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Design of New Thiadiazole Derivatives with Improved Antidiabetic Activity

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Abstract

Diabetes is a serious, long-term (or chronic) disease that occurs when a person's blood sugar levels are high because their body cannot produce enough insulin, or does not produce enough insulin or that it cannot effectively use the insulin it produces. According to the literature, this disease has several causes, but certain types of diabetes such as type 2 diabetes are most closely linked to a metabolic disorder due to abdominal obesity. Thus, the number of individuals with type 2 diabetes is increasing. It is with this in mind that we work to improve human health. The aim of this study is to design new derivatives of 1,3,4-thiadiazole with improved antidiabetic activity by the mathematical model of multiple linear regression (MLR) established previously. The analysis of the effect on the substituents influencing the antidiabetic activity, fourteen (14) new molecules coded CDTH were generated and presenting values of the potential of inhibitory concentration higher than that of the base compound (pIC_{50} = 2.526). But thirteen (13) of these new compounds belong to the domain of applicability of the MLR model established previously. In addition, the thermodynamic quantities of formation formed at 298K have been calculated. Lipinski's rule and pharmacokinetic properties proved that five (5) (TH4, TH9, TH10, TH13 and TH14) new molecules can be used as diabetes medicine.

Keywords

Design, Antidiabetic Activity, 1,3,4-Thiadiazole, Lipinski's Rule

1. Introduction

Diabetes is one of the oldest diseases known to mankind whose devastating ef-

fect is increasing day by day and seriously to an epidemic level [1]. It is a disease of disordered carbohydrate metabolism, which also affects proteins and fats which are caused by the total or relative insufficiency of the action of insulin [2]. Today, more than 420 million people have diabetes worldwide. This number is estimated to increase to 570 million by 2030 and 700 million by 2045 [3]. The hyperglycemia seen in diabetes mellitus is the result of a mismatch between the amount of insulin needed to regulate metabolic processes and the amount of insulin secreted by β cells. Insulin treatment is the mainstay of patients with type 1 diabetes mellitus, while dietary and lifestyle modifications are the mainstay of the treatment and management of type 2 diabetes mellitus in his beginnings. Insulin is also important in type 2 diabetes mellitus when blood sugar levels cannot be controlled by diet, weight loss, exercise, and oral medications [4]. Most diabetic patients have type 2 diabetes. Simple lifestyle changes can prevent or delay the onset of type 2 diabetes and its complications. In addition to these preventions, there are Oral Antidiabetics (OAD) that affected patients use. Despite these preventions and treatments, there is resistance to this disease. It is therefore urgent to find new molecules with new mechanisms of action to meet these needs. Thus, in their work Pattan *et al.* [5] also showed that 1,3,4-thiadiazoles exhibit antidiabetic activity. In addition, 1,3,4-thiadiazole and derivatives possess a wide range of therapeutic activities like antimicrobial [6], antifungal, diuretic, antiulcer [7], antimycobacterial [8], antioxidant/radioprotective [9], anti-inflammatory, anticonvulsant, antidepressant, anticancer, anti-leshmanic [10] [11]. To do so, the scientific community is moving towards new research methods that consist in predicting the activities of molecules even before they are synthesized. These modeling methods have been recommended by the Organization for Economic Cooperation and Development (OECD) in the design of new molecules with therapeutic properties [12]. This approach is increasingly used to reduce the excessive number of experiments, which are sometimes long, dangerous and costly in terms of time and finance [13] [14]. As part of our work, the mathematical model of multiple linear regression (MLR) and the domain of applicability (DA) previously established [15] by the Quantitative Structure-Activity Relationship were used. The general objective of this work is to use the mathematical model established by Dou *et al.* [15] to design new antidiabetic derivatives of 1,3,4-thiadiazole within the scope of applicability.

2. Materials and Methods

2.1. Computer Aided Design

The new approach, known as Fragment-Based Drug Design (FBDD), or FBDD, appeared in the late 1990s in pharmaceutical research [16] [17] [18]. This approach involves the screening of organic molecules of very low molecular mass, the fragment molecules. The latter are distinguished from molecules traditionally present in the chemical libraries of pharmaceutical companies and academic laboratories by their low molecular complexity and their moderate size. Frag-

ment molecules can in fact be considered as fractions of molecules commonly called "lead-like" and "drug-like", used for high-throughput screening campaigns.

