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STRUCTURAL INVESTIGATION, DRUG LIKENESS SCORING AND STRUCTURE ACTIVITY/PROPERTY RELATIONSHIPS APPLIED ON 1,2,3-THIADIAZOLE DERIVATIVES, WITH KINASE INHIBITORS ACTIVITY

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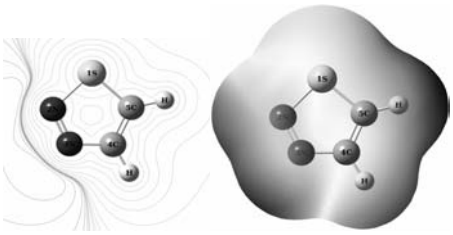
All calculations and the equilibrium geometries of 1,2,3-thiadiazole have been performed using *ab initio*/HF, MP2 and DFT methods with different basis sets. The molecular electrostatic potential surface (MESP) that reveals centers of reactivity of the molecule and substitution effects of the molecular system have been studied using the HSAB principle (Hard Soft Acid and Base). Also, the multi-parameter optimization (MPO) methods and structure activity/property relationship studies were carried out on twenty-one molecules of 1,2,3-thiadiazole derivatives which are potent VEGFR-2/KDR kinase inhibitors. In the present work results such as net charges, bond lengths, dipole moments, QSAR properties, Lipinski's parameters, Lipophilic Efficiency (LipE), have been calculated and discussed.



INTRODUCTION

The rise in the resistance against drugs became a global phenomenon, which led to the need to design new compounds in order to deal with this resistance. In the most important areas of nowadays research,[1] thiadiazoles are of special interest as potential active compounds because of their structural similarity to natural and synthetic compounds possessing high biological activity.[2,3] As a member of five membered aromatic systems that have three heteroatoms at symmetrical positions thiadiazoles have been studied extensively owing to their interesting pharmacological activities.[4] The thiadiazole nucleus has several important activities such as: antimicrobial, anti-inflammatory, anticancer, anticonvulsant, antidepressant, antioxidant, radio protective, and anti-leishmanial activities.[5]

In organic synthesis and medicinal chemistry, the 1,2,3-thiadiazole derivatives represent a remarkable class of molecules.[2] They have an impressive attention to reinforce kinase inhibitory activity, which is an intense area of investigation in anti-tumor research.[6]

The contributions to this series of thematic issues provide an insight into an emerging and most exciting area of drug discovery, while highlighting success stories as well as challenges for computational models in medicinal chemistry. In 1997, Lemont B. Kier stated that "It is no longer just sufficient to synthesize and test; experiments are played out in silico with prediction,

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classification and visualization being the necessary tools of medicinal chemistry"[7] Without doubt, computer-based simulation of biochemical processes and molecular model building will increasingly drive molecular design and decision in drug discovery. There are ample evidences that computational medicinal chemistry has become an important pillar of modern drug research.[8,9]

Drug development requires a lot of effort in addition to a considerable funding; it takes so many years for lead identification, optimization, in vitro and in vivo testing, before the starting of the first clinical trials.[10,11] More than ever, the volume of complex data produced by drug discovery activities is larger, which is in need of certainty. Here comes the role of multi-parameter optimization which improves the use of this data to fast the targeting of the compounds with a good balance of properties.[12] The most known rules from MPO methods for compounds prediction with best balance of properties are calculated metrics and rules of thumb.

Among the diverse rules which have been proposed, Lipinski and Veber rules are the most popularly used.[13,14] On the other side, we found that the calculated metrics which integrate the potency with other parameters in order to get a single metric give through optimization. The oldest compound and most widely used metrics are the Ligand Efficiency (LE) and the Lipophilic Efficiency (LipE).[12] Therefore, discovering drugs is a process which realizes a sustained balanced search for molecules that have structural features that produce: 1) strong target binding using structure-activity relationship (SAR) and 2) high performance at in vivo barriers, using structure property relationship (SPR).

By a similar way that design of structural features using SAR is known as structure-based design, the design of structural features using SPR has become known as property-based design. The matter of the way that medicinal chemists deal with balancing these often disparate processes is a question of experience and strategy.[15] The Structure Activity/Property Relationship (SAR/SPR)[16,17] are studies to ameliorate the grasp of fundamental processes and phenomena in medicinal chemistry and drug design.[18-21] They are also intended to show the liaison between molecular structures and molecular properties [22-24] such as lipophilicity, polarizability, electronic and steric parameters. During this correlation, the characteristics of a molecule to the main physicochemical processes happened in the target activity.

This research aims to study molecular geometry, electronic properties and substitution effects of 1,2,3-thiadiazole nucleus using *ab initio*/HF, MP2 and DFT methods.[25-34] Afterward, in order to determine compounds with elevated strength, the dataset of 1,2,3-thiadiazole derivatives has been prolonged, by using rules of thumb, calculated metrics and structure activity/property relationships (SAR/SPR) respectively related to their kinase inhibition activity.

