



## AROMATICITY STUDY OF HETEROCYCLIC ANTICANCER COMPOUNDS THROUGH COMPUTATIONAL S-NICS METHOD

## ESTUDIO DE LA AROMATICIDAD DE LOS COMPUESTOS ANTICANCERÍGENOS HETEROCÍCLICOS MEDIANTE EL MÉTODO COMPUTACIONAL S-NICS

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### ABSTRACT

In this study, we have suggested a theoretical approach via computing of nucleus-independent chemical shifts (S-NICS) in view point of probes motions in a sphere of de-shielding and shielding spaces of rings of anticancer contain heterocyclic rings. Few research in theoretical of a statistical approach in NMR shielding and nucleus independent chemical shifts for study of anticancer drugs. S-NICS method is an accurate method for estimation the amount of aromaticity in the non-benzene rings such as heterocyclic rings which is a famous for organic chemical compounds as anti-cancer disease. Theoretical of a statistical method of NICS-nucleus independent chemical shift in small distance and are alternate in large distance in the center of heterocyclic rings. In this research, we have explored the statistical approaches through nucleus-independent chemical shifts-SNICS calculations in view point of Bq motions in the center of sphere spaces of heterocyclic rings of some anticancer drugs. The S-NICS method is an accurate computing method for estimation the aromaticity in the non-benzene rings such as heterocyclic rings which are standard molecules in organic anti-cancer compounds. Although NICS values for benzene and naphthalene and so on can be indicated as aromaticity criterion, for other molecules such as heterocyclic rings and their derivatives, S-NICS values are much more accurate compare to NICS index. Heterocyclic compound with good  $\pi$  stacks are good candidate for anticancer medicines. Presence of Nitrogen, oxygen and sulfur in these compounds make them similar biochemical parts such as nucleic acids and. Aromaticity of heterocyclic ring. This similarity especially their  $\pi$  stacks give them the ability of interaction with DNAs and RNAs and the heterocyclic compounds.

**Keywords:** Heterocyclic Compounds; Anticancer drug; Aromaticity study; Computational S-NICS method.

## RESUMEN

En este estudio, hemos sugerido un enfoque teórico a través de la computación de los cambios químicos independientes del núcleo (S-NICS) en el punto de vista de los movimientos de las sondas en una esfera de espacios de desprotección y protección de anillos de anticancerígenos que contienen anillos heterocíclicos. Pocas investigaciones teóricas sobre un enfoque estadístico en el blindaje de RMN y los cambios químicos independientes del núcleo para el estudio de medicamentos contra el cáncer. El método S-NICS es un método preciso para estimar la cantidad de aromaticidad en los anillos sin benceno, como los anillos heterocíclicos, que es famoso por los compuestos químicos orgánicos como la enfermedad anticancerígena. Teórico de un método estadístico de desplazamiento químico independiente del núcleo NICS a pequeña distancia y se alternan a gran distancia en el centro de los anillos heterocíclicos. En esta investigación, hemos explorado los enfoques estadísticos a través de cálculos de SNICS-cambios químicos independientes del núcleo en el punto de vista de los movimientos Bq en el centro de los espacios de esfera de los anillos heterocíclicos de algunos medicamentos contra el cáncer. El método S-NICS es un método computacional preciso para estimar la aromaticidad en los anillos que no son de benceno, como los anillos heterocíclicos, que son moléculas estándar en los compuestos orgánicos contra el cáncer. Aunque los valores de NICS para benceno y naftaleno, etc., pueden indicarse como criterio de aromaticidad, para otras moléculas como los anillos heterocíclicos y sus derivados, los valores de S-NICS son mucho más precisos en comparación con el índice de NICS. Los compuestos heterocíclicos con buenas pilas  $\pi$  son buenos candidatos para medicamentos contra el cáncer. La precedencia de nitrógeno, oxígeno y azufre en estos compuestos los convierte en partes bioquímicas similares, como los ácidos nucleicos y. Aromaticidad del anillo heterocíclico. Esta similitud, especialmente las pilas  $\pi$ , dan la capacidad de interacción con ADN y ARN y los compuestos heterocíclicos.

**Palabras clave:** Compuestos heterocíclicos; Medicamento contra el cáncer; Estudio de aromaticidad; Método computacional S-NICS.

