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Original article

Exploration of electronic properties, radical scavenging activity and QSAR of oxadiazole derivatives by molecular docking and first-principles approaches

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ABSTRACT

Eight new oxadiazole derivatives were designed then geometries for ground state were optimized through Density Functional Theory (DFT) at B3LYP/6-31G** level. Single electron transfer mechanism has been studied to understand the antioxidant ability of the oxadiazole derivatives. Then molecular electrostatic potential and quantitative structure–activity relationship (QSAR) was probed. Additionally, we shed light on different molecular descriptors, e.g., electrophilicity(ω), electronegativity(χ), electrophilicity indices(ωi), hardness(η), softness(S) and chemical potential(μ).The smaller value of ionization potential for **5a** is showing that it might be efficient antioxidant candidate. The electrophilic reactive sites in **2a, 3a, 4a**, **5a** and **7a** derivatives might be a good choice for reactivity that would be advantageous to improve the biological activity. The polar surface area of **3a**, **4a** and **5a** derivatives was found < 60 A^2 which is enlightening that these drugs might be suitable as orally active and for brain penetration. First-principles calculations and molecular docking results revealed that **5a** would lead to superior antioxidant activity.

1. Introduction

Heterocyclic azole derived products gained noteworthy attention for multifunctional purposes (Sauer et al., 2017; Abd-Ellah et al., 2017; Desai et al., 2016). Their unique properties make them appropriate to be used as biological active compounds (Genc et al., 2016; Hou et al., 2014; Kendre et al., 2019; Rauf and Farshori, 2012), sensors (Oliveira et al., 2011) and semiconducting devices likewise organic field effect transistors (OFETs). The heterocyclic five-membered compounds like pyrazoles, 1,3,4-oxadiazole and isoxazoles rings nucleus gained importance because of their versatile biological properties such as anti-HIV, antitubercular and antioxidant (El-Emam et al., 2004; Padmavathi et al., 2010). The cardiovascular, atherosclerosis, cancer, neurodegenerative diseases resulted during oxidative stress damage of biological macromolecules with Reactive oxygen species (ROS) and neutral molecules (hydrogen peroxide; Pisoschi and Pop, 2015; Kotaiah et al., 2012). The biological substrates oxidation, malignant changes, DNA mutations were prevented with aids of antioxidants that are able to scavenge free radical species. Furthermore potent radical scavengers discovered through heterocyclic pharmacophores combination with well-known phenolic antioxidants like 1,3,4-oxadiazole substituted scaffold having broad spectrum biological activity (Lukin et al., 2016). Alzheimer, Parkinson and atherosclerosis type lethal diseases associated with generation of elevated concentrations of reactive nitrogen and oxygen species (RNS and ROS) (Uttara et al., 2009). In this connection, numerous study information exhibited that exogenous antioxidant substances supplementation are operational to decrease the tissue damage along with reduction of oxidative stress (Nogueira et al., 2004).

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Recently, we have designed eight 1,3,4-oxadiazole derivatives namely, [5-(4-chlorophenyl)-1,3,4-oxadiazol-2-yl] (3-methyl-1,6-diphenyl-1*H*-pyrazolo pyridin-4-yl) methanone (**1a**), (3-methyl-1,6-diphenyl-1*H*-pyrazolo pyridin-4-yl) [5-(4-nitrophenyl)-1,3,4-oxadiazol-2-yl] methanone **(2a)**, [5-(4-fluorophenyl)-1,3,4-oxadiazol-2-yl] (3-methyl-1,6-diphenyl-1*H*-pyrazolo pyridin-4-yl) methanone (**3a**), [5-(4-bromophenyl)-1,3,4-oxadiazol-2-yl] (3-methyl-1,6-diphenyl-1*H*-pyrazolo pyridin-4-yl) methanone (**4a**), (3-methyl-1,6-diphenyl-1*H*-pyrazolo pyridin-4-yl) [5-(4-methyl phenyl)-1,3,4-oxadiazol-2-yl] methanone (**5a**), [5-(2-furyl)-1,3,4-oxadiazol-2-yl] (3-methyl-1,6-diphenyl-1*H*-pyrazolo pyridin-4-yl) methanone (**6a**), (3-methyl-1,6-diphenyl-1*H*-pyrazolo pyridin-4-yl) [5-(4-pyridinyl)-1,3,4-oxadiazol-2-yl] methanone (**7a**) and [5-(2-chloro-4-nitrophenyl)-1,3,4-oxadiazol-2-yl] (3-methyl-1,6-diphenyl-1*H*-pyrazolo pyridin-4-yl) methanone (**8a**) then their antioxidant and anti-lipoxygenase activities were measured experimentally. Additionally, we also calculated their electronic properties, structure–activity relationship (SAR) and quantitative structure–activity relationship (QSAR).

