ISSN 1814-9758. Ukr. Bioorg. Acta, 2020, Vol. 15, N 1
UDC 544.182.32+547.31.39+547.787.1+547.874.8
DOI: hpps://doi.org/10.15407/bioorganica2020.01.012

Ukrainica Bioorganica Acta
www.bioorganica.org.ua

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RESEARCH ARTICLE

In silico binding affinity studies of phenyl-substituted 1,3-oxazoles with protein molecules

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Abstract: The new model approach of interaction between the pharmacophores with bio-molecules, fragment-to-fragment, is presented. It is a new step of the molecular modeling that takes correctly into consideration not only the spatial complementarity of the interacted molecules but also the contribution of the stacking π-π-electron interaction and hydrogen bonds. As an example, the correct analysis of the interaction of the biological active phenyl-substituted 1,3-oxazoles with protein fragments is performed. It was shown that the length and energy of the hydrogen bond uniquely depend on the chemical constitution of both components in the created complex [*Pharmacophore*(Oxazole)-*Biomolecule* (H-X)]. The binding energy decreases in the series X → O, S, NH (fragments of the corresponding biomolecules). It should be pointed out that introduction of the conjugated phenyl groups at positions 2 and 5 of oxazoles increase the stability of the generated complex *Pharmacophore-Biomolecule* [*Pharm-BioM*] with fragments of the corresponding biomolecules along the core of oxazole by 0.2 and 0.5 kcal/mole. At the same time, modeling of the generated complex [*Pharm-BioM*] by phenyl substituents at position 2 and 5 of 1,3-oxazole with phenylalanine as a fragment of protein molecules additionally stabilizes complex by 2.5 kcal/mole by π-stacking mechanism. The observed biological activity of the phenyl substituted 1,3-oxazole is rather connected with ability to generate the stable complex due to the formation of additional bonds with other fragments (conjugated phenyl core). The calculations demonstrated that such substituents do not cause spatial hindrances with the polypeptide chain.

Keywords: biological affinity, 1,3-oxazoles, quantum chemical calculations, [*Pharm-BioM*] complex, π-stacking interaction, hydrogen bonds.

Introduction

The oxazole-based five-membered heterocycles exhibit various pharmacologically interesting properties that have recently been reported in several reviews **[1-2]**. It enabled the wide introduction of novel pharmacological drugs into medicine. The 1,3-oxazoles with branched conjugated systems demonstrated high biological activity, including antibacterial and antiviral activities [3-4], and multiple drug resistance pump inhibition [5-6]. The substituted 1,3-oxazoles with branched π-conjugated systems also were studied *in vitro* at the National Cancer Institute in the USA, as part of a therapeutic program for the development of DTP. It was found that these compounds are promising component in the development of new biologically active substances exhibiting antitumor activity which is strongly dependent on the nature of the substituents in heterocyclic core [7-10]. That leads to additional research activity toward developing new pharmaceuticals [11-12].

The QSAR models for a wide range of 1,3-oxazole derivatives showed an inhibitory effect on several cancer cell lines. A good correlation between many descriptors and biological activity was established [8]. Therefore, the planar oxazole core can be regarded as an applicable biologically active fragment. Its lone electron pair (LEP) at the two-coordinated nitrogen atom can promote the additional stabilization of [*Pharm-BioM*] complex by hydrogen bonds.

Received: 20.03.2020
Revised: 03.04.2020
Accepted: 10.04.2020
Published online: 30.06.2020

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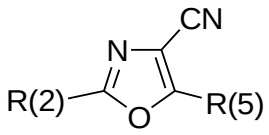
At the same time, the introduction of substituents with a conjugated π-electron system in the 1,3-oxazole ring increases the stabilization of resulted complex [*Pharm-BioM*] by π-stacking interaction. The presence of the phenyl substituent in 1,3-oxazole substrate increases biological activity, particularly, the inhibitory effect on the cancerous tumors [9-10]. These molecular fragments can generate an additional complementary structure with many biopolymers, which is considered an important condition for increasing selectivity for potential targets.

This paper presents the results of the *in silico* investigations of the connection between biological properties and electronic structure of phenyl substituted 1,3-oxazoles, including the steric features as well as additional stabilization of the model [*Pharm-BioM*] complex by stacking interaction and by generation hydrogen bonds.