MATERIALS AND METHODS

The molecular modeling calculations for all the 1,2,3-thiadiazole derivatives are performed by HyperChem 8.08,[35] Gaussian 09[36] and MarvinSketch 6.2.1.[37] Firstly, we realized the calculation of some geometric and electronic parameters, using various computational levels; *ab initio*/HF, MP2 and DFT with different basis sets such as 6-311G++(2d,p), 6-311G++ (3d,2p) and CC-pVDZ. This work also involves calculation of 3D MESP surface map and 2D MESP contour map to reveal the information regarding charge transfer within the molecule.[38-40] Finally, using Chemaxon,[37] Molinspiration[41] and QSAR module from HyperChem software, the following physicochemical properties were calculated for the investigated molecules: Polar surface area (PSA) which is formed by polar atoms of a molecule, surface area grid (SAG) with a grid calculation (solvent accessible or Van der Waals)[42] much slower method than the approximate calculation, but is more accurate for a given set of atomic radii. It is recommended to use this method as a benchmark for the approximate surface area calculation. The grid method used is described by Bodor *et al.*[43] Molecular volume (V) calculation is very similar to the Surface Area (Grid) calculation; it uses a grid method described by Bodor *et al.* The hydration energy (HE) is a key factor determining the stability of different molecular conformations. The calculation is based on exposed surface area.[44] Calculation octanol-water partition coefficient (logP) is carried out using atomic parameters derived by Ghose, Pritchett and Crippen and later extended by Ghose and coworkers.[45,46] The molecular refractivity (MR) is estimated by the same method as logP. Ghose and Crippen presented atomic contributions to the refractivity in exactly the same manner as to the hydrophobicity.[46,47]

The polarizability (Pol) is estimated from an additivity scheme presented by Miller, different increments are associated with different atom types. For a variety of organic molecules, the

estimates are accurate to within 1 to 3%.[48] The molecular weight (MW) of a system calculation is based on a general applicability method.[35]

RESULTS AND DISCUSSION

GEOMETRIC AND ELECTRONIC STRUCTURE OF 1,2,3-THIADIAZOLE

In order to get optimized geometrical parameters [49-51] (bond lengths and valence angles) of 1,2,3-thiadiazole (Fig. 1), we used different methods; *ab initio*/HF, MP2 and DFT with different basis sets (Table 1).

We found good agreement between predicted geometries (bond lengths and bond angles) and corresponding experimental data from double resonance modulation microwave (DRM) spectroscopy values,[52] especially for the DFT/B3LYP results. From that, we can say the DFT method is more appropriate for further study on 1,2,3-thiadiazole ring and its derivatives. Furthermore, net charge analysis results as shown in Table 2, we observed the values which were calculated by both DFT and MP2 methods with 6-311G++ (3d,2p) basis are similar for NBO and Mulliken. Regarding our results, NBO was chosen as the best approximation to perform the electronic study on the investigated series. The molecular electrostatic potential surface MESP is a piece of electrostatic potential mapped onto the iso-electron density surface,[53] the importance of the MESP lies in the fact that at the same time it shows the molecular size and form whether positive, negative and neutral electrostatic potential areas in terms of the electrostatic surface, which illustrate the investigation of the molecular structure with its physicochemical properties relationships.[54-56]

The MESP surface map and contour map of 1,2,3-thiadiazole (Fig. 2) display the two regions characterized by red color (negative electrostatic potential) around the two cyclic nitrogen atoms which expound the ability for an electrophilic attack on these positions, also by blue color (positive electrostatic potential) around the two hydrogen atoms which explain that these regions are susceptible for a nucleophilic attack. Finally, for the green color located between the red and blue regions explain the neutral electrostatic potential surface. The variation in electrostatic potential produced by a molecule is largely responsible for binding of a drug to various active sites of the receptor (VEGFR-2/KDR), as the binding site in general is expected to have opposite areas of electrostatic potential.[57]

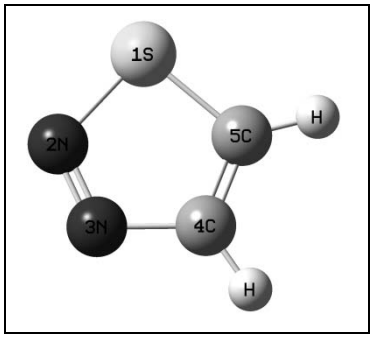


Fig. 1 – 3D structure of 1,2,3-thiadiazole.

Table 1

Bond lengths (in angstrom, Å) and valence angles (in degrees, º) of 1,2,3-thiadiazole

Comp.	EXP.[52]	*ab initio*/ HF			DFT/ B3LYP			*ab initio*/MP2		
		6 311 ++ G (2d,p	6 31 1 ++ G (3d,2p)	CC-pVDZ	6 311 ++ G (2d,p	6 31 1 ++ G (3d,2p)	CC-pVDZ	6 311 ++ G (2d,p	6 31 1 ++ G (3d,2p)	CC-pVDZ
S-N2	1,692	1,664	1,654	1,691	1,732	1,718	1,782	1,702	1,684	1,740
S-C5	1,689	1,694	1,689	1,705	1,698	1,693	1,708	1,687	1,680	1,697
N2-N3	1,290	1,244	1,247	1,242	1,273	1,276	1,266	1,319	1,320	1,308
C4-C5	1,369	1,343	1,345	1,348	1,366	1,368	1,373	1,385	1,387	1,393
N3-C4	1,366	1,369	1,368	1,376	1,367	1,366	1,374	1,353	1,352	1,363
C5-H	1,078	1,069	1,067	1,077	1,078	1,076	1,088	1,080	1,076	1,091
N2-S-C5	92,90	92,22	92,48	91,68	91,84	92,18	90,85	93,39	93,79	92,58
S-N2-N3	111,20	112,43	112,61	112,29	110,64	110,88	110,16	110,42	110,74	110,37

Table 1 (continued)

