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Heterocyclic Anticancer Compounds: Using S-NICS Method

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Abstract

This work is done for developing of modern anticancer drugs. Many of heterocyclic compounds are known as anticancer drugs such as alkylating agents which have targeted cell DNA causing cell death. Heterocycles' ring structures are in essence composed by atoms other than carbon, where the most frequent substituents are sulfur, oxygen and nitrogen. In our previous work it has been exhibited that S-NICS method is an accurate method for estimation the amount of aromaticity in the non-benzene rings similar heterocyclic rings which are popular molecules in organic chemical compounds as anti-cancer disease. 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.

***Keyword**: S-NICS, NICS, heterocyclic anticancer compounds,*

1. Introduction:

Cancer is a disease dating as far back as the dinosaurs has found cancerous lesions on dinosaur bones. Egyptians also drew examples of breast cancer in their hieroglyphics on papyrus, and by the 4th century B.C. many types of tumors such as stomach and uterine cancer had been described. In 1775 Percival Pott, a London physician, linked the incidence of scrotal cancer in men to their jobs as chimney sweeps when they were young boys. It was not, however, until the 19th century that scientists began to study cancer systematically, looking at what causes cancer and how it can be cured. Cancer is one of the important causes of death in the new century. his work is done for developing of modern anticancer drugs. Many of heterocyclic compounds are known as anticancer drugs such as alkylating agents which have targeted cell DNA causing cell death. Heterocycles ring structures are in essence composed by atoms other than carbon, where the most frequent substituents are sulfur, oxygen and nitrogen [1, 2].The model size of heterocycles ring, together with the substituent groups of the core scaffold, impact tightly on the chemical and physical properties [3-5] while among the clinical applications, heterocyclic compound has an active role as anti-bacterial, anti-viral [6], anti-fungal [7], anti-inflammatory [8] and anti-tumor drugs. Among the heterocyclic compounds the pyridine, thiophene and Thiazole derivatives exhibited large amount cytotoxicity towards the cancer cell lines. Structure activities relationship was reduced [9] from biological results and will be used in further design [10] of new active compounds. Currently, a number of drugs are used in the treatment of the cancer, but most of them were produced controlled effect on the cancer cells. The usual applications of heterocycles are as vast as they are diverse and are not extensively encompassed in the scope of this study [10, 11]. The most drugs belong to a class of hetero-genius structures. Heterocyclic structures played an important role in the metabolism of all cells; large number of them are six (or sometimes 5) membered hetero-cycles having one to three heteroatoms [11]. Recently, imidazole fragments have been attracting much concentration due to its role as attractive scaffolds for biochemical active heterocyclic drugs [12]. Generally, chemical-physics and biochemical properties like donor-acceptor capability, hydrogen bond, π-π stacking interactions, van der Waals, co-ordination bonds with metals and in total hydrophobic forces have caused the increasing interest in anticancer studies for such compounds. These properties are important of understanding for their reactivity enable derivatives to readily bind with various nucleic acids, enzymes and biological structures [13, 14]. A large number of the common heterocyclic compounds used in the medical activities such as proline, histidine which are amino acids. It is notable the vitamins and coenzymes precursors such as thiamine, riboflavin, pyridoxine, folic acid, biotin, B_{12} and E families of the vitamins are included of heterocyclic structures. For investigation of antifungal activity compounds, Singh et al have synthesized 1,3, 4oxadiazolo-(3,2a)-s-triazin-7-thione[13,14] and Abdle et al have synthesized some novel 1, 3, 4-oxadiazole derivatives. Fungi[13] are hetero-tropic micro-organisms that are distinguished from algae by lack of photosynthetic abilities which includes yeast. Gogia et al have synthesized 1, 3, 4-oxa / thiadiazolo – (3, 2a) pyrimidin-5-one which shows antifungal activity. x=O, S. Ahluwalia et al have studied the N-benzylidene-3, 4-dihydro-2, 2, 8-trimethyl- 2H-1-benzopyran-7-yloxyacetie acid hydrazide, Dhar et al have synthesized 1,3,4-oxadiazolo-[3,2-a]- 1,3,4-dithiazines and found anti-fungal. In compound Ar=2- ClC6H4, Ar'=2- ClC6H4OCH2.Methyl 5-(l-hydroxy-2-propenyl)-3-thiophenecarboxylate was stirred at room temperature with 10 equivalents of freshly prepared manganese dioxide to give methyl 5-(2-propenoyl)-3- thiophene carboxylatein 60% yield. The proton NMR spectrum exhibits explicitly a doublet for two hydrogens due to the de-shielding effect of the carbonyl. Infra-red spectroscopy helps to confirm the structure of two carbonyls around 1650 cm^{-1} for the allylic ketone and 1700 cm^{-1} for the ester Figs1-3. Since a carcinogen is applied into a body, cancerous cell will not immediately result. This is due to the "latency effect" where certain of time elapses before there is growth of the tumor. The initial application of a carcinogen will result in the formation of the irreversible initiated cells. Time may then elapse before a second agent, known as the promoter, will act reversibly on the initiated cell giving a

