COMMUNICATION

A C G publications

Bioorg. Med. Chem. Rep. 1:1 (2018) 29-36

Bioorganic & Medicinal Chemistry Reports

Analyzing of some druggable properties of hydrazono-pyridazinones

Burak Kuzu and Nurettin Menges*

Department of PharmaceuticalChemistry, Van Yüzüncü YilUniversity, 65080, Van,Türkiye

(Received December 03,2018; Revised December 21, 2018 ; Accepted December 26,2018)

Abstract: Some pyridazinones with *ortho* hydroxy hydrazone were investigated using DFT/B3LYP 6-311 G(d,p) method. Optimized molecules were taken account for NBO analysis by using DFT/B3LYP 6-311+G(d,p) method and information gained NBO analysis gave some important point for predicton of polarization of atoms. Furthermore, electrostaticpotential surfaces (MEP) were calculated and visualized in order to predict charge distribution as well as the shape/volume of the surface of the pyridazinones. HOMO-LUMO orbitals were computed and with these information hardness, electronegativity and global electronegativity index were calculated. For aromaticity of pyridazinone ring HOMA, BIRD and NICS indexes were calculated and aromaticity indexes revealed that which heterocyclic ring was the most aromatic and stable against metabolization effect of enzymes. Electron density map with projection for **2** was plotted and its localization of electron density was discussed. Lipinski's rule of five was calculated for investigated molecules for prediction of oral uptake and drug candidates.

Keywords: Pyridazinone; aromaticity; nbo analysis; physicochemical properties; drug design.

1. Introduction

Diazinones (pyrazinone, pyridazinone, pyrimidinone) have emerged as useful starting materials for the elaboration of different types of skeletons of biologically interesting compounds[1]. Some alkaloids, Hamacanthin A and B, Aureusimine A and B, have diazinone moiety. Furthermore, some pharmacologically important compounds carry a diazinone unit. Such compounds inhibit the hepatitis C-virus (HCV)NS5B[2] and HCVNS3[3] as well as being an active inhibitor of the human α-thrombin that is potentially useful for the acute and chronic treatment of venous and arterial thrombosis (Figure 1)[4].

2. Computational method

The calculations of the geometrical parameters were performed using the Gaussian 09W program package[5] and B3LYP (Becke's Three Parameter Hybrid Functional using the LYP Correlation Functional) approach in conjunction with the 6-311G(d,p) basis set. The harmonic vibrational frequencies were calculated at the same level of theory for the optimized structure. Calculated vibrational frequencies ascertained that the structures were the stable structure (no imaginary frequencies). The geometry of the

*Corresponding author: E-mail: nurettinmenges@yyu.edu.tr, Phone: + 90 432 2251025

The article was published by ACG Publications
http://www.acgpubs.org/journal/bioorganic-medicinal-chemistry-reports © January-December 2018
DOI: http://doi.org/10.25135/bmcr.10.18.12.1104

selected compounds, together with that of tetramethylsilane (TMS), were fully optimized. ^{1}H-NMR chemical shifts were calculated using the standard GIAO/B3LYP/6-311++G(d,p) (Gauge-Independent Atomic Orbital) approach[6-7] with the Gaussian 09W program package.

To investigate the reactive sites of compounds, the molecular electrostatic potential surfaces (MEP) were evaluated using the B3LYP/6-311+G(d,p) method. The NBO analysis was performed at the B3LYP/6-311+G(d,p) level by means of the NBO 3.1 program within the Gaussian 09W package [8]. HOMA and BIRD aromaticity indexes and electron density map with projection were calculated by means of Multiwfn software program[9-10].

