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RESEARCH PAPER

Synthesis, computational study, and antibacterial activity of rhodanine and thiazolidine-2,4-dione scaffolds

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A B S T R A C T:

In this research, different thiazolidine-2,4-dione and 2-thioxothiazolidin-4-one derivatives **(1-13)** have been synthesized by Knoevenagel Condensation (**1-13**). Thiazolidine-2,4-dione and 2-thioxothiazolidin-4-one derivatives have an important role in medicinal chemistry and drug design. All synthesized compounds (**1-13**) have been confirmed by IR, ^{1}H and ^{13}C-NMR spectral data. A computational study was used to determine values of the lowest unoccupied molecular orbital and highest occupied molecular orbital energy gap to show the chemical stability, and reactivity of compounds (**1-13**). Small values of energy between a lowest unoccupied molecular orbital and a highest occupied molecular orbital energy gap indicate chemical stability and reactivity of synthesized compounds. $E_{LUMO-HOMO}$ ranged between 0.004-0.306 eV indicated high reactivity of the prepared molecule. Thermodynamic energies have been calculated for synthesized compounds including Enthalpy, Entropy, and Gibbs free energy, negative values have been detected for all synthesized compounds (**1-13**).

Antibacterial activity has done for all synthesized compounds (**1-13**) against Gram-positive *Staphylococcus aureus* and Gram-negative *Escherichia coli* by the method of disc diffusion show that all synthesized compounds except **7**, **8**, **11** and **13** have antibacterial effect for both or one type of bacteria. Antibacterial activity is observed as a clear circular **zone of inhibition** for selected synthesized compounds by disc Inhibition zones of *Staphylococcus aureus*, and *Escherichia coli bacteria.* The range for *Staphylococcus aureus* were between (6-24)mm and for *Escherichia coli* were between (6-18)mm, the measuring of the zones were with the discs.

KEY WORDS:Synthesis, computational study, 2-thioxothiazolidin-4-one, antibacterial activity, and thiazolidine-2,4-dione.
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INTRODUCTION

Five-membered multi-heterocyclic rings like hydanoin derivatives play important roles in medicinal chemistry and biological activity (Syldatk et al., 1990, Faghihi and Hagibeygi, 2003, Yu et al., 2004, Jawhar et al., 2018). Drugs based on five-membered heterocyclic include thiohydantoins, thiazolidine-2, 4-dione and 2-thioxothiazolidin-4-one, are used in drug discovery (Sun et al., 2001, Murugan et al., 2009, Bhatti et al., 2013).

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5-substituted 2-thioxothiazolidin-4-one and thiazolidine-2, 4-dione were synthesized by Knoevenagel condensation reaction with different substituted aldehydes (Scheme 1) (Sandhu, 2013, Ahn et al., 2006, Murugan et al., 2009, Veisi et al., 2015).

Potential (*IP*) and electron affinity (*EA*) have been obtained by orbital energies calculation to obtain ionization values for neutral molecules. Ionization potential and electron affinity are the negative values of the highest occupied molecular orbital energy (-*E*HOMO) and the lowest unoccupied molecular orbital energy (-*E*LUMO), respectively (i.e., IP =-*E*HOMO and *EA* =-*E*LUMO) (Yadav et al., 2015, Wang et al., 2017, Rajamanikandan et al., 2017).

We aimed to synthesize, and computational study of several thiazolidine-2,4-dione and 2-thioxothiazolidin-4-one derivatives. The reactivity and polarity of prepared compounds will be changed by various substituents on benzylidine at position 5. Therefore, computational study has been used to show their reactivity based on substituents. The computational study gives information about hardness, softness, and electronegativity of our synthesized compounds. We tried to give details about the effect of substituent's differences on the antibacterial activity. We imply to obtain difference between more polar compounds with less polar compounds to have antibacterial activities.

2. Experimental

2.1. Chemistry experimental section

2.1.1. Material and methods

All starting compounds obtained from Fisher Scientific, Sigma-Aldrich, Acemec Biochemical, CHEM-LAB and Scharlau. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on 500 MHZ spectrometer and FT-IR instrument was used for identification. ^{1}H-NMR and ^{13}C-NMR spectra were recorded on Brukeravance (500 MHz) spectrometer. Parts per million is a unit of chemical shift and tetra-methylsilane expressed as a standard. NMR spectram were recorded in solutions in the deuterated solvent mentioned in the method section.

2.1.2. General procedure

Method 1: Commercially available Thiazolidine-2,4-dione with corresponding aldehydes, piperidine were dissolved in ethanol in a round bottom flask. The mixture was stirred at 150 ℃. The solid product was filtered and washed several times by ethanol. All pure compounds were collected. Recrystallization was done by ethanol (Ghosh et al., 2011).

Method 2: Commercially available 2-thioxothiazolidin-4-one was placed with corresponding aldehydes, piperidine was dissolved in ethanol in a round bottom flask using a magnetic stirrer and reflux condenser. The mixture was stirred at 150 ℃. The solid product was filtered off and washed with ethanol. The pure compounds were collected. Recrystallization was done by ethanol (McNulty et al., 1998).

2.2. Antibacterial activity

The antibacterial activity was performed by method disc diffusion. All synthesized compounds were screened in against two types of bacterial strains namely *Staphylococcus aureus*, and *Escherichia coli* prepared by our self. The comparison was used with known antibiotics such as Amikacin, Amoxcillin-clavulanic acid, Ampicillin, and cefotaxime. The inhibition zone was measured for each synthesized compound in millimeters (Chaudhari et al., 2012).

The clinical sample was taken from urinary catheterized patients in Rizgari hospital. Bacteria identification were by VITEK II compact system, and molecular approach using 16S rRNA, nuc and coa gen. Bacterial strains Identified according to conventional test such as gram stain, and cultural characteristics like colony properties on bacterial culture media. Biochemical tests analysis like detection of different and special enzymes. Molecular approach using 16S rRNA, nuc and coa genes (Jonas et al., 1999).

3. Discussion

3.1. Chemistry

Different 5-substituted 2-thioxothiazolidin-4-one and thiazolidine-2,4-dione were synthesized by the reaction of Knoevenagel condensation reaction, 2-thioxothiazolidin-4-one or thiazolidine-2,4-dione were dissolved in ethanol with corresponding aldehydes in the base medium (by using piperidine) based on the process previously (Scheme 2) (Ahn et al., 2006, Murugan et al., 2009, Sandhu, 2013, Veisi et al., 2015).

