Research Article

BIOMEDICAL Journal of Scientific & Technical Research

ISSN: 2574 -1241

DOI: 10.26717/BJSTR.2023.53.008459

Exploring the Molecularity of Specific Olfactory and Gustatory Perceptive Phenotypes–A Computational Approach

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ARTICLE INFO

Received: November 10, 2023

Published: November 17, 2023

Citation: Chiquito Crasto, Hirva Bhayani, Sona Sara Thomas, Roshan Thilakarathne and Neranjan Perera. Exploring the Molecularity of Specific Olfactory and Gustatory Perceptive Phenotypes–A Computational Approach. Biomed J Sci & Tech Res 53(5)-2023. BJSTR. MS.ID.008459.

ABSTRACT

We have identified specific molecular electronic-structural aspects of odorants and tastants that elicit a specific olfactory or gustatory response from an individual. Our approach goes beyond functional groups or gross molecular features such as aromatic rings, aliphatic rings, or the chain lengths of these compounds. We target specific, reproducible electronic-structural features at the interatomic level. We identify atom pairs, even if the atoms are non-bonded. For structural features, we use interatomic distances from a distance matrix of all atoms. For the electronic features, we use chemical shifts–from theoretically determined NMR (nuclear magnetic resonance) spectra. The chemical shift is a representation of the atom's electronic environment. The perceptive phenotype is the odor or taste that this molecule elicits in the individual. We illustrate this approach for two molecules that are additives in the perfume industry: heptyl acetate and isopropyl salicylate. This paper also describes a method that enhances the structural aspects of molecular features by including angles and dihedral angles.

Abbreviations: QSAR: Quantitative Structure-Activity Relationship; SDAR: Spectroscopic Data Activity Relationships; DFT: Density Functional Theory; NCTR: National Center for Toxicology Research

Introduction and Background

Understanding olfaction–providing a mechanistic basis for odor perception, and by extension, taste perception–is challenging. The discovery of olfactory receptors was published in 1991. [1] This was indeed momentous. It resulted in the 2004 Nobel Prize in Physiology and Medicine. [2] Mining the olfactory- and taste-, or collectively, chemosensory receptors from the human and other mammalian genomes resulted in breaking new ground in our understanding of gene superfamilies. Several research groups identified (and, subsequently, refined) the number of olfactory receptors in the human genome. Their efforts revealed that humans have approximately 850 olfactory receptor genes, more than 50% of which are pseudogenic. [3-5] Subsequent identification of the olfactory repertoires of other well-known or model mammalian organisms such as those for mouse [6,7], rat, dog, [8] and elephant [9,10] showed that the ratio of non-pseudogenic and functional genes to pseudogenes was high-

er than that for humans. The number of pseudogenes in each family was not insignificant. The most accepted theory posits that as other senses and faculties developed and became more acute, humans relied less on smell for the survivalist, fight-or-flight, response. [11,12]

A scan of the Olfactory Receptor Database (https://ordb.biotech.ttu.edu/ORDB) shows that humans have approximately 287 taste receptors. [13,14] Humans have four taste sensations: sweet, sour, salty, and bitter, [15] with the umami perception [16] being restricted to specific population groups. Despite only having four overall tastes localized to different parts of the tongue, with some overlap, humans can discern a wide range of specific tastes. This is because olfaction and taste are inextricably linked, and olfaction contributes to the nuances of taste. [17-19] Olfactory and taste receptors contribute to the first biochemical interactions that take place between odorants and tastants, respectively. These interactions catalyze a cascade of reactions resulting in the perception of the odor and taste. The challenges in functionally assessing the specific roles of olfactory and taste receptors are stymied by several factors. Both sets of receptors are membrane receptors and are difficult to express separately from the lipid bi-membrane layers in which they are embedded. [20, 21] These proteins are difficult to purify, which is one reason why the crystal structure of a chemosensory receptor is not currently available. Computation provides a mechanistic glimpse into the molecularity of odorant-olfactory receptor or tastant-gustatory receptor interactions. A combination of ab initio and semi-empirical methods is needed to create a putative structure of the receptor. Next, the odorant or tastant ligand is computationally docked into the putative binding pocket of the receptor. [22-24] This static docking is a prelude to all-atom, nano-second scale molecular dynamics simulation of these interactions. One must apply a cautionary approach to making sweeping statements of these interactions given the possible limitations of computational methods and the challenges of comprehensively mimicking a biological system. Experimental, functional analysis is needed to test and validate these computationally driven hypotheses.