## 1. INTRODUCTION

Heterocyclic compounds (HCs) and families are good candidates for anticancer drug Heterocyclic compounds are known as anticancer drugs due they have targeted DNA and causing cancer cell demise. Heterocyclic compound played a vital actions in the metabolism of all cells; 6 (or sometimes 5) membered hetero-cycles including one to three heteroatoms. Recently, imidazole fragment has been attracting much concentration because of its role as attractive scaffold for biochemical active heterocyclic drugs (Mohammadian, N. K. et al, 2017).

Anticancer property of Heterocycles structures is Due to ambidentate nucleophilic centers i.e. mercapto and amino groups. thiadiazine derivatives, as heterocyclic compound, have been reported to have antimicrobial activity mainly due to N–C–S linkage in the skeleton of triazolothiadiazine and also possess anticancer activity (Fathima et al, 2019).

Subsequently, the study of intercommunication of complexes contain heterocyclic ligand with DNA has gained increasing interest, owing to its use in tumour treatment and molecular biology. DNA is the key component of the antitumor agent and stacking interaction with metal complexes is used to identify drug interaction strategy. Schiff base metal complexes liking with DNA by cleavage or binding mechanism. In common, the ternary compounds can be bonded to the nucleic acid via the groove and electrostatic binding mode, leading to intercalation (Nakhaei, E et al, 2018).

Literature review also exposes that a minor change in the structure of anticancer drugs can lead to quantitative and qualitative variations in biological action (Hokmabady, L et al , 2016).

The basis in DNA or RNA as Cytosine, thymine, and uracil, the basal are contain heterocyclic compound and also contain many consecutive hydrogen bond-donor and acceptor groups, which makes it ideal for studying of interaction of heterocyclic drug with them.[5]. Structurally, pyrimidines are heterocyclic, aromatic organic compounds with two nitrogen containing carbon ring structures at positions 1 and 3 of the six membered ring (Nakhaei, E et al, 2018).

The investigation of the drug–DNA bases interactions is essential and will recovered regarding the action mechanism of antitumor, antiviral drugs, and some carcinogenic compounds. A range of techniques have been engaged for the interactions study of some anticancer drugs with DNA. The antitumor activity of a drug is related to its molecular properties as well as to its interactions with different targets in cells (Spiegel, K, 2006).

A large number of the important heterocyclic compounds are used in the medical activities such as histidine and proline which are amino acids. It is notable pyridoxine, folic acid, thiamine, riboflavin B12 and E families of the vitamins are included of heterocyclic structures. heterocyclic-(2H)-1,2,3triazoles CA-4 analogues are generally classified as tubulin polymerization inhibitors with an anti-mitotic mechanism of 35 action, due to their ability to disrupt microtubule dynamics and hence mitotic spindle formation by binding to the same site as colchicine on tubulin dimers. These small molecule VDAs also induce hypoxia-driven necrosis of solid tumors, and are able to induce apoptosis by cell-cycle arrest (Joshi, M, 2019).

The nucleus-independent chemical shift (NICS) is a computational method that calculates the absolute magnetic shielding at the center of the ring taken with reversed sign. Negative NICS values indicate aromaticity and positive values antiaromaticity (Schleyer, 1972).

The nucleus-independent chemical shift (NICS) is a computational method that calculates the absolute magnetic shielding at the center of the ring taken with reversed sign. Negative NICS values indicate aromaticity and positive values antiaromaticity. For further investigation of aromaticity, another method called the harmonic oscillator model of aromaticity (HOMA) (Kruszewski,1972). It has been applied, and is distinguished as a normalized sum of the squared deviations of bond length from the normal value (Stępień, 2004). An aromatic compound has a HOMA value of one whereas a non-aromatic compound has the value (Jiao, 1998).

Schleyer et al. have proposed the use of the negative of the computed magnetic shieldings at or above the ring center, referred to as ‘nucleus-independent chemical shifts’ (NICS), as a simple and effective criterion for aromaticity. NICS, as an indicator of aromaticity, agrees well with the energetic, geometric, and magnetic criteria, and does not require increment systems for other references (Schreyer, 1998). To date, a new generation of molecularly targeted drugs is eagerly expected who’s rational for suggestion new structure for anticancer drug or other type of drugs to investigate the activity to bibding DNA or cancer cell. (Skander, 2012). The NICS values for molecules could be indicated as the aromaticity criterion, for other cases such as antidepressant and anticancer compounds and their derivatives, S-NICS values are much more accurate compare to NICS index (Mollaamin, 2012).