2.2. Basic Structure

Figure 1 below is the molecular structure of 1,3,4-thiadiazole (TH) which was used for modeling.

2.3. Molecular Model

The equation and the statistical parameters of the model established by Dou *et al.* [15] are presented below:

$$\begin{aligned} \mathrm{pIC}_{50} = &-11.36472 + 0.18089 * \alpha(\text{S-C-N}) - 5.70651 * I(\text{C=N}) \\ &+ 0.02973 * \mu(\text{D}) - 0.40993 * \Delta S_f^0 \end{aligned} \quad (1)$$

This equation will be used to predict the antidiabetic activity of new 1,3,4-thiadiazole derivatives.

2.4. Structures Selected

The effects of substituents on the antidiabetic activity of the molecules were studied in order to detect the substituents which influence the pIC_{50}. The approach adopted is as follows:

- ✓ Classification of 1,3,4-thiadiazole derivatives in decreasing order of pIC_{50};
- ✓ Identification of substituents of molecules with the highest pIC_{50} values.

Thus, by ranking all the 1,3,4-thiadiazole derivatives in decreasing order of the potential for inhibiting antidiabetic activity (pIC_{50}), the first five (5) were selected. Those compounds with the best values of antidiabetic activity will serve as the basic structure for the design. Table 1 includes the 2D structures of these molecules and the pIC_{50} values.

2.5. Thermodynamic Quantities of Formation

The calculation of the thermodynamic quantities of the molecules was carried out from optimization and calculation of the frequencies at the level of theory DFT/B3LYP/6-31+G (d, p) [19] [20] [21]. The quantities such as the variation of entropy, the variation of enthalpy and the variation of the free enthalpy of formation of the new derivatives of antimalarial activity were determined by means of the following formulas proposed by Otchersky *et al.* [22].

$$\Delta H_f^0(M,0K) = \sum_{atoms} x\Delta H_f^0(X,0K) - \sum D_0 \quad (2)$$

$$\begin{aligned} \Delta H_f^0(M,298K) = &\Delta H_f^0(M,0K) + \left(H_M^0(298K) - H_M^0(0K)\right) \\ &- \sum_{atoms} x\left(H_X^0(298K) - H_X^0(0K)\right) \end{aligned} \quad (3)$$

Avec:

$$\sum D_0 = \sum x\varepsilon_0 - \varepsilon_0(M) - \varepsilon_{ZPE} \quad (4)$$

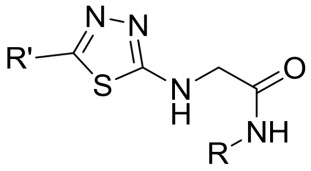
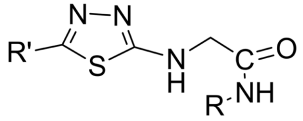
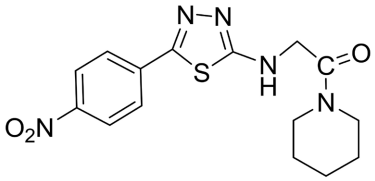
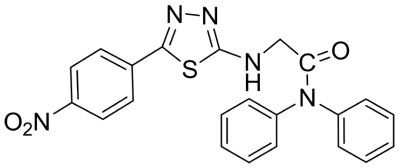
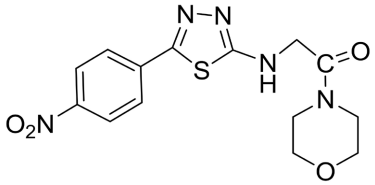
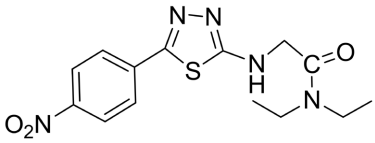
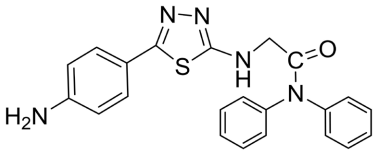


Figure 1. Common structure of 1,3,4-thiadiazole (TH) molecules.