S-C5-C4	107,80	107,46	107,38	107,73	108,44	108,26	109,15	107,63	107,41	108,04
N2-N3-C4	114,00	114,19	113,94	114,52	115,11	114,79	115,91	113,83	113,50	114,41
N3-C4-C5	114,20	113,69	113,59	113,78	113,97	113,89	113,93	114,73	114,56	114,60
S-C5-H	122,90	124,02	124,01	123,97	123,56	123,68	123,48	124,26	124,06	124,14
N3-C4-H	119,20	118,99	119,03	118,91	119,28	119,40	119,38	119,38	119,45	119,52

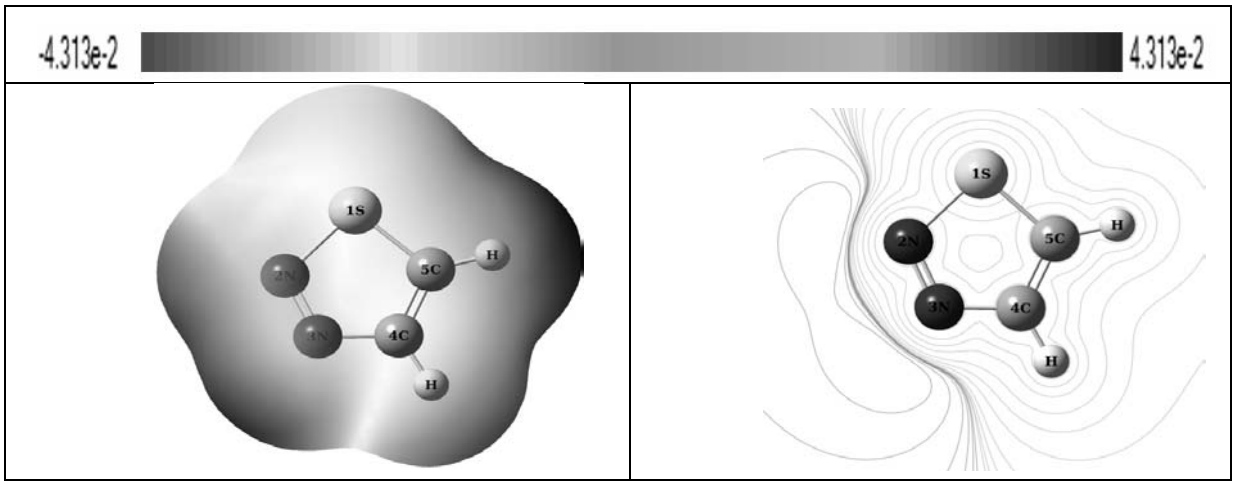


Fig. 2 – 3D MESP surface map and 2D MESP contour map of 1,2,3- thiadiazole.

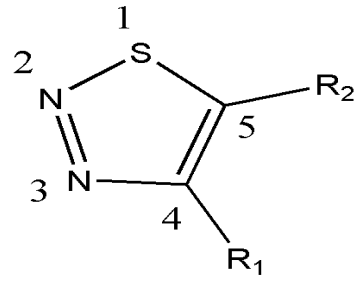
Table 2

Net charges distribution of 1,2,3-thiadiazole

ATOMS	**DFT/ B3LYP (6311G++3D2P)**		***ab initio*/MP2 6 31 1 ++ G (3d,2p)**	
	NBO	**MULLIKEN**	**NBO**	**MULLIKEN**
S1	0,589	0,066	0,643	0,096
N2	-0,354	-0,405	-0,403	-0,476
N3	-0,198	-0,277	-0,214	-0,400
C4	-0,072	0,381	-0,047	0,505
C5	-0,425	-0,018	-0,415	0,066
H6	0,218	0,129	0,205	0,090
H7	0,242	0,124	0,231	0,118

SUBSTITUTION EFFECTS ON 1,2,3-THIADIAZOLE STRUCTURE

The calculated values such as heat of formation, dipole moment (μ) and the frontier molecular orbitals energies HOMO (Highest Occupied Molecular Orbital) and LUMO (Lowest Unoccupied Molecular Orbital) of 1,2,3-thiadiazole systems (Fig. 3) are given in Table 3, net atomic charges of 1,2,3-thiadiazole derivatives are also reported in Table 4 for the first series, which contains methyl, ethyl and propyl groups and in Table 5 for the second series. which, contains chloride, cyanide, bromide and fluoride groups. For the comparative study between the electron donors and acceptors effects, in each addition of methyl, ethyl, propyl, chloride and fluoride radical, the heat of formation decreases of approximately 8, 14, 21, 5 and 39 (kcal/mol) respectively. However, the addition of the cyanide and bromide groups leads to the increase of the heat of formation with 35 and 5 (kcal/mol), respectively. Among the various substitutions on1,2,3-thiadiazolenucleus, we found that the compound **A1** (4-methyl-1,2,3-thiadiazole) with electro-donor effect has the lowest energy gap HOMO-LUMO (0.2092 a.u.). For the electro-acceptor effect, the compound **B6** (4-fluoro-1,2.3,-thiadiazole) has the lowest energy gap (0.2037a.u, see Table 4). From HSAB (Hard Soft Acid and Base) principle the lowest energetic gap allows an easy flow of electrons which makes the molecule soft and more reactive which means that **A1** and **B6** compounds are the most reactive in the two series of 1,2,3-thiadiazole derivatives.[58] The compound **B1** (4-cyano-1,2,3-thiadiazole) show the maximum dipole moment value, which would be resulting from a resonance effect.

