

Computing Wiener-Type Indices for Virtual Combinatorial Libraries Generated from Heteroatom-Containing Building Blocks

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The expensive and time-consuming process of drug lead discovery is significantly accelerated by efficiently screening molecular libraries with a high structural diversity and selecting subsets of molecules according to their similarity toward specific collections of active compounds. To characterize the molecular similarity/diversity or to quantify the drug-like character of compounds the process of screening virtual and synthetic combinatorial libraries uses various classes of structural descriptors, such as structure keys, fingerprints, graph invariants, and various topological indices computed from atomic connectivities or graph distances. In this paper we present efficient algorithms for the computation of several distance-based topological indices of a molecular graph from the distance invariants of its subgraphs. The procedures utilize vertex- and edge-weighted molecular graphs representing organic compounds containing heteroatoms and multiple bonds. These equations offer an effective way to compute for weighted molecular graphs the Wiener index, even/odd Wiener index, and resistance-distance index. The proposed algorithms are especially efficient in computing distance-based structural descriptors in combinatorial libraries without actually generating the compounds, because only distance-based indices of the building blocks are needed to generate the topological indices of any compound assembled from the building blocks.

INTRODUCTION

The current acceleration of the drug discovery process is a result of the extensive use of combinatorial chemistry^{1,2} to generate large libraries of structurally diverse molecules, which are subsequently used in the high-throughput screening (HTS) process. These techniques can be used at different stages of the drug discovery process, i.e. in lead generation and in lead optimization. Each of these stages requires different types of combinatorial libraries (CL): in lead generation the CL must offer for HTS a large collection of chemical compounds with a wide structural diversity, while for lead optimization the ideal CL is focused on the chemical space around the lead compounds.^{3–6} The use of CL and HTS in the last years dramatically extended the structural diversity of the compounds tested in the drug discovery process and demonstrated that this approach is able to identify biologically active molecules far more rapidly than with the conventional approaches. Because the combinatorial synthesis offers huge numbers of compounds in a short time, the bottleneck of this stage of drug discovery process is the HTS. An efficient way to reduce the number of compounds that enter the HTS process is the *in silico* screening of CL, a process applied both to diverse and focused libraries with the aim to select for HTS the compounds with potential “drug-like” characteristics and sufficient diversity.^{7–13}

The process of virtual screening of combinatorial libraries (VSCL) starts from a wide selection of reactants which are used to generate *in silico* a huge number of chemical compounds, according to a multicomponent reaction¹⁴ (e.g., as that of Ugi, Biginelli, or Passerini). In the next step, for each chemical compound a comprehensive set of structural

descriptors is computed, followed by a dimensionality reduction by selecting from the descriptors set a chemical space that is relevant for the investigated biological target. Finally, the compounds for chemical synthesis and HTS are selected with a statistical algorithm that implements a similarity, diversity, or drug-like paradigm.

To transform into a numerical form the structural features of chemical compounds, the VSCL uses a large number of structural descriptors, many of them traditionally used in QSPR and QSAR: physicochemical or empirical (log *P*, molecular polarizability); constitutional (number of aromatic rings, number of rotatable bonds, number of hydrogen-bond donors, number of hydrogen-bond acceptors); structure keys and fingerprints; graph invariants (cyclomatic number, atom pairs, path counts); topological indices^{15–17} (Wiener,^{18,19} Randić,²⁰ Kier and Hall,²¹ Balaban,^{22,23} Harary^{24,25}); geometric (polar surface area, molecular volume); quantum (HOMO energy, atomic charges); and grid (various steric, electrostatic, and lipophilic fields). Although SAR and QSAR studies offer a rich variety of structural descriptors, not all of them are optimally fit for use in VSCL. While the typical number of compounds in SAR and QSAR is usually between 10 and 100, a virtual library can easily exceed 10⁶ compounds. To be efficient, the *in silico* compound screening most conveniently uses descriptors that require small computational resources, thus explaining the wide popularity of counts of atom types, counts of functional groups, fingerprints, constitutional descriptors, graph invariants, and topological indices.^{13,26–28} This trend is apparent from the examination of several recent papers relevant to VSCL, including the following: selection of drug-like compounds;^{29,30} characterization of drug classes;³¹ property distribution in drug databases;³² classification of compounds according to the

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biological activity;³³ Focus-2D, which uses simulated annealing and genetic algorithms to generate targeted libraries;³⁴ design of immunosuppressive compounds;¹³ characterization of building blocks chemical space;³⁵ design of libraries with CNS activity;³⁶ and ChemGPS, a chemical global positioning system.³⁷

Due to the extremely large number of compounds that can be generated *in silico*, the selection of chemical synthesis candidates is time-consuming whenever it involves hard to compute descriptors, such as 3D pharmacophores, quantum indices, grid descriptors, or other relevant 3D descriptors. Therefore, a first compound selection step in VSCL uses simple structural descriptors to implement a fast and efficient filtering method intended to eliminate inappropriate reactants or products before going to more sophisticated structural descriptors and screening methods. Recently, Shi et al. introduced a promising technique of achieving an efficient sampling of the virtual chemical library by computing the structural descriptors of reaction products without actually assembling the molecules from the building blocks.³⁸ This effective method can be applied to obtain the structural descriptors of reaction products for all additive or nearly additive descriptors or for descriptors that can be generated with a simple algorithm from the corresponding descriptors of reactants or building blocks and a proper representation of the chemical process that takes place. We give here a list of simple structural descriptors that can be readily obtained from the corresponding descriptors of the reagents or building blocks: atom types, number of various functional groups, molecular weight, total number of atoms, number of atoms with a given atomic number Z , mass percent of atoms with a given atomic number Z , number of hydrogen-bond donors, number of hydrogen-bond acceptors, number of rotatable bonds, number of rings, number of aromatic rings, total number of bonds, number of single, double, triple, or aromatic bonds. An alternative approach for computing product descriptors based on the building blocks structure is to use simplified algorithms and equations for those important QSAR descriptors that traditionally require the examination of the whole 2D or 3D molecular structure: octanol–water partition coefficient obtained from atomic contributions;³⁹ calculation of molecular polar surface area as a sum of N, O, P, and S atoms contributions;⁴⁰ approximate van der Waals molecular surface area computed from the atomic connectivity information;⁴¹ molecular polar surface area computed from the number of hydrogen bond donors and acceptors;⁴² and fast log P computation from the sum of polar atoms, sum of nonpolar atoms, and sum of hydrogen bond donors and acceptors.⁴³

Although molecular graph invariants and topological indices represent highly used structural descriptors efficiently employed to measure the similarity and diversity of chemical libraries^{13,26,32–37} or to quantify the drug-like character of compounds,^{29–31} their computation from reactants or building blocks has not previously been recognized as a major way to speed-up the VSCL process. In a recent paper we have presented several algorithms for computing distance-based topological indices of combinatorial compounds from the distance invariants of the building blocks.⁴⁴ These procedures afford a very fast calculation of the Wiener index, even/odd Wiener index, resistance distance index, Wiener polynomial, and even/odd Wiener polynomial but in this previous work

were restricted to simple (nonweighted) molecular graphs.

In the present paper we extend the building block computation of these distance-based topological indices for combinatorial compounds containing heteroatoms and multiple bonds, thus increasing the utility of these structural descriptors in encoding the molecular similarity and diversity of CL. Molecules containing heteroatoms and multiple bonds can be represented as vertex- and edge-weighted graphs, with special parameters for vertices (atoms) and edges (bonds).^{16,17,45–49} The vertex weights depend on atom type, while the bond weights depend on the bond multiplicity and the types of atoms they interconnect. Using weighted graphs one can compute relevant structural descriptors representing weighted analogues to graph invariants and topological indices familiar for unweighted graphs. To reveal the efficiency of the procedures proposed in this paper, we present detailed computation algorithms as well as an illustrative example of computations of these indices for a small combinatorial library of α -ketoamides, which was recently generated through a multicomponent Ugi reaction.⁵⁰

VERTEX- AND EDGE-WEIGHTED MOLECULAR GRAPHS

In this section we briefly introduce some useful definitions regarding weighted molecular graphs, together with a more detailed presentation for the weighting schemes used in this paper. Relevant developments from the chemical literature are also mentioned.

Molecular Graphs. Let G be a simple (nonweighted) connected graph consisting of the vertex set $V(G)$ and the edge set $E(G)$ and having $|V(G)|$ vertices and $|E(G)|$ edges. A cut edge of G is an edge which if deleted breaks G into two disconnected subgraphs. A cut vertex of G is a vertex which if deleted breaks G into two disconnected subgraphs. Molecular graphs are nondirected connected graphs that represent organic compounds.^{15,51} In the graph representation of organic compounds their geometrical features, such as bond lengths or bond angles, are not considered and the chemical bonding of atoms is regarded as being their most important characteristic. In molecular graphs each vertex corresponds to an atom, while each edge represents a covalent bond of the chemical compound. Alkanes and cycloalkanes are usually represented as simple molecular graphs in which each vertex corresponds to a carbon atom and each edge corresponds to a carbon–carbon single bond. In this paper chemical compounds are represented as hydrogen-suppressed weighted graphs. We must emphasize that even organic compounds containing heteroatoms and multiple bonds can be represented as simple molecular graphs whenever one is interested in computing topological indices and graph invariants that reflect only the molecular connectivity and are free from the influence of various heteroatoms and different types of bonding. Almost all commercial programs that compute distance-based topological indices use this convention, and due to this situation all VSCL applications of these indices use this simplification. Compared to these applications, the approach proposed in this paper for computing distance-based topological indices represents a significant improvement, because the computing time needed is considerably smaller, and all algorithms are developed for heteroatom-containing molecular graphs.

Weighted Molecular Graphs. An organic compound containing heteroatoms and multiple bonds can be represented as a vertex- and edge-weighted molecular graph.^{16,17} A vertex- and edge-weighted (VEW) molecular graph consists of a vertex set $V = V(G)$, an edge set $E = E(G)$, a set of chemical symbols for vertices $Sy = Sy(G)$, a set of topological bond orders for edges $Bo = Bo(G)$, a vertex weight set $Vw(w) = Vw(w, G)$, and an edge weight set $Ew(w) = Ew(w, G)$. The elements of the vertex and edge weight sets are computed with the weighting scheme w . Several procedures (weighting schemes) for computing vertex and edge weights in molecular graphs were proposed in the literature.^{45–49} These weighted molecular graphs are then represented as weighted graph matrices, which are transformed into topological indices using various mathematical operations. The computation of the distance-based topological indices for weighted molecular graphs is presented in several recent papers.^{52–56}

The Topological Weighting Scheme t . The most simple model for organic compounds is obtained with the topological weighting scheme t , in which all (non-hydrogen) atoms are considered to be carbons and all bonds are considered single. The weight of a vertex corresponding to a carbon atom is $Vw(t) = 0$, while the weight of an edge corresponding to a carbon–carbon single bond is $Ew(t) = 1$. This weighting scheme is useful in computing topological indices that consider only the molecular connectivity and are free from heteroatom and bonding-type information. Such topological indices can be used as reference in computing difference topological indices that measure the influence of heteroatoms and multiple bonds. In this approach all acyclic compounds are represented as alkanes, while cyclic compounds are symbolized as cycloalkanes.

The Graph Weighting Scheme g . In the graph weighting scheme g all atoms are considered to be carbons, and the multiplicity of each bond is considered in computing the corresponding weight. The weight of a vertex corresponding to a carbon atom is $Vw(g) = 0$, while the edge parameter $Ew_{ij}(g)$ that characterizes the bond between atoms i and j (represented in the molecular graph by the edge $\{i, j\}$ between vertices i and j) is

$$Ew_{ij}(g) = 1/Bo_{ij} \quad (1)$$

where Bo_{ij} is the topological bond order of the edge between vertices i and j . The topological bond order Bo takes the value 1 for single bonds, 2 for double bonds, 3 for triple bonds, and 1.5 for aromatic bonds. The graph weighting scheme considers all saturated acyclic compounds as alkanes and all saturated cyclic compounds as cycloalkanes. An unsaturated organic compound is considered to be equivalent to the corresponding hydrocarbon having the same skeleton.