Table 1. 2D structure of the five selected 1,3,4-thiadiazole derivatives.

N°	Common structure	pIC_{50} exp
		
1		2.526
2		2.524
3		2.387
4		2.320
5		2.376

$\sum D_0$: Atomization energy;

$\varepsilon_0(M)$: Total energy of the molecule;

ε_{ZPE} : Energy of the zero point of the molecule;

$H_X^0(298K)-H_X^0(0K)$: Enthalpy corrections of atomic elements. These values are included in Janaf's table [23];

$H_M^0(298K)-H_M^0(0K)=H_{corr}-\varepsilon_{ZPE}(M)$: Molecule enthalpy correction;

H_{corr} : Thermal correction enthalpy.

$$\Delta S_f^0(M,298K)=S_M-\sum_{atoms} x\Delta S(298K) \tag{5}$$

x : Number of Atoms of X in the Molecule

$$\Delta G_f^0(M,298K) = \Delta H_f^0(M,298K) - T\Delta S_f^0(M,298K) \quad (6)$$

2.6. Lipinski's Rules (Rule of Five)

Lipinski defined a set of rules for estimating the oral bioavailability of a compound from its two-dimensional (2D) structure. These rules concerning physico-chemical activities were defined after the analysis of 2245 drugs on the market or in the final phase of development [24].

- The molecular molar mass which must be less than 500 g/mol;
- The number of hydrogen bond acceptor atoms which must be less than or equal to 10;
- The number of hydrogen bond donor atoms which must be less than or equal to 5;
- The M LogP coefficient which must be less than or equal to 5.

Compounds whose physico-chemical activities do not satisfy at least 2 of the rules are highly likely to present absorption problems. These criteria correlate the physico-chemical activities with oral administration and a molecule for which two of the criteria are outside these limits is less likely to be absorbed orally [24]. New compounds with better pIC_{50} values than existing ones can be developed with the aim of improving research on antidiabetic drugs.

2.7. Area of Applicability of the Established Model

Figure 2 below represents the domain of applicability, the area in which the model can predict.

The values of the levers of the molecules are lower than the value of the threshold lever h*(h* = 0.882). Also, all molecules are inside the domain of applicability of the model.

Note that the alphabetical letters in the diagram are the molecule codes used to establish the mathematical model.

2.8. Prediction of Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET)

- **AIH (Human Intestinal Absorption)** refers to the ability of the human intestine to absorb the drug. The greater the human intestinal absorption percentage, the better the human intestine absorbs the drug (0% - 20%) poor absorption; 20% - 70% medium absorption, 70% - 100% strong absorption.
- **Caco-2** (nm/s) and MDCK (nm/s) predicts the intestinal permeability of a compound on Caco-2 cells (<4 poor permeability, between 4 - 70 average permeability, >70 high permeability) and MDCK.
- **BBB (Blood Brain Barrier)**, this descriptor indicates the penetration of a compound to cross the blood-brain barrier which controls the passage of most compounds from the blood to the Central Nervous System (CNS).
- **PBB (Plasma Protein Binding)** predicts the degree of drug binding to proteins in the blood (<90 low binding, >90 high binding).

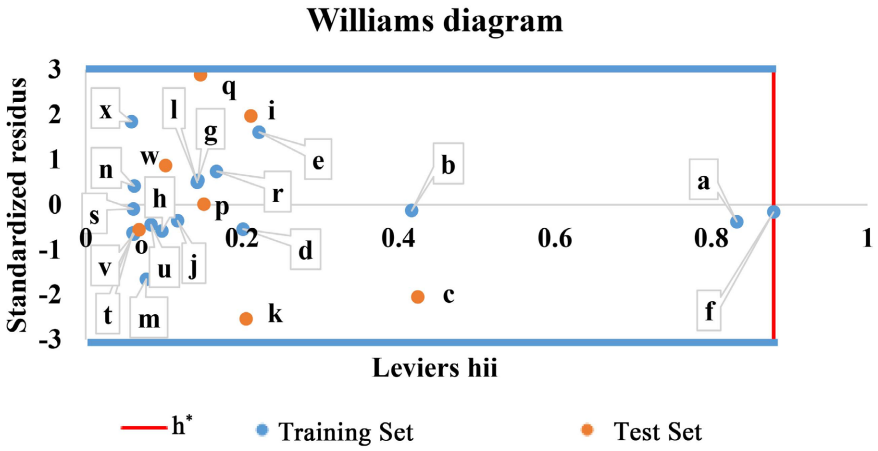


Figure 2. Domain of applicability of the MLR model.

