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Biological evaluation of selected metronidazole derivatives as anti-nitroreductase via *in silico* approach

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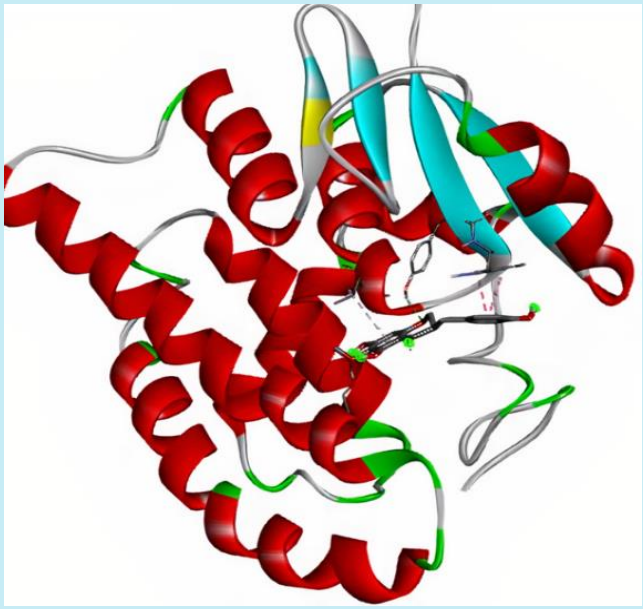
ABSTRACT: The 1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole (2HMN) is a powerful antibacterial and antiparasitic drug used alongside other drugs against *Helicobacter pylori* infection and was investigated the effects of substituents: –OH (A), H (B), –SPh (C), –COOH (D), $–NO_2$ (E) and $–OCH_3$ (F) on the interactions of 2HMN with the target nitroreductase Rdxa protein for the treatment of the infection. Spartan 14 (optimization), PyMOL 1.7.4.4 (to treat downloaded protein), Autodock Tool (locate protein binding site), Autodock vina 1.1.2 (docking calculation) were used to discover the nonbonding interaction between docked complexes using SWISSADME and Pre-ADMET software. The band gaps order for the studied compounds were C < A < F < B < D < E, a probability of highest charge distribution and activity for SPh substituted derivatives and the ligands conformed to the Lipinski's rule of five. Compounds D and E are noninhibitors and nonsubstrate for cytochrome P450 2C9, P450 2D6, P450 2C19 with the same efficient calculated binding affinity (–21.3 kJ mol^{-1}) and inhibition constant (7.8) comparable to the standard compound A.



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1. Introduction

Helicobacter pylori (*H. pylori*), a microaerophilic gram-negative bacterium, has been described as the first formally recognized carcinogenic bacterial, and one of the most successful human pathogens which is believed to be transmitted from person to person through closed contact and exposure to fecal matters or vomit (Fig. 1) (Bürgers *et al*., 2008; Kayali *et al*., 2018). These bacteria are typically found in the mucous layer that covers and protects the stomach and small intestine's tissues (Houghton and Wang, 2005). Its infection, by inflaming the stomach's inner layer, which is a complicated interplay between the bacterial, the host, and environmental factors, has been established to be the key factor with various gastric diseases such as chronic gastritis, peptic ulcers, and gastric mucosa-associated lymphoid tissue (MALT) lymphoma (Jemilohun and Otegbayo, 2016; Wu *et al*., 2009). Although, many other factors, such as the persistent use of anti-inflammatory pain relievers, including aspirin, are responsible for peptic ulcer diseases (Bürgers *et al*., 2008).

The clinical use of many 5-nitroimidazoles derivatives, especially metronidazole [1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole] (2HMN) as antibiotic for the effective treatment of patients with *H. pylori* linked gastritis and peptic ulcer ailment, has been listed and approved by the World Health Organization. Metronidazole (A) (Fig. 2) has also been used in combination with other antibiotics such as tetracycline, amoxicillin and clarithromycin to treat ulcer. However, it is uncommon to find both bacteria and protozoa to cause ulcer (Houghton and Wang, 2005). Some studies (Ghotaslou *et al*., 2015; Kim *et al*., 2020) in the last few years have reported that *H. pylori* is exhibiting an increasing double resistance to metronidazole and this has drawn the attention many researchers to study physiological and pharmacological significance of some metronidazole and its derivatives (Alawadi *et al*., 2015). To contribute to this ongoing area of research, this study investigates the relative substituents' effects on the interactions of some nitroimidazole derivatives on the target; nitroreductase Rdxa proteins (PDB ID: 3qdl).

