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Dedicated to Niculae I. Ionescu PhD
on the occasion of his 85th anniversary

COMPUTATIONAL ELECTRONIC PROFILE OF THE INSECTICIDE IMIDACLOPRID AND ANALOGUES

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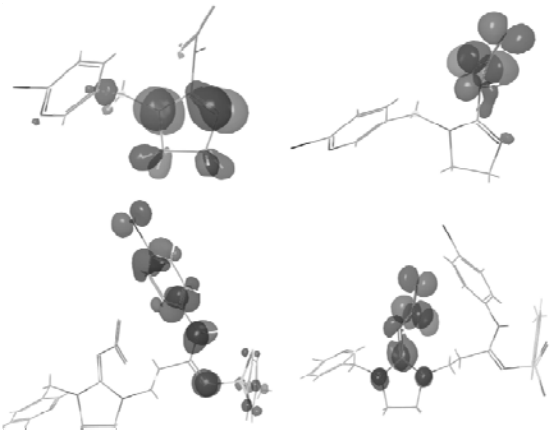
Neonicotinoids, a class of neuro-active insecticides acting on the nicotinic acetylcholine receptors (nAChRs), are of great interest because of their high efficiency, low toxicity, broad insecticidal spectra and unique mode of action. The nAChRs ligands available on the market are involved in various pharmacological and pathophysiological processes.
In this study, the molecular structures of imidacloprid, sulfoxaflor, and two analogues were investigated by means of Density Functional Theory and semiempirical quantum chemical methods including Austin Model 1 (AM1), Parametric-Method number 3 (PM3), and Re-parametrization of AM1 (RM1). In order to identify the key structural features responsible for the insecticidal activity, the electronic parameters (heat of formation, molecular electrostatic potential, reactivity Fukui indices, HOMO and LUMO energies) and ADME profiles were computed and analyzed for all neonicotinoids. The computation's outcome supports the experimental evidence regarding the importance of substituents and their positions at the heterocyclic rings for the insecticidal activity.



INTRODUCTION

The discovery of neonicotinoids, an important family of insecticides, represents a key achievement in agrochemical research domain and environmental protection.[1] Since their discovery, in the 1980s, and introduction of imidacloprid in 1990s, have attracted considerable attention due to their high efficiency, low mammalian toxicity, broad insecticidal spectra and versatile application methods.[2] Following the imidacloprid development, new compounds such as acetamiprid, clothianidin, nitenpyram, thiacloprid, thiamethoxam, dinotefuran have been certified as agricultural insecticides.[3] All neonicotinoids act as agonists on their molecular target, the nicotinic acetylcholine receptor (nAChR), having important applications in crop protection and animal health.[4] The problem of significant increases in resistance and detrimental effect on agriculture productivity urged the development of novel neonicotinoid candidates with new chemical structure, mode of action and improved insecticidal activity.[5-7] Generally, the

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chemical structure of the neonicotinoids shares several common molecular features such as (i) five/six-membered ring or non-cyclic systems, (ii) guanidine or amidine cycle, (iii) electron withdrawing group (*e.g.* nitro or ciano group). The subclass of the N-nitroguanidine derivatives is the most prominent one accounting approximately 85% of the neonicotinoid insecticide market. Imidacloprid remains the forerunner of this class and the best-selling ambassador. It is well known and experimented that small modifications to the chemical structure of the neonicotinoids could lead to significant modifications in their insecticidal activity. Likewise, modification of the structure can be an adequate strategy to overcome resistance. These affirmations are sustained by several experimental and theoretical studies.[8-11] More specifically, several articles reported that small modifications of the bioactive functional fragments or skeleton of the imidacloprid could improve or change the biological activity of the chemicals.[12,13] Subsequent modification in neonicotinoid chemical structures conducted to a new class of acyclic neonicotinoids from which sulfoxaflor compound emerged as an appropriate alternative to overcome drawbacks of imidacloprid.[14,15] In this context, computational chemistry in conjunction with experimental information represents valuable tools for understanding the structural factors involved in the insecticidal activity, selectivity, and diversity of neonicotinoid actions. The computational methods help to predict compound properties economically, to provide appropriate molecular geometries, and accurate structural information.[16-18] Owing to the neonicotinoids importance in agriculture and environmental health, a better understanding of their structures, their reactivity and chemical properties in addition to the mechanisms of action appears essential to create novel insecticide agents with the improved physicochemical profile.