In a concurrent study, NICS is also an actual probe of the individual rings in polycyclic systems.<sup>12</sup> Most lately, Lecea et al.<sup>13</sup> used NICS to characterize the in-plane aromaticity of 1,3-dipolar cycloaddition transition states, and only found evidence for the in-plane delocalization; the p (out-of plane) effects are negligible (Jiao, 1998). In recent years Computation study in biological field especially on drugs attract the research attention (Mollaamin, 2012).

Newly aromaticity in terms of nucleus-independent chemical shifts in long distances of NICS (1, 2.5, 3, and 3.5) Å, around the ring center, NICS (0), at the center of ring plane and aromatic ring current shielding (ARCS) were compared in numerous research. In small range of distances ( $r < 0.3$ ) there are no theoretical or mathematical reports of statistical tactic in nucleus independent chemical shift calculations, while the asymmetry ( $\mu$  and skew ( $k$ . parameters fluctuate in behavior around the center of rings. Several research in recent years were done by S-NICS Investigation for drug development. Zakeri and monajemmi recently developed S-NICS Investigation for

Neurology and Psychiatry, Antidepressant and Antihistamine Drugs. They used theoretical of a statistical approach in NMR shielding and nucleus independent chemical shifts for study of antidepressant and antihistamine drugs (Zakeri, 2018). This research group also S-NICS method is an accurate method for estimation the amount of aromaticity in the non-benzene rings such as heterocyclic rings which is a famous for organic chemical compounds as anti-cancer disease. SamieiSoofi and coworkers Studied Gilan's environmental plants & natural products as anti-cancer drugs by S-NICS method. They have optimized and discussed about several active compounds which are extracted from famous plants through NMR study. There are no works in theoretical of a statistical approach in NMR shielding and nucleus independent chemical shifts for study of antidepressant and antihistamine drugs, while the asymmetry ( $\eta$ ) and skew ( $\kappa$ ) parameters are fluctuated in small distances and are alternative in large distances in the center of heterocyclic rings for Matrine, Cytarabine, Gemcitabine and Vidarabine (Neda SamieiSoofi, 2018).

The majority of heterocycle compounds and typically common heterocycle fragments present in most pharmaceuticals currently marketed, alongside with their intrinsic versatility and unique physicochemical properties, have poised them as true cornerstones of medicinal chemistry (Zakeri., 2018).

We have now employed the computed geometric properties and especially magnetic enhancements and NICS to characterize the aromaticity of several heterocyclic anticancer drugs with different structure and groups. In this study, the major components of active parameters erocyclic rings and their aromaticity were investigating. The numerous random points around the center of those molecules have been produced by generation of pseudo-random numbers, which are distributed in a Gaussian function in the interval [0, 1). At last the aromaticity was used as parameter for anticancer activity.

## 2. THEORETICAL BACKGROUND

The total chemical shielding tensor  $\sigma$  is a non-symmetric tensor which could be separated into three independent parameters: asisotropic, traceless symmetric, and traceless anti-symmetric (Aime, 1996). [The spherical tensor has been showed by Haeberlen and Mehring (Monajjemi, 2019). They have investigated fundamental tensors as

$$\sigma = \sigma^{\text{iso}(0)} + \sigma^{\text{anti}(1)} + \sigma^{\text{sym}(2)} \quad (1)$$

Aromaticity of nucleus-independent chemical shifts, with NICS (0) For any further argument of statistical methods in S-NICS mainly in short range of distances, we exhibited that the asymmetry( $\zeta$ )15 and skew( $\hat{\epsilon}$ )15 fluctuate around the center of rings.

The reduced anisotropy as:

$$[\zeta = (\sigma_{zz} - \sigma_{\text{iso}}) = (\sigma_{33} - \sigma_{\text{iso}})] \quad (2)$$

[ $z = (s_{zz} - s_{\text{iso}}) = (s_{33} - s_{\text{iso}})$ ] (3) and anisotropy ( $\Delta\sigma$ ) with relation of  $\Delta\sigma = \frac{3}{2} \zeta$  including shielding asymmetry (h) could be distinct as:

$$\Delta\sigma = \sigma_{xx} - \frac{1}{2}(\sigma_{xx} + \sigma_{yy}) \quad (4)$$

$$\eta = \left(\frac{\sigma_{xx} - \sigma_{yy}}{\zeta}\right) = \frac{3(\sigma_{xx} - \sigma_{yy})}{2\Delta\sigma} \quad (5)$$