The roles of computational chemistry for the qualitative and quantitative evaluation of substances and in almost every field of chemistry cannot be overstated. Of recent, it is routinely used to accelerate the long and costly drug discovery/design activities, from drug target identification, commonly a receptor or an enzyme, to the design and optimization of new drug-like compounds. Thus, each computational chemistry method can impact and accelerate a given phase of the drug discovery process, from structure-based drug design technique molecular docking (stimulation of molecular interaction and generation of potent inhibitory ability, i.e., binding affinity), molecular dynamics for hit identification and lead generation to quantitative structure-activity relationship (QSAR) (Adejoro *et al*., 2016).

The quantum mechanically derived molecular descriptors and physicochemical variables also dictate the pharmacokinetics of any studied compounds (Venkatesh and Aravinda, 2017). These calculated descriptors affect their drug-likeness and, ultimately, their absorption, distribution, metabolism, excretion and toxicity (ADMET) properties, which are the key factors to be optimized to generate drug candidate in clinical trials (Palermo and Vivo, 2015). ADMET properties influence the drug levels and the kinetics of drug exposures to the tissues, and, hence, the performance and pharmacological activities of compounds as drugs (Patil, 2016). This study, therefore, determines the ADME properties of the studied 2HMN and some other derivatives of nitroimidazole to investigate their oral-bioavailability and drug-likeness properties.

Figure 1. Pictorial view of *H. pylori*.
Source: Bürgers *et al*. (2008).

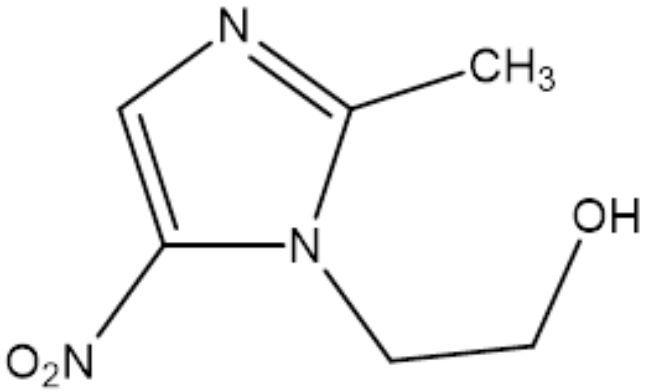

Figure 2. Structure of metronidazole [A].

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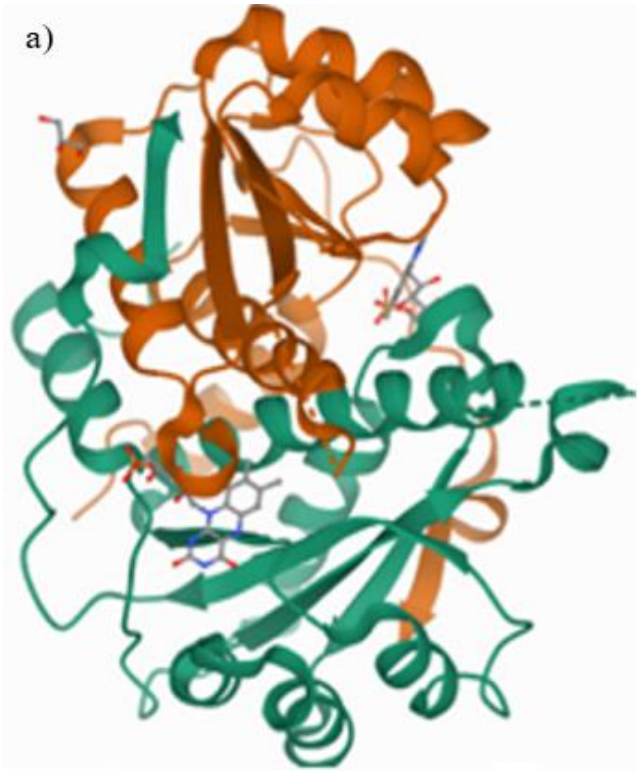
2. Materials and Methods