Identification of functional groups were done by using FTIR spectroscopy. Obtained NH stretching vibrations were lower value for carbonyl (X=O) in compounds (1-**8**) than thiocarbonyl group (X=S) in compounds (**9-13)** (Katritzky et al., 1988, Martínez-Mayorga et al., 2004), respectively. The NH stretching vibrations are calculated at (2971-3239) cm^{-1}, and (3012-3409) cm^{-1} in the spectra for compounds 1-**8** and **9-13**. Compounds (**1-8**) show appearance of (1715-1750)) cm^{-1} belong to ν(C=O) carbonyl group and appear at (1671-1691) cm^{-1} due to the second (C=O) of carbonyl group, (1500-1672) cm^{-1} due to the ν(C=C) and (3012-3409) cm^{-1} belong to ν(NH) group. While, compounds (**9-13**) show appearance of (1677-1725) cm^{-1} belong to ν(C=O) carbonyl group and appear absorption at (1475-1598) cm^{-1} because of the (C=S) group, (1428-1598) cm^{-1} for the presence of the ν(C=C) group and (2971-3239) cm^{-1} belong to (NH) group. ^{1}H-NMR spectrum for hydrogen (NH) peak for 2-thioxothiazolidin-4-one derivatives are higher values than thiazolidine-2,4-dione derivatives, Chemical shift for hydrogen NH are (12.61, 12.61, 12.48, 12.30, 12.39,12.45, 12.58, 12.30, 13.82, 13.96, 13.54, 13.83, 13.78) for (**1-13**), respectively. Compound **12** has a CH_2 peak at 5.22, compound **11** has $2CH_3$ (6H) at 3.02, and compound **6** has an OH peak at 10.32. In ^{13}C –NMR, there is (C-F) peak in 164.29, (C-O) at 167.94, (CH_3) at 40.15 for compounds **2**, **3**, and **8**, respectively(Alizadeh et al., 2009, Barakat et al., 2014)

3.2. Computational study

The LUMO-HOMO energy gap is the most important parameter for the chemical reactivity (Jalbout and Fernandez, 2002). The shorter LUMO-HUMO energy gap is considered as the high reactivity (Johansson et al., 2004), The LUMO-HOMO energy gap for all synthesized compounds were calculated by Gaussian using HF- 6-31G (Abdullah et al., 2016, Abdallah, 2019) (Figure 1).

Values of 0.00418 and 0.00391are the ΔE for compounds **5** and **10** respectively, small values of **5**, and **11** indicated that the presence of electron attracting group (NO_2) attached to the benzyl ring on the 5-position could affect the energy gap (Vikneshvaran and Velmathi, 2017, Ahmad, 2015). The highest energy gap value compared with the other synthesized compounds is 0.306 for compound **3** indicated low reactivity. Hydroxyl group attached to benzyl ring as an electronic donating group expected to have an effect on the reactivity. While, the lowest energy differences for compound **5**, and **10** are 0.00418 eV , and 0.00391 eV indicated more reactive than compound **6** with energy gap difference 0.0276 eV and the other synthesized compounds. The reactivity of synthesized compounds indicated as follow **10 >5 > 2 > 1, 9 > 11 > 8 > 4 > 6 > 12 > 13> 7 > 3**. (Table 1).

Ionization potential was calculated by Koopmans's theory (Chong et al., 2002) using orbital energies which is equal to a negative value of HOMO energy. Electron affinity is a negative value of LUMO energy(Shankar et al., 2009, Rocha et al., 2015). The chemical hardness η of the molecule based on the molecular orbital can be calculated by the following equation (equation 1) (Pearson and Pearson, 2005, Galván et al., 2015).

(Pearson and Pearson, 2005, Galván et al., 2015).

$\eta = \frac{ELUMO-EHOMO}{2}$	……….(Equation 1)

While electro negativity χ can be obtained by equation 2

$\chi = \frac{ELUMO+E\ HOMO}{2}$	………..(Equation 2)

Chemical hardness η for compound **1** is equal to the energy gap between LUMO-HOMO and LUMO-HOMO divided by two and the half between the HOMO and LUMO corresponds to electro negativity χ of the molecule. Hardness η and softness η values give information about the molecule about reactivity and stability. Therefore, Other chemical properties were calculated by using HOMO and LUMO energy values such as; hardness which is equal to η = IP-EA/2, electrophilicity index ω = μ2 /2η, electro-negativity χ = IP+EA/2, chemical potential μ=-χ, and softness s = 1/2η (Table 2) (Rocha et al., 2015).

Hardness of compound **1** is equal to 0.13196 which is a measure of the resistance of a chemical species to changes in it is electronic configuration, stability and reactivity (Makov, 1995). It has also been claimed that the interaction between hard species is predominantly electrostatic, while between soft species (3.789) it is predominantly covalent (Pearson and Pearson, 2005).

Thermodynamic parameters

Thermodynamic parameters for all synthesized compounds have been calculated by using B3LYP/6-31G level in Gaussian 09 W. Molar heat capacity constant volume (Cv), Gibbs free energy (ΔG), enthalpies (ΔH), entropies (S) and energy (E), have been calculated for compounds

(**1-13)** (Table 3). In all reactions the values of ΔG are negative and S > 0 that's mean the reactions occur spontaneously (Romero-Gonzalez et al., 2005), energy is released during an exothermic process because of the negative value of ΔH (ΔH < 0) (Kuhlman and Raleigh, 1998).

3.3.Antibacterial activity

All synthesized compounds (**1-13**) were used against *Staphylococcus aureus*, a Gram-positive and *Escherichia coli* as Gram-negative bacterial strains by the process of diffusion. Discs for all (**1-13**) were formed for the study by mixing 10 mg of each compound with 490 mg of KBr under pressure, because the synthesized compounds were powder and we needed to make it as a disc (Figure 2) (Samad and Hawaiz, 2019).

Antibacterial activity is observed as a clear circular **zone of inhibition** around selected synthesized compounds disc Inhibition zones of *Staphylococcus aureus*, and *Escherichia coli* **(Table 4)**. ANOVA (turkeys multiple comparisons) were used for statistical analysis in the study (Oses et al., 2016).

Compounds (**7**, **8**, **11** and **13)** have no antibacterial activity neither with *S. aureus as* or *E. coli* ,because of the presence of tertiary amine and chlorine atoms in compound attached in the benzyl ring inhibit the response of synthesized compound against Gram positive and Gram negative bacteria. Previously studies showed that tertiary amine alone has a high antibacterial activity, because of covalent bonds between polystyrene and fiber (TAF) with tertiary amines (Endo et al., 1987).

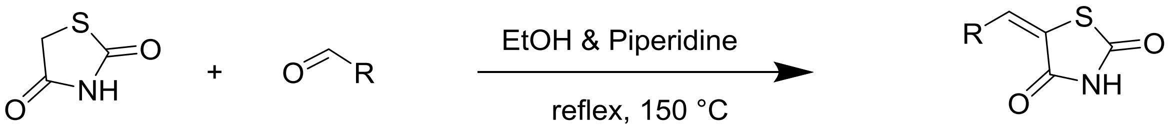
No substituents on benzyl ring attached to 5-position in both thiazolidine-2,4-dione and rhodanine (**1** and **9**) have potent against *S. aureus as* and *E. coli*, while presence of hydroxyl and fluorine atoms (**3** and**12**) have a power of positive and Gram negative bacteria. Compare with the other compounds have higher inhibition zone in both type of bacteria. In previous study showed that compounds containing fluoro group show a higher antibacterial activity than the other compounds against *E. coli*, and *S. aureus* (Naeem, 2010).

Substituents attached on compound **2** and 4 are fluorine and methoxy which give a potency against gram negative bacteria while, fluorine in compound **12** has a response for both type of bacteria.