premalignant lesion. Changes in the premalignant lesion, such as increased growth rate, increased invasiveness and metastases, result from the 3rd stage of the process known as progression. Those changes are usually associated with the changing in the number and arrangement of genes which encode for various proteins. In all parts of the world, cancer disease is one of the important main reasons of human death due to unknown treatment and difficulty for curing. The main cause for this problem is that cancer results from the uncontrolled and huge proliferation of normal cells. Chemotherapy and cell-killing (cytotoxic) is one of the major methods of cancer treatment which acts through intervening in somehow with the operation of the cell's DNA. Cancer is a disease dating as far back as the dinosaurs has found cancerous lesions on dinosaur bones. Egyptians also drew examples of breast cancer in their hieroglyphics on papyrus, and by the 4th century B.C. many types of tumors such as stomach and uterine cancer had been described. In 1775 Percival Pott, a London physician, linked the incidence of scrotal cancer in men to their jobs as chimney sweeps when they were young boys. Cytotoxic compounds that selectively, but not solely, attack to tumor cells include various groups such as anti-metabolites, intercalating agents, DNA-alkylating agents, and mitotic inhibitors. Anti-metabolites molecules are nucleotides and are polymerized into DNA for destroying the functional of DNA. Alkylating agent are such molecules which attach to the DNA permanently and distorting its structure. Unfortunately, these agents destroy many other molecules in cells. DNA-binding agents are such molecules that bind to the DNA chain for breaking it and subsequently attaching to another string then repeat the process. In some items, cell's DNA appears a resistance to treatment with several of cytotoxic drugs so necessarily, DNA-binding agents are given by a combination of drugs from several groups consequently various side effects. Obviously, using a wide range of cytotoxic drugs make them dangerous for human that can only be endured for short periods. In fact the side effects of the treatment may sometimes cause more stress than the cancer problem. These side-effects include losing hair, flaky skin, decreasing of the appetite, dry skin, change in taste, vomiting, fatigue, depression, decreasing of immune system and blood clotting. Generally, although the advantages of using cytotoxic drugs in cancer therapy are much more than the disadvantages, it is important to decrease the side effects of these kind drugs as possible which are the subject of this work. The root of many cytotoxic drugs is the natural products which are extracted from the plants. They can be classified into three major groups due to their mode and site of action basically including anti-metabolites, genotoxic agents and mitotic inhibitors. Cancer is one of the important causes of death in the new century. This work is done for developing of modern anticancer drugs. Many of heterocyclic compounds are known as anticancer drugs such as alkylating agents which have targeted cell DNA causing cell death. This study is highlighted by new and efficient drugs with focusing on the development of cytotoxic drugs through the aromaticity function. In recent decade about 100,000 natural and synthetic chemical compounds have been examined as a strong antioxidant agent, but only less than 100 of them are widely applied to combat with cancer today. It means that for many cancers the cytotoxic drugs are used randomly without any diagnosis about their characterization and reaction mechanisms. A mechanism that might be utilized by tumor's cell to resist cytotoxic compounds is perhaps evolved in normal cells as a defense mechanism against environmental carcinogens which include genetic responses, Potential of DNA repairing, metabolic effect, growth factor and access to target cells. Although nowadays cancer drugs significantly decrease the mortality rates for several cancers, there is a long way to go before truly curative drugs are available for most cancers. Because tumor's cells not only aren't alien to human bodies but also are simply subtly mutated forms of normal cells and obviously it is very different to synthesize drugs that can tell the difference. 5-Flourouracil, Carabine, Gemcitabine, Capecitabine are important drugs in the first class of anti-metabolites (Pyrimidine Antagonists) from Cytotoxic agents which block pyrimidine nucleotide formation by incorporation into newly synthesized DNA which are using for Basal cell skin cancer, GIT adenocarcinoma, Cancers of breast-colonstomach-rectum-pancreas, Cancer of prostate and bladder. 6-Mercaptopurine and 6-Thioguanine are cytotoxic agents in the second class of anti-

metabolites (Purine Antagonists) which act as fraud substrate for biochemical reactions and inhibit the synthetic steps during S-phase of replication. Methotrexate, and are Cytotoxic agents in the third class of anti-metabolites (Folate Antagonists) which inhibits the di-hydro-folate reductive and thus affect nucleoside metabolism. Temazolomide, Cisplatin, Cyclophosphamide, Melphalan, Carmustine, Ifosfamide, Streptozotocin are Cytotoxic agents in the first class of GENOTOXIC AGENTS (Alkylating Agents) which binds to DNA and directly affect the replication which induces the apoptosis and create cross linking between two DNA strands and inhibit protein synthesis. Melphalan (trade name Alkeran, in former USSR also known as Sarcolysin) is belonging to the second class of nitrogen mustard alkylating agents. An alkylating agent adds an alkyl group (C_nH_{2n+1}) to DNA. It attaches the alkyl group to the guanine base of DNA, at the number 7 nitrogen atom of the imidazole ring. Ifosfamide (IFO), is a medicine for chemotherapy that used to treat a number of types of cancer, including testicular cancer, soft tissue sarcoma, osteosarcoma, bladder cancer, small cell lung cancer, cervical cancer, and ovarian cancer. IFO is in the alkylating agent and nitrogen mustard family of medications. It works by disrupting the duplication of DNA and the creation of RNA.-It is on the World Health Organization's List of Essential Medicines, the most effective and safe medicines needed in a health system. Epirubicin is an anthracycline medicine applied for chemotherapy. It can be applied to combination with other drugs for treating breast cancer in patients who have had surgery to remove the tumor. It is marketed by Pfizer under the trade name Elene in the US and Epirubicin elsewhere which acts by intercalating DNA strands (Figs 1-3).