In several belongings of an axially symmetric tensor, ( $\sigma_{yy} - \sigma_{xx}$ ) will be zero and later  $\eta = 0$ . However, the asymmetry ( $\eta$ ) parameter specifies that how much the line figure deviates since an axially symmetric tensor,

The shielding tensor could be stated as the sum of a symmetric, an anti-symmetric, and a scalar terms, which are rank 2, rank 1 and rank zero tensors individually as:

$$\Omega = \Omega^{(0)} + \Omega^{(1)} + \Omega^{(2)} \quad (6).$$

The total chemical shielding tensor “ $\sigma$ ” is a non-symmetric tensor that could be decayed into three independent tensors as:

(1), an isotropic component,

(2) a traceless symmetric component,

and (3) a traceless anti-symmetric component .

In spherical tensor illustration, as Haeberlen have pointed out, at a fundamental level tensors are better represented in spherical fashion, such that a general second-order property “ $s$ ” may be engraved as  $s = s_{iso}(0) + s_{anti}(1) + s_{sym}(2)$  (7), where the number in brackets denotes to tensor rank. Spherical tensors

This study is based on dummy atom in de-shielding spaces of heterocyclic rings for seeing the most abundant of points. The major purpose random data of several probes inside of de-shielding spaces is for understanding of anisotropic spin-spin interaction in short distances. A random points near to the center of those rings have been generated by Gaussian function between the interval [0, 1)

### 3. COMPUTATIONAL DETAILS

All calculations were carried out by using Gaussian program. Among various functionals for DFT calculation, Becke’s three parameter hybrid functional combined with Lee–Yang–Parr correlation functional designated B3LYP was used. Were optimized at the B3LYP/6-311+G\* level of theory. Geometry optimizations and frequency calculations were carried out at B3LYP/6-311+G.

The NICS values at the geometrical centers of interest were calculated at the B3LYP/6–31G\* level with B3LYP/6–311G\* geometries using the Gaussian 94 program

### 4. RESULTS AND DISCUSSION

As declared above It should be illustrious that NMR parameters mainly depend on the local chemical bonding environment, inside a few angstroms of the nucleus under thought (Esrafil, 2009).

Optimization and NMR shielding constants with orientations of the principal data such as standard components, Haeberlen-Mehring and Herzfeld-Berger parameters for Buclizine, Cetirizine, loratacline, and Promethazine compounds in various statistical situations have been calculated and the data are listed in tables 1. The isotropy in all NMR calculations are positive which shows negative values for aromaticity, but the slopes are decreased from the replacing from 0.1 to center. It is obvious that the difference between isotropies for NICS data can explain the quality.

Nuclear magnetic resonance (NMR) spectroscopy provides a sensitive measure of electronic charge distribution about the nucleus of interest. Many of NMR observables are caused from anisotropic chemical shielding interaction between nuclear spin and its environment (Sack, 1998).

For calculating NMR shielding tensors at both the Hartree-Fock and DFT levels of theory, using functionals which do not include a specific magnetic field dependent term, but which have yielded good accuracy for other chemical properties (Cheeseman, 1996).

Aromaticity in terms of nucleus-independent chemical shifts in long distances of NICS (1, 2.5, 3, and 3.5) Å, around the ring center, NICS (0), at the center of ring plane and aromatic ring current shielding (ARCS) were compared in several studies. In short range of distances ( $r < 0.3$ ) there are no theoretical or mathematical reports of statistical approach in nucleus independent chemical shift calculations, while the asymmetry and skew parameters fluctuate in behavior around the center of rings.

The isotropy in NMR calculations are positive which indicates negative values for aromaticity. It is obvious that the isotropies for NICS data would illuminate the quantity and quality of the aromaticity for some molecules, but those are not capable for expressing the mechanism as well as S-NICS.

In slight distance around the center, the asymmetric-parameter  $\chi$  (h), and the skew  $\chi$  (k), exhibited gaussian distribution based on their fluctuation behavior, which is relate on its distance of molecular ring. In contrast, of that parameters, the isotropy  $\chi$  (16-18) has not a fluctuating behavior and increase in around the midpoint of the rings with a direct relationship. The slopes of that line is changed for various distances of heterocyclic compounds.