Materials

The 4-cyano substituted 1,3-oxazole derivatives were investigated (Figure 1) as biologically active compounds for interaction with protein fragments. Typically, electron accepting groups at the 4th position of 1,3-oxazoles increase the stability of the 5-membered electron-rich oxazole cycle. Moreover, oxazole derivatives containing similar substituents have demonstrated high biological activity [9].



Compd	$R_{(2)}$	$R_{(5)}$
1	Me	Me
2	Ph	Me
3	Me	Ph
4	Ph	Ph

Figure 1. Structures of compounds **1-4**.

The dimethyl substituted oxazole **1** was chosen as a reference molecule; the one- and two-phenyl substituted derivatives **2-4** were compared to oxazole **1**. Compounds **1-4** were evaluated at the National Cancer Institute (NCI) for anticancer activity *in vitro*. Primary *in vitro* one dose anticancer assay was performed in full NCI 60 cell panel representing leukemia, melanoma, and cancers of lung, colon, brain, breast, ovary, kidney, and prostate in accordance with the protocol of the NCI, USA [9].

The main characteristics of the electron structure (optimized molecular geometry, charge distribution, energies and shapes of molecular orbitals) were calculated by DFT computation utilizing wB97XD function and 6-31G(d,p) basis set as implemented in GAUSSIAN 03 program [13].

Binding affinity by fragment-to-fragment approach

Typically, the biological affinity of pharmacophores evaluated by their ability to effectively interact with biological molecules. The pharmacophore (*Pharm*) and biomolecule (*BioM*) should form a stable complex, namely [*Pharm-BioM*]. The stability of such complex depends on the geometrical characteristics of both complex components. The complex can be additionally stabilized by creating hydrogen bonds and stacking interactions with phenyl substituents. The oxazole and its conjugated substituted derivatives are planar molecules and, hence, should be attracted to protein fragments. The amino acids with the aromatic groups as part of its structural characteristics can create a π-complex [*Pharm-BioM*] with oxazole derivatives **1-5**. Therefore the ability to form the π-complex can be considered as a π-electron affinity component. Similarly, the ability to form a complex by hydrogen bonds can be considered as an [H-B] affinity component. As a result, the oxazole π-electron cycle can manifest the π-affinity whereas the two-coordinated nitrogen atom of the oxazole ring can manifest its [H-B]-affinity. These properties can be evaluated by a direct quantum-chemical modeling.

Many events of the [*Pharm-BioM*] interactions can be modeled by elementary interactions between the pharmacophore fragments (1,3-oxazoles) and some fragments of the complex biological molecules by taking into consideration the complementarity of the complex components. We will call this approach a fragment-to-fragment approach.

Results and Discussion

Molecular geometry of substituted 1,3-oxazoles and charge distribution

The 1,3-oxazoles are conjugated planar molecules. The optimization of the molecular geometry of phenyl substituted oxazoles **2-4** with variable substituents in positions 2 and 5 confirmed planar configuration. According to the complementarity rule such compounds should predominantly form complexes [*Pharm-BioM*] with protein fragments that contain conjugated aromatic amino acids (phenylalanine, tyrosine, tryptophan, histidine). These complexes are additionally stabilized by stacking interaction between π-electron systems of both complex components.

Earlier, we have demonstrated that the binding energy of the complex [Pharm-Fullerene] depends on the nature of the substituent in the oxazole ring [14]. We hypothesized that the binding energy of complex [*Pharm-BioM*] formation depends on the nature of the substituent at the 2- and 5-positions of 1,3-oxazoles **1-4**. This dependence should be similar for all types of donor/acceptor characteristics of these biomolecules. The complex formation of 1,3-oxazole