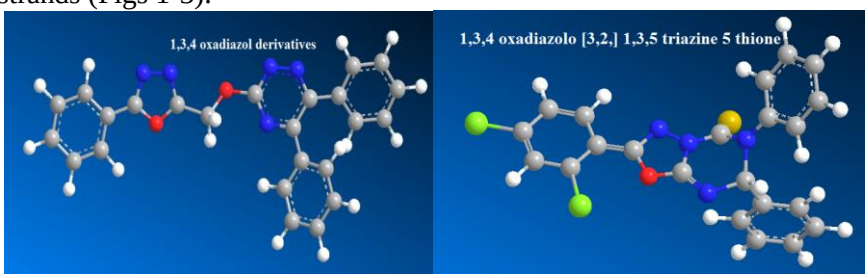

Figure1. *Optimization of 1, 3, 4 oxadiazol derivatives and 1, 3, 4 oxadiazolo [3, 2] 1, 3, 5 triazine 5 thione*

It also triggers DNA cleavage via topoisomerase II, resulting in mechanisms that leads to cell death. Binding to cell membranes and plasma proteins may be involved in the compound's cytotoxic effects. Epirubicin also produces free radicals which cause cell and DNA damage.

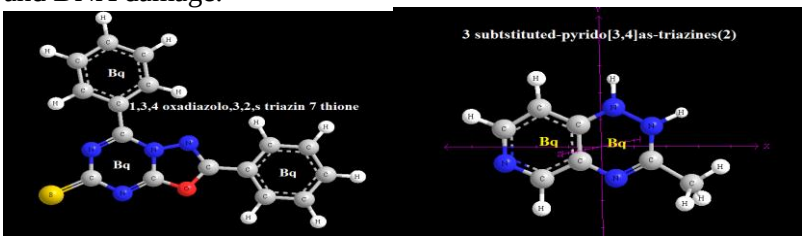

Figure2. Optimization of 1, 3, 4 oxadiazolo, 3, 2, s triazin 7 thione and 3 subtstituted-pyrido [3, 4] as-triazines

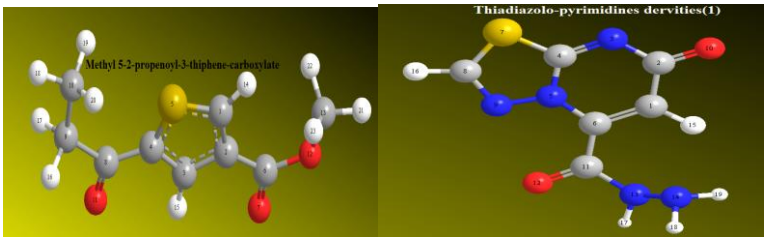

Figure3. Optimization of Methyl 5-2-propenoyl-3-thiphene-carboxylate and Thiadiazolo-pyrimidines derivatives

Epirubicin is interested over doxorubicin, the most popular anthracycline, in some cancer therapy regimens as it shows to cause fewer side-effects. Epirubicins have the different spatial direction of the OH group at the 4' carbon of the sugar - it has the opposite chirality - which might , counting for its quicker deletion and reduced the toxicities. Epirubicins groups are primarily applied against breast and ovarian cancer, gastric cancer, lung cancer and lymphomas. These consist of testicular cancer, lung cancer, lymphoma, leukemia, and ovarian cancer. It is used by mouth or injection into a vein. Side effects are very general and they consist of low blood cell counts, vomiting, and fever. Etoposide is in the topoisomerase inhibitor family of medication and it was confirmed for drug use in the world. Topotecan is a chemotherapeutic agent that is a topoisomerase inhibitor. It is a synthetic, water-soluble analog of the natural medicine. It is applied in the form of its hydrochloride salt to treat ovarian cancer, lung cancer and other cancer systems. Anastrozole, sold under the brand name Arimidex among others, is a medication used in addition to other treatments for breast cancer. Particularly it is used for hormone receptor-positive breast cancer. It has also been used to prevent breast cancer in those at high risk. General side effects include hot flashes, altered mood, joint pain, and nausea. Various side effects consist of an increased risk of heart disease and osteoporosis. Use during pregnancy is known to harm the baby. Anastrozole is in the aromatase-inhibiting family of medications. It works by blocking the creation of estrogen. Exemestane, or Aromasin , is a medication used to treat breast cancer. It is a member of the class of antiestrogens known as aromatase inhibitors. Some breast cancers require estrogen to grow. Those cancers have estrogen receptors (ERs), and are called ER-positive. They may also be called estrogen-responsive, hormonally-responsive, or hormone-receptor-positive. Aromatase is an enzyme which synthesizes estrogen. Aromatase inhibitors block the synthesis of estrogen. This lowers the estrogen level, and slows the growth of cancers. Bortezomib (BAN, INN and USAN; marketed as Velcade by Millennium . Pharmaceuticals; Neomib by Getwell and Bortecad by Cadila Healthcare) is an anti-cancer drug and the first therapeutic proteasome inhibitor to be used in humans. Proteasomes are cellular complexes that break down proteins. In some cancers, the proteins that normally kill cancer cells are broken down too quickly. Bortezomib interrupts this process and lets those proteins kill the cancer cells. In multiple myeloma, complete clinical responses have been obtained in patients with otherwise refractory or rapidly advancing disease. Traditional drugs for anticancer such as alkylating agent has targeted cell DNA causing cell death. Demethoxyviridin (A) and Wortmannin (B) are natural products which basically, have been used for the development of novel anticancer drugs. In addition a series of thiophene (C) and furan (D) derivatives modelled on the suspected pharmacophore have therefore been synthesized . It was not, however, until the 19th century that scientists began to study cancer systematically, looking at what causes cancer and how it can be cured. The most drugs belong to a class of hetero-genius structures. Heterocyclic structures played an important behavior in the metabolism of all cells; maximum number of them is 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. Generally, chemical-physics and biochemical properties like acceptor and donor capabilities, hydrogen bond, π-π interactions, van der Waals, coordination [12] bond with a metal and in total hydrophobic force has caused much interest in anticancer studies for such compounds. These properties are important of understanding for its reactivity enable derivative for binding with various nucleic acids, enzymes and biological structures [13, 14]. 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, biotin, B_{12} and E families of the vitamins are included of heterocyclic structures. For investigation of antifungal activity compounds, Singh et al have synthesized 1, 3, 4oxadiazolo-(3, 2a)-s-triazin-7-thione [13, 14] and Abdle et-al have synthesized some novel 1, 3, 4oxadiazole derivatives [12, 13].