The aim of the present research is to extend the experimental observations regarding the insecticidal activity of imidacloprid and its analogues, through a theoretical study of the electronic and structural parameters through semi-empirical quantum chemical methods including Austin Model 1 (AM1), Parametric-Method Number 3 (PM3), Re-parametrization of AM1 (RM1) and density functional theory (DFT/B3LYP). Imidacloprid (1), sulfoxaflor (2), compounds (3), and (4) (Fig. 1) were selected owing to their distinct chemical features and different insecticidal activity. In order to identify the key structural features responsible for the insecticidal activity, the electronic parameters (*e.g.* heat of formation, molecular electrostatic potential, reactivity Fukui indices, HOMO and LUMO energies, chemical hardness, electrophilicity, etc.) were computed and analyzed for all neonicotinoids. The outcomes of the present research are expected to be useful for understanding the key features by which these compounds act and can be further utilized to obtain agents with improved insecticidal activity by rational modifications.

COMPUTATIONAL DETAILS

Molecular geometry optimization. We optimized the geometries of the **1** (imidacloprid), **2** (sulfoxaflor), **3** and **4** molecules (Fig.1) using the following protocol: (i) the 3D geometries selected from PubChem database were optimized at semiempirical level using AM1, PM3 and RM1 methods and (ii) were further used for DFT calculations. Thus, we carried out complete optimization of the preoptimized RM1 structures by applying hybrid DFT with B3LYP (Becke, three-parameter, Lee-YangParr) exchange-correlation functional and using the basis set 6-31G(d,p) level to calculate the electronic properties of the investigated compounds.[19,20] Each geometry was confirmed as true minimum energy structure by the absence of any imaginary frequencies. All semiempirical and DFT calculations were carried out using semiempirical NDDO[21] and Jaguar[22] modules of Schrodinger software.

Computation of electronic parameters. Density functional theory was employed to calculate electronic properties of the studied neonicotionid molecules, such as heat of formation (ΔH_f^{θ}), HOMO-LUMO energies, ionization potential (IP), electron affinity (EA), electronegativity (χ), chemical potential (μ), global hardness (η), softness (S), electrophilicity (ω) and the Fukui indices. These global descriptors are used to describe reliably the reactive behavior of the molecules.

ΔH_f^{θ} represents an important indicator regarding the thermodynamic stability or instability of a molecule. High negative values of ΔH_f^{θ} indicate a very stable molecule and slightly negative or positive values indicate a relatively unstable molecule.[23]

