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ONE-POT SYNTHESIS, PHARMACOLOGICAL EVALUATION, DOCKING STUDY, AND DFT CALCULATIONS FOR SELECTED IMIDAZOLIDINE-2,4-DIONES

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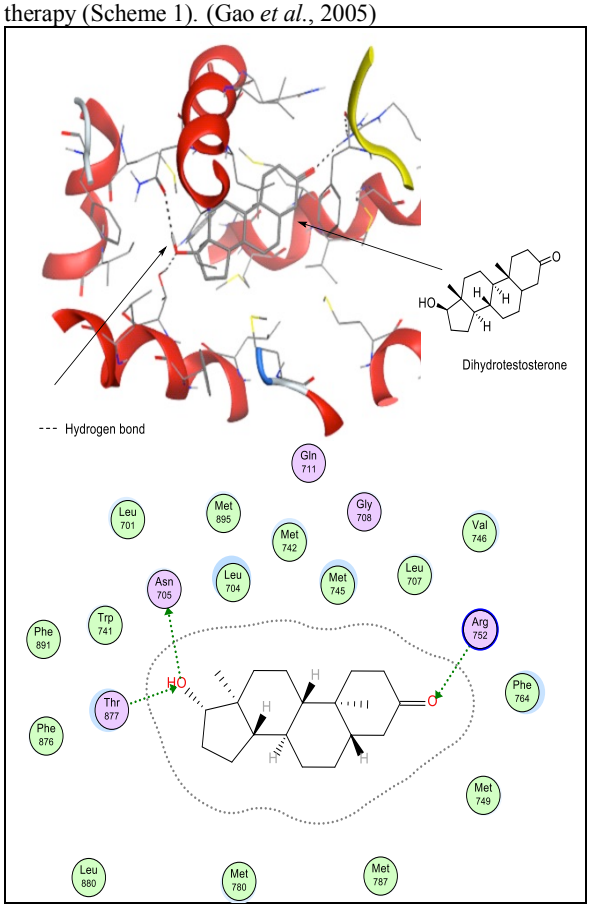
ABSTRACT:
The title compounds with different 5-substituted imidazolidine-2,4-dione were synthesized through a solvent-free reaction. Imidazolidine-2,4-dione derivatives are found to be an active pharmacophore for design and development of various bioactive lead compounds. Positive values of energy obtained for compound **1** and **3**, while a negative value for compound **2** was calculated by DFT in Gaussian. keto-enol tautomerism was supported by energy values and indicated the most stable tautomeric form. The biological evaluation has been supported by docking studies using molecular operating environment program to show binding with androgen receptor.

KEYWORDS: imidazolidine-2,4-dione derivatives, Prostate cancer, computational study, Energy, biological activity.

1. INTRODUCTION

The imidazolidine-2,4-dione (hydantoin) is a common 5-membered ring containing a reactive cyclic used in medicinal chemistry because of its broad spectrum of biological activity. They have a number of biological activities as anti-arrhythmic, anti-inflammatory, antitumor, and antidiabetic properties, in addition to the herbicidal and fungicidal activity (Cheng *et al*., 2008; Colacino *et al*., 2007; Ghanbari *et al*., 2014; Katritzky *et al*., 1998; Nefzi *et al*., 2000). There were a number of methods have been reported for the synthesis of 5- substituted analogs of hydantoins including multi-step methods, one-pot, solid-phase and microwave-assisted. (Li, 2010; J Safari *et al*., 2009; Javad Safari *et al*., 2010) H-bonds are the most important supramolecular synthons for assembling complex system and binding in vivo and vitro. (Bisello *et al*., 2017) Two N−H and two C=O acceptors are present to form intermolecular H-bonding in imidazolidine-2,4-dione derivatives (Bisello *et al*., 2017; Etter, 1990).

Several marketed hydantoin moieties are present as drugs such as anticonvulsant medications phenytoin (Tikhonov & Zhorov, 2017) and etotoin, nilutamide, a postsynaptic muscle relaxant dantrolene, or an aldose reductase inhibitor sorbinil with different substituents at 1-, 3-, and 5-, positions. These substituents are giving different chemical and physical properties to the molecules. (Law *et al*., 2013) Baeyer company in 1861 has first achieved hydantoin, namely imidazolidine-2,4-dione. (Baeyer, 1861) Substituents on the 5- position have found to increase potency, while, substituent at position-1 decreases potency. Therefore, type of polar and polar group that were substituted on the position 1 and 5 affect the potency of hydantoin against cancer. A bulky group on the position 3 will also decrease activity rather than methyl group (M. Zhang *et al.*, 2017). Androgen receptor AR antagonists is a soluble protein that used widely in a series of clinical application such as agonists are employed for hypogonadism, while antagonists are used for prostate cancer therapy (Scheme 1). (Gao *et al*., 2005)



Scheme 1. AR-DHT co-crystal structure (PDB ID: 2AMA). The key residues around the ligand were shown. Hydrogen bonds were shown as dashed lines.