Optimization & NMR constants with orientations of the principal components & parameter for some heterocyclic target in has been calculated through DFT methods. In small distance around the center, the asymmetric-parameter. NMR calculations are positive which specifies negative values for aromaticity. It is obvious that the isotropies for NICS data could elucidate the quantity and quality of the aromaticity for these molecules, but those are not proficient for maintaining the mechanism as well as S-NICS.

For an aromatic compound, HOMO–LUMO gaps must be large enough to prevent electron localization and fixation rather than the preferable and more stable delocalization bonding agreement (Jalbout, 2002).

The results showed that aromaticity differs depending on the criterion used. The NICS (0.5), HOMO–LUMO gap predict that aromaticity increases in heterocyclic species and anti-aromaticity decreases in other part of anticancer molecule

Table 1: Nucleus-independent chemical shifts (NICS, and Anisotropy) properties related to aromaticity for. Studied anticancer drugs.

| Molecule | $\chi$ (anniso) | NICS (0.0) |
|----------|-----------------|------------|
| 1        | 3.3011          | 7.3089     |
|          | 22.8291         | 11.2267    |
|          | 1.5534          | 11.0180    |
| 2        | 2.061           | 8.7939     |
|          | 10.868          | 9.4343     |
| 3        | 6.8668          | 9.9182     |
|          | 33.2676         | -5.6579    |
|          | 12.1921         | 9.5627     |
| 4        | 2.0619          | 8.739      |
|          | 10.8680         | 9.4343     |
| 5        | 18.5042         | 0.7274     |
|          | 1.7318          | 11.0327    |
| 6        | 3.0295          | 10.356     |
|          | 3.4972          | 8.9144     |
|          | 15.2492         | 1.6786     |
| 7        | 1.1257          | 12.3185    |
|          | 15.2066         | -1.5720    |
|          | 33.0340         | 1.61169    |
| 8        | 14.9072         | 3.5817     |
|          | 8.7459          | 0.6561     |
|          | 19.8843         | 2.8910     |



Contributions perpendicular to the ring plane. The NICS (0.0) values for molecule 1, suggesting the nonaromatic or weakly aromatic. Molecule 3 in middle ring showed negative NICS value that showed it would have high interaction with cancer cell and DNA and its pyridine and purine bases. In molecule 7 there is 3ring one ring contain hydroxyl group hase NICs negative and has aromaticity and other rings with oxygen and ketone group hase a few antiaromaticity and other ring with 5 Carbone has high antiaromaticity Molecule 8 has weakly antiaromaticity and has high ability to interact with DNA bases.

The isotropy in all NMR calculations are positive which indicates negative values for aromaticity. It is obvious that the isotropies for NICS data can explain the quantity and quality of the aromaticity for some molecules, but those are not able for expressing the mechanism as well as S-NICS.

The isotropy (iso\*) which is related to all of (h\*), (k\*), (W\*) and ( $\zeta^*$ ) is suitable criterion for the aromatic molecules both hetero or regular rings through the S-NICS method. Similar to the NICS method, in S-NICS15, mines nucleus-independent-chemical-shifts indicates the aromaticity. Therefor “+” values indicate the anti-aromaticity quantitative. In S-NICS15 methods, the shielding & de-shielding spaces are important for discussing the mechanism of the aromatic molecules in point of ring currents (Monajjemi, 2015).

Nucleus-independent chemical shift values (NICS) show a little and no evidence of ring currents, indicating with no aromaticity for molecule due to the high Anisotropy parameter.

Some criteria for explanation of aromaticity can be reflected and may divide into five categories, which are: (1) the energetic approach to aromaticity (2) geometrical considerations (3) reactivity of aromatic compounds (4) magnetic parameters of aromaticity, 8–10 and the (5) Statistical-Nucleus-Independent Chemical Shifts approach (SNICS) which is the subject of this study.

The stabilities S-NICS criterion is strongly affected on the greatest places in shielding spaces which is related to the composition of hetero aromatic rings. It is noticeable that geometry factors cause changes in the magnetic field by the nuclei and variation the resonant frequencies. Therefore, the chemical shielding and several factors as the same electronegativity, magnetic anisotropy of p-systems will be changed due to the number of electrons the chemical shielding is a vector orientation function for all of the shielding parameters that may change in several places inside the shielding region.

Analogous to the NICS method, in S-NICS, negative nucleus-independent-chemical-shifts denote aromaticity. There for positive values denote anti-aromaticity. In S-NICS methods, the shielding and de-shielding spaces are important to discuss the mechanism of the aromatic molecules in point of ring currents, which are the circulating  $\pi$  electrons in an aromatic molecule produce reverse to the functional magnetic field (Zakeri, 2018).