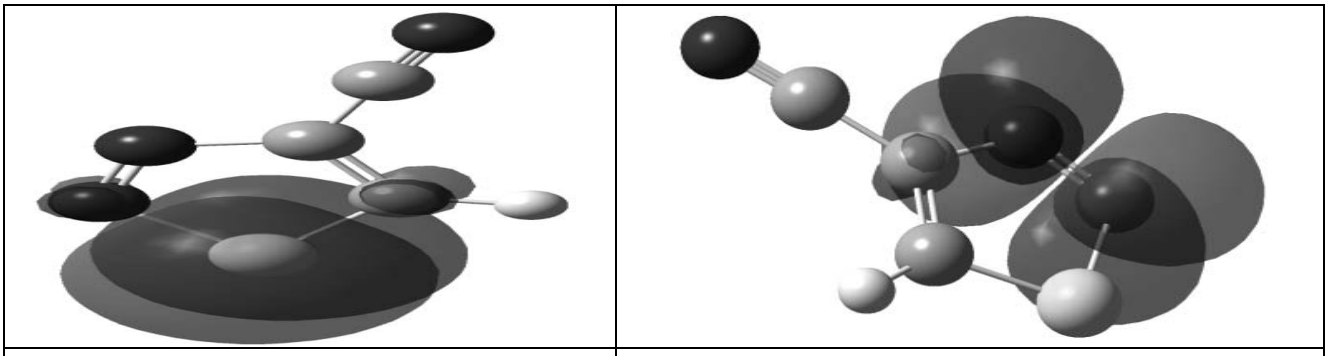


Series 1	series 2
(A_1) R_1=CH_3, R_2=H	(B_1) R_1=CN, R_2=H
(A_2) R_1= R_2=CH_3	(B_2) R_1=Cl, R_2=H
(A_3) R_1=C_2H_5, R_2=H	(B_3) R_1=H, R_2=Cl
(A_4) R_1= R_2= C_2H_5	(B_4) R_1=Br, R_2=H
(A_5) R_1=C_3 H_7, R_2=H	(B_5) R_1=H, R_2=Br
(A_6) R_1= R_2= C_3 H_7	(B_6) R_1=F, R_2=H

Fig. 3 – 1,2,3-thiadiazole systems.

The contour plots of the □-like frontier orbital for the ground state of the compound **B1** are shown in (Fig. 4). From the plots, we can observe that the HOMO mainly concentrates on S1 with some delocalization along N2-N3, whereas, the LUMO distributes over the whole molecule. These further demonstrate the existence of the delocalization of the conjugated □-electron system in the 4-cyano-1,2,3-thiadiazole molecule.[59]

The negative atomic charge on N2 and N3 has increased considerably for methyl, ethyl and propyl groups (Table 4) for the first series. The opposite was observed in cyanide group (Table 5) of the second series. As shown in Table 5, the carbon C4 has the highest positive charges (0.104) and (0.520) in the compound **A3** (4-ethyl-1,2,3-thiadiazole) from the first series and compound **B6** (4-fluoro-1,2.3,-thiadiazole) from the second series, respectively. These positions of C4 ATOMS with the highest positive charges lead to preferential sites of nucleophilic attack.



HOMO	LUMO

Fig. 4 – Π-like frontier molecular orbitals of the compound **B1**.

Table 3

Electronic parameters of 1,2,3-thiadiazole systems

Comp. ID	Compound structure	Heat of formation(kcal/mol)	HOMO (a.u.)	LUMO (a.u.)	ΔE (a.u.)	μ(D)
	1,2.3,-thiadiazole	59,77	-0,2745	-0,0654	0.2091	3,55
A1	4-methyl -1,2.3,-thiadiazole	51,46	-0,2691	-0,0596	0.2092	3,63
A2	4,5 -dimethyl -1,2.3,-thiadiazole	43,67	-0,2633	-0,0537	0.2093	4,32

Table 3 (continued)

A3	4-ethyl -1,2.3,-thiadiazole	45,34	-0,2684	-0,0588	0.2096	3,57
A4	4,5 -diethyl-1,2.3,-thiadiazole	31,80	-0,2612	-0,0518	0.2094	4,30
A5	4 -propyl -1,2.3,-thiadiazole	38,45	-0,2680	-0,0582	0.2098	3,55
A6	4,5 -dipropyl-1,2.3,-thiadiazole	17,97	-0,2602	0,0508	0.3110	4,36
B1	4-cyano-1,2.3,-thiadiazole	94,88	-0,3011	-0,0902	0.2109	4,69
B2	4-chloro -1,2.3,-thiadiazole	54,01	-0,2859	-0,0796	0.2063	3,36
B3	5-chloro-1.2.3-thiadiazole	54,75	-0,2834	-0,0749	0.2085	2,52
B4	4-bromo-1,2.3,-thiadiazole	64,30	-0,2858	-0,0797	0.2061	3,31
B5	5-bromo-1.2.3-thiadiazole	63,89	-0,2825	-0,0747	0.2078	2,67
B6	4-fluoro-1,2.3,-thiadiazole	20,37	-0,2899	-0,0862	0.2037	3,46

Table 4

NBO charges of 1,2,3-thiadiazole systems (series 1)

