



Original Article

New Resorcinol Derivatives: Preparation, Characterization and Theoretical Investigation

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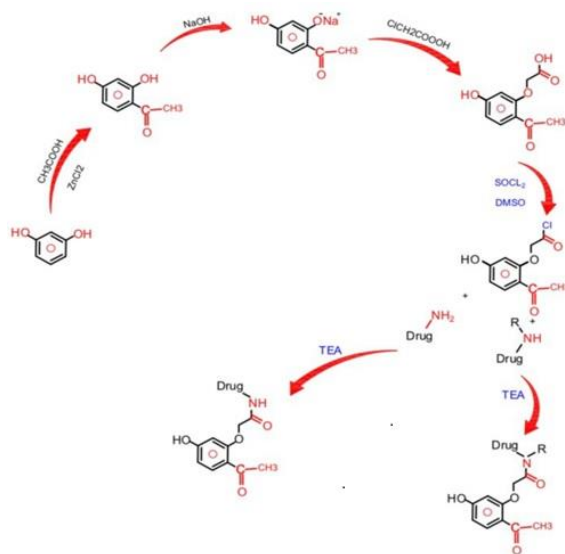
Theoretical investigation

Transition state

ABSTRACT

Our interest in this area has been to employ organic synthesis methods to prepare new resorcinol derivatives with high yields. The precursor material has been used to prepare di-substituted molecule pharmaceutical compounds by reacting with acetic acid and zinc dichloride as catalysts at the first step. At second step reaction the product with chloro acetic acid using the sodium hydroxide to converting the carboxyl group in the last product to an acid chloride by SOCl₂. The acid chloride was then dissolved in DCM and reacted with four amino drugs (Sulfadiazine, Theophylline, Paracetamol, and 4-amino antipyrine) to produce the new preparative compounds. All the organized compounds have been characterized with the aid of using FT-IR, and ¹H-NMR. The physical properties of the synthesized compounds have been additionally decided, and their solubility in distinctive solvents. A theoretical investigation is done to prove the nature of the acylation reaction of resorcinol through the suggestion of three different transition states. Three suggested transition states are examined for the most probable pathway of the acylation reaction. The calculation proves that the acylation reaction is done through the para position of aromatic ring with high yield present than other positions.

GRAPHICAL ABSTRACT



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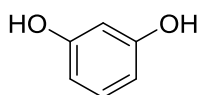
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Introduction

In the last years, applications of new drug derivatives have been accelerated to increase the treatment effect towards a wide range of microbial organism that causes disease. One of the famous chemical compounds is resorcinol, a solid organic compound [1] with less toxic than phenol [2].

Resorcinol is widely used in industry but is also used as a pharmaceutical agent for topically in dermatological remedies, pimples, associated pores and skin conditions. It can also be utilized in aggregate with the opposite pimples remedy retailers, which include Sulfur [3, 4] and used as a chemical intermediate for manufacturing of m-aminophenol, manufacturing of mild stabilizers for plastics [5], manufacturing of sunscreen arrangements for the pores and skin, manufacturing of dyes (fluorescein, eosin) [6], and anti-cancer agents [7, 8].

Resorcinol (Scheme 1) can also be used in many applications as floor coatings, silt, anti-corrosion coatings and adhesives when it interacts with formaldehyde and the formation of resorcinol-formaldehyde (RF) resin as a product of the reaction [9].



Scheme 1: Chemical structure of resorcinol

In this work, new derivatives of resorcinol will prepare depending on acylation reaction to get on four different derivatives of resorcinol as the primary molecule in all organized compounds (Scheme 2). Spectral analysis methods will be characterized all these derivatives. In the theoretical investigation, the acylation reaction of resorcinol is carried out using semi-empirical methods (PM₃) (Figure 1), where the Geometrical structures are calculated. One-of-a-kind transition states were counseled, and the maximum probable transitions state was investigated, relying upon the energetic and electronic characteristics to indicate the maximum probable pathway of the reaction (Table 2). That Table 3 show the calculations of transition states, energy

barrier and $\epsilon\Delta H$ for the resorcinol derivatives (Scheme 3).