2.1 Ligand Preparation

The ligands preparation and computational analyses of the studied compounds were carried out with Spartan-14 software package at DFT/B3LYP/6-311G** level of theory. Using molecular editor builder of Spartan 14, the equilibrium geometries of each of these compound A–F (Tab. 1), were modeled, and their structures were minimized. The compounds were fully optimized (Fig. 3) using equilibrium geometry at ground state, with the features in the personal computer Spartan 14 software at HF-DFT self-consistent field level of theory, to estimate the physicochemical properties; dipole moment, polarizability, solvation energy, partition coefficient (log P), a measure of lipophilicity/ hydrophobicity, frontier orbital energies (E_{HOMO} and E_{LUMO}) of the studied compounds. Following their geometry optimization, their energy gaps (E_{HOMO}–E_{LUMO}) were computed. The E_{HOMO} and E_{LUMO} of the modeled molecules were related to the ionization potential (IP), the electron affinity (EA), and the global hardness (η), using Koopman's theorem (1–3) (Adeoye *et al*., 2019). These descriptors help to predict, on theoretical basis, the chemical activities of these compounds.



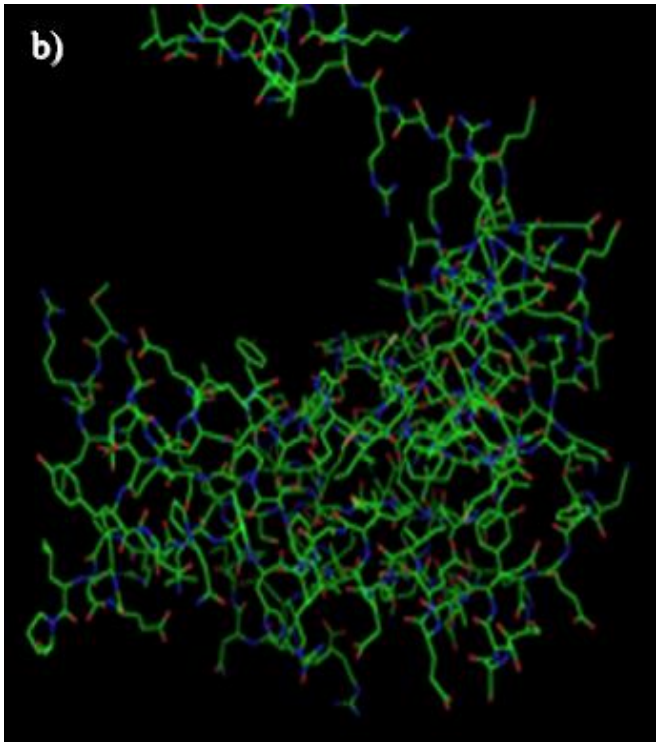
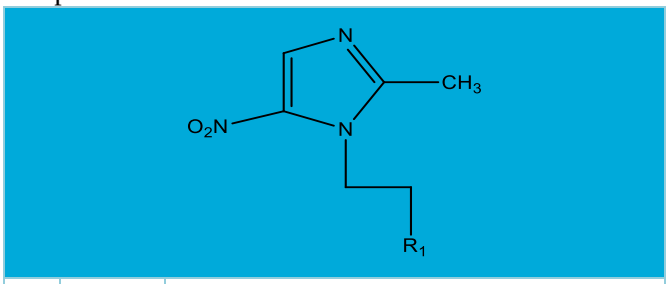


Figure 3. Structures of **(a)** [raw protein (3dql)] and **(b)** [cleaned protein].
Source: Martínez-Júlvez *et al*. (2012).

Table 1. Two-dimensional (2D) structures of the studied compounds.



	R_1	Name
A	OH	1-(2-hydroxyethyl)-2-methyl-5-nitroimidazole
B	H	N-ethyl-2-methyl-5-nitroimidazole
C	SPh	1-(2-thiophenylethyl)-2-methyl-5-nitroimidazole
D	COOH	1-(2-carboxylethyl)-2-methyl-5-nitroimidazole
E	NO_2	1-(2-nitroethyl)-2-methyl-5-nitroimidazole
F	OCH_3	1-(2-methoxylethyl)-2-methyl-5-nitroimidazole

2.2 Preparation of the Studied Receptor (Protein)

The target protein for this study was nitroreductase Rdxa protein (PDB ID: 3QDL) (Martínez-Júlvez *et al*., 2012). The 3D structure (X-ray diffraction) was obtained from the protein data bank and treated with PyMOL 1.7.4.4 for the removal of water molecules and any other residues apart from the desired molecule. Schrödinger (Maestro 12.7) (Morakinyo *et al*., 2022) and the