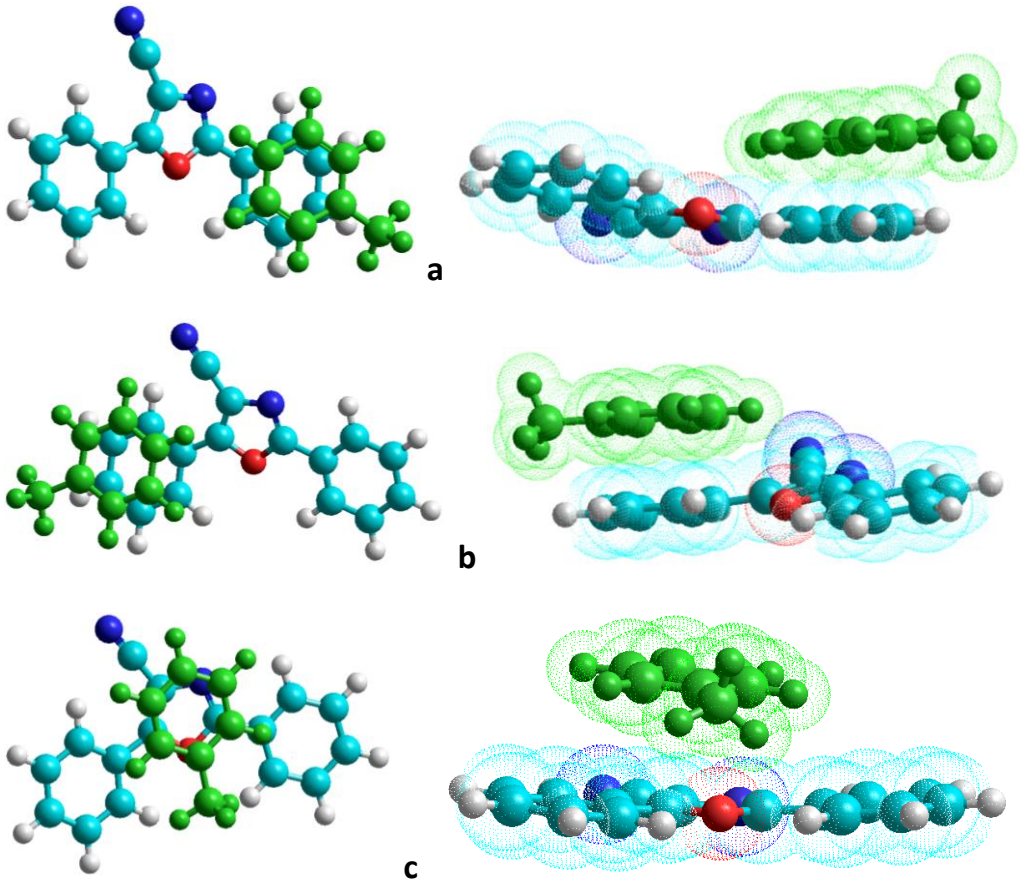


Figure 2. Optimized molecular geometry of three possible complexes of 1,3-oxazole **4** with a model phenylalanine (toluene): a) π-stacking by phenyl group at position 2; b) π-stacking by phenyl group at position 5; v) π-stacking by 1,3-oxazole cycle.

4 with phenylalanine [oxazole-Phe] was examined. Phenylalanine in a polypeptide chain was modeled by toluene, i.e. only conjugated system was taken into consideration. The geometrical characteristics of phenyl group of toluene is similar to the fragments of the phenyl-substituted 1,3-oxazole **4**. As a result, we calculated different possible versions of the generated complex: (i) when the central heterocycle is oriented to model phenylalanine or (ii) when one of the phenyl-group of oxazole **4** is oriented toward model phenylalanine. Three possible complexes of diphenyl substituted oxazole with toluene are presented in Figure 2.

It is noteworthy that the thickness of π-electron systems is 3.4 Å, the distance between the components in the studied complex [*Pharm-BioM*] (i.e., between 1,3-oxazole cycle, phenyl substitutes in the 2- and 5-positions of 1,3-oxazole **4** and model phenylalanine – toluene) is 3.4 Å. Similar founding was reported for deoxyribonucleic acid helix [16] and for polymethine dyes aggregates [17].

*Positions of the frontier orbitals of compounds **1-4** and its donor/acceptor properties*

We assumed that biological activity is connected to the position of frontier orbitals as it was reported previously [15]. The oxazole ligand produces complex with peptide fragments by protein-ligand complex binding [*Pharm-BioM*] [18]. These results indicates the stacking interaction between the π-systems of both complex components: A (*Pharmacophore*) and B (*Biomolecule*). According to the perturbation theory [19], a similar interaction depends on the relative positions of the molecular orbitals of both molecules as well as the overlapping of their π-systems and can be calculated by Equation 1:

$$\Delta E \approx \sum_{\mu}^{A}\sum_{i}^{A}\sum_{\nu}^{B}\sum_{j}^{B}\left[\frac{C_{i\mu}C_{j\nu}}{\varepsilon_i - \varepsilon_j}\right] \qquad (1)$$

where ε_i and ε_j are MO energies; $C_{i\mu}$ and $C_{j\nu}$ are MO coefficients; indices i, μ is energy system A; indices j, ν is energy system B.

