1586.736	1626.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	43
33	<i>cis-p</i> -Menth-8-en-2-ol	89-79-2	1180.423	1193.1	1145	1146	1146	1146	1146	1146	1146	1146	1146	1146	1146	47-49
34	Isopulegol	89-79-2	1200.764	1141.3	1879	1879	1879	1879	1879	1879	1879	1879	1879	1879	1879	43
35	Menthol	89-78-1	1190.85	1113.6	1173	NA	NA	NA	1626	NA	NA	NA	NA	1646	NA	41
36	<i>cis</i> -Sabinene hydrate	15 537-55-0	1144.655	975	1069	1101	1070	1070	1070	1070	1070	1070	1070	1070	1070	14 and 43
37	Cedrol	77-53-2	1583.856	1544.5	1596	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	15, 41, 42 and 46-49
38	( <i>Z</i> )-Isosafrole	17 627-76-8	1271.586	1391.8	1308	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
39	Nona-trans, <i>cis</i> -2,6-dienal	557-48-2	1102.993	1130.7	NA	NA	NA	NA	1597 1605	NA	NA	NA	NA	NA	NA	51
40	Howeveranediol	25 265-75-2	761.5132	733.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
41	Ethyl-2-hexenol	50 639-00-4	993.1246	1003.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
42	Hept- <i>trans</i> -3-en-2-one	1119-44-4	940.3034	900.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	51

Table 3 (Contd.)

No.	Name	CAS number	R <sub>i</sub> <sup>predicted</sup> (this study)	R <sub>i</sub> <sup>predicted</sup> (Rojas <i>et al.</i> )	Experimental R <sub>i</sub> <sup>literature</sup>										Ref.
					DB-5 column	HP-5MS stationary phase	HP-5 column	DB-Wax stationary phase	BPX5 column	RTX-Wax stationary phase	HP-20M column	DB-5MS stationary phase	BP20 column		
43	Nona- <i>trans</i> , <i>trans</i> -2,5-dien-4-one	61 759-51-1	1101.811	1085.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	51
44	Hex- <i>trans</i> -2-enal	6728-26-3	838.5927	850.3	854	NA	857	1201	NA	NA	1209	848	NA	NA	51
45	( <i>E</i> )-2-Hexenal	4938-52-7	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
45	1-Hepten-3-ol	4938-52-7	902.912	925.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
46	( <i>E</i> )-3-Octenol	18 185-81-4	1063.265	1043.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
47	2-Heptanone	110-43-0	900.1747	971.3	888	889	882	1160	889	NA	NA	NA	NA	NA	51
48	Non- <i>trans</i> -2-en-4-one	32 064-72-5	1115.155	1156.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	51
49	Non-1-en-4-one	61 168-10-3	1084.331	1154.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	51
50	$\alpha$ -Ethyl hexanoate	123-66-0	1021.078	1118	996	1001	997	1224	1229	1244	1270	980	1438	1465	6
51	1-Octen-3-ol	3391-86-4	990.474	1013.3	942	975	977	980	991	NA	1423	NA	NA	NA	41
52	2,4-Decadienoic acid	42 997-42-2	1235.616	1736.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
53	Piperidine	18 836-52-7	1519.16	1624.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
54	Deca- <i>trans</i> , <i>cis</i> -2,4-dienal	25 152-83-4	1189.996	1212.5	1291	NA	NA	1758	NA	NA	NA	NA	NA	NA	51
	Deca- <i>trans</i> , <i>trans</i> -2,4-dienal	2363-88-4	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	51
	Deca-2,4-dienal	25 152-84-5	—	—	1311	NA	NA	1820	1832	NA	NA	NA	NA	NA	51
55	( <i>E</i> )-2-Octenal	2363-89-5	1010.999	1023.6	NA	1060	NA	NA	NA	NA	NA	NA	NA	NA	41
56	<i>N</i> -Isobutyl-(2 <i>E</i> ,4 <i>E</i> ,12 <i>E</i> )-octadecatrienamide	943 546-17-6	2222.115	2290	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
57	<i>N</i> -Isobutyl-(2 <i>E</i> ,4 <i>E</i> ,14 <i>Z</i> )-eicosatrienamide	—	2397.239	2448.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14

Table 3 (Contd.)