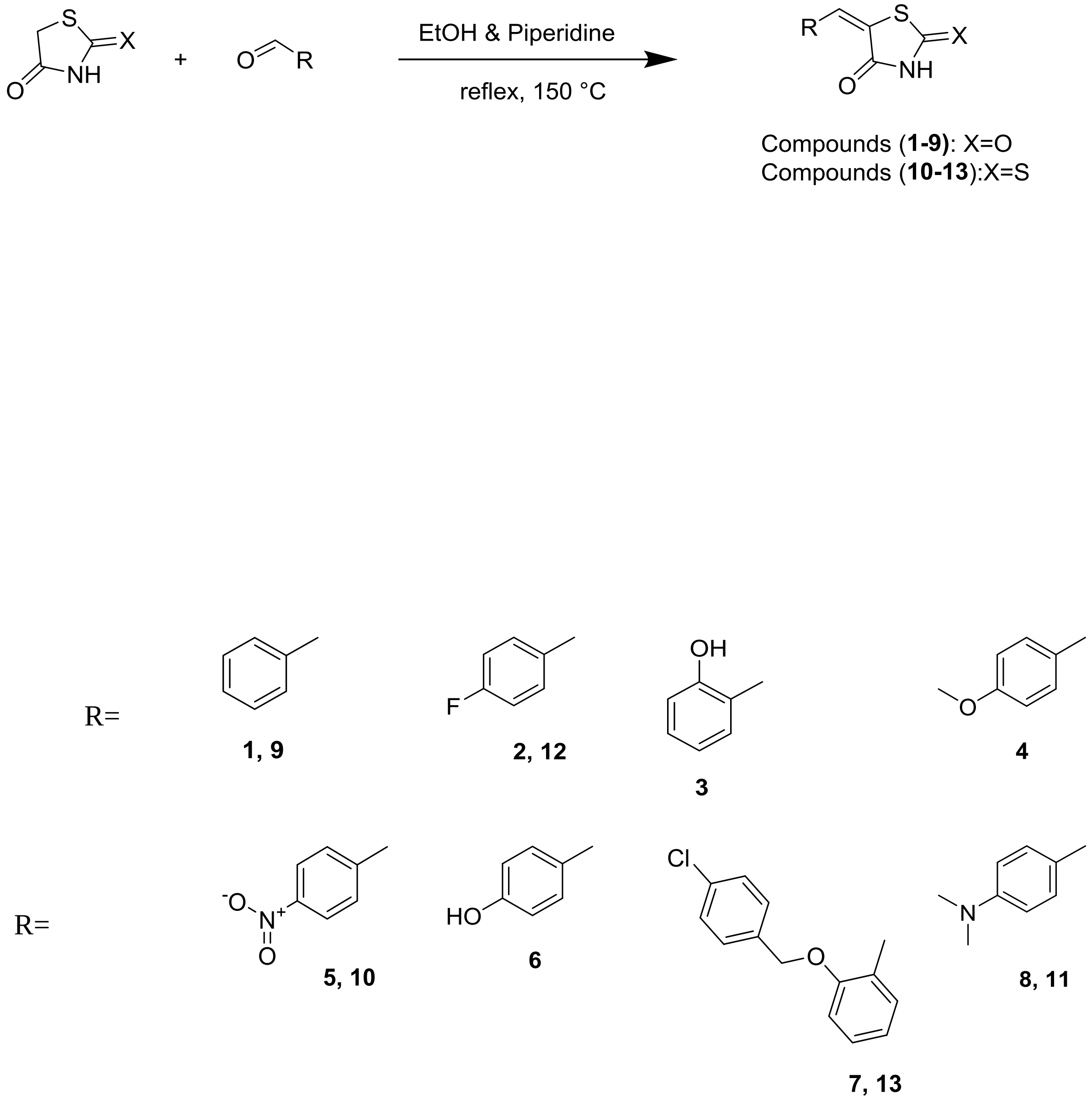
Nitro substituent attache to compound **10** and **5** has a different effect. In compound **10** has the inhibition of Gram negative. While in compound **5** which is thiazolidine-2,4-dione (C=O) might has inhibition zone against Gram positive.

Conclusions

Several compounds (**1-13**) have been prepared by the Knoevenagel condensation with different substituents on the position 5. We found that 5-substituents of thiazolidine-2,4-dione and rhodanine have different rate constant and time duration of the reaction . Therefore, the approximately rate constant of reactions were different from compounds to other. The precipitation of compound (**10**) after mixing of starting materials was produced in 25 minutes, while the slowest precipitation has been identified for compounds (**2** and **3**). All synthesized compounds (**1-13**) have been confirmed via the spectrum of IR, ^{1}H and ^{13}C-NMR. The small values of $\Delta E_{LUMO-HOMO}$ gap are 0.00418 eV and 0.00391 eV for compounds **10** and **5** respectively, small values of **5**, and **10** indicated that the presence of electron attracting group (NO_2) substituted to the benzyl ring on the 5-position can affect the energy gap. While compound **1** and **9** have the same ΔE (0.263 eV) because both have not substituent on the Benzaldehyde. The reactivity of synthesized compounds indicated as follow **10 >5 > 2 > 1, 9 > 11 > 8 > 4 > 6 > 12 > 13> 7 > 3**. The synthesized compounds (**1-13**) were objected to *Staphylococcus aureus* as a Gram positive and *Escherichia coli* as Gram negative bacteria. We identified that different functional groups have different potent against Gram positive *S. aureus* and Gram negative *E. coli*. 5-subistitited of thiazolidine-2,4-dione and rhodanine has a good inhibition zone against both type of bacteria, and with their substituents showed different inhibition zone, in 5-subistituated thiazolidine-2,4-dione presence of hydroxyl group and in rhodanine derivatives presence of flouro group has a inhibition zone with both type of bacteria. Attaching of (F and OCH_3) in the benzyl ring at position 5 of thiazolidine-2,4-dione and rhodanine with (NO_2) as a substituent has inhibition zone only with Gram positive bacteria, while thiazolidine-2,4-dione with (NO_2) has antibacterial activity only with Gram negative bacteria *Escherichia coli*.

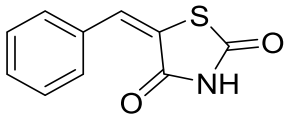


Scheme 1: Knoevenagel condensation reaction for thiazolidine-2,4-dione derivates



Scheme 2: Synthesis of thiazolidine-2,4-dione (X=O) and 2-thioxothiazolidin-4-one (X=S) derivative

Synthesize of 5-benzylidenethiazolidine-2,4-dione

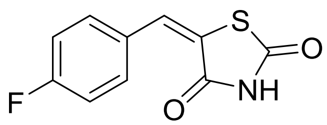


1

Method 1: Thiazolidine-2,4-dione (1.0 g, 8.6 mmol), piperidine (0.3 ml, 0.3 mmol), and benzaldehyde (2. 0 ml, 19.7 mmol) were dissolved in 20 ml of ethanol, reflex for 6 hrs at 150 °C.