- **Cytochromes** P450 are key enzymes involved in the metabolism of different endogenous or exogenous molecules. They exist in several iso-forms (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4) but the most important are the last two. The prediction of the interaction of our best inhibitors with these iso-forms was also. essential since the inhibition of these iso-enzymes is certainly one of the main causes of drug interactions resulting in toxic or adverse effects [25].
- **hERG (human Ether-to-go-go-Related Gene)** hERG (human Ether-à-go-go-Related Gene) is a gene encoding a voltage-gated potassium channel that moves potassium out of the cell. The blockage of this channel leads to fibrillations in cardiology which can lead to cardiac arrest.
- **AMES-Test (Salmonella typhimurium reverse Mutation Assay)** AMES-Test (Salmonella typhimurium reverse Mutation Assay) is a simple method to test the mutagenicity of a compound. It uses several strains of the bacterium Salmonella typhimurium carrying mutations in genes involved in the synthesis of histidine, so that they require histidine for their growth. This test consists in evaluating the ability of a compound to cause a mutation allowing a return to growth on a medium without histidine.

These different parameters were determined from the PreADMET online server [26] (https://preadmet.bmdrc.kr/).

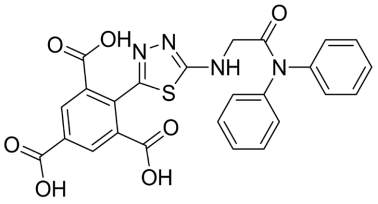
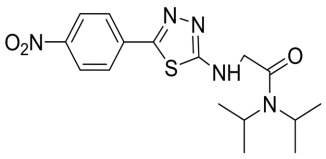
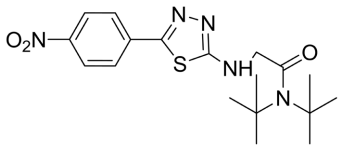
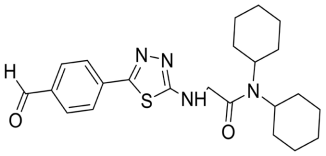
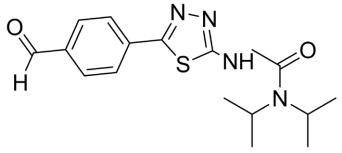
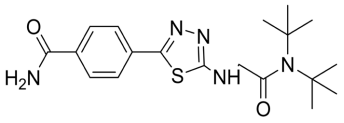
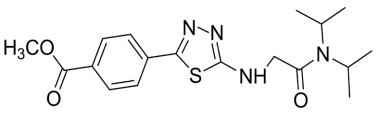
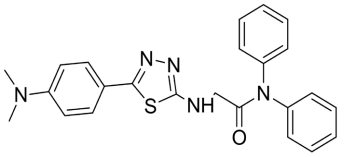
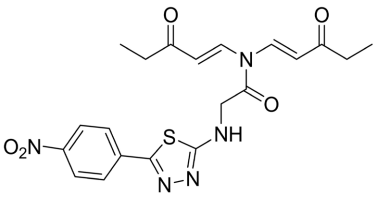
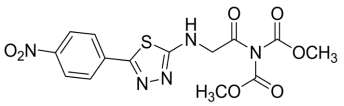
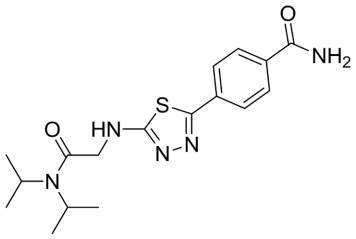
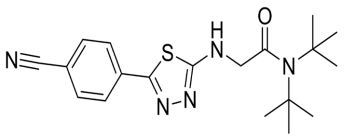
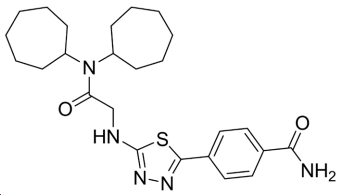
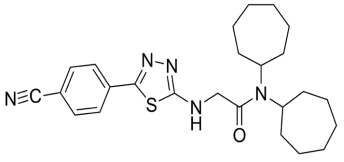
3. Results and Discussion

3.1. Molecular Structures of New Thiadiazole Derivatives

The modification made to the molecular structures of the compounds in Table 1 according to the form and nature of the substituents enabled us to propose new molecules. The different structures obtained codified (TH) are presented in Table 2.

