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Original Research Article

Designing Novel Molecule (V-NNC) based on Voxelotor (GBT-440) against Sickle Cell Disease (SCD) Via Binding to Carbonmonoxy Hemoglobin S

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ABSTRACT

Sticking cell disease is a defect in hemoglobin structure that leads to deficiency in oxygen transferring to tissues. Voxelotor is a new compound that achieved FDA-approved to treat SCD, recently. In this study, we aimed to introduce novel structure based on the voxelotor to cure the mentioned condition more effectively. At the beginning, various properties of Voxelotor including electronic properties, reactivity and stability were assessed via B3LYP/6-311++G(d,p) method and Global Reactivity in said method that revealed Voxelotor is a stable compound with low reactivity. In addition, docking potential of Voxelotor into active site of hemoglobin S was investigated. Then, several molecules were designed and optimized based on the Voxelotor structure. Docking and physicochemical properties of investigated molecules were analyzed. Results of presented study revealed that between four molecules (V-NNC, V-NNN, V-CNC and V-CNN) with higher potential to interact with Hemoglobin S in comparison with Voxelotor, only V-NNC has the optimum physicochemical features. So, molecular structure screening and evaluating of Voxelotor and designing novel compounds based on it leads to introducing an optimized molecule with suitable potential to treat SCD.

***Keywords*:** *Stricking cell disease (SCD); Drug design; Molecular docking; Molecular simulation; Hemuglobin S; Voxelotor.*

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Introduction

Hemoglobin, a globular and quaternary protein, is well known as a main protein of Red Blood Cells with responsibility to bind to oxygen atoms and carry them through blood flow [1]. Its tetramer structure consists two different types of chains, Beta and Alpha and each group includes two similar chains [2]. Each of them is bound to an arrangement called "Heme" [3], the crucial structure for transporting diatomic gasses through blood, which made of a porphyrin and a Fe^{2+} ion that located in the center of the porphyrin [4]. Porphyrin also has quaternary assembly including four pyrrolic groups which bind together with Methine Bridge and built a large heterocyclic ring [2, 5]. The structure of hemoglobin has been shown in Figure 6. Hemoglobin has not remarkable affinity to bind to oxygen, this property makes hemoglobin as an appropriate molecule to transfer oxygen, due to its ability to release it at the demand region [6]. At the beginning of the hemoglobin journey in blood, the high amount of oxygen in lung makes it possible to bind to the hemoglobin (not affinity), therefore, existence of other gases such as monoxide carbon with stronger affinity to hemoglobin could disturb the main duty of hemoglobin [6, 7].

The other suitable property of hemoglobin is its sigmoidal form and ability to attend the other functional parts to bind to oxygen when one group is bounded to this atomic gas. It happens via intracellular signaling that leads to increasing affinity of hemoglobin to oxygen. In fact, changing configuration of hemoglobin could affect its affinity to oxygen. This molecule has two different state, T (Tensed), R (Relaxed) [8]. The high affinity to oxygen occurs in R-state, when hemoglobin fully is bounded to oxygen that called "oxyhemoglobin" [9]. While, lacking an oxygen binding in hemoglobin structure decreased its oxygen affinity, in this situation it is "deoxyhemoglobin" [8, 10].

Hemoglobin as other proteins, could be affected by various molecules that stimulate or inhibit its functions [11]. 2,3 bisphosphoglycerate is one allosteric molecules [12] which seems to be necessary for hemoglobin actions. It works as an allosteric inhibitor because when binds to the central area of the hemoglobine's curve, could stabilize the T-state and reduced the affinity of hemoglobin to oxygen and facilitates oxygen releasing in tissues [11].

The other factor which could regulate the activities of hemoglobin is pH [13]. Low pH value leads to decreasing oxygen affinity and high pH values could increase it. These effects are because of formation salt bridges [14] (for example between Histidine 146 and Alpha Lyzine 40)

and stabilizing T-state which induce low oxygen affinity [15]. While, completely opposite situation could be happened in high pH environments. High level of carbon dioxide in interaction with water produces bicarbonate and proton that decreases pH and reduces the affinity of hemoglobin to bind to oxygen. The mention situation occurs in tissues where the hemoglobins should release their oxygen content [16]. So, as mentioned before, various features of hemoglobin and its allosteric regulators are pivotal for efficient transferring oxygen in blood. In diverse conditions the function of hemoglobin is disrupted and leads to various diseases such as Sickle Cell Anemia (SCA) [17].

Hemoglobin in SCA patients has Sickle or crescent form and occurs when Glutamate at position 6 in amino acid sequence is instituted with Valin [18]. This mutation in hemoglobin leads to decrease its solubility resulting in appearance hydrophobic patch is created by lieing residue Valin on the surface of T-state hemoglobin [19]. The hemoglobin with the mentioned properties is called “Hemoglobin S ” (HbS) [20]. These types of hemoglobin are incapable in transferring oxygen into tissues, so the various symptoms are reveals including oxygen delivery deficiencies, growth disturbing, painful edema, pain crisis that individuals suffer from pain in various parts of the body, fever, uandice, tachycardia and etc. The specific structure of hemoglobin S increased their attending to making clot that cessation of blood flow leads to various organ failure and stroke as the major reason of the patient death [21].