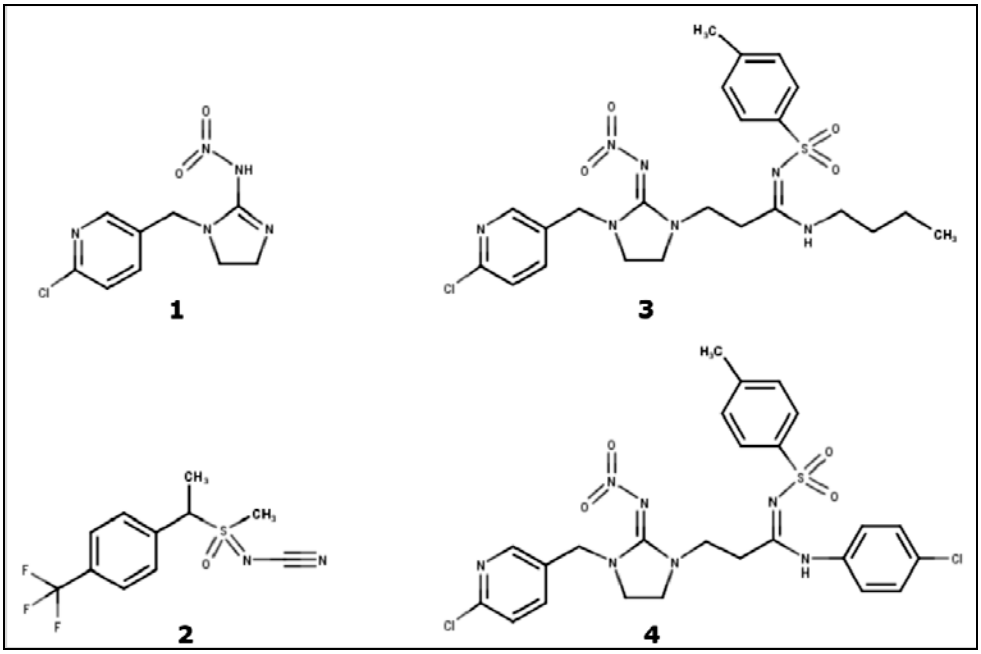

Fig. 1 – Chemical structures of the four insecticides **1** (imidacloprid, IMI), **2** (sulfoxaflor), **3** ((Z)-N-butyl-3-[(2Z)-3-[(6-chloropyridin-3-yl)methyl]-2-(nitroimino)imidazolidin-1-yl]-N'-(4-methylbenzenesulfonyl)propanimidamide), **4** ((Z)-N-(4-chlorophenyl)-3-[(2Z)-3-[(6-chloropyridin-3-yl)methyl]-2-(nitroimino)imidazolidin-1-yl]-N'-(4-methylbenzenesulfonyl)propanimidamide).

The highest occupied molecular orbital (HOMO) and the lowest unoccupied molecular orbital (LUMO) play an important role in the chemical reactivity of a molecule and suggest the electron-donating or electron-affinity capacity of a molecule. The other two parameters, ionization potential (IP, eq.1) and electron affinity (EA, eq.2), can estimate the same predisposition of a molecule. The HOMO-LUMO gap, calculated as the energy difference between HOMO and LUMO orbitals, is also an important stability and chemical reactivity indicator.[24,25]

Chemical potential (μ, eq.3) measures the tendency of a particle to diffuse.[26] Electronegativity (χ, eq.4), the negative of chemical potential, describes the tendency of an atom to attract electrons (or electron density) towards itself.[26] The global hardness (η, eq. 5) corresponds to the gap between the occupied and unoccupied orbitals. The larger is the HOMO-LUMO energy gap the harder the molecule. The inverse of hardness is defined as softness, (S, eq.6).[27,28] The electrophilicity index (ω, eq.7) measures the propensity of a species to accept electrons. The larger value of ω indicates higher reactivity of the chemical system.[29] Atomic Fukui indices or reactivity indices specify which atoms in a molecule are more likely to undergo a nucleophilic (high positive value of Fukui for LUMO) or an electrophilic attack (high positive value of Fukui for HOMO). This affirmation is equivalent with the tendency of an atom to either loose or accept an electron.[30,31] The calculated values are compared with the available experimental data for the investigated molecules.

The global descriptors were computed according to the equations:

$$IP = -E_{HOMO} \quad (1)$$

$$EA = -E_{LUMO} \quad (2)$$

$$\mu = -\frac{IP+EA}{2} = \frac{E_{HOMO}+E_{LUMO}}{2} \quad (3)$$

$$\chi = \frac{IP+EA}{2} = -\frac{E_{HOMO}+E_{LUMO}}{2} \quad (4)$$

$$\eta = IP - EA = E_{LUMO} - E_{HOMO} \quad (5)$$

$$S = \frac{1}{\eta} \quad (6)$$

$$\omega = \frac{\mu^2}{2\eta} \quad (7)$$

ADME profile estimation. The ADMET properties (Absorption, Distribution, Metabolism, Excretion, and Toxicity) are important key players in the drug development process. By calculating these properties it is ensured that compounds with poor ADMET properties are eliminated and, also, the research and development costs of the drug

development process are reduced. The ADME profile of all four insecticides was computed using QikProp[32] tool of Schrodinger package. The QikProp[32] predicts a relevant number of descriptors and pharmaceutical properties such as molecular weight (MW), QPlogPo/w, QPlogS, QPlogHERG, QPPCaco, QPlogBB, QPlogKp, QPPMDCK, the percent human oral absorption (%HOA), and the polar surface area (PSA) (Table 2).