## 5. CONCLUSION

By the S-NICS, we have developed a steady method based on NMR performance of the magnetic components. Although this method is not simple compared to NICS, it has many benefits, such as its individuality of the shape and structure of the molecule, and independence of the center of the molecule. It is, more logically, dependent on inspection of the shielding area around each molecule or bio-molecule. Not only does this method work as a new criterion of aromaticity, but also it is potentially very useful in other fields such as nano-biotechnology, including protein folding, protein structure determination, DNA pairing mechanism, and t-RNA-amino acid binding, that are sensitive to proton chemical shifts from structural and conformational changes. Molecule 3 and 7 showed more aromaticity than other molecules and expect have extra interaction with DNA and genome of cancer cells. High aromaticity of heterocyclic rings results the high interaction of anticancer drug with DNA and cancer cell. The charge density as aromaticity of bioactive atoms in anticancer drugs. Decreases the amount of such a significant interaction and then the pharmacological characteristics of these drugs would be decreased. Charge

and aromaticity have an important role in determining the binding affinity and then reactivity of these ligands with the cancer cell receptor or mutant DNA of cancer cell genetics.

*Fig.1: Optimization of structure of anticancer drugs*

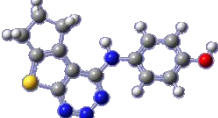
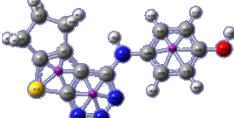
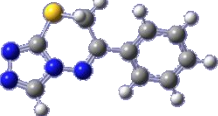
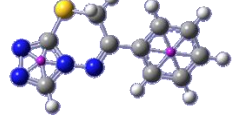
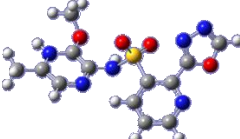
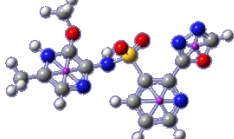
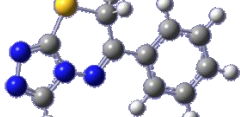
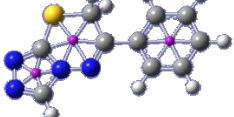
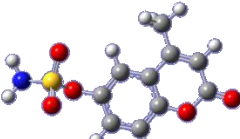
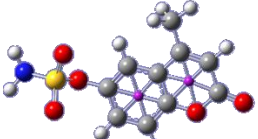
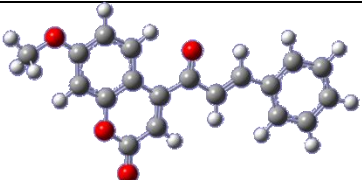
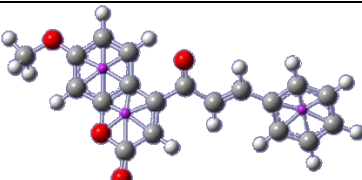
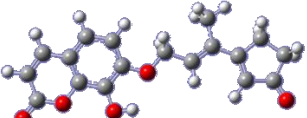
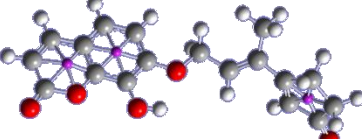
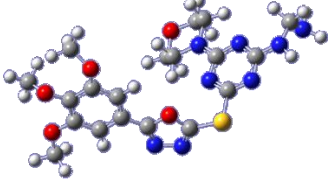
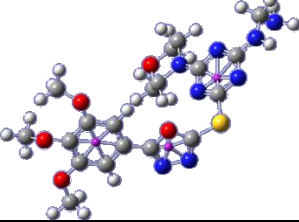
| molecule | Chemical structure  | Bq atom   |
|----------|---|---|
| 1        |    |    |
| 2        |    |    |
| 3        |    |    |
| 4        |    |    |
| 5        |   |   |
| 6        |  |  |
| 7        |  |  |
| 8        |  |  |



