Novel Approach for the Numerical Characterization of Molecular Chirality†

Ramanathan Natarajan,‡ Subhash C. Basak,*,‡ and Terrence S. Neumann§

Natural Resources Research Institute, University of Minnesota Duluth, 5013 Miller Trunk Highway, Duluth, Minnesota 55811, and Department of Chemistry and Biochemistry, University of Minnesota Duluth, 1039 University Drive, Duluth, Minnesota 55812

Received December 1, 2006

The use of chiral compounds as pharmaceuticals and agrochemicals continues to increase, warranting numerical characterization of chirality in order to develop structure−activity relationship models involving these compounds. Enantiomers are identical in all scalar properties and, hence, are not differentiated by topological indices and 3-D descriptors. Three distinct measures of chirality were developed to discriminate diastereomers and enantiomers. The novel topological indices treat chirality as a continuous measure, and hence we prefer to call it the Relative Chirality Index (RCI). Application of RCI in developing SAR is illustrated with the repellency data for the diastereomers of picaridin and AI3-37220.

INTRODUCTION

Biological discrimination of stereoisomers is well-known and has been illustrated with examples such as (*R*)-(+)-limonene which has orange-like odor, while the (*S*)-(−)-limonene has the smell of lemon. Several reviews and monographs highlight the pharmacological implications of chiral discrimination.[1,2] However, one of the incidents that had a very high impact and changed the line of thinking of the pharmaceutical industry and the policy makers was the thalidomide episode. Racemic thalidomide was introduced as a sedative and an antinausea agent. The teratogenicity of (*S*)-(−)thalidomide led to the high incidence of fetal abnormalities and children born to women who used thalidomide had deformities of limbs. The less potent or the inactive enantiomer present in a racemate affects nontarget cells and to avoid this risk enantiopure or single isomer drugs should be used. The Food and Drug Administration (FDA) requires that both enantiomers of a racemate be studied in detail before marketing a racemate. Several pharmaceutical companies are going for the redevelopment in single-isomer forms of chiral drugs that were originally approved for marketing as racemates. This practice is called a racemic switch. Other important factors that gave impetus in using 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 also there is an increasing trend to use single isomer or enantiopure compounds,[3] and this reduces loading the environment with isomers that have low or no efficacy. Recently Klun et al.[4] demonstrated the stereospecificity of insect repellants in the case of AI3-37220 and picaridin.

Computational chemists are now facing the challenge of developing models to predict the beneficial as well as adverse effects of diastereoisomers (diastereomers). In such situations quantitative stereochemical structure−activity relationship modeling (QSSAR) approach is necessary rather than simple quantitative structure−activity relationship (QSAR). Conventional QSAR modeling using simple computed molecular descriptors or physicochemical properties fail in handling compounds that exhibit polychiral diastereomerism. The reason for the limitation of the molecular descriptors derived from adjacency and distance matrices of molecular graphs in differentiating enantiomers is their identical scalar properties. In other words, enantiomers are isometric, and for each distance between two given atoms in one isomer there is a corresponding identical distance between a pair of atoms in the other. Thus, distance matrices for the enantiomers have identical entries, and consequently the various topological indices derived from the distance matrices could not differentiate enantiomers. The same is true for three-dimensional (3-D) distance matrices of enantiomers.

In order to develop QSSAR, descriptors that encode the stereochemical features of a molecule are the primary requisite. Some attempts have been made by Schultz and co-workers[5] to develop topological indices to differentiate *cis*(*Z*) and *trans*(*E*) isomers as well as diastereomers arising out of chirality of molecules. They used vertex weighted distance matrices to compute descriptors and then added to the descriptors correction terms for different diastereomers. Golbraikh, Bonchev, and Tropsha[6] used a similar approach, applying chirality corrections to Zagreb indices, molecular connectivity indices, extended connectivity indices, overall connectivity indices, and topological charge indices. They implemented these chirality indices in QSAR modeling of ecdysteroids and compared the results with that of Comparative Molecular Field Analysis (CoMFA). Randić's[7] approach to the problem of chirality was confined to two-dimensional chirality and is applicable to benzenoid hydrocarbons. Recently, Fujita[8−10] suggested sphericity indices for the enumeration of stereoisomers. Aires-de-Sousa et al.[11−12]

† Dedicated to Professor Nenad Trinajstić on the occasion of his 70th birthday.