The main contributions to the frontier molecular orbitals (MO) are made by the highest occupied MO (HOMO) and the lowest unoccupied MO (LUMO). The geometry of the frontier molecular orbitals contribute to the donor and acceptor ability of the conjugated molecules. The influence of the phenyl groups on the energy level of both HOMO and LUMO are presented in Table 1.

Table 1. Energies of frontier MO of substituted 1,3-oxazoles **1-4**.

Compd	$R_{(2)}$	$R_{(5)}$	ε(MO), eV		Δ, eV	φ_0[a]
			HOMO	LUMO		
1	Me	Me	-8.822	1.137	9.958	0.472
2	Ph	Me	-8.307	0.386	8.694	0.454
3	Me	Ph	-8.228	0.049	8.277	0.436
4	Ph	Ph	-8.004	-0.173	7.830	0.433

[a] φ_0 calculated by Equation 2.

The introduction of the phenyl groups in position 2 or 5 of oxazole ring are accompanied by converging of the frontier orbitals so that energy gap (difference between the energy of highest occupied orbital and lowest vacant orbital) decreases. Phenyl group in position 5 causes the greater effect (1.68 eV) compared to the phenyl substituent in position 2 (1.26 eV). There is no additive effect found upon simultaneous introduction of two phenyl groups to positions 2 and 5 (2.12 eV).

It was proposed [20] to calculate the donor/acceptor ability of the molecules as a relative position of the frontier orbitals by the following Equation 2:

$$\varphi_0 = (\varepsilon_{LUMO} - (\varepsilon_F)/((\varepsilon_{LUMO} - (\varepsilon_{HOMO}) \quad (2)$$

Where ε_{LUMO} is an energy of the lowest unoccupied MO, ε_{HOMO} is an energy of the highest occupied MO, ε_F (α) is an energy of non-bonding MO (α = -3.561 eV) [21].

The calculated values φ_0 for studied compounds are presented in Table 1. The data shows that this parameter is slightly sensitive to introduction of phenyl groups. The phenyl substituent generates the equal number of occupied and unoccupied MO, which symmetrically positioned from the non-bonding MO (Fermi level α) [21]. The acceptor property (φ_0 < 0.5) is caused by cyano group (-CN) in position 4, although the oxazole *per se* is molecule with donor properties as an electron rich system [18].

Binding energies of π-complex [Pharm-BioM]

In the first approximation, the binding energy $E_{binding}$ can be calculated as the difference of the total energy of the complex [*Pharm-BioM*] and the energies of both its components (Eq. 3):

$$E_{binding} = E_{[Pharm\text{-}BioM]} - E_{Pharm} - E_{BioM} \quad (3)$$

where $E_{[Pharm-BioM]}$ is the energy of optimized complex, while E_{Pharm} and E_{BioM} are energies of optimized components.

This work focuses on the protein fragment in the form of model phenylalanine (Phe-CH_3), which can create a π-complex. The calculations of the donor/acceptor parameter φ_0 of the phenylalanine amino acid gives φ_0 = 0.52; while this parameter of the model fragment, Phe-CH_3, is equal to φ_0 = 0.53. We are investigating the influence of the phenyl substitution in positions 2 and 5 that resulted in change of a π-contribution as well as total affinity of the oxazoles **1-4** in a model complex [Oxazole:Phe-CH_3].

Figure 2 depicted three possible geometries of both components in the model complex. The optimization showed that the distance between components in the stable complex is approximately 3.4 Å. The calculated binding energies of the optimized complexes [Oxazole:Phe-CH_3] are presented in Table 2.

As it can be seen (Table 2 and Figure 2c) that one phenyl group (compounds **2** and **3**) increases the complex stability by orienting the phenyl group to the heterocyclic fragment; in the complex that is formed from di-phenyl-substituted 1,3-oxazole **4**, the binding energy is less than in the complex with the reference molecule **1**.

The stabilization energy of the complex **2c** [Oxazole:Phe-CH_3] is significantly lower compared to other complexes' geometries (Figure 2, Table 2). It is noteworthy that the stabilization energy of the complex that is formed from two phenyl substituted oxazole is minimum among all possible complexes. However, the preferential formation of

Table 2. Binding energies of complexes [Oxazole:Phe-CH_3], where oxazole corresponds to compounds **1-4**.

