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Original Article

New Resorcinol Derivatives: Preparation, Characterization and Theoretical Investigation

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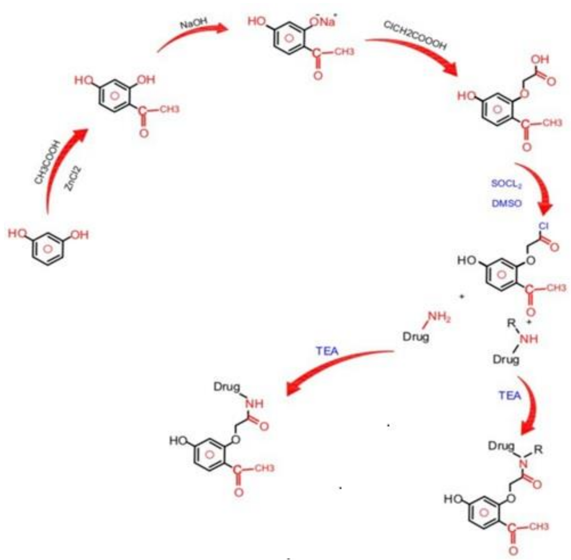
ABSTRACT

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 ^{1}H-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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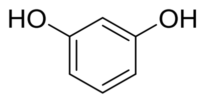
Introduction

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 (PM_3) (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 ƐΔH 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. ^{1}H-NMR decided with the aid of using the use of a Bruker AC four hundred NMR spectrometer set to 500 MHz for ^{1}H-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 (TS$_2$)

Anhydrous $ZnCl_2$ (15 g, 110 mmol) was added to 30 ml of CH_3COOH and heated at 140 °C. After all the $ZnCl_2$ has been dissolved, resorcinol (10 g, 90 mmol) has been stirred and heated for 3 hours at 150 °C in an oil bath. The $ZnCl_2$ complex broke down by adding 50% HCI (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: $C_8H_8O_3$, M.wt=152.15 g/mol [10].

Synthesis of compound (TS$_3$)2-(2-acetyl-5-hydroxyphenoxy) acetic acid

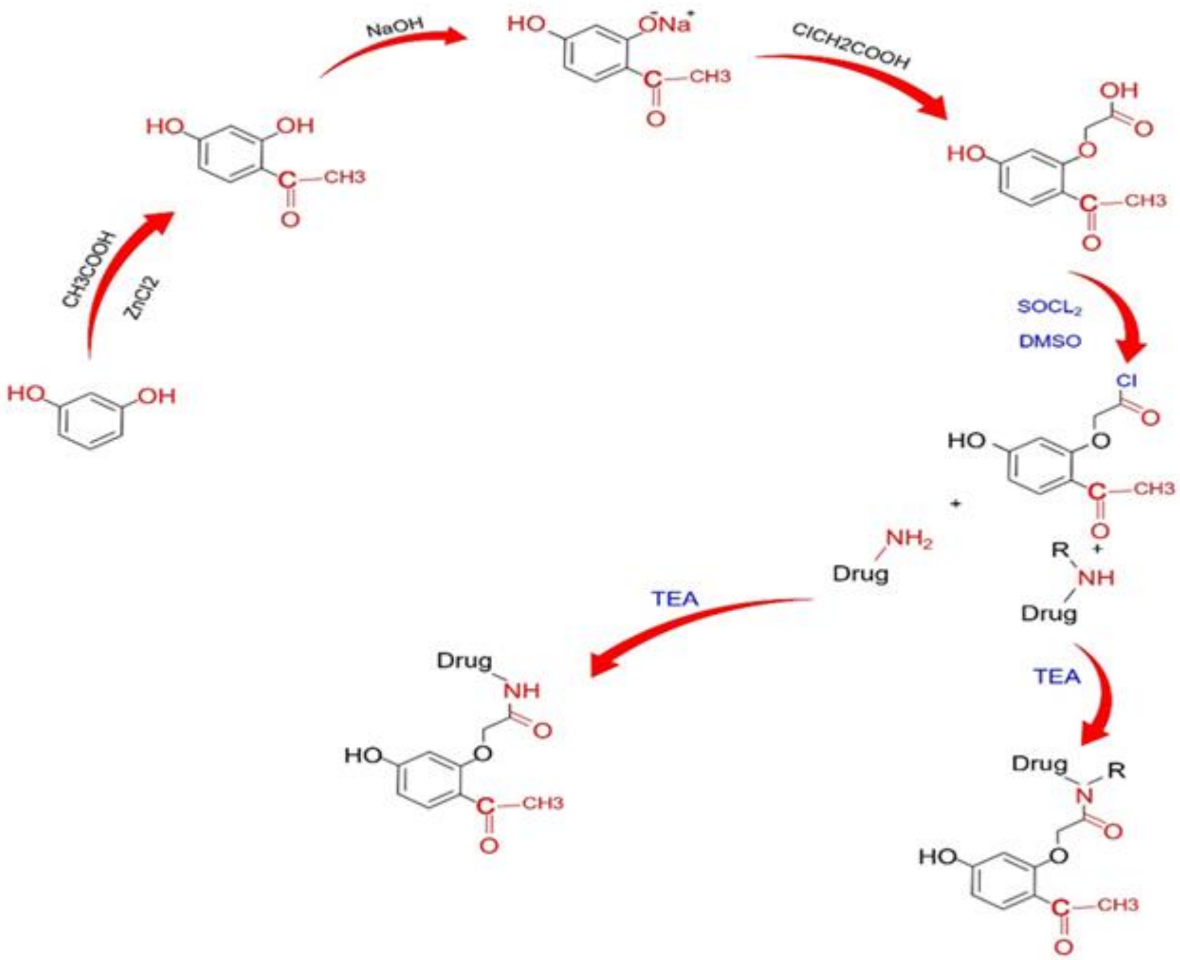
Dissolved 2 g of KOH in 4 mL of water in a 50 mL spherical flask, and 0.5 g of 2,4-dihydroxyacetophenone was delivered to the spherical flask. The aggregate changed into stirred till a homogeneous solution resulted. Fit the flask with a reflux condenser and warmth to a mild boil. Add 6 mL of a 50% aqueous 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 TS_3. The response became observed using the TLC approach of ethyl acetate: acetone (1:1). FT-IR was used to represent TS_3. Solid, Color: white, molecular formula:$C_{10}H_{10}O_5$, M.wt=210.19 g/mol [11].