* Corresponding author phone: (218)720-4230; fax: (218)720-4328; e-mail: sbasak@nrri.umn.edu.

‡ NRRI-UMD.

§ UMD.

10.1021/ci600542b CCC: $37.00
Published on Web 04/05/2007

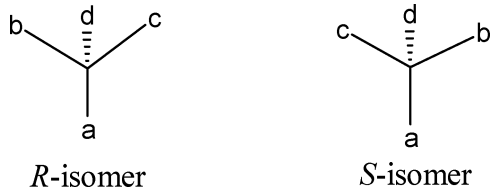


Figure 1.

attempted to describe chirality using a "chirality code". A chirality-sensitive flexibility (CSF) descriptor based on the distance between a pharmacophore point and a plane defined by three pharmacophore points was introduced by Dervarics et al.[13] Capozziello and Lattanzi[14] derived algebraic structures of molecular chirality from simple Fischer projections. They used the approach to define a chirality index[15,16] to characterize the global chirality of a structure and suggested an aufbau (built up) method to predict the same property for a new compound. Yang and Zhong[17] suggested that a chirality factor be applied to several commonly used topological indices to calculate molecular descriptors for chiral molecules and tested their applicability in QSAR studies. However, these indices are calculated by applying the chiral correction to the commonly used topological indices. Hence, they depend on the computation of other topological indices.

In several of these studies, chirality is treated as an either−or property, i.e., on a black or white scale. Activities of many enzymes and biological activities of chiral molecules are not either−or properties, and so, chirality must be treated as a continuous measure in developing structure−activity relationships. This could be substantiated with the insect repellency of picaridin and AI3-37220[5,18,19] and the HIV protease inhibition activity of chiral sulfonamide-substituted cyclooctylpyranones.[20] Hence, there is a need to develop molecular descriptors that could not only differentiate enantiomers and diastereomers but also treat chirality as a continuous measure. Natarajan and Basak[21] attempted to develop such indices using ^{1}H NMR chemical shift values by converting a NMR spectrum into a linear graph. However, this method requires NMR data for a compound under investigation. The present study describes the calculation of new chirality descriptors to discriminate enantiomers and diastereoisomers. Application of the new chirality descriptors in SAR modeling is illustrated with mosquito repellency of the diastereomers of picaridin and AI3-37220.

METHODS

Calculation of Chirality Indices. Three-point interaction models are always proposed for biodiscrimination of enantiomers, and this formed the basis for the calculation of the new indices. Instead of considering all possible spatial orientations for a given configuration we preferred to use the single representation of spatial arrangement of groups around a given chiral center (Figure 1) in calculating the chirality measure. The reasons for our preference to use a single representation are as follows: Although there are 24 (4! permutations) possible planar projections (Fischer projections) for the four chemical groups (12 for each of the enantiomers, *R* or *S*), three-point correlation is important. The importance of three point correlation for tetrahedral chiral centers was discussed in detail by Harris et al.[22−24] According to the Cahn-Ingold-Prelog rule, different degrees of priorities are assigned to the four chemical groups attached to the chiral carbon, "*a*" being given highest priority, then "*b*", etc. Difference in the disposition of the groups *a*, *b*, *c*, and *d* around the asymmetric carbon is given in Figure 1. The least important chemical group (*d*) is placed at the rear, and the clockwise or the anticlockwise arrangement of the other three groups (*a*, *b*, *c*) is considered to assign the configuration as *R* or *S*. So, all the 12 projections of an enantiomer are reduced to only one representation to assign the absolute configuration.