Figure	Complex	$R_{(2)}$	$R_{(5)}$	Energy (E)[a], a.u.		ΔE[b], kcal/mole
				Oxazole	Complex	
2c	[Oxazole **1**:Phe-CH_3]	Me	Me	-416.825544294	-688.327544051	-12.18
2c	[Oxazole **2**:Phe-CH_3]	Ph	Me	-608.502926733	-880.005254882	-12.38
2a	[Oxazole **2**:Phe-CH_3]	Ph	Me		-880.002988419	-10.96
2c	[Oxazole **3**:Phe-CH_3]	Me	Ph	-608.502469135	-880.005254882	-12.67
2b	[Oxazole **3**:Phe-CH_3]	Me	Ph		-880.000764847	-9.85
2c	[Oxazole **4**:Phe-CH_3]	Ph	Ph	-800.180950747	-1071.68207547	-11.63
2a	[Oxazole **4**:Phe-CH_3]	Ph	Ph		-1071.67606230	-7.86
2b	[Oxazole **4**:Phe-CH_3]	Ph	Ph		-1071.67528637	-7.37
	Phe-CH_3			-271.482591603		

[a] E is total energy.

[b] ΔE is binding energy increases only the stability of the formed complex.

various complexes with the orientation at the heterocycle (Figure 2c) will be difficult because of spatial hindrances with the polypeptide chain.

The formation of hydrogen bonding in [H-B] complex

The oxazole cycle contains a coordinated nitrogen atom (with the lone electron pair – LEP) in position 3. It can be considered as an acceptor center for the formation of hydrogen bonds, while the hydrogen atom of the amino group of some acids (lysine, arginine, histidine, etc.) or groups containing hydrogen (-NH, -OH and -SH) can provide the required proton, i.e. the hydrogen bonds can be formed during complex's formation. This interaction should result in the additional stabilization energy of complexes [Oxazole:H-X] that are formed between oxazole molecules and suitable fragments of biomolecules, where X is a N, O, S atoms.

In our study, the donor centers were modeled by the simplest molecules: methanol HO-CH_3, methylamine H_2N-CH_3 and methanethiol HS-CH_3. Possible complexes of the model bio-fragments with the 1,3-oxazoles **1-4** are shown in Figure 3.

The model peptide fragment and oxazole cycle are positioned perpendicularly. Moreover, the formation of hydrogen bond should depends on the charge at the nitrogen atom as well as on the relative position of the LEP (*n*-MO). Calculation revealed that the *n*-MO is localized near the nitrogen atom, and it actively interacts with the σ-orbital, as it presented in Figure 4. *n*-MO is located directly below of the frontier orbitals: HOMO-1. In the case of phenyl derivatives, the local orbital (MOs localized only on phenyl molecular fragment) are situated between the delocalized HOMO and the *n*-MO. Nevertheless, the energy level of *n*-MOs remains practically the same after every change in the reference oxazole cycle. The calculated atomic charges and *n*-MO energies are presented in Table 3.

Table 3. Charge at nitrogen atom (z) and *n*-MO energy (ε) of substituted oxazoles **1-4**.

Compd	$R_{(2)}$	$R_{(5)}$	z, e.u.	*n*-MO	
				number	ε, eV
1	Me	Me	-0.457	HOMO-1	-10.63
2	Ph	Me	-0.454	HOMO-3	-10.69
3	Me	Ph	-0.491	HOMO-3	-10.70
4	Ph	Ph	-0.458	HOMO-5	-10.77

Table 3 shows that introducing of phenyl group in position 2 slightly decreases a negative charge at the nitrogen atom whereas the phenyl in position 5 causes the opposite effect.

The energy of three complexes of the reference molecule **1** with three model compounds H-X-CH_3 where X is a N, O, S atoms as well as three complexes of one model bio-fragment, H_2N-CH_3, with substituted 1,3-oxazoles **2-4** were calculated and presented in Table 4.

It was found that the length of the hydrogen bond and the binding energy depends on the chemical structure of both components in the generated [Oxazole:H-X] complex. Thus, the change of heteroatoms in a model bio-fragment [H-B(X)] decreases the binding energy and, therefore, the stabilization of the corresponding complex in series: X → O, S, NH. The length of a hydrogen bond is shorter during the interaction with –OH group, whereas the lengths of a hydrogen bond with $–NH_2$ and –SH groups are essentially the same.