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

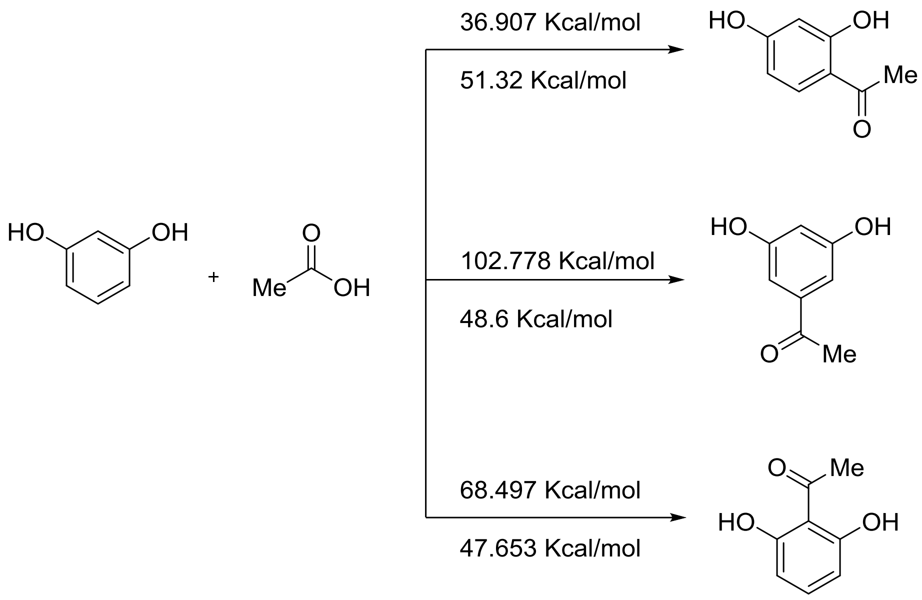
1 mmol of the carboxylic acid is brought to 1 mmol of amine and 3 mmol of triethylamine (Et_3N) in dichloromethane, then 1 mmol of $SOCl_2$ is delivered at room temperature. The aggregate is stirred for 5–20 mins at room temperature. The recovery of the mixture into executed by evaporating the solvent 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 ^{1}H-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 (TS_5-TS_8). FT-IR, and ^{1}H-NMR spectrum fixed eyeglass synthesized compounds [15].