M.P.=244-245 ℃, ^{1}H NMR (500 MHz, d_6-DMSO) δ 12.61 (s, 1H, N**H**), 7.77 (s, 1H, **H**CCS), 7.58 (d, *J* = 7.3 Hz, 2H, Ar), 7.55 – 7.49 (m, 2H, Ar), 7.49 – 7.44 (m, 1H, Ar). ^{13}C- NMR (126 MHz, d_6-DMSO). δ 168.3 (**C**OS), 167.7 (**C**ON), 133.5 (**C**-CH), 132.3 (**C**H-C), 130.4 (Ar), 129.7 (Ar) , 123.9 (**C**-S). IR (neat): vmax=1736 cm^{-1} (C=O), 1684 cm^{-1} (C=O), 3120 cm^{-1} (NH), 1662 cm^{-1} (C=C).

Synthesis of (E)-5-((4-fluorocyclohexa-2,4-dien-1-yl)methylene)thiazolidine-2,4-dione



2

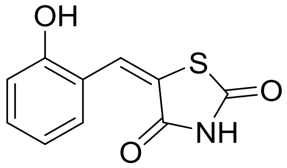
Method 1: Thiazolidine-2,4-dione (1.0 g, 8.6 mmol), piperidine (0.3 ml, 0.3 mmol), and 4-Flurobenzaldehyde (2.0 ml, 18.7 mmol) were dissolved to 20 ml of ethanol, reflex overnight at 150 °C.

(500 MHz, d6-dmso):

M.P.= 219-220 ℃. ^{1}H -NMR (500 MHz, d_6-DMSO): δ 12.61 (s, 1H, N**H**), 7.79 (s, 1H, C**H**CS), 7.68 – 7.63 (m, 2H, Ar), 7.38 (d, *J* = 8.6 Hz, 2H, Ar).^{13}C-NMR (126 MHz, d_6-DMSO): δ 168.2 (**C**OS), 167.8 (**C**ON), 164.3 (**C**F), 162.3 (**C**HCS), 132.9 (**C**CH), 131.1 (Ar), 130.2 (**C**S), 123.8 (Ar), 117.0(Ar). IR (neat): vmax =1725 cm^{-1} (C=O), 16

86 cm^{-1} (C=O), 3118 cm^{-1} (NH), 1606 cm^{-1} (C=C).

Scheme (2.3). Synthesis of (E)-5-(2-hydroxybenzylidene)thiazolidine-2,4-dione

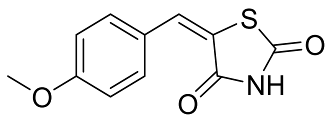


3

Method 1: Thiazolidine-2,4-dione (1.0 g, 8.5 mmol), piperidine (0.3 ml, 0.3 mmol), and 2-hydroxy benzaldehyde (0.91 gm, 7.45 mmol) were dissolved to 20 ml of ethanol, reflex overnight at 150 °C.

M.P.=274-276 ℃. ^{1}H- NMR (500 MHz, d_6-DMSO δ 12.48 (s, 1H, N**H**), 10.48 (s, 1H, O**H**), 8.01 (d, *J* = 19.7 Hz, 1H, C**H**CS), 7.29 (dd, *J* = 16.0, 7.6 Hz, 2H, Ar), 6.98 – 6.86 (m, 2H, Ar). ^{13}C- NMR (126 MHz, d_6-DMSO): δ 168.6(**C**OS), 167.9 (**C**O), 132.6 (**C**OH), 128.7 (H**C**CS), 127.5 (Ar), 122.3 (Ar),, 120.1 (Ar),, 116.6 (C-S). IR (neat): vmax=1721 cm^{-1} (C=O), 1680 cm^{-1} (C=O), 3409 cm^{-1} (NH), 3172 cm^{-1} (OH), 1662 cm^{-1} (C=C).

Synthesis of (E)-5-(4-methoxybenzylidene)thiazolidine-2,4-dione

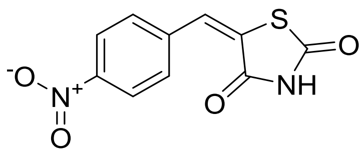


4

Method 1: Thiazolidine-2,4-dione (1.0 g, 8.6 mmol), piperidine (0.3 ml, 0.3 mmol), and 4-methoxy benzaldehyde (2.0 ml, 17.0 mmol) were dissolved to 20 ml of ethanol, reflex for 4 hrs. at 150 °C**.**

M.P.= 260-261℃. ^{1}H -NMR (500 MHz, d_6-DMSO): δ 12.79 (s, 1H, N**H**), 8.32 (d, *J* = 8.6 Hz, 3H, C**H**CS), 8.04 – 7.63 (m, 4H, Ar), 3.38 (d, *J* = 46.7 Hz, 3H, C$\mathbf{H}_3$). ^{13}C- NMR (126 MHz, d_6-DMSO): δ 167.6 (**C**O), 166.9 (**C**O), 147.2 (**C**OCH3), 139.7 (**C**HCS), 131.5 (Ar), 129.4 (Ar), 125.0 (**C**-S), 39.4 (**C**H_3). IR (neat): vmax=1750 cm^{-1} (C=O), 1714 cm^{-1} (C=O), 3186 cm^{-1} (NH), 1161cm^{-1} (C-O), 1672 cm^{-1} (C=C).

Synthesis of (E)-5-(4-nitrobenzylidene)thiazolidine-2,4-dione

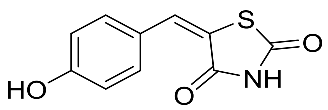


5

Method 1: Thiazolidine-2,4-dione (1.0 g, 8.5 mmol), piperidine (0.3 ml, 0.3 mmol), and 4-nitro benzaldehyde (1.0 gm, 8.6 mmol) were dissolved to 20 ml of ethanol, reflex for 2 hrs at 150 ℃

M.P.=297-298 ℃. ^{1}H- NMR (500 MHz, d_6-DMSO): δ 12.30 (s, 1H, N**H**), 8.06 – 7.45 (m, 1H, C**H**CS), 7.41 (d, *J* = 8.6 Hz, 2H, Ar), 6.80 (d, *J* = 8.6 Hz, 2H,Ar). ^{13}C- NMR (126 MHz, d_6-DMSO): δ 168.7 (**C**OS), 167.9 (CO), 151.9 (**C**N), 133.7 (**C**H), 132.0 (**C**CH), 120.5 (Ar), 116.6 (Ar), 112.2 (**C**S). IR (neat): vmax=1720 cm^{-1} (C=O), 1677 cm^{-1} (C=O), 3090 cm^{-1} (NH), 1326 cm^{-1} (C-N), 1611cm1^{-1} (C=C).

Synthesis of (E)-5-(4-hydroxybenzylidene)thiazolidine-2,4-dione

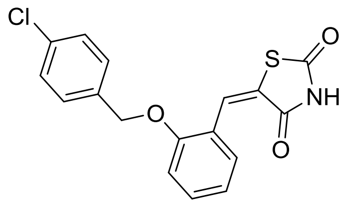


6

Method 1: Thiazolidine-2,4-dione (1.0 g, 8.6 mmol), piperidine (0.3 ml, 0.3 mmol), and 3-nitro benzaldehyde (1.0 gm, 8.6 mmol) were dissolved to 20 ml of ethanol, reflex for 2 hrs. at 150 ℃

M.P.= 296-297 ℃. ^{1}H NMR (500 MHz, d_6-DMSO): δ 12.39 (s, 1H, N**H**), 10.32 (s, 1H, O**H**), 7.67 (s, 1H, C**H**CS), 7.42 (d, *J* = 8.2 Hz, 2H), 6.90 (d, *J* = 8.3 Hz, 2H). ^{13}C NMR (126 MHz, d_6-DMSO) δ 168.7 (**C**=O), 168.4 (**C**=O), 160.5 (**C**-O), 133.0m (**C**H-C), 124.1 (Ar), 116.6 (Ar). IR (neat): vmax=1719 cm^{-1} (C=O), 1671cm^{-1} (C=O), 3110 cm^{-1} (NH), 3399 cm^{-1} (OH), 1570 cm1^{-1} (C=C).