Material and Methods

All the chemical substances used in this study have been Sigma Aldrich and Fluka supported with the very best purity available. Samarra Company for drug manufacturing produced drugs. Gallenkamp MFB-600-Melting factor Stuart apparatus was used to determine organized compounds' melting factors. The FT-IR spectra changed into measured in a Bruker spectrometer. ¹H-NMR decided with the aid of using the use of a Bruker AC four hundred NMR spectrometer set to 500 MHz for ¹H-NMR, the chemical shifts (δ) have been expressed in components consistent with million (ppm) relative to tetramethylsilane (TMS) as a default.

Synthesis of resorcinol derivatives

Synthesis of 2,4-dihydroxyacetophenone (TS₂)

Anhydrous ZnCl₂ (15 g, 110 mmol) was added to 30 ml of CH₃COOH and heated at 140 °C. After all the ZnCl₂ has been dissolved, resorcinol (10 g, 90 mmol) has been stirred and heated for 3 hours at 150 °C in an oil bath. The ZnCl₂ complex broke down by adding 50% HCl (50 mL). In an ice bath, a bright yellow precipitate formed and cooled, then filtered. A yield was washed with 5% HI and thus recrystallized through hot water, a white solid formed (7.99 g, 80%), m.p. 144-146 °C, molecular formula: C₈H₈O₃, M.wt=152.15 g/mol [10].

Synthesis of compound (TS₃)2-(2-acetyl-5-hydroxyphenoxy) acetic acid

Dissolved 2 g of KOH in 4 mL of water in a 50 mL spherical flask, and 0.5 g of 2,4-dihydroxyacetophenone was delivered to the spherical flask. The aggregate changed into stirred till a homogeneous solution resulted. Fit the flask with a reflux condenser and warmth to a mild boil. Add 6 mL of a 50% aqueous solution (g/mL) of chloro acetic acid dropwise and boil and boil the mixture for 10 min. The aggregate cooled to room temperature and acidified the solution with sensible drop addition of focused HI, revealing the pH with pH paper. The combination turned into

cooled in an ice bath and filtered the precipitate through vacuum filtration. The crude strong changed into recrystallized from boiling water to have the funds for compound TS₃. The response became observed using the TLC approach of ethyl acetate: acetone (1:1). FT-IR was used to represent TS₃. Solid, Color: white, molecular formula: C₁₀H₁₀O₅, M.wt=210.19 g/mol [11].