In the approach developed in this paper, the three groups of highest priority attached to a chiral center were viewed from a reference point to calculate the new chirality metric. The groups/atoms *a*, *b*, *c*, and *d* are then assigned valence delta values of atoms (δ^v) according to the method of Hall and Kier.[25] When the group has more than one atom, δ^v for the group *a*, *b*, or *c* 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 (δ^v_i) attached to a chiral carbon is calculated as

$$\delta^v_i = \delta^v_{n1} + (\delta^v_{n2}/2) + (\delta^v_{n3}/4) + (\delta^v_{n4}/8) + ...$$

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

$$^V\mathrm{RCI}_R = \delta^v_a + (\delta^v_a + \delta^v_a\delta^v_b) + (\delta^v_a + \delta^v_a\delta^v_b + \delta^v_a\delta^v_b\delta^v_c) + \delta^v_a\delta^v_b\delta^v_c\delta^v_d$$

$$^V\mathrm{RCI}_S = \delta^v_a + (\delta^v_a + \delta^v_a\delta^v_c) + (\delta^v_a + \delta^v_a\delta^v_c + \delta^v_a\delta^v_b\delta^v_c) + \delta^v_a\delta^v_b\delta^v_c\delta^v_d$$

For example,

$$^V\mathrm{RCI}_R = 5 + (5 + 5(3)) + (5 + 5(3) + 5(3)1) + 0 = 60$$

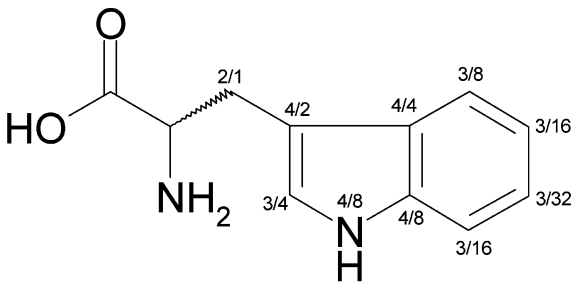
$$^V\mathrm{RCI}_S = 5 + (5 + 5(1)) + (5 + 5(1) + 5(1)3) + 0 = 40$$

To obtain ^{V}RCI for molecules containing more than one chiral center, root-mean-square of ^{V}RCI for all the chiral centers is taken.

$$^V\mathrm{RCI} = \sqrt{\frac{1}{N}\sum_{i=1}^{N}(^V\mathrm{RCI}_i)^2}$$

Calculation of group δ^v values for cyclic structures is illustrated with tryptophan (Figure 2). Figure 2 examples the calculation of ^{V}RCIs for *R* and *S* isomers of tryptophan. Information regarding the fourth group is encoded 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.

In addition to the valence connectivity, we also used the formula weights of the groups and the electrotopological state of the various atoms[26] and groups in *a*, *b*, *c*, and *d* to calculate ^{W}RCI and ^{I}RCI, respectively. In order to calculate ^{I}RCI, one



$$\delta_a = 3$$

$$\delta_b = \frac{4}{1} + \frac{6}{2} + \frac{5}{2} = 9.5$$

$$\delta_c = \frac{2}{1} + \frac{4}{2} + \frac{3}{4} + \frac{4}{4} + \frac{3}{8} + \frac{4}{8} + \frac{4}{8} + \frac{3}{16} + \frac{3}{16} + \frac{3}{32} = 7.59375$$

$${}^{V}RCI_R = 288.42$$

$${}^{V}RCI_S = 270.98$$

Figure 2. Calculating of group δ and RCI for tryptophan. $\delta_a = 3$, $\delta_b = 4/1 + 6/2 + 5/2 = 9.5$, $\delta_c = 2/1 + 4/2 + 3/4 + 4/4 + 3/8 + 4/8 + 4/8 + 3/16 + 3/16 + 3/32 = 7.59375$, ${}^{V}\mathrm{RCI}_R = 288.42$, ${}^{V}\mathrm{RCI}_S = 270.98$.

has to replace δ^v of the groups *a*, *b*, *c*, and *d* by their δ^I (electrotopological state) in the formula to calculate ^{V}RCIs. In the same way, ^{W}RCI for enantiomers and diastereomers can be calculated using the formula weights of *a*, *b*, *c*, and *d*. However, while calculating formula weights for groups we considered the whole substituent instead of using diminishing importance of contribution of atoms based on their neighborhood. It is to be noted that simple connectivity and bond order connectivity of vertices (atoms) were not useful in generating RCI due to their inability to differentiate atom types and this consequently gave degenerate values for several structures.