Children can inherit this gene from their parents and if the both parents be SCA patients, their child also has it [22]. The most prevalence regions are Africa and areas with high prevalence of Malaria while CSA patients are resistance to malaria [23].

Recently various studies have been performed to find a new efficient approach to cure this disease and at least on November 2019, the US Food and Drug Administration (FDA) has approved voxelotor oral tablets (Oxbryta, Global Blood Therapeutics) for the treatment of sickle cell disease (SCD) in adults and children aged 12 years and older [24]. This molecule could prevent sickling of sickle cell traid red blood and increasing the half-life of erythrocytes. Voxelotor also rises the affinity of hemoglobin for oxygen and subsequently restrains its polymerization during hypoxic situations [25]. In the present study we tried to design novel molecule based on the Voxelotor to treat SCA more efficiently. We used drug design science and chemical computation to introduce new compounds based on changing of pentet ring in isosteric isomers. Then we choose the most effective molecules with the highest potential to bind

selectively to hemoglobin S (not normal hemoglobin) resulting in HbS' lipophilic surface. This capacity makes them extraordinary efficient drugs against Sickle Cell disease. Also, assessing toxicity of the nominated molecules via simulation methods proves its safety.

Computational methods

Drug Design is a new process to discover novel chemical compounds for smart treatment of diseases [26]. This drug field is a foundation of various branches of science like chemistry, pharmacy, medicine, biotechnology and pharmacology. Drug design is basically done in one of three ways: a) screening available compounds for a specific receptor, b) investigating different substituents on a known medicinal compound, c) investigation of changes in the main backbone of a known medicinal compound [27-30]. Here, the third method was used to design new compounds. Designing the novel molecular structures was done via changing the atoms of the pentet ring with their isosters. All molecular structures were optimized using B3LYP/6-311++G(d,p) level of theory at room temperature by Gaussian 03 software. Stability and reactivity of these designed molecules were studied by global reactivity indices. These parameters were calculated using energy levels of the frontier molecular orbitals (HOMO and LUMO). Molecular docking analysis was carried out to determine the type and probability of the interactions of the molecular structures with the hemoglobin. The docking studies were done using Molecular Virtual Docker (MVD) software. On the other hand, the physicochemical and bioavailability properties of the designed molecular structures were predicted using SwissADME web tool.

Results and discussion

Evaluation of Voxelotor's physical and electrical features

At the first step in molecular designing to locate it properly in an active section of especial receptor, optimization of length and angle of bands seems crucial. The mentioned optimization is implemented via theoretical methods that various methods based on theoretic exist in computational chemistry field. The method should be chosen that its results have the highest level of converging with experimental data. Hence, due to that Voxelotor is known as a small molecule, Mechanical Quantum is the best choice for structural optimization [31].

There are various Mechanical Quantum methods and we chose Density Functional Theory (DFT) computational method. In this schema we used different DFT methods with various basis sets, and then we evaluated Voxelotor structure (Figure 1). After implementation of each method, the lengths of the bonds in molecular structure were comprised strictly with experimental data [32] and its scheme has been presented in Figure 2. The highest level of convergence (R^2=0.9137) happened using B3LYP/6-311++G (d,p) computational method. It is important to mention that the dependence is displayed by the equation y=0.9964x-0.0084. So, all of our measurements for this molecule or others, those are based on Voxelotor have been designed via the pointed computational method. As the Figure 1 have represented, none of three rings are on a same page but screwed which is resulting in the volume of electron density through the rings.

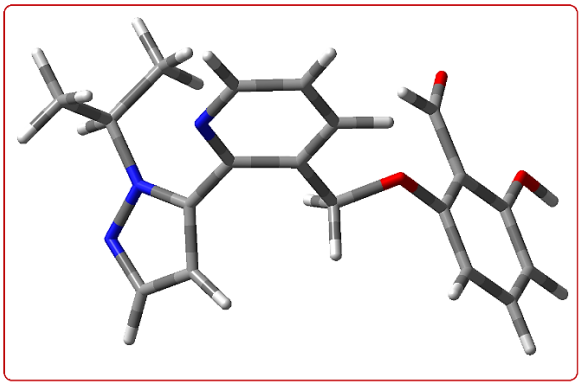


Figure 1. The optimized molecular structure of Voxelotor

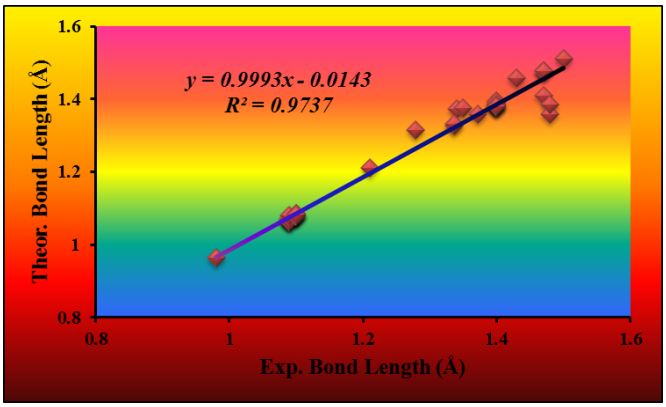


Figure 2. The experimental and theoretical bond lengths relationship of Voxelotor