RESULTS AND DISCUSSION

In the following part of the manuscript, the electronic features of the titled neonicotinoids obtained through semiempirical and DFT calculations are presented and analyzed in conjunction with the experimental information.

As can be seen from Table 1, the heat of formation energies obtained from all the applied semiempirical methods are in the same range of values, excepting those from AM1 calculations. Neonicotinoids **1** and **4** are the compounds with the positive values of the heat of formation (case of the RM1 and PM3 methods) which indicates a low stability of the compounds that might rapidly react or decompose into their elements. All three semiempirical methods suggest sulfoxaflor (**2**) as being the most stable compound. Based on these observations, the trend for the stability of compounds is the following: 2>3>4>1. For superior DFT optimization, the RM1 preoptimized geometries were used. The electron donating or accepting capability of compounds is in accordance with the stability or instability trend. These compound capabilities can be also estimated by the HOMO and LUMO values. The high HOMO values of compounds **1** and **4** reflect a strong capability to donate electrons and therefore a high availability to react with an electrophilic molecule. The HOMO values mimic the tendency of the insecticidal activity of compounds **3** and **4** as determined by Wang *et al.*[33] From the experimental results, the insecticidal activity of compounds **1**, and **4** (LC50 of 0.08856mmol/L and 0.00895mmol/L) tested against *Aphis craccivora* suggested the compound **4** as being the most active and the compound **3** as less active ones. Both compounds showed superior insecticidal activity as compared with imidacloprid (LC50 of 0.03602mmol/L). The increased values of the insecticidal activity and of the HOMO value for compounds **4** may be due to the replacement of the alkyl chain (of compound **3**) with an aromatic ring. This tendency is also supported by the introduction of the second halogen atom into the molecule (as compared with compound **3**). The high influence of the halogens on the activity is confirmed by around 96% of the launched compounds on the market (herbicides, fungicides, insecticides/ acaricides and nematicides).[34] Imidacloprid (**1**) have the lowest LUMO values which recommended it as the most electrophilic compound from the titled insecticides and also the most reactive one toward nucleophiles attack. The higher values of LUMO energies for compound **4** suggest a low capacity to accept electrons. This low capacity to accept electrons is also sustained by the low values of the electronegativity and electrophilicity indexes. The band gap energy is related to the stability and the reactivity of the system. Compounds **1**, **3** and **4** have the lower values of ΔE comparing to the compounds **2**. In this case, the systems are highly reactive and with a great insecticidal activity.

Looking at Fig. 2, it can be observed that the HOMO frontier orbitals of the compounds **3** and **4** are mainly distributed on the $–N=SO_2-C_6H_5R$ region, while the LUMO frontier orbitals are allocated to the 4,5-dihydroimidazol-2-yl-nitramide system as for imidacloprid. The ESP plots of the compounds show that the negative contours (red shade or dark grey shade for black-white version, Fig 2. (E)) are distributed around electronegative atoms (S, F, Cl, CF3, the Ns of the imidazole ring) and nitro unit, indicating areas susceptible to the electrophilic attack. The positive contours (blue shade) are spread on the rest of the molecule suggesting that these regions are prone to the nucleophilic attack. The charge distribution plots are in accordance with the ESP plots showing that the S atom, the SO_2 and NO_2 units have an excess of negative charges (red shades; nucleophilic center) while the blue shades indicate units as CF_3 with charge deficiency (electrophilic center). The Fukui plots alongside with the Fukui indices values emphasize the significant atoms within the molecule. The Fukui graphic plots of compound **3** and **4** (Fig. 3) highlight the importance of the N atoms close to the SO_2 unit and the N atom of the nitro unit for the insecticidal activity. The well-known importance of the nitro unit for the insecticidal activity is also supported by the Fukui values of the corresponding atoms. In case of imidacloprid, all N atoms within the molecule contributed equally to the insecticidal activity.