Synthesis of (E)-5-(2-((4-chlorobenzyl)oxy)benzylidene)thiazolidine-2,4-dione

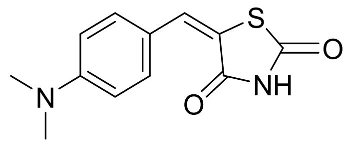


7

Method 1: Thiazolidine-2,4-dione (1.0 g, 8.6 mmol), piperidine (0.3` ml, 0.3 mmol), and 4-chloro benzaldehyde (1.7 gm, 6.9 mmol) were dissolved to 20 ml of ethanol, reflex for 4 hrs. at 150 ℃.

M.P.=197-198 ℃. ^{1}H- NMR (500 MHz, d_6-DMSO): δ 12.58 (s, 1H, N**H**), 8.01 (s, 1H, C**H**CS), 7.48 (s, 4H, Ar), 7.45 (d, *J* = 8.1 Hz, 1H, C**H**CCH), 7.42 (s, 2H,C**H**Cl), 7.11 (t, *J* = 7.5 Hz, 1H C**H**CO), 5.24 (s, 2H, CH_2). ^{13}C -NMR (126 MHz, d_6-DMSO): δ 168.5 (**C**=O), 167.9 (**C**=O), 157.4 (C-O), 136.0 (**C**-H), 133.2 (**C**-H), 132.7 (**C**-Cl), 130.1 (**C**-CH_2), 129.1 (Ar), 128.8 (Ar), 126.5 (**C**-S), 124.2 (Ar), 122.4 (Ar), 121.8 (**C**HCO), 69.4 (**C**H_2). IR (neat): vmax=1759. cm^{-1} (C=O), 1691 cm^{-1} (C=O), 3012 cm^{-1} (NH), 805 cm^{-1} (C-Cl), 1588 cm1^{-1} (C=C), 1250 cm^{-1} (C-O).

Synthesis of (E)-5-(4-(dimethylamino)benzylidene)thiazolidine-2,4-dione



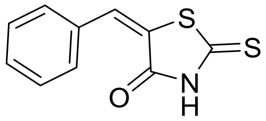
8

Method 1: Thiazolidine-2,4-dione (1.0 g, 8.6 mmol), piperidine (0.3 ml, 0.3 mmol), and 4-(dimethylamino) benzaldehyde (1.3 gm, 8.7 mmol) were dissolved to 20 ml of ethanol, reflex for 2 hrs. at 150 ℃.

M.P.= 295-298 ℃. ^{1}H- NMR (500 MHz, d_6-DMSO): δ 12.30 (s, 1H, N**H**), 7.65 (s, 1H, C**H**CS), 7.41 (d, *J* = 8.7 Hz, 2H, Ar), 6.80 (d, *J* = 8.7 Hz, 2H, Ar), 3.00 (s, 6H, CH_3). ^{13}C- NMR (126 MHz, d_6-DMSO) δ 168.7 (**C**=O), 167.6

(**C**=O), 151.6 (**C**NCH$_3$), 134.0 (**C**H), 120.0 (Ar), 115.5 (Ar), 113.3 (**C**-S), 40.2 (**C**H$_3$). IR (neat): vmax= 1720 cm^{-1} (C=O), 1677 cm^{-1} (C=O), 3089 cm^{-1} (NH), 1500 cm1^{-1} (C=C), 1100 cm^{-1} (C-N), 2760 cm^{-1} (C-H).

Synthesis of (E)-5-benzylidene-2-thioxothiazolidin-4-one

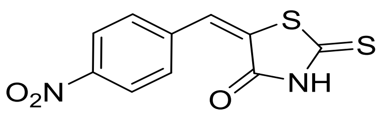


9

Method 2: 2-thioxothiazolidin-4-one (1.0 g, 7.5 mmol), piperidine (0.3 ml, 0.3 mmol), and benzaldehyde (2.0 ml, 18.7 mmol) were dissolved to 20 ml of ethanol at 150 ℃ for 6 hrs.

M.P.= 198-200 ℃. ^{1}H -NMR (500 MHz, d$_6$-DMSO): δ 13.82 (s, 1H, N**H**), 7.63 (s, 1H, C**H**CS), 7.58 (d, *J* = 7.1 Hz, 3H Ar,), 7.50 (ddd, *J* = 9.7, 3.7 Hz, 2H, Ar). ^{13}C -NMR (126 MHz, d$_6$-DMSO): δ 195.83 (**C**=S), 169.44 (**C**=O), 133.40 (**C**H), 132.08, (**C**CH), 131.17 (Ar), 130.91(Ar), 129.88(**C**-S). IR (neat): vmax= 2971cm^{-1} (NH), 1698 cm^{-1} (C=O), 1475 cm^{-1} (C=S), 1598 cm^{-1} (C=C).

Synthesis of (E)-5-(4-nitrobenzylidene)-2-thioxothiazolidin-4-one

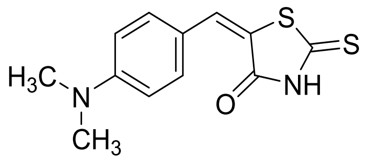


10

Method 2: 2-thioxothiazolidin-4-one (1.0 g, 7.5 mmol), piperidine (0.3 ml, 0.3 mmol), and 4-nitro benzaldehyde (1.3 gm, 8.6 mmol) were dissolved to 20 ml of ethanol, reflex for 25 mines at 150 ℃.

M.P.= 269-270 ℃. ^{1}H- NMR (500 MHz, d$_6$-DMSO): δ 13.96 (s, 1H, N**H**), 8.43 (s, 1H, C**H**CS), 8.30 (d, *J* = 8.2 Hz, 2H, Ar), 7.99 (d, *J* = 7.8 Hz, 2H, Ar). ^{13}C NMR (126 MHz, d$_6$-DMSO): δ 195.8 (**C**=S), 170.2 (**C**=O), 148.3 (**C**-N), 136.6 (**C**-H), 134.8 (**C**CH), 131.2 (Ar), 130.8 (Ar), 125.1 (**C**-N). IR (neat): vmax= 3239 cm^{-1} (NH), 1725 cm^{-1} (C=O), 1598 cm^{-1} (C=S), 1428 cm^{-1} (C=C), 1222 cm^{-1} (C-N).

Synthesis of (Z)-5-(4-(dimethylamino)benzylidene)-3-thioxoisothiazolidin-4-one

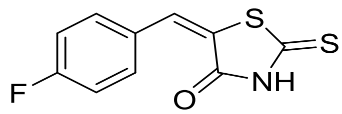


11

Method 2: 2-thioxothiazolidin-4-one (1.0 g, 7.5 mmol), piperidine (0.3` ml, 0.3 mmol), and 4-(dimethylamino) benzaldehyde (1.3 gm, 8.7 mmol) were dissolved to 20 ml, reflex for 3 hrs. at 150℃.