Compound TS_5

Dark brawn, mp 92-94 °C, yield 97%, FT-IR (KBr) (ν_{max}/ 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 sp^3), 1313 and 1253 (C-O), 1437 (O-H), 1157 (S=O). ^{1}H-NMR (500 MHz, DMSO): δ 9.98 (s, O-H, alcohol), 9.96 (s, N-H, amid), 11.3 (s, *N*sulfonamide), 6.4-7.6 (d, C-H, aromatic), 4.6 (s, methylene), 2.6 (s, methyl) 7.7-8.4 (d, CH pyrimidine).

Compound TS_6

Dark green, mp 120-123 °C, yield 89%, FT-IR (KBr) (ν_{max}/ cm^{-1}): 1720 (C=O ketones), 1647 (CO amide), 3674 (O-H alcohol), 3100 (C-H aromatic), 2976 (C-H sp^3). ^{1}H-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 TS_7

Black, mp 108-111 °C, yield 80%, FT-IR (KBr) (ν_{max}/ 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 sp^3), 1430 (O-H). ^{1}H-NMR

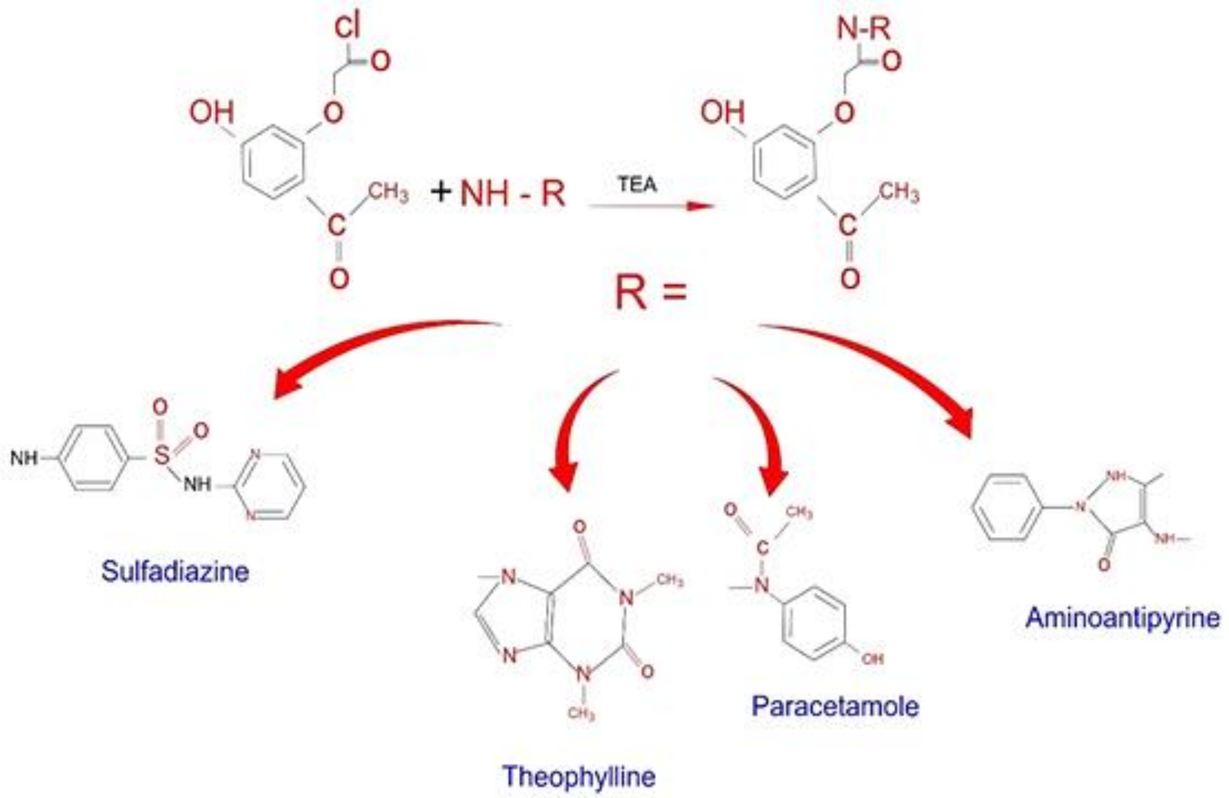
(500 MHz, DMSO): Singlet 2.2 (s, methyl), 2.7 (s, methyl), 4.7 (s, methylene), 6.3 (s, C-H, aromatic), 7.4 (d, C-H, aromatic), 9.9 (s, O-H, alcohol), and 9.5 (s, O-H, alcohol).