Methodology

The work described here contributes to a novel approach to assessing chemosensory receptor-ligand interactions–from the perspective of the ligand. One methodology explores the conformational space of ligands, identifying specific conformations adopted by the ligands that are responsible for receptor activation. These assessments go beyond the chemical nature of the ligand, such as the nature of functional groups, ring versus straight chains, aromatic versus aliphatic systems. Here, we mean that the dynamic motion of a ligand molecule adopts a conformation that is conducive to receptor activation. We posit that this is one possible reason why seemingly disparate ligands activate the same receptor. [25] Another approach, and the one described here, is to explore the molecularity of a ligand by identifying specific regions of known odorants and tastants that have reproducible structural-electronic features. As described in the above paragraph, these features are not restricted to gross features such as functional groups, etc. By molecular features, we mean atom pairs that may or may not be bonded; and indeed, the atom pairs might include atoms that are located remotely within the molecule. For each atom pair, we explore the interatomic distance–the structure, and the electronic environment determined by the chemical shift on the NMR (nuclear magnetic resonance) spectrum. We then determine whether ligands that had the same perceptive phenotypes contained atom pairs with reproducible structural-electronic features. [26]

Similar notions have been advanced in the pharmaceutical industry. Quantitative Structure-Activity Relationship (QSAR) has been used to identify similar features from known pharmaceutical products in the quest to produce novel drugs. [27-29] Similarly, SDAR (Spectroscopic Data Activity Relationships) methodologies (1D-SDAR–which includes only reproducible chemical shifts, and 3D-SDAR–which includes chemical shifts and interatomic distances) have been used to identify toxicities in compounds. Here we have used the principles of SDAR in this work. [30,31] We have, however, independently developed our protocols, and when necessary, custom-designed software, and applied them to the domain of the chemical senses.

Computational Approaches

We use ab initio methodologies based on quantum chemistry calculations, specifically Density Functional Theory (DFT), to determine theoretical chemical shifts from the NMR calculations for 13C, 15N, and 31P isomers in cohorts of molecules. Proton (1H)-NMR chemical shifts are ignored in our protocols. For this representation of the structural-electronic aspects of an atom whether in an isolated or bonded state, the functional is also used to determine a Z-matrix. This matrix represents the interatomic distances for all atoms in the molecule. These are the electronic-structural features of the odorant and tastant molecules. [32]

Perceptive Phenotypes

To identify the intramolecular features of specific olfactory and gustatory responses, the odor and taste perception profiles of these molecules must be explored. Good Scents Company (https://www.thegoodscentscompany.com/) is a valuable and comprehensive resource that catalogs the odor and flavor profiles of many molecules. In QSAR or SDAR, the molecular attributes must be mapped to specific activities like pharmacophores–the part of the molecule that gives it efficacy in addressing a clinical condition, or toxicophores–the part of the molecule responsible for potential adverse effects. Here, we map an odorant or tastant molecule to its various distinct odors and tastes as determined by super-smellers and -tasters and cataloged in the Good Scents Company resource. We tested our methodology on 75 odorant molecules that were used in perfumes. For each molecule, the GAUSSIAN program [33] was used to determine the interatomic distances and NMR chemical shifts using DFT calculations. Each

molecule was mapped to its perceptive odor. We listed all the atom pairs identifying the chemical shifts for each atom and the interatomic distance based on the perceived odors. We developed and deployed customized software that for each atom pair, scanned all other atom pairs for all the 75 odorant molecules. To identify atom-pairs, whether in the same molecule or in different molecules, we established two criteria: the difference in interatomic distances for the compared atom-pairs less than or equal to 0.1 Å and the differences between the chemical shifts for the atoms less than or equal to 1 ppm (parts per million). This ensured that the two atom pairs were electronically and structurally (almost) identical. If these atom pairs belonged to molecules whose odors or tastes were the same, then those atom pairs would likely solely (or in combination with other reproducible atom pairs) contribute to that odor or taste. If an atom pair belonged to a molecule that exhibited a specific odor while its "identical" atom pair belonged to another molecule that exhibited another odor, those were also listed. We surmised that these perceptions were not distinct. For example, the generic odors "fruity", "sweet" and "floral" especially when perceived for the same molecule are largely based on individual perceptions, and, in some cases, are likely not distinguishable at a molecular level.