Researchers recently summarized a large number of drug and drug-like molecule that bind to the AR including substituted

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hydantoin and thiohydantoins. (Nique *et al*., 2012; X. Zhang *et al*., 2006; Zuo *et al*., 2017) The aim of this study is free solvent synthesis of selected 5-substituted moiety of hydantoins by using corresponding amino acids reacting with urea. The biological activity of the synthesized compounds was studied on some of gram positive bacteria and gram negative bacteria. Hydantoins have shown a wide spectrum of biological activity because of 5-cyclic ring containing carbonyl and N-H groups.

We are also involved to study energetics of hydantoin compounds including thermodynamic experiments and provide an insight on the effect of substitution on the C5 in the hydantoin ring, using wide range of substituents on protonation.

The molecular geometry was done for several compounds by Gaussian 09w program in a gas phase using different level of theory. MOE program has used to study between hydantoin and AR based the molecular structure.

2. EXPERIMENTAL SECTION

2.1 Materials and Methods

Infrared spectra were recorded in the range 4000-600 cm^{-1} using a Shimadzu Scientific Instruments' IR, as KBr disc. Samples were either thin films or powders. All absorptions are quoted in cm^{-1}. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brukeravance (500 MHz) spectrometer. Chemical shifts are expressed in parts per million downfield from tetra-methylsilane as an internal standard. NMR spectra were recorded in solutions in the deuterated solvent mentioned.

2.2 Molecular Modeling

Gaussian 09 W was used to perform standard initio molecular orbital calculations. (Frisch *et al.*, 2016) employing the B3LYP1 functional and the 6–31(p,d,f) basis set for all atoms. (Becke, 1993)

The enthalpy of formation of these compounds was estimated after the consideration of the following gas-phase working reactions:

2.3 Energy Minimization Procedure

The chemical compounds with the correct stereochemistry were drawn on Chemdraw professional 16.0 and stored in mol format in Gaussian view 5.0. The structure was recalled in molecular operating environment (MOE), and all hydrogen atoms were added.

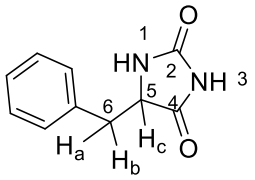
2.4 Docking Study

All the molecular modeling calculations and docking simulation studies were performed utilizing Molecular Operating Environment (MOE®) 2014.091. The three-dimensional X-ray structure of AR (PDB code 2AMA) was downloaded from protein Data banking. (Pereira de Jesus-Tran *et al*., 2006)

2.5 Chemistry

2.5.1 General procedure for the synthesis of 5- substituted imidazolidine-2,4-diones: Corresponding amino acids and urea were mixed in a round bottom flask together at 160 °C. After 5 minutes, the temperature was increased to 190 °C and a yellow vapour was observed inside the condenser. The mixture was allowed to heat under reflux at the same temperature for 20 minutes. Water was then added to the hot mixture. The mixture was then put in a refrigerator for the product to precipitate. The precipitant was collected and dried at room temperature. The product was purified by column chromatography on silica gel using CH_2Cl_2/ethyl acetate (80:20).

5-benzylimidazolidine-2,4-dione (1)

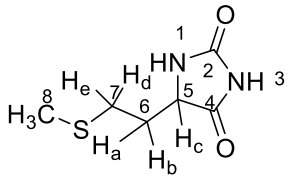


1

L-phenylalanine (1.0 g, 6.05 mmol) and urea (2.3 g, 38.20 mmol) were mixed together and heated under stirring.

yield 30%, M.p. 188-189 °C. HRMS calculated for $C_{10}H_{10}N_2O_2$ m/z [MS EI]$^+$ 190.0742; found 190.0742); ^{1}H-NMR (500 MHz DMSO): δ 7.55 (br s, 1H, N**H**$_3$), δ 7.35-7.16 (m, 5H, C6H5), δ 5.27 (br s, 1H, N**H**$_1$), δ 4.28 (ddd J=9.5, 3.7, 1.2 Hz, 1H, **H**$_c$), δ 3.27 (dd J=14.0, 3.7 Hz, 1H, **H**$_{6a}$), δ 2.84 (dd, J=13.9, 9.4 Hz, 1H, **H**$_{6b}$); 13C NMR (100 MHz, CDCI3): δ 175.1 (C_2), δ 157.0 (C_4), δ 135.6-126.6 (Ar), δ 58.3 (C_5), δ 36.4 (C_6). IR (neat): vmax= 1706, 1775 cm^{-1} (C=O).