Previous studies exposed that density functional theory (DFT) and quantum chemical methods are rational to compute the parameters which would help to understand the radical scavenging activity of antioxidant compounds (Antonczak, 2008; Kalita et al., 2012; Sadasivam et al., 2012; Najafi et al., 2013; Mikulski et al., 2014; Najafi and Naqvi, 2014). In the present study, we have designed eight new oxadiazole derivatives of **1a**-**8a** by incorporating the keto (-C = O) group between oxadiazole and pyridine moieties, see Fig. 1. We studied in detail the electro-optical and molecular properties of newly designed 1,3,4-oxadiazole derivatives (**1a**-**8a**) then compared their scavenging activity and physiochemical properties. We investigated the effect of keto incorporation on the electronic properties, ionization potential and physiochemical properties. The DFT methods (Kohn et al., 1996; Becke, 1993; Miehlich et al., 1989; Abbas et al., 2018; Kooh et al., 2014; Irfan et al., 2020; Irfan et al., 2019; Irfan et al., 2020) is good approach for calculating the ionization potentials (IPs), antioxidant behavior and ability of the oxadiazole derivatives. Moreover, we have studied SAR, QSAR (Ghasemi and Nemati-Rashtehroodi, 2015), molecular electrostatic potentials (MEPs), different molecular descriptors, e.g., electrophilicity indices(ωi), hardness(η), softness(S), electronegativity(χ), electrophilicity(ω) and chemical potential(μ) by DFT and molecular docking to understand the active sites which have been explored and discussed in the current study.

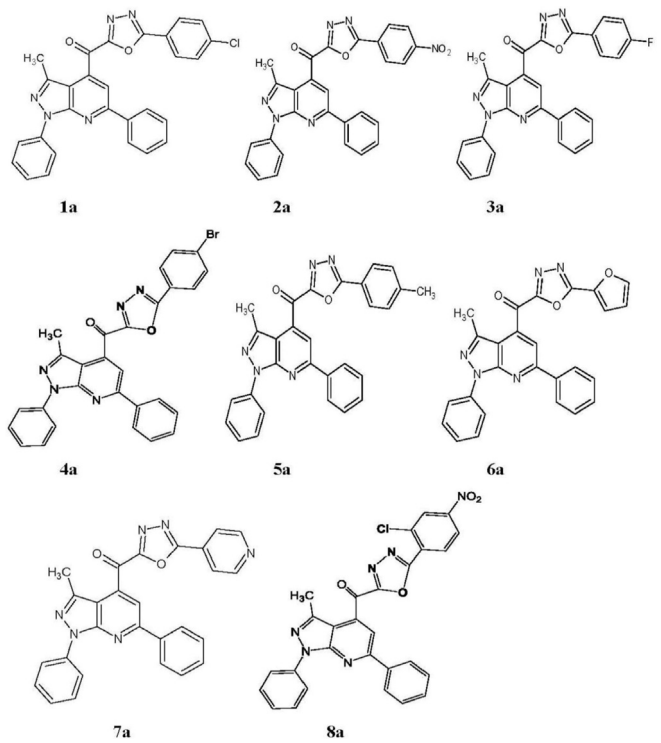

Fig. 1. The structures of 1,3,4-oxadiazoles (**1a**-**8a**).

2. Computational details

The process of radical scavenging can be better understood by the frequently used single-electron and H-atom transfer mechanisms (Belcastro et al., 2006; Wright et al., 2001). Molecules contains hydroxyl groups its H-atom transfer pathway is accustomed to comprehend radical scavenging action, as within these molecules the transfer of hydrogen atom would be more promising. The 1,3,4-oxadiazole substituted scaffold which have been studied in the ongoing research work without the presence of hydroxyl group/groups. Currently, we elucidate the detailed one-electron transfer mechanism for various 1,3,4-oxadiazole scaffold. The experimental data is presented using B3LYP functional that has been proven an efficient computation procedure (Irfan et al., 2018). The B3LYP/6-31G** level is used for the optimization of ground state geometries in the current study. The various reactivity descriptors were computed through DFT method from the equations (1)–(8).

