

# Numerical Characterization of Molecular Chirality of Organic Compounds

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**Abstract:** In 2006, 80% of the small molecule drugs approved by Food and Drug Administration (FDA) of USA were chiral and 75% were single enantiomers. It is expected that 200 chiral compounds could enter the development process every year. In order to keep pace with the industry, computational chemists are trying to develop chirality measures to assist and direct asymmetric synthesis and chiral catalysis. Parameterization of chirality and development of chirality metrics, are very important in QSAR approach to be applied to chiral molecules. There are several attempts in the development of chirality measurements and earlier reviews on chirality measures concentrated more on the mathematics involved in their calculations. This review presents in-depth discussions of various chirality measures from the perspective of a QSAR modeler.

**Keywords:** Chirality, chirality measures, chirality index, enantiomers, diastereoisomers, quantitative structure-activity relationship.

## INTRODUCTION

Structural isomerism and stereoisomerism are the two types of isomerism exhibited by organic compounds. Structural isomers differ in connectivity of atoms, while stereoisomers have the same connectivity but differ in the 3-dimensional orientations (configurations) of atoms. Enantiomers and diastereomers are the two subclasses of stereoisomers. Enantiomers are isomers such that the object and its mirror image are not superimposable, while diastereomers differ from one another only in the 3-dimensional architecture but have no mirror-image relationship. Diastereomerism is exhibited by molecules with: a) more than one chiral center, b) hindered rotation about a single bond (chiral axis), c) olefinic bonds of the type  $abC=Cde$ , and d) ring structure (cyclophanes) with two or more ring atoms with substituents. Hence, diastereomerism arises out of differences in configuration and/or conformation, and chirality is not an essential condition to exhibit diastereomerism. In the present review we are concerned exclusively with chirality arising out of asymmetry of tetrahedral carbon and diastereomerism (diastereomerism and diastereoisomerism are used interchangeably by several authors) due to polychiral centers.

van 't Hoff and Le Bel developed the concepts of "asymmetry" in 1874 [1, 2] based on Louis Pasteur's experiments on the resolution of two different types of sodium ammonium tartrate crystals [3]. Pasteur went on to confirm the difference in the interaction of the two isomers with plane polarized light, one rotated the plane of polarization to the left and the other to the right. van 't Hoff and Le Bel realized that the two forms differ in the spatial orientation of the four groups attached to the tetrahedral carbon. A carbon atom attached to four different groups or ligands is called an

asymmetric carbon atom and the two possible arrangements of the four ligands lead to two isomeric forms that differ in their interaction with plane polarized light. The two isomers are related to each other as the object and the non-superimposable mirror image and are called enantiomers (*enantio* means opposite).

Though the concept of chirality is known since 1870, the term chirality was introduced by Lord Kelvin in 1904 for the first time in his Baltimore Lectures on Molecular Dynamics and the Wave Theory of Light [4] in which he stated, "I call any geometrical figure, or group of points, chiral, and say it has chirality, if its image in a plane mirror, ideally realized, cannot be brought to coincide with itself". The term chiral is derived from the Greek name *kheir* meaning "hand" and Lord Kelvin used it for the first time. In fact, even Eliel started using the term more in the later edition [5] of his monograph (Stereochemistry of Carbon Compounds) than in its first edition published in 1962 [6].

Enantiomers were identified from the difference in their interaction with plane polarized light. The enantiomers were specified by *d*- (dextrorotatory) or *l*- (laevorotatory) based on the direction of rotation of the plane of polarization (*dextro*-right; *laevo*-left). This *dl*-notation is different from the upper case *DL*-notation that was used to differentiate configuration at the chiral centers for the planar Fischer projection formulae. The *DL*-system is now confined only for the  $\alpha$ -amino acids and carbohydrates. In  $\alpha$ -amino acids the configuration is *L* if the amino group is on the left of the Fischer projection formula with the carboxylate group on the top, and the enantiomer (mirror image) is *D*. For sugars, the notation is assigned based on the configuration of the highest numbered chiral CHOH group (this is the farthest carbon from the carbonyl group as the number starts from the carbonyl group). If the hydroxyl group (OH) is on the right of the CHOH the configuration is *D*, if the OH is on the left the configuration is *L*.

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Cahn, Ingold and Prelog [7] developed a system to assign absolute configurations to Fischer projection formulae based on a set of sequence rules. The Cahn-Ingold-Prelog (CIP) rules are based on decreasing atomic number and number of atoms of same atomic number attached in the successive spheres from the chiral center. The CIP system is the accepted and universally used method to describe configuration for chiral center(s) for projection formulas that allows the absolute configuration assignments of *R* (for *rectus*, Latin for right) and *S* (for *sinister*, Latin for left). Several commercial software such as the chirality monitor of Accelrys DS Viewer [8], and the CambridgeSoft's ChemDraw Ultra [9] have the CIP rules incorporated in them. The freeware ACD-Chemsketch [10] also assigns the absolute configurations at each chiral center while giving the IUPAC name. Thus, it is possible to establish the R/S configuration at each asymmetric atom for a given molecular structure even without knowing the Cahn, Ingold and Prelog sequence rules.