The calculation of the frequencies of these different molecules at the level of the B3LYP 6-31+G (d, p) theory after geometric optimization, provides information

Table 2. Molecular structures of new thiadiazole derivatives.

Codes	Molecular structure	Codes	Molecular structure
TH1		TH2	
TH3		TH4	
TH5		TH6	
TH7		TH8	
TH9		TH10	
TH11		TH12	
TH13		TH14	

on the value of the bond angle (α(S-C-N)), the length of the bond L(C=N), the standard entropy of formation (ΔS_f^0 298K), and the dipole moment μ(D). Obtaining these values allowed us to predict the antidiabetic activity (pIC_{50}) of these different molecules from the QSAR model obtained. Table 3 presents the different values of the descriptors and the predicted pIC_{50} of these compounds.

The study of Table 3 indicates fourteen (14) new molecules obtained. With pIC_{50} values between 2.532 and 2.751, the new molecules present pIC_{50} higher than the pIC_{50} of the base compound ranging from 2.320 to 2.526. This

Table 3. Model descriptors, predicted values of inhibitor concentration potential pIC_{50}.

Molecules	*l*(C=N) (Å)	*α*(S-CN)(ua)	ΔS_f^0 (kcal/moLK)	*μ*(D)	pIC_{50}	h_{ii}
TH1	1.317	113.907	−1.523	8.299	2.591	0.222
TH2	1.321	113.761	−1.246	12.004	2.539	0.262
TH3	1.320	113.983	−1.416	8.752	2.558	0.140
TH4	1.318	114.191	−1.639	7.987	2.674	0.413
TH5	1.319	113.783	−1.242	11.737	2.544	0.202
TH6	1.316	114.01	−1.467	6.722	2.546	0.234
TH7	1.318	113.804	−1.350	10.410	2.561	0.181
TH8	1.300	113.995	−1.197	7.614	2.551	**0.944**
TH9	1.317	114.034	−1.410	7.776	2.553	0.141
TH10	1.318	114.008	−1.090	12.047	2.540	0.768
TH11	1.317	113.788	−1.296	11.765	2.579	0.188
TH12	1.318	113.977	−1.386	7.940	2.532	0.172
TH13	1.317	114.204	−1.696	5.994	2.648	0.379
TH14	1.315	113.882	−1.614	12.129	2.751	0.755

highlights that all new thiadiazole derivatives may be more active than the compounds in the experimental database.

Figure 3 below gives us an idea of the appearance of the different levers of the 14 new compounds.

However, the lever of the TH8 molecule (h_{ii} = 0.944) is greater than the threshold lever of the model (h^* = 0.882). The prediction of the antidiabetic activity of this compound from the model is therefore doubtful.

3.2. Determination of Thermodynamic Quantities of Formation

The standard thermodynamic quantities of formation, such as the enthalpy of formation ΔH_f^0 (kcal/mol), the entropy of formation ΔS_f^0 (kcal/mol) and the free enthalpy of formation ΔG_f^0 (kcal/mol) have were determined from the formula of Otchersky *et al.* in order to demonstrate the possibility of formation of new, more active 1,3,4-thiadiazole derivatives. It should be known that a variation of the enthalpy translates the thermicity of a chemical reaction, when that of the entropy provides information on the level of disorder in the system. On the other hand, a change in free enthalpy reflects the spontaneity with which the reaction occurs. The values of these calculated quantities are given in Table 4.