The Atomic Number Weighting Scheme Z . A general approach for computing parameters for VEW graphs was developed by Trinajstić and co-workers⁴⁵ by weighting the contributions of atoms and bonds with parameters based on the atomic number Z and the topological bond order; a large variety of structural descriptors were computed with this method.⁵⁵ In the atomic number weighting scheme Z the

Table 1. Selected Set of Atomic Properties Used with Different Weighting Schemes and Corresponding Atomic Parameters Vw^a

element	Z	X	Y	$Vw(Z)$	$Vw(X)$	$Vw(Y)$
B	5	0.851	1.038	−0.200	−0.175	0.037
C	6	1.000	1.000	0.000	0.000	0.000
N	7	1.149	0.963	0.143	0.130	−0.038
O	8	1.297	0.925	0.250	0.229	−0.081
F	9	1.446	0.887	0.333	0.308	−0.127
Si	14	0.937	1.128	0.571	−0.067	0.113
P	15	1.086	1.091	0.600	0.079	0.083
S	16	1.235	1.053	0.625	0.190	0.050
Cl	17	1.384	1.015	0.647	0.277	0.015
As	33	0.946	1.379	0.818	−0.057	0.275
Se	34	1.095	1.341	0.824	0.087	0.254
Br	35	1.244	1.303	0.829	0.196	0.233
Te	52	0.954	1.629	0.885	−0.048	0.386
I	53	1.103	1.591	0.887	0.093	0.371

^a The atomic number Z , the relative electronegativity X , and the relative covalent radius Y .

vertex parameter $Vw_i(Z)$ of the vertex i (representing atom i from a molecule) is

$$Vw_i(Z) = 1 - Z_C/Z_i = 1 - 6/Z_i \quad (2)$$

where Z_i is the atomic number Z of the atom i , and $Z_C = 6$ is the atomic number Z of carbon. The bond between atoms i and j is characterized by the edge parameter $Ew_{ij}(Z)$

$$Ew_{ij}(Z) = Z_C Z_C / Bo_{ij} Z_i Z_j = 6 \times 6 / Bo_{ij} Z_i Z_j \quad (3)$$

where Bo_{ij} is the topological bond order of the edge between vertices i and j . In Table 1 column 5 we present the atomic parameters $Vw(Z)$ for a selected set of atoms.

The Relative Electronegativity Weighting Scheme X . In the relative electronegativity X weighting scheme^{46,47} the vertex parameter $Vw_i(X)$ of the vertex i is

$$Vw_i(X) = 1 - 1/X_i \quad (4)$$

where X_i is the relative electronegativity of atom i , with carbon having $X_C = 1$. The edge parameter $Ew_{ij}(X)$ that characterizes the bond between atoms i and j is

$$Ew_{ij}(X) = 1/Bo_{ij} X_i X_j \quad (5)$$

In Table 1 we present for a selected set of atoms the relative electronegativities X in column 3 and the atomic parameters $Vw(X)$ in column 6.

The Relative Covalent Radius Weighting Scheme Y . In the relative covalent radius Y weighting scheme^{46,47} the vertex parameter $Vw_i(Y)$ of the vertex i is

$$Vw_i(Y) = 1 - 1/Y_i \quad (6)$$

where Y_i is the relative covalent radius of atom i , with carbon having $Y_C = 1$. The edge parameter $Ew_{ij}(Y)$ that characterizes the bond between atoms i and j is

$$Ew_{ij}(Y) = 1/Bo_{ij} Y_i Y_j \quad (7)$$

In Table 1 we present for a selected set of atoms the relative covalent radius Y in column 4 and the atomic parameters $Vw(Y)$ in column 7.

While the atom and bond parameters computed with the Z weighting scheme vary monotonically with the number of

electrons, those derived from the X and Y weighting schemes have a periodic variation versus the atomic number Z . Other methods of numerically encoding the presence of heteroatoms in computing topological indices are found in the literature.^{21,23,52,57}

THE WIENER INDEX

The Wiener index W ,^{18,19} one of the most widely used graph descriptors in QSAR and VSCL, was initially defined only for alkanes and extended with the aid of the distance matrix \mathbf{D} for cyclic hydrocarbons by Hosoya.⁵⁸ This extension of the Wiener index W to cyclic graphs is not unique, and alternative ways have been proposed, e.g., the resistance-distance index W' defined by Klein and Randić as the sum for all pairs of vertices of the corresponding elements in the resistance distance matrix Ω ⁵⁹ and the Szeged index Sz proposed by Gutman⁶⁰ and computed from molecular matrices by Diudea.⁶¹ The actual definition of the Wiener index, which is valid for any vertex- and edge-weighted molecular graphs representing organic compounds with heteroatoms and multiple bonds, is based on the distance matrix of weighted molecular graphs.⁴⁸ A weighted distance-matrix analogue $\mathbf{D}(w) = \mathbf{D}(w, G)$ for a vertex- and edge-weighted molecular graph G with N vertices is the symmetric square $N \times N$ matrix with real elements defined with the formula

$$\mathbf{D}_{ij}(w, G) = \begin{cases} d_{ij}(w, G) & \text{if } i \neq j \\ V_{w_i}(w) & \text{if } i = j \end{cases} \quad (8)$$

where $d_{ij}(w, G)$ is the weighted-graph distance between vertices i and j , $V_{w_i}(w)$ is the weight of the vertex i , and w is the weighting scheme used to compute the parameters V_w and E_w . The Wiener index $W(w) = W(w, G)$ of a vertex- and edge-weighted graph G with N vertices is

$$W(w, G) = \sum_{i=1}^N \sum_{j=i}^N \mathbf{D}_{ij}(w, G) \quad (9)$$

where the distance matrix $\mathbf{D}(w, G)$ is computed with the weighting scheme w .

The aim of our investigation is to propose fast and efficient algorithms for computing distance-based topological indices for combinatorial libraries, and therefore it is important to estimate the computational complexity for obtaining the Wiener index W with eq 9. For a molecular graph consisting of N atoms and M bonds, and starting from an $N \times N$ matrix with all elements equal to zero, the connection table is translated into the adjacency matrix \mathbf{A} in $O(M)$ computer operations. We have to consider that organic compounds have the maximum degree four, so M could not be larger than $2N$, and we can approximate that the adjacency matrix \mathbf{A} is obtained in $O(N)$ operations. For each chemical compound the computation of the distance matrix \mathbf{D} from the adjacency matrix \mathbf{A} needs $O(N^3)$ operations, i.e. the computer time is proportional to N^3 , indicating that when N increases this part of the algorithm will consume the largest part of the computational resources. The computation of the Wiener index W from \mathbf{D} with eq 9 is accomplished in $O(N^2)$ steps. From this analysis it is clear that the most computa-

tional demanding step is the generation of the distance matrix \mathbf{D} from the adjacency matrix. Chemical compounds generated for combinatorial libraries are fairly large, and the above analysis demonstrates that the standard algorithm for the Wiener index is not efficient for VSCL, when usually much more than 10^6 compounds must be evaluated in a short period of time.

We denote by $W_i(w, G)$ the sum of all distances between vertex i and all other vertices from G

$$W_i(w, G) = \sum_{\substack{i \neq j \\ j \in V(G)}} d_{ij}(w, G) \quad (10)$$

where w is the weighting scheme used to compute the shortest-path distances between two atoms. We have to point that, in general, $W_i(w, G)$ is different from the distance sum of vertex i , $\mathbf{DS}_i(w, G)$,^{16,46,48} because the later graph invariant contains also the vertex contribution $V_{w_i}(w)$, which is not considered in eq 10.

For the computation of the Wiener index from subgraphs (building blocks) we extend for vertex- and edge-weighted molecular graphs a well-known graph decomposition formula for W ,^{62,63} and we give a detailed algorithm for the computer implementation of this procedure.

Theorem 1. Let $\{a, b\}$ be a cut edge between two subgraphs A and B of G such that $a \in A$ and $b \in B$. The atom and bond parameters are computed with the weighting scheme w , and the distance between vertices a and b is $d_{ab}(w)$. Denote various subgraphs of $G = A - B$ as in the Figure 1. Then the Wiener index of graph G is

$$W(w, G) = W(w, A - B) = W(w, A) + |V(B)|W_a(w, A) + d_{ab}(w)|V(A)||V(B)| + |V(A)|W_b(w, B) + W(w, B) \quad (11)$$

Proof. The Wiener index of graph $G = A - B$ is the sum of three types of distances, namely between pairs of vertices from A , between pairs of vertices from B , and between a vertex from A and another vertex from B . Then, the shortest-path distance between a vertex i from A and another vertex j from B is partitioned into three terms: the distance between vertex i and the cut vertex a , the distance between cut vertices a and b , and the distance between cut vertex b and the vertex j . The substitution of eqs 9 and 10 in this equality completes the demonstration of Theorem 1:

$$\begin{aligned} W(w, G) = W(w, A - B) &= \sum_{\substack{i \leq j \\ i, j \in V(A)}} d_{ij}(w, A) + \\ &\sum_{i \in V(A)} \sum_{\substack{j \neq b \\ j \in V(B)}} d_{ij}(w, G) + \sum_{\substack{i \leq j \\ i, j \in V(B)}} d_{ij}(w, B) = W(w, A) + \\ &\sum_{i \in V(A)} \sum_{\substack{j \neq b \\ j \in V(B)}} (d_{ia}(w, A) + d_{ab}(w) + d_{bj}(w, B)) + W(w, B) = \\ &W(w, A) + |V(B)| \sum_{\substack{i \neq a \\ i \in V(A)}} d_{ia}(w, A) + d_{ab}(w)|V(A)||V(B)| + \\ &|V(A)| \sum_{\substack{j \neq b \\ j \in V(B)}} d_{bj}(w, B) + W(w, B) \end{aligned}$$

Equation 11 is the core of an efficient algorithm for the fast computation of the Wiener index for compounds from

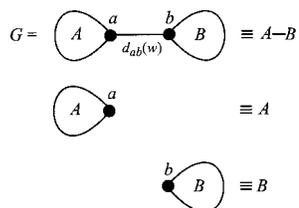


Figure 1. A heteroatom-containing molecular graph G with a cut edge between vertices a and b and its relevant subgraphs. The graph distance between cut vertices a and b , computed with the weighting scheme w , is $d_{ab}(w)$.

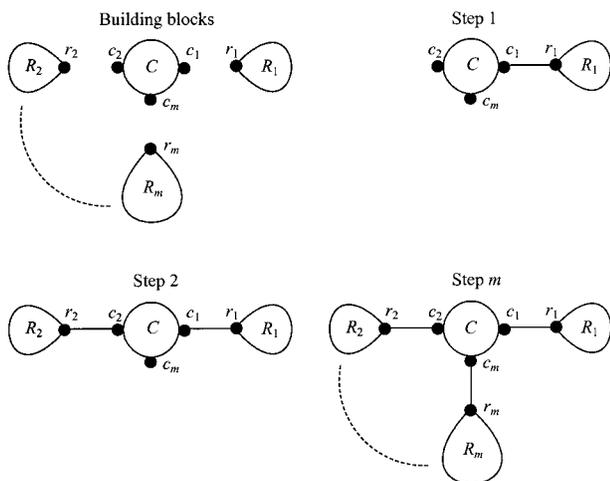


Figure 2. Generation of combinatorial compounds from a core structure C and m substituents R_1, R_2, \dots, R_m .

combinatorial libraries. The description of this algorithm for computing the Wiener index from building blocks is presented for the general case when a chemical compound $CR_1 \dots R_m$ is generated from a core structure C and m substituents R_1, R_2, \dots, R_m , as presented in Figure 2.

Algorithm 1. 1. Consider a core structure C with m substitution atoms c_1, c_2, \dots, c_m and m substituents R_1, R_2, \dots, R_m , each having one substitution atom r_1, r_2, \dots, r_m , respectively. The final molecular graph is presented in Figure 2.

2. Compute the Wiener indices for the core structure C and the m substituents R_1, R_2, \dots, R_m , i.e. $W(w, C), W(w, R_1), W(w, R_2), \dots, W(w, R_m)$.

3. Compute the sum of all distances to the substitution atoms $c_1, c_2, \dots, c_m, r_1, r_2, \dots, r_m$, i.e. $W_{c_1}(w, C), W_{c_2}(w, C), \dots, W_{c_m}(w, C), W_{r_1}(w, R_1), W_{r_2}(w, R_2), \dots, W_{r_m}(w, R_m)$.