Chirality leads to two-way classification of objects as left-handed and right-handed. However, there is no absolute way to classify objects as "left" or "right". In the case of two-dimensional objects, this can be illustrated using benzenanthracene. Benzenanthracene and its mirror image are chiral objects as the mirror image is not superimposable on the object. However, it is difficult to classify them as right-handed and left-handed. Moreover, this example also brings out another important concept that an object which is chiral in a lower-dimensional space need not be chiral in a higher dimensional space. In the case of 3-D objects, one can consider potatoes. Potatoes are chiral as they lack symmetry due to the presence of "bumps" and "eyes" but it is not possible to classify them as right-handed potatoes and left-handed potatoes. Handedness of objects is analogous to shoes where it is possible to classify as left and right shoes without considering the attributes of the shoes, and absence of symmetry is analogous to potatoes where an unambiguous classification as right and left is impossible. Hence, all handed objects are chiral, but all chiral objects are not handed. These phenomena are discussed by Ruch [11-12] and King [13]. However, in the case of chiral organic molecules, classification into left-handed and right-handed is possible as they are tetrahedron with four different substituents; and CIP method of assigning absolute configuration facilitates such a classification based on a set of arbitrary rules.

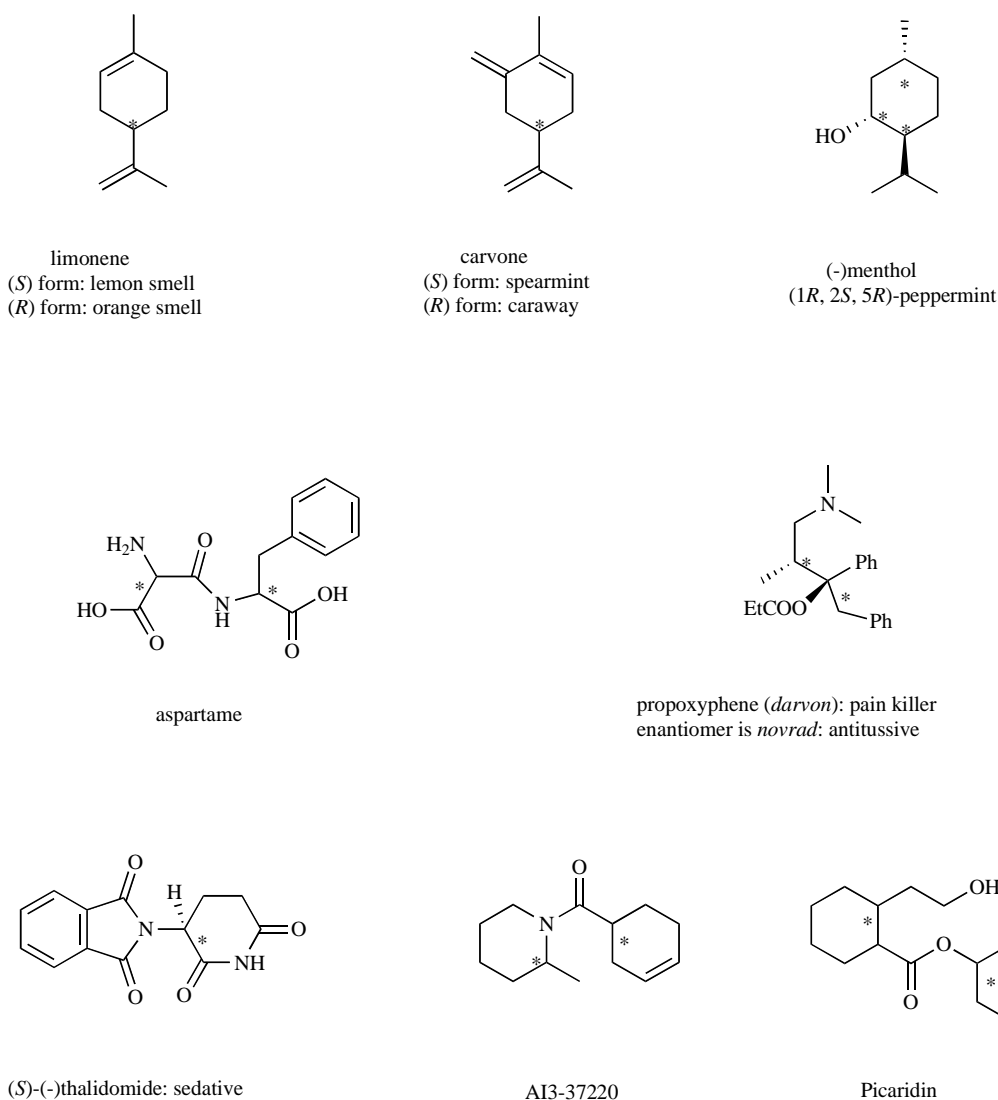
### **BIOLOGICAL DISCRIMINATION OF STEREOISOMERS**

Biological discrimination or recognition of enantiomers and diastereomers is a well-known phenomenon and plays a vital role in several biological processes from microorganisms to human beings, and plants are no exception. Discrimination of odor and taste differences of enantiomers by humans offers some striking examples of bio-discrimination of stereoisomers. The most commonly cited examples are limonene, carvone, menthol, and aspartame where the enantiomers differ in their taste and/or smell (see Fig. (1) for chemical structures). In the case of insects, the differential biological recognition of stereoisomers is very striking and their olfactory receptors are highly specific in differentiating pheromone, kairomone and chemical cues from hosts [14]. The high stereospecificity for olfactory cues in insects might be attributed to the evolution of these specific receptors as

the organisms' survival (food and reproduction) critically depends on the recognition of these chemicals.