Results

We illustrate our methodology using the example of two molecules used in the perfume industry: heptyl acetate and isopropyl salicylate. The primary odors for heptyl acetate are green and fruity. The primary and single odor for isopropyl salicylate is green. These are listed in the Good Scents Company web resource. In Figures 1 & 2, either bold or dotted lines connect different atoms. The bold lines connect atoms-pairs whose interatomic distances and chemical shifts meet our criteria for atom pairs to be found in virtually identical electronic-structural environments and exclusively point to molecules that have the odor-perception of "green". The bold, green lines for heptyl acetate and isopropyl salicylate depict atom pairs that are associated with the perception of "green." The bold, blue lines in heptyl acetate are associated with the perception of "fruity." The dotted lines indicate where atom pairs are for molecules that show both "fruity" and "green" odor perceptions. It is critical to note that while we have represented just two examples here, the atom-pairs are unique for a specific odor "green" and "fruity" over our test cohort of 75 odorants used as adducts in perfumes. Figures 1 & 2, and the examples of using this methodology illustrate how and why atom-pairs can be identified that elicit the same olfactory response though the structures of isopropyl salicylate and heptyl acetate are structurally disparate, with different functional groups.

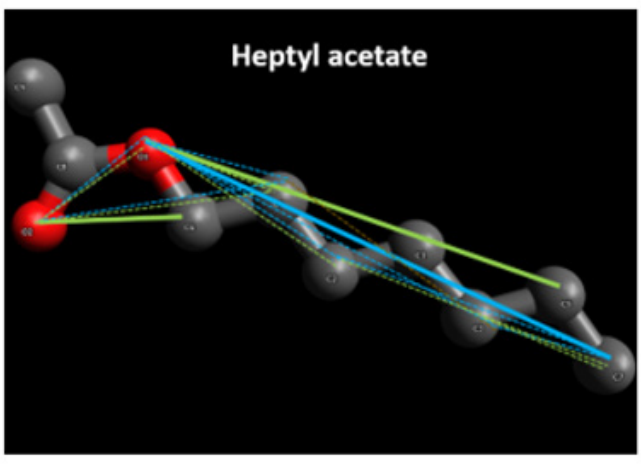

Figure 1: Heptyl acetate: The solid blue and green lines depict atoms pairs that are exclusively associated with molecules that have the perceived odor of fruity and green, respectively. The dotted lines where the blue and green lines show the same atom pairs are where atom pairs related to one perceived odor are virtually identical to atom pairs associated with another odor.

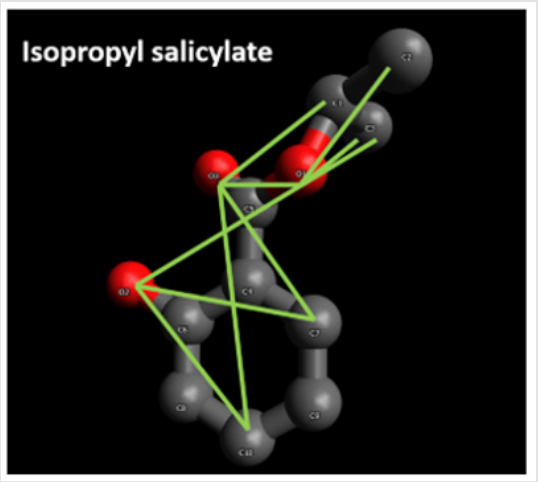

Figure 2: Isopropyl salicylate: All the highlighted atom pairs for this odorant molecule are associated with the perceived odor of green. This means that they are only associated with atom pairs of other molecules that have the odor of green.