For the next step, we tried to evaluate the electron density and charge distribution of molecule to estimate stability and chemical reactivity through its journey to attach the receptor and influence

on it. The greatest methods to evaluate the both mentioned features are Frontier Molecular Orbitals (FMOs) theories. These methods developed by Kenichi Fukui in 1950's [33] and the most powerful advantages of this method are its attention to the highest occupied and lowest unoccupied molecular orbitals (HOMO and LUMO) [34]. FMO provides to scientists to focus on the localization of the HOMO orbital resulting in its available free electrons to contribute in a specific reaction. In addition, the region with the Lowest Unoccupied orbital, an appropriate electrophilic site, could be recognized using FMO [33]. So, frontier orbitals of Voxelotor could be accessible by density job in Gaussian softwre. As we mentioned before, B3LYP/6-311++G(d,p) is the greatest calculation method, so it was used to study about the molecular orbitals. The results have been presented in Figure 3. Based on Figure 3, the pentet and sixtet rings contribute to create HOMO. Furthermore, the molecule that placed at the write section of the Figure 3, shows that the third ring (benzene ring and its substances) participates in an electrophilic reactivity with amino acids of hemoglobin chains (act as LOMO). Based on the table 1, the energies of HOMO and LOMO structures are "-9 eV" and "2.3 eV", respectively and the gap energy between orbitals is "11.38 eV" that is presented in Figure 4 and DOS graph. The density of states (DOS) graph demonstrates the quantity of permissible electron (or hole) states for each system at a certain level of energy [35]. This high level of gap energy leads to the suitable stability of molecule that protects it against electron transition in presentation of oxidase agents and free radicals. In fact the electron transferring from HOMO to LOMO do not occurred. Also, the DOS could reveal the probable density of occupied and virtual orbitals presented in Figure 3. Occupied orbitals which are distinguishable with green lines have the much more density. So, this molecule has remarkable tendency of contributing in nucleophilic interactions. Therefore, our compound based on its molecular structure is capable to participate in both electrophilic and nucleophilic reactions with more affinity to nucleophilic ones especially in existence of electron poor residues.

The other important factor helps us to discover the molecular structure is Molecular Electrostatic Potential (MEP) that could determine the charge distribution of a compound that relates to dipole moment, electronegativity, and partial charges of it and in fact this method offers a graphic method to determine the virtual polarity of a molecule [36]. The MEP structure of Voxelotor has been shown in Figure 5. In this map, the colors reveal data about the potential distributions of various regions of the molecule. The red, green and blue colors of the molecule in this map

express the negative, zero and positive charge, respectively. The red site is related to the electronegative atoms specially oxygen that induce nucleophilic reactions. Also, the Figure 5 revealed that the potential distribution is approximately uniform.

Reactivity potential is the other factor that could be evaluated using Global Reactivity in Disease (GRD) method. The following equation and HOMO and LOM data are used to calculate the reactivity. For efficient illustration of the stability and reactivity features of the Voxelotor, the global reactivity descriptors including energy gap (Eg), ionization potential (IP), electron affinity (EA), chemical hardness (η), chemical softness (S), electronegativity (χ), electronic chemical potential (μ) and electrophilicity index (ω) will be identified using frontier orbitals' energies [37]. The mentioned global reactivity indexes are calculated via several formula including [38]:

$$E_g = E_{LUMO} - E_{HOMO}$$

$$IP = -E_{HOMO}$$

$$EA = -E_{LUMO}$$

$$\eta = \frac{(\varepsilon_{LUMO} - \varepsilon_{HOMO})}{2}$$

$$\chi = \frac{-(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\mu = \frac{(\varepsilon_{LUMO} + \varepsilon_{HOMO})}{2}$$

$$\omega = \frac{\mu^2}{2\eta}$$

$$S = \frac{1}{\eta}$$

The results have been shown in Table 1. Based on the presented data, the energies of HOMO and LOMO have been calculated "-9 eV" and "2.38 eV", in turn. So, the stability of molecule is resulting in low energy of the frontier molecular orbitals. The gap between HOMO and LOMO energies is "11.38 eV" that leads to inhibition of electron transferring from HOMO to LOMO. In addition, chemical hardness and softness are the most important parameters which both of them are in normal (middle) range. The pointed data revealed that beside the high level of stability of molecular against free radical agents, our compound could contribute in reactions with HbS'

active site. Furthermore, the low value of electrophilicity index of molecule describes its affinity to participant in reactions with electron poor residues instead of electron rich ones.