M.P.=197-198℃. ^{1}H- NMR (500 MHz, d$_6$-DMSO): δ 13.54 (s, 1H, N**H**), 7.50 (s, 1H, C**H**CS), 7.40 (d, *J* = 8.7 Hz, 2H, Ar), 6.80 (d, *J* = 8.7 Hz, 2H, Ar), 3.02 (s, 6H, C**H**$_3$). ^{13}C -NMR (126 MHz, d$_6$-DMSO) δ 195.5 (**C**=S), 170.4 (**C**=O), 151.6 (**C**NCH$_3$), 133.3 (**C**HCS), 120.1 (Ar), 117.6 (Ar), 111.9 (C-S) 43.4 (**C**H$_3$) . IR (neat): vmax= 3150 cm^{-1} (NH), 1677 cm^{-1} (C=O), 1561 cm^{-1} (C=S), 1519 cm^{-1} C=C), 1250 cm^{-1} (C-N).

Synthesis of (E)-5-(4-fluorobenzylidene)-2-thioxothiazolidin-4-one



12

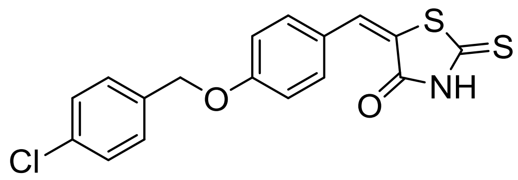
Method 2: 2-thioxothiazolidin-4-one (1.0 g, 7.5mmol), piperidine (0.3 ml, 0.3 mmol), and 4-floro benzaldehyde (2.0 ml, 18.7 mmol) were dissolved to 20ml of ethanol, reflex for 3 hrs. at 150 ℃.

^{1}H NMR (500 MHz, dmso) δ 13.83 (s, 1H), 7.66 (dd, *J* = 7.8, 5.6 Hz, 1H), 7.37 (t, *J* = 8.4 Hz, 1H).

^{1}H NMR (500 MHz, dmso)

M.P.=224-225 ℃, ^{1}H NMR (500 MHz, d$_6$-DMSO) δ 13.83 (s, 1H, N**H**), 7.70 – 7.65 (m, 1H, C**H**CS), 7.66 (s, *J* = 7.8, 5.6 Hz, 2H), 7.36 (s, 2H). ^{13}C NMR (126 MHz, d$_6$-DMSO) δ 195.8 (**C**=S), 169.4 (**C**=O), 164.8 (**C**-F), 162.3 (**C**H), 133.7 (Ar), 130.8 (**C**-S), 117.3 (Ar). IR (neat): vmax= 3015cm-1 (NH), 1699 cm-1 (C=O), 1584 cm^{-1} (C=S), 1482 cm^{-1} (C=C), 534 cm^{-1} (C-F).

Synthesis of (E)-5-(2-((4-chlorobenzyl)oxy)benzylidene)-2-thioxothiazolidin-4-one



13

Method 2: 2-thioxothiazolidin-4-one (1.0 g, 7.5mmol), piperidine (0.3` ml, 0.3 mmol), and 1-((4-chlorobenzyl)oxy)-2-vinylbenzene (1.7 gm, 12.09 mmol) were dissolved to 20 ml of ethanol reflex for 4hrs at 150℃.

M.P.=239-240℃, ^{1}H NMR (500 MHz, d_6-DMSO) δ 13.78 (s, 1H, N**H**), 7.84 (s, 1H, C**H**CS), 7.47 (d, *J* = 11.5 Hz, 4H, Ar), 7.39 (d, *J* = 7.6 Hz, 2H, Ar), 7.21 (d, *J* = 8.3 Hz, 2H, Ar), 7.12 (t, *J* = 7.5 Hz, 1H), 5.25 (s, 2H, C$\mathbf{H}_2$). ^{13}C NMR (126 MHz, d_6-DMSO) δ 196.5 (**C**=S), 170.1 (**C**=O), 157.6 (**C**-O), 136.2 (**C**-H), 133.0 (**C**CH_2), 129.7 (**C**Cl), 128.7 (2***C**H), 126.2 (**C**-CH), 121.9 (C-S), 114.0 (2X**C**H), 69.4 (**C**H_2). IR (neat): vmax= 3036 cm^{-1} (NH), 1699 cm^{-1} (C=O), 1584 cm^{-1} (C=S), 1482 cm^{-1} (C=C), 800 cm^{-1} (C-Cl).