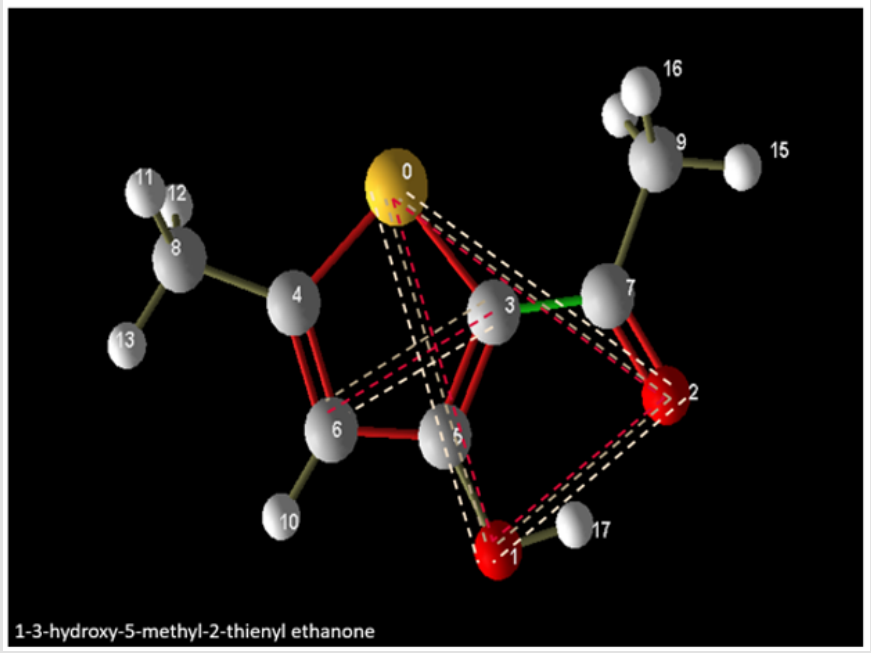

Figure 3: The atom pairs for 1,3-hydroxy-5-methyl-2-thienyl ethenone, a molecule that elicits the smell of "brown." The atom pairs are highlighted by dotted lines that are colored: red for "cooked", beige for "meaty", and cream for "roasted." All identified atom pairs show these bonds—when compared to 18 other compounds that elicited the "brown" smell.

Discussion

The methodology that we have used is a novel approach when applied to the domain of the chemical senses. The notions have been previously used in identifying molecular toxicities in the clinical domain and beyond. This work is also novel as it echoes recent efforts to approach studies related to receptor-ligand interactions from the perspective of the ligand. In the work described here, we treat the ligand molecularity as separate and independent from any associations with the receptor. This work is universally applicable to any molecule or cohort of molecules when associated with a phenomenon or a phenotype, in this case, the perception of odor or taste. In the clinical domain, this behavior or result might be an efficacious or toxic effect from a pharmaceutical product. If this methodology can validly be associated with a salutary effect that can be pointed to a particu-

lar molecular feature, then novel molecules that reproduce that molecular feature can be designed and synthesized. Our methodology is currently being tested to discern and distinguish subtle differences in odorant and gustatory perceptions. From the Good Scents Company resource, we identified all the compounds that had odors and tastes of "green" and "brown." These perceptions are unique. There is no odor or taste molecule that is green and brown. Green and brown are perceptions of smell and taste that arise by combining the chemical senses with visual perception–most often from stored memory. It is possible, however, to identify what molecular features produce the chemosensory perceptions of green and brown by using our methodology (e.g., isopropyl salicylate (Figure 2 & 3)). Table 1 lists all the other odors and tastes identified for the molecules associated with the smell and tastes of "green" and brown."

Table 1: All the other smells and tastes associated with molecules that had the common smells and tastes of green and brown.