The electronegativity (χ) was computed through Mulliken procedure as:

$$\chi=(E_{HOMO} + E_{LUMO})/2 \quad (1)$$

The eq. (2) used to figure out the hardness (η) in 1,3,4-oxadiazole scaffold:

$$\eta=(E_{LUMO} - E_{HOMO})/2 \quad (2)$$

Using eq. (3) the electrophilicity (ω) of 1,3,4-oxadiazole derivative was calculated:

$$\omega=(E_{HOMO} + E_{LUMO}/2)^2/2\eta \quad (3)$$

The eq. (4) used to measure the Softness (S) of studied molecules:

$$S = 1/_{2\eta} \quad (4)$$

The values of electrophilicity index (ωi) was computed through eq. (5):

$$\omega i = \mu^2/2\eta \quad (5)$$

Substances chemical potential (μ) was determined with the help of eq. (6):

$$\mu=-(E_{HOMO} + E_{LUMO}/2) \quad (6)$$

The values of (IP and EA) were calculated as per eq. (7) and (8), respectively

$$IP = -E_{HOMO} \quad (7)$$

$$EA = -E_{LUMO} \quad (8)$$

All the computations were carried out through Gaussian16 software (Frisch et al., 2016) besides SAR, QSAR examinations which have been accomplished with the aid of Spartan '14 v1.1.8′ at B3LYP/6-31G* level of theory. The molecular docking was performed in Autodock version 4.2. The H_2O molecules were deleted from the enzyme before performing the calculations. Moreover,

polar hydrogen atoms were added in the enzyme. The compound was docked with enzyme by selecting grid coordinates (X, Y, and Z-axis).

3. Results

The antioxidant inhibition with standard 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging activity (RSA) assay were evaluated which can provide a quick procedure for the RSA screening of targeted molecules. The basic 1,3,4-oxadiazoles skeleton with electron-withdrawing (–NO2) or electron-donating groups (–N $(CH_3)_2$) substituted phenyl moieties favor the biological activity particularly the antioxidant inhibition. In order to understand its electron or hydrogen radical providing potential to DPPH radical, ensure to get stable diamagnetic compounds that gives higher antioxidant potential (Musad et al., 2011). The pyrazoline amidoximes and their 1,2,4-oxadiazole scaffold were examined for *in vitro* antimicrobial, antioxidant as well as anti-inflammatory potential. The obtained results showed excellent anti-lipid peroxidation potential along with superb DPPH radical scavenging inhibition, potent antimicrobial and anti-inflammatory activities compared with standard drug. Based one antioxidant, antibacterial, antifungal and anti-inflammatory potential they are considered as promising candidates for *in-vivo* studies (Ningaiah et al., 2013). Antioxidant properties of 1,3,4-oxadiazole/thiadiazole substituted (S and Se) scaffold, were evaluated with DPPH and phosphomolybdenium inhibition. The antioxidant potential signifying that substituents inclusion may permit electron donation out of that DPPH radical (Farghaly et al., 2014). The pyrazolo[3,4-b] pyrazines containing, thiadiazolyl, thiazolidinonyl, 1,2,4-oxadiazolylsubstituents along with related substituents were evaluated for anticonvulsant inhibition alongside Pentylenetetrazole (PTZ) prompted convulsions in mice. The results revealed that compounds exhibited excellent anticonvulsant inhibition ($p < 0.01$) compared with standard. The anticonvulsant inhibition against PTZ-induced tonic seizures, molecules having 2-phenyl group within thiazolidinone moiety is unsubstituted, exhibited noteworthy protective inhibition. The insertion of two Cl, NO_2 or methoxyl moieties within phenyl ring rendered molecules with highest inhibition (Ma et al., 2013). The 1,3,4-oxadiazole along with thieno [2,3-d] pyrimidine derivatives were screened for *in vitro* antioxidant inhibition and showed significant nitric oxide (NO), DPPH and hydrogen peroxide (H_2O_2) radical scavenging potential. With DPPH radical method studied compounds exhibited IC_{50} value 16.35–17.70 mg/ml compared with standard ascorbic acid IC_{50} 15.11 mg/ml. Furthermore, radical scavenging potential becomes more significand with NO, DPPH and H_2O_2 methods as the concentration increases. The thienopyrimidine ring substituted along both sides with electron donating substituent improves the activity potential whereas electron withdrawing groups (–NO2) decrease its potential (Kotaiah et al., 2012). The substituted 1,3,4-oxadiazole scaffold with 1,4-benzodioxan groups were evaluated for *in vitro* antioxidant potential with DPPH, ABTS and FRAP scavenging bioassays compared with standard Trolox and BHT. These were further screened towards antioxidant inhibition against lipid peroxidation (LPO) of mice liver microsomes and AAPH induced supercoiled DNA breakage (Mihailović et al., 2017). The 1,3,4-oxadiazoles scaffold with diacylhydrazine precursors having DPPH activity (IC_{50} values 13.59–22.17 mM) were also further screened for ABTS radical, H_2O_2 scavenging potential along with strong ferric ion reducing aptitude. *In vitro* antioxidant potential of active compounds showed their defensive impacts in ordinary lung fibroblasts MRC-5 contrary to H_2O_2 induced oxidative stress (Ayhan-Kılcıgil et al., 2007). The oxadiazolyl benzimidazole derived-products were also examined for antioxidant potential with estimation of microsomal NADPH-dependent activity with microsomal ethoxyresorufin O-deethylase (EROD assay) and lipid peroxidation (LP assay) activity. The results revealed the inhibitory effects (28%) with LP assay at 10^{-3}M concentration lower than BHT standard (65%) (Kelder et al., 1999). In order to explore the antioxidant potential of designed compounds (**1a** and **8a**), theoretical, SAR, SPAR and QSAR methodologies were employed to recognize bioactive substituted 1,3,4-oxadiazole scaffold in present work. The screening strategies employed to endorse its significant role towards identification of bioactive molecules useful for the purpose of new drug discovery.