4. Calculate the distances $d_{c_i c_j}(w)$ between all $m(m-1)/2$ pairs of substitution atoms from the core C .

5. Determine the bond distances $d_{r_i c_j}(w)$ between all m pairs of connection atoms, where r_i belongs to the substituent R_i , and c_j belongs to the core structure C .

6. To an intermediate structure $CR_1 \dots R_{i-1}$ add the substituent R_i by inserting a bond between atoms r_i and c_i and obtain in this way $CR_1 \dots R_i$.

7. Compute the Wiener index of $CR_1 \dots R_i, W(w, CR_1 \dots R_i)$:

$$W(w, CR_1 \dots R_i) = W(w, CR_1 \dots R_{i-1}) + |V(R_i)| W_{c_i}(w, CR_1 \dots R_{i-1}) + d_{r_i c_i}(w) |V(CR_1 \dots R_{i-1})| |V(R_i)| + |V(CR_1 \dots R_{i-1})| W_{r_i}(w, R_i) + W(w, R_i) \quad (12)$$

8. Determine the number of vertices in the subgraph $CR_1 \dots R_i$:

$$|V(CR_1 \dots R_i)| = |V(CR_1 \dots R_{i-1})| + |V(R_i)| \quad (13)$$

9. Update the sum of all distances for the core atoms $c_j, i < j \leq m$, that are not yet substituted in the intermediate structure $CR_1 \dots R_i$ using the equation:

$$W_{c_j}(w, CR_1 \dots R_i) = W_{c_j}(w, CR_1 \dots R_{i-1}) + (d_{c_j c_i}(w) + d_{r_i c_j}(w)) |V(R_i)| + W_{r_i}(w, R_i) \quad (14)$$

Repeat steps 6–9 until $W(w, CR_1 \dots R_m)$ is computed.

We give an equivalent formula for computing the updated distance sum for the atom c_k after the first i substituents have been added to the core structure C :

$$W_{c_k}(w, CR_1 \dots R_i) = W_{c_k}(w, C) + \sum_{j=1}^i [(d_{c_j c_k}(w) + d_{r_j c_j}(w)) |V(R_j)| + W_{r_j}(w, R_j)] \quad (15)$$

From a thorough examination of the above algorithm we can easily divide the computational expenses in two types: computation of several distance-based graph invariants for the building blocks and m times application of eq 11 for computing W of $CR_1 \dots R_m$. The computation of the Wiener index with eq 9 for the building blocks C, R_1, R_2, \dots, R_m , sum of distances W_j for atoms $c_1, c_2, \dots, c_m, r_1, r_2, \dots, r_m$, and distances between all pairs of atoms c_1, c_2, \dots, c_m , is the most computational demanding step, but we have to consider that the size of the building blocks is much smaller than that of the final compound, and this computation is performed only once for the whole combinatorial library. The second part of the algorithm involves in step 7 the m -fold application of eq 11 which has a time expense of $O(m)$, where m , in general, is smaller than 5. One important feature of the second step, which is repeated for each compound generated, is that the computational expenses do not depend on the number of atoms N from the final compound but on the number of building blocks m , which is small and constant for a given virtual library. At the i th stage, step 9 involves $m-i$ computations, so that as i ranges from 1 to m . Thus this step involves overall $m(m-1)/2$ such computations for each compound, i.e., a time $O(m^2)$ arises. It is now clear that the usual algorithm for computing the Wiener index with eq 9, which involves $O(N^3)$ operations per compound, is much less efficient than the algorithm that uses eq 11 and involves $O(m^2)$ operations per compound. Also, the larger is the combinatorial library the greater the relative efficiency of our algorithm that uses eq 11 compared with the standard one.

This fast procedure for computing the Wiener index for compounds generated from building blocks is now applied to a 100-member combinatorial library of α -ketoamides, which was recently generated by a parallel solution-phase synthesis.⁵⁰ A one-pot two-step synthesis was developed for the synthesis of this library. In Figure 3 we present the general reaction, performed in THF, which involves a Ugi four-component reaction followed by a PDC oxidation that delivers the α -ketoamides. The reagents for the Ugi four-component reaction are DL-lactic acid, 5 aldehydes **A**, 5 amines **B**, and 4 isocyanides **C**, giving a total of 100 products. In Figure 4 we present the structure of the aldehydes, amines, and isocyanides used in synthesis. The

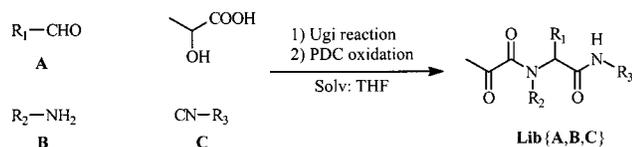


Figure 3. General four-component one-pot synthesis of the 100 α -ketoamides library $\text{Lib}\{A,B,C\}$.

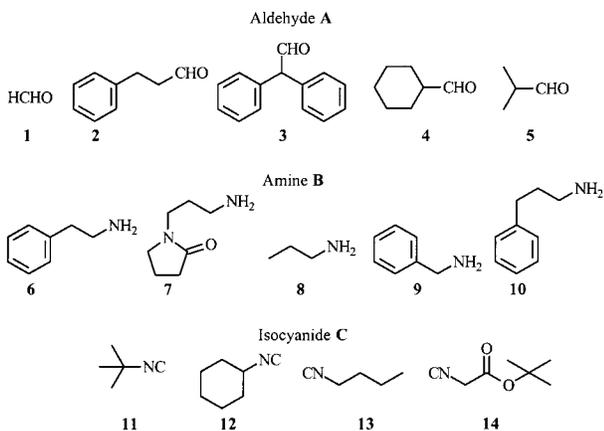


Figure 4. Reagents for the synthesis of the 100 α -ketoamides library $\text{Lib}\{A,B,C\}$: 5 aldehydes **A**, 5 amines **B**, and 4 isocyanides **C**.

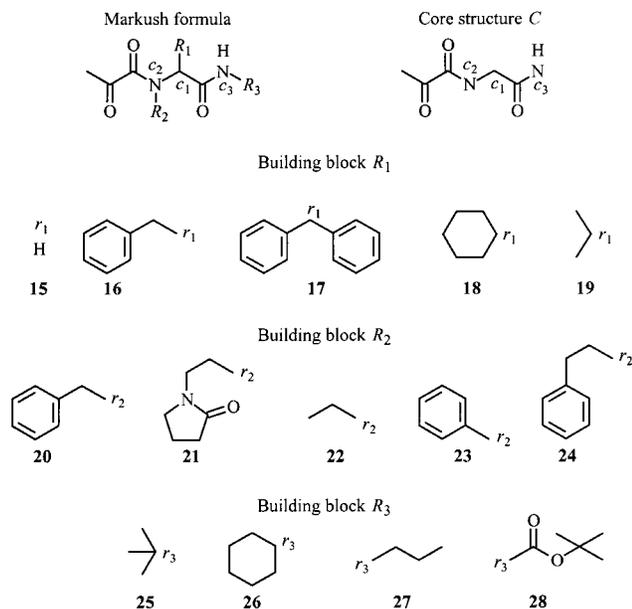


Figure 5. Markush-type formula of the α -ketoamides library, core structure **C**, and structures of the building blocks **R**₁, **R**₂, and **R**₃. For each building block the attachment atom is labeled with r_i , i taking the value 1 for aldehydes, 2 for amines, and 3 for isocyanides. In generating the combinatorial library a building block **R** _{i} is connected to the core structure **C** by joining atom r_i with the corresponding atom c_i .

N-pyruvoyl amino acid derivatives can be conveniently represented by a Markush-type formula, as presented in Figure 5, showing that the general formula can be conveniently separated into four building blocks, namely a core structure **C** and the three substituents **R**₁, **R**₂, and **R**₃. The core structure **C** is presented in Figure 5, having labels c_1 , c_2 , and c_3 for the atoms connected to the three substituents. The molecular graphs of the substituents **R**₁, **R**₂, and **R**₃, which can be easily obtained from the structure of the corresponding reagents in Figure 4, are also presented in

Table 2. Shortest-Path and Resistance Distance-Based Structural Descriptors for the Core Structure **C** (Figure 5) Computed with the Weighting Schemes **X**, **Y**, and **Z**

descriptor	weight		
	X	Y	Z
$W(w,C)$	112.834	125.503	111.875
$W'(w,C)$	111.887	125.823	110.839
$W_{c_1}(w,C) = W'_{c_1}(w,C)$	18.600	21.083	18.411
$W_{c_2}(w,C) = W'_{c_2}(w,C)$	16.860	19.006	16.696
$W_{c_3}(w,C) = W'_{c_3}(w,C)$	29.563	33.390	29.268
$d_{c_1c_2}(w) = \Omega_{c_1c_2}(w)$	0.870	1.038	0.857
$d_{c_1c_3}(w) = \Omega_{c_1c_3}(w)$	1.870	2.038	1.857
$d_{c_2c_3}(w) = \Omega_{c_2c_3}(w)$	2.741	3.077	2.714

Table 3. Shortest-Path Distance-Based Structural Descriptors for the Building Blocks **R**₁, **R**₂, and **R**₃ (Figure 5) Computed with the Weighting Schemes **X**, **Y**, and **Z**

R	$ V(R) $	$W(X,R)$	$W(Y,R)$	$W(Z,R)$	$W_r(X,R)$	$W_r(Y,R)$	$W_r(Z,R)$
15	0	0.000	0.000	0.000	0.000	0.000	0.000
16	8	49.000	49.000	49.000	19.000	19.000	19.000
17	13	204.000	204.000	204.000	24.000	24.000	24.000
18	6	27.000	27.000	27.000	9.000	9.000	9.000
19	3	4.000	4.000	4.000	2.000	2.000	2.000
20	8	49.000	49.000	49.000	19.000	19.000	19.000
21	9	79.996	87.819	79.393	26.959	28.963	26.804
22	3	4.000	4.000	4.000	3.000	3.000	3.000
23	7	30.000	30.000	30.000	12.000	12.000	12.000
24	9	76.000	76.000	76.000	27.000	27.000	27.000
25	4	9.000	9.000	9.000	3.000	3.000	3.000
26	6	27.000	27.000	27.000	9.000	9.000	9.000
27	4	10.000	10.000	10.000	6.000	6.000	6.000
28	8	55.058	65.135	54.375	17.325	20.270	17.125

Figure 5; for each substituent R_i the connection atom is labeled with r_i , i taking the value 1 for aldehydes, 2 for amines, and 3 for isocyanides. In generating the combinatorial library a building block R_i is connected to the core structure **C** by joining atom r_i with the corresponding atom c_i . Although this combinatorial library is small compared with those currently used in virtual screening of compounds, it represents a convenient example for the algorithms proposed in this paper.

As outlined in Algorithm 1, the application of Theorem 1 for the computation of the Wiener index uses several distance-based indices for the core structure and substituents. In Table 2 we present the set of invariants computed for the core structure with the three weighting schemes **X**, **Y**, and **Z**: the Wiener index $W(w,C)$, the sum of distances to a connection atom c_i , $W_{c_1}(w,C)$, $W_{c_2}(w,C)$, and $W_{c_3}(w,C)$, and the distances between pairs of connection atoms $d_{c_1c_2}(w)$, $d_{c_1c_3}(w)$, and $d_{c_2c_3}(w)$. For the substituents **15**–**28** we present in Table 3 all structural descriptors needed in the Algorithm 1, i.e. the number of vertices $|V(R)|$, the Wiener index $W(w,R)$, and the sum of distances to a connection atom r , $W_r(w,R)$. These indices presented in Tables 2 and 3 are solely needed to compute the Wiener indices of all members from the combinatorial library of α -ketoamides.

To further demonstrate the utility and easiness of use of Algorithm 1 we present below all steps from the computation of the Wiener index for an α -ketoamide with the general formula $CR_1R_2R_3$ assembled from the core structure **C** and three substituents **R**₁, **R**₂, and **R**₃, representing the aldehyde **2**, the amine **7**, and the isocyanide **14** (Figure 4), corresponding to the building blocks **16**, **21**, and **28** (Figure 5), respectively. The steps of this computation use the distance indices from Tables 2 and 3, and follow the steps outlined in Algorithm 1:

1. Compute the Wiener indices for the four building blocks: $W(X,C) = 112.834$, $W(X,R_1) = 49.000$, $W(X,R_2) = 79.996$, $W(X,R_3) = 55.058$.