Table 1

The computed electronic features heat of formation (ΔH_f^{θ}), HOMO and LUMO energies, gap energy (ΔE), chemical potential (μ), electronic hardness (η), global softness (S), electronegativity (χ) and electrophilicity index (ω), for all four insecticides

Parameters		Compounds			
		1 (imidacloprid)	2 (sulfoxaflor)	3	4
ΔH_f^{θ} (kcal/mol)	AM1	102.26	-96.86	48.94	95.52
	RM1	63.361	-122.25	-22.6	12.26
	PM3	55.857	-96.85	-11.41	29.28
(eV)	E_{HOMO}	-6.309	-6.847	-6.479	-6.418
	E_{LUMO}	-2.060	-1.722	-1.721	-1.598
	ΔE	4.249	5.125	4.758	4.820
	IP	6.309	6.847	6.479	6.418
	EA	2.060	1.722	1.721	1.598
	χ	4.185	4.285	4.100	4.008
	η	4.249	5.125	4.758	4.820
	S	0.235	0.195	0.210	0.207
	μ	-4.185	-4.285	-4.100	-4.008
	ω	2.061	1.791	1.766	1.666

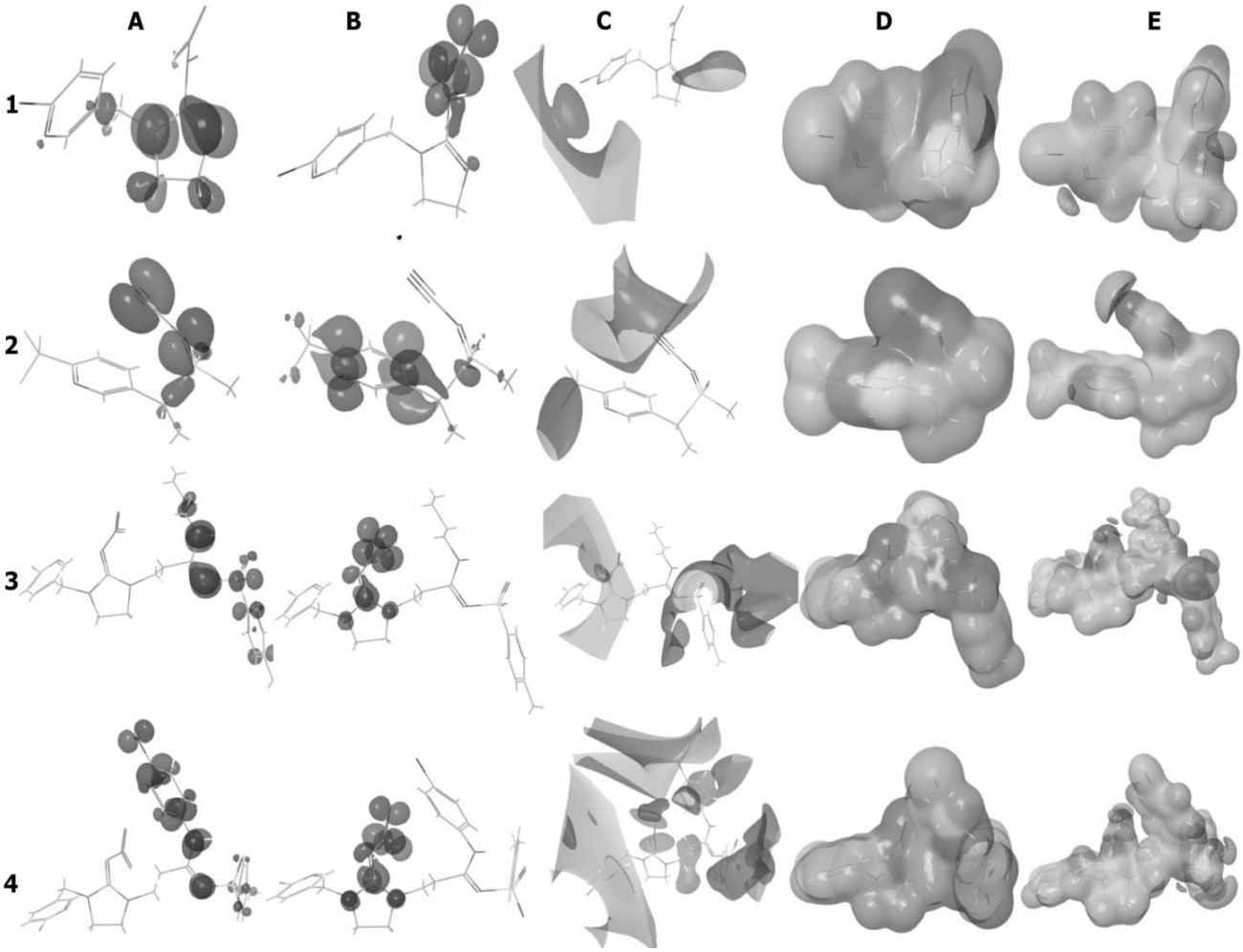

Fig. 2 –The three dimensional HOMOs (A) and LUMOs orbitals (B), average local ionization energy (C), charge distributions (D) and electrostatic potential profiles (E) plots of the four insecticides.