Biological activities such as enzymatic reactions and metabolic changes are also highly stereospecific, hence, enantiomers and diastereomers may have entirely different pharmacological activities and the extent to which they differ in their activities depends on their differential interaction with the receptors. Enantiomers might have additive, antagonistic or even synergistic biological activities. For example, propoxyphene (Darvon) (Fig. 1) is a pain killer, while its enantiomer (marketed as Novrad, *Darvon*-spelled backward) is an anticough agent (antitussive). Sometimes the less potent or the inactive enantiomer present in a racemate affects non-target cells and, to avoid this risk, enantiopure or single isomer drugs should be administered. Racemic thalidomide (Fig. 1) was introduced as a sedative and an anti-nausea agent. The teratogenicity of (*S*)-(-) thalidomide led to high incidence of fetal abnormalities, and children born to women who used thalidomide had deformities of limbs. The thalidomide episode was one of the incidents that had a very high impact and changed the line of thinking of the pharmaceutical industry and the policy makers. Ariens' critical reviews on the importance of stereochemistry on biological activities [15-17] added impetus to the importance of stereochemistry in drug development. The Food and Drug Administration (FDA) changed its policy on chiral drugs and requires the pharmacological and toxicological profiling of both enantiomers before marketing a racemate. Several pharmaceutical companies are involved in the redevelopment, in single-isomer form, of a chiral drug that was originally approved for marketing as a racemate. In 2006, 80% of the small molecule drugs approved by FDA were chiral and 75% were single enantiomers. It is expected that 200 chiral compounds could enter the development process every year [18]. Other important factors that contributed to such an increase in the synthesis of enantiopure drugs are the new analytical tools to separate enantiomers and improved methodologies to synthesize enantiopure compounds. In addition to this, there are methods available to monitor the therapeutic action of the chiral drugs and their metabolites. In the case of agrochemicals, there is also an increasing trend to use single isomers or enantiopure compounds [19], and this reduces loading of the environment with the inactive or less potent isomers that may have adverse impacts. For this reason European countries allow the use of only the active (*R*)-enantiomers of phenoxypropionic acid herbicides. Chiral agrochemicals and pharmaceutical drugs finally will reach the environment and the environmental fate of the chiral pollutants needs to be investigated [20].

Conventional quantitative structure-activity relationship (QSAR) modeling of pharmacological, biological or toxicological properties cannot be extended to studies involving enantiomers and diastereomers because the majority of physicochemical properties and calculated descriptors will have the same value for enantiomeric pairs. Quantitative stereochemical structure-activity relationship (QSSAR) needs chirality descriptors developed to satisfactorily extend the QSAR approach to data sets involving chiral molecules. A successful QSSAR approach is also expected to assist the synthesis of chiral drugs. Quantification of chirality and defining new chirality descriptors has always attracted chemists, physicists and mathematicians. Hence, several attempts



**Fig. (1).** Biodiscrimination of enantiomers and diastereomers.

were made over the years in the discrimination of enantiomers and quantifying molecular chirality and appeared in mathematics, physics and chemistry journals. Thus, most of the literature available on chirality is distributed over these three basic fields of physical science. There were some earlier reviews on chirality measures but they were oriented more for mathematicians and physicists rather than structure-activity modelers and predictive toxicologists, who always look for better chirality measures to use for real-world chemical systems. In the present review, approaches in quantifying molecular chirality and chirality descriptors congenial to QSAR development are discussed in more detail than other approaches that placed their emphasis on the mathematical sophistication involved rather than the application in the real-world chemistry systems.

#### CHIRALITY MEASURES: EARLY APPROACHES

In their review Buda, Heyde and Mislow classified [21] chirality measures into two types: those that measure the extent to which a chiral molecule differs from an achiral reference (measure of the first kind) and those that measure the extent to which the two enantiomers of a chemical differ

from one another (measure of second kind). Wienberg and Mislow [22] classified twenty-one different chirality measures from literature. These comprehensive reviews [21-23] in the area cover most of the chirality measures reported by physicists and mathematicians. Many of these approaches articulate the mathematical aspects of geometric chirality more, rather than applying them to chiral molecules or using them in property prediction. As the objective of the present review is to discuss methods that are more relevant to QSAR modelers, only a very brief overview of these earlier methods is given below:

The asymmetry product suggested by Guye [24] in the late 19<sup>th</sup> Century is one of the oldest chirality measures. The asymmetry product calculated using Eq. (1) was correlated with optical rotatory power of optically active compounds. The asymmetry product ( $P_A$ ) is an algebraic function and  $P_A$  for a regular tetrahedron (there is no change in the bond angle from 109° 28') is:

$$P_A = \prod_{i=1}^6 d_i \quad (1)$$

where  $d_i$  are the distances of the molecular center of mass to the six planes of symmetry. If the mass of the four ligands (groups) attached to the asymmetric carbon are  $m_1$ ,  $m_2$ ,  $m_3$  and  $m_4$  then  $P_m$  is proportional to the asymmetric product.

$$P_m = \prod_{i>j}^{1-4} (m_i - m_j) \quad (2)$$

Thus the asymmetric product can be expressed as a product of differences between any appropriate parameters of the ligands. These were called the 'chirality functions' and the generalization was introduced by Ruch *et al.* [25]. Detailed discussion on the generalized chirality functions and the controversies about ligand properties are given in [23]. Rassat proposed [26] chirality measures based on Hausdorff distances. A volume overlap-related measure was introduced by Gilat [27]. In 1991 Mezey proposed [28, 29] a resolution-based similarity measure to quantify chirality using equally-sized contiguous cells. The chirality measure was obtained from the minimum number of cells to be removed or added to obtain an achiral structure or a polycube.