2. Compute the sum of all distances for the six connection atoms: $W_{c_1}(X,C) = 18.600$, $W_{c_2}(X,C) = 16.860$, $W_{c_3}(X,C) = 29.563$, $W_{r_1}(X,R_1) = 19.000$, $W_{r_2}(X,R_2) = 26.959$, $W_{r_3}(X,R_3) = 17.325$.

3. Compute the shortest-path distances $d_{c_i c_j}(X)$ between all pairs of connection atoms from the core structure C : $d_{c_1 c_2}(X) = 0.870$, $d_{c_1 c_3}(X) = 1.870$, $d_{c_2 c_3}(X) = 2.741$.

4. Determine the bond distances $d_{r_i c_j}(X)$ between all pairs of connection atoms, where the first atom belongs to the substituent R_i , and the second atom belongs to the core structure C : $d_{r_1 c_1}(X) = 1.000$, $d_{r_2 c_2}(X) = 0.870$, $d_{r_3 c_3}(X) = 0.870$.

5. Get the number of vertices in all four building blocks: $|V(C)| = 10$, $|V(R_1)| = 8$, $|V(R_2)| = 9$, $|V(R_3)| = 8$.

6. Connect the substituent R_1 to C by joining vertices r_1 and c_1 , obtaining in this way CR_1 .

7. Compute the Wiener index of CR_1 , $W(CR_1)$:

$$W(X,CR_1) = W(X,C) + |V(R_1)|W_{c_1}(X,C) + d_{r_1 c_1}(X)|V(C)||V(R_1)| + |V(C)|W_{r_1}(X,R_1) + W(X,R_1) \quad (16)$$

$$W(X,CR_1) = 112.834 + 8 \times 18.600 + 1.000 \times 10 \times 8 + 10 \times 19.000 + 49.000 = 580.637$$

8. Determine the number of vertices in the subgraph CR_1 :

$$|V(CR_1)| = 10 + 8 = 18$$

9. Compute the distance sum of atom c_2 in the intermediate structure CR_1 :

$$W_{c_2}(X,CR_1) = W_{c_2}(X,C) + (d_{c_1 c_2}(X) + d_{r_1 c_1}(X))|V(R_1)| + W_{r_1}(X,R_1) \quad (17)$$

$$W_{c_2}(X,CR_1) = 16.860 + (0.870 + 1.000) \times 8 + 19.000 = 50.822$$

10. Compute the distance sum of atom c_3 in the intermediate structure CR_1 with the equation:

$$W_{c_3}(X,CR_1) = W_{c_3}(X,C) + (d_{c_1 c_3}(X) + d_{r_1 c_1}(X))|V(R_1)| + W_{r_1}(X,R_1) \quad (18)$$

$$W_{c_3}(X,CR_1) = 29.563 + (1.870 + 1.000) \times 8 + 19.000 = 71.526$$

11. Connect the substituent R_2 to CR_1 by joining vertices r_2 and c_2 , obtaining in this way CR_1R_2 .

12. Compute the Wiener index of CR_1R_2 , $W(CR_1R_2)$, with eq 7:

$$W(X,CR_1R_2) = W(X,CR_1) + |V(R_2)|W_{c_2}(X,CR_1) + d_{r_2 c_2}(X)|V(CR_1)||V(R_2)| + |V(CR_1)|W_{r_2}(X,R_2) + W(X,R_2) \quad (19)$$

$$W(X,CR_1R_2) = 580.637 + 9 \times 50.822 + 0.870 \times 18 \times 9 + 18 \times 26.959 + 79.996 = 1744.289$$

13. Determine the number of vertices in the subgraph CR_1R_2 :

$$|V(CR_1R_2)| = 18 + 9 = 27$$

14. Compute the distance sum of atom c_3 in the intermediate structure CR_1R_2 with the equation:

$$W_{c_3}(X,CR_1R_2) = W_{c_3}(X,CR_1) + (d_{c_2 c_3}(X) + d_{r_2 c_2}(X))|V(R_2)| + W_{r_2}(X,R_2) \quad (20)$$

$$W_{c_3}(X,CR_1R_2) = 71.526 + (2.741 + 0.870) \times 9 + 26.959 = 130.983$$

15. Connect the substituent R_3 to CR_1R_2 by joining vertices r_3 and c_3 , obtaining in this way $CR_1R_2R_3$.

16. Compute the Wiener index of $CR_1R_2R_3$, $W(CR_1R_2R_3)$, with the equation:

$$W(X,CR_1R_2R_3) = W(X,CR_1R_2) + |V(R_3)|W_{c_3}(X,CR_1R_2) + d_{r_3 c_3}(X)|V(CR_1R_2)||V(R_3)| + |V(CR_1R_2)|W_{r_3}(X,R_3) + W(X,R_3) \quad (21)$$

$$W(X,CR_1R_2R_3) = 1744.289 + 8 \times 130.983 + 0.870 \times 27 \times 8 + 27 \times 17.325 + 55.058 = 3502.966$$

In this section we have presented a theorem, an algorithm, computational examples, and a comparative analysis of the computational complexity, all representing realistic arguments demonstrating that for very large combinatorial libraries the Wiener index can much faster be computed with eq 11 than with the customary eq 9. The approach proposed here is even more general than so far indicated, and in the following two sections we extend it for other related molecular descriptors.

EVEN/ODD WIENER INDEX

In a recent study⁶⁴ we have partitioned all graph distances into two classes, i.e. even and odd distances, which are separately summed to give two distinct structural descriptors, $W^e(G)$ and $W^o(G)$.^{64,65} The sum of even graph distances $W^e(w,G)$ from the molecular graph G is

$$W^e(w,G) = \sum_{i,j \in V(G)} d_{ij}^e(w,G) \quad (22)$$

where the even distance $d_{ij}^e(w,G)$ represents the distance between vertices i and j computed with the weighting scheme w having the property that the distance $d_{ij}(t,G)$ computed with the topological weighting scheme t has an even value (i.e., vertices i and j are separated by an even number of edges), and the summation goes over all such distances from G . In a similar way we define $W^o(w,G)$, the sum of odd graph distances from the molecular graph G , by collecting together all odd graph distances

$$W^o(w,G) = \sum_{i,j \in V(G)} d_{ij}^o(w,G) \quad (23)$$

where the odd distance $d_{ij}^o(w,G)$ represents the distance

between vertices i and j computed with the weighting scheme w having the property that the distance $d_{ij}(t,G)$ computed with the topological weighting scheme t has an odd value (i.e., vertices i and j are separated by an odd number of edges), and the summation goes over all such distances from G . A simple relationship exists between the Wiener index $W(w,G)$ and the even/odd indices $W^e(w,G)$ and $W^o(w,G)$:

$$W(w,G) = W^e(w,G) + W^o(w,G) \quad (24)$$

We introduce four notations related to even/odd graph distances: $d_i^e(w,G)$, the set of even graph distances from G that have vertex i as an endpoint; $d_i^o(w,G)$, the set of odd graph distances from G that have vertex i as an endpoint; $|d_i^e(w,G)|$, the number of elements in the set $d_i^e(w,G)$, equal with the number of atoms separated from atom i by an even number of bonds; and $|d_i^o(w,G)|$, the number of elements in the set $d_i^o(w,G)$, equal with the number of atoms separated from atom i by an odd number of bonds. In a graph G , the sum of even distances that have vertex i as an endpoint is

$$W_i^e(w,G) = \sum_{j \in V(G)}^{i \neq j} d_{ij}^e(w,G) \quad (25)$$

Similarly, the sum of odd distances that have vertex i as an endpoint is

$$W_i^o(w,G) = \sum_{j \in V(G)}^{i \neq j} d_{ij}^o(w,G) \quad (26)$$

From eqs 22–26 we notice a significant similarity between the Wiener index W and the even/odd variants presented in this section. Therefore, it is no surprise that for W^e and W^o one can devise two theorems, equivalent with Theorem 1, for computing the respective topological indices from subgraphs obtained by deleting a cut edge.

Theorem 2. Let $\{a,b\}$ be a cut edge between two subgraphs A and B of G such that $a \in A$ and $b \in B$. Denote various subgraphs of $G = A - B$ as in the Figure 1. Then the even Wiener index of graph G is

$$\begin{aligned} W^e(w,G) = W^e(w,A-B) = W^e(w,A) + \\ |d_b^o(w,B)|W_a^e(w,A) + d_{ab}(w)|d_a^e(w,A)||d_b^o(w,B)| + \\ |d_a^e(w,A)||W_b^o(w,B) + |d_b^o(w,B)|W_a^o(w,A) + \\ d_{ab}(w)|d_a^o(w,A)||d_b^e(w,B)| + |d_a^o(w,A)||W_b^e(w,B) + \\ W^e(w,B) \end{aligned} \quad (27)$$

Proof. The even Wiener index of graph $G = A - B$ is the sum of three types of even distances, namely between pairs of vertices from A , between pairs of vertices from B , and between a vertex from A and another vertex from B . Subsequently, the even distance between a vertex i from A and a vertex j from B can arise in two situations:

(1) an even distance between vertex i and the cut vertex a combined with an odd distance between vertex j and the cut vertex b and (2) an odd distance between vertex i and the cut vertex a combined with an even distance between vertex j and the cut vertex b . Substituting then in this equality eqs 22–26 completes the demonstration of Theorem 2:

$$\begin{aligned} W^e(w,G) = W^e(w,A-B) = \sum_{i,j \in V(A)}^{i \leq j} d_{ij}^e(w,A) + \\ \sum_{i \in V(A)j \in V(B)} d_{ij}^e(w,G) + \sum_{i,j \in V(B)}^{i \leq j} d_{ij}^e(w,B) = W^e(w,A) + \\ \sum_{i \in V(A)j \in V(B)}^{i \neq a \quad j \neq b} [d_{ia}^e(w,A) + d_{ab}(w) + d_{bj}^o(w,B)] + \\ \sum_{i \in V(A)j \in V(B)}^{i \neq a \quad j \neq b} [d_{ia}^o(w,A) + d_{ab}(w) + d_{bj}^e(w,B)] + \\ W^e(w,B) = W^e(w,A) + |d_b^o(w,B)| \sum_{i \in V(A)}^{i \neq a} d_{ia}^e(w,A) + \\ d_{ab}(w)|d_a^e(w,A)||d_b^o(w,B)| + |d_a^e(w,A)| \sum_{j \in V(B)}^{j \neq b} d_{bj}^o(w,B) + \\ |d_b^e(w,B)| \sum_{i \in V(A)}^{i \neq a} d_{ia}^o(w,A) + d_{ab}(w)|d_a^o(w,A)||d_b^e(w,B)| + \\ |d_a^o(w,A)| \sum_{j \in V(B)}^{j \neq b} d_{bj}^e(w,B) + W^e(w,B) \end{aligned}$$

Theorem 3. Let $\{a,b\}$ be a cut edge between two subgraphs A and B of G such that $a \in A$ and $b \in B$. Denote various subgraphs of $G = A - B$ as in the Figure 1. Then the odd Wiener index of graph G is

$$\begin{aligned} W^o(w,G) = W^o(w,A-B) = W^o(w,A) + \\ |d_b^e(w,B)|W_a^o(w,A) + d_{ab}(w)|d_a^o(w,A)||d_b^e(w,B)| + \\ |d_a^o(w,A)||W_b^e(w,B) + |d_b^e(w,B)|W_a^e(w,A) + \\ d_{ab}(w)|d_a^e(w,A)||d_b^o(w,B)| + |d_a^e(w,A)||W_b^o(w,B) + \\ W^o(w,B) \end{aligned} \quad (28)$$

Proof. The odd Wiener index of graph $G = A - B$ is the sum of three types of odd distances, namely between pairs of vertices from A , between pairs of vertices from B , and between a vertex from A and another vertex from B . Subsequently, the odd distance between a vertex i from A and a vertex j from B can arise in two situations: (1) an even distance between vertex i and the cut vertex a combined with an even distance between vertex j and the cut vertex b and (2) an odd distance between vertex i and the cut vertex a combined with an odd distance between vertex j and the cut vertex b . Substituting then in this equality eqs 22–26 completes the demonstration of Theorem 3:

$$\begin{aligned}
W^o(w, G) = W^o(w, A-B) &= \sum_{i,j \in V(A)}^{i \leq j} d_{ij}^o(w, A) + \\
&\sum_{i \in V(A), j \in V(B)} d_{ij}^o(w, G) + \sum_{i,j \in V(B)}^{i \leq j} d_{ij}^o(w, B) = W^o(w, A) + \\
&\sum_{i \in V(A), j \in V(B)}^{i \neq a, j \neq b} [d_{ia}^e(w, A) + d_{ab}(w) + d_{bj}^e(w, B)] + \\
&\sum_{i \in V(A), j \in V(B)}^{i \neq a, j \neq b} [d_{ia}^o(w, A) + d_{ab}(w) + d_{bj}^o(w, B)] + \\
W^o(w, B) &= W^o(w, A) + |d_b^e(w, B)| \sum_{i \in V(A)}^{i \neq a} d_{ia}^e(w, A) + \\
d_{ab}(w) &|d_a^e(w, A)| |d_b^e(w, B)| + |d_a^e(w, A)| \sum_{j \in V(B)}^{j \neq b} d_{bj}^e(w, B) + \\
|d_b^o(w, B)| &\sum_{i \in V(A)}^{i \neq a} d_{ia}^o(w, A) + d_{ab}(w) |d_a^o(w, A)| |d_b^o(w, B)| + \\
&|d_a^o(w, A)| \sum_{j \in V(B)}^{j \neq b} d_{bj}^o(w, B) + W^o(w, B)
\end{aligned}$$

Theorems 2 and 3 afford the computation of even and odd Wiener indices for combinatorial libraries, using a procedure similar to Algorithm 1.