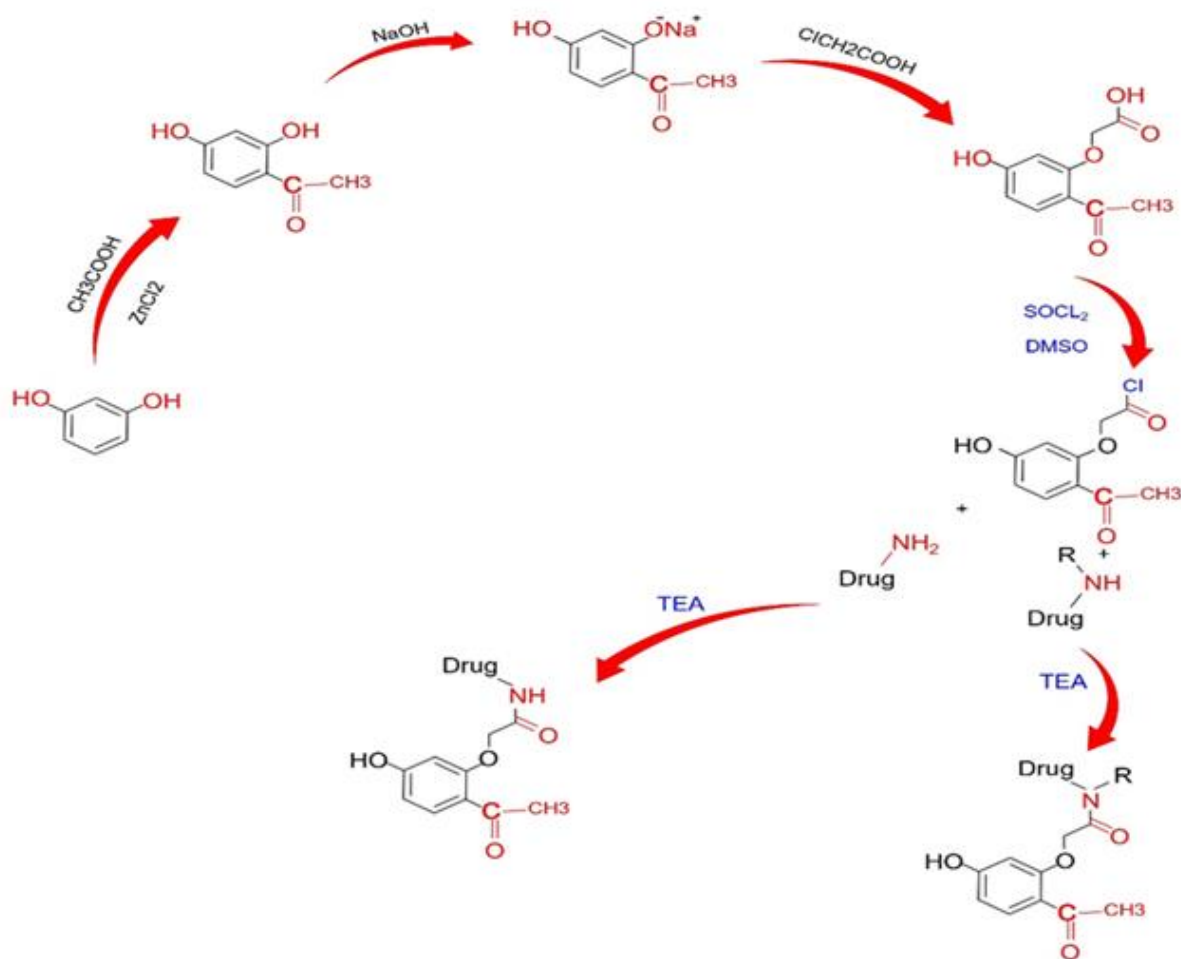
A general technique for one-pot synthesis of amides (Synthesis of TS5-TS8)

1 mmol of the carboxylic acid is brought to 1 mmol of amine and 3 mmol of triethylamine (Et₃N) in dichloromethane, then 1 mmol of SOCl₂ is delivered at room temperature. The aggregate is stirred for 5–20 mins at room temperature. The recovery of the mixture into executed by evaporating the solvent under decreased pressure. The ensuing residue is taken up in