Eclética Química Journal, vol. 47, n. 4, 2022, 27-36
ISSN: 1678-4618
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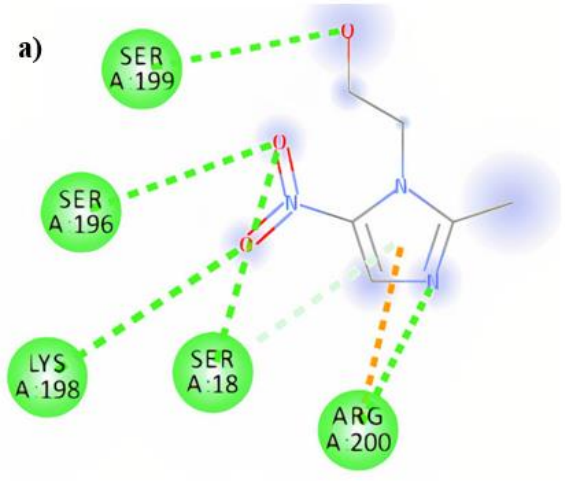
references therein attached journals were used to determine the target protein's active site, in preparation for site specific docking. The structure of the raw protein (3dql) from the data bank and the cleaned protein are as presented in Figs. 4a and b.

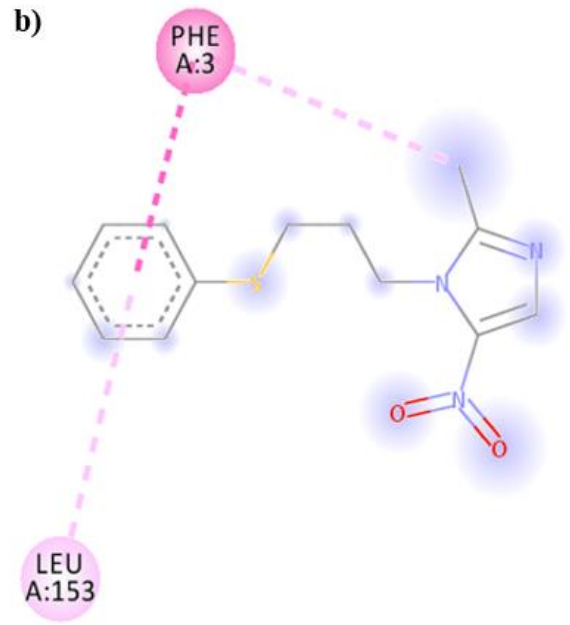
2.3 Molecular Docking Analysis

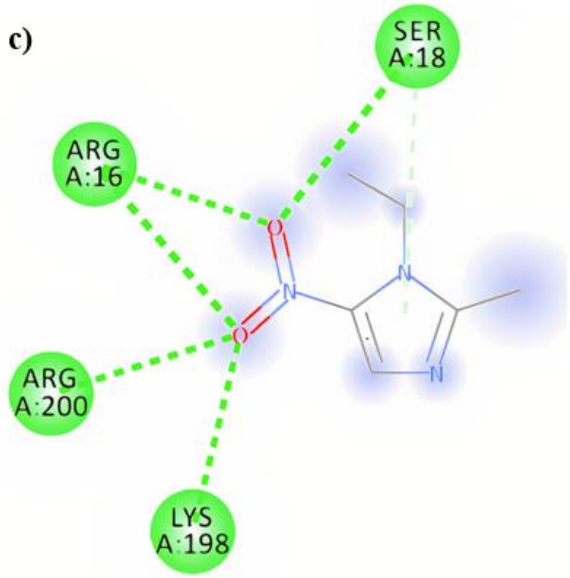
The optimized compounds were docked into the active pockets of the target *H. pylori* protease; nitroreductase Rdxa protein (PDB ID: 3QDL), using two softwares with different algorithm profiles (Autodock Vina and Discovery studio) to predict their binding abilities with the studied receptor (Forli *et al*., 2016; Roche *et al*., 2015). The docking process mainly involves spatial matching and energy matching (Meng *et al*., 2011) between the ligand and the receptor (cleaned protein) for optimal conformation. The grid center (X = 16.082, Y = 4.657, Z = 10.976) and box size (X = 84, Y = 94, Z = 46) were used. And the spacing was set to be 1.00 Å.