Electronic Properties. The Fig. 2, displayed frontier molecular orbitals (FMOs) arrangement along with to explore the highest occupied and lowest unoccupied molecular orbitals (HOMOs/LUMOs) of 1,3,4-oxadiazole compounds. In all the studied derivative **1a-8a**, the HOMO is delocalized on the phenylpyrazole moiety. The LUMO is distributed on the 1,3,4-oxadiazole-pyridinmethanone parts excluding **2a** and **8a** where nitrophenyl oxadiazole substituents are contributing. The intra-molecular charge transfer (ICT) was noted within phenylpyrazole substituent to the 1,3,4-oxadiazole among all the computed molecules excluding **2a** and **8a**.

The HOMO/LUMO energies (E_{HOMO}, E_{LUMO}) and HOMO–LUMO (E_{gap})energy gaps, electrophilicity indices (ωi), hardness (η), softness (S), electrophilicity (ω) and electronegativity (χ) through B3LYP/6-31G** theory level were formulated within Table 1. The computed tendency within E_{HOMO} *is* **5a > 3a > 1a = 4a > 7a > 2a > 8a > 6a**, E_{LUMO} **5a > 3a > 1a > 4a > 7a > 6a > 2a > 8a** and E_{gap} **5a > 3a > 1a > 4a > 7a > 6a > 2a > 8a**. The highest energies for the HOMO and LUMO as well as largest E_{gap} has been observed for the **5a** derivative among all the studied compounds. Larger E_{gap} of **5a** derivative revealed that it would be thermodynamically more stable as compared to the other counterparts. The radical scavenging activity of antioxidant compounds is correlated with the HOMO energies as well.