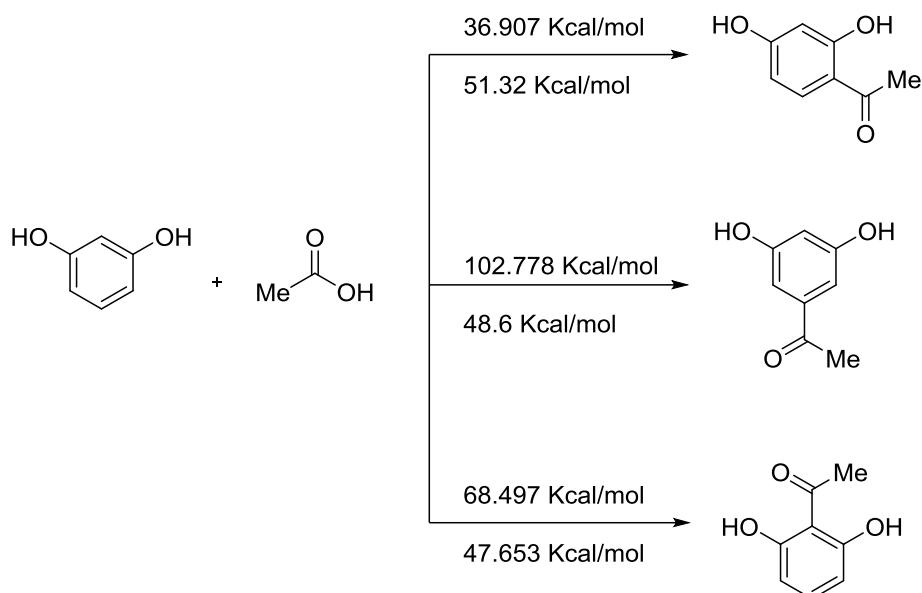
dichloromethane and washed first with 1 N HCl with 1 N NaOH. The development of reactions becomes monitored through TLC. Solid precipitates had been fashioned, and all products were characterized through FT-IR and ¹H-NMR (Scheme 4) [12].

Antibacterial activity

Antimicrobial susceptibility tests of a few synthesized compounds have been completed consistent with the “nicely diffusion technique”. Synthesized compounds were evaluated on bacterial strains, one gram-notable bacteria (*staphylococcus aureus*) and one gram-terrible bacteria (*Klebsiella pneumonia*). Samples have been cultured on Muller Hinton agar medium at a temperature of 37 °C for 24 hours, and the outcomes have been precise for a few compounds [13].



Scheme 2: Interaction diagram



Scheme 3: Calculation of transition states of acylation reaction

Antioxidants activity

The solution changed from moderate to shielding the check tubes with aluminum foil. DPPH (four mg) has become dissolved in 100 mL of methanol. Some of the produced compounds have been used to make numerous concentrations of 25, 50, and 100 ppm. It was made by dissolving 1 milligram of the chemical in 10 mL of methanol to make one hundred elements in step with million, then diluting it to 50 and 25 components regular with million. The concentrations were made with inside the same way. 1 mL of the diluted or everyday answer (25, 50, 100) ppm modified into delivered to at least one mL of DPPH answer in a test tube. After 30 min of incubation at 37 °C, every answer's absorbance becomes measured using a spectrophotometer at 517 nm. The following equation has become used to decide the capacity to scavenge DPPH radicals [14].

$$I\% = \frac{\text{Absorption control} - \text{Absorption sample}}{\text{Absorption clean}} \times 100$$

The solubility

The solubility of all synthesized derivatives in different solvents turned into was studied and listed in Table 1.

Results and Discussion

The reaction between resorcinol and drugs produces a bi-molecular compound composed of three drug molecules (TS₅-TS₈). FT-IR, and ¹H-NMR spectrum fixed eyeglass synthesized compounds [15].

Compound TS₅

Dark brown, mp 92-94 °C, yield 97%, FT-IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 3300 (N-H groups), 1618 (N-H bend), 1770 (C=O ketones), 1680 (CO amide), 3742 (O-H groups), 3049 (C-H aromatic), 2939 (C-H sp³), 1313 and 1253 (C-O), 1437 (O-H), 1157 (S=O). ¹H-NMR (500 MHz, DMSO): δ 9.98 (s, O-H, alcohol), 9.96 (s, N-H, amid), 11.3 (s, Nsulfonamide), 6.4-7.6 (d, C-H, aromatic), 4.6 (s, methylene), 2.6 (s, methyl) 7.7-8.4 (d, CH pyrimidine).

Compound TS₆

Dark green, mp 120-123 °C, yield 89%, FT-IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1720 (C=O ketones), 1647 (CO amide), 3674 (O-H alcohol), 3100 (C-H aromatic), 2976 (C-H sp³). ¹H-NMR (500 MH, DMSO): δ 9.98 (s, O-H, alcohol), 9.3 (d, imidazol), 6.4 (d, C-H aromatic), 6.5 (s, C-H aromatic), 1.19 (s, methylene), 3.4-3.6 (s, methyl).