Compound TS$_8$

Light brawn, 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 sp^3), 1219 (C-O), 1440 (O-H). ^{1}H-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	-l	-	+	-	-	-
TS8	+	-	+	+	+	-	+	+	+	-	-	+



Scheme 4: Synthesis of compounds (TS$_5$-TS$_8$)

Table 2: Calculations of transition states, energy barrier and ƐΔH for the acylation reaction

Total energy of reactants Kcal/mol	Transition states Kcal/mol	Energy barrier Kcal/mol	ƐΔH 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 ƐΔH 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	ƐΔH Kcal/mol
TS5 /Sulfadiazine	-64899.190	-65093.767	-122334.280	-7671.757	-129836.039	-129641.462	-13.081
TS6/ Theophylline	-64899.190	-50483.469	-107717.387	-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-Aminoantipyrine	-64899.190	-49201.640	-106443.587	-7671.757	-113994.386	106.44	-14.519

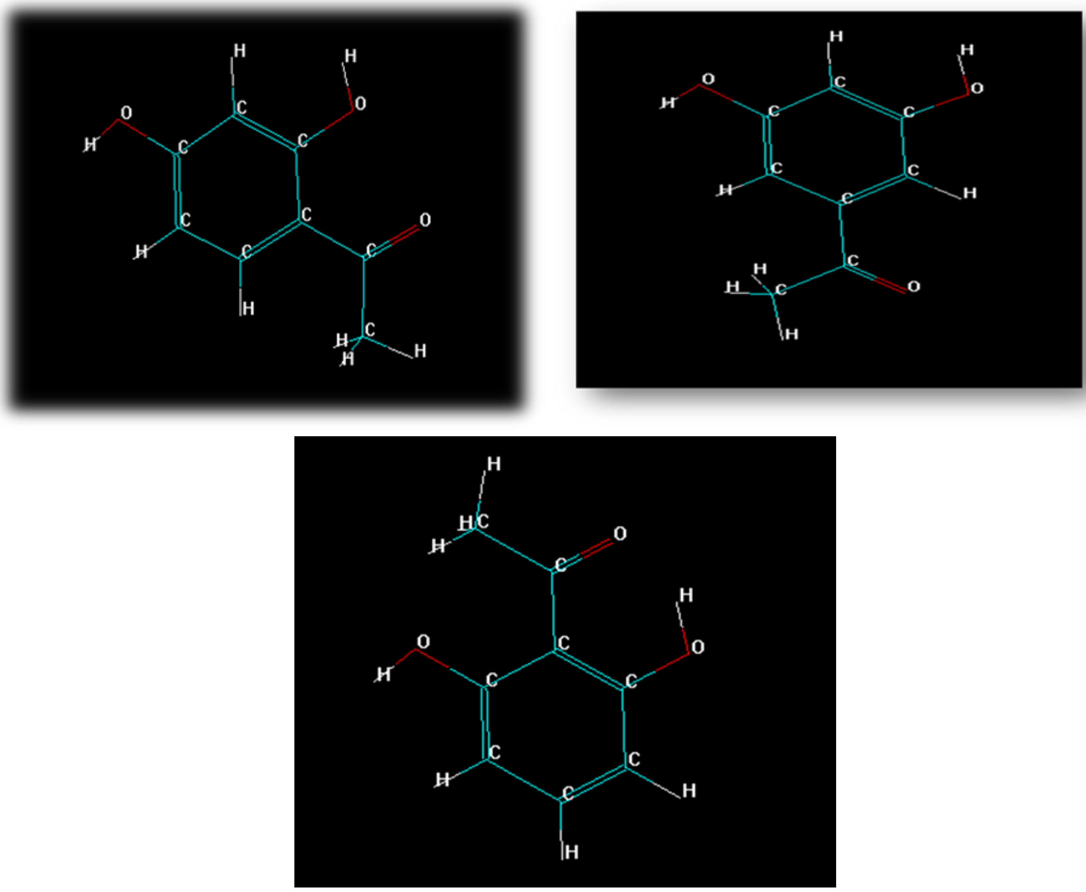


Figure 1: The geometrical suggested transition state for acylation reaction calculated by PM_3-semi empirical method

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 compounds (TS_5-TS_8) with a sizable hobby. Ascorbic acid, a common medication, with an IC_{50} of 4.02 M. The forces for the antioxidant hobby of the take a look at materials is with inside the following order whilst in comparison to the reference

Table 4: Antibacterial activity for compound (TS_5-TS_8)

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

Table 5: Antioxidants activity for compounds (TS_5-TS_8)

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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Disclosure Statement

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.