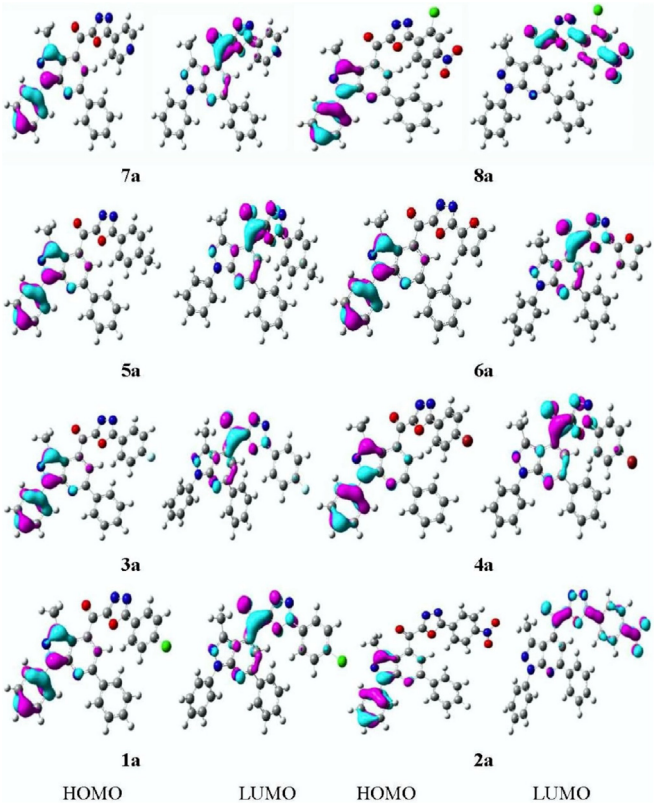

Fig. 2. Charge density of HOMOs and LUMOs of 1,3,4-oxadiazoles.

Table 1
Different chemical descriptors (in eV) of oxadiazole derivatives obtained at B3LYP/6-31G** level of theory.

	1a	2a	3a	4a	5a	6a	7a	8a
E_{HOMO}	−5.95	−6.05	−5.93	−5.95	−5.88	−6.22	−5.99	−6.07
E_{LUMO}	−2.90	−3.31	−2.85	−2.91	−2.75	−3.29	−3.03	−3.44
E_{gap}	3.05	2.74	3.08	3.04	3.13	2.93	2.96	2.63
IP	5.95	6.05	5.93	5.95	5.88	6.22	5.99	6.07
EA	2.90	3.31	2.85	2.91	2.75	3.29	3.03	3.44
χ	4.42	4.68	4.39	4.43	4.31	4.75	4.51	4.75
η	1.52	1.37	1.54	1.52	1.57	1.46	1.48	1.31
ω	6.43	7.99	6.26	6.45	5.92	7.73	6.87	8.61
S	0.33	0.36	0.32	0.33	0.32	0.34	0.34	0.38
μ	−4.42	−4.68	−4.39	−4.43	−4.31	−4.75	−4.51	−4.75
ωi	6.43	7.99	6.26	6.45	5.92	7.73	6.87	8.61

Table 2
Different SAR descriptors of oxadiazole derivatives obtained at B3LYP/6-31G** level of theory (μD = dipole moment; HBD = hydrogen bond donor; HBA = hydrogen bond acceptor; PSA = polar surface area; S.E. = solvation energy; Pol. = Polarizability).

	μD (Debye)	Area (A^2)	Volume (A^3)	Log P	HBD	HBA	Pol.	PSA (A^2)	S.E. (KJ/mol)
1a	6.12	484.34	472.76	7.93	0	7	79.06	55.658	−32.23
2a	3.15	494.28	480.65	7.40	0	10	79.72	94.589	−33.3
3a	6.09	474.28	463.66	7.53	0	7	78.31	55.576	−27.71
4a	5.72	488.76	477.18	8.20	0	7	78.13	55.553	−33.74
5a	8.37	488.54	477.35	7.86	0	7	79.41	55.591	−33.81
6a	8.27	450.24	437.71	5.50	0	8	76.21	63.786	−41.06
7a	5.06	463.39	452.74	6.03	0	8	77.46	62.937	−44.04
8a	4.48	507.83	494.17	7.96	0	10	80.88	93.356	−29.95

The chemical hardness (η) and electronegativity (χ) are the resistance degree to charge transfer and to fascinate electronic tendency of an atom within chemical bond (-ive of the chemical potential), respectively. Stabilization energy that measure the electrons affinity is called as electrophilicity index. The larger hardness (η) value of **5a** is enlightening that it may be not worthy reactive compound.