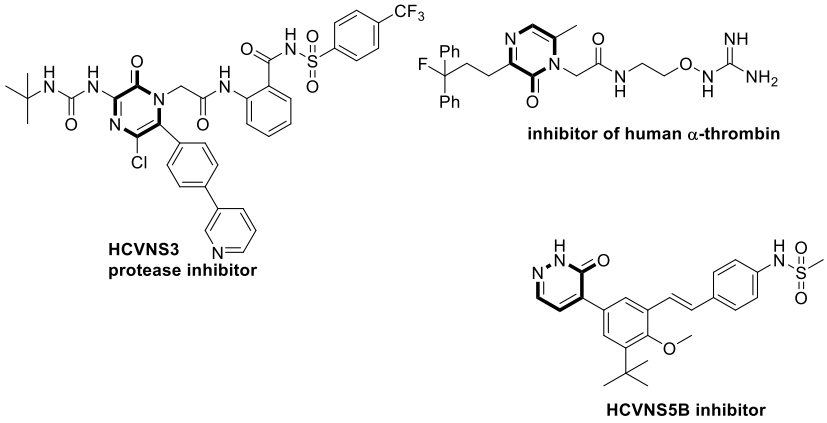

Figure. 1. Some important diazinone derivatives

In order to investigate the effect on the activity of the *ortho*-hydroxy N-acyl hydrazone fragment and diazinone skeleton, which is the active part of the PAC-1 compound, we wanted to analyze some physicochemical and electronic properties of the hydrazono-pyridazinone structure by means of computational chemistry.

3. Result and Discussion

3.1. Molecular structure

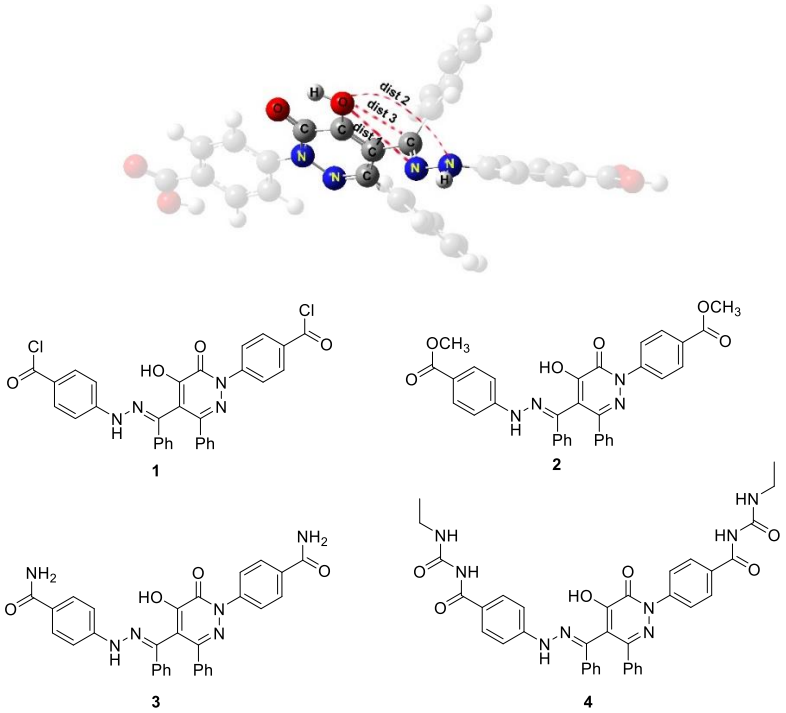

Figure 2. General structure of pyridazinones

Distances between atoms have been extracted from theoretical calculations (Figure 2, Figure S1). With this result, a few valuable points have been revealed (Table S1). The oxygen atom in the hydroxyl group, nitrogen atoms in the hydrazone group and the carbon atom adjacent to the pyridazinone ring have been realized. By measuring the distances between two atoms in Angstrom (A^o), some distances have been obtained. Reference compound, PAC-1, has 4.01, 4.90, 2.70 A^o for dist 1, 2 and 3 respectively. It is seen in Table S1, PAC-1 has longer distances for dist 1 and dist 2 than but shorter distance for dist 3. For pyridazinones, hydroxy group is closer to nitrogen atom of **N**=CH and **N**HN=CH groups (dist 1 and dist 2) than that of PAC-1. On the other hand, pyridazinones have slightly different distances between themselves.