RESULTS AND DISCUSSION

Calculation of RCI for α-Amino Acids. The RCI calculated from all three methods for the 17 biologically important chiral α-amino acids are given in Table 1. In the case of α-amino acids having 2 chiral centers the values for the two pairs of enantiomers are given in Table 2. RCI can be calculated considering chirality at a given center in the case of a polychiral molecule, and this will be very useful in finding out the relative importance of chirality of the various centers with respect to one another. Hence, it is possible to calculate a set of RCI for a polychiral system taking into consideration one chiral center only at a time. This is illustrated in the case of isoleucine and threonine, and the values are given in Table 2. Calculation of the new chiral metric considering specific chiral centers is expected to bring out the importance of chirality at a particular chiral atom. Distribution of atoms according to their mass around a chiral center is encoded in ^{W}RCI, while ^{V}RCI and ^{I}RCI quantify the distribution of groups based on branching and electrotopological states, respectively. Thus the "handedness" based on three different measures are encoded by the chirality indices. For example, bioisosteric amino acids, serine and cysteine have the same set of ^{V}RCI (${}^{V}\mathrm{RCI}_R = 194.250$; ${}^{V}\mathrm{RCI}_S = 164.250$). However, the other two RCI values are different for these two amino acids indicating their difference with respect to chemical nature and other aspects of chirality. ^{V}RCI is degenerate for aspartic acid and histidine, and this type of degeneracy can be handled by using correction factors for cyclic structures. RCI values for the diastereomers of tartaric acid (Table 2) showed that the two *meso* forms have the same RCI values indicating that they are nondistinguishable. The primary objective of a molecular descriptor is to map the structural information into a set of real numbers, and the descriptors thus generated must be able to discriminate different structures. The above discussion shows that the new chirality indices satisfy this requirement. However, their applicability in SAR modeling is the next most important test of their usefulness.

Table 1. RCI Values for Amino Acids Containing a Single Chiral Center

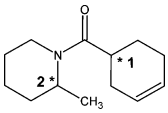
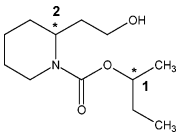
		^{W}RCI		^{V}RCI		^{I}RCI	
no.	amino acid	*R*	*S*	*R*	*S*	*R*	*S*
1	alanine	23088	22128	94.50	43.50	142.67	93.34
2	arginine	145488	147248	193.36	163.17	185.89	147.14
3	asparagine	85008	85424	244.13	224.63	333.24	330.57
4	aspartic acid	86448	86896	258.38	241.88	259.74	239.07
5	cysteine	69312	69379	194.25	164.25	178.97	138.52
6	glutamic acid	106608	107504	219.19	194.44	217.54	186.54
7	glutamine	99408	100144	212.06	185.81	209.37	176.37
8	histidine	118128	119280	258.38	241.88	216.18	184.84
9	leucine	83568	83952	180.00	147.00	180.78	140.78
10	lysine	105168	106032	178.22	144.84	177.38	136.55
11	methionine	109632	110595	197.81	168.56	173.98	132.31
12	phenylalanine	132528	134000	235.22	213.84	197.81	161.98
13	proline	75777	74791	252.50	187.50	122.56	84.10
14	serine	46128	45680	194.25	164.25	224.34	195.01
15	tryptophan	188688	191408	282.42	270.98	215.85	184.43
16	tyrosine	155568	157552	255.70	238.64	203.94	169.60
17	valine	61968	61872	186.22	147.55	151.50	112.50