The results show that all the values of the standard thermodynamic quantities of molecule formation are negative. The negative values of the enthalpy and the free enthalpy translate respectively an exothermic reaction and a spontaneous reaction under the conditions of the study. With regard to entropy, a negative value reflects a decrease in disorder. Thus, the formation of all compounds occurs spontaneously with a release of heat and a decrease in disorder. At this

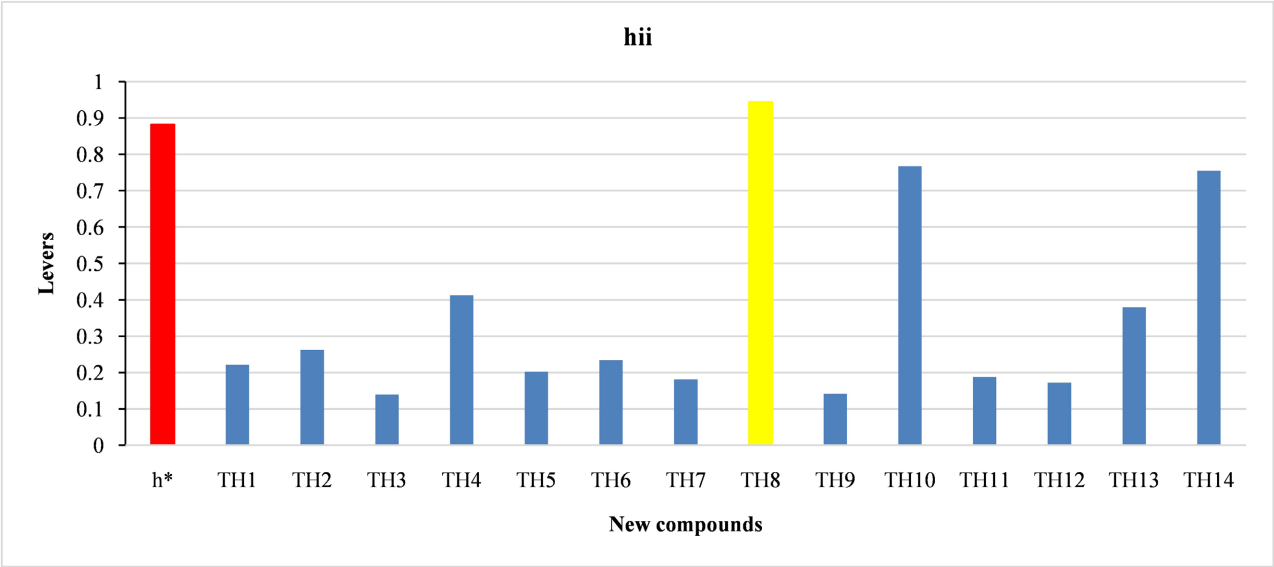


Figure 3. Diagram of the levers of the new compounds compared to the threshold lever.

Table 4. Thermodynamic quantities of TH formations optimized at the B3LYP/6-31+G (d, p) level.

Molecules	ΔH_f^0 (kcal/mol))	ΔG_f^0 (kcal/mol)	ΔS_f^0 (kcal/mol/K^{-1})
TH1	−1820.237	−1365.870	−1.523
TH2	−1141.650	−769.943	−1.246
TH3	−1205.114	−782.789	−1.416
TH4	−1292.445	−803.531	−1.639
TH5	−1078.268	−707.824	−1.242
TH6	−1219.628	−782.111	−1.467
TH7	−1234.409	−831.811	−1.350
TH8	−1024.165	−667.092	−1.197
TH9	−1437.125	−1016.463	−1.410
TH10	−1437.534	−1112.385	−1.090
TH11	−1156.447	−769.929	−1.296
TH12	−1080.590	−667.214	−1.386
TH13	−1370.291	−864.531	−1.696
TH14	−1233.948	−752.657	−1.614

level, we note that the quantities determined at the B3LYP/6-31+G (d, p) theory level confirm the formation of all these new compounds at the temperature of 298.15 K and 1 atm.

3.3. Determination of Lipinski Parameters

The determination of the Lipinski parameters, the values of which are recorded in Table 5, enabled us to verify the oral bioavailability of the molecules.

Table 5. Lipinski parameters of new thiadiazole derivatives with improved antidiabetic activities.