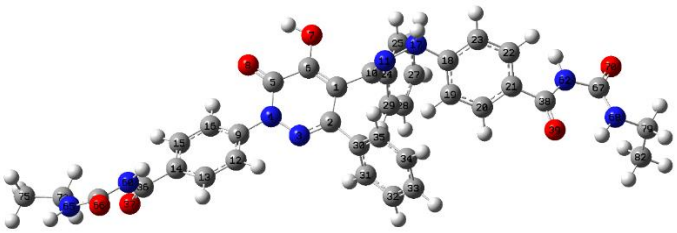

Figure 3. Bond and dihedral angles for **4**

Bond and dihedral angles for compound **4** are acceptable and they are comparable with those related structures. There is not a crystal structure of compound **4** and the optimized structure can therefore only be compared with other similar systems. With comparison bond angles were handled (for bond angles see table S2 in supporting information). For example, bond angles for pyridazinone ring (Figure 3) for N3-N4-C9, C2-N3-N4, N4-C5-C6, C5-N4-N3, O8-C5-N4 of pyridazinone ring are 114.27, 120.50, 114.57, 123.06, 123.78 º respectively which are in good agreement with a similar molecular structure (113.09, 118.68, 115.18, 123.40, 121.53 º)[11].

After search out the some dihedral angles we have observed that some deviations take place from planarity of whole system such as -151.51 º for C16-C9-N4-N3, 0.42 ºfor C30-C2-C1-C10 and 0.20 º for N11-N17-C18-C19 because of some steric hinderances of hydrogens and aromatic rings (Table S2). It was seen that planarity of pyridazinone ring was retained when analyzed dihedral angles of the ring such as C6-C1-C2-N3:0.28 º; C1-C2-N3-N4:0.02 º; C2-N3-N4-C5:0.07 º. Furthermore, hydrazone unit is almost perpendicular to pyridazine skeleton because of the fact that dihedral angle of C6-C1-C10-N11 is 97.42 º.

3.2. Electronic parameters

HOMO (High Occupied Molecular Orbitals) and LUMO (Low Unoccupied Molecular Orbitals) orbitals show important properties for predictivity of drug metabolization. The frontier molecular orbitals of the pyridazinones, **1-4**, show that for all five HOMO, the coefficient density is predominantly located on the hydrazone, benzene ring attached to NH group of hydrazone and the other benzene ring adjacent to hydrazone whereas pyridazinone and the other rest of benzene rings do not possess coefficient density. Conversely, for LUMO of pyridazinones, **1-4,** the coefficient density is located on the pyridazinone, and benzene attached to nitrogen atom of pyridazinone ring (Figure S2). Furthermore, HOMOs and LUMOs energy of compounds **1-4** have been calculated by using DFT/B3LYP 6-311+G (d,p) method (Table1).

Table1. HOMOs and LUMOs of hydrazono-pyridazinones

Compound	Calculated HOMO energy (eV)	Calculated LUMO energy (eV)	Calculated DE (HOMO-LUMO)(eV)
1	-6.008	-2.427	-3.581
2	-5.643	-1.918	-3.726
3	-5.635	-1.755	-3.880
4	-5.795	-1.916	-3.878

HOMOs and LUMOs of selected pyridazinones have been calculated and outcomes showed that alteringcarboxylic acid with acyl chloride**1**, methoxy **2**, amine **3**, ethyl urea **4** slightly increased the energy gap (DE) of pyridazinones. The most change was seen for the amide derivative **3**, -3.880, when compared tothe others**.**According to calculated DE (energy gap), the most stable compound against metabolization is compound **3.**