Comp.	T	A1	A2	A3	A4	A5	A6
S1	0,589	0,588	0,593	0,585	0,582	0,585	0,582
N2	-0,354	0,352	-0,364	-0,353	-0,359	-0,353	-0,360
N3	-0,198	-0,209	-0,209	-0,209	-0,209	-0,208	-0,208
C4	-0,072	0,099	0,089	0,104	0,094	0,096	0,097
C5	-0,425	-0,425	-0,224	-0,421	-0,211	-0,420	-0,205
C-methyl-4	-	-0,595	-0,600	-	-	-	-
C-methyl-5	-	-	-0,596	-	-	-	-
C-ethyl-4	-	-	-	-0,405	-0,403	-	-
C-ethyl-5	-	-	-	-	-0,413	-	-
C-propyl-4	-	-	-	-	-	-0,404	-0,402
C-propyl-5	-	-	-	-	-	-	-0,411

Table 5

NBO charges of 1,2,3-thiadiazole systems (series 2)

Comp.	T	B1	B2	B3	B4	B5	B6
S1	0,589	0,628	0,623	0,613	0,623	0,625	0,633
N2	-0,354	-0,326	-0,346	-0,351	-0,346	-0,352	-0,355
N3	-0,198	-0,155	-0,213	-0,189	-0,215	-0,189	-0,235
C4	-0,072	-0,036	0,055	-0,091	0,006	-0,091	0,520
C5	-0,425	-0,363	-0,437	-0,309	-0,438	-0,391	-0,491
chloro -4	-	-	0,065	-	-	-	-
chloro-5	-	-	-	0,100	-	-	-
C-cyamide-4	-	0,265	-	-	-	-	-
N-cyamide-4	-	-0,269	-	-	-	-	-
bromo-4	-	-	-	-	0,129	-	-
bromo-5	-	-	-	-	-	0,172	-
fluoro-4	-	-	-	-	-	-	-0,320

DRUG LIKENESS SCORING OF 1,2,3-THIADIAZOLE DERIVATIVES

In this part, we have applied rules of thumb and calculated metrics on twenty-one derivatives of 1,2,3-thiadiazole (Fig.5) with respect to their VEGFR-2/KDR kinase inhibition activity (pIC_{50}).[6] The properties involved are: partition coefficient octanol/water (logP), molecular weight (MW), hydrogen bond donors (HBD), hydrogen bond acceptors (HBA), number of rotatable bonds (NRB), polar surface area (PSA), Ligand efficiency (LE) and Lipophilic efficiency (LipE). The results using HyperChem 8.0.8 and MarvinSketch 6.2.1 software are shown in Table 6. At first, we have studied Lipinski and Veber rules to identify "drug-like" compounds. Rich absorption or permeability is more likely when:[13,14]

(1) There are less than 5 H-bond donors (expressed as the sum of OHs and NHs).

(2) The molecular weight is under 500 DA.

(3) The logP is under 5.

(4) There are less than 10 H-bond acceptors (expressed as the sum of Ns and Os).

(5) Rotatable bonds are under 10.

(6) Polar surface area is under 140 $Å^2$.

We used the Lipinski's rules to identify compounds with problems of absorption and permeability if these compounds do not validate at least two of its rules.[60] In addition, Veber's rules

suggest that molecular flexibility and polar surface area (PSA) are important to determine the oral bioavailability.[14]

Lipinski and Veber rules are based on a strong physicochemical rationale. Hydrogen bonds increase solubility in water and help the water-soluble molecules of low molecular weight to pass through the aqueous pores of biological membranes with passive diffusion. Table 6 shows that all the studied derivatives are compatible with rules number (**1**) and (**4**). Therefore, it is possible to say that they are less polar and more absorbed. Molecular weight (MW) is related to the size of the molecule, with its increasing, a larger cavity should be formed in water to solubilize the compound.[61] It exists an inverse relationship between MW and the compound concentration at the surface of the intestinal epithelium and its absorption. The fact that the size will rise creates obstacles such as preventing passive diffusion through the tightly packed aliphatic side chains of the bilayer membrane. We have all series compounds of 1,2,3-thiadiazole derivatives with molecular weights less than 500 Da (rule number **2**), so they are probably soluble and easily pass through cell membranes. However the increasing logP decreases aqueous solubility, which minimizes absorption. Consequently, membrane transporters can either reinforce or reduce compound absorption by either active uptake transport or efflux, respectively. 1,2,3-Thiadiazole derivatives satisfy also the rule number (**3**) thus these compounds could have a good solubility in aqueous and lipidic solutions.[16]

It is well known that high oral bioavailability is a significant factor for the progress of bioactive molecules as therapeutic agents. Reduced molecular flexibility (measured by the number of rotatable bonds) and low polar surface areas are found to be important predictors of good oral bioavailability.[62,63] Whereas, rotatable bonds and polar surface area tend to increase with molecular weight may in part explain the success of these two parameters in predicting the oral bioavailability and the transport across membranes.

The number of rotatable bonds (NRB) was defined as any single bond, not in a ring, bound to a heavy atom (non-hydrogen). Excluded from the count the amide bonds (C–N), because of their high rotational energy barrier.[14] The low number of rotatable bonds (reduced flexibility) in the studied series indicates that these ligands upon binding to a protein change their conformation only slightly. On the other hand, the polar surface area (PSA) is formed by polar atoms of a molecule. It is a descriptor that shows good correlation with passive molecular transport through membranes, and so allows estimation of transport properties of drugs. In the studied series of 1,2,3-thiadiazole derivatives, the very high values of PSA result in worsening of the absorption of a drug. Indeed, all the 21 molecules with PSA values between 75 and 140, belong to the compounds with reduced absorption (Table 6).