Compound TS₇

Black, mp 108-111 °C, yield 80%, FT-IR (KBr) ($\nu_{\max}/\text{cm}^{-1}$): 1678 (C-N), 1739 and 1790 (C=O), 1627 (C=O amide), 3742 (O-H groups), 3100 (C-H aromatic), 2924 (C-H sp³), 1430 (O-H). ¹H-NMR

(500 MHz, DMSO): Singlet 2.2 (s, methyl), 2.7 (s, methyl), 4.7 (s, methylene), 6.3 (s, C-H, aromatic), 7.4 (d, C-H, aromatic), 9.9 (s, O-H, alcohol), and 9.5 (s, O-H, alcohol).

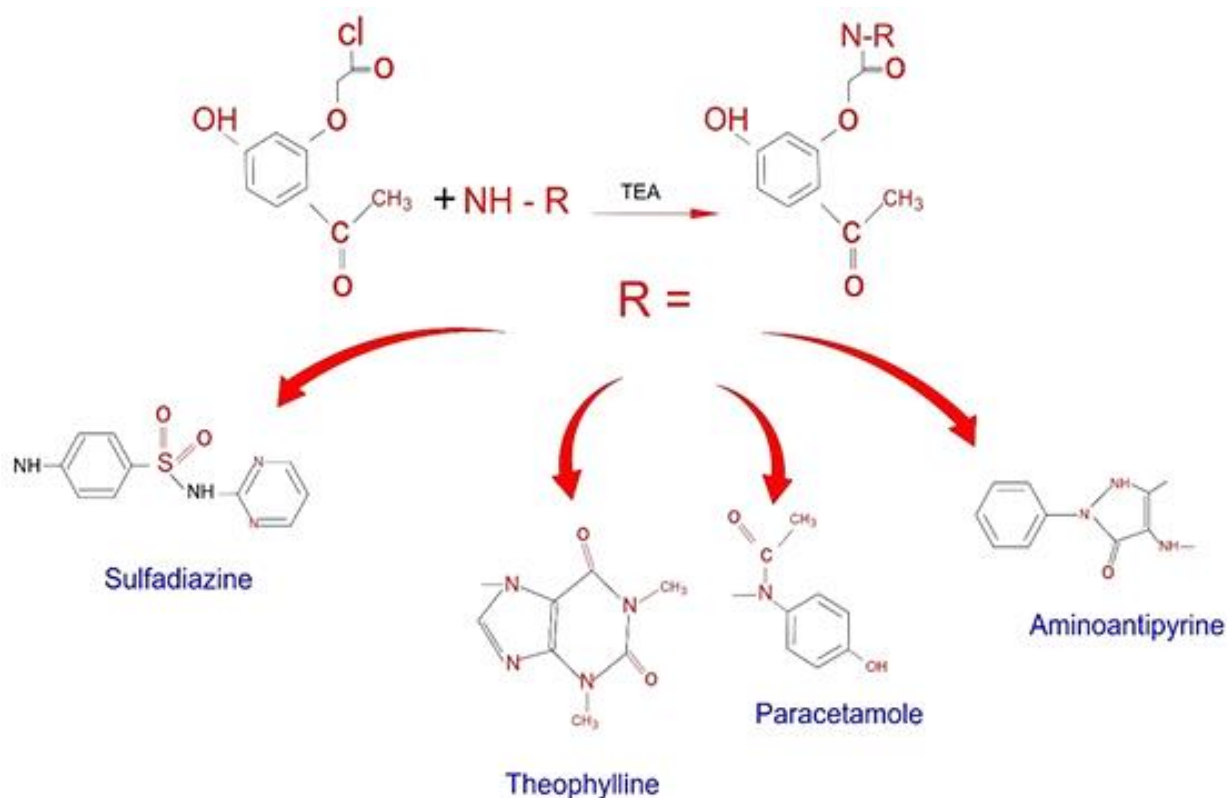
Compound TS₈

Light brown, mp 146-150 °C, yield 71%, FT-IR (KBr) (ν_{\max} / cm⁻¹): 3394 (N-H groups), 1566 (N-