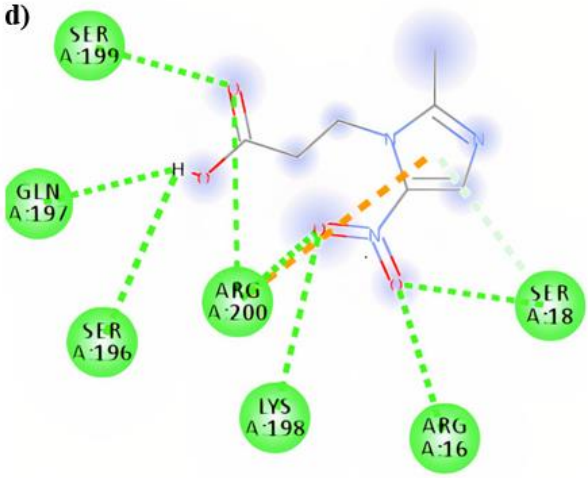
2.4 ADMET Prediction

The absorption, distribution, metabolism, excretion and toxicology of a substance in and through the human body are dealt with by ADMET characteristics (Balani *et al*., 2005). The modeled ligands (A–F) were evaluated for their ADME properties using SwissADME software (Daina *et al*., 2017; Oyebamiji *et al*., 2022) for accessing their oral-bioavailability and drug-likeness features. These assist in studying the ligands' pharmacokinetics and pharmacodynamics properties (Iwaloye *et al*., 2021). Molecular weight, hydrogen bond donor (HBD), hydrogen bond acceptor (HBA), blood–brain barrier (BBB), human intestinal absorption (HIA) are all predicted significant ADME properties.









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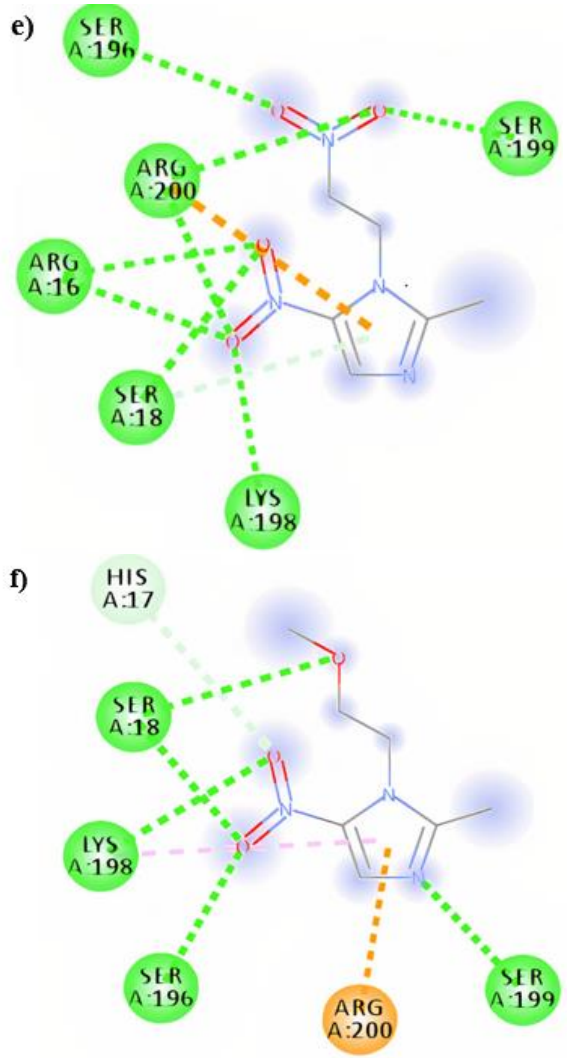

Figure 4. 2D structure of interaction between compound (**a–f)** and nitroreductase Rdxa protein (PDB ID: 3QDL).

3. Results and Discussion

3.1 Calculated Descriptors

The frontier orbital electron densities of atoms in a molecule can be used to analyze the electron donor acceptor interaction (Akintelu *et al*., 2021). The 2D structures for the studied compounds are as shown on Tab. 1. The frontier molecular orbital energies (E_{HOMO} and E_{LUMO}) are used to determine how a molecule interacts with the other species. The E_{HOMO} orbital energy donates electron, since it is the outermost (highest energy) orbital containing electrons. In contrast, the E_{LUMO} orbital accepts electrons since it is the innermost (lowest energy) orbital that can accept electrons (Raj *et al*., 2015). According to the frontier molecular orbital theory, the interaction between the HOMO and LUMO of reactants formed the transition state.