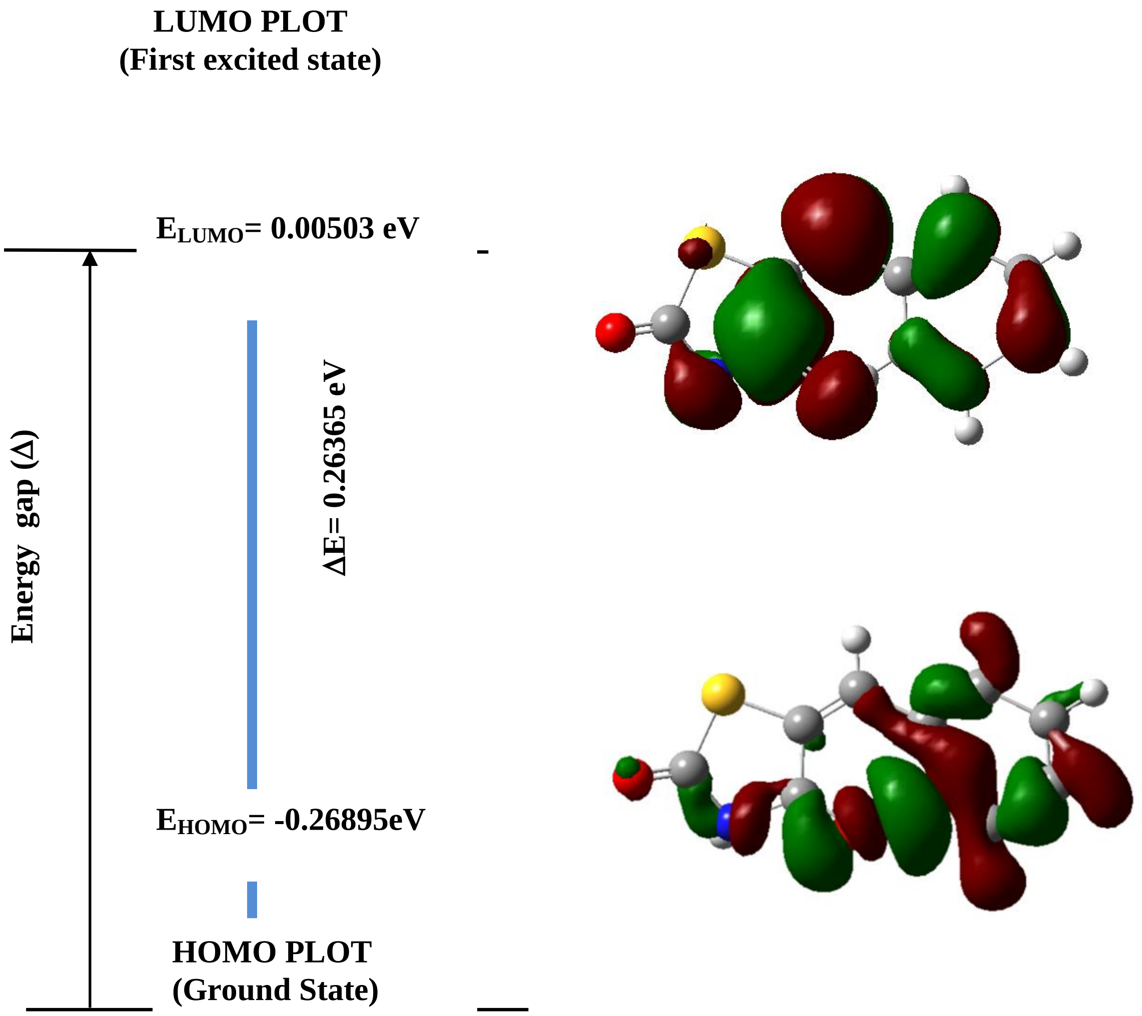


Figure 1.Molecular orbitals and LUMO and HOMO energy gap of compound **1**

Table 1: Data for HOMO, LUMO, and LUMO- HOMO gap (ΔE) for compounds **1-13**

No.	Compounds	HOMO/eV	LUMO/eV	ΔE, (LUMO-HOMO)
1.	5-benzylidenethiazolidine-2,4-dione (**1**)	-0.26895	0.00503	0.26365
2.	5-((4-fluorocyclohexa-2,4-dien-1-yl)methylene)thiazolidine-2,4-dione (**2**)	-0.29539	0.03306	0.26233
3.	5-(2-hydroxybenzylidene)thiazolidine-2,4-dione (**3**)	-0.31383	0.00768	0.30615
4.	5-(4-methoxybenzylidene)thiazolidine-2,4-dione (**4**)	-0.27636	0.00314	0.27322

5.	)-5-(4-nitrobenzylidene)thiazolidine-2,4-dione (**5**)	-0.28395	-0.28786	0.00391
6.	5-(4-hydroxybenzylidene)thiazolidine-2,4-dione (**6**)	-0.2771	0.00081	0.27629
7.	5-(2-((4-chlorobenzyl)oxy)benzylidene)thiazolidine-2,4-dione (**7**)	-0.31564	0.01359	0.30205
8.	5-(4-(dimethylamino)benzylidene)thiazolidine-2,4-dione (**8**)	0.02120	-0.29169	-0.27049
9.	5-benzylidene-2-thioxothiazolidin-4-one (**9**)	-0.26389	0.01121	0.26389
10.	5-(4-nitrobenzylidene)-2-thioxothiazolidin-4-one (**10**)	-0.27706	-0.28124	0.00418
11.	(E)-5-(4-(dimethylamino)benzylidene)-2-thioxothiazolidin-4-one (**11**)	-0.29483	0.02493	0.2699
12.	(E)-5-((4-fluorocyclohexa-2,4-dien-1-yl)methylene)-2-thioxothiazolidin-4-one (**12**)	-0.28119	-0.00279	0.2784
13.	(E)-5-(2-((4-chlorobenzyl)oxy)benzylidene)-2-thioxothiazolidin-4-one (**13**)	-0.30933	0.01967	0.28966

Table 2: Reactivity properties, HOMO and LUMO energies, LUMO-HOMOenergy gap of compound **1**.

Molecular parameters	**B3LYP/6-31G(d,p)**
EHOMO (eV)	**-0.26895**

ELUMO (eV)	**0.00503**
ΔE LUMO-HOMO (eV)	**0.26365**
Ionization potential, IP (eV)	**0.26895**
Electron affinity, EA (eV)	**-0.00503**
Electronegativity, χ (eV)	**0.27398**
Chemical potential, μ (eV)	**-0.27398**
Chemical hardness, η (eV)	**0.13196**
Chemical softness, s (eV-1)	**3.789**
Global electrophilicity index ω	**2.84177**

Table 3: Thermodynamic parameters of **1-13**

Compounds	**E(Kcal/mol)**	**ΔG(Kcal/mol)**	**ΔH(Kcal/mol)**	**S(Kcal/mol)**	**CV(Kcal/mol)**
1	-619887.329	-619915.6718	-619886.737	0.097046	0.039226
2	-682879.094	-682910.954	-682878.501	0.044261	0.108848
3	-664154.296	-664182.5245	-664153.703	0.097444	0.039904
4	-691698.407	-691728.458	-691697.814	0.102778	0.044273
5	-745110.057	-745140.6766	-745109.465	0.106307	0.043715
6	-469732165.8	-748597.067	-748565.1032	0.107209	0.044823
7	-664092.506	-664121.686	-664091.913	0.099859	0.040958
8	-1120477.18	-1120513.987	-1120476.594	0.125417	0.063167
9	-819607.569	-819634.802	-819606.977	0.093325	0.035416
10	-951220.205	-951251.196	-951219.613	0.105931	0.043889
11	-903082.448	-903113.669	-903081.855	0.106706	0.04577
12	-881627.256	-881655.96	-881626.663	0.098266	0.038311
13	-1322938.49	-1322975.165	-1322937.897	0.124995	0.062528

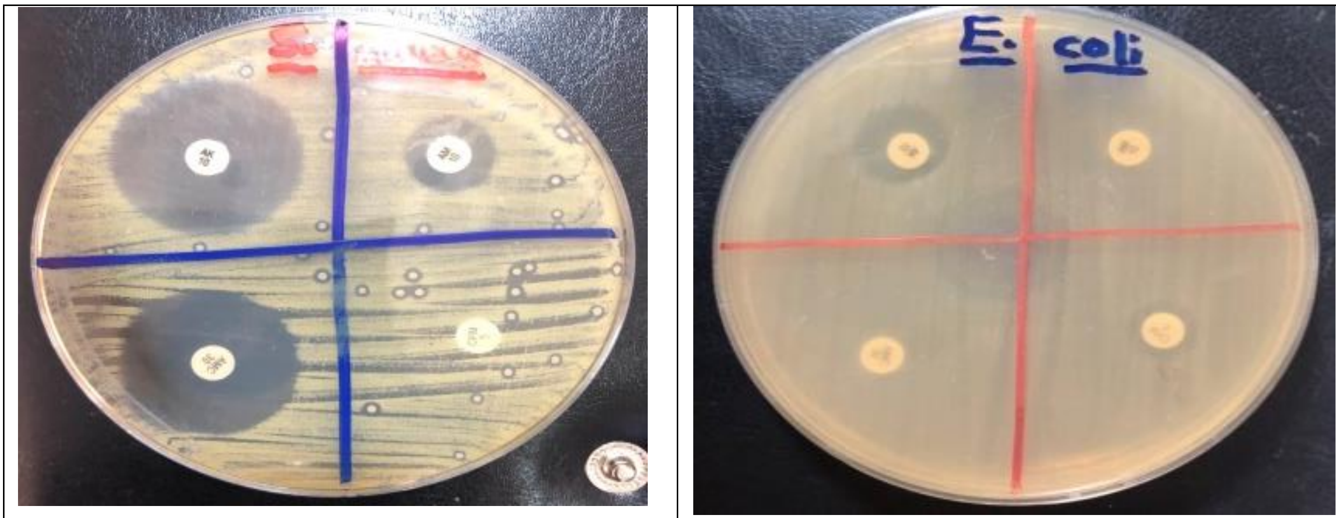


Figure 2-a : Antibacterial activities of Amikacin, Amoxcillinclavulanic acid, Ampicillin, and Cefotaxime with *Staphylococcus aureus*, and *Escherichia coli* by disc diffusion method