Green Taste	Floral, fruity, muguet, tropical, berry, melon, rind, waxy, fatty, nutty, walnut, lactonic, nut, skin, oily, cooling, minty, mentholic, herbal, terpenic, camphoreous, bitter, musty, citrus, sandalwood, estery, ethereal, winey, passion-fruit, solvent, fermented, aldehydic, sweet, plastic, metallic, weedy, earthy, mushroom, fungal, umami, savory, brothy, pine, spicy, balsamic, mossy, woody, cocoa, vegetable, roasted, creamy, cucumber, chicken, mutton, coffee, burnt, hazelnut, currant-bud, black, apple, almond, honey, acacia, caramellic, hawthorn, astringent, radish, beany, cheesy, coconut, bell-pepper, pea, galbanum, pineapple, coffee, grape, sulfurous, soapy, dairy, dirty, buttery, tomato, horseradish, fishy, ketonic, onion, yeasty, bready, watercress, cortex, hyacinth, phenolic, red-rose, nasturtium, privet, sappy, chrysanthemum, foliage, citrus-like-fatty, durian, grassy, asparagus, clover, fresh, pear, alcoholic, fusel, rummy, egg-nog-whiskey, nauces, guava, celery, aromatic, cinnamon, cherry, peach, lovage, licorice, hay, magnolia, mango, petal, apricot, melon-rind, sharp, macadamia, nut-flesh, greasy, dried-fruit, plum, lime, peptigrain, rooty, turnup, capers, tutti-frutti, strawberry, juicy, saffron, tobacco, medicinal, leathery, alliaceous, cilantro, artichoke, ripe, banana, candy, starfruit, papaya, bubble-gum, grain, spearmint, boulillon, lemon-peel, dark-chocolate, cumin, costus, watery, pulpy, green-onion, jasmin, powdery, raisin, cognac, sour, tart, asafetida, fried, potato, greasy-undertone, coriander, pork, citrus-peel, beefy, mandarin, tangerine, watermelon-rind, jammy, quince, wintergreen, violet-leaf, humus, juicy-fruit, kiwi, wasabi, lavender, rasberry, orchid, unripe-banana, plum-skin, dusty, clean, rue, oak-wood, spruce, malty, sauerkraut, mahogany, juniper, ylang, gooseberry, bergamot, milky, peppermint, rancid, origanum, coumarinic, thyme, fir, needle, orange-flower, cooked-onion, rindy, greenbean, filbert, apple, skin, cooked, apple, fig, fleshy, tea, honeydew, cabbage, fennel, kimchi, chamomile
Green Odor	herbal, coumarinic, cooling, pine, minty, camphoreous, terpenic, eucalyptus, woody, fruity, earthy, mushroom, geranium, leafy, marine, floral, melon, musty, violet, sweet, peony, pungent, vegetable, apple, banana, metallic, oily, tomato, spicy, rummy, ethereal, fatty, creamy, raw, chicken, fungal, horseradish, radish, chrysanthemum, mild-fruity, astringent, muguet, lily, mangolia, linden, flower, grape, cucumber, aldehydic, sulfurous, onion, citrus, orange, fresh, skin-like, petal, gardenia, almond, nutty, marzipan, waxy, fat, nuance, tropical, fruit, pear, buttery, baked, mango, leaf, goaty, watery, sweaty, roasted, savory, rose, mandarin, sharp, powerful-floral, apricot, dried-papaya, lemon-grass, coconut, cheesy, ketonic, bitter, plum, pea, pepper, galbanum, fermented, tea, burnt, mustard, cabbage, undernotes, soapy, weedy, cereal, fusel-oil, winey, ripe-apple, alcoholic, hyacinth, narcissus, foliage, honey, carrot, dry, peppery, potato, cortex, clean, tallow, fried, fishy, petitgrain, lilial, cyclamen, grapefruit, spice, neroli, green-apple, milky, jasmin, grassy, caraway, medicinal, solvent, pineapple, cider, tart, concord, buchu, currant-bud, black, peely, cognac, cocoa, basil, vinyl, garlic, meaty, clam, alliaceous, cooked, reseda, moss, brothy, celery, bell-pepper, chemical, berry, gooseberry, diffuse, lilac, coup, tangerine, passion-fruit, gassy, peach, levender, bergamot, myrrh, black-pepper, ambroxide, amber, ambergris, paper, musk, cedar, estery, resinous, hay, nutmeg, balsamic, opoponax, malty, fir, needle, currant-black, currant-natural, anise, yeasty, cherry, leathery, nut, rancid, brown, chocolate, butter, skin, vanilla, cumin, prune, seedy, powdery, cinnamon, watermelon, plastic, unripe-banana, cilantro, natural, guava, sassafrass, fennel, phenolic, orchid, thujonic, tobacco, lavender, rhubarb, catty, cedarwood, spearmint, bois-de-rose, soft, greasy, clove, lime, privet, nasturtium, animal, stem, warm, caramellic, clary, sage, pumpkin, parsley, wet, anisic, orris, cloth, laundered, aspirin, sawdust, ozone, painty, corn, honeydew, bean, whiskey, walnut, rind, acidic, dairy, turnip, cantaloup, juicy, beeswax
Brown Taste	meaty, sulfurous, brothy, creamy, caramellic, fatty, sweet, fruity, vegetable, cooked, beefy, coffee, toffee, maple, sugar, brown-sugar, molasses, buttery, milky, potato, baked, oily, shellfish, vanilla, nutty, woody, bready, burnt, astringent, alcoholic, apple, fermented, roasted, green, herbal, beefy, bloody, chicken, ethereal, rummy, nut, skin, tequila, fenugreek, sour, tropical, strawberry, berry
Brown Odor	almond, baked, beefy, bread, bready, brothy, burn, sugar, burnt, buttermilk, butterscotch, buttery, caramellic, celery, cherry, chicory, chocolate, cocoa, coffee, cooked, cortex, creamy, dry, ethereal, fatty, fenugreek, fruity, herbal, lactonic, lard, lovage, maple, meaty, molasses, musty, nutty, phenolic, praline, pungent, roasted, rummy, savory, Sugar, sweet, syrup, tequila, toffee, tropical, vanilla, vegetable, whiskey, winey