Molecules (d)	M (g/mol)	HBD	HBA	MlogP
Rule	**<500**	**<5**	**<10**	**<4.15**
TH1	510.50	4	9	2.25
TH2	363.43	1	5	1.16
TH3	391.49	1	5	1.64
TH4	426.57	1	4	2.79
TH5	346.45	1	4	1.44
TH6	389.51	2	4	1.78
TH7	376.47	1	5	1.96
TH8	429.54	1	3	3.44
TH9	443.48	1	7	3.15
TH10	395.35	1	9	−0.17
TH11	361.46	2	4	1.31
TH12	371.5	1	4	1.91
TH13	441.59	2	4	2.67
TH14	423.57	1	4	2.79

The quantities characterizing the determined Lipinski rule are the molar mass (M), the number of hydrogen donors (HBD), the number of hydrogen acceptors (HBA) and the lipophilicity (MlogP) were determined.

Analysis of the data in the table shows that the values of the molar mass of the compounds are less than 500 g/mol except for compound TH1 (510.50 g/mol) Also, the values of the number of hydrogen bond donor atoms (HBD) are all less than 5. As for the numbers of hydrogen bond acceptor atoms (HBA), they are all less than 10. At the level of (M Logp), all the values of our studied series are less than or equal to 4.15 (≤4.15). This parameter gives good intestinal absorption due to a good balance between solubility and permeability by passive diffusion according to this characteristic. Therefore, these compounds can be orally administrable drugs.

3.4. Prediction of the Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) of New Molecules

The prediction of the absorption, distribution, metabolism, excretion and toxicity of the new molecules was carried out from the online server PreADMET. We determined parameters such as, Human Intestinal Absorption (HIA), in vitro cell permeability caco-2, in vitro cell permeability MDCK (Mandin Darby Canine Kidney), plasma protein binding (PPB), penetration blood-brain barrier (BBB), inhibition of cytochrome P450 enzyme (CYP2D6, CYP2C9, CYP2C19, CYP2A4), inhibition of hERG (human Ether-à-go-go-Related Gene), carcinogenicity and mutagenicity. These different parameters are listed in **Table 6**.

Table 6. Prediction of absorption, distribution, metabolism, excretion and toxicity (ADMET) parameters of new compounds with improved antidiabetic activity.

	Absorption			Distribution		Metabolism							Toxicity		
Molecules	HIA	Caco-2	MDCK	PPB	BBB	CYP2C19 Inhibition	CYP2C9 Inhibition	CYP2D6 Inhibition	CYP2D6 Substrat	CYP3A4 Inhibition	CYP3A4 Substrat	hERG Inhibition	Cancérogénicité		Mutagénicité
													Mouse	Rat	(AMES-Test)
TH1	80.314	0.954	0.065	100.000	0.059	No	Inhibition	No	No	Inhibition	No	Ambiguous	negative	negative	Mutagen
TH2	78.105	3.942	0.129	83.349	0.110	No	No	No	No	No	Substrate	Weak	negative	negative	Mutagen
TH3	81.331	5.884	0.048	84.334	0.157	No	No	No	No	No	Substrate	Risk	negative	negative	Mutagen
TH4	97.856	19.830	37.217	93.969	0.029	No	No	No	No	No	Weak	Weak	negative	negative	Mutagen
TH5	96.479	24.365	0.237	77.440	0.022	No	No	No	No	No	Substrate	Risk	negative	negative	Mutagen
TH6	92.604	9.640	0.058	61.973	0.017	No	No	No	No	No	Substrate	AVERAGE	negative	Positive	Mutagen
TH7	95.681	22.157	0.251	75.553	0.019	No	No	No	No	No	Substrate	Risk	negative	Positive	Mutagen
TH9	75.262	2.251	1.457	84.178	0.046	No	No	No	No	No	No	AVERAGE	Positive	negative	Mutagen
TH10	27.749	0.391	4.519	82.465	0.027	No	No	No	No	No	No	Risk	negative	negative	Mutagen
TH11	90.746	2.880	0.448	59.640	0.017	No	No	No	No	No	Substrate	Medium Risk	negative	negative	Mutagen
TH12	97.561	57.095	24.302	91.127	0.095	No	No	Yes	Yes	Yes	Weak	Medium Risk	negative	Positive	Mutagen
TH13	95.282	2.441	11.789	89.656	0.023	No	No	No	No	No	No	Medium Risk	negative	negative	Mutagen
TH14	97.866	16.659	53.574	92.374	0.025	No	No	No	No	No	No	Low Risk	negative	negative	Mutagen