Table1. Classification of anti-cancer agents

Class	Molecular name	Mechanism	Kind uses of cancer
anti-metabolite	Methotrexate	Inhibits the di-hydro-folate reeducates for affecting of nucleoside metabolism.	Cancer of breast-neck head-lungs-cervical.
	5-Flourouracil Cytarabine Gemcitabine Capecitabine	Block nucleotide formation of pyrimidine through incorporation into newly synthesized DNA	Skin cancer, Cancer of prostate and bladder, Cancers of breast, Cancers of rectum and pancreas and Cancers of colon and stomach
	6-Tioguanine 6-Mercaptopurine	Act as fraud substrate for biochemical reactions and inhibit the synthetic steps during S-phase of replication.	Acute cancer of lymphocytic and Acute myelomonocytic leukaemia
Alkylating Agents	Temazolomide Ifosfamide Melphalan	Insert an alkyl group into DNA to create a cross linking between two DNA strands for inhibiting protein synthesis.	Brain Cancer, Testicular cancer, Neck cancer, Ovarian and bladder cancer
Intercalating Agents	Epirubicin Doxorubicin	Binding to DNA via intercalation between related base pair for blocking the DNA synthesis.	Breast cancer, Endometrial cancer, Thyroid cancer , Acute leukaemia,
Enzyme Inhibitors	Etoposide	Inhibitor for topoisomerase II, Consequently this enzyme prevents resealing of DNA which leads to cell death.	lung cancer, Breast cancer
	Topotecan	Inhibitor for topoisomerase I, Consequently this enzyme allows single strands break in DNA but not affect resealing.	Cancers of lung, ovary, colon
EPIDERMAL GROWTH FACTOR RECEPTOR (EGFR) INHIBITORS:	Erlotinib Gefitinib	Epidermal growth factor receptor (EGFR) will be active and causes the intracellular activation of protein tyrosine kinase	lung cancer and solid tumors.
PROTEIN TYROSINE KINASE INHIBITORS	Imatinib	By inhibiting this enzyme, inhibit proliferation of myeloid cel	Chronic myeloid leukaemia (CML), GIT stromal cell tumor.
PROTEOSOME INHIBITORS:	Bortezomib	Prevents degradation of intracellular protein leading to activation of signaling cascade, cell cycle arrest and apoptosis	Refractory and relapsed multiple myeloma
AROMATASE INHIBITORS:	Anastrozole Letrozole Exemestane	Aromatase, responsible for conversion of testosterone to estradiol	Estrogen Receptor (ER) positive metastatic breast cancer in post-menopausal women that are resistant to tamoxifen therapy.

Fungi [13] are hetero-tropic micro-organisms that are distinguished [13]. Dhar has synthesized 1, 3, 4-oxadiazolo-[3, 2-a]-1, 3, 4-dithiazines and found anti-fungal. In compound Ar=2- ClC6H4, Ar'=2- ClC6H4OCH2. Methyl 5-(l-hydroxy-2-propenyl)-3-thiophenecarboxylate was stirred at room temperature with 10 equivalents of freshly prepared manganese dioxide to give methyl 5-(2-propenoyl)-3- thiophene carboxylatein 60% yield. The proton NMR spectrum exhibits explicitly doublets for two hydrogens due to the de-shielding effect of the carbonyl (Table 1). Infra-red spectroscopy helps to confirm the structure of two carbonyls around 1650 cm^{-1} for the allylic ketone and 1700 cm^{-1} for the ester Figs1-3. Since a carcinogen is applied into a body, cancerous cell will not immediately result. This is due to the "latency effect" where certain of time elapses before there is growth of the tumor. The initial application of a carcinogen will result in the formation of the irreversible initiated cells. Time may then elapse before a second agent, known as the promoter, will act reversibly on the initiated cell giving a premalignant lesion. Changes in the premalignant lesion, such as increased growth rate, increased invasiveness and metastases, result from the 3rd stage of the process known as progression. Those changes are usually associated with the changing in the number and arrangement of genes which encode for various proteins.