References

[1]. Körbahti B.K., Demirbüken P., Electrochemical oxidation of resorcinol in aqueous medium using boron-doped diamond anode: reaction kinetics and process optimization with response surface methodology, *Frontiers in Chemistry*, 2017, **5**:75 [Crossref], [Google Scholar], [Publisher]

[2]. Jeżewska A., Kondej D., Resorcinol-determination method in the workplace air,

Medycyna Pracy, 2022, **73**:135 [Crossref], [Google Scholar], [Publisher]

[3]. Khodari M., Mersal G.A.M., Rabie E.M., Assaf H.F., Electrochemical sensor based on carbon paste electrode modified by TiO_2 nano-particles for the voltammetric determination of resorcinol, *International Journal of Electrochemical Science*, 2018, **13**:3460 [Crossref], [Google Scholar], [Publisher]

[4]. Hassan K.M., Hathoot A.A., Azzem M.A., Simultaneous and selective electrochemical determination of hydroquinone, catechol and resorcinol at poly (1, 5-diaminonaphthalene)/glassy carbon-modified electrode in different media, *RSC Advances*, 2018, **8**:6346 [Crossref], [Google Scholar], [Publisher]

[5]. Ngamchuea K., Tharat B., Hirunsit P., Suthirakun S., Electrochemical oxidation of resorcinol: mechanistic insights from experimental and computational studies, *RSC Advances*, 2020, **10**:28454 [Crossref], [Google Scholar], [Publisher]

[6]. da Silva A.R.L., Dos Santos A.J., Martínez-Huitle C.A., "Electrochemical measurements and theoretical studies for understanding the behavior of catechol, resorcinol and hydroquinone on the boron doped diamond surface," *RSC Advances*, 2018, **8**:3483 [Crossref], [Google Scholar], [Publisher]

[7]. Eftekhari A., Ahmadian E., Dizaj S.M., Investigating anti-cancer mechanism of phenolic compounds of water mint in cancer cells, *Eurasian Chemical Communications*," Eurasian Chem. Commun., 2022, **4**:197 [Crossref], [Google Scholar], [Publisher]

[8]. Mohammed J.H., Aowda S.A., "The synthesis and biological evaluation of prodrug amide derivatives based on phenylene dioxy di acetic acid," in *AIP Conference Proceedings*, 2020, **2213**:020157 [Crossref], [Google Scholar], [Publisher]

[9]. Kuraimid Z.K., Amoury Q.M., Majeed H.M., Jebur H.Q., Khaleel B., Mohammed M., "Synthesis and characterization of fast curing polymeric coating for Iraqi oil tank bases," *Eurasian Chemical Communications*, 2021, **3**:831 [Crossref], [Google Scholar], [Publisher]

[10]. Patil R.B., Sawant S.D., Thombare P.A., "Design, synthesis and pharmacological evaluation of chromenones and related analogues," *International Journal of Advances in Pharmacy, Biology and Chemistry*, 2012, **4**:375 [Google Scholar], [Publisher]

[11]. Kulangiappar K., Anbukulandainathan M., Raju T., "Synthetic communications: an international journal for rapid communication of synthetic organic chemistry," *Synthetic Communications*, 2014, **1**:2494 [Crossref], [Google Scholar], [Publisher]

[12]. Leggio A., Belsito E.L., De Luca G., Di Gioia M.L., Leotta V., Romio E., Siciliano C., Liguori A., One-pot synthesis of amides from carboxylic acids activated using thionyl chloride, *Rsc Advances*, 2016, **6**:34468 [Crossref], [Google Scholar], [Publisher]

[13]. T. Hagr and I. Adam, "Phytochemical Analysis, Antibacterial and antioxidant Activities of Essential Oil from Hibiscus sabdariffa (L) Seeds, (Sudanese Karkadi)," *Progress in Chemical and Biochemical Research*, 2020, **3**:194 [Crossref], [Google Scholar], [Publisher]

[14]. Hussein N.A., Abbas A.K., "Synthesis, spectroscopic characterization and thermal study of some transition metal complexes derived from caffeine azo ligand with some of their applications," *Eurasian Chemical Communications*, 2022, **4**:67 [Crossref], [Google Scholar], [Publisher]

[15]. Salih A.R., Al-Messri Z.A.K., Synthesis of pyranopyrazole and pyranopyrimidine derivatives using magnesium oxide nanoparticles and evaluation as corrosion inhibitors for lubricants, *Eurasian Chemical Communications*, 2021, **3**:533 [Crossref], [Google Scholar], [Publisher]

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