## QUANTUM CHEMICAL METHODS

In the realm of quantum chemical methods, various approaches were proposed to define chirality measures and almost all of them used electron density distributions. Mezey suggested the use of scalar products of electron densities [30]. He also used fuzzy set theory and Hausdorff-type distances between electron density contours [31]. Grimme suggested a continuous symmetry measure using the hermitian product of the electronic wave function and its inverted image [32]. Molecular isodensity contours were converted into sequence graphs with rooted tree structure. The topological symmetry lattice tree code was used by Mezey to compute the symmetry deficiency [33]. Luzanov and Babich proposed a chirality index ( $\kappa$ -index) from the spatial curves of electron paths in molecules [34, 35]. Realizing the limitation of the approach to natural chemical systems, an one-electron invariant was proposed [36]. The revised  $\kappa$ -index is a matrix invariant. Quantum chemical approaches are not usually applicable to the real-world systems, and work within a small framework of theoretical considerations. In our opinion, they lack practical applications in the realm of structure-activity modeling and property prediction. Moreover, quantum chemical calculations are computer intensive and are almost impossible to use in data sets containing thousands of chemical candidates.

## ALGEBRAIC APPROACH USING FISCHER PROJECTIONS

Capozziello and Lattanzi developed [37] an algebraic approach using the 24 possible Fischer projections (12 for each enantiomer). They constructed matrix operators based on  $O(4)$  orthogonal group algebra for each of the 24 matrices corresponding to the Fischer projections. Though they were able to classify enantiomers, diastereoisomers or achiral molecules, no chirality measure was put forward. However, they proposed a chirality index  $\chi$  in their geometric approach [38] wherein the ligands around a chiral atom were projected on a  $\{x; y\}$ -plane. The chirality index  $\chi$  was obtained using complex numbers to define bond lengths and bond angles

(angular positions of the ligands). The approach was extended as a building-up (*aufbau*) procedure to predict the chiral features of a new molecule by "adding-up" [39]. The chirality index  $\chi \equiv \{n, p\}$ ; where  $n$  is the number of stereogenic centers and  $p$  the number of inversions (at most one for each center). Adding up a chiral center to the structure gives rise to a new molecule, where  $\chi \equiv \{n + 1, p + \Delta p$ , the variation of  $p$ ,  $\Delta p$  ( $\Delta p = 0, 1$ ) gives the chiral feature of the new molecule. Applications of this approach to predict properties of chiral molecules were not illustrated and moreover, the approach cannot handle *meso* compounds where the added chiral center is not different from the first chiral center.

## CHIRALITY MEASURES FROM MOLECULAR SIMILARITY

Seri-Levy *et al.* [40, 41] calculated shape similarities by superimposing molecular structures using electrostatic potential and the shape similarities were converted to chirality coefficients defined as (1-similarity). They correlated the eudismic ratio, the relative potency of the two enantiomers of a drug, to the chirality coefficient. The approach was similar to chirality coefficients introduced by Gilat. See [42] for the various chirality functions used to calculate the geometric chirality measures. Basak *et al.* [43] reported a molecular overlay method for ordering the insect repellency of diastereomers of AI3-37220 (1-(cyclohex-3-ene-1-ylcarbonyl)-2-methylpiperidine) and Picaridin (2-(2-hydroxyethyl)-1-piperidinecarboxylic acid 1-methylpropyl ester). Instead of defining chirality coefficients, the root mean square distances (RMSD) of the overlaid structures were used as similarity/ dissimilarity measure. In their hierarchical overlay approach, the geometry of the low-energy conformer of each diastereomer was optimized in a graded manner of theory or basis set (AM1 to HF/STO3G to HF/ 3-21G to HF/6-31G to HF/6-311G to B3LYP/6-31G to B3LYP/6-311G) using Gaussian 03 [44]. The insect repellencies of the diastereomers were ordered properly and the results were much better than those arrived in an earlier study [45] using molecular mechanics method for geometry optimization. The approach used by Benigni *et al.* [46] was similar to that of Servi *et al.* [40] but they used Principal Component Analysis (PCA) of the complete  $N \times N$  pair-wise similarity matrices. Electrostatic potential and shape indices were used to measure the similarity. They applied the PCA of the complete  $N \times N$  pair-wise similarity matrices of a series of dihydropyridine calcium channel antagonists to analyze the chirality component and order eudismic activity of the enantiomeric pairs.

## CONTINUOUS SYMMETRY/CHIRALITY MEASURES (CSM/CCM)

In 1992, Zabrodsky, Peleg and Avnir introduced Continuous Symmetry Measures (CSM) and Continuous Chirality Measures (CCM) [47, 48]. In their approach they treated chirality as a continuous structural property rather than a binary quality, i.e. chirality was treated on a grey scale rather than a black-or-white scale. From their arguments it is clear that CSM is associated with a given symmetry while CCM is associated with reflection and improper rotation axis. Several papers have been published by Avnir and his co-workers on the topic (see [23] and references therein). In one of their papers they used CCM as a shape descriptor to analyze five

receptor/substrate systems, namely: trypsin/arylammonium inhibitors; the D2-dopamine receptor/dopamine derivative agonists; trypsin/organophosphate inhibitors; acetylcholinesterase/organophosphates; and butyrylcholinesterase/organo-phosphates [49]. A computer program to calculate the chirality measure was developed by Avnir's group [50].

### TOPOLOGICAL INDICES-BASED CHIRALITY MEASURES

Topological indices have been widely used in quantitative structure-property/activity relationships (QSPR/QSAR) studies and their frontiers of application are always expanding. There are quite a large number of them and conventional topological indices (refer to [51] and [52] for detailed accounts of various topological indices) have limitations in their application to enantiomers and diastereomers because the stereoisomers arising out of chiral center(s) have the same connectivity and all of them have the same molecular graph and 3-D geometry. Several approaches were tried over the years to overcome this limitation.