2. Materials and methods

2.1. Theoretical background

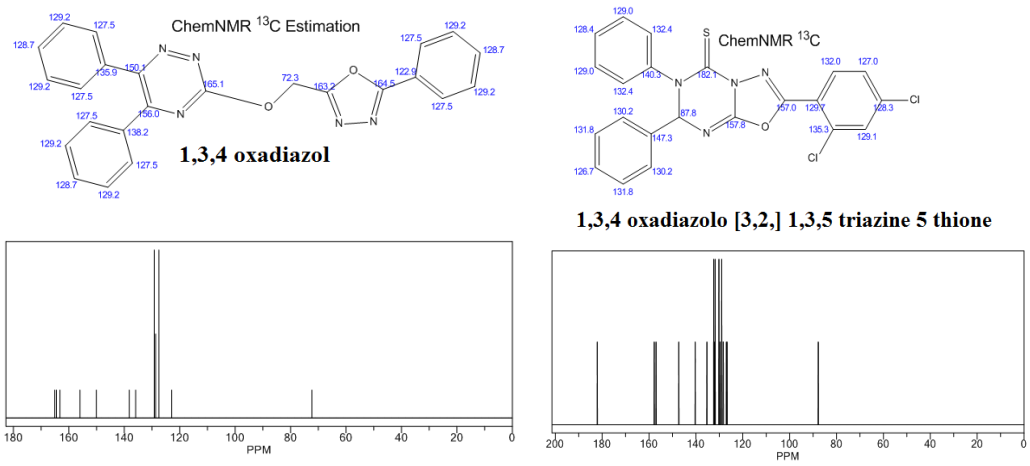

Figure4. NMR estimation of some oxadiazol compounds

Aaromaticity in point of nucleus-independent chemical shifts, with NICS (0), at the center of ring plane were compared in several studies in long distances. In small range of distance a few works have been done in theoretical and reports the statistical approach in our works[15]. For anyfurther discussion of statistical methods in S-NICS especially in short range of distances, we exhibited that the asymmetry(η)[15] and skew(κ)[15] fluctuate around the center of rings. The maximum fluctuations[15] are visible around the extremums functions mathematically[15]. The fundamental of this work is based on random motions of dummy atom in de-shielding spaces of heterocyclic rings for considering the most abundant of points. The major purpose of random data of several probes inside of de-shielding spaces is for understanding of anisotropic spin–spin interaction in short distances. In this study, the major components[16-18] of Haeberlen[17] parameters[16-18], has been calculated for heterocyclic rings. A large number of random points near to the center of those rings have been generated by pseudo-random numbers [15] generation, which is distributed in a Gaussian function between the interval [0, 1) [15]. The results have been compared through

the energy-decomposition-analyzation (EDA).The π bond energy and conjugation of π between heteroatoms bonds of rings are significantly accurate. We have optimized the geometries and calculated the carbon NMR for various heterocyclic molecules for understanding which members of rings are more stable (Figs 1-8). Our methods and physical chemistry approach have been done based on our previous works [19-73].

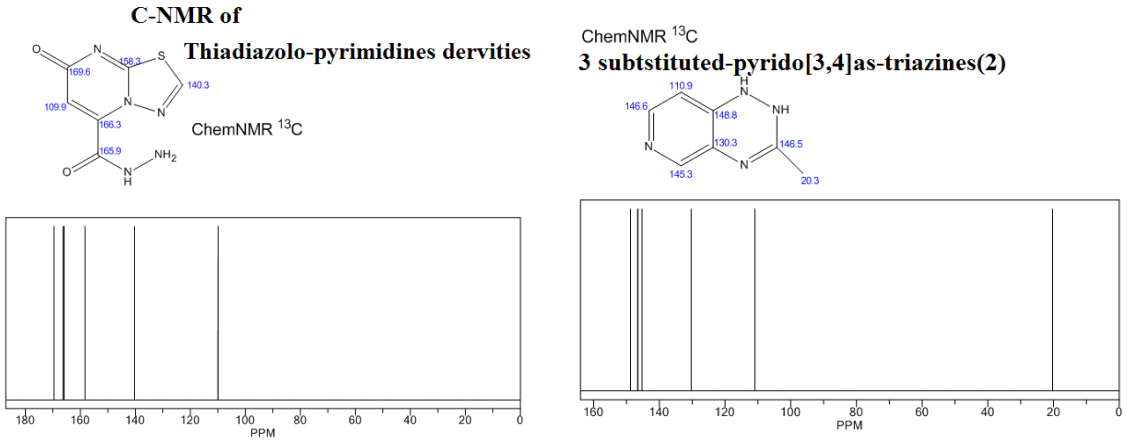

Figure5. NMR estimation of some Thiadiazol compounds

2.2. Computational chemistry

We applied density functional theory with the van der Waals density functional to model the exchange-correlation energies of heterocyclic compounds· The double ζ-basis set with polarization orbitals (DZP) were used for x natural gases inside the cages. For non-covalent interactions, the "B3LYP" method is unable to describe van der Waals adsorbed systems by medium-range interactions such as the interactions of two cylinders. The B3LYP and most other functional are correctly insufficient to illustrate the exchange and correlation energy for distant non-bonded medium-range systems. Moreover, some recent studies have shown that inaccuracy for the medium-range exchange energies leads to large systematic errors in the prediction of molecular properties. The charge transfer **a**nd electrostatic potential-derived charge were also calculated using the Merz-Kollman-Singh, chelp, or chelpG. The charge calculation methods based on molecular electrostatic potential (MESP) fitting are not well-suited for treating larger systems whereas some of the innermost atoms are located far away from the points at which the MESP is computed. Calculations were performed using Gaussian and GAMESS-US packages. The ONIOM methods including three levels from (1)-high calculation (H), (2)-medium calculation (M), and (3)-low calculation (L) have been performed in this study. The "advanced DFT" methods are used for high layer of the model and the semi empirical methods of "Pm6" including pseudo=lanl2 and "Pm3MM" are used for the medium and low layers, respectively. The semi empirical method has been used in order to treat the non-bonded interactions between two parts of gases diffused and cages. There are various situations of non-covalent interaction in this system between hydrogen diffused. For non-covalent interactions, the classical "B3LYP" methods are unable to describe van der Waals systems. In this study, we have mainly focused on getting the optimized results for each item from "advanced DFT" methods including the "m06" and "m06-L". The "m062x", "m06-L", and "m06-HF" are a novel Meta hybrid DFT functional with a good correspondence in non-bonded calculations and are useful for calculating the energies of the distance between gases and cages."Pm6", "Extended-Huckel" and "Pm3MM" including pseudo=lanl2 calculations using Gaussian program have done for the non-bonded interaction between two tubs. "M06" and "m06-L (DFT)" functional is based on an iterative solution of the Kohn-Sham equation of the density functional theory in a plane-wave set with the projector-augmented wave pseudo-potentials. The "Perdew-Burke-Ernzerhof" (PBE) exchange-correlation (XC) functional of the generalized gradient approximation (GGA) is adopted. In such a condition, variations of the