No. Name	CAS number	R <sub>i</sub> <sup>predicted</sup> (this study)	R <sub>i</sub> <sup>predicted</sup> (Rojas <i>et al.</i> )	Experimental R <sub>i</sub> <sup>literature</sup>										Ref.
				DB-5 column	HP-5MS stationary phase	HP-5 column	DB-Wax stationary phase	BPX5 column	RTX-Wax stationary phase	HP-20M column	DB-5MS stationary phase	BP20 column		
58 Hexanal	66-25-1	836.3585	921.5	784	805	800	1067	NA	NA	1075	NA	NA	NA	16 and 51
				797		803	1093							
				799										
				800										
				819										
59 2-Octanol	25-339-16-6	1019.923	981.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
60 Nonane	111-84-2	964.4392	965.9	899	900	NA	NA	NA	NA	900	NA	NA	NA	41
61 ( <i>E</i> )-2-Tridecenal	7774-82-5	1448.809	1429.9	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	43
62 Tetradecane	629-59-4	1402.249	1372.2	1116	NA	NA	1399	1400	NA	1400	NA	NA	NA	14
63 <i>N</i> -Isobutyl-(2 <i>E</i> ,4 <i>E</i> )-octadecadienamide	54-794-70-6	2219.656	2266	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
64 Pentadecanal	2765-11-9	1624.416	1660.3	1513	1711	NA	NA	NA	NA	NA	NA	NA	NA	50
				1687										
				1710										
65 Hexadecane	544-76-3	1577.373	1531.4	1600	NA	NA	NA	NA	NA	1600	NA	NA	NA	14
66 Palmitic acid	57-10-3	1755.653	1811.2	1984	NA	NA	NA	NA	NA	2860	NA	NA	NA	14
Palmitic acid glyceride		–	–	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
67 Heptadecane	629-78-7	1664.935	1610.7	1700	NA	NA	NA	NA	NA	1700	NA	NA	NA	14
68 1-Octadecene	112-88-9	1759.766	1711.6	1793	NA	NA	NA	1774	NA	NA	NA	NA	NA	14
				1794										
69 Octadecane	593-45-3	1752.497	1689.9	1800	NA	NA	1805	NA	NA	1800	NA	NA	NA	14
70 Nonadecane	629-92-5	1840.059	1768.9	1900	NA	NA	NA	NA	NA	1900	NA	NA	NA	14
71 1-Eicosene	3452-07-1	1934.889	1869.5	1990	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
				1994										
72 Eicosane	112-95-8	1927.621	1847.8	2000	NA	NA	NA	NA	NA	2000	NA	NA	NA	14
73 Heneicosane	629-94-7	2015.183	1926.7	2100	NA	NA	NA	NA	NA	2100	NA	NA	NA	14
74 Docosane	629-97-0	2102.745	2005.4	2200	NA	NA	NA	NA	NA	2200	NA	NA	NA	14
75 Nonadecanol	1454-84-8	2015.34	1901.6	NA	2156	NA	NA	NA	NA	NA	NA	NA	NA	50
76 Hexanol	111-27-3	877.0338	846.4	867	NA	865	1351	NA	NA	1325	869	NA	NA	41
				884			1354							
							1360							
							1379							
							1392							
77 Amyl alcohol	71-41-0	789.4719	751.3	766	NA	766	1244	NA	NA	NA	NA	NA	NA	41
				768										
78 Benzenepropanoic acid, ethyl ester	2021-28-5	1339.896	1411.3	1390	NA	NA	1897	NA	NA	NA	NA	NA	NA	43

Table 3 (Contd.)