The introduction of the phenyl substituents does not change the length of hydrogen bonds in the corresponding complex: $l_{N^-\ldots H} \approx 2.01\pm 0.01$ Å. Moreover, the binding energy is considerably more sensitive to position of the introduced phenyl groups as well as to the number of

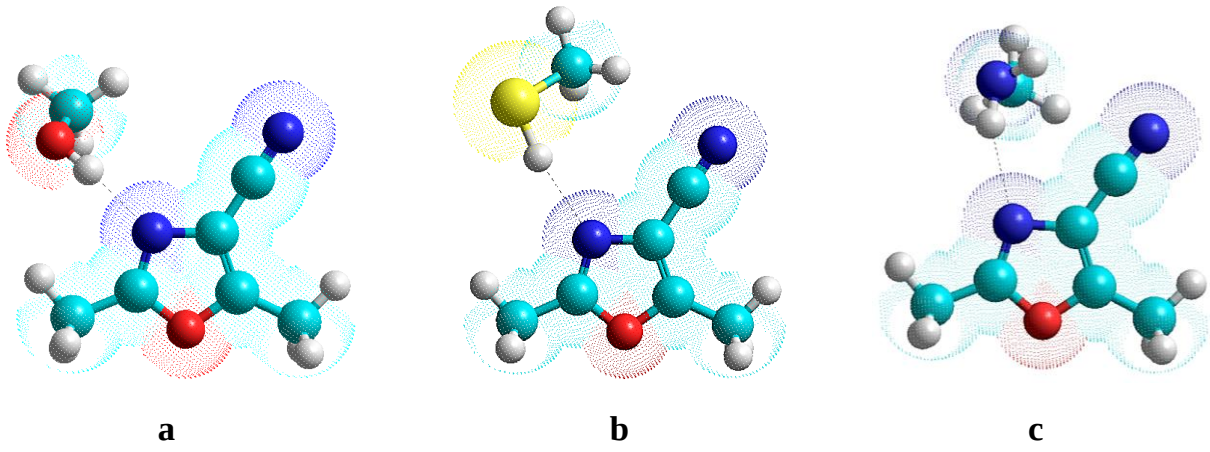


Figure 3. Calculated geometry of 1,3-oxazole molecule **1-4** and model fragments of biomolecules: a) methanol; b) methanethiol; c) methylamine.