5-(2-(methylthio) ethyl) imidazolidine-2,4-dione (2)

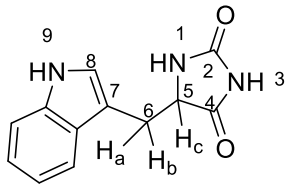


2

L-methionine (1.5g, 10.05 mmol) and urea (1.8 g, 29.90 mmol) were mixed together and heated under stirring.

Yield= 25.0 %, M.p. 107-109 °C, HRMS calculated for $C_6H_{10}N_2O_2S$ m/z [MS EI]$^+$ 174.0462; found 174.0463;^{1}H-NMR (500 MHz DMSO): δ 10.69 (br s, 1H, N**H**$_3$), δ 8.04 (br s, 1H, N**H**$_1$), δ 4.15 (ddd, *J* = 7.9, 4.6, 1.3 Hz, 1H, **H**$_c$), δ 2.60 (t, *J* = 7.5 Hz, 2H, **H**$_d$ and **H**$_e$), δ 2.32 (s, 3H, **H**$_8$), δ 2.04 – 1.94 (m, 1H, **H**$_a$), δ 1.88 – 1.75 (m, 1H, **H**$_b$).^{13}C-NMR (126 MHz, d_6-DMSO): δ 176.2 (C_2), δ 156.3 (C_4), δ 57.0 (C_5), δ 31.5 (C_6), δ 31.5 (C_7), δ 14.40 (C_8).

5-((1H-indol-3-yl) methyl) imidazolidine-2,4-dione (3)



3

L-tryptophan (0.5 g, 2.4 mmol) and urea (0.4 g, 7.3 mmol) were mixed together and heated under stirring.

Yield= 40.0 %, M.p. 112-113°C, HRMS calculated for $C_{12}H_{11}N_3O_2$ m/z [ES]$^-$ 229.0853; found 229.0851; ^{1}H-NMR (500 MHz DMSO): δ 7.97 (br s, 1H, N**H**$_3$), δ 7.61 (d, *J* = 7.9 Hz, 1H, Ar), δ 7.37 (d, *J* = 1.2 Hz, 1H, Ar), δ 7.18 (d, *J* = 2.4 Hz, 1H, **H**$_8$), δ 5.49 (br s, 1H, N**H**$_1$), δ 7.11 (ddd, *J* = 8.2, 7.0, 1.2 Hz, 1H, Ar), δ 7.03 (ddd, *J* = 8.0, 6.9, 1.1 Hz, 1H, Ar), δ 5.49 (br s, 1H, N**H**$_9$), δ 4.37 (td, *J* = 4.9, 1.2, 1H, **H**$_c$), δ 3.13 (d, *J* = 4.9 Hz, 2H, H_a and H_b).^{13}C-NMR (101 MHz, d_6-DMSO): δ 175.7 (C_2), δ 157.3 (C_4), δ 135.9 (Ar), δ 127.5 (Ar), δ 124.1 (C_8), δ 120.8 (Ar), δ 118.5 (Ar), δ 118.3 (Ar), δ 111.2 (Ar), δ 108.0 (C_7), δ 58.3 (C_5), δ 30.6 (C_6). IR (neat): vmax = 1704, 1776 cm^{-1} (C=O).

3.1 Biological Activity

Antibacterial activity was studied by Mueller-Hinton agar medium for the synthesized compounds (**1-3**). 0.0512 g of each test compound was dissolved in 10 mL of 20 % of DMSO. Two different concentrations were prepared by using half of prepared solution with 5 ml of 20 % DMSO with 256 and 512 µg/mL including another concentration to prepare it by 5 ml of 20 % DMSO 128 µg/mL. Sterile cork borer (6 mm) was used to prepare cups constructed in petri plates and 0.1 ml of each tested compound was added separately into each well and then bacterial plates were incubated at 37C in 24 hrs. The Zone of inhibition fashioned by each compound was measured in mm (Table 1).