No. Name	CAS number	RI <sub>predicted</sub> (this study)	RI <sub>predicted</sub> (Rojas <i>et al.</i> )	Experimental RI <sub>literature</sub>										
				DB-5 column	HP-5MS stationary phase	HP-5 column	DB-Wax stationary phase	BPX5 column	RTX-Wax stationary phase	HP-20M column	DB-5MS stationary phase	BP20 column	Ref.	
79 Methyl salicylate	119-36-8	1160.501	1248.3	1190	1190	NA	NA	NA	NA	NA	NA	NA	NA	51
				1191										
				1206										
80 Guaiacol	90-05-1	1001.29	1087.9	1086	NA	NA	1872	NA	NA	NA	NA	NA	NA	41
				1091			1875							
							1883							
81 2-Methoxy-3-isobutylpyrazine	24 683-00-9	1055.625	1291	1135	NA	NA	1540	NA	NA	NA	NA	NA	NA	51
				1171										
82 Thymol	89-83-8	1189.021	1203.6	1290	1290	1308	NA	NA	NA	NA	NA	NA	NA	41 and 43
83 2-Methylnaphthalene	91-57-6	1210.977	1379.3	1281	NA	1295	NA	NA	NA	NA	NA	NA	NA	51
84 1-Methylnaphthalene	90-12-0	1163.889	1355.6	1298	NA	1312	NA	NA	NA	NA	NA	NA	NA	51
85 Piperamide C 9:1 (8E)	62 510-52-5	2232.683	2552.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
86 4,5-Dihydropiperettine	583-34-6	2105.33	2419.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
87 Dehydropiperonaline	107 584-38-3	2279.967	2579.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
88 Piperine	94-62-2	1928.943	2235.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
89 Piperanine	23 512-46-1	1932.372	2211.5	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
90 1-Cinnamoyl piperidine	5422-81-1	1597.08	1759.2	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
	1													
91 Piperolein B	30 505-89-6	2301.005	2626.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	14
92 Geranial	5392-40-5	1182.447	1151.7	1240	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
Neral	106-26-3	–	–	1235	NA	NA	1630	NA	NA	NA	1658	NA	NA	41
				1240			1690							
				1294			1695							
93 Citronella	106-23-0	1155.695	1216.9	1153	NA	NA	1425	NA	NA	NA	NA	NA	NA	41, 42 and 46–49
				1159			1485							
				1161			1488							
94 Phenylacetaldehyde	122-78-1	1046.275	1112.2	1043	NA	NA	1609	NA	NA	NA	1615	NA	NA	51
				1049			1671							
95 Furfural	98-01-1	753.1899	858.1	830	NA	NA	1474	832	NA	NA	NA	NA	NA	51
							1485							
96 Oxalic acid	144-62-7	740.7731	852.3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
97 $\alpha$ -Hydroxypropionic acid	50-21-5	699.8166	862.4	NA	NA	NA	NA	1058	NA	NA	NA	NA	NA	6
98 Howevedioic acid	110-16-7	888.9371	943.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
99 Dihydrolimonen-10-al	3269-90-7	1223.518	1236	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
100 Gluconate anion	608-59-3	1350.775	1570.7	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6

Table 3 (Contd.)

No. Name	CAS number	R <sub>i</sub> <sup>predicted</sup> (this study)	R <sub>i</sub> <sup>predicted</sup> (Rojas <i>et al.</i> )	Experimental R <sub>i</sub> <sup>literature</sup>										Ref.	
				DB-5 column	HP-5MS stationary phase	HP-5 column	DB-Wax stationary phase	BPX5 column	RTX-Wax stationary phase	HP-20M column	DB-5MS stationary phase	BP20 column			
101 Erythritol	149-32-6	943.4734	1041.8	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
102 Glycerin	56-81-5	758.5946	864.6	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
103 Myrtenol	515-00-4	1159.949	1118.5	1194	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	42, 44 and 47–49
				1196											
				1202											
				1214											
104 <i>cis</i> - <i>p</i> -Menth-2-en-7-ol		1185.016	1202.4	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
105 Glucopyranose	492-62-6	1317.003	1440.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	6
106 Geraniol	106-24-1	1175.015	1171.8	1255	NA	1240	1788	1850	1862	NA	1770	NA	NA	NA	41
				1276											
Nerol	106-25-2	—	—	1228	NA	NA	1753	1862	1862	NA	1770	NA	NA	NA	41 and 50
107 (2 <i>E</i> ,6 <i>E</i> )-Farnesol	106-28-5	1606.869	1597.8	1706	NA	NA	2371	1722	1722	NA	NA	NA	NA	NA	43
( <i>E</i> , <i>E</i> )-Farnesol	—	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
$\alpha$ -Farnesol	—	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	44
( <i>Z</i> , <i>Z</i> )-Farnesol	4602-84-0	—	—	1689	1713	1713	NA	NA	NA	NA	NA	NA	NA	NA	41
				1713											
				1718											
(2 <i>Z</i> ,6 <i>Z</i> )-Farnesol	—	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	43
(2 <i>E</i> ,6 <i>Z</i> )-Farnesol	3879-60-5	—	—	1734	1742	1743	NA	NA	NA	NA	NA	NA	NA	NA	43
				1742											
				1748											
( <i>E</i> , <i>Z</i> )-Farnesol	3790-71-4	—	—	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
( <i>Z</i> , <i>E</i> )-Farnesol	—	—	—	1697	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
108 Phytol	150-86-7	1941.848	1928.7	1949	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	43
109 ( <i>E</i> )-Cinnamyl alcohol	4407-36-7	1155.272	1238.7	1305	NA	NA	NA	NA	NA	NA	2571	NA	NA	NA	41
110 2-Methyl cinnamyl alcohol	1504-55-8	1212.211	1285.1	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	41
111 Isoamyl alcohol	123-51-3	764.7509	679.6	734	NA	737	1169	1206	1206	NA	1182	NA	NA	NA	41
				735											
112 Hex- <i>cis</i> -3-enol	928-96-1	880.2674	870.4	857	NA	NA	1378	1401	1401	NA	1357	849	NA	NA	51
3-Hexenol	544-12-7	—	—	NA	NA	NA	NA	1407	1407	NA	NA	NA	NA	NA	41
113 Cuminal alcohol	536-60-7	1204.248	1262.4	1287	NA	NA	2099	NA	NA	NA	NA	NA	NA	NA	41
114 Biphenyl	92-52-4	1283.923	1486.7	1381	NA	1385	NA	NA	NA	NA	NA	NA	NA	NA	51
115 Naphthalene	91-20-3	1131.721	1316	1179	NA	NA	NA	NA	NA	NA	1718	NA	NA	NA	51