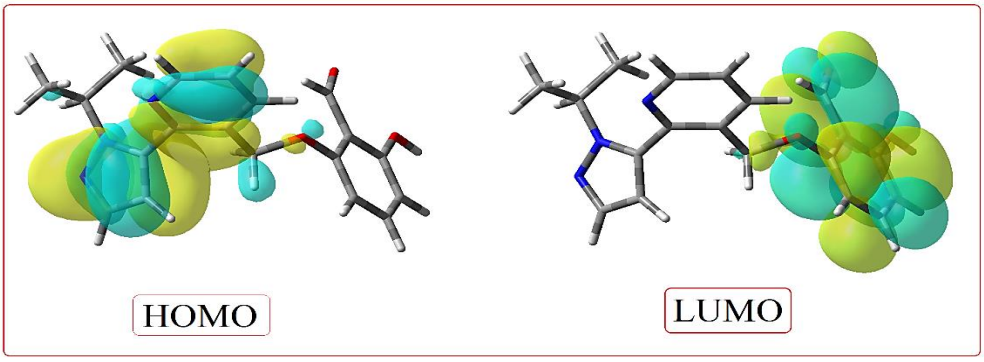


Figure 3. The frontier molecular orbitals of Voxelotor

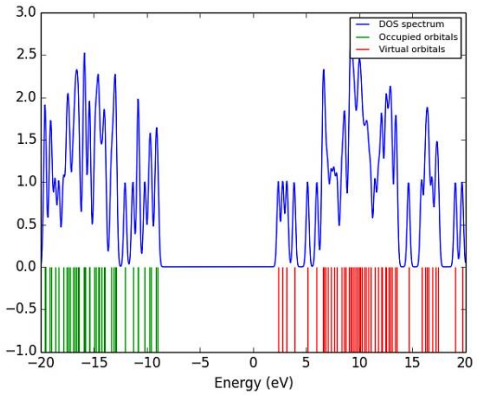


Figure 4. The DOS graph of Voxelotor

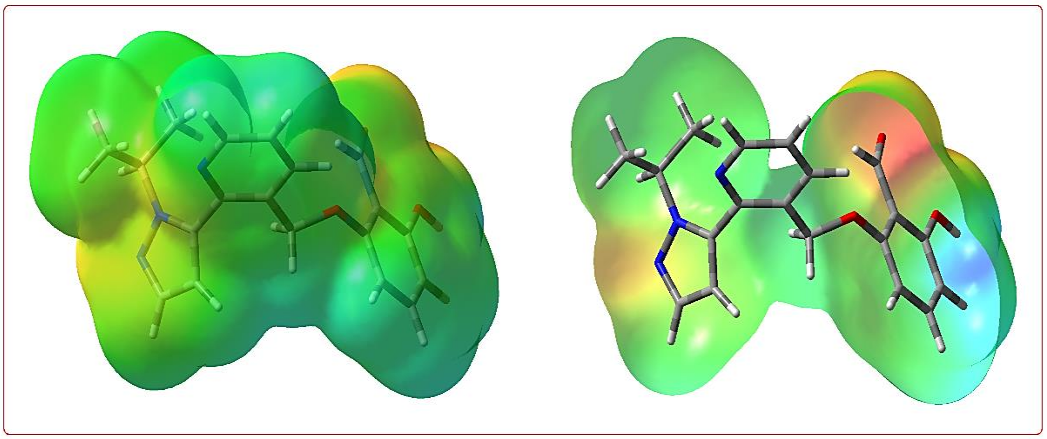


Figure 5. The MEP graph of Voxelotor

Table 1. Global reactivity indices of Voxelotor

Parameter	Energy value (eV)
HOMO	-9.00
LUMO	2.38
Ionization Potential (IP)	9.00
Electron Affinity (EA)	-2.38
Energy Gap (Eg)	11.38
Electronegativity (χ)	3.31
Chemical Potential (μ)	-3.31
Chemical Hardness (η)	5.69
Chemical Softness (S)	0.176
Electrophilicity index (ω)	0.963

Molecular docking analysis of Voxelotor binding to the Hbs:

Docking potential is a critical parameter in designing a molecule and molecular biology [39]. For this aim, docking potential of Voxelotor to locate at the HbS' active site was evaluated using Molecular Virtual Docking (MVD) and its results have been presented in Table 2. This parameter is "-119.814" (MolDock score) which is sufficient for creating bonds with active site strongly. Docking occurs via steric (score = -94.127) and hydrogen bonds (score = -4.999). Based on our results, Voxelotor creates steric bonds with Leu 2 (C), Ser 131 (C), Ala 130 (C), Lys 127 (C), Ser 131 (A), Pro 77 (A), Val 135(A), Val 1(C), Thr 134 (A), Ser 138(A), Thr 134(C), Ala 130(A), Val 1(A), Pro 77(C), Val 135(C), Val 132(C) and Met 76(C) and hydrogen bond with Thr 134(C) and Ser 131(A).