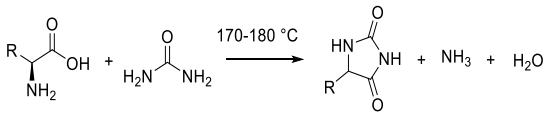
Table 1. Diameter of inhibited zones in millimeters as a measure of antibacterial activity of the synthesized compounds (**1**, **2**, and **3**) and some standard drugs

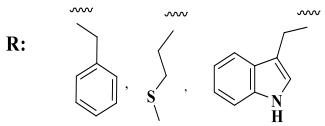
Compounds	*Escherichia coli*		*Staphylococcus aureus*	
	256 µg	512 µg	256 µg	512 µg
	1 -	-	-	17
	2 **NA**	NA	NA	NA
	3 -	-	-	12
Amikacin	19–26		20–26	
Cefalotin	15–21		29–37	
Tetracycline	18–25		24–30	
Chloramphen	21–27		19–26	
Nalidixic acid	22–28		-	
Vancomycin	-		17–21	

3. DISCUSSION

3.1 Chemistry

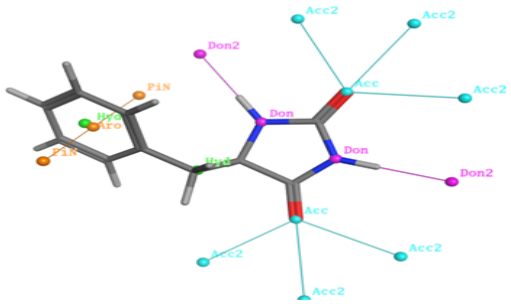
In this study, we synthesized 5-substituted hydantoin with different substituent by reacting corresponding amino acids with urea in a free solvent. (Ware, 1950) The reaction successfully proceeded under melting condition at 170-180 °C with washing by water to remove urea and amino acids. No acids and bases were used during this reaction (Scheme 2)





Scheme 2. Synthesis of compound **1-3**

Three amino acids were used as starting materials to prepare different functional groups attached to the stereogenic center. All synthesized compounds were elucidated by IR and NMR spectroscopy. Imidazolidine-2,4-dione contain two nitrogen donors and two carbonyl accepters. These functional groups have a vital role to produce hydrogen bond with the receptors. N-H hydrogen has role to bind with solvent (Scheme 3). (Bisello *et al.*, 2017; Etter, 1990)



Scheme 3. 5-benzylimidazolidine-2,4-dione constraints are shown in bond acceptor, hydrogen bond donor, aromatic part of the molecule.

The hydrogen atom attached to the stereogenic center is an acidic hydrogen, Cys76 (in thiolate form) acts as a base and retrieves a proton (*vide supra*), when a D-isomer of a 5-monosubstituted hydantoin is available, While, Cys181 acts as an acid, inserting a proton in the opposite side of the substrate, thus producing L-monosubstituted hydantoin. (Heras-Vazquez *et al.*, 2008) Several tautomeric form could exist for 5-monosubstituted imidazolidine-2,4-dione because of presence numbers of acidic hydrogen on the structure (*vide infra*).

3.2 Computational study

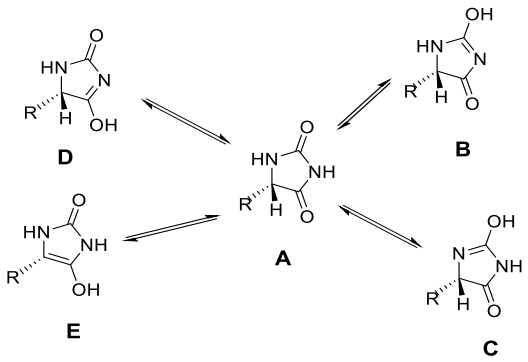
The geometry of compounds were optimized using semi empirical SCF, AM1. (Dewar *et al.*, 1985) The relative, Enthalpies and Gibbs free energies for the neutral species of compound **1**, **2**, and **3** have been obtained. The energy levels for all compounds were calculated by Gaussian and showed in Table 2.

Table 2. Energy profile (in kcal/mol) calculated at AM1

Compounds	Energy/ kcal/mol
1	133.21
2	-627.509
3	180.0727

Table 2 shows the positive values of energy for compound **1** and **3** with a dipole moments of 6.4074, and 6.4636 debye, respectively, while a negative value for compound **2** with a dipole moment of 5.3957 debye. Substituent groups attached to position 5 predict similarity between aromatic ring substitutes such as benzene and indole rings for compound **1**, and **3**, respectively. There is aliphatic carbon and sulfur atom presence on the stereogenic centre for compound **2**.