<sup>a</sup> Not available.



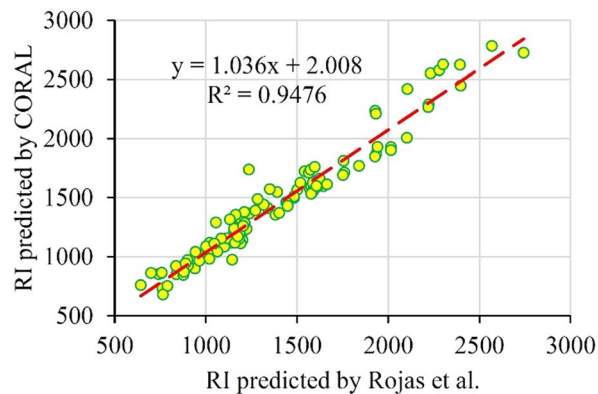


Fig. 3 Plot of the RI of external set predicted by CORAL software versus the RI predicted by Rojas *et al.*

## 4. Conclusions

In the present study, 40 QSPR models for the prediction of RI of 273 VOCs were developed from 10 random splits. The balance of correlation algorithm was used to design QSRR models. Four target functions, *i.e.* TF<sub>0</sub> (without IIC or CII), TF<sub>1</sub> (with IIC alone), TF<sub>2</sub> (with CII alone) and TF<sub>3</sub> (with IIC and CII, simultaneously) were employed to verify the significance of the present statistical method of QSPR model generation. The simultaneous use of IIC and CII (TF<sub>3</sub>) improves the predictive potential of the QSPR model. All suggested models render satisfactory predictive QSPR models for the RI of the VOCs, but the best predictive potential was computed with TF<sub>3</sub> for split 6; thus it is specified as the best model. To evaluate the reliability and prediction ability of all created models, various statistical parameters, such as  $R^2$ , IIC, CII, CCC,  $Q^2$ ,  $Q_{F1}^2$ ,  $Q_{F2}^2$ ,  $Q_{F3}^2$ ,  $s$ , MAE,  $F$ , RMSE,  $\overline{R_m^2}$ ,  $\Delta R_m^2$ ,  $CR_p^2$  and Y-test were utilized. A comparison of some statistical parameters of the present study, as analyzed by the QSPR model developed by Rojas *et al.*<sup>32</sup> reveals that the  $R^2$  value for the training set has shown an improvement, increasing from 0.879 to 0.900. Similarly, the  $R^2$  value for the test set has also demonstrated an enhancement, rising from 0.915 to 0.931. In addition, the RMSD has exhibited a reduction, decreasing from 72.1 to 62.7 for the training set and from 55.4 to 54.4 for the test set. The applicability domain (AD) was studied based on “statistical defect”  $d(A)$ . The structural attributes based on graph invariants and SMILES notation were also extracted from the split 6 (best model) and employed to recognize the promoters of RI increase and decrease. Morgan extended connectivity of zero-order for hydrogen atom as 1 (ec0-h...1...), Morgan extended connectivity of first-order for hydrogen atom as 4 (ec1-h...4...), Morgan extended connectivity of first-order for carbon atom as 7 (ec1-c...7...), Morgan extended connectivity of zero-order for carbon atom as 3 (ec0-c...3...), Morgan extended connectivity of first-order for carbon atom as 4 (ec1-c...10...) *etc* were some significant promoters of endpoint increase. The nearest neighbours codes for carbon equal to 413 (nnc-c...413), the nearest neighbours codes for carbon equal to 440 (nnc-c...440), a combination of the carbon atom, oxygen and branching (c...o...(...)), and 28 as a sum of

vertex degrees which take place at a topological distance of 2 relatively to carbon vertex (*vs.* 2-c...28) *etc* are some significant promoters of endpoint decrease.

## Data availability

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## Conflicts of interest

There are no conflicts to declare.

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