The MDS value which is related to interaction between molecule and Hbs is -124.173 that shows Voxelotor contributes in interactions with active site and water molecules, exist around the hemoglobin, without any interaction with cofactors (MDS value is zero). Beside external interactions, electronegative atoms and screwed structure lead to creating internal interactions which reduce the potency of molecule and receptor interactions. Generally, voxelotor interacts with various chains of HbS including 5E83 [A] and 5E83 [C] proteins of alpha chains and 5E83 [B] and 5E83 [D] proteins of beta chains.

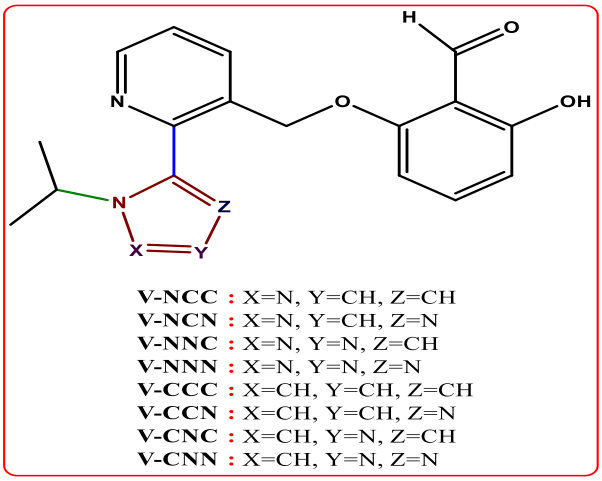
In addition to molecular and electron structural study of Voxelotor and evaluation of its interaction with HbS, we tried to design novel molecules based on voxelotor with much more

affinity to HbS. The designing performed on the pentet ring and via insertion of one or more nitrogen atoms in different sites of this ring.

Figure 6. Ligand Voxelotor embedded in the active site of the hemoglobin S

Docking analysis of the novel designed molecular structures

As described before, Voxelotor can create bonds (mostly steric bonds) with active site of the HbS. In this section we aim to design novel molecules based on the Voxelotor backbone with much more interaction capacity to enhance the efficacy of the drug. For this respect, the pentetring was chosen and one or more nitrogen atoms placed instead of carbon in this ring. The molecular structures of Voxelotor and designed molecules are shown in Scheme 1. Seven molecules including V-NCC, V-NCN, V-NNC, V-NNN, V-CCC, V-CCN, V-CNC and V-CNN were designed by mentioned methods.



Scheme 1. The designed molecular structures based on Voxelotor

For beginning, all designed molecules were adjusted at B3LYP/6-311++G(d,p) level of theory. Then, the docking of the adjusted molecules into the active site of the HbS were analysed (Table 2). Based on the data presented in Table 2, V-NNC, V-NNN, V-CNC and V-CNN showed enhanced interaction with HbS than the Voxelotor and interaction capacity of V-NNN is remarkably stronger that the others.

Table 2. Docking analysis data of the designed molecular structures

Molecules	MolDock Score
V-NCC (Voxelotor)	-119.814
V-NCN	-119.135
V-NNC	-121.702
V-NNN	-129.767
V-CCC	-118.531
V-CCN	-118.540
V-CNC	-121.345
V-CNN	-124.127

Physicochemical descriptors and ADME parameters of the designed compounds

As mentioned before, structural and docking properties assessment revealed that V-NNC, V-NNN, V-CNC and V-CNN have the highest level of interaction potential with HBs in comparison with Voxelotor. Physicochemical characteristics and ADME parameters are crucial to evaluate the behavior of compounds as a drug. To predict these features, we used SwissADME web tools.

Oral bioavailability of molecules has been assessed and presented in Figure 7. Six parameters which are necessary for a compound to be a drug, demonstrated for each designed molecule. These factors for all compounds are in pink region, the region with suitable level of bioavailability. So, presented result shows that our proposed molecules have appropriate bioavailability.

Results of the physicochemical characteristics and ADME parameters have been shown in Table 3 and various properties of molecule have been evaluated. Csp3 fraction, the ratio of sp3 hybridized carbons to the entire carbon count of the molecule [40], was assessed in this study. The results show that all the four compounds are similar to Voxelotor in this parameter. The

other pointed factor is TPSA (Topological Polar Surface Area) [40] which reveals the area of a molecule that contributes in interactions. In comparison with Voxelotor, all designed structures except V-CNC have higher TPSA value than Voxelotor. So, V-CNC was deleted from the study and we continued with the other three compounds.