The E_{HOMO} and E_{LUMO} are directly related to the IP and EA respectively (Eqs. 1 and 2). Higher E_{HOMO} signify that the compound has stronger ability to donate electron(s) to the neighboring compound, the better ability of its drug-likeness properties, as well as the ability of such compound to inhibit receptor (Gao *et al*., 2010). The band gap (E_g/E_{HOMO}–E_{LUMO}) is also an important parameter that reflects the chemical activity of the molecules. The E_g and associated molecular/ physicochemical properties are as presented in Tab. 2. More so, the HOMO π-electrons are delocalized on the 5-nitroimidazole ring in compounds A, B, D and E, delocalized on the entire molecules in compound F, but localized on thiophenylethyl substituent of compound C. However, the LUMO π-electrons are more localized on the nitro (NO_2) group substituent of the nitroimidazole ring in compounds A, B, D, E and F, but are more localized on the 5-nitroimidazole ring in compound C. This attests to studied compounds' intramolecular charge transfer characteristic properties (Kulhánek *et al*., 2012). The lowest and highest E_g values were recorded for compound C (3.94 eV) and E (4.63 eV) respectively; a strong indication of highest distribution of charges, and hence, the probability of higher chemical activity of compound C (R = SPh_3) compared with the other compounds (Oyebamiji *et al*., 2021a).

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

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

The partition coefficient (lipophilicity / log P) plays important roles in drugs design (Méndez-Lucio *et al*., 2017). It has been described as the main physicochemical determinant that influences the bioavailability, permeability, and penetrability of pharmacophore in biological membranes, and toxicity of the compounds. Their values are therefore used as determinants in some industrial processes, such as agricultural chemistry, drug formulation and flavoring of finished products (Lipinski *et al*., 2020; Oyebamiji *et al*., 2021b). According to the Lipinski's rule of 5 (MW ≤ 500 amu, LogP [octanol-water partition coefficient] ≤ 5, HDB [total number of N–H and O–H bonds] ≤ 5 and HBA [total number of N and O atoms] ≤ 10) (Erazua *et al*., 2021), problem is likely to be encountered in the oral usage of this drug-like compound if log P value is higher than 5 (Stefaniu and Pintilie, 2018). The log P for all the studied compounds (Tab. 2) were within the acceptable range, which therefore showed that the compounds can be taken

Eclética Química Journal, vol. 47, n. 4, 2022, 27-36
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orally. Compounds D, E, F have their log P values (0.59–0.7) less than 1, being closer to that of the standard—metronidazole (0.42). Furthermore, for compounds to be useful in drug formulation targeted at central nervous system, and intestinal absorption, their log P should fall in the range; 1.35–1.8 (Adegoke *et al*., 2020). This was observed for compounds B (1.28), while the log P for compound C is slightly greater than 3 (Tab. 2).

Table 2. Calculated descriptors for the studied compounds.

Mol		A	B	C	D	E	F
MW (amu)	Molecular weight	171.15	155.15	277.34	199.16	200.15	185.18
DM (Debye)	Dipole moment	4.55	4.89	2.98	4.29	3.88	3.59
E_{HOMO} (eV)	Highest occupied molecular orbital	–6.80	–6.90	–6.26	–7.03	–7.35	–6.95
E_{LUMO} (eV)	Lowest unoccupied molecular orbital	–2.26	–2.29	–2.32	–2.41	–2.72	–2.39
Band Gap	Band gap	4.54	4.61	3.94	4.62	4.63	4.56
HBA	Hydrogen bond accept	5	4	5	5	5	5
HBD	Hydrogen bond donor	1	0	0	1	0	0
Log p	Lipophilicity	0.42	1.28	3.45	0.70	0.59	0.78
Ovality	Ovality	1.30	1.29	1.47	1.35	1.35	1.36
PSA (A^2)	Polar surface area	65.15	46.30	46.06	80.15	85.44	53.77
SE (KJ/mol)	Solvation energy	–37.24	–27.70	–45.09	–43.64	–34.32	–31.80

Note: Referenced drug = Compound A = metronidazole.