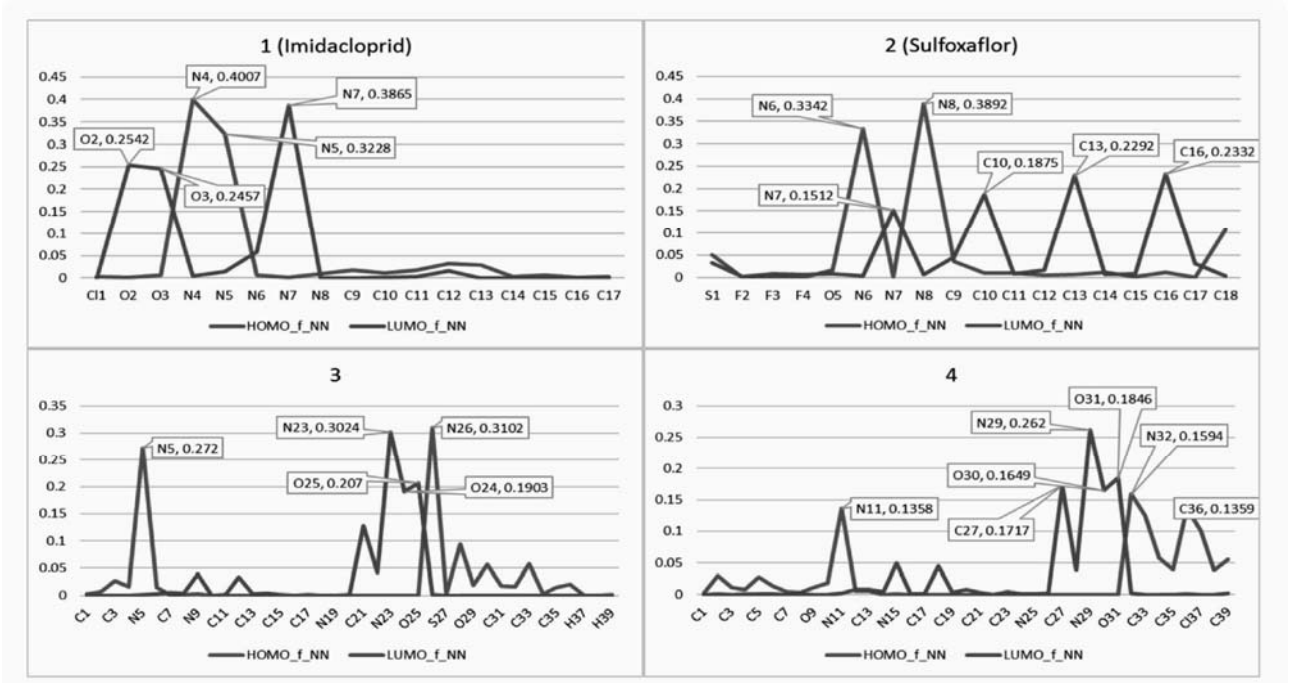

Fig. 3 – The Fukui plots of all four insecticides which emphasize the significant atoms within the molecule.

Table 2

The predicted ADME parameters or all four insecticides using QikProp module

Parameter*	Compound			
	1 (imidacloprid)	**2** (sulfoxaflor)	**3**	**4**
N atom	5	3	7	7
O atom	2	1	4	4
Cl atom	0	0	1	2
F atom	0	3	0	0
MW	255.663	277.264	536.047	590.483
PSA	91.617	70.099	143.644	143.79
%HOA	76.884	55.824	65.146	70.256
QPlogPo/w	0.932	0.686	4.341	4.978
QPlogS	-2.320	-0.004	-6.301	-6.837
ClQPlogS	-2.619	-1.842	-6.708	-8.224
QPlogHERG	-3.884	-3.907	-6.728	-7.139
QPPCaco	305.675	24.493	145.308	173.491
QPlogBB	-0.857	-0.475	-2.359	-1.899
QPPMDCK	346.735	1360.702	157.05	463.063
QPlogKp	-5.786	-3.166	-3.043	-2.640
LV	0	0	2	2

*where: MW: molecular weight; PSA: polar surface area (<140Å^2); %HOA: predicted human oral absorption on 0 to 100% scale, (acceptable range: <25% poor, >80% high); QPlogPo/w: predicted octanol-water partition coefficient, logP (acceptable range -2 to 6.5; QPlogS: the predicted aqueous solubility, logS; S in moldm^{-3} (acceptable range -6.5 to 0.5); QPlogHERG: the predicted IC50 value for blockage of HERG K^+ channels, (acceptable range: below -5); QPPCaco: predicted apparent Caco-2 cell permeability in nm/sec (acceptable range: <25 poor, >500 great); QPlogBB: predicted brain/blood partition coefficient (acceptable range: -3.0 to 1.2); QPMDCK: predicted cell permeability(acceptable range: <25 poor, >500 great); QPlogK_p: predicted skin permeability, log K_p (-8.0 to -1.0); LV: Lipinski's rule of five.