Lipophilicity is the other parameter that plays a pivotal role in various aspects of novel drug designing including prediction of solubility, biological membrane permeability, safety, and efficacy and toxicity features of compounds [41]. In this study we demonstrated log $P_{O/W}$, the partition coefficient between n-octanol and water, to estimate the lipophilicity of molecules. The results revealed that all three designed molecules (V-CNN, V-NNC and V-NNN) have similar lipophilicity feature to Voxelotor.

In this project we use ESOL (log s) to evaluate the water solubility of investigated compounds. There are six group to categories solubility property of molecules: 1) Insoluble (Log S < -10), 2) Poorly soluble (-10 < Log S < -6), 3) Moderately soluble (-6 < Log S < -4), 4) Soluble (-4 < Log S < -2), 5) Very soluble (-2 < Log S < 0) and 6) Highly soluble (Log S > 0) [39-41]. As is presented in table 3, log s value of all compounds is lower than Voxelotor's that indicates all of them are more water soluble than Voxelotor.

Voxelotor is a molecule with potential to permeate through Blood Brain Barrier [32]. The results show that our novel investigated molecules have limited capacity to cross from BBB that leads to its higher safety than Voxelotor.

Cytochrome p450 is a family of enzymes that play an important role in drug metabolism which leads to reduction or increase in clearance of molecules that any changes in their activity could be associate with drug toxicity and adverse events [39-41]. Between three remained molecules, only V-NNC could inhibit CYP450 as Voxelotor.

Lipinski's rule is one of the rules that demonstrate the drug likeness and the most important ones. This rule also is called Pfizer's rule or rule of five (RO5).

In fact, this rule is used to evaluate pharmacokinetics parameters (including absorption, distribution, metabolism, and excretion ("ADME")) of molecule in body to describe that physicochemical properties of a specific molecule make it a probable orally active drug in humans [42-50]. Our data shows that all of the investigated molecules obey the Lipinski's rule (MLOGP ≤4.15, relative MW ≤ 500, N or O ≤ 10, NH or OH ≤ 5). In addition, bioavailability of designed compounds is 0.55 as same as Voxelotor.

Table 3. ADME properties of the designed molecules

Physiochemical descriptors and ADME parameters	Compounds							
	V-NCC	V-NCN	V-NNC	V-NNN	V-CCC	V-CCN	V-CNC	V-CNN
Fraction Csp3	0.21	0.22	0.22	0.24	0.20	0.21	0.21	0.22
TPSA (Å2)	77.24	90.13	90.13	103.02	64.35	77.24	77.24	90.13
Log PO/W	2.59	2.22	2.19	2.02	3.02	2.50	2.45	2.14
Log S (ESOL)	-3.73	-3.59	-3.39	-3.32	-4.00	-3.60	-3.60	-3.23
Class	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble	Soluble
GI Absorption	High	High	High	High	High	High	High	High
BBB permeant	Yes	No	No	No	Yes	Yes	Yes	No
P-gp substrate	No	No	No	No	No	No	No	Yes
CYP450 inhibitor	Yes	Yes	Yes	No	Yes	Yes	Yes	No
Druglikeness (Lipinski)	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55