Solvation energy, a measure of interaction of solute with solvent that leads to stabilization of species in solution, is also highly significant in drugs development. The highest solvation energies recorded for compound C is an indication that its interaction with solvent will be more thermodynamically favored than other studied molecules (Choi *et al*., 2013). The trends in the polar surface area of the compounds (C < B < F< A < D < E) differ from their volumes (B < A< E < F < D < C), and molecular weight (B < A< F < D < E < C) variations. Ovality is related to molecular surface area and van der Waal's volume; it increases with increasing structural linearity and deviate from spherical form, which is usually 1 for spherical shape molecules (Abdul-Hammed *et al*., 2020). The reported trend in the ovality values of the studied compounds: B (1.29) < A (1.30) < D (1.35) =E (1.35) < F (1.36) < C (1.49), suggests that compound C vary more greatly from spherical shape than the other compounds. The dipole moment and polarizability of molecule which measure the bond properties (induction polarization), charge densities and nonbonding interactions between ligand and receptor of molecules follow the trend: B > A > D > E > F > C. As reported by Adeoye *et al*. (2017) and Oyewole *et al*. (2020), the unpredictable properties of drug-like molecules may arise as a result of large dipole moment value, molecules with better charge distribution and increasing distance will have higher dipole moment and polarizability. Thus, the studied compounds may possibly have strong nonbonded connections with the target nitroreductase Rdxa proteins (PDB ID: 3qdl).

3.2 Molecular Docking and ADME Studies

A docking study was used to predict the preferred orientation or correct conformation of the ligand in the active site of the protein. The binding energy measure of binding affinity is an important parameter generated from molecular docking to provide information on the strength of the interaction between the ligand and receptor. The interaction is spontaneous; the greater the binding affinity (in term of negativity), the better the inhibition (Adeoye *et al*., 2022; Ibrahim *et al*., 2019). Consequently, the five studied compounds (B–F) were docked against the target (PDB ID: 3qdl) to determine the nonbonding interactions present in the studied complex using metronidazole (A) as the standard. The calculated binding affinities for the compounds A–F were –18.8, –18.0, –17.2, –21.3, –21.3 and –18.4 kJ mol^{-1}, respectively. Compounds D and E have the same binding affinity (–21.3 kJ mol^{-1}) and inhibition constant (7.8) which were compared with the referenced drug (compound A [metronidazole]) (Tab. 3 and Fig. 4). It was observed that the addition of –COOH and $–NO_2$ to the parent compound enhanced it inhibit activity. Also, as shown in Tab. 2, lower ability of compounds D and E to donate electron to target compounds as well as their greater capacity to receive from the nearby compounds enhanced it capability to inhibit nitroreductase Rdxa proteins than others studied compound as well as the referenced drug (compound A).

Eclética Química Journal, vol. 47, n. 4, 2022, 27-36
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Table 3. Calculated scoring, residues, inhibition constant and types of non-bonding interactions between 2HMN derivatives and Nitroreductase Rdxa Protein (PDB ID: 3qdl).

Compounds	Binding Affinity (kJ mol^{-1})	Residue involved in the interaction	Inhibition constant K_1 (nmol L^{-1})	Types of nonbonding interaction involved
A	–18.8	SER 199, SER 196, LYS 198, SER 18, ARG 200	6.1	Conventional hydrogen bond π-carbon, π-donor hydrogen bond
B	–18.0	ARG 16, LYS 198, ARG 200, SER 18	5.6	π- π stacked, π-alkyl C
C	–17.2	PHE 3, LEU 153	5.2	Conventional hydrogen bond, π-donor hydrogen bond
D	–21.3	ARG 16, GLN 17, SER 199, SER 196, LYS 198, SER 18, ARG 200	7.8	Conventional hydrogen bond, π-carbon π-donor hydrogen bond
E	–21.3	SER 199, SER 196, LYS 198, ARG 16, SER 18, ARG 200	7.8	Conventional hydrogen bond, π-carbon π-donor hydrogen bond
F	–18.4	HIS 17, SER 199, SER 196, LYS 198, SER 18, ARG 200	5.9	Conventional hydrogen bond, π-alkyl, π-cation carbon-hydrogen bond

Note: Referenced drug = Compound A = metronidazole.

These compounds proved to possess highest tendency to inhibit nitroreductase Rdxa proteins (PDB ID: 3qdl) and may likely be more potent than other studied ligands. The amino acid residues involved in the interactions and the types of nonbonding interactions involved are as displayed in Fig. 4 and Tab. 3. Furthermore, compounds D and E's ADME features with the best efficient calculated binding affinity were comparable with the standard metronidazole (Tab. 4).

Table 4. Drug-likeness prediction.