Table 2: S-NICS calculation for center rings

|              |  |
|--------------|--|
| <b>Mol 1</b> | <p>33 Bq Isotropic = 7.3089 Anisotropy = 3.3011<br/>           XX= 8.9990 YX= 0.5127 ZX= 0.7365<br/>           XY= 1.0475 YY= 4.4994 ZY= 0.3037<br/>           XZ= 0.7122 YZ= -1.6082 ZZ= 8.4284<br/>           Eigenvalues: 4.2268 8.1903 9.5097</p> <p>34 Bq Isotropic = 11.2267 Anisotropy = 22.8291<br/>           XX= 9.8265 YX= 5.6476 ZX= -1.2200<br/>           XY= 3.4396 YY= 25.0071 ZY= 3.0936<br/>           XZ= -1.5137 YZ= 2.3058 ZZ= -1.1536<br/>           Eigenvalues: -1.7351 8.9690 26.4461</p> <p>35 Bq Isotropic = 11.0180 Anisotropy = 1.5534<br/>           XX= 11.4526 YX= -0.1603 ZX= 0.1610<br/>           XY= -0.2122 YY= 11.9956 ZY= -0.1265<br/>           XZ= 0.1223 YZ= 0.2558 ZZ= 9.6056<br/>           Eigenvalues: 9.5922 11.4081 12.0536</p>        |
| <b>Mol 2</b> | <p>24 Bq Isotropic = 8.7939 Anisotropy = 2.0619<br/>           XX= 8.3213 YX= -0.1685 ZX= -0.0088<br/>           XY= -0.2659 YY= 8.6096 ZY= -1.1112<br/>           XZ= -0.6515 YZ= -0.9765 ZZ= 9.4508<br/>           Eigenvalues: 7.6907 8.5225 10.1685</p> <p>25 Bq Isotropic = 9.4343 Anisotropy = 10.8680<br/>           XX= 16.4578 YX= 2.2656 ZX= 0.0777<br/>           XY= -0.1960 YY= 9.1607 ZY= -2.3813<br/>           XZ= 2.8407 YZ= -4.3570 ZZ= 2.6843<br/>           Eigenvalues: 1.0510 10.5722 16.6796</p>  |
| <b>Mol 3</b> | <p>38 Bq Isotropic = 9.9182 Anisotropy = 6.8668<br/>           XX= 8.6725 YX= 0.2872 ZX= 1.3348<br/>           XY= 1.5632 YY= 7.9683 ZY= 1.1418<br/>           XZ= 4.0181 YZ= -0.0215 ZZ= 13.1139<br/>           Eigenvalues: 6.9980 8.2606 14.4961</p> <p>39 Bq Isotropic = -5.6579 Anisotropy = 33.2676<br/>           XX= 11.8994 YX= -7.4329 ZX= 13.0170<br/>           XY= -7.2409 YY= 4.0631 ZY= 16.1839<br/>           XZ= 11.8736 YZ= 16.1535 ZZ= -32.9361<br/>           Eigenvalues: -42.7213 9.2271 16.5205</p> <p>40 Bq Isotropic = 9.5627 Anisotropy = 12.1921<br/>           XX= 9.1856 YX= -3.3443 ZX= 3.1778<br/>           XY= -3.4212 YY= 9.4596 ZY= -5.2563<br/>           XZ= 2.5222 YZ= -6.0538 ZZ= 10.0429<br/>           Eigenvalues: 4.0195 6.9779 17.6907</p> |
| <b>Mol4</b>  | <p>24 Bq Isotropic = 8.7939 Anisotropy = 2.0619<br/>           XX= 8.3213 YX= -0.1685 ZX= -0.0088<br/>           XY= -0.2659 YY= 8.6096 ZY= -1.1112<br/>           XZ= -0.6515 YZ= -0.9765 ZZ= 9.4508<br/>           Eigenvalues: 7.6907 8.5225 10.1685</p> <p>25 Bq Isotropic = 9.4343 Anisotropy = 10.8680<br/>           XX= 16.4578 YX= 2.2656 ZX= 0.0777<br/>           XY= -0.1960 YY= 9.1607 ZY= -2.3813<br/>           XZ= 2.8407 YZ= -4.3570 ZZ= 2.6843<br/>           Eigenvalues: 1.0510 10.5722 16.6796</p>  |
| <b>Mol5</b>  | <p>27 Bq Isotropic = 0.7274 Anisotropy = 18.5042<br/>           XX= 5.8888 YX= 2.2319 ZX= 3.8466<br/>           XY= 0.2745 YY= 12.8426 ZY= -1.1163</p>   |