ADME profile estimation. The ADME parameters values (Table 2) have shown that two (compounds **3** and **4**) out of four compounds are defying some of the ADME properties. It is known that for a molecule to cross the blood-brain barrier and thus to act on the central nervous system of an insect, a PSA less than 90Å is required. So, the PSA values of the uncharged molecules **1** and **2** indicate their abilities to penetrate the insect BBB while the PSA values of the compounds **3** and **4**

denote the opposite action. The predicted values for compound's distribution and absorption showed that compounds **3** and **4** have exceeded the acceptable range of the cell and membrane permeability (values of QPlogHERG, QPlogS, and ClQPlogS). The same compounds did not meet two of the Lipinski's rule of five. The outcomes of the ADME descriptors in conjunction with the electronic parameters suggested that compounds **3** and **4** display improved profiles as compared with the imidacloprid.

CONCLUSIONS

In the present study, the molecular structures of imidacloprid, sulfoxaflor, and two analogues were investigated by means of the computational methods. The electronic parameters in conjunction with the ADME descriptors were computed to better describe the key structural features responsible for the insecticidal activity of the neonicotionids. As an important conclusion, the potency of the compounds depends significantly upon the nature and the position of the substituent at the aromatic ring. The nitro unit was suggested as indispensable for the insecticidal activity. The present conclusions will be helpful in the design of the new insecticides with the enhanced profile.

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