Table 2. RCI Values for Amino Acids Containing Two Chiral Centers and Tartaric Acid

amino acid	absolute configuration	^{W}RCI	^{V}RCI	^{I}RCI
D-allo-threonine	*RR*	54857.8	199.76	225.49
D-threonine	*RS*	54134.4	174.99	200.55
L-threonine	*SR*	54857.8	187.48	213.07
L-allo-threonine	*SS*	54134.4	160.83	186.48
D-isoleucine	*RR*	76583.3	158.09	153.43
D-allo-isoleucine	*RS*	75659.7	150.61	151.17
L-allo-isoleucine	*SR*	76793.0	140.21	130.71
L-isoleucine	*SS*	75872.0	131.72	128.05
tartaric acid	*RR*	117861.0	596.88	528.43
	RS	**118389.2**	**600.64**	**529.93**
	SR	**118389.2**	**600.64**	**529.93**
	SS	118915.0	604.38	531.42

Application of RCI in SAR. In order to test the application of RCI in structure−activity relationship modeling we considered the insect repellency data for diastereomers of AI3-37220 and picaridin. Both picaridin and AI3-37220 have two asymmetric centers (structures are given in Table 3), and the four diastereoisomers (1*R*,2′*R*, 1*R*,2′*S*, 1*S*,2′*R*, and 1*S*,2′*S*) of each compound were shown to have differing degrees of mosquito-repellent activity.[5] The order of repellency (proportion of biting) of the diastereomers of AI3-37220 and picaridin are given in Table 3. In situations such as this where activities of diastereomers are to be modeled, conventional QSAR using calculated molecular descriptors failed to discriminate chemicals. In our earlier attempt[19] to

Table 3. RCI and Repellency Data for AI3-37220 and Picaridin Diastereomers

chemical	biting[a] proportion	^{W}RCI	^{V}RCI	^{I}RCI
AI3-37220				
				
1*R*,2′*R*	0.56c	332358.4	249.32	100.19
1*R*,2′*S*	0.32b	329904.3	233.86	96.59
1*S*,2′*R*	0.51c	332519.1	242.07	100.89
1*S*,2′*S*	0.18a	330066.2	226.11	97.31
control	0.83d			
picaridin				
				
1*R*,2′*R*	0.22a	407664.0	242.38	121.92
1*R*,2′*S*	0.18a	407081.2	230.49	112.82
1*S*,2′*R*	0.40b	406731.3	234.29	119.08
1*S*,2′*S*	0.44b	406147.2	221.96	109.74
control	0.72c			

[a] Proportions followed by the different letters are significantly different from one another at $P = 0.05$. Repellency data are from refs 4 and 15. Lower the biting proportion higher the repellency.

use the Schultz method of discriminating diastereomers, we found that the *RR* isomer always had the largest numerical value of the index and the *SS* the smallest irrespective of the substituents attached to the asymmetric carbon. This limitation in using the Schultz approach is eliminated in the new indices described in this paper. However, the order of repellency of diastereomers with the order of RCI is reversed in the case of AI3-37220 and picaridin (see Table 3). In the case of AI3-37220, the increasing order of RCI matches with the increasing order of repellency of the diastereomers; for picaridin diastereomers, the lower the RCI the higher the repellency. It is to be noted that AI3-37220 is an amide and picaridin is a carbamate. The difference in their chemical nature might be one of the possible reasons for the inverse relation observed between their repellencies. In SARs we try to find the mathematical association of structure/properties of molecules and chemical/ biological activities. The key to identifying the 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. The CIP rule uses atomic number ($\approx$ size) to distinguish different substituents if one follows the approach to develop quantitative indices that will lead to numerical discrimination of diastereomers and enantiomers. 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 the ordering of them by the receptor, then and only then can we expect a correlation between the calculated RCI and the bioactivity. Otherwise, the indices will only discriminate the structures without any necessary correlation with biological function.