Algorithm 2. 1. Consider a core structure C with m substitution atoms c_1, c_2, \dots, c_m and m substituents R_1, R_2, \dots, R_m , each having one substitution atom r_1, r_2, \dots, r_m , respectively. The final molecular graph is presented in Figure 2.

2. Compute the even Wiener indices for the core structure C and the m substituents R_1, R_2, \dots, R_m , i.e. $W^e(w, C)$, $W^e(w, R_1)$, $W^e(w, R_2)$, ..., $W^e(w, R_m)$.

3. Compute the odd Wiener indices for the core structure C and the m substituents R_1, R_2, \dots, R_m , i.e. $W^o(w, C)$, $W^o(w, R_1)$, $W^o(w, R_2)$, ..., $W^o(w, R_m)$.

4. Compute the sum of even graph distances for the substitution atoms $c_1, c_2, \dots, c_m, r_1, r_2, \dots, r_m$, i.e. $W_{c_1}^e(w, C)$, $W_{c_2}^e(w, C)$, ..., $W_{c_m}^e(w, C)$, $W_{r_1}^e(w, R_1)$, $W_{r_2}^e(w, R_2)$, ..., $W_{r_m}^e(w, R_m)$.

5. Calculate the sum of odd graph distances for the substitution atoms $c_1, c_2, \dots, c_m, r_1, r_2, \dots, r_m$, i.e. $W_{c_1}^o(w, C)$, $W_{c_2}^o(w, C)$, ..., $W_{c_m}^o(w, C)$, $W_{r_1}^o(w, R_1)$, $W_{r_2}^o(w, R_2)$, ..., $W_{r_m}^o(w, R_m)$.

6. For all $m(m-1)/2$ pairs of substitution atoms from the core C compute the topological distance $d_{c_i c_j}(t)$ between atoms c_i and c_j , determine the type of each distance (i.e., even if atoms c_i and c_j are separated by an even number of bonds, or odd if atoms c_i and c_j are separated by an odd number of bonds), and compute the corresponding even $d_{c_i c_j}^e(w)$ or odd $d_{c_i c_j}^o(w)$ distance.

7. Determine the bond distances $d_{r_i c_i}(w)$ between all m pairs of connection atoms, where r_i belongs to the substituent R_i , and c_i belongs to the core structure C .

8. To an intermediate structure $CR_1 \dots R_{i-1}$ add the substituent R_i by inserting a bond between atoms r_i and c_i , and obtain in this way $CR_1 \dots R_i$.

9. Compute the even Wiener index of $CR_1 \dots R_i$, $W^e(w, CR_1 \dots R_i)$:

$$\begin{aligned}
W^e(w, CR_1 \dots R_i) &= W^e(w, CR_1 \dots R_{i-1}) + \\
&|d_{r_i}^o(w, R_i)| W_{c_i}^e(w, CR_1 \dots R_{i-1}) + \\
d_{r_i c_i}(w) &|d_{c_i}^e(w, CR_1 \dots R_{i-1})| |d_{r_i}^o(w, R_i)| + \\
|d_{c_i}^e(w, CR_1 \dots R_{i-1})| &W_{r_i}^o(w, R_i) + \\
|d_{r_i}^e(w, R_i)| &W_{c_i}^o(w, CR_1 \dots R_{i-1}) + \\
d_{r_i c_i}(w) &|d_{c_i}^o(w, CR_1 \dots R_{i-1})| |d_{r_i}^e(w, R_i)| + \\
|d_{c_i}^o(w, CR_1 \dots R_{i-1})| &W_{r_i}^e(w, R_i) + W^e(w, R_i) \quad (29)
\end{aligned}$$

10. Compute the odd Wiener index of $CR_1 \dots R_i$, $W^o(w, CR_1 \dots R_i)$:

$$\begin{aligned}
W^o(w, CR_1 \dots R_i) &= W^o(w, CR_1 \dots R_{i-1}) + \\
&|d_{r_i}^e(w, R_i)| W_{c_i}^o(w, CR_1 \dots R_{i-1}) + \\
d_{r_i c_i}(w) &|d_{c_i}^o(w, CR_1 \dots R_{i-1})| |d_{r_i}^e(w, R_i)| + \\
|d_{c_i}^o(w, CR_1 \dots R_{i-1})| &W_{r_i}^e(w, R_i) + \\
|d_{r_i}^o(w, R_i)| &W_{c_i}^e(w, CR_1 \dots R_{i-1}) + \\
d_{r_i c_i}(w) &|d_{c_i}^e(w, CR_1 \dots R_{i-1})| |d_{r_i}^o(w, R_i)| + \\
|d_{c_i}^e(w, CR_1 \dots R_{i-1})| &W_{r_i}^o(w, R_i) + W^o(w, R_i) \quad (30)
\end{aligned}$$

11. Determine the number of vertices in the subgraph $CR_1 \dots R_i$:

$$|V(CR_1 \dots R_i)| = |V(CR_1 \dots R_{i-1})| + |V(R_i)| \quad (31)$$

12. Update the even distance sum of atoms c_j , $i < j \leq m$, in the intermediate structure $CR_1 \dots R_i$. The set of atoms c_j represents those substitution atoms from the core structure C that are not bonded to substituents in $CR_1 \dots R_i$. After adding the substituent R_i to C the distance sums of all atoms c_j must be updated. In computing the even distance sum of vertex c_j from $CR_1 \dots R_i$ one can distinguish two cases, namely when the shortest-path distance between c_i and c_j is even (vertices c_i and c_j are separated by an even number of bonds):

$$\begin{aligned}
W_{c_j}^e(w, CR_1 \dots R_i) &= W_{c_j}^e(w, CR_1 \dots R_{i-1}) + (d_{c_i c_j}^e(w) + \\
&d_{r_i c_i}(w)) |d_{r_i}^o(w, R_i)| + W_{r_i}^o(w, R_i) \quad (32)
\end{aligned}$$

and the case when the shortest-path distance between c_i and c_j is odd (vertices c_i and c_j are separated by an odd number of bonds):

$$\begin{aligned}
W_{c_j}^o(w, CR_1 \dots R_i) &= W_{c_j}^o(w, CR_1 \dots R_{i-1}) + (d_{c_i c_j}^o(w) + \\
&d_{r_i c_i}(w)) |d_{r_i}^e(w, R_i)| + W_{r_i}^e(w, R_i) \quad (33)
\end{aligned}$$

13. Update the odd distance sum of atoms c_j , $i < j \leq m$, in the intermediate structure $CR_1 \dots R_i$. In updating the odd distance sum of vertex c_j from $CR_1 \dots R_i$ there are two cases, namely when the shortest-path distance between c_i and c_j is even

$$\begin{aligned}
W_{c_j}^o(w, CR_1 \dots R_i) &= W_{c_j}^o(w, CR_1 \dots R_{i-1}) + (d_{c_i c_j}^e(w) + \\
&d_{r_i c_i}(w)) |d_{r_i}^e(w, R_i)| + W_{r_i}^e(w, R_i) \quad (34)
\end{aligned}$$

and the case when the shortest-path distance between c_i and c_j is odd:

$$W_{c_j}^o(w, CR_1 \dots R_i) = W_{c_j}^o(w, CR_1 \dots R_{i-1}) + (d_{c_i, c_j}^o(w) + d_{r_i, c_i}(w)) |d_{r_i}^o(w, R_i)| + W_{r_i}^o(w, R_i) \quad (35)$$

Repeat steps 8–13 until $W^e(w, CR_1 \dots R_m)$ and $W^o(w, CR_1 \dots R_m)$ are computed.

The computational complexity of Algorithm 2 is comparable with that of Algorithm 1; a similar analysis of computer operations clearly demonstrates that the computation of even/odd Wiener indices with eqs 27 and 28 involves $O(m^2)$ operations per compound (depending only on the number m of radicals R_i attached to the core structure C), while eqs 22 and 23 require $O(N^3)$ operations per compound (depending on the number N of atoms in the molecular graph, which is very large compared to m).

RESISTANCE DISTANCE INDEX

Klein and Randić introduced a new distance function on graphs named resistance distance,⁵⁹ applying some results from the electrical network theory; this novel graph distance was utilized to define the resistance-distance matrix Ω , proposed as an alternative to the distance matrix \mathbf{D} .^{66–68} For the computation of the molecular matrix Ω , Klein and Randić superposed onto the molecular graph G an electrical network of resistors, in such a way that carbon atoms become nodes in the network and carbon–carbon single bonds are represented as 1 ohm resistors; the matrix element Ω_{ij} is equal to the effective electrical resistance between the vertices i and j . From the theory of electrical networks it is easy to determine that in the case of acyclic hydrocarbons (i.e. alkanes, alkenes, alkynes, etc.), the resistance-distance matrix Ω is identical with the distance matrix \mathbf{D} , while in the case of cyclic compounds the two matrices are different. We present here a more general definition and procedure for the computation of the resistance-distance matrix Ω of weighted molecular graphs, corresponding to organic compounds with heteroatoms and multiple bonds. Consider an electrical network of resistors in which a node (vertex) i corresponds to a vertex (with the same label) in the molecular graph G , while each chemical bond $\{i, j\}$ from the molecular graph is represented as a resistor between nodes i and j . Each resistor has a value $Ew_{ij}(w)$ (in ohm) depending on the chemical nature of the atoms represented by vertices i and j and on the type of the chemical bond between them; the $Ew_{ij}(w)$ parameter is computed using the weighting schemes w proposed in the literature. The computation of the resistance-distance matrix of a vertex- and edge-weighted molecular graph comprises the following steps:

1. Set up the edge-weighted adjacency matrix of the molecular graph G that contains heteroatoms and multiple bonds

$$\mathbf{A}_{ij}(w, G) = \begin{cases} 0 & \text{if } i = j \\ Ew_{ij}(w) & \text{if } \{i, j\} \in E(G) \\ 0 & \text{if } \{i, j\} \notin E(G) \end{cases} \quad (36)$$

where $Ew_{ij}(w)$ is the weight of the edge $\{i, j\}$ computed with the weighting scheme w .

2. Compute the reverse adjacency matrix $\mathbf{A}^-(w, G)$:

$$\mathbf{A}_{ij}^-(w, G) = \begin{cases} 0 & \text{if } i = j \\ 1/\mathbf{A}_{ij}(w, G) & \text{if } \{i, j\} \in E(G) \\ 0 & \text{if } \{i, j\} \notin E(G) \end{cases} \quad (37)$$

3. Obtain the Laplacian matrix of the reverse adjacency matrix:

$$\mathbf{L}_{ij}(w, G) = \begin{cases} \sum_{\{i, k\} \in E(G)} \mathbf{A}_{ik}^-(w, G) & \text{if } i = j \\ -\mathbf{A}_{ij}^-(w, G) & \text{if } \{i, j\} \in E(G) \\ 0 & \text{if } \{i, j\} \notin E(G) \end{cases} \quad (38)$$

4. Calculate the eigenvalues and eigenvectors of the weighted Laplacian matrix $\mathbf{L}(w, G)$ of the molecular graph G with N vertices

$$\mathbf{L} = \mathbf{U}\mathbf{\Lambda}\mathbf{U}^t \quad (39)$$

where \mathbf{U} is an $N \times N$ column matrix of eigenvectors of the weighted Laplacian matrix \mathbf{L} , \mathbf{U}^t is the transpose matrix, and $\mathbf{\Lambda}$ is an $N \times N$ diagonal matrix containing on the main diagonal the eigenvalues of \mathbf{L} ; the eigenvalue $[\mathbf{\Lambda}]_{ii}$ corresponds to the eigenvector from the i th column of matrix \mathbf{U} . For any connected molecular graph the Laplacian matrix \mathbf{L} has all eigenvalues positive except for one which is 0.