Here, we have also compared the electron injection energy of oxadiazole derivatives **1a-8a**. The following eq. (9) can be used to evaluate the electron injection energy of a compound:

$$\text{Electron injection energy}=(=-E_{\text{LUMO}} - (-\text{work function of metal})) \quad (9)$$

In this study aluminum metal was considered which has − 4. 08 eV work function. The electron injection energy would be 1.18, 0.77, 1.23, 1.17, 1.33, 0.79, 1.05 and 0.64 eV from the **1a**-**8a** to aluminum electrode, respectively. It can be found from above results that lowest energy has been observed for **2a**, **6a** and **8a** which needed 0.77, 0.79 and 0.64 eV to overcome the injection barrier. Thus it is predictable that **2a**, **6a** and **8a** derivatives might be better electron charge transported than the other counterparts. Moreover, hole injection energy has also been anticipated as 1.87, 1.97, 1.85, 1.87, 1.80, 2.14, 1.91 and 1.99 eV from **1a** to **8a** to aluminum electrode, respectively. It is expected that **1a, 3a, 4a** and **5a** might be better hole transport materials than the other derivatives.

Single Electron Transfer Mechanism. The single electron transfer can lead to the free radicals scavenging potential. The electron transfer phenomena can be estimated from the value of ionization potential that is an imperative physical factor. When electron is removed from the HOMO then radical cation can gained the benefit of one-electron transfer. The computed ionization potential (IP) values were presented within Table 1. The ionization potential (IP) trend has been observed as **5a < 3a < 1a = 4a < 7a < 2 a < 8a < 6a** enlightening that in **5a** electron transfer pathway might be more promising for the free radicals scavenging than those of the other 1,3,4-oxadiazole substituted scaffold.

Molecular Electrostatic Potential. The molecular electrostatic potential (MEP) is being usually accustomed to understand the molecular interactions particularly in order to know the reactivity sites towards electrophilic and nucleophilic attack 3-D mapping is the worthy appliance. The MEP surface maps of all the studied oxadiazole derivatives have been illustrated in Fig. 3. The + ive and -ive electrostatic potential (ESP) regions are represent with blue and red color parts whereas zero potential regions with the green color parts. The + ive/-ive ESP is accompanying to nucleophilic/electrophilic reactivity, *i.e.*, site might be more encouraging towards nucleophile/electrophile attack.

QSAR Study. The SAR, structure–property–activity relationship (SPAR) and QSAR are the worthy procedures to comprehend the medicinal performance as well as nature of antimicrobial (antibacterial, antifungal) and antichagasic drugs. Among SAR, SPAR and QSAR, the later one is often used to know the correlations between the biological potential of drug and its various physicochemical properties. In Table 2, we have recorded the various QSAR descriptors e.g., volume, hydrogen bond donor (HBD), area, hydrogen bond acceptor (HBA), μD = dipole moment, partition coefficient (LogP), solvation energy, polar surface area (PSA) and Polarizability of all the studied 1,3,4-oxadiazole scaffold. Kelder et al. observed linear relationship between the brain penetration and PSA (Palm et al., 1998) that showed dissimilarity with reported sigmoidal curve of Palm and coworkers investigations for oral absorption (van de Waterbeemd et al., 1998). When the value of PSA rises then brain penetration decreases. Formerly it has been observed that value of PSA may not overcome 120 A^2 value for the orally active drug which are conveyed by transcellular route whereas <100 A^2 for brain penetration or <60–70 A^2 (Palm et al., 1998).

Molecular docking. According to our understanding, no results are reported showing NADPH (PDB ID-2CDU) enzyme resistance against **5a** by simulation means. The 2CDU NADPH crystal was downloaded from Worldwide Protein Data Bank (https://www.rcsb.org/structure/2CDU, xxxx), see Fig. 4. We proceeded to explore the interactions of **5a** with NADPH crystal structure to accomplish the interpretation on the effectiveness of this compound as antiox-