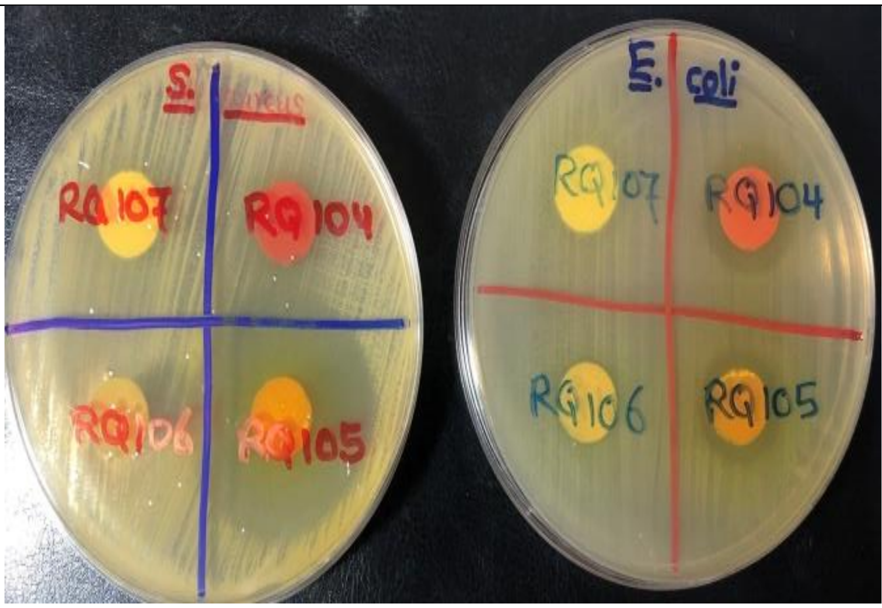


Figure 2-b : Antibacterial activities of synthesized compounds (R.Q.104 = comp **11**and R.Q.106 = Comp **12**) with *Staphylococcus aureus*, and *Escherichia coli* by disc diffusion method

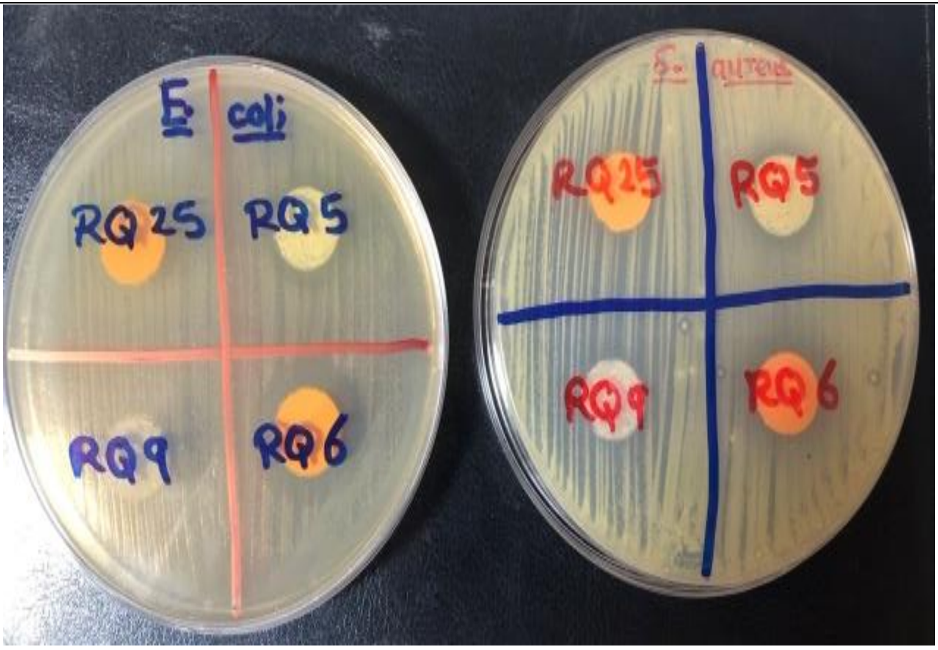


Figure 2-c : Antibacterial activities of synthesized compounds (R.Q.5 = comp **4,** R.Q.6 = comp. **5**, R.Q.9 = comp **7**, and R.Q.25 = comp. **8** with *Staphylococcus aureus*, and *Escherichia coli* by disc diffusion method

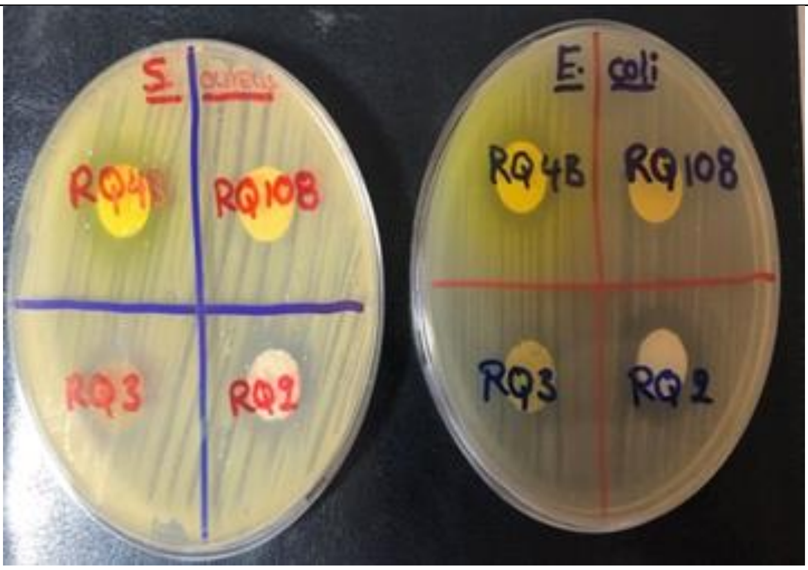


Figure 2-d : Antibacterial activities of synthesized compound (R.Q.2= comp **1**, R.Q.3= comp **2**, R.Q.4-B= comp **3** and R.Q.108= comp **13**) with *Staphylococcus aureus,* and *Escherichia coli* by disc diffusion method

Table 4: Inhibition zone of the tested compounds against *Staphylococcus aureus*, and *Escherichia coli*		
Compounds	Inhibition zones of *S. aureus* and *E. coli* for the tested compound (mm)	
	E-coli	***S. aureus***
1	18	15
2	6	13
3	15	14
4	6	14
5	18	6
7	6	6
8	6	6
9	12	22
10	6	24
11	6	6
12	12	17
13	6	6

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