5. The $N \times N$ diagonal matrix \mathbf{V} is computed from the eigenvalues of \mathbf{L} :

$$[\mathbf{V}]_{ij} = \begin{cases} 0 & \text{if } [\mathbf{\Lambda}]_{ij} = 0 \\ [\mathbf{\Lambda}]_{ij}^{-1} & \text{if } [\mathbf{\Lambda}]_{ij} \neq 0 \end{cases} \quad (40)$$

6. The generalized inverse of \mathbf{L} is the matrix $\mathbf{\Gamma}$ which is 0 on its null eigenspace and the “true” inverse on the subspace orthogonal to this null space:

$$\mathbf{\Gamma} = \mathbf{U}\mathbf{V}\mathbf{U}^t \quad (41)$$

7. The resistance-distance matrix is obtained from $\mathbf{\Gamma}$:

$$\Omega_{ij}(w, G) = \begin{cases} \Gamma_{ii}(w, G) - 2\Gamma_{ij}(w, G) + \Gamma_{jj}(w, G) & \text{if } i \neq j \\ 0 & \text{if } i = j \end{cases} \quad (42)$$

The resistance-distance matrix is the source of a topological index related to W , namely the resistance-distance index W' :

$$W'(w, G) = \sum_{i, j \in V(G)}^{i < j} \Omega_{ij}(w, G) \quad (43)$$

Because the objective of this section is to introduce a new and fast algorithm for computing the resistance-distance index W' , it is relevant to estimate the computational complexity for obtaining W' with the above described algorithm that uses eqs 36–43. For a molecular graph containing N atoms and M bonds and starting from an $N \times N$ matrix with all elements equal to zero, the connection table is translated into the Laplacian matrix of the reverse

adjacency matrix $\mathbf{A}^-(w,G)$ in $O(M)$ computer operations. For each chemical compound the computation of the eigenvalues and eigenvectors of the Laplacian matrix $\mathbf{L}(w,G)$ needs $O(N^3)$ operations, representing the most expensive part of the algorithm regarding the computing time. Starting from an $N \times N$ matrix with all elements equal to zero, the diagonal matrix \mathbf{V} is obtained in $O(N)$ operations, while the matrix Γ is computed in $O(N^3)$ operations, representing another costly step of the algorithm. Finally, the resistance-distance matrix Ω is obtained in $O(N^2)$ computer operations with eq 42 and another $O(N^2)$ computer operations are needed in eq 43 to obtain the resistance-distance index W' . The conclusion of the above complexity analysis for obtaining W' is that the computation of the eigenvalues and eigenvectors of the Laplacian matrix $\mathbf{L}(w,G)$ and the generation of the matrix Γ are the most computationally intensive steps, each one involving $O(N^3)$ operations. Obviously, the algorithm for computing the resistance-distance index W' , presented in eqs 36–43, requires large computational resources for VSCL, because combinatorial compounds contain a fairly large number of atoms, and much more than 10^6 such molecules must be evaluated in a short period of time. In the following part of this section we present a novel algorithm for computing the resistance-distance index W' for organic compounds assembled from building blocks, algorithm that is especially efficient for large combinatorial libraries.

With $W'_i(G)$ we denote the sum of the resistance distances between vertex i and all other vertices from G :

$$W'_i(w,G) = \sum_{j \in V(G)}^{i \neq j} \Omega_{ij}(w,G) \quad (44)$$

For the computation of the resistance-distance index W' for molecular graphs that can be decomposed in building blocks (subgraphs) by deleting one edge one can use an equation similar to that presented in Theorem 1 for the decomposition of the Wiener index W .

Theorem 4. Let $\{a,b\}$ be a cut edge between two subgraphs A and B of G such that $a \in A$ and $b \in B$. The atom and bond parameters are computed with the weighting scheme w , and the resistance distance between vertices a and b is $\Omega_{ab}(w)$. Denote various subgraphs of $G = A-B$ as in the Figure 1. Then the resistance-distance index of graph G is

$$W'(w,G) = W'(w,A-B) = W'(w,A) + |V(B)|W'_a(w,A) + \Omega_{ab}(w)|V(A)||V(B)| + |V(A)|W'_b(w,B) + W'(w,B) \quad (45)$$

Proof. The resistance-distance index of graph $G = A-B$ is the sum of three types of resistance distances, namely between pairs of vertices from A , between pairs of vertices from B , and between a vertex from A and another vertex from B . Then, the resistance distance between a vertex i from A and another vertex j from B is partitioned into three terms: the resistance distance between vertex i and the cut vertex a , the resistance distance between cut vertices a and b , and the resistance distance between the cut vertex b and vertex j . Substituting then in this equality eqs 43 and 44 completes the demonstration of Theorem 4:

$$\begin{aligned} W'(w,G) = W'(w,A-B) &= \sum_{i,j \in V(A)}^{i \leq j} \Omega_{ij}(w,A) + \sum_{i \in V(A)} \sum_{j \in V(B)} \Omega_{ij} \\ (w) + \sum_{i,j \in V(B)}^{i \leq j} \Omega_{ij}(w,B) &= W'(w,A) + \sum_{i \in V(A)}^{i \neq a} \sum_{j \in V(B)}^{j \neq b} (\Omega_{ia}(w,A) + \\ &\Omega_{ab}(w) + \Omega_{bj}(w,B)) + W'(w,B) = W'(w,A) + |V \\ &(B)| \sum_{i \in V(A)}^{i \neq a} \Omega_{ia}(w,A) + \Omega_{ab}(w)|V(A)||V(B)| + |V \\ &(A)| \sum_{j \in V(B)}^{j \neq b} \Omega_{bj}(w,B) + W'(w,B) \end{aligned}$$

We present now all steps for an algorithm that allows one to compute the resistance-distance index W' with eq 45 for the general case when a chemical compound $CR_1 \dots R_m$ is generated from a core structure C and m substituents R_1, R_2, \dots, R_m .

Algorithm 3. 1. Consider the generation of a combinatorial library from a core structure C with m substitution atoms c_1, c_2, \dots, c_m and m substituents R_1, R_2, \dots, R_m , each having one substitution atom r_1, r_2, \dots, r_m , respectively. The final molecular graph is presented in Figure 2.

2. Compute the resistance-distance indices for the core structure C and the m substituents R_1, R_2, \dots, R_m , i.e. $W'(w,C), W'(w,R_1), W'(w,R_2), \dots, W'(w,R_m)$.

3. Compute the resistance-distance sum for the substitution atoms $c_1, c_2, \dots, c_m, r_1, r_2, \dots, r_m$, i.e. $W'_{c_1}(w,C), W'_{c_2}(w,C), \dots, W'_{c_m}(w,C), W'_{r_1}(w,R_1), W'_{r_2}(w,R_2), \dots, W'_{r_m}(w,R_m)$.

4. Calculate the resistance distances $\Omega_{c_i c_j}(w)$ between all $m(m-1)/2$ pairs of substitution atoms from the core C .

5. Determine the resistance distances $\Omega_{r_i c_i}(w)$ between all m pairs of connection atoms, where r_i belongs to the substituent R_i , and c_i belongs to the core structure C .

6. To an intermediate structure $CR_1 \dots R_{i-1}$ add the substituent R_i by inserting a bond between atoms r_i and c_i and obtain in this way $CR_1 \dots R_i$.

7. Compute the resistance-distance index of $CR_1 \dots R_i$, $W'(w,CR_1 \dots R_i)$:

$$\begin{aligned} W'(w,CR_1 \dots R_i) &= W'(w,CR_1 \dots R_{i-1}) + \\ &|V(R_i)|W'_{c_i}(w,CR_1 \dots R_{i-1}) + \\ &\Omega_{r_i c_i}(w)|V(CR_1 \dots R_{i-1})||V(R_i)| + \\ &|V(CR_1 \dots R_{i-1})|W'_{r_i}(w,R_i) + W(w,R_i) \quad (46) \end{aligned}$$

8. Determine the number of vertices in the subgraph $CR_1 \dots R_i$:

$$|V(CR_1 \dots R_i)| = |V(CR_1 \dots R_{i-1})| + |V(R_i)| \quad (47)$$

9. Update the resistance-distance sum of atoms $c_j, i < j \leq m$, in the intermediate structure $CR_1 \dots R_i$ with the equation:

$$\begin{aligned} W'_{c_j}(w,CR_1 \dots R_i) &= W'_{c_j}(w,CR_1 \dots R_{i-1}) + (\Omega_{c_i c_j}(w) + \\ &\Omega_{r_i c_i}(w))|V(R_i)| + W'_{r_i}(w,R_i) \quad (48) \end{aligned}$$

Repeat steps 6–9 until $W'(w,CR_1 \dots R_m)$ is computed.

Table 4. Resistance Distance-Based Structural Descriptors for the Building Blocks R_1 , R_2 , and R_3 (Figure 5) Computed with the Weighting Schemes X , Y , and Z

R	$W'(X,R)$	$W'(Y,R)$	$W'(Z,R)$	$W'_r(X,R)$	$W'_r(Y,R)$	$W'_r(Z,R)$
15	0.000	0.000	0.000	0.000	0.000	0.000
16	38.444	38.444	38.444	16.889	16.889	16.889
17	161.778	161.778	161.778	19.778	19.778	19.778
18	17.500	17.500	17.500	5.833	5.833	5.833
19	4.000	4.000	4.000	2.000	2.000	2.000
20	38.444	38.444	38.444	16.889	16.889	16.889
21	67.164	73.991	66.636	25.004	26.689	24.873
22	4.000	4.000	4.000	3.000	3.000	3.000
23	21.556	21.556	21.556	9.889	9.889	9.889
24	63.333	63.333	63.333	24.889	24.889	24.889
25	9.000	9.000	9.000	3.000	3.000	3.000
26	17.500	17.500	17.500	5.833	5.833	5.833
27	10.000	10.000	10.000	6.000	6.000	6.000
28	54.600	65.297	53.875	17.325	20.270	17.125

The procedure outlined above for the fast computation of the resistance-distance index W' is especially efficient for large chemical libraries of combinatorially generated compounds. Because Algorithm 3 is similar with Algorithm 1 (for computing the Wiener index W), the number of computer operations needed per compound is proportional to $O(m^2)$, which is a significant improvement over the “classical” and more general algorithm presented in eqs 36–43.

We present here an example for the computation of W' for the 100-member combinatorial library of α -ketoamides⁵⁰ used in the section dedicated to the Wiener index W . As outlined in Algorithm 3, the application of Theorem 4 for the computation of the resistance-distance index W' uses several distance-based indices for the core structure and substituents. In Table 2 we present the set of invariants computed for the core structure with the three weighting schemes X , Y , and Z : the resistance-distance index $W'(w,C)$, the resistance-distance sums to a connection atom c_i , $W'_{c_i}(w,C)$, $W'_{c_2}(w,C)$, and $W'_{c_3}(w,C)$, and the resistance distances between pairs of connection atoms $\Omega_{c_1c_2}(w)$, $\Omega_{c_1c_3}(w)$, and $\Omega_{c_2c_3}(w)$. For the substituents **15**–**28** we present in Table 4 all indices needed in the Algorithm 3, i.e. the resistance-distance index $W'(w,R)$, and the resistance-distance sums to a connection atom r , $W'_r(w,R)$. These indices presented in Tables 2 and 4 are solely needed to compute the resistance-distance index of all members from the combinatorial library of α -ketoamides.