In the second part, we have studied the Ligand Efficiency (LE) to penalize large compounds over small compounds with similar potency because larger compounds tend to have poorer physicochemical and ADME properties.[64,65] In addition, we have studied Lipophilic Efficiency (LipE) to maximize potency while maintaining as low as possible the lipophilicity, due to the association between high lipophilicity and several issues including poor solubility, membrane permeation, metabolic stability, etc.[66,67] Ligand efficiency (LE) and Lipophilicity efficiency (LipE) are defined as follows:

$$LE = 1.4\, pIC_{50} / NH \quad (1)$$

$$LipE = pIC_{50} - logP \quad (2)$$

where*: NH* is the number of heavy atoms.

Following to the kinase inhibitor activity of the 1,2,3-thiadiazole derivatives series, high LE favors compounds that have the affinity-based selection and optimization towards smaller ligands. Our focus directed towards the generation of compounds that employ their atoms most efficiently. As regards LipE, it chooses compounds that gain a lot of their affinity through directed interactions, thus making the interaction with the receptor more specific. While one can say that LipE shows how efficient a Ligand exploits its lipophilicity, no explicit measure of molecular size is exploited.

From the results obtained in Table 6 the compound **3** has the highest LE (0.493) with pIC_{50} (8.097). However, the compound **1**, which has the highest pIC_{50} (8.222) and its LE (0.460) lower than compound **3**. As lipophilicity is the major factor for the promiscuity of compounds, LipE optimized compounds should be more selective. It is suggested to target a LipE in a range of 5–7 or even higher.[68] In the series studied LipE is changing during optimization (Table 6). From our results, we found that we have compounds **11**, **17**, **19** and **20** are in the range of 5-7. For the rest compounds, LipE is found to take values above the discussed range. From these molecules, the most hydrophilic is the compound **1**, which shows the highest LipE value.

The logP values of the compounds (**2**, **3**, **10** and **17**) are in the range of optimal values ($0<logP<3$) reach a LipE of (7.199, 7.857, 7.116 and 6.802) respectively. We can say that these compounds have

good oral bioavailability and an optimal biological activity. For logP too high the drug has a weak solubility and for logP too low the drug has difficulties to penetrate through lipidic membranes.[69]

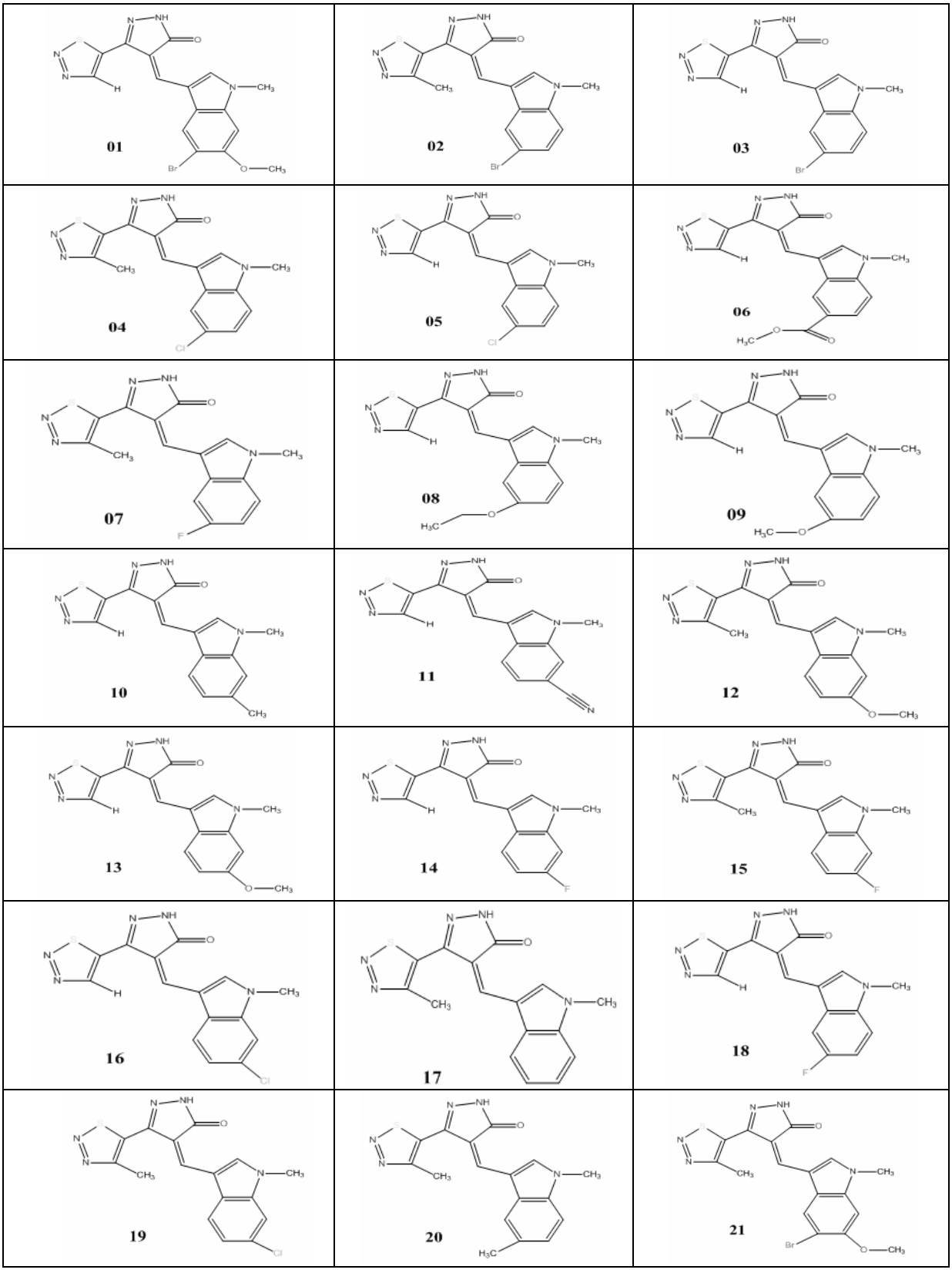


Fig. 5 – 2D structures of 1,2,3-thiadiazole derivatives.