|             |   |
|-------------|---|
|             | <p>XZ= 3.8743 YZ= -0.7095 ZZ= -16.5492<br/> Eigenvalues: -17.2357 6.3543 13.0635<br/> 28 Bq Isotropic = 11.0327 Anisotropy = 1.7318<br/> XX= 9.9300 YX= -0.4244 ZX= -0.5949<br/> XY= -0.2243 YY= 11.8880 ZY= 0.2720<br/> XZ= -0.9446 YZ= 0.3139 ZZ= 11.2801<br/> Eigenvalues: 9.5676 11.3432 12.1872</p>  |
| <b>Mol6</b> | <p>38 Bq Isotropic = 10.1356 Anisotropy = 3.0295<br/> XX= 11.3059 YX= 1.2794 ZX= -0.3279<br/> XY= 0.6071 YY= 10.9663 ZY= -0.5011<br/> XZ= -0.4013 YZ= -0.1671 ZZ= 8.1345<br/> Eigenvalues: 8.0736 10.1779 12.1553<br/> 39 Bq Isotropic = 8.9144 Anisotropy = 3.4972<br/> XX= 7.7778 YX= 0.1167 ZX= -0.5726<br/> XY= 0.3435 YY= 8.7527 ZY= 1.8924<br/> XZ= 0.1799 YZ= 1.3164 ZZ= 10.2128<br/> Eigenvalues: 7.4476 8.0498 11.2459<br/> 40 Bq Isotropic = 1.6786 Anisotropy = 15.2492<br/> XX= 10.5675 YX= 2.1072 ZX= -5.4420<br/> XY= -0.2894 YY= 9.6071 ZY= 0.2248<br/> XZ= -5.2183 YZ= 1.8698 ZZ= -15.1389<br/> Eigenvalues: -16.2564 9.4474 11.8447</p>      |
| <b>Mol7</b> | <p>40 Bq Isotropic = 12.3185 Anisotropy = 1.1257<br/> XX= 12.6349 YX= 0.0980 ZX= 0.2033<br/> XY= 0.3022 YY= 11.8211 ZY= -0.1739<br/> XZ= 0.7387 YZ= 0.2598 ZZ= 12.4995<br/> Eigenvalues: 11.7660 12.1205 13.0690<br/> 41 Bq Isotropic = 1.5720 Anisotropy = 15.2066<br/> XX= 9.0830 YX= 4.5689 ZX= -2.0545<br/> XY= 2.4921 YY= 6.8852 ZY= 3.6795<br/> XZ= -2.5185 YZ= 5.0451 ZZ= -11.2523<br/> Eigenvalues: -12.6727 5.6790 11.7097<br/> 42 Bq Isotropic = -1.6169 Anisotropy = 33.0340<br/> XX= 1.5941 YX= 4.9983 ZX= 15.6048<br/> XY= 5.4978 YY= -14.7943 ZY= -0.9006<br/> XZ= 13.9020 YZ= 0.7638 ZZ= 8.3495<br/> Eigenvalues: -17.4348 -7.8216 20.4058</p> |
| <b>Mol8</b> | <p>58 Bq Isotropic = 3.5817 Anisotropy = 14.9072<br/> XX= 10.6533 YX= 0.5431 ZX= 8.4295<br/> XY= 2.2866 YY= 7.2273 ZY= 0.0102<br/> XZ= 5.9209 YZ= 0.6736 ZZ= -7.1355<br/> Eigenvalues: -9.6702 6.8954 13.5199<br/> 59 Bq Isotropic = 0.6561 Anisotropy = 8.7459<br/> XX= 4.7690 YX= 1.0372 ZX= 2.1422<br/> XY= 3.7845 YY= -0.9709 ZY= 6.6931<br/> XZ= -0.6529 YZ= 2.6301 ZZ= -1.8296<br/> Eigenvalues: -6.1925 1.6742 6.4867<br/> 60 Bq Isotropic = 2.8910 Anisotropy = 19.8843<br/> XX= 13.2438 YX= 3.4598 ZX= 5.0488<br/> XY= 7.1119 YY= 0.4581 ZY= 10.8660<br/> XZ= -0.8623 YZ= 3.3564 ZZ= -5.0289<br/> Eigenvalues: -9.9828 2.5086 16.1471</p>            |

Theoretical back ground NMR Shielding and S-NICS method there are not theoretically or mathematically reports for the statistical approaches in NMR shielding and nucleus-independent-chemical-shift (S-NICS), Since the asymmetry ( $\eta$ ) and skew (K) parameters have fluctuated in a short distances and in contrast are alternative in long distances.

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