Compounds	Molecular weight	Log P	HBD	HBA	Violations
A	171.156	0.42	1	5	0
B	155.157	1.28	0	4	0
C	277.348	3.45	0	5	0
D	199.166	0.70	1	5	0
E	200.154	0.59	0	5	0
F	185.183	0.78	0	5	0

The higher the HIA, the better the compound's tendency to be absorbed upon oral administration (Oyebamiji *et al*., 2020). As observed in Tab. 5, the values of HIA for the studied compounds are positive and correlated with the standard. This further proved that the selected compounds have capacities to be absorbed in the intestine. The ability to cross the BBB for compounds D and E are also closer to the existing standard drug (metronidazole), while the molar solubility in aqueous state (log S) values of the selected compounds and standards fall within the recommended range of 1 to 5 (Ibrahim *et al*., 2018). The observed ADME factors indicate that the selected compounds and the standards have better absorption and distribution properties. The Caco-2 permeability reveals the permeability on lipid absorption and metabolism of the studied compounds (Semire *et al*., 2017). The probability of this was higher in compound D, but little lower than the standard in the ligand E. Also, in terms of metabolic activities of the selected ligands, compounds D and E are non-inhibitors and nonsubstrates for microsomal enzymes (CYP450 2C9, CYP450 2D6 and CYP450 2C19), similar to the standard. A noninhibitor of CYP450 means that the molecule will not hamper the biotransformation of the drugs metabolized by CYP450 enzyme (Nisha *et al*., 2016).

Eclética Química Journal, vol. 47, n. 4, 2022, 27-36
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Table 5. Predicted ADME properties of the studied compounds.

	Compound D		Compound E		Compound A (Metronidazole)	
Mode	Result	Probability	Result	Probability	Result	Probability
Blood-Brain Barrier	BBB+	0.114253	BBB+	0.12801	BBB+	0.173454
Human Intestinal Absorption	HIA+	High	HIA+	High	HIA+	High
Caco-2 Permeability	Caco-2	High	Caco2+	High	Caco2+	High
Log S	ESOL	–0.67	ESOL	–0.86	ESOL	–1.00
Solubility (mg/ml)	Very soluble	4.32+01	Very soluble	2.76+01	Very soluble	1.72+01
Log S	Ali	–1.00	Ali	–1.49	Ali	–1.29
P-gp substrate	Substrate	No	Substrate	No	Substrate	No
Log p	ILOGP	0.77	ILOGP	0.59	ILOGP	1.16
Lipinski's rule		Yes		Yes		Yes
CYP450 2D6 Substrate	Noninhibitor	No	Substrate	No	Noninhibitor	No
CYP450 2C9 Inhibitor	Noninhibitor	No	Noninhibitor	No	Noninhibitor	No
CYP450 2D6 Inhibitor	Noninhibitor	No	Noninhibitor	No	Noninhibitor	No
CYP450 2C19 Inhibitor	Noninhibitor	No	Noninhibitor	No	Noninhibitor	No
CYP450 3A4 Inhibitor	Inhibitor	No	Inhibitor	No	Inhibitor	No
CYP450 3A4 Substrate	Substrate	No	Substrate	Substrate	Substrate	Substrate
Synthetic accessibility		2.23		2.53		2.30
Ghose		0		0		0
Vegar		0		0		0
Pain		0, Alert		0.12801		0, Alert

4. Conclusions

This study was carried out to determine the effects of substituents: –OH, H, –SPh, –COOH, $–NO_2$ and $–OCH_3$ on the chemical activities and interactions of six nitroimidazole derivatives on the target nitroreductase Rdxa protein (PDB ID: 3qdl) for the treatment of *H. pylori* infection. The nonbonding interactions and the calculated binding affinities that exist between the six compounds and the nitroreductase Rdxa protein were identified. The ADME features showed that substituted –COOH and $–NO_2$ nitroimidazole derivatives has the same binding energies (kJ $mol^{–1}$) and higher tendency to inhibit target nitroreductase Rdxa protein (PDB ID: 3qdl) than the referenced drug despite their higher band gaps. The compounds are also noninhibitors and non-substrates for microsomal enzymes (CYP450 2C9, CYP450 2D6 and CYP450 2C19), with capacities to be absorbed in the intestine and ability to cross the BBB comparable with the standard.

Authors' contribution

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Data availability statement

All data sets were generated or analyzed in the current study.

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