Information gleaned from the electrostaticpotential surface map is a powerful tool that has provided insights into intermolecular association and molecular properties of small molecules. This tool can analyze interaction of protein-ligand, protein-protein and enzymes catalysis[15] thus, some pyridazinones were put througha process that creates MEPs of all compounds[12]. The charge distribution of compounds were searched and it was observed that electron density of carbonyl group placed on the end of compounds were highly dense (red and yellow regions). MEP shape of all compounds looks like similar but there are some exception because of different functional groups. For instance, compound **4** has two red regions due to urea group. At MEPs there are some highly electropositive regions (blue regions) which are responsible for hydrogens of OH and NH of hydrazone groups. Red region of the end of compound **2** belongs to ester carbonyl group and electron density is more localized on carbonyl oxygen than methoxy oxygen because of conjugation with benzene. This information was proved by NBO charge of two different oxygen (-0.527 for carbonyl oxygen; -0.511 for methoxy oxygen). Compound **3** and **4** have blue regions (electropositive) on the end of molecules which belongs to hydrogens of amide and urea groups (Figure 4). All of this information reveal good points for possible binding with drug targets.

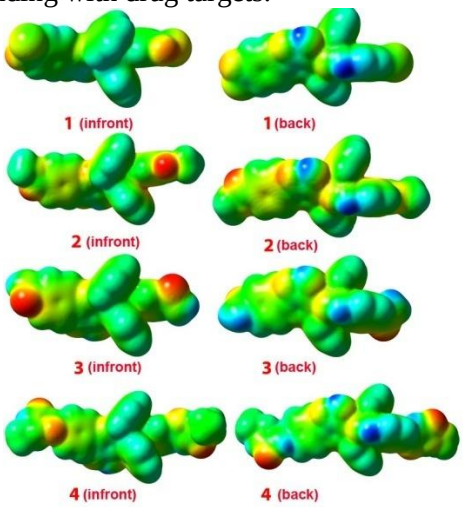

Figure 4. Electrostatic Potential map (MEP) on molecular surface. Isosurface value: 0.004. Color scheme ranges from red (-9.215 eÅ^{-3}) via green (zero) to blue (9.215 eÅ^{-3}) (-29.7-29.7 kcal/(e mol)). Gaussian view 5.09 program was used to plot the data .

NBO analyze for compound **4** showed that C5-O8 bond was polarized toward to oxygen atom and coefficient of oxygen 2p orbital for corresponding bond was 0.8398. In addition, C6-O7 bond has similar properties and coefficient of sp orbital for oxygen is higher than that of carbon as expected. Analyze of N11-N17 bond gave information that N17 gained more nucleophilic character than N11 and this outcome might be because of conjugation of N11 with C10. Coefficient of carbon 2p orbital for C10-N11 bond is 0.6401 and that of nitrogen is 0.7684. This result is expected but coefficient differences between two atoms are smaller than the others which are polarized. This means that C-10 atom has less electrophilic character than the other polarized carbon atoms which mentioned in Table S3 in supporting information. It might be due to delocalization with benzene and pyridazinone ring. NBO analysis indicated that the carbonyl group (C38-O39) placed on the end of compound **4** was more electropositive (more electrophilic site) than C36-O37 because coefficient of π anti-bond orbital of C38-O39 (0.8363p) is slightly larger than that of C36-O37 (0.8297p) (for detail see Table S3).

3.3. Electron density map with projection

To analyze the electron density of pyridazinone ring electron density map with projection was plotted by means of Multiwfn software. Gaussian output file of energy job (DFT/B3LYP G(d,p)) was converted into fch file with gaussian and this file was used as an input file for Multiwfn software. Density map shows that there are some points in which electron density is localized. Some covalent bonds are polarized toward more electronegative atoms and π-electron delocalization through the ring do not occur and this means lacking of fully delocalization which results in decreasing of aromaticity. This issue was clarified by calculating of ring aromaticity using by NICS aromaticity index (Table 2). According to NICS calculation, aromaticity of ring center of pyridazinone for **2** is -3.21, this value is very low when compared to the benzene ring Ph(1) of same molecule whose value is -10.36 (Table 2).Electron density between some atoms was very low thus their bond lengths were calculated. The lowest electron density was seen between CO-COH whose bond length was 1.495 Aº which was the longest distance between two atoms in molecule. The other distances were 1.457, 1.421, 1.369, 1.366, 1.323 Aº and these distances reflect the electron density between relevant atoms (Figure 5). This kind of electron density map might be useful for prediction of active side of ligand and/or of metabolization pathway.