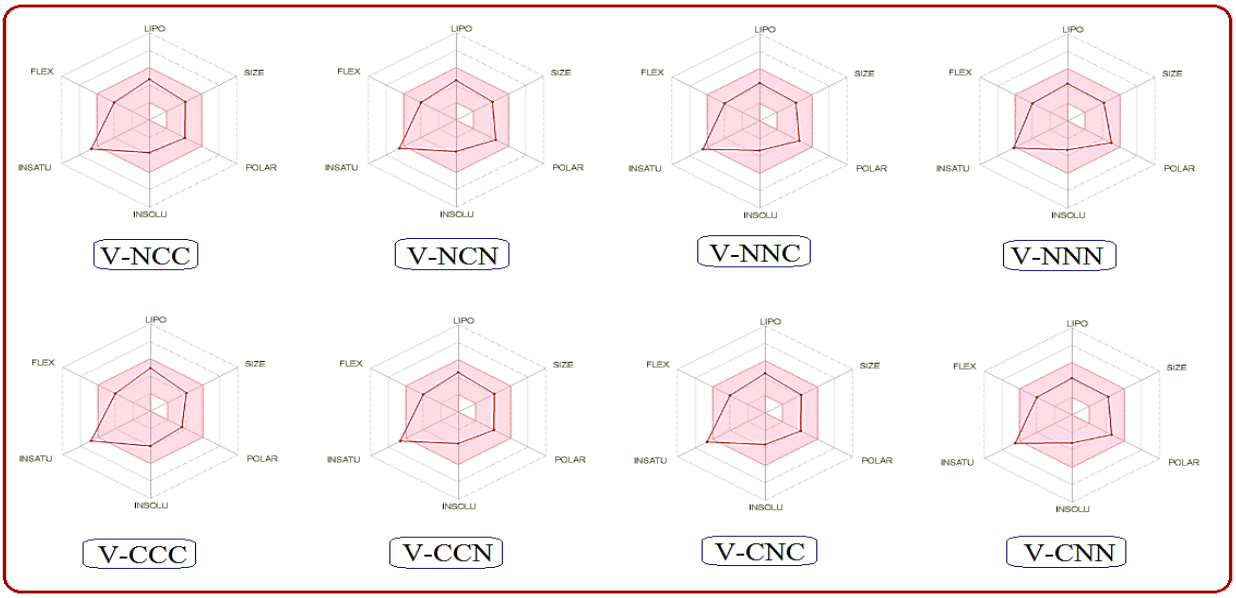


Figure 7. The oral bioavailability zone of the designed molecules

Conclusions

Scientific efforts to find a new drug to cure the Sickle Cell disease leads to developing Voxelotor. This molecule achieved FDA approve on 26 November 2019. Various analysis have been shown that this compound is effective to prevent sickling procedure of red blood cells,

enhancing the half-life of erythrocytes, increasing affinity of hemoglobin for oxygen and preventing hemoglobin polymerization in hypoxic conditions.

In the presented article, we tried to design novel molecules based on Voxelotor to treat sickling cell disease more effectively. To reach this aim, as the first step, the electronic properties, reactivity and stability of Voxelotor and its docking properties into the active site of the hemoglobin S were evaluated. In the next step, designing new compounds based on the Voxelotor structure were performed. Then, docking study was used to examine the interaction of designed molecules with active site of the hemoglobin. Our result showed four molecules including V-NNC, V-NNN and V-CNC could create more efficient binds with hemoglobin s in comparison with Voxelotor. In addition, the physicochemical properties of the designed molecules were studied and the data revealed that V-NNC is the only molecule that has higher drug potential than Voxelotor. We intensely believe that this method of Voxeotor-based structure assessing and evaluating will be of great interest in future endeavors in drug design and drug delivery.

Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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References

[1] I. Rehman, S. Botelho, Secondary Protein Structure in Biochemistry, *StatPearls Publishing*, (2018).

[2] Y. Morita, T. Yamada, M. Kureishi, K. Kihira, T. Komatsu, *J. Phys. Chem. B* 122, 12031 (2018).

[3] R. Macdonald, M. Phillips, D. Cascio, M. Collazo, R. T. Clubb, *The FASEB Journal* 32, 613 (2018).

[4] J.-K. Hong, E. H. Jho, H. S. Choi, G. Kang, *Sci. Total Environ.* 627, 1174 (2018).

[5] M. Khoshouei, R. Danev, J. M. Plitzko, W. Baumeister, *J. Mol. Biol.* 429, 2611 (2017).

[6] E. Duscio, F. Vasques, F. Romitti, F. Cipulli, L. Gattinoni, *J. Thorac Dis.* 10, 81 (2019).

[7] M. Bellizzi and M. Bonello, *J. Emerg. Med. Intens. Care* 3, 1 (2018).

[8] E. I. Kvasyuk, T. I. Kulak, O. V. Tkachenko, I. A. Mikhayelopulo, A. I. Zinchenko, V. N. Barai, S. B. Bokut, S. S. Marennikova, E. V. Chekunova, *Khimiko Farmatsevtichskii Zhurnal,* 23, 699 (1989).

[9] J. J. Yan, T. Kroll, M. L. Baker, S. A. Wilson, R. Decréau, M. Lundberg, D. Sokaras, P. Glatzel, B. Hedman, K. O. Hodgson, *Proc. Natl. Acad. Sci.* 116, 2854 (2019).

[10] R. Ramachandran, C. Zhao, D. Luo, K. Wang, F. Wang, *Appl. Surf. Sci.* 460, 33 (2018).

[11] S. Sakurai, D. Sawada, T. Yonetani, A. Tsuneshige, *Biophys. J.* 110, 48a (2016).

[12] M. Rossetti, S. Ranallo, A. Idili, G. Palleschi, A. Porchetta, F. Ricci, *Chem. Sci.* 8, 914 (2017).

[13] B. Jensen, A. Fago, *J. Inorg. Biochem.* 182, 133 (2018).

[14] W. A. Eaton, E. R. Henry, J. Hofrichter, S. Bettati, C. Viappiani, A. Mozzarelli, *IUBMB life* 59, 586 (2007).

[15] A. Bellelli, M. Brunori, *Biochim. Biophys. Acta* 1807, 1262 (2011).

[16] a) W. Yan, Y. Xie, X. Wang, F. Jia, X. Li, *Food Res. Int.* 106, 885 (2018); b) H. Kaya, O. Hisar, S. Yılmaz, M. Gürkan, Ş. A. Hisar, *Environ. Toxicol. Pharmacol.* 44, 114 (2016).

[17] I. Benenson, S. Porter, *Orthop. Nurs.* 37, 221 (2018).

[18] S. K. Tossea, E. G. Adji, B. Coulibaly, B. A. Ako, D. N. Coulibaly, P. Joly, S.-B. Assi, A. Toure, R. Jambou, *BMC Res. notes* 11, 215 (2018).