CONCLUSION

The three distinct classes of indices of chirality take into account the distribution of groups around a chiral center based on different measures of "handedness". They are able to discriminate diastereomers and enantiomers very well. Singularity of *meso* compounds is also addressed because the *meso* compounds have the same values for all three RCIs. As they are computed based on a three-point fitting in receptors, they are expected to perform well in SAR modeling of biological activities of diastereomers. The new indices might be used along with the other commonly used topological indices to handle enantiomeric and diastereomeric compounds. The new chiral indices are conceptually very simple and can be computed easily for simple molecules. However, for large molecules like peptides and proteins we need to develop a computer program.

ACKNOWLEDGMENT

Research was supported by Grant F49620-02-1-0138 from the United States Air Force. The U.S. Government is authorized to reproduce and distribute reprints for governmental purposes notwithstanding any copyright notation thereon. The views and conclusions contained herein are those of the authors and should not be interpreted as necessarily representing the official views, policies, or endorsements, either expressed or implied, of the Air Force Office of Scientific Research or the U.S. Government. We acknowledge Natural Resources Research Institute, University of Minnesota Duluth for the financial support for one of the authors (R.N.). This paper is contribution number 444 from the Center for Water and the Environment, Natural Resources Research Institute, University of Minnesota Duluth, Duluth, U.S.A.

REFERENCES AND NOTES

(1) Ariens, E. J. Racemic therapeutics: problems all along the line. In *Chirality in Drug Design and Synthesis*; Brown, C., Ed.; Academic Press: New York, 1990; pp 29−43.
(2) Ariëns, E. J. Stereoselectivity in bioactive agents: general aspects. In *Stereochemistry and Biological Activity of Drugs*; Ariëns, E. J., Soudijn, W., Timmermans, P. B. M. W. M., Eds.; Blackwell Scientific Publications: Oxford, U.K., 1983; pp 11−32.
(3) *Chirality in Agrochemicals;* Kurihara, N., Miyamoto, J., Eds.; Wiley Series in Agrochemicals and Plant Protection, John Wiley & Sons: New York, 1998; p 269.
(4) Klun, J. A.; Schmidt, W. F.; Debboun, M. Stereochemical Effects in an Insect Repellent. *J. Med. Entomol*. **2001**, *38*, 809−812.
(5) Schultz, H. P.; Schultz, E. B.; Schultz, T. P. Topological Organic Chemistry. 9. Graph Theory and Molecular Topological Indices of Stereoisomeric Organic Compounds. *J. Chem. Inf. Comput. Sci*. **1995**, *35*, 864−870.
(6) Golbraikh, A.; Bonchev, D.; Tropsha, A. Novel Chirality Descriptors Derived from Molecular Topology. *J. Chem. Inf. Comput. Sci*. **2001**, *41*, 147−158.
(7) Randić, M. Graph Theoretical Descriptors of Two-Dimensional Chirality with Possible Extension to Three-Dimensional Chirality. *J. Chem. Inf. Comput. Sci*. **2001**, *41*, 639−649.
(8) Fujita, S. Graphs to Chemical Structures 1. Sphericity Indices of Cycles for Sterochemical Extension of Polaya's Theorem. *Theor. Chem. Acc.* **2005**, *113*, 73−79.
(9) Fujita, S. Graphs to Chemical Structures 2. Extended Sphericity Indices of Cycles for Sterochemical Extension of Polaya's Coronas. *Theor. Chem. Acc.* **2005**, *113*, 80−86.
(10) Fujita, S. Graphs to Chemical Structures 3. General Theorems with the Use of Different Sets of Sphericity Indices for Combinatorial Enumeration of Nonrigid Stereoisomers. *Theor. Chem. Acc.* **2006**, *115*, 37−53.
(11) Aires-de-Sousa, J.; Gasteiger, J. New Description of Molecular Chirality and Its Applications to the Prediction of the Preferred