Table 6

Inhibitory activities and properties involved in MPO method for

Comp	MW (a.u)	logP	NBD	NBA	Lipinski score of 4	NRB	PSA	PIC50	LE	LipE
1	418,27	-0,75	1	6	4	3	85,71	8,222	0,460	8,972
2	402,27	0,27	1	5	4	2	76,47	7,469	0,436	7,199
3	388,24	0,24	1	5	4	2	76,47	8,097	0,493	7,857
4	357,82	-0,01	1	5	4	2	76,47	7,347	0,429	7,357
5	343,79	-0,03	1	5	4	2	76,47	7,796	0,475	7,826
6	367,38	-0,40	1	5	4	4	102,78	7,658	0,412	8,058
7	341,36	-0,39	1	5	4	2	76,47	6,863	0,400	7,253
8	353,40	-0,46	1	5	4	4	85,71	7,602	0,426	8,062
9	339,37	-0,81	1	5	4	3	85,71	7,886	0,460	8,696
10	323,37	0,34	1	4	4	2	76,47	7,456	0,454	7,116
11	334,35	-0,09	1	5	4	2	100,26	6,759	0,394	6,849
12	353,40	-0,78	1	5	4	3	85,71	7,046	0,395	7,826
13	339,37	-0,81	1	5	4	3	85,71	7,553	0,441	8,363
14	327,34	-0,41	1	5	4	2	76,47	7,319	0,446	7,729
15	341,36	-0,39	1	5	4	2	76,47	7,004	0,409	7,394
16	343,79	-0,03	1	5	4	2	76,47	7,469	0,455	7,499
17	323,37	0,22	1	4	4	2	76,47	7,022	0,427	6,802
18	327,34	-0,41	1	5	4	2	76,47	7,796	0,475	8,206
19	357,82	-0,01	1	5	4	2	76,47	6,818	0,398	6,828
20	337,40	0,37	1	4	4	2	76,47	7,237	0,422	6,867
21	432,29	-0,73	1	6	4	3	85,71	7,638	0,411	8,388

PSA, NRB calculated by Molinspiration

STRUCTURE ACTIVITY/PROPERTY RELATIONSHIP FOR 1,2,3-THIADIAZOLE DERIVATIVES

For the series of 1,2,3-thiadiazole derivatives (Fig. 5) we have studied seven physicochemical properties with respecting their kinase inhibitory activity.[6] The involved properties are: Surface area grid (SAG), molar volume (V), hydration energy (HE), partition coefficient octanol/water (logP), molar refractivity (MR), polarizability (Pol) and molecular weight (MW). The results using HyperChem 8.0.8 software are shown in Tables 6 and 7.[70,71] From the results obtained in Tables 6 and 7 the molecular refractivity and polarizability increases proportionally with the molecular weight of 1,2,3-thiadiazole derivatives. This explains the accordance of our results with Lorentz- Lorenz expression.[72-75] This relation shows that the molecular refractivity and polarizability increase with the volume and molecular weight, for example, the compound **21** (with bulky substituents which are Br and OCH_3) has highest values of molecular refractivity and polarizability (115.71$Å^3$), (39.77$Å^3$), respectively, while the compounds **14** and **18** which are the smallest molecules have the smallest values of the molecular refractivity (96.14$Å^3$) and polarizability (32.74$Å^3$). We have also noticed that the volume and the surface of distribution of our molecules are different, we found that the volume of compound **21** takes the biggest value (1007.47$Å^3$) and compound **14** the smallest one (837.66 $Å^3$), and the surface of compound **21** also is bigger (591.89A^2) than the one of compound **14** (505.35 A^2).

The highest value of hydration energy is of the compound **11** (21.74 Kcal/mol) and the smallest value is of the compound **20** (14.59 Kcal/mol). In the biological environments the polar molecules are surrounded by water molecules. They are establishing hydrogen bonds between them. Hydrophobic groups in 1,2,3-thiadiazole derivatives induce a decrease of hydration energy, however, the presence of hydrophilic groups as in compound **11** "1-methyl-3-{(z)-[5-oxo-3-(1,2,3-thiadiazol-5-yl)-1,5-dihydro-4H-pyrazol-4-ylidene]methyl}-1H-indole-6-carbonitrile" (Fig.7) possessing one (HBD) hydrogen bond donors (NH) and four (HBA) hydrogen bond acceptors (three N and one O), result in the increase of the hydration energy. Otherwise, the lipophilicity increases proportionally with the hydrophobic features of

substituent. As seen in Tables 6 and 7 the compound **20** has the highest value of hydration energy (-14.59 kcal/mol) and the highest value of logP (0.37). The results obtained by calculating logP of 1,2,3- thiadiazole derivatives show that the compounds **9** and **13** present small coefficients of lipophilicity (−0.81) and (−0.81) respectively. Although these molecules should have a good permeability because of their small molecular weights,[76] these compounds provide a good solubility and a weaker absorption and penetration in cellular membranes, caused by the weaker permeability of the passive diffusion.