innermost atomic charges will not lead towards a significant change of the MESP outside of the molecule, meaning that the accurate values for the innermost atomic charges are not well-determined by MESP outside the molecule. This approach (CHELP-G) is shown to be considerably less dependent upon molecular orientation than the original CHELP program. The results are compared to those obtained by using CHELP. In the CHELP-G (Charges from Electrostatic Potentials using a Grid based method), atomic charges are fitted to reproduce the molecular electrostatic potential (MESP at a number of points around the molecule. The MESP is calculated at a number of grid points spaced 3.0 pm apart and distributed regularly in a cube. Charges derived in this way don't necessarily reproduce the dipole moment of the molecule. CHELPG charges are frequently considered superior to Mulliken charges as they depend much less on the underlying theoretical method used to compute the wave function (and thus the MESP). The representative atomic charges for molecules should be computed as average values over several molecular conformations.

2.3. S-NICS method

There are no theoretical or mathematical reports for the statistical approaches in NMR shielding and nucleus independent chemical shifts (S-NICS), while the asymmetry (η) and skew (κ) parameters are fluctuated in short distances and are alternative in long distances. In the case of axially symmetric tensor, σ_{22} equals either σ_{11} or σ_{33}, skew is $\kappa = \pm 1$ and by changing asymmetry between $0 \leq \eta \leq +1$ skew will be changed between $-1 \leq \kappa \leq +1$, meanwhile the parameter "κ" is zero when $\sigma_{22} = \sigma_{iso}$. In this work, we have investigated a statistical method by computing of nucleus-independent chemical shifts (S-NICS) in point of probes motions in a sphere of shielding and de-shielding spaces of hereto rings in some antibiotics. The reduced anisotropy defined as: [$\zeta = (\sigma_{zz} - \sigma_{iso}) = (\sigma_{33} - \sigma_{iso})$]**(1):** Anisotropy ($\Delta\sigma$) with relation of $\Delta\sigma = \frac{3}{2}\ \zeta$ including shielding asymmetry (η) is defined as: $\eta = \left(\frac{\sigma_{yy}-\sigma_{xx}}{\zeta}\right) = \frac{3(\sigma_{yy}-\sigma_{xx})}{2\Delta\sigma}$ **(2)** and $\Delta\sigma = \sigma_{zz} - \frac{1}{2}(\sigma_{xx} + \sigma_{yy})$ **(3).** In several cases of an axially symmetric tensor, (σ_{yy} -σ_{xx}) will be zero and hence η = 0. However, the asymmetry (η) parameter indicates that how much the line figure deviates from an axially symmetric tensor, therefore, ($0 \leq \eta \leq +1$). The shielding tensor is expressed as the sum of a symmetric, an anti-symmetric, and a scalar terms, which are ranks 2, 1 and zero tensors which defined as: $\Omega = \Omega^{(0)} + \Omega^{(1)} + \Omega^{(2)}$**(4).** The total chemical shielding tensor {r} is a non-symmetric tensor that can be decomposed into three independent tensors as: (1) a traceless symmetric component, (2) an isotropic component, and (3) a traceless anti-symmetric component. In a spherical tensor representation, as Haeberlen [168] have pointed out, at a fundamental level tensors are better represented in spherical fashion, such that a general second-order property "σ" may be written as $\sigma = \sigma^{iso(0)} + \sigma^{anti(1)} + \sigma^{sym(2)}$ **(5)** , where the number in brackets refers to tensor rank. Spherical tensors are intrinsically involved in considering the effects of tensor quantities on density matrix evolution , so the use of this representation is inevitable for such work. It is worth noting that: $\sigma_0^{iso(2)} = \sqrt{3/2}\,\zeta$ **(6)** and $\sigma_{\pm 2}^{sym(2)} = \frac{1}{2}\zeta$ **(7)** . The symmetric component of the shielding tensor has tensor elements with $r_{ij} = r_{ji}$. This tensor is responsible for the CSA relaxation most often described in the literature and can be diagonalsed by rotation into the shielding tensor principal coordinate system. The anti-symmetric tensor also induces CSA relaxation but this is almost impossible to measure because the induced effects are close to parallel to the external magnetic field which cannot be diagonalsed. By this manuscript, in a statistical calculation we have shown that a time independent average of (Ω^{*}) can be replaced of all above sum of asymmetric, an anti-symmetric, and a scalar terms, which are rank 2, rank 1 and rank zero tensors respectively. These methods are based on random motions of probes in the shielding and de-shielding spaces of aromatic and anti-aromatic molecules to consider maximum abundant of relaxations points in due to spin –dipole and dipole–dipole interactions. The magnetic environment of a spin is seldom isotropic. Therefore, is

represented by a tensor of Span: $(\Omega) = \sigma_{33} - \sigma_{11}$ **(8)** *and* $\kappa = \frac{3(\sigma_{iso} - \sigma_{22})}{\Omega}$ **(9)** .In the Herzfeld-Berger notation, tensors have explained by three parameters, which they are combination of the major components in the standard notations. These are including, the span (Ω), which describes the maximum width of these models, (Ω ≥ 0), and the skew (**κ**) of the tensors which are a magnitude of these values. The accurate formulation of the span (Ω), including the factor of (1-σ_{ref}) has been described by Ω = (σ_{33}- σ_{11}) (1-σ_{ref}) **(10)**. In the Haeberlen- Mehring notation, different combinations of the major components are used for explaining the line figure, and is needed the major components become orderly according to their segregation from the isotropic value in this convention [15] (Fig. 6).