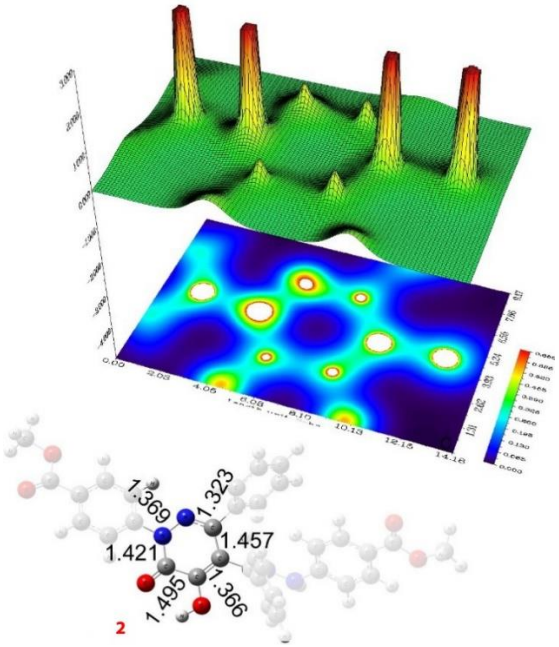

Figure 5. Electron density map with projection for compound **2** (pyridazinone ring). Numbers refer bond distances in Angstrom.

Furthermore, it can be seen that highest localization of electron density is observed on the nitrogen atom and it might be because of lone pair electrons. It does not share its lone pair electrons very effectively through the ring and it results in lower aromaticity.

3.4. Aromaticity and stability

Some selected compounds having same skeleton exception for different functional groups such as **1-4** were objected to investigate the aromaticity and stability. Stability is concerned due to metabolization of drug candidates. HOMA[13] and BIRD[14] aromaticity indexes were calculated by using Multiwfn software[9-10]. NICS[15] values were calculated by means of Gaussian 09 and for this purpose optimized compounds were calculated by using GIAO/B3LYP/6-311++G(d,p) (Gauge-IndependentAtomic Orbital) approach and isotropic values (meaning $NICS_{iso}$) were extracted from corresponding files. HOMA value goes to 1 when aromaticity of ring rises. Selected compounds have not good enough HOMA value to be mentioned as aromatic. BIRD value of benzene ring is 100 and it is reference for BIRD. When the aromaticity rises, BIRD value is clouse to 100. For NICS method the more compound has negatif value the more compound will be aromatic. Advantage of NICS method is that the aromaticity/antiaromaticity/nonaromaticity of any desired point of any place of the ring can be calculated. NICS indexes showed that aromaticity of center of the ring of pyridazinones is smaller than that of the point above 0.5 Aº of the ring center (Table S5 NICS(0) and NICS(0.5)). All mentioned methods indicated that the most aromatic pyridazinone ring belonged to **3** (HOMA: 0.0924; BIRD: 52.406; $NICS_{iso}(0.5)$: -5.15; Table 2). Hardness indicates the stability of compounds against to electrophilic or nucleophilic attacks and furthermore hardness and electronegativity work together to enlighten stability of molecules so G. E. Index(Global electrophilicity index) including electronegativity and hardness values gives more accurate result as to stability of molecules. G.E. index value of **3** is 0.129 and it is the more stabilized molecule within studied pyridazinones. Aromaticity values and G.E. index proved that more stabilized molecule was **3**. Another point that should be mentioned is that magnetic field of compounds rises when gone far from the ring of the pyridazinone. This means that aromaticity of the point above 0.5 A º of the ring is higher than that of the ring center (for **3** NICS(0):-3.21, NICS(0.5):-4.83 see Table 2). The data given in Table 2 can be good reference for pyridazinone types of molecules for researchers.