Walters and Yalkowsky [53] developed a computer program called ESCHER to determining the rotational symmetry number for rigid molecules from a SMILES string (Simplified Molecular Input Line Entry Scheme) [54]. However, the drawback was that the program could not fully deal with stereochemistry or conformation. Moreau [55] came up with a measure of chirality based on an atom's environment in a molecule. The environment was defined both by the geometry of the closest atoms and by a property of those atoms. Thus, the new chirality measure depended on the position of the atom with respect to the principal planes of the environment. Moreau did not attempt any QSAR modeling using the chirality measure proposed by him. Unlike Moreau's method that gave an atomistic chirality measure, the method developed by Wildman and Crippen [56] assigned a chirality-metric to the whole molecule. A 3D QSAR program called DAPPER developed by them [57] was used for conformational search. The new chirality measure was used in QSAR modeling of three different data sets of dihydrofolate reductase (DHFR) [58-60], angiotensin-converting enzyme (ACE) [61] and acetylcholinesterase (AChE) inhibitors [62].

Schultz and co-workers [63] developed topological indices to differentiate *cis*(*Z*) and *trans*(*E*) diastereoisomers as well as diastereomers arising out of chirality of molecules. They used vertex weighted distance matrices to compute descriptors. A correction term (chiral modifier) was applied to the topological indices to take care of configuration around stereocenter(s). Following operations are carried out to calculate the chiral modifier:

1. The distance matrix  $D(G_{V_{vw}})$  of the vertex weighted graph is converted into a matrix for chiral correction ( $D_s$ ) which is nothing but the sum of  $D(G_{V_{vw}})$  and its transpose.
2. The chiral correction matrices are formed from the chiral factors (CF) of the vertices. A stereocenter with *R* configuration is assigned a chiral factor +1, while that with *S* configuration is assigned -1. All other vertices are assigned chiral factor values of zero. The number of chiral correction matrices thus formed is equal to the number of diastereoisomers.

3. Chiral modifier is obtained from the sum of the elements of a matrix obtained as a result of pre-multiplying  $D_s$  with  $D(\text{CF})$  for a particular stereoisomer.

The chiral modifier is then used to alter the value of the topological indices. Irrespective of the groups or the atoms attached to the stereocenter, the order of numerical values of the diastereoisomers will be  $R > S$  for a compound with one chiral center, and  $RR > RS/SR > SR/RS > SS$  for a compound with two chiral centers. This limited the application of chirality indices calculated using the Schultz approach in QSAR.

Similar to the Schultz approach, Julian-Ortiz *et al.* [64] proposed a set of new descriptors by introducing a weight of +1 for an (*R*) carbon or -1 for an (*S*) carbon into the corresponding entries of the main diagonal of the adjacency matrix. They used the descriptors in modeling the dopamine D2 and  $\sigma$  receptor affinities of seven enantiomeric pairs of 3-(3-hydroxyphenyl)piperidines (3-HPP) [65]. Randić and Razinger [66, 67] considered a quantitative characterization of molecular chirality based on the binary code that describes the shape of the molecular periphery; their approach was limited to chirality in two-dimensional space, hence confined to benzenoid forms that are chiral. Randić [68] came up with an index (*F*-index) to account for the direction of circumference of planar structures and explained how the 2-D approach could be extended to the characterization of chiral objects in a 3-D space using *n*-alkane rotamers as examples. Randić strongly advocated that the chirality indices for a pair of enantiomers should have opposite sign. Lukovits and Linert [69] corrected the first-order valence connectivity index  ${}^1\chi^v$  [51] with a chiral function *F* that satisfied the condition  $F(D) = -F(L)$ , where D and L denote enantiomers of the same structure. The resulting index was called  $\chi_c$  and its application was tested to model the thin-layer chromatographic retention indices for eight hydroxy acids (4 pairs) and ten  $\alpha$ -amino acids (5 pairs) [70]. Their approach failed in the case of cyclic molecules and molecules with very bulky substituents. Golbraikh *et al.* [71, 72] modified the vertex degree of asymmetric atoms in a molecular graph using a term called chirality correction. For each asymmetric atom in *R*-configuration, the vertex degree  $a_i$  was substituted with  $(a_i + c)$ , and for each atom in *S*-configuration  $a_i$  was substituted with  $(a_i - c)$ . They calculated a series of descriptors based on Zagreb group indices, extended connectivity, overall connectivity, and topological charge indices for molecules containing chiral atoms using chirality correction *c* for each chiral atom. The chirality descriptors thus calculated were used in the QSAR studies of a set of ecdysteroids [73] and they compared the results obtained with comparative molecular field analysis (CoMFA) [73, 74]. They extended the application of the chirality descriptors to four more data sets using the k-nearest neighbor (kNN) QSAR method [75]. The chirality correction *c* used by them is an empirical parameter and its best value depends on the descriptors used and the compounds in the training and test sets. Hence, the chirality descriptors developed by Golbraikh *et al.* had limitations in their application. Randić [68] was critical about the approach and argued that invariants extracted from modified adjacency matrices did not qualify as chirality indices as they did not satisfy the requirement that enantiomers have indices of the same magnitude but opposite signs. As mentioned previ-

ously, Randić strongly believed this was necessary. However, we differ from this view because there are several situations where the activities of enantiomers are either or-like properties. Two specific examples can be found in the insect repellency of diastereomeric repellents [76] and the HIV protease inhibition of sulfonamide-substituted cyclooctylpyranones [77]. The difference in activities between enantiomers depends on the extent to which the receptor interacts with the chiral molecule and recognizes the spatial distribution of ligands with respect to a property.