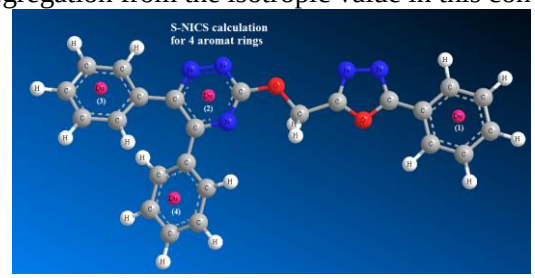

Figure6. S-NICS calculation for 4 rings through dummy atoms

2.3. NMR shielding

The CSA relaxation rates depend on the anisotropy parameter in the standard parameters, of the shielding tensor, (σ_{11}, σ_{22}, σ_{33}), are labeled according to the IUPAC rules, and they formalized and adopt the high frequency-positive order. Therefore, σ_{33} corresponds to the direction of minimum shielding, with the highest frequency, whenever σ_{11} corresponds to the direction of maximum shielding, with the lowest frequency. Moreover the orientation of asymmetry tensor is given by ($\kappa = \frac{3a}{\Omega}$) *and the skew is* $\kappa = \frac{3(\sigma_{iso} - \sigma_{22})}{\Omega}$; (-1 ≤ κ ≤ +1), and related on the position of

σ_{22} with consideration of σ_{iso}, the sign of κ is either positive or negative. In our calculations of various heterocyclic Rings, Benzene and naphthalene, (κ) is mostly positive, and the negative values are belong to some critical or boundary points. In the case of an axially symmetric tensor, σ_{22} equals either σ_{11} or σ_{33} and κ= ±1 therefore ***a*** = Ω/3, and the parameter "***a***" and "**κ**" are zero when $\sigma_{22} = \sigma_{iso}$ and the parameter "μ" used with the Herzfeld-Berger is related to the span of a tensor. Meanwhile, the spinning rate is given by $\mu = \Omega * \nu_{ref,}$. For a non-zero anti-symmetric tensor give the relaxation rates

$$R_1^{dia,CSA} = \frac{2}{15}\gamma_s^2 B_0^2 \left[5\rho^2 . \frac{\tau_{r,1}}{1+\omega_s^2\tau_{r,1}^2} + \Delta\sigma^2\left(1+\frac{\eta^2}{3}\right)\frac{\tau_{r,2}}{1+\omega_s^2\tau_{r,2}^2}\right] \quad (11)$$

and ρ^2 is defined by: $\rho^2 = (\frac{\sigma_{xy} - \sigma_{yx}}{2})^2 + (\frac{\sigma_{xz} - \sigma_{zx}}{2})^2 + (\frac{\sigma_{yz} - \sigma_{zy}}{2})^2$ **(12)**

$$R_2^{dia,CSA} = \frac{5}{45}\gamma_s^2 B_0^2 \left[15\rho^2 . \frac{\tau_{r,1}}{1+\omega_s^2\tau_{r,1}^2} + \Delta\sigma^2\left(1+\frac{\eta^2}{3}\right)\left(4\tau_{r,2} + \frac{3\tau_{r,2}}{1+\omega_s^2\tau_{r,2}^2}\right)\right] \quad (13)$$

Where $\tau_{r,1}$ and $\tau_{r,2}$ correspond to the correlation times for isotropic tumbling and small-step molecular rotation, respectively and in the case of axial symmetry or for isotropic $\tau_{r,1} = 3\tau_{r,2}$. The NMR parameters (such as isotropic magnetic shielding tensors (σ_{iso}), anisotropic magnetic shielding tensors (σ_{aniso}) and Chemical shifts (δ) were also evaluated on the optimized geometries .In all calculations the default gauges-including atomic orbital (GIAO) orbitals were used to obtain molecular magnetic susceptibilities, NMR shielding with Gaussian program. Optimization & NMR constants with orientations of the principal components& Haeberlen-Mehring, or Herzfeld-Berger parameter for several heterocyclic compounds in random situations has been calculated through DFT methods tables 2, 3. In small distance around the center, the asymmetric-parameter (η), and the skew[17](**κ**), exhibited. Gaussian distribution based on their fluctuation behavior[15], which is relate on its distance of molecular ring**.** In contrast, of that parameters, the

isotropy[16-18] $\sigma_{iso}(r)$ Has not a fluctuating behavior and increase in around the center of the rings with a linear relationship[15]. The slopes of that line is changed for various distances of heterocyclic compounds.The isotropy[16-18] in all NMR calculations are positive which indicates negative values for aromaticity[15] (Fig.7).