Enantiomer in Stereoselective Reactions. *J. Chem. Inf. Comput. Sci.* **2001**, *41*, 369−375.
(12) Aires-de-Sousa, J.; Gasteiger, J.; Gutman, I.; Vidović, D. Chirality Code and Molecular Structure. *J. Chem. Inf. Comput. Sci.* **2004**, *44*, 831−836.
(13) Dervarics, M.; Otvos, F.; Martinek, T. A. Development of a Chirality-Sensitive Flexibility Descriptor for 3+3D-QSAR. *J. Chem. Inf. Model.* **2006**, *46*, 1431−1438.
(14) Capozziello, S.; Lattanzi, A. Algebraic Structure of Central Molecular Chirality Starting From Fischer Projections. *Chirality* **2003**, *15*, 466−471.
(15) Capozziello, S.; Lattanzi, A. Molecular Approach to Central Molecular Chirality: A Chirality Selection Rule. *Chirality* **2003**, *15*, 227−230.
(16) Capozziello, S.; Lattanzi, A. Description of chiral tetrahedral molecules via an Aufbau approach. *Theochem* **2003**, *671*, 205−209.
(17) Yang, C.; Zhong, C. Chirality Factors and Their Application to QSAR Studies of Chiral Molecules. *QSAR Comb. Sci.* **2005**, *24*, 1047−1055.
(18) Basak, S. C.; Natarajan, R.; Nowak, W.; Miszta, P, Klun, J. A. Three Dimensional Structure-activity Relationships (3D-QSAR) for Insect Repellency of Diastereoisomeric Compounds: A Hierarchical Molecular Overlay Approach. *SAR QSAR Environ. Res*. **2007**, in press.
(19) Natarajan, R.; Basak, S. C.; Balaban, A. T.; Klun, J. A.; Schmidt, W. F. Chirality Index Molecular Overlay and Biological Activity of Diastereoisomeric Mosquito Repellents. *Pest Manage. Sci.* **2005**, *61*, 1193−1201.
(20) Skulnick, H. I.; Johnson, P. D.; Aristoff, P. A.; Morris, J. K.; Lovasz, K. D.; Howe, W. J.; Watenpaugh, K. D.; Janakiraman, M. N.; Anderson, D. J.; Reischer, R. J.; Schwartz, T. M.; Banitt, L. S.; Tomich, P. K.; Lynn, J. C.; Horng, M.-M.; Chong, K.-T.; Hinshaw, R. R.; Dolak, L. A.; Seest, E. P.; Schwende, F. J.; Rush, B. D.; Howard, G. M.; Toth, L. M.; Wilkinson, K. R.; Kakuk, T. J.; Johnson, C. W.; Cole, S. L.; Zaya, R. M.; Zipp, G. L.; Possert, P. L.; Dalga, R. J.; Zhong, W. Z.; Williams, M. G.; Romines, K. R. Sulfonamide-Substituted Cyclooctylpyranones. *J. Med. Chem.* **1997**, *40*, 1149−1164.
(21) Natarajan, R.; Basak, S. C. NMR Spectral Invariants − A New Class of Descriptors for Diastereomers and Enantiomers. *Croat. Chem. Acta* **2007** (submitted).
(22) Harris, A. B.; Kamien, R. D.; Lubensky, T. C. Molecular chirality and chiral parameters. *Rev. Mod. Phys*. **1999**, *71*, 1745−1757.
(23) Harris, A. B.; Kamien, R. D.; Lubensky, T. C. Microscopic Origin of Cholesteric Pitch. *Phys. Rev. Lett*. **1997**, *78*, 1476−1479.
(24) Harris, A. B.; Kamien, R. D.; Lubensky, T. C. Microscopic Origin of Cholesteric Pitch. *Phys. Rev. Lett*. **1997**, *78*, 2867(erratum).
(25) Kier, L. B.; Hall, L. *Molecular Connectivity Analysis*; Research Studies Press: Letchworth, U.K., 1986; pp 1−26.
(26) Kier, L. B.; Hall, L. H *Molecular Structure Description*; Academic Press: New York, 1999; pp 13−36.

CI600542B