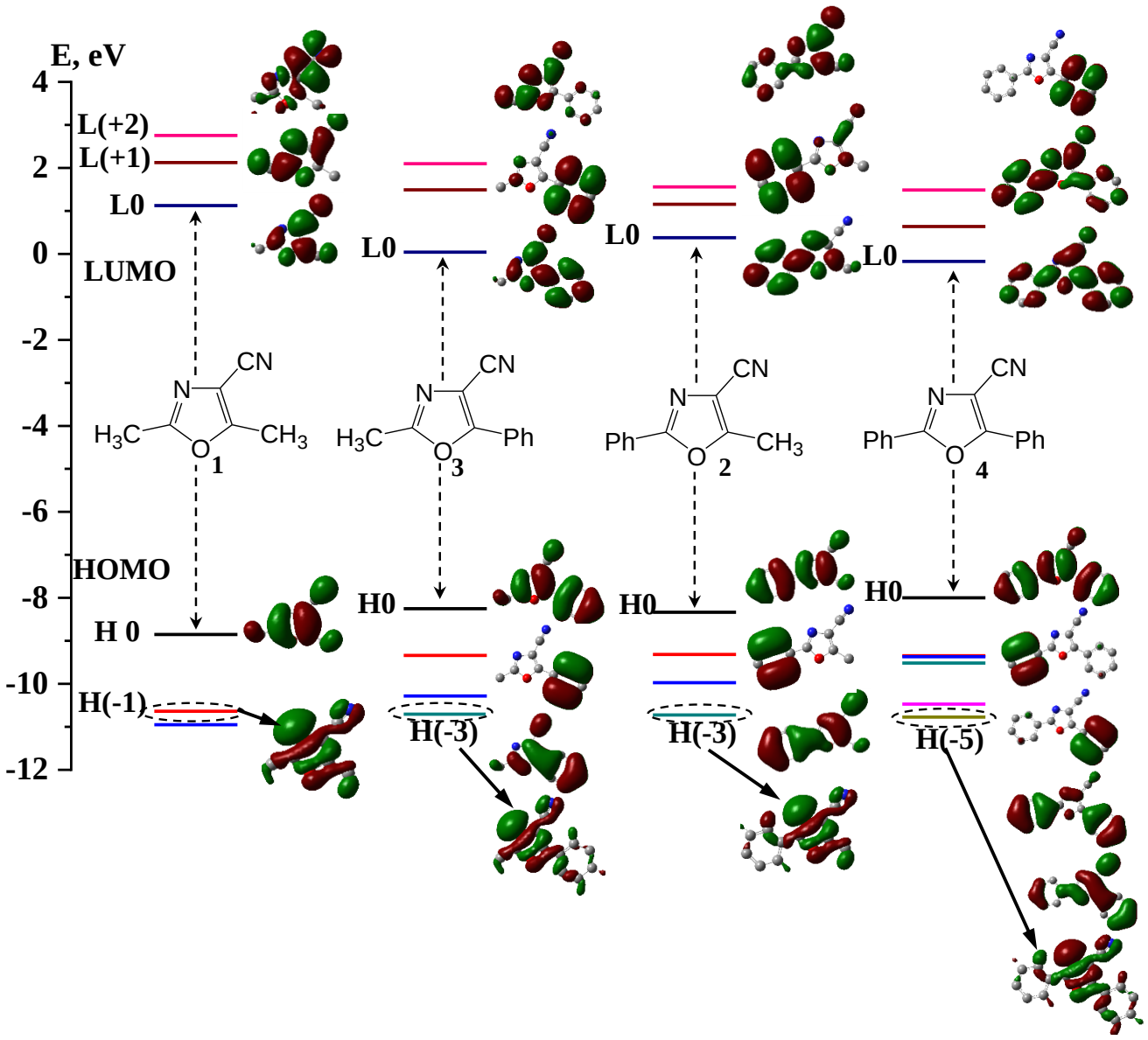


Figure 4. Position and shape of frontier and nearest MOs in 1,3-oxazoles **1-4**.

Table 4. Hydrogen bond energy of complex [Oxazole:H-X] with model methanol, methylamine, and methanethiol.

Complex	$R_{(2)}$	$R_{(5)}$	X	$l_{N-\cdots H}$[a], Å	Energy (E), a.u.		$\Delta E_{binding}$[b], kcal/mole
					Oxazole	Complex	
[Oxazole **1**:H-X]	Me	Me	-O	1.838	-416.82554429	-532.52885310	-11.47
[Oxazole **1**:H-X]	Me	Me	-HN	2.252	-416.82554429	-512.66886008	-7.68
[Oxazole **1**:H-X]	Me	Me	-S	2.232	-416.82554429	-855.50852371	-9.11
[Oxazole **2**:H-X]	Ph	Me	-O	1.989	-608.50292673	-724.20719212	-12.08
[Oxazole **3**:H-X]	Me	Ph	-O	2.018	-608.50246913	-724.20876140	-13.34
[Oxazole **4**:H-X]	Ph	Ph	-O	1.996	-800.18095074	-915.88462187	-11.70
H-O-CH_3						-115.68502789	
H-HN-CH_3						-95.831078854	
H-S-CH_3						-438.66846361	

[a]$l_{N-\cdots H}$ is hydrogen bond length.
[b]$\Delta E_{binding}$ is binding energy.

Table 5. Anticancer activity of synthesized compounds [22] model 1,3-oxazoles **2-4**, and their theoretical characteristics.

Compd	$R_{(2)}$	$R_{(5)}$	φ_0	π-stack interaction	H-bond interaction	Anti-Cancer Activity [22], %	
				E, kcal/mol		Leukemia (RPMI-8226)	Non-Small Cell Lung Cancer (EKVX)
1	Me	Me	0.472	-12.18	-9.11	-	-
2	Ph	Me	0.454	-12.4[a]/10.9[b]	-12.08	99.2	73.1
3	Me	Ph	0.436	-12.7[a]/9.9[c]	-13.34	79.3	94.3
4	Ph	Ph	0.433	-11.6[a]/-7.9[b]/-7.4[c]	-11.70	75.0	85.3

[a]π-stack interaction according to Figure 2c. [b]π-stack interaction according to Figure 2a. [c]π-stack interaction according to Figure b.

substituents. The maximum stabilization energy of complex [Oxazole:H-X] (Table 4) reached when the 1,3-oxazole contains phenyl group in position 2 (compound **2**). The introduction of second phenyl group (compound **4**) decreases binding energy so that two phenyl substituents in positions 2 and 5 do not change the stability of the [Oxazole:H-X] complex, in compare with the reference molecule **1** ($R_1 = R_2 = CH_3$).