H), 1305.85 (C-N), 1770 (C=O), 1701 (C=O), 3740 (O-H), 2935 (C-H sp³), 1219 (C-O), 1440 (O-H). ¹H-NMR (500 MHz, DMSO): 5.3 (s, O-H, alcohol), 8.1 (s, N-H), 6.0 (t, C-H aromatic), 7.8 (d, C-H aromatic), 4.6 (s, methylene), 2.2 (s, methyl), and 2.4 (s, methyl).

Table 1: Solubility of synthesized compounds in different solvents

Solv. Comp.	DMSO	Water	Etha.	Ace.	Meth.	Haxe.	1,4-dioxan	DCM	DMF	Diet. ether	Petr. Ether	Ethyl ace.
TS5	+	-	+	+	Partial	-	+	partial	+	-	-	-
TS6	+	Partial	+	+	+	-	+	+	+	-	-	Partial
TS7	+	-	+	-	Partial	partial	-	-	+	-	-	-
TS8	+	-	+	+	+	-	+	+	+	-	-	+



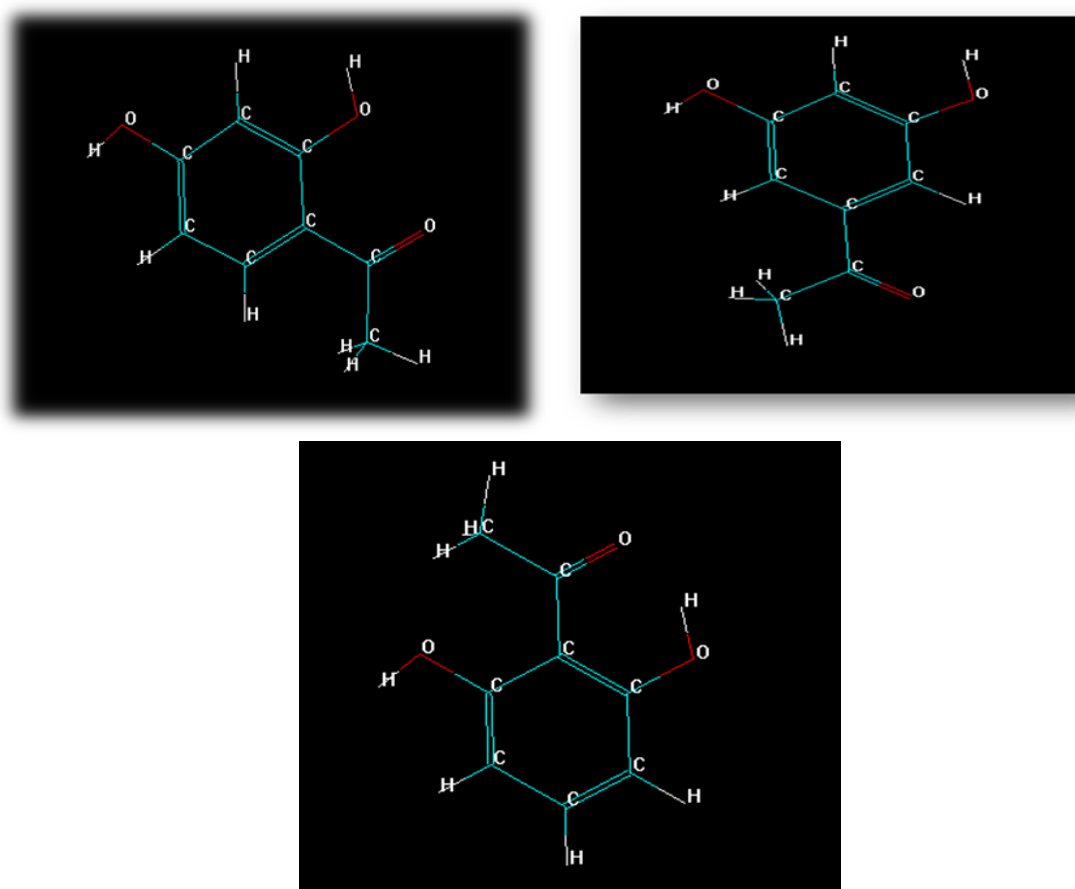
Scheme 4: Synthesis of compounds (TS₅-TS₈)