HIA (%) is the percentage of human intestinal absorption (from 0% - 20% poor absorption; from 20% - 70% medium absorption, from 70% - 100% strong absorption). Caco-2 (nm/s) and MDCK (nm/s) predict the intestinal permeability of a compound on Caco-2 (<4 poor permeability, between 4 - 70 medium permeability, >70 high permeability) and MDCK cells. PPB (Plasma Protein Binding%) predicts the degree of drug binding to proteins in the blood (<90 low binding, >90 high binding). BBB (Blood–Brain Barrier %) predicts the penetration of the blood-brain barrier (<0.1 low absorption in the Central Nervous System (CNS), 0.1 - 2 medium absorption in the CNS and >2 high absorption in the CNS). Cytochromes of P450 (CYP2D6, CYP2C19, CYP2C9 and CYP2A4) are important in the oxidative metabolism of compounds. hERG (human Ether-à-go-go-Related Gene) is an ion (potassium) channel moving potassium out of its cell. AMES-Test (Salmonella typhimurium reverse Mutation Assay) predicts the mutagenic potential of a molecule.

Examination of the table shows us that at the level of absorption for values of human intestinal absorption (HIA) greater than 70%, suggests that these compounds are efficiently absorbed in the human intestine. Regarding the permeability on the Caco-2 cell, the values of the compounds (TH1, TH2, TH9, TH10, TH11) are less than 4 nm/s, therefore poor permeability and the other compounds have values between 4 and 27.4619 nm/s. These latter compounds have an average permeability as regards the permeability on the MDCK cell, the values are between 0.048 and 57.2175 nm/s, this shows that the new compounds are permeable on the Caco-2 and MDCK cells. Concerning the binding of plasma proteins (PPB), the values are greater than 90% for the compounds TH10 (93.969%), TH8 (97.752%), TH1 (100.000) and TH13 (92.374) hence a strong binding on plasma proteins. It is clear that the other compounds have poor BBB permeability, *i.e.* low absorption at the blood-brain barrier (CNS), except compound TH7, which has average BBB permeability.

Concerning the metabolism of xenobiotics, not all the compounds are inhibitors of the CYP2C19 and CYP2C9 enzymes except compound TH1 which inhibits the CYP2C9 enzyme. Not all the compounds are inhibitors and substrates of the CYP2D6 enzyme and only compound TH12 is an inhibitor and substrate of

the CYP3A4 enzymes. We can say that all molecules can easily be metabolized by CYP2D6 and CYP3A4 enzymes.

For the toxicity test, the compounds present a low and medium risk for Herg inhibition except for the TH1 molecule which presents an ambiguity for Herg inhibition. Compounds TH3, TH4, TH5, TH8, TH13, TH14 are non-carcinogenic in mice and rats, and mutagenic according to the AMES test. As a result, the proposed new molecules can therefore be like drugs because they have good properties of absorption, distribution, metabolism and toxicity.

4. Conclusion

The calculations carried out at the theoretical level DFT/B3LYP/6-31G+(d, p) were used to establish the model which enabled us to design 14 new compounds with higher activity values than those of the base molecules. The new thiadiazole derivatives belong to the domain of applicability except the TH8 molecule, so their predicted activity values are low. However, all fourteen (14) new molecules designed had inhibitory concentration potential (pIC_{50}) values greater than the inhibitory concentration potential (pIC_{50}) of the parent compound. Then the analysis of the thermodynamic quantities of formation showed that out of all fourteen (14) compounds can be formed. In addition, the data analysis respects Lipinski's rule, and these molecules can therefore be administered orally. The study of the parameters of absorption, distribution, metabolism, excretion and toxicity (ADMET) showed that the compounds have a good pharmacokinetic profile and can therefore be used as a drug. In perspective, the synthesis and in vitro tests of these new molecules could be useful in the fight against diabetes.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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