To further demonstrate the utility and easiness of use of Algorithm 3 we present below all steps from the computation of the Wiener index for an α -ketoamide with the general formula $CR_1R_2R_3$ assembled from the core structure C and three substituents R_1 , R_2 , and R_3 , representing the aldehyde **2**, the amine **7**, and the isocyanide **14** (Figure 4), corresponding to the building blocks **16**, **21**, and **28** (Figure 5), respectively. The steps of this computation use the resistance-distance indices from Tables 2 and 4 and follow the stages outlined in Algorithm 3:

1. Compute the resistance-distance indices for the four building blocks: $W'(X,C) = 111.887$, $W'(X,R_1) = 38.444$, $W'(X,R_2) = 67.164$, $W'(X,R_3) = 54.600$.

2. Compute the resistance-distance sums for the six connection atoms: $W'_{c_1}(X,C) = 18.600$, $W'_{c_2}(X,C) = 16.860$, $W'_{c_3}(X,C) = 29.563$, $W'_{r_1}(X,R_1) = 16.889$, $W'_{r_2}(X,R_2) = 25.004$, $W'_{r_3}(X,R_3) = 17.325$.

3. Compute the resistance distance between all pairs of connection vertices from the core structure C : $\Omega_{c_1c_2}(X) = 0.870$, $\Omega_{c_1c_3}(X) = 1.870$, $\Omega_{c_2c_3}(X) = 2.741$.

4. Determine the resistance distances $\Omega_{r_i c_i}(X)$ between all pairs of connection atoms, where the first atom r_i belongs to the substituent R_i , and the second atom c_i belongs to the core structure C : $\Omega_{r_1 c_1}(X) = 1.000$, $\Omega_{r_2 c_2}(X) = 0.870$, $\Omega_{r_3 c_3}(X) = 0.870$.

5. Get the number of vertices in all four building blocks: $|V(C)| = 10$, $|V(R_1)| = 8$, $|V(R_2)| = 9$, $|V(R_3)| = 8$.

6. Connect the substituent R_1 to C by joining vertices r_1 and c_1 , obtaining in this way CR_1 .

7. Compute the resistance-distance index of CR_1 , $W'(X,CR_1)$, with the equation:

$$W'(X,CR_1) = W'(X,C) + |V(R_1)|W'_{c_1}(X,C) + \Omega_{r_1 c_1}(X)|V(C)||V(R_1)| + |V(C)|W'_{r_1}(X,R_1) + W'(X,R_1) \quad (49)$$

$$W'(X,CR_1) = 111.887 + 8 \times 18.600 + 1.000 \times 10 \times 8 + 10 \times 16.889 + 38.444 = 548.024$$

8. Determine the number of vertices in the subgraph CR_1 :

$$|V(CR_1)| = 10 + 8 = 18$$

9. Compute the resistance-distance sum of atom c_2 in the intermediate structure CR_1 :

$$W'_{c_2}(X,CR_1) = W'_{c_2}(X,C) + (\Omega_{c_1c_2}(X) + \Omega_{r_1 c_1}(X))|V(R_1)| + W'_{r_1}(X,R_1) \quad (50)$$

$$W'_{c_2}(X,CR_1) = 16.860 + (0.870 + 1.000) \times 8 + 16.889 = 48.711$$

10. Compute the resistance-distance sum of atom c_3 in the intermediate structure CR_1 :

$$W'_{c_3}(X,CR_1) = W'_{c_3}(X,C) + (\Omega_{c_1c_3}(X) + \Omega_{r_1 c_1}(X))|V(R_1)| + W'_{r_1}(X,R_1) \quad (51)$$

$$W'_{c_3}(X,CR_1) = 29.563 + (1.870 + 1.000) \times 8 + 16.889 = 69.414$$

11. Connect the substituent R_2 to CR_1 by joining vertices r_2 and c_2 , obtaining in this way CR_1R_2 .

12. Compute the resistance-distance index of CR_1R_2 , $W'(X,CR_1R_2)$:

$$W'(X,CR_1R_2) = W'(X,CR_1) + |V(R_2)|W'_{c_2}(X,CR_1) + \Omega_{r_2 c_2}(X)|V(CR_1)||V(R_2)| + |V(CR_1)|W'_{r_2}(X,R_2) + W'(X,R_2) \quad (52)$$

$$W'(X,CR_1R_2) = 548.024 + 9 \times 48.711 + 0.870 \times 18 \times 9 + 18 \times 25.004 + 67.164 = 1644.651$$

13. Determine the number of vertices in the subgraph CR_1R_2 :

$$|V(CR_1R_2)| = 18 + 9 = 27$$

14. Compute the resistance-distance sum of atom c_3 in the intermediate structure CR_1R_2 :

$$W'_{c_3}(X, CR_1R_2) = W'_{c_3}(X, CR_1) + (\Omega_{c_2c_3}(X) + \Omega_{r_2c_2}(X))|V(R_2)| + W'_{r_2}(X, R_2) \quad (53)$$

$$W'_{c_3}(X, CR_1R_2) = 69.414 + (2.741 + 0.870) \times 9 + 25.004 = 126.917$$

15. Connect the substituent R_3 to CR_1R_2 by joining vertices r_3 and c_3 , obtaining in this way $CR_1R_2R_3$.

16. Compute the resistance-distance index of $CR_1R_2R_3$, $W'(X, CR_1R_2R_3)$:

$$W'(X, CR_1R_2R_3) = W'(X, CR_1R_2) + |V(R_3)|W'_{c_3}(X, CR_1R_2) + \Omega_{r_3c_3}(X)|V(CR_1R_2)||V(R_3)| + |V(CR_1R_2)|W'_{r_3}(X, R_3) + W'(X, R_3) \quad (54)$$

$$W'(X, CR_1R_2R_3) = 1644.651 + 8 \times 126.917 + 0.870 \times 27 \times 8 + 27 \times 17.325 + 54.600 = 3370.341$$

Chemical libraries of combinatorially generated molecules represent the current source of drug leads, efficient catalysts, or new materials, and their use creates impressive computational and experimental challenges. One of them is the efficient generation of structural descriptors that represent in a numerical way the molecular size and shape together with steric, electronic, and lipophilic characteristics. This section presented an efficient way of computing the resistance-distance index W' for molecules assembled from building blocks. Our approach, presented in detail in Algorithm 3, represents a major improvement over the usual method of computing W' , presented in eqs 36–43. The computational complexity of this novel algorithm is $O(m^2)$, significantly smaller than $O(N^3)$, required by the method from eqs 36–43. Our method belongs to the novel trend of computing structural descriptors for combinatorial compounds without assembling the product structure but from structural indices of the reactants or building blocks.

CONCLUSIONS

Together with other classes of structural descriptors (i.e., LFER substituent constants, geometrical descriptors, and quantum indices), graph invariants and topological indices are extensively used in QSPR, SAR, and QSAR studies as effective numerical descriptors of the chemical structure. Their recent applications in the investigation of chemical libraries revealed their efficiency in quantifying the similarity, diversity, and the drug-like character of chemicals. In all QSPR and QSAR studies the topological indices are computed with general numerical methods (i.e., one can use them for any chemical structure), but often such algorithms require significant computational resources. For example, for a molecule with N atoms, the calculation of the distance matrix from the adjacency matrix requires $O(N^3)$ computer operations, and as the number of atoms increases the generation of the distance matrix consumes the largest part of the computational effort required to obtain distance-based topological indices. As an alternative to the computation of graph invariants and topological indices with numerical methods, mathematical chemists developed recurrence rela-

tionships or subgraph decomposition equations that calculate a graph invariant from the invariants of selected subgraphs, usually obtained after deleting a vertex, edge, or cycle.^{15,51} Although such algorithms are efficient in terms of computational expenses, these subgraph decomposition equations have not previously found an application in computing topological indices for QSAR studies, due to the relatively small number of compounds, usually between 10 and 100, in the QSAR studies. In such cases, when the computation time for obtaining the structural descriptors is not critical, the topological indices are obtained with numerical methods because this is the most straightforward and general procedure. However, the process of screening virtual and synthetic combinatorial libraries has some special characteristics that make attractive and time-effective the computation of topological indices with subgraph decomposition equations. Using a relative small number of reactants that are combined following a general reaction scheme, a virtual library can easily exceed 10^6 compounds. Therefore, the time needed to compute the structural descriptors becomes critical, so that recent investigations have been dedicated to the development of simplified algorithms for the calculation of descriptors, such as the molecular polar surface area approximated as the sum of N, O, P, and S atoms contributions,⁴⁰ or the van der Waals molecular surface area computed from the atomic connectivity information.⁴¹

An equally efficient approach is represented by a group of algorithms for computing the structural descriptors of reaction products without actually assembling the molecules from the building blocks,^{38,44} an approach that was further developed in this paper. Using heteroatom-containing molecular graphs we have demonstrated several subgraph decomposition equations for distance-based topological indices and graph invariants: the Wiener index, even/odd Wiener index, and resistance-distance index. We have proposed simple and fast algorithms for the computation of these topological indices for very large virtual combinatorial libraries without generating the reaction products. The procedure uses numerical methods to compute distance-based graph invariants only for the building blocks. The values are stored and used to compute topological indices for the reaction products with the subgraph decomposition equations proposed in this paper. In this way, the most expensive step in computing distance-based topological indices, namely the generation of the individual distance matrices, is avoided, and the time investment, proportional to the total number of compounds, scales as $O(m^2)$ when there are m substituent positions around a core structure.

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REFERENCES AND NOTES

- (1) Gallop, M. A.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gordon, E. M. Application of Combinatorial Technologies to Drug Discovery. 1. Background and Peptide Combinatorial Libraries. *J. Med. Chem.* **1994**, *37*, 1233–1251.
- (2) Gordon, E. M.; Barrett, R. W.; Dower, W. J.; Fodor, S. P. A.; Gallop, M. A. Application of Combinatorial Technologies to Drug Discovery. 2. Combinatorial Organic-synthesis, Library Screening Strategies, and Future Directions. *J. Med. Chem.* **1994**, *37*, 1385–1401.