[19] B. J. Kumar, A. B. Kumar, L. L. Reddy, *World J. Parm. Res.* 5, 328 (2016).

[20] M. Bender, *GeneReviews,* 2017, 1993 (2017).

[21] R. E. Ware, M. de Montalembert, L. Tshilolo, M. R. Abboud, *The Lancet* 390, 311 (2017).

[22] A. Habara, M. H. Steinberg, *Exp. Biol. Med.* 241, 689 (2016).

[23] a) E. Depetris-Chauvin, D. N. Weil, *Econ. J.* 128, 1207 (2017); b) S. D. Grosse, I. Odame, H. K. Atrash, D. D. Amendah, F. B. Piel, T. N. Williams, *Am. J. Prev. Med.* 41, S398 (2011).

[24] B. Metcalf, C. Chuang, K. Dufu, M. P. Patel, A. Silva-Garcia, C. Johnson, Q. Lu, J. R. Partridge, L. Patskovska, Y. Patskovsky, *ACS Med. Chem. Lett.* 8, 321 (2017).

[25] N. M. Elmaki, I. A. Al Sadawi, A. M. Gbaj, A. Hermann, *Drug. Des. Intellect. Prop. Int. J.* 2, 191 (2018).

[26] M. El-Naggar, H. A. Sallam, S. S. Shaban, S. S. Abdel-Wahab, E. Amr, A. El-Galil, M. E. Azab, E. S. Nossier, M. A. Al-Omar, *Molecules* 24, 1066 (2019).

[27] M. Nabati, V. Bodaghi-Namileh, *Int. J. New. Chem*. 6, 254 (2019).

[28] M. Nabati, *J. Med. Chem. Sci.* 3, 22 (2020).

[29] M. Nabati, *Chem. Methodol.* 2, 223 (2018).

[30] M. Nabati, *Iran. Chem. Commun.* 7, 324 (2019).

[31] M. Nabati, H. Sabahnoo, *J. Med. Chem. Sci.* 2, 118 (2019).

[32] B. Metcalf, C. Chuang, K. Dufu, M. P. Patel, A. Silva-Garcia, C. Johnson, Q. Lu, J. R. Partridge, L. Patskovska, Y. Patskovsky, S. C. Almo, M. P. Jacobson, L. Hua, Q. Xu, S. L. Gwaltney, C. Yee, J. Harris, B. P. Morgan, J. James, D. Xu, A. Hutchaleelaha, K. Paulvannan, D. Oksenberg, Z. Li, *ACS Med. Chem. Lett.* 8, 321 (2017).

[33] M. Nabati, *Asian J. Green Chem.* 3, 258 (2019).

[34] M. Nabati, V. Bodaghi-Namileh, *J. Phys. Theor. Chem. IAU Iran* 15, 149 (2018).

[35] M. D. Esrafili, *ChemistrySelect* 3, 12072 (2018).

[36] H. Nazemi, M. Mirzaei, E. Jafari, *Adv. J. Chem. B* 1, 3 (2019).

[37] Z. S. Alidoosti, M. Mirzaei, *Adv. J. Chem. B* 1, 23 (2019).

[38] M. Nabati, V. Bodaghi-Namileh, *Eurasian Chem. Commun.* 2, 234 (2020).

[39] A. De, H. P. Ray, P. Jain, H. Kaur, N. Singh, *J. Mol. Struct.* 1199, 1 (2020).

[40] M. Nabati, V. Bodaghi-Namileh, *J. Phys. Theor. Chem. IAU Iran* 15, 159 (2018).

[41] M. Nabati, H. Sabahnoo, E. Lohrasbi, M. Mazidi, *Chem. Methodol.* 3, 383 (2019).

[42] M. Nabati, V. Bodaghi-Namileh, *Adv. J. Chem. A* 3, 58 (2020).

[43] S. Samadi, R. Ahmadi, M. Kohi, *Int. J. New. Chem*. 2, 8 (2015).

[44] E. Hegin, J. Shalini, A. Subramaniyan, *Int. J. New. Chem*. 5, 181 (2018).

[45] M. Mozafarjalali, M. Hajiani, A. Haji, *Int. J. New. Chem*. 7, 111 (2020).

[46] M. S. Nagar, *Int. J. New. Chem*. 7, 150 (2020).

[47] Z. Sarikhani, M. Manoochehri, *Int. J. New. Chem*. 7, 30 (2020).

[48] F. Z. Benhachem, T. Attar, F. Bouabdallah, *Chem. Rev. Let*. 2, 33 (2019).

[49] M. Nabati, E. Pournamdari, V. Bodaghi-Namileh, Y. Dashti-Rahmatabadi, S. Sarshar, *Adv. J. Chem. B* 2, 64 (2020).

[50] F. Krika, A. Krika, A. Azizi, *Chem. Rev. Let*. 2, 59 (2019).

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