Yang and Zong [78] came up with chirality factors (CF) that were then used to modify the Kier-Hall topological indices [51, 52] into chiral topological indices using the relation.

$$TI_{CF_n} = TI \times {}^nCF \quad (3)$$

where  $TI_{CF_n}$  is a chiral topological index,  $TI$  is the conventional Kier-Hall topological index and  ${}^nCF$  is the  $n$ -order chirality factor. The four substituents attached to a chiral center, were assigned priority according to the CIP-rule. The lowest priority substituent (D) was placed away from the plane and the other three substituents, which form a plane, were defined as A, B and C clockwise. The chirality factor of  $n^{\text{th}}$  order was calculated using Eq. (4).

$${}^nCF = \frac{N}{M} \sum_{i=1}^m \left( \frac{{}^n f_{iA} - {}^n f_{iB}}{{}^n f_{iA} {}^n f_{iB}} \right) \left( \frac{{}^n f_{iA} - {}^n f_{iC}}{{}^n f_{iA} {}^n f_{iC}} \right) \left( \frac{{}^n f_{iA} - {}^n f_{iD}}{{}^n f_{iA} {}^n f_{iD}} \right) \left( \frac{{}^n f_{iB} - {}^n f_{iC}}{{}^n f_{iB} {}^n f_{iC}} \right) \left( \frac{{}^n f_{iB} - {}^n f_{iD}}{{}^n f_{iB} {}^n f_{iD}} \right) \left( \frac{{}^n f_{iC} - {}^n f_{iD}}{{}^n f_{iC} {}^n f_{iD}} \right) \quad (4)$$

where  $N$  is the number of non-hydrogen atoms,  $M$  is the number of chiral centers,  ${}^n f_{iA}$  is the chiral index of substituent A attached to chiral center  $i$ . The chiral index  ${}^n f_i$  is given by Eq. (5).

$${}^n f_i = \sum_{j=1}^m \frac{\delta_j}{d_{ij}^2} d_{ij} \leq n \quad (5)$$

where  $m$  is the number of non-hydrogen atoms in the ligands (A, B, C or D) whose distance to chiral center  $i$  is less than or equal to  $n$  and the hydrogen atoms directly attached to the chiral center,  $d_{ij}$  is the graph distance of vertex  $j$  to chiral center  $i$ , (the shortest path between the vertex  $i$  and  $j$ , and  $d_j$  is the degree of vertex  $j$ ) and this is for 0 for hydrogen. The chiral correction factor becomes zero for achiral molecules and the chirality topological indices calculated for a pair of enantiomers using this approach has the same numerical values but opposite sign. Thus, they satisfied Randić's condition [68] for chirality indices. The chirality factor  $CF$  defined by Eq. (4) is a modified form of the asymmetry product defined in Eq. (2). The authors have taken into consideration the contribution by the least priority group and the importance of distance of an atom from the chiral center. They applied the new chirality indices in the QSAR modeling of the data sets from [65, 70, 79].

Aires-de-Sousa and Gasteiger [80] came up with a chirality code to distinguish enantiomers. The chirality code was a sequence of numbers equal to the value of a certain "chirality function" at equidistant points. In their approach the 3-D structure of a molecule was transformed into an atomic radial distribution function consisting of properties such as atomic numbers, partial atomic charges and atomic po-

larizability. They used the computer program CORINA [81] to generate the 3-D structures, and the physicochemical atomic properties were calculated using the computer program PETRA (Parameter Estimation for the Treatment of Reactivity Applications) [82] that works in Molecular Networks [81] (Molecular Networks GmbH, Erlangen, Germany). They used the chirality codes generated in the counter-propagation neural networks prediction of the major enantiomer in (a) the catalytic addition of diethylzinc to benzaldehyde, and (b) the reduction of ketones by DIP-chloride. The two sets were collected from the literature such that the results were from the same laboratory and products with more than one chiral carbon atom were excluded. References for the original data references can be obtained from [80]. The chirality code generated peaks (maxima and minima) for each quartet of atoms, and for molecules of moderate size the chirality function has thousands of peaks. Hence, the authors thought that the chirality code would not represent the molecular structure comprehensively, and came up with a revised chirality code. In their revised approach [83], the functional groups present in the molecule resulted in clusters of near-lying and partially overlapping peaks, whose position in the chirality code was characteristic for the particular functional group. Aires-de-Sousa and his group appeared to have preference to counter propagation neural networks hence always tried to generate a series of descriptors. As in their earlier studies they used the 3-D QSAR program CORINA and PETRA to calculate the physicochemical properties of the ligands attached to the chiral center. Aires-de-Sousa's group [84] recently came up with Physicochemical Atomic Stereo-descriptors (PAS) based on twenty-one physicochemical properties of the ligands attached to a chiral center. The R/S-like descriptor related to the physicochemical property under consideration was computed. The conventional R/S-like is derived from the CIP- and CIP-like used by several authors, where CIP-R/S refers to the assignment of priority based on CIP rules while CIP-like R/S (R/S-like) refers to the priority assigned using any other property (physicochemical or atomic). The PASs calculated were used in profiling chiral compounds. Similar to their previous studies they applied the new chiral measures to the prediction of preferred enantiomers in the stereoselective reactions of forty-eight enantiomeric pairs of chiral amino alcohols with diethylzinc to benzaldehyde, and a series of eighty-six enantiomeric pairs of primary alcohols involved in racemic resolutions by trans-esterifications, or hydrolyses catalyzed by *Pseudomonascepacia* lipase. However, their predictions for primary alcohols that have an oxygen atom attached to the chiral center were not good. In order to address this, the highest priority in the generation of PAS descriptors was assigned to the  $\text{CH}_2\text{OH}$  group involved in the reaction.