- (3) Fauchère, J.-L.; Boutin, J. A.; Henlin, J.-M.; Kucharczyk, N.; Ortuno, J.-C. Combinatorial Chemistry for the Generation of Molecular Diversity and the Discovery of Bioactive Leads. *Chemom. Intell. Lab. Syst.* **1998**, *43*, 43–68.
- (4) Drewry, D. H.; Young, S. S. Approaches to the Design of Combinatorial Libraries. *Chemom. Intell. Lab. Syst.* **1999**, *48*, 1–20.
- (5) Agrafiotis, D. K.; Myslik, J. C.; Salemme, F. R. Advances in Diversity Profiling and Combinatorial Series Design. *Mol. Diversity* **1999**, *4*, 1–22.
- (6) Beno, B. R.; Mason, J. S. The Design of Combinatorial Libraries Using Properties and 3D Pharmacophore Fingerprints. *Drug Design Today* **2001**, *6*, 251–258.
- (7) Sheridan, R. P.; Kearsley, S. K. Using a Genetic Algorithm to Suggest Combinatorial Libraries. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 310–320.
- (8) Taylor, R. Simulation Analysis of Experimental Design Strategies for Screening Random Compounds as Potential New Drugs and Agrochemicals. *J. Chem. Inf. Comput. Sci.* **1995**, *35*, 59–67.
- (9) Gillet, V. J.; Willett, P.; Bradshaw, J. The Effectiveness of Reactant Pools for Generating Structurally-Diverse Combinatorial Libraries. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 731–740.
- (10) Good, A. C.; Lewis, R. A. New Methodology for Profiling Combinatorial Libraries and Screening Sets: Cleaning Up the Design Process with HARPick. *J. Med. Chem.* **1997**, *40*, 3926–3936.
- (11) Pickett, S. D.; Luttmann, C.; Guerin, V.; Laoui, A.; James, E. DIVSEL and COMPLIB – Strategies for the Design and Comparison of Combinatorial Libraries Using Pharmacophoric Descriptors. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 144–150.
- (12) Gillet, V. J.; Willett, P.; Bradshaw, J.; Green, D. V. S. Selecting Combinatorial Libraries to Optimize Diversity and Physical Properties. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 169–177.
- (13) Grassy, G.; Calas, B.; Yasri, A.; Lahana, R.; Woo, J.; Iyer, S.; Kaczorek, M.; Floc'h, R.; Buelow, R. Computer-Assisted Rational Design of Immunosuppressive Compounds. *Nature Biotechnol.* **1998**, *16*, 748–752.
- (14) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. Multiple-Component Condensation Strategies for Combinatorial Library Synthesis. *Acc. Chem. Res.* **1996**, *29*, 123–131.
- (15) Ivanciuc, O.; Balaban, A. T. The Graph Description of Chemical Structures. In *Topological Indices and Related Descriptors in QSAR and QSPR*; Devillers, J., Balaban, A. T., Eds.; Gordon and Breach Science Publishers: Amsterdam, 1999; pp 59–167.
- (16) Ivanciuc, O.; Ivanciuc, T.; Balaban, A. T. Vertex- and Edge-Weighted Molecular Graphs and Derived Structural Descriptors. In *Topological Indices and Related Descriptors in QSAR and QSPR*; Devillers, J., Balaban, A. T., Eds.; Gordon and Breach Science Publishers: Amsterdam, 1999; pp 169–220.
- (17) Ivanciuc, O.; Ivanciuc, T. Matrices and Structural Descriptors Computed from Molecular Graph Distances. In *Topological Indices and Related Descriptors in QSAR and QSPR*; Devillers, J., Balaban, A. T., Eds.; Gordon and Breach Science Publishers: Amsterdam, 1999; pp 221–277.
- (18) Wiener, H. Structural Determination of Paraffin Boiling Points. *J. Am. Chem. Soc.* **1947**, *69*, 17–20.
- (19) Wiener, H. Correlation of Heats of Isomerization and Differences in Heats of Vaporization of Isomers among the Paraffin Hydrocarbons. *J. Am. Chem. Soc.* **1947**, *69*, 2636–2638.
- (20) Randić, M. On Characterization of Molecular Branching. *J. Am. Chem. Soc.* **1975**, *97*, 6609–6615.
- (21) Kier, L. B.; Hall, L. H. *Molecular Connectivity in Chemistry and Drug Research*; Academic Press: New York, 1976.
- (22) Balaban, A. T. Highly Discriminating Distance-Based Topological Index. *Chem. Phys. Lett.* **1982**, *89*, 399–404.
- (23) Balaban, A. T. Chemical Graphs. Part 48. Topological Index J for Heteroatom-Containing Molecules Taking Into Account Periodicities of Element Properties. *MATCH (Commun. Math. Chem.)* **1986**, *21*, 115–122.
- (24) Plavšić, D.; Nikolić, S.; Trinajstić, N.; Mihalić, Z. On the Harary Index for the Characterization of Chemical Graphs. *J. Math. Chem.* **1993**, *12*, 235–250.
- (25) Ivanciuc, O.; Balaban, T.-S.; Balaban, A. T. Design of Topological Indices. Part 4. Reciprocal Distance Matrix, Related Local Vertex Invariants and Topological Indices. *J. Math. Chem.* **1993**, *12*, 309–318.
- (26) Pearlman, R. S.; Smith, K. M. Metric Validation and the Receptor-Relevant Subspace Concept. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 28–35.
- (27) Ivanciuc, O.; Taraviras, S. L.; Cabrol-Bass, D. Quasi-Orthogonal Basis Sets of Molecular Graph Descriptors as a Chemical Diversity Measure. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 126–134.
- (28) Taraviras, S. L.; Ivanciuc, O.; Cabrol-Bass, D. Identification of Groupings of Graph Theoretical Molecular Descriptors Using a Hybrid Cluster Analysis Approach. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1128–1146.
- (29) Ajay; Walters, W. P.; Murcko, M. A. Can We Learn to Distinguish between “Drug-like” and “Nondrug-like” Molecules? *J. Med. Chem.* **1998**, *41*, 3314–3324.
- (30) Sadowski, J.; Kubinyi, H. A Scoring Scheme for Discriminating between Drugs and Nondrugs. *J. Med. Chem.* **1998**, *41*, 3325–3329.
- (31) Ghose, A. K.; Viswanadhan, V. N.; Wendoloski, J. J. A Knowledge-Based Approach in Designing Combinatorial or Medicinal Chemistry Libraries for Drug Discovery. 1. A Qualitative and Quantitative Characterization of Known Drug Databases. *J. Comb. Chem.* **1999**, *1*, 55–68.
- (32) Oprea, T. I. Property Distribution of Drug-related Chemical Databases. *J. Comput.-Aided Mol. Design* **2000**, *14*, 251–264.
- (33) Xue, L.; Bajorath, J. Molecular Descriptors for Effective Classification of Biologically Active Compounds Based on Principal Component Analysis Identified by a Genetic Algorithm. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 801–809.
- (34) Zheng, W.; Cho, S. J.; Tropsha, A. Rational Design of a Targeted Combinatorial Chemical Library with Opiate-like Activity. *Int. J. Quantum Chem.* **1998**, *69*, 65–75.
- (35) Linusson, A.; Gottfries, J.; Lindgren, F.; Wold, S. Statistical Molecular Design of Building Blocks for Combinatorial Chemistry. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1320–1328.
- (36) Ajay; Bemis, G. W.; Murcko, M. A. Designing Libraries with CNS Activity. *J. Med. Chem.* **1999**, *42*, 4942–4951.
- (37) Oprea, T. I.; Gottfries, J. Chemography: The Art of Navigating in Chemical Space. *J. Comb. Chem.* **2001**, *3*, 157–166.
- (38) Shi, S.; Peng, Z.; Kostrowicki, J.; Paderes, G.; Kuki, A. Efficient Combinatorial Filtering for Desired Molecular Properties of Reaction Products. *J. Mol. Graphics Modell.* **2000**, *18*, 478–496.
- (39) Wildman, S. A.; Crippen, G. M. Prediction of Physicochemical Parameters by Atomic Contributions. *J. Chem. Inf. Comput. Sci.* **1999**, *39*, 868–873.
- (40) Ertl, P.; Rohde, B.; Selzer, P. Fast Calculation of Molecular Polar Surface Area as a Sum of Fragment-Based Contributions and Its Application to the Prediction of Drug Transport Properties. *J. Med. Chem.* **2000**, *43*, 3714–3717.
- (41) Labute, P. A Widely Applicable Set of Descriptors. *J. Mol. Graph. Modell.* **2000**, *18*, 464–477.
- (42) Österberg, T.; Norinder, U. Prediction of Polar Surface Area and Drug Transport Processes Using Simple Parameters and PLS Statistics. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1408–1411.
- (43) Oprea, T. I. Rapid Estimation of Hydrophobicity for Virtual Combinatorial Library Analysis. *SAR QSAR Environ. Res.* **2001**, *12*, 129–141.
- (44) Ivanciuc, O.; Klein, D. J. Building-Block Computation of Wiener-Type Indices for the Virtual Screening of Combinatorial Libraries. *Croat. Chem. Acta* **2002**, *75*, 000–000.
- (45) Barysz, M.; Jashari, G.; Lall, R. S.; Srivastava, V. K.; Trinajstić, N. On the Distance Matrix of Molecules Containing Heteroatoms. In *Chemical Applications of Topology and Graph Theory*; King, R. B., Ed.; Elsevier: Amsterdam, 1983; pp 222–227.
- (46) Ivanciuc, O.; Ivanciuc, T.; Balaban, A. T. Design of Topological Indices. Part 10. Parameters Based on Electronegativity and Covalent Radius for the Computation of Molecular Graph Descriptors for Heteroatom-Containing Molecules. *J. Chem. Inf. Comput. Sci.* **1998**, *38*, 395–401.
- (47) Ivanciuc, O.; Ivanciuc, T.; Cabrol-Bass, D.; Balaban, A. T. Comparison of Weighting Schemes for Molecular Graph Descriptors: Application in Quantitative Structure-Retention Relationship Models for Alkylphenols in Gas-Liquid Chromatography. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 732–743.
- (48) Ivanciuc, O. Design of Topological Indices. Part 12. Parameters for Vertex- and Edge-Weighted Molecular Graphs. *Rev. Roum. Chim.* **2000**, *45*, 289–301.
- (49) Ivanciuc, O. Design of Topological Indices. Part 14. Distance-Valency Matrices and Structural Descriptors for Vertex- and Edge-Weighted Molecular Graphs. *Rev. Roum. Chim.* **2000**, *45*, 587–596.
- (50) Nakamura, M.; Inoue, J.; Yamada, T. A Two-Step, One-Pot Synthesis of Diverse *N*-Pyruvoyl Amino Acid Derivatives Using the Ugi Reaction. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 2807–2810.
- (51) Ivanciuc, O.; Balaban, A. T. Graph Theory in Chemistry. In *The Encyclopedia of Computational Chemistry*; Schleyer, P. v. R., Allinger, N. L., Clark, T., Gasteiger, J., Kollman, P. A., Schaefer, H. F., III, Schreiner, P. R., Eds.; John Wiley & Sons: Chichester, U.K., 1998; pp 1169–1190.
- (52) Diudea, M. V.; Silaghi-Dumitrescu, I. Molecular Topology. I. Valence Group Electronegativity as a Vertex Discriminator. *Rev. Roum. Chim.* **1989**, *34*, 1175–1182.

- (53) Kier, L. B.; Hall, L. H. An Electrotopological-State Index for Atoms in Molecules. *Pharm. Res.* **1990**, *7*, 801–807.
- (54) Balaban, A. T.; Kier, L. B.; Joshi, N. Correlations Between Chemical Structure and Normal Boiling Points of Acyclic Ethers, Peroxides, Acetals, and their Sulfur Analogues. *J. Chem. Inf. Comput. Sci.* **1992**, *32*, 237–244.
- (55) Ivanciuc, O.; Balaban, A. T. Design of Topological Indices. Part 5. Precision and Error in Computing Graph Theoretic Invariants for Molecules Containing Heteroatoms and Multiple Bonds. *MATCH (Commun. Math. Chem.)* **1994**, *30*, 117–139.
- (56) Ivanciuc, O. QSAR Comparative Study of Wiener Descriptors for Weighted Molecular Graphs. *J. Chem. Inf. Comput. Sci.* **2000**, *40*, 1412–1422.
- (57) Balaban, A. T.; Ivanciuc, O. FORTRAN 77 Computer Program for Calculating the Topological Index J for Molecules Containing Heteroatoms. In *MATH/CHEM/COMP 1988*; Graovac, A., Ed.; Studies in Physical and Theoretical Chemistry; Elsevier: Amsterdam, 1989; Vol. 63, pp 193–212.
- (58) Hosoya, H. A Newly Proposed Quantity Characterizing the Topological Nature of Structural Isomers of Saturated Hydrocarbons. *Bull. Chem. Soc. Jpn.* **1971**, *44*, 2332–2339.
- (59) Klein, D. J.; Randić, M. Resistance Distance. *J. Math. Chem.* **1993**, *12*, 81–95.
- (60) Gutman, I. A Formula for the Wiener Number of Trees and Its Extension to Graphs Containing Cycles. *Graph Theory Notes New York* **1994**, *27*, 9–15.
- (61) Diudea, M. V. Cluj Matrix Invariants. *J. Chem. Inf. Comput. Sci.* **1997**, *37*, 300–305.
- (62) Polansky, O. E.; Bonchev, D. The Wiener Number of Graphs. I. General Theory and Changes Due to Some Graph Operations. *MATCH (Commun. Math. Chem.)* **1986**, *21*, 133–186.
- (63) Diudea, M. V.; Kacsó, I. E. Molecular Topology. 9. Composition Rules for Some Topological Indices. *MATCH (Commun. Math. Chem.)* **1991**, *26*, 255–269.
- (64) Ivanciuc, O.; Ivanciuc, T.; Klein, D. J.; Seitz, W. A.; Balaban, A. T. Wiener Index Extension by Counting Even/Odd Graph Distances. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 536–549.
- (65) Ivanciuc, O.; Ivanciuc, T.; Klein, D. J. Quantitative Structure–Property Relationships Generated with Optimizable Even/Odd Wiener Polynomial Descriptors. *SAR QSAR Environ. Res.* **2001**, *12*, 1–16.
- (66) Zhu, H.-Y.; Klein, D. J. Graph-Geometric Invariants for Molecular Structures. *J. Chem. Inf. Comput. Sci.* **1996**, *36*, 1067–1075.
- (67) Klein, D. J. Graph Geometry, Graph Metrics, & Wiener. *MATCH (Commun. Math. Comput. Chem.)* **1997**, *35*, 7–27.
- (68) Klein, D. J.; Zhu, H.-Y. Distances and Volumina for Graphs. *J. Math. Chem.* **1998**, *23*, 179–195.

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