Table 2. Aromaticity and stability values for selected pyridazinones

Compound	**1**	**2**	**3**	**4**
HOMA	0.0603	0.0773	**0.0924**	0.0849
BIRD	51.308	51.870	**52.406**	52.160
$NICS_{iso}(0)$	-3.07	-3.21	**-3.58**	-3.31
$NICS_{iso}(0.5)$	-4.84	-4.83	**-5.15**	-4.89
HOMO	0.2208	0.2074	**0.2071**	0.2129
LUMO	0.0892	0.0705	**0.0645**	0.0704
Hardness	0.0658	0.0684	**0.0715**	0.0720
G. E. Index	0.182	0.141	**0.129**	0.140
Electronegativity	-0.155	-0.139	**-0.136**	-0.142

3.5. Lipinski's Rule of Five

Lipinski's rule of five is a rule of thumb to evaluate druglikeness or determine whether a compound has a propriate chemical properties and physical properties that would make it a likely orally active drug.

Table 3. For compound 1-4, Lipinski's Rule of Five

Compound	H-Bond Donor	H-Bond Acceptor	Molecular Mass	Calculated LogP
1	8	2	582	5.09
2	10	2	574	6.49
3	10	6	544	3.47
4	15	6	686	5.76

Physicochemical parameters of hydrazone derivatives of this manuscript showed that these molecules can not be considered for orally active (Table 3). LogP (lipophilicity) of compounds are higher than 5 except for compound **3**. This is a problem because this type of molecules might bind with plasma proteins such as serum albumine resulting in lower amount of free drug. Furthermore, molecular mass of compounds which should be below 500, are higher than Lipinski's rule of five. H-bond donor and H-bond acceptor numbers are acceptable according to Lipinski's rule.

4. Conclusions

Some pyridazinones containing *ortho*-hydroxyhydrazone unit which resembles active core of PAC-1 which is procaspase-activated molecule were theoretically investigated. Molecular structure, electronic parameters, stability and aromaticity of compounds were calculated. These calculations gave us a few valuable points as to the position of atoms in pyridazinones. MEPs were created and visualized to examine their electron distributions and shapes. This is a powerful approach to reveal intermolecular specificity. This process could be useful as it shows promise in having predictive value in drug design. In addition, aromaticity parameters brought into the light some valuable discussions so that this study might open an access for prediction of aromaticity and stability for these types of molecules. Electron density map for pyridazinone ring of **2** was plotted and localization of the ring electrons were discussed. Lipinski's rule was discussed and some of physicochemical parameters was shown. We assume that this study might be a good perspective for drug candidates in which hydrazono-pyridazinone structures are focused.

Supporting Information

Supporting information accompanies this paper on http://www.acgpubs.org/journal/-bioorganic-medicinal-chemistry-reports

Acknowledgement

This study wascompleted by means of support of Van YuzuncuYil University, Council of Scientific Research.

ORCID
Burak Kuzu: 0000-0002-7305-7177
Nurettin Menges: 0000-0002-5990-6275

References

[1] (a) Pawar, V. G.; De Borggraeve, V. M. 3,5-Dihalo-2(1*H*)-pyrazinones: **v**ersatile scaffolds in organic synthesis. *Synthesis*, **2006**, *17*, 2799-2814. (b) Mehta, V. P.; Appukkuttan, P.; Van der Eycken, E. Microwave-assisted chemistry of 2(1H)-pyrazinones. *Curr. Org. Chem*. **2011**, *15* (2), 265-283.