Recently we came up with a relative chirality index (RCI) [85] and the limitations in many of the attempts discussed above were considered in their formulation. Though the approach has some similarity with the PAS [84], it was developed simultaneously and independently. There are two major differences:

1. We used mainly a connectivity-based topological approach and proposed possible extensions of using physicochemical properties or any computable property of the ligands attached to the chiral center. On

the other hand, calculation of PASs *exclusively* used physicochemical properties.

- We followed CIP-R/S and PASs used CIP-like R/S assignment of priority for the ligands.

The four ligands attached to a chiral center were assigned priorities according to the CIP-rules. The least priority group D was kept away from the plane and the other three groups (A, B and C) on the plane were viewed from a reference point to calculate the new chirality metric. The groups/atoms A, B, C and D were then assigned valence delta-values of atoms ( $\delta^v$ ) according to the method of Hall and Kier [51]. When the group has more than one atom,  $\delta^v$  for the group A, B, C or D is calculated considering the relative proximities of the atoms to the chiral center and decreasing importance with increasing topological distance (through bond) was assigned while calculating the contribution of atoms other than hydrogen in a group. The group delta value for any group ( $\delta_i^v$ ) attached to a chiral carbon is calculated as:

$$\delta_i^v = \delta_{n_1}^v + \left(\delta_{n_2}^v/2\right) + \left(\delta_{n_3}^v/4\right) + \left(\delta_{n_4}^v/8\right) + \dots \quad (6)$$

where  $n_1$  is the atom attached directly to the chiral center (nearest neighbor),  $n_2$  is separated by one atom,  $n_3$  by two atoms etc. Relative chirality indices ( ${}^V RCI$ ) for a pair of enantiomers are calculated as:

$${}^V RCI_R = \delta_a^v + (\delta_a^v + \delta_a^v \delta_b^v) + (\delta_a^v + \delta_a^v \delta_b^v + \delta_a^v \delta_b^v \delta_c^v) + \delta_a^v \delta_b^v \delta_c^v \delta_d^v \quad (7)$$

$${}^V RCI_S = \delta_a^v + (\delta_a^v + \delta_a^v \delta_c^v) + (\delta_a^v + \delta_a^v \delta_c^v + \delta_a^v \delta_b^v \delta_c^v) + \delta_a^v \delta_b^v \delta_c^v \delta_d^v \quad (8)$$

Information regarding the least priority group (D) was also included in the new index by the fourth term  $\delta_a \delta_b \delta_c \delta_d$ . When D is hydrogen,  $\delta_a \delta_b \delta_c \delta_d$  becomes zero; otherwise it contributes to the RCI for the chiral center. From Eq. 7 and Eq. 8 the difference between the values of RCI for R and S isomers is  $2\delta_a(\delta_b - \delta_c)$ . Several other approaches did not consider compounds with more than one chiral center, which was not the case in the calculation of RCI. We used a root mean square method to obtain RCI for molecules containing more than one chiral center i.e. for diastereomers. In addition to the valence connectivity, we used formula weights of the groups and the electrotopological state of the various atoms and groups in A, B, C and D to calculate  ${}^W RCI$  and  ${}^E RCI$ , respectively. Thus, three different scales were proposed and the approach could be extended for any computable property. RCIs were calculated for the common  $\alpha$ -aminoacids and were found to differentiate enantiomers and diastereomers. The application to model mosquito repellency of AI3-37220 and Picaridin diastereomers was tried.

**Table 1. Comparison of Chiral Indices According to Shultz Approach and RCI for a Set of Enantiomers and Diastereomers**

| Compound                | CM <sup>a</sup> | S <sup>b</sup> | PRSc        | <sup>V</sup> RCId | <sup>W</sup> RCI <sup>e</sup> | <sup>E</sup> RCIf |
|-------------------------|-----------------|----------------|-------------|-------------------|-------------------------------|-------------------|
| 3-methylhexane          |                 | 294            | 2464862400  |                   |                               |                   |
| (R)-                    | +44             | 338            | 2464862444  | 34.13             | 35.75                         | 35.85             |
| (S)-                    | -44             | 250            | 2464862356  | 24.38             | 33.00                         | 35.03             |
| bromohlorofluoromethane |                 | 3707           | 103680000   |                   |                               |                   |
| (R)-                    | +193            | 3900           | 103680193   | 462.00            | 121.31                        | 143.08            |
| (S)-                    | -193            | 3514           | 103679807   | 462.00            | 142.69                        | 172.26            |
| 2-butanol               |                 | 302            | 933120      |                   |                               |                   |
| (R)-                    | +29             | 331            | 933149      | 52.50             | 78.00                         | 83.07             |
| (S)-                    | -29             | 273            | 933091      | 37.50             | 72.00                         | 82.10             |
| 2-aminopropanoic acid   |                 | 1400           | 9172942848  |                   |                               |                   |
| (R)-                    | +87             | 1487           | 9172942935  | 94.50             | 142.67                        | 142.75            |
| (S)-                    | -87             | 1313           | 9172942761  | 43.50             | 93.33                         | 81.46             |
| 2,3-butanediol          |                 | 742            | 522991161   |                   |                               |                   |
| (R,R)-                  | +108            | 850            | 522991269   | 120               | 145.92                        | 155.01            |
| (S,S)-                  | -108            | 634            | 522991053   | 44.43             | 74.93                         | 76.14             |
| (R,S)- meso             | 0               | 742            | 522991161   | 94.87             | 127.52                        | 133.46            |
| (S,R)- meso             | 0               | 742            | 522991161   | 94.87             | 127.52                        | 133.46            |
| 2,3-pentanediol         |                 | 1034           | 84321972000 |                   |                               |                   |
| (R,R)-                  | +131            | 1165           | 84321972131 | 134.19            | 156.99                        | 163.06            |
| (S,S)-                  | -131            | 903            | 84321971869 | 41.54             | 77.05                         | 80.45             |
| (R,S)-                  | +5              | 1039           | 84321972005 | 115.63            | 140.45                        | 140.21            |
| (S,R)-                  | -5              | 1029           | 84321971995 | 113.91            | 138.00                        | 140.00            |