Table 2: Calculations of transition states, energy barrier and $\epsilon\Delta H$ for the acylation reaction

Total energy of reactants Kcal/mol	Transition states Kcal/mol	Energy barrier Kcal/mol	$\epsilon\Delta H$ Kcal/mol
52521.261	-52484.354	36.907	51.32
52521.261	-52418.483	102.778	48.6
52521.261	-52452.764	68.497	47.653

Table 3: Calculations of transition states, energy barrier and $\epsilon\Delta H$ for the resorcinol derivatives

Derivatives	Total Energy of Reactant 1	Total Energy of Reactant 2	Total Energy of Product 1	Total Energy of product 2	Transition State	Energy barrier	$\epsilon\Delta H$ Kcal/mol
TS5 /Sulfadiazine	-64899.190	-65093.767	-	-7671.757	129836.039	129641.462	-13.081
TS6/ Theophylline	-64899.190	-50483.469	-	-7671.757	115320.468	62.191	-6.485
TS7/ Paracetamole	-64899.190	-42346.383	-99583.684	-7671.757	107047.767	197.806	-9.868
TS8 / 4-Aminoantipyrene	-64899.190	-49201.640	-	-7671.757	113994.386	106.44	-14.519

**Figure 1:** The geometrical suggested transition state for acylation reaction calculated by PM₃-semi empirical method

Antibacterial activity

The findings found that almost all of the compounds examined to have a top antibacterial pastime. These microorganisms have been selected due to their extensive significance in the medical field, as they motive many illnesses further to their various antibiotic and chemical drug resistance. Table 4 exhibits that the produced compounds have an organic pastime towards the microorganism because they'll suppress the

microorganism through various quantities of the compounds.

Antioxidants activity

Compounds antiradical operation achieved with the usage of the usual DPPH method.

Table 5 in comparison to the normal (ascorbic acid) hobby ($IC_{50}=4.02$ mg/mL), the bulk of compounds confirmed mild to the excessive antioxidant hobby. Most hobbies become a

consequence of the OH organization in the take a look at materials is with inside the compounds (TS₅-TS₈) with a sizable hobby. following order whilst in comparison to the Ascorbic acid, a common medication, with an IC₅₀ reference of 4.02 M. The forces for the antioxidant hobby of

Table 4: Antibacterial activity for compound (TS₅-TS₈)

No. of Comp.	Antibacterial activity test	
	<i>Staphylococcus aureus</i> (Gram-positive bacteria)	<i>klebsiella pneumonia</i> (Gram-negative bacteria)
Control	-	-
TS5	10	-
TS6	17	-
TS7	20	-
TS8	16	-

Table 5: Antioxidants activity for compounds (TS₅-TS₈)

Sample No.	Scaving %		
	25 mg/mL	50 mg/mL	100 mg/mL
1	39.25	58.83	64.83
2	34.25	52.25	58.58
3	25.25	33.25	44.58
4	45.00	72.08	91.08
Ascorbic acid	80.95	89.25	93.54

Conclusion

In this study, it is possible to prepare new, developed, and suitable drug derivatives for infection prevention treatment because most prepared derivatives gave good biological activity and antioxidant results. The prepared compounds gave a large proportion of the output and were prepared from simple and available materials. All prepared compounds were stable in various conditions.

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No potential conflict of interest was reported by the authors.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

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