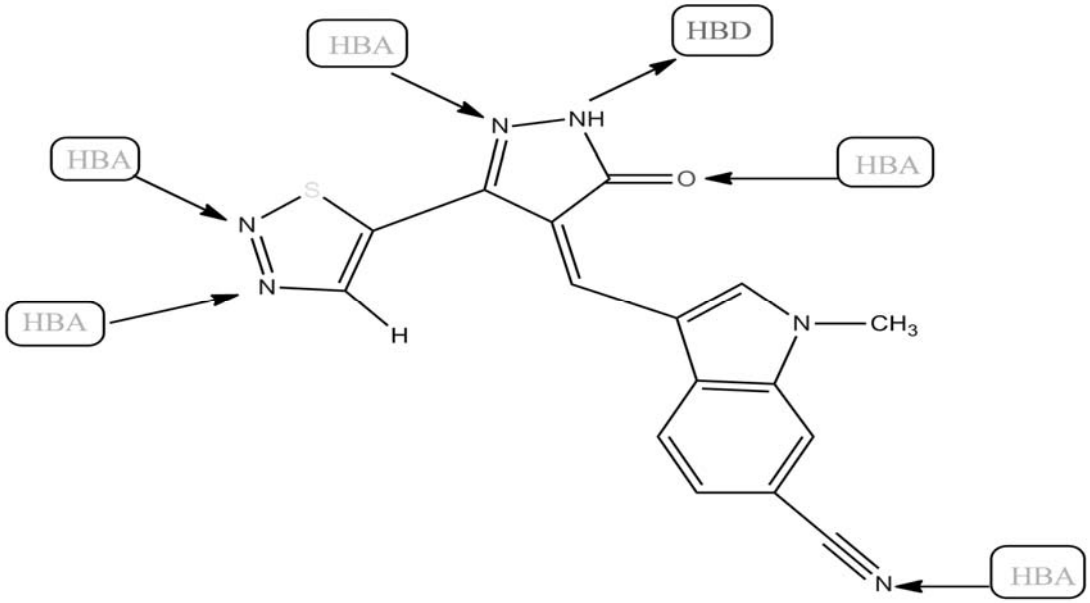


Fig. 7 – Donor and acceptor sites of compound **11**"1-methyl-3-{(z)-[5-oxo-3-(1,2,3-thiadiazol-5-yl)-1,5-dihydro-4H-pyrazol-4-ylidene]methyl}-1H-indole-6-carbonitrile".

Table 7

Physicochemical properties of 1,2,3-thiadiazole derivatives

Comp.	Molecular Volume (A^3)	Molecular Surface (A^2)	Molecular Mass (Amu)	logP	Hydration Energy (Kcal/Mol)	Polarizability (A^3)	Refractivity (A^3)
1	956,31	563,96	418,27	-0,75	-18,08	37,93	109,92
2	934,98	549,86	402,27	0,27	-15,33	37,29	109,33
3	882,33	522,97	388,24	0,24	-17,12	35,46	103,55
4	910,06	539,38	357,82	-0,01	-15,37	36,60	106,52
5	864,81	513,68	343,79	-0,03	-17,14	34,76	100,73
6	959,32	570,97	367,38	-0,40	-17,80	37,23	106,78
7	884,01	524,81	341,36	-0,39	-15,39	34,58	101,93
8	955,67	589,85	353,40	-0,46	-17,85	37,14	107,13
9	898,19	535,05	339,37	-0,81	-18,68	35,31	102,39
10	874,56	520,83	323,37	0,34	-16,35	34,67	100,29
11	885,63	533,96	334,35	-0,09	-21,74	34,69	100,99
12	942,86	559,26	353,40	-0,78	-17,32	37,14	108,17
13	899,33	534,89	339,37	-0,81	-19,09	35,31	102,39
14	837,66	505,35	327,34	-0,41	-17,25	32,74	96,14
15	885,12	525,93	341,36	-0,39	-15,40	34,58	101,93
16	865,82	515,36	343,79	-0,03	-17,15	34,76	100,73
17	876,07	524,17	323,37	0,22	-15,63	34,67	101,80
18	837,77	505,44	327,34	-0,41	-17,24	32,74	96,14
19	917,75	544,27	357,82	-0,01	-15,36	36,60	106,52
20	925,25	545,19	337,40	0,37	-14,59	36,50	106,08
21	1007.47	591,89	432,29	-0,73	-16,29	39,77	115,71

CONCLUSION

Different *ab initio* calculation methods have been performed for 21 derivatives of 1,2,3-thiadiazole ring and the resulted structural data have been compared with experimental data. The best agreement was obtained by the DFT/B3LYP method. The influence of radical substitution in R_1 and R_2 positions of 1,2,3-thiadiazole was studied through electron-donating and attracting groups. Thereafter, this search emphasizes on the study of molecular geometry and electronic properties, which are considered as the responsible for binding of a drug to various active sites of the target protein (VEGFR-2/KDR). This permits to expect the impact of some structural modifications on the biological activity. Moreover, this study provides the capacity to guide design and selection in order to fast identify compounds from the 1,2,3-thiadiazole derivatives series which are mostly to achieve outcome in the clinic and make a considerable profit. As well, it's allowed to discuss different approximations of the structure activity/property relationship, in order to find the favorites conformations and comparing them with the kinase inhibitory activities of 1,2,3-thiadiazole derivatives. This permitted to create a correlation between structural parameters and various properties of the investigated molecules in order to ameliorate the concept of new therapeutic drugs.

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