<sup>a</sup>Chiral modifier.

<sup>b</sup>Schultz index.

<sup>c</sup>Product of row sum.

<sup>d</sup>Relative chirality indices based on valence degree.

<sup>e</sup>Relative chirality indices based on atom related intrinsic state (I-state) [86].

<sup>f</sup>Relative chirality indices based on electrotopological state (E-state) [86].

\*Values from [63].

RCI values and chirality indices calculated using the Schultz approach for a few chiral molecules are given in Table 1 for comparison. Three different scales, namely valence degree, intrinsic state (I-state) and electronic state (E-state), were used to calculate RCI according to Eq. (7) and Eq. (8), and if a molecule contains more than one chiral center then the root mean squares of the RCI value for each center were calculated. The chiral modifier used in the Schultz approach has the same numerical value for a given molecule irrespective of the topological index used, even though they differ in several orders of magnitude. For the examples given in Table 1, Schultz indices ( $S$ ) are of the order of  $10^2$  to  $10^3$  while the product of row sums (PRSs) are of the order of  $10^6$  to  $10^{11}$ . In most of the cases of PRS, correction factors are almost insignificant comparing to the values of PRSs. *meso*-Isomers are given a correction factor of zero and therefore the values of the topological descriptors remain unaltered for them. Yang and Zong's approach [78] is very similar to this and the chiral correction (chirality factor  $CF$ ) is zero for *meso* isomers. The topological chiral descriptors for *meso* isomers themselves become zero because the chiral topological index is  $TI_{CF} = TI \times CF$ . Unlike these two methods, the RCI approach gives chiral descriptors for *meso* isomers and both the isomers have the same RCI values (Table 1, entries for the *meso* isomers of 2,3-butanediol). The optical rotatory power of *meso* isomers is zero and this should not be taken as a proof for zero biological activity. Hence, we believe in assigning chirality descriptors for *meso* isomers. As opposed to several of the other approaches, the RCI approach does not have a predetermined order of enantiomers or diastereomers. For example in the case of stereoisomers of tartaric acid the order of RCI was found to be  $SS > RS = SR > RR$  while the orders for the stereoisomers of threonine and isoleucine were  $RR > SR > RS > SS$  and  $RR > RS > SR > SS$ , respectively [85].

RCI were found to have the following advantages:

1. The effect of weighting the atoms according to their distance to the central atom is significant because the farther the atom from the chiral center, the lower its contribution; it was shown by Mills and Klyne that optical activity of analogues reaches a constant value with increase in carbon atom chains [87]. This fact was considered in the approach by Yang and Zong [78].
2. Bioisosterism was addressed by  $^VRCI$  and was exemplified by the same set of  $^VRCI$  values for the bioisosteric amino acids, serine and cysteine.
3. Singularity of *meso* compounds was addressed. The *meso* tartaric acids is optically inactive because of it is achiral by intramolecular configuration.
4. Diastereomers were also addressed and enantiomers did not get the same set of values with opposite sign as observed in most of the chirality measures.
5. Unlike several other topological chirality indices, RCI are stand-alone descriptors. They do not require prior computation of other indices, as they are not meant as modifiers. Thus RCI are independent and can be calculated easily.

6. Different fundamental properties of the atoms in the four ligands were considered. Hence, the distribution of ligands around the chiral center was given based on different properties, i.e. different measures of "handedness" are given.

The new descriptors attempt to map the distribution of the four substituents around a chiral centre into a set of real numbers and it is entirely based on the structure of the molecule. However, there will be some contraction of data due to the mathematical operations involved in the computation of the descriptors.

## CONCLUSION

Several chirality measures and their success and limitations in application to structure- activity relationship (SAR) modeling were presented in the review. In SARs we try to find the mathematical association between structure/properties of molecules and chemical/ biological activities. The key to identify most relevant molecular descriptors depends on the understanding of the mechanism of action. Correlation of a descriptor to a biological activity does not guarantee causality (mechanism of action). Moreover, there is no reason to assume *a priori* that steric effects will totally determine bioactivity. What a particular biological receptor senses in a chiral molecule may vary from one receptor to another. If the ordering of a set of chiral molecules by calculated indices parallels their ordering by the receptor in terms of observed bioactivity, then and only then we can expect a strong correlation between the calculated index and the bioactivity. Otherwise, the indices will only discriminate the structures without any necessary correlation with biological function. A chirality measure will be very successful only when it takes into account the asymmetry of the distribution of a property the receptor is looking for.

As mentioned earlier, the literature on chirality measures and their applications is spread over journals in mathematics, physics, chemistry and toxicology; the diversity of applications and the challenges involved therein are immensely fascinating. We apologize if any important piece of work is not covered in the review, the major reason being the wide variety of places for the publication of such papers.

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