Based on the previous study for hydantoin derivatives, (Zaki S Safi *et al.*, 2018; Zaki Sulieman Safi, 2012) there are several tautomeric forms could exist for imidazolidine-2,4-dione as shown in Scheme 4.



Scheme 4. Schematic representation of the tautomeric forms of 5-monosubstituted imidazolidine-2,4-dione.

The energy optimization geometry by AM1 were calculated when R=H for tautomeric form from A to E (Table 3).

Table 3. Energy profile (in kcal/mol) calculated at AM1

Tautomeric form	Energy/ kcal/mol	Energy/ A.U	Dipole moment/ Debye
A	202.91	0.323364	6.6575
B	243.69	0.388347	8.0747
C	247.85	0.394971	7.1316
D	206.77	0.32950748	5.9771
E	137.13	0.218525	3.1113

Table 3 shows the highest number of energy for tautomeric form C of 247.85 kcal/mol, and the lowest energy value of 137.13 kcal/mol, for compound E. The relative stability order of the tautomeric forms of the compound (when R=H) under probe is as follows: E >D>B>C.

B3LYP with the 6-311þG (d,p) has been also used to calculate energy profile for A and E tautomers when R=H shown in supporting information.

A value of -405805.11 (kcal/mol) revealed of electronic and thermal enthalpies for compound **1** (support information). The transition from keto to enol A-E is indicated in our result to show the most stable tautomor form is E based on the lowest energy value (Table 3). B3LYP with the 6-311þG (d,p) has been also used to calculate energy profile for A and E tautomers when R=benzyl (Compound 1 form as keto and enol form) (Table 4).

Table 4. Energy profile (in kcal/mol) calculated at B3LYP with the 6-311þG(d,p) (R=benzyl)

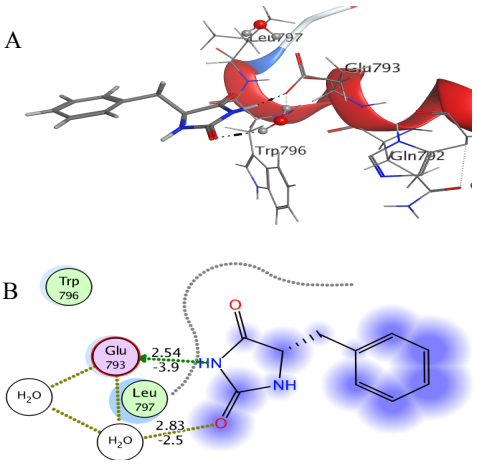
Tautomeric form	Energy/ kcal/mol	Energy/ A.U	Dipole moment/ Debye
A	-406019.05	-647.0324	6.9032
E	-405978.95	-646.9685	7.9245

Table 3 shows a low negative value for E (enol form) for compound **1** compare with A (keto form) showed in Scheme 4.

Finally, the IR and NMR spectra are also undertaken to study the absorption spectra of the studied compounds under probe using the time-dependent– DFT method at the B3LYP optimized structure in the gas phase.

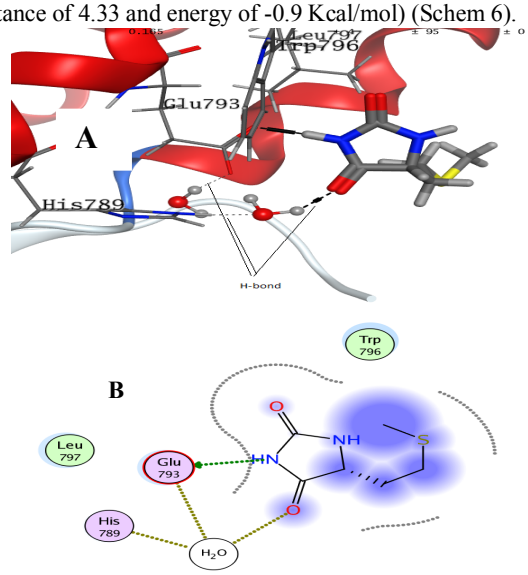
3.3 Docking study

Compound **1**, **2** and **3** were docked into the active site of AR (PDB ID: 2AMA) using MOE program. Glu 793 binds with compound **1** by hydrogen bond in the present of water as a solvent. In addition, Tryp 796 can also act as a base to take hydrogen attached to the streogenic centre and cause keto-enol tautomerism process (*vide supra*).Therefore, isomer of hydantoin as *R* or *S* shape will cause greater influence on the type and affinity of the binding (Scheme 5).