Table 1 shows that molecules that elicit the taste and smell of "green" and "brown" are also associated with other tastes and smells. Is it possible then, within the "brown" taste to identify the atom-pairs that contribute to "brown-sugar" versus "molasses"? Or are these two tastes too close to discern and are based on the perceptions of the individual, his or her experiences, and possible cultural background? Within the odor perception of "brown," meaty, roasted, and cooked are identified with the same atom-pairs. Can a vegetarian be able to identify the "meaty" odor? Even if these tastes are not distinguishable, we can identify the atom pairs that contribute to these tastes. For 1,3-hydroxy-5-methyl-2-thienyl ethanone, the atom pairs that are reproducible among molecules that elicited an odor response of "cooked," "meaty," and "roasted" are two sulfur-oxygen pairs, the oxygen-oxygen pairs, and the carbon atoms marked atom "3" and "6" in the compound's thienyl ring. (Figure 3) Another group of molecules that can be studied using our method, and still within the domain of

the chemical senses, are spices. Good Scents Company lists odor and flavor indices that contain all the spices. While a lot of the responses on searching this resource are natural products–which are a combination of chemicals, the resource also contains molecules that elicit the spice odor and taste response. The resource lists approximately, a hundred different compounds and mixtures are listed in response to the cinnamon odor. Roughly, a third of these are individual molecules. It is possible to extract the atom pair(s) that are responsible for the cinnamon odor and flavor. Likewise, for molecules that elicit a cardamom flavor and odor, among others.

Conclusions: Beyond 3-D

The strength of the method proposed in this paper is that it is universally applicable. We have shown that it is possible to identify atom pairs from molecules that have disparate structures, but which elicit similar smells and tastes, that have nearly identical structural-electronic aspects. Our methodology borrows from notions first developed at the National Center for Toxicology Research (NCTR) in Arkansas, USA, which was used to identify toxicophores in pharmaceutical products and clinical applications. We extended these ideas to the domain of the chemical senses. We developed customized software to process the data and identify the atom pairs. The electronic-structural properties were obtained by using established (and Nobel Prize-winning) quantum chemistry software, GAUSSIAN. Researchers at NCTR tested their methods by first developing 1d-SDAR (NMR chemical shifts) [30] and extending it to 3d-SDAR [31] by combining chemical shifts with interatomic distances.

One of the challenges in identifying a chemical marker that can point to a phenotype or an outcome (e.g., olfactory, or gustatory response) with high specificity is the relatively large number of putative features. This is observed in gene expression analysis of high throughput data that arise from next-generation sequencing experiments. A smaller number of differentially expressed genes (ideally, a single gene) corresponding to a phenotype is preferred. This is no different from our work described here. [34,35] Ideally, one would like a single atom pair (or consistently unique atom pairs) that is reproducible and unique for every odorant or tastant molecule that elicits a specific odor or taste response. We can extend our studies beyond 3D by extending the notion of reproducible atom pairs to atom triads and atom tetrads. An atom triad would involve three atoms whose interatomic distances, angles, and chemical shifts would be measured. Atom triads of molecules that elicited the same smell and taste would be scanned. A reproducible atom triad would be chemical shifts within a specific bin (1 to 10 ppm depending on the nature of the atom), interatomic distances of 0.1 Å and angles between 0.5° to 1°. This would reduce the number of features that point to a specific odor or taste. This notion could be further extended to include reproducible electronic-structural planarity, in addition to distances and angles, by identifying atom-tetrads in molecules that elicited the same smell and tastes. Each atom tetrad would have reproducible chemical shifts for the involved atoms, reproducible distances, angles, and dihedral angles. Thus, a three-dimensional region of a molecule with reproducible structure electronic features abstracted from any other aspect of the molecule could be identified. The implications for these notions in any field, especially in the pharmaceutical field are immense.

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ISSN: 2574-1241

DOI: 10.26717/BJSTR.2023.53.008459

Chiquito Crasto. Biomed J Sci & Tech Res