[2] Schoenfeld, R. C.; Bourdet, D. L.; Brameld, K. A.; Chin, E.; Vicente, J.; Fung, A.; Harris, S. F.; Lee, E. K.; Pogam, S. L.; Leveque, V.; Li, J.; Lui, A. S. T.; Najera, I.; Rajyaguru, S.; Sangi, M.; Steiner, S.; Talamas, F. X.;

Taygerly, J. P.; Zhao. J. Discovery of a novel series of potent non-nucleoside inhibitors of hepatitis C virus NS5B. *J. Med. Chem.* **2013**, *56*, 8163-8182.

[3] Gising, J.; Belfrage, A. K.; Alogheli, H.; Ehrenberg, A.; Åkerblom, E.; Svensson, R.; Artursson, P.; Karlén, A.; Danielson, U. H.; Larhed, M.; Sandström, A. Achiral pyrazinone-based inhibitors of the hepatitis C virus NS3 protease and drug-resistant variants with elongated substituents directed toward the S2 pocket. *J. Med. Chem*. **2014**, *57*, 1790-1801.

[4] Lu, T.; Markotan, T.; Ballentine, S. K.; Giardino, E. C.; Spurlino, J.; Brown, K.; Maryanoff, B. E.; Tomczuk, B. E.; Damiano, B. P.; Shukla, U.; End, D.; Gordon, P. A.; Bone, R. F.; Player, M. R. Discovery and clinical evaluation of 1-{*N*-[2-(amidinoaminooxy)ethyl]amino}carbonylmethyl-6-methyl-3-[2,2-difluoro-2-phenylethylamino]pyrazinone (RWJ-671818), a thrombin inhibitor with an oxyguanidine P1 motif. *J. Med. Chem*. **2010**, *53*, 1843-1856.

[5] Gaussian 09, Revision C.01, Gaussian, Inc., Wallingford CT, **2010**.

[6] Ditchfield, R. Molecular orbital theory of magnetic shielding and magnetic susceptibility. *J. Chem. Phys*. **1972**, *56*, 5688-5691.

[7] Wolinski, K.; Hinton, J. F.; Pulay, P. Efficient implementation of the gauge-independent atomic orbital method for NMR chemical shift calculations. *J. Am. Chem. Soc*. **1990**, *112*, 8251-8260.

[8] Glendening, E. D.; Badenhoop, J. K.; Reed, A. E.; Carpenter, J. E.; Weinhold, F.; NBO.Version 3.1, Theoretical Chemistry Institute, University of Wisconsin, Madison, 1995.

[9] Lu, T.; Chen, F. Multiwfn: a multifunctional wavefunction analyzer. *J. Comp. Chem*. **2012**, *33*, 580-592.

[10] Lu, T.; Chen, F. Quantitative analysis of molecular surface based on improved marching tetrahedra algorithm. *J. Mol. Graph. Model.* **2012**, *38*, 314-323.

[11] Sowmya, H. B. V.; Suresha Kumara, T. H.; Nagendrappa Jerry, G.; Jasinski, P.; Millikan, P.; Jose, G.; Dileep, R.; Sujan Ganapathy, P. S. Solvent free synthesis, crystal studies, docking studies and antibacterial properties of some novel fluorinated pyridazinone derivatives. *J. Mol. Struct.* **2013**, *1054-1055*, 179-187.

[12] Weiner, P. K.; Langridge, R.; Blaney, J. M.; Schaefer, R.; Kollman, P. A. Electrostatic potential molecular surfaces. *Proc. Natl. Acad. Sci. USA*. **1982**, *79*, 3754-3758.

[13] Kruszewski, J.; Krygowski, T. M. Definition of aromaticity basing on the harmonic oscillator model. *Tetrahedron Lett.* 1**972**, *13*, 3839-3842.

[14] Bird, C. W. A new aromaticity index and its application to five-membered ring heterocycles. *Tetrahedron*. **1985**, *7*, 1409-1414.

[15] Schleyer, P. R.; Maerker, C.; Dransfeld, A.; Jiao, H.; Hommes, N. J. R. Nucleus-independent chemical shifts: a simple and efficient aromaticity probe. *J. Am. Chem. Soc*. **1996**. 118, 6317-6318.