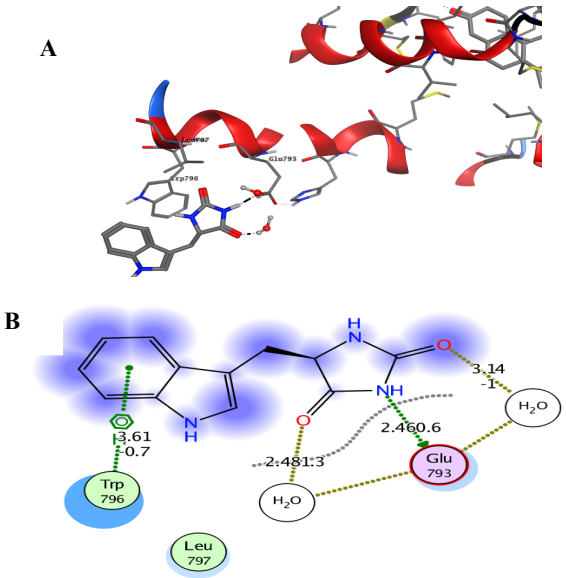
Scheme 5. Compound 1 docking with AR. Dot line show hydrogen bond between compound and amino acids or water. B) Cycled line shows a Latch interaction between Leu 797 and compound 1. Values over the dot lines show distance of the bond, while negative values under dot lines indicate energy of the bond.

Compound **2** has been also docked with AR and shows complex with Glu 793 by hydrogen bond in the presence of water as a solvent in the position of N-3. Sulfur atom attached to the ethyl group on the position 5 can also bind with ARG 786 by a weak bond (H-Accepter) and a distance of the bond 5.30, and -0.7 Kcal/mol). Trp 796 binds with molecule by H-pi bond with the distance of 4.33 and energy of -0.9 Kcal/mol) (Schem 6).



Scheme 6. A) Compound 2 docking with AR. Dot line show hydrogen bond between compound and amino acids or water. B) Cycled line shows a Latch interaction between Leu 797 and compound 2.

Compound **3** has similar docking at N-3 position by H-bond with Glu 793 with the distance of 2.46 and energy of 0.6 Kcal/mol. Two carbonyl groups at the positions of 2, and 4 act as electron accepters and accept hydrogens from water in addition of the connection with Glu 793 by hydrogen bonds. Trp 796 binds with aromatic ring by H-pi bond at the distance of 3.61 and energy of -0.7 Kcal/mol (Scheme 7).



Scheme 7. A) Compound **3** docking with AR. Dot line show hydrogen bond between compound and amino acids or water. B Cycled line shows a Latch interaction between Glu793 and compound **3**. Values over the dot lines show distance of the bond, while negative values under dot lines indicate energy of the bond.

3.4 Biological activity

Biological activity of the present compounds in terms of anti-bacterial property was analyzed against two well-known

pathogenic gram-negative and gram-positive organisms such as *Escherichia coli*, and *Staphylococcus aureus*, respectively.

The activity was tested after dissolution of all the compounds **1** and **3** in DMSO, which was used as a negative control in the experiment. The results of the bacterial growth inhibition are shown in Table 1 (vide *supra*) along with the corresponding positive and negative controls. Compounds **1**, and **3** showed significant growth inhibition of 17 and 12 mm, respectively against *Staphylococcus aureus*, indicating that the experimental set and procedures are appropriate for the test (Table 1).

4. CONCLUSIONS

In this study, three 5-substituted imidazolidine-2,4-diones have been synthesized under free solvent condition. We have performed a theoretical study on the stability order and the prototrophic isomerization processes of using Gaussian program with B3LYP with the 6-311þG (d,p) and AM1. The cyclic imidazolidine-2,4-dione derivatives have been investigated. Molecular docking was performed to simulate the modes of interactions between the drugs and Androgen receptor. Two carbonyl groups at the positions of 2, and 4 act as electron accepters and accept hydrogens from water in addition of the connection with Glu 793 by hydrogen bonds from N-3 position. The best output poses of the ligands generated were analyzed on the basis of Molecular operating environment (MOE), feasibility of hydride transfer process, and H-bonding to the enzyme. Compounds **1**, and **3** showed significant growth inhibition of 17 and 12 mm, respectively against gram positive bacteria, *Staphylococcus aureus*, and resistance to the gram-negative bacteria.

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