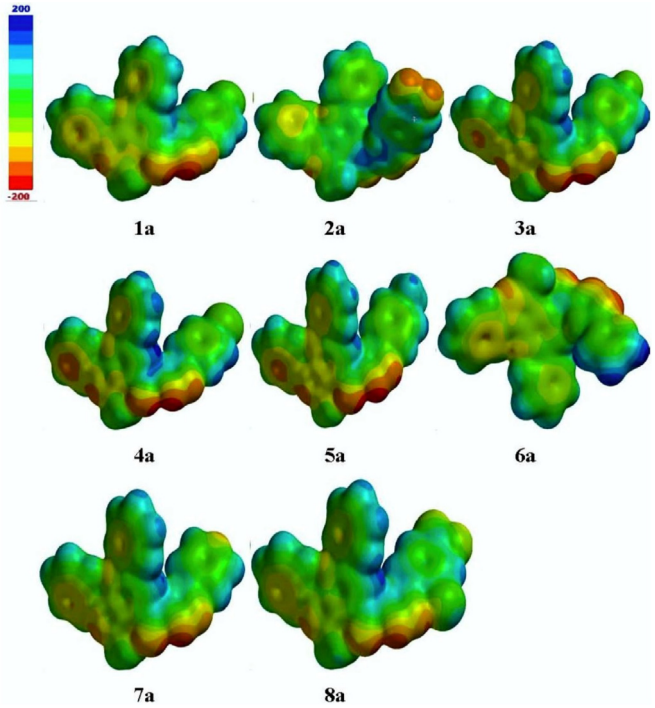

Fig. 3. The molecular electrostatic potential surfaces of 1,3,4-oxadiazoles.

Fig. 4. Crystal structure of the NADPH (PDB ID-2CDU) enzyme without H_2O and inhibitors.

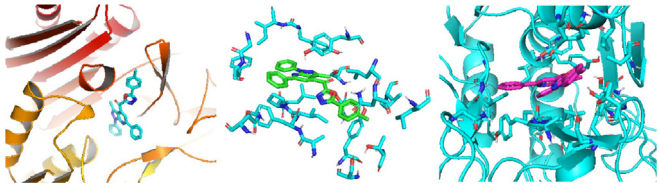

Fig. 5. Docking simulation between **5a** and NADPH enzyme.

idant. Molecular docking was done by introducing **5a** in the 2CDU NADPH enzyme, see Fig. 5.

4. Discussion

In **2a** and **8a** significant ICT can be comprehended from phenylpyrazole substituent to the *p*-nitrophenyl and 2-chloro-4-nitrophenyl units, respectively. The enhanced ICT value within **2a** and **8a** is because of significant push–pull effect whereupon nitrophenyl group is serving as strong acceptor and phenylpyrazole substituent is acting as donor. The higher HOMO energy exposed that the compound would have strong electron donating ability, *i.e.*, **5a** might have greater electron donor potential compared with the other investigated derivatives. The lower electrophilicity of **5a** followed by **3a**, **1a** and **4a** are displaying that these compounds would be more susceptible for electrophilic attack in the following order **5a** > **3a** > **1a** > **4a**. The MEP careful investigations exposed that 1,3,4-oxadiazole substituent may be provide the electrophile attack favorable site within studied compounds. In addition to this, negative region can be observed on nitro group in **2a** and in **7a**; on the phenylpyrazole substituent in **3a**, **4a** and **5a**, -ive charge on pyrazole unit and nitrogen atom of end-core pyridine unit can be comprehended. More electrophilic reactive sites might lead to derivatives more reactive and biological active.

Furthermore, these compounds would be more susceptible for electrophilic attack than other studied derivatives. The smaller ionization potential (IP) of **5a** in comparison to added counterparts shown that aforementioned derivative might be superior antioxidant substance ultimately might be effective against COVID19. The PSA value for calculated 1,3,4-oxadiazole substituted scaffold is<120 A^2 displaying that these may be orally active drugs. Moreover, the PSA of **3a**, **4a**, and **5a**<60 A^2 is revealing that these drugs would be better brain penetration. The binding energy value between ligand and 2CDU NADPH enzyme (active sites in the title compounds and enzyme) was found −8.59 which illuminated that **5a** might be good anti-oxidant compound with better binding ability with enzyme.

5. Conclusions

The nature of the activity of designed drugs has been explored and discussed on the bases of charge density distribution, energies of frontier molecular orbitals, molecular electrostatic potential, one-electron transfer mechanism, quantitative structure–activity relationship, hydrogen bond donor (HBD), polar surface area, hydrogen bond acceptor (HBA), dipole moment and partition coefficient (LogP). The intra-molecular charge transfer was detected within **1a**-**8a** 1,3,4-oxadiazole scaffold. The greater HOMO energy of **5a** is enlightening its better electron donor ability than other investigated derivatives. The smallest ionization potential of **5a** is leading to this drug as efficient antioxidant material. The electrophilic reactive sites in **2a, 3a, 4a**, **5a** and **7a** derivatives would be beneficial to enhance biological activity. <60 A^2 polar surface area of **3a**, **4a** and **5a** derivatives would lead to the better orally active and brain penetration drugs than other counterparts. Molecular docking studies revealed that **5a** would be efficient antioxidant drug.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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