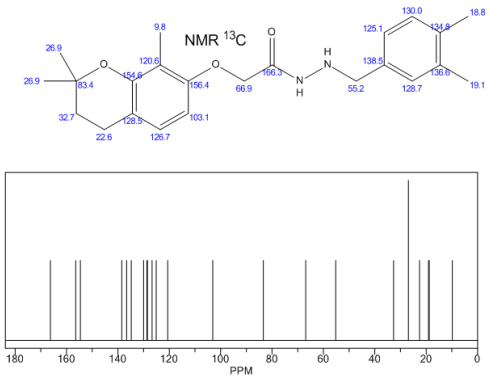

Figure7. *Carbon NMR diagram of N-benzylidene-3, 4-dihydro-2, 2,8-trimethyl-2H-1-benzopyran-7-yloxyacetie acid hydrazide*

3. Results and discussion

It is obvious that the isotropies[15] 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[15]. In the S-NICS method the suitable shielding space near to the center of hetero rings are enables to evaluate the aromaticity[15] as a criterion data. and in this method the expectation of the (η*)[16-18] and (*κ**)[16-18] have been estimated via the Gaussian curve. The isotropy(σ_{iso}^{*}) which is related to all of (η*),(κ *),(Ω*) and (*ζ**) is suitable criterion for the aromatic molecules both hetero or regular rings through the S-NICS method. Similar to the NICS method, in S-NICS[15], mines nucleus-independent-chemical-shifts indicates the aromaticity. Therefor "+" values indicate the anti-aromaticity quantitative. In S-NICS[15] methods, the shielding& de-shielding[15] spaces are important for discussing the mechanism of the aromatic molecules in point of ring currents. The stabilities S-NICS criterion is strongly affected on the best places in shielding spaces which is related to the composition of hetero aromatic rings. It is obvious that geometry factors cause changes in the magnetic-field[15] by the nuclei and change the resonant frequencies. Therefore the chemical shielding and several factors as the same electronegativity, magnetic anisotropy of π-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 can change in several places inside the shielding region .

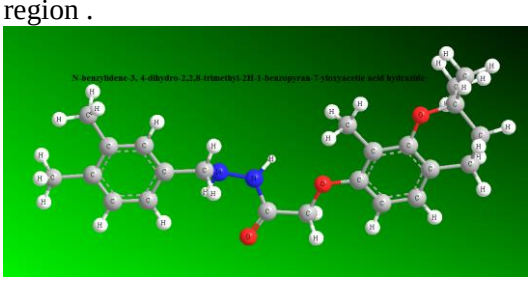

Figure.8 *optimization of N-benzylidene-3, 4-dihydro-2,2,8-trimethyl-2H-1-benzopyran-7-yloxyacetie acid hydrazide*

Table 2: the principal data such as standard components, Haeberlen-Mehring (Isotropic and Anisotropy) for oxadiazol derivatives

49 Bq	Isotropic =	9.6670	Anisotropy =	5.0148	
XX=	9.4293	YX=	3.3067	ZX=	1.0248
XY=	1.9426	YY=	9.7601	ZY=	-2.9706
XZ=	-0.0460	YZ=	-1.8228	ZZ=	9.8115
Eigenvalues:	5.8663	10.1245	13.0102		
50 Bq	Isotropic =	8.0983	Anisotropy =	5.5104	
XX=	5.8732	YX=	2.2708	ZX=	1.3457
XY=	2.6023	YY=	7.2310	ZY=	0.0328
XZ=	2.2751	YZ=	-0.9279	ZZ=	11.1908
Eigenvalues:	3.6297	8.8933	11.7720		
51 Bq	Isotropic =	10.3139	Anisotropy =	4.0072	
XX=	10.2125	YX=	2.4504	ZX=	0.5820
XY=	1.0666	YY=	10.8610	ZY=	-2.2914
XZ=	-0.6321	YZ=	-1.2240	ZZ=	9.8682
Eigenvalues:	7.9371	10.0193	12.9854		
52 Bq	Isotropic =	8.9431	Anisotropy =	3.8663	
XX=	9.8499	YX=	2.8955	ZX=	1.4619
XY=	2.1835	YY=	7.0215	ZY=	-2.2300
XZ=	0.2536	YZ=	-2.0714	ZZ=	9.9580
Eigenvalues:	4.5560	10.7527	11.5207		

Table3. S-NICS calculation for 14 center rings

Dummy atoms in Rings(number)	σ_{11}	σ_{22}	σ_{33}	S-NICS	NICS
BQ_1	5.8663	10.1245	13.0102	-9.667	-9.122
BQ_2	3.6297	8.8933	11.7720	-8.098	-9.051
BQ_3	7.9371	10.0193	12.9854	-10.313	-9.265
BQ_4	4.5560	10.7527	11.5207	-8.943	-9.034
BQ_5	4.9321	9.3453	11.3456	-8.541	-9.01
BQ_6	5.0031	9.1267	10.9934	-8.374	-8.756
BQ_7	4.9835	9.3476	11.4523	-8.594	-8.765
BQ_8	5.1211	9.8745	10.9874	-8.661	-9.001
BQ_9	4.9135	11.84312	10.8734	-9.211	-9.324
BQ_{10}	6.6345	10.9833	11.9823	-9.866	-9.545
BQ_{11}	7.3462	11.0987	10.9872	-9.811	-9.934
BQ_{12}	4.9932	10.9453	11.9352	-9.291	-9.012
BQ_{13}	5.0923	10.9542	10.9987	-9.015	-9.241
BQ_{14}	6.9345	9.4581	11.0187	-9.137	-9.345

4. Conclusion

Many of heterocyclic compounds are known as anticancer drugs such as alkylating agents which have targeted cell DNA causing cell death. Heterocycles ring structures are in essence composed by atoms other than carbon, where the most frequent substituents are sulfur, oxygen and nitrogen .The model size of heterocycles ring, together with the substituent groups of the core scaffold, impact tightly on the chemical and physical properties while among the clinical applications, heterocyclic compound has an active role as anti-bacterial, anti-viral, anti-fungal, anti-inflammatory and anti-tumor drugs. This work is done for developing of modern anticancer drugs. Many of heterocyclic compounds are

known as anticancer drugs such as alkylating agents which have targeted cell DNA causing cell death. Heterocycles ring structures are in essence composed by atoms other than carbon, where the most frequent substituents are sulfur, oxygen and nitrogen.

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