*The tendency of the quantum-chemical approaches and the anticancer activity of oxazole derivatives **1-4**.*

The synthesized compounds **1-4** were screened for anticancer activity in the 60 cell panel in accordance with the protocol of the NCI, USA, under the Developmental Therapeutic Program DTP [22]. Table 5 presents data from anticancer activity of synthesized compounds [9, 22] and their theoretical characteristics from quantum-chemical model fragment-to-fragment approach.

As can be seen from Table 5, the oxazole derivatives **2-4** inhibits of cell line EKVX (Non-Small Cell Lung Cancer) growth due to the formation of hydrogen bonds and stable [*Pharm-BioM*] complexes with regulatory proteins, which on the outer sphere have free residues of proton donor amino acids.

The growth's inhibition of cell line RPMI-8226 (Leukemia) happened due to the interaction with regulatory proteins that occurs by π-stack interaction of oxazole derivatives **2-4** with regulatory proteins that have open aromatic amino acid residues.

Conclusions

The theoretical analysis of the interaction of biologically active phenyl-substituted 1,3-oxazoles in the framework of the fragment-to-fragment approach (beside the spatial complementarity of the interacted molecules, the contribution of the stacking π-π-electron interaction and hydrogen bonds is taken into consideration) reviled that introduction of conjugated phenyl groups into main heterocyclic platform will not increase the stability of generated complexes. The observed biological activity of substituted 1,3-oxazoles **2-4** can be explained by the formation of additional bonds with other fragments (conjugated phenyl core) during complex formation, so as they do not cause the stearic hindrances with the polypeptide chain.

Notes

The authors declare no conflict of interest.

Author contributions. **M. Yu. Zh.**: provision of study materials, computing resources, or other analysis tools. **N. V. O.**: formulation or evolution of overarching research goals and aims, application of statistical, mathematical, computational, or other formal techniques to analyze study data. **S. G. P.**: development and design of methodology; creation of models, provision of study materials, computing resources, or other analysis tools. **M. V. K.**: preparation, creation and presentation of the published work, specifically visualization. **O. D. K.**: ideas; formulation or evolution of overarching research goals and aims, development or design of methodology; creation of models. **V. S. B.** ideas; formulation or development of common goals and objectives of the research, verification of results, responsibility for managing and coordinating the planning and implementation of research activities.

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In silico дослідження афінності зв'язування фенілзаміщенних 1,3-оксазолів з молекулами білків

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Резюме: Представлений новий пофрагментний підхід моделювання взаємодії фармакофорів з біомолекулами. Це новий, наступний крок молекулярного моделювання, який враховує не тільки просторову відповідну комплементарність взаємодіючих молекул, але й внесок π-електронів при стекінговій взаємодії та *n*-електронів при формуванні водневих зв'язків. Як приклад, проведено повний аналіз взаємодії біологічно активних феніл-заміщених 1,3-оксазолів з білковими молекулами. Було показано, що довжина та енергія водневого зв'язку однозначно залежать від хімічної конституції обох компонентів в утвореному комплексі [*Фармакофор(оксазол)-Біомолекула(H-X)*]. Енергія зв'язку регулярно зменшується у ряді X ⟶ O, S, NH (фрагменти відповідних біомолекул). Введення спряжених фенільних груп в положення 2 та 5 оксазолу збільшує стабільність згенерованого комплексу *Фармакофор-Біомолекула* [*Фарм-БіоМ*] з фрагментами відповідних біомолекул по ядру оксазола на 0.2 ккал/моль та 0.5 ккал/моль. При моделюванні утворення комплексу [*Фарм-БіоМ*] по фенільних замісниках 1,3-оксазолу в положенні 2 та 5 з фенілаланіном як фрагментом білкових молекул спостерігається додаткова його стабілізація на 2.5 ккал/моль за механізмом π-стекінгової взаємодії. Скоріш за все, біологічна активність феніл- заміщених 1,3-оксазолів, яка спостерігається, пов'язана з можливістю генерувати стійкий комплекс [*Фарм-БіоМ*] за рахунок утворення додаткових π-зв'язків з іншими фрагментами, що мають кон'юговане ядро. Розрахунки показують, що такі замісники не викликають просторових утруднень з поліпептидними молекулами.

Ключові слова: біологічна афінність, 1,3-оксазоли, квантово-хімічні розрахунки, комплекс [*Фарм-БіоМ*], π-стекінгова взаємодія, водневі зв'язки.