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REGULAR ARTICLE

Synthesis and characterization of (E)-2-(1-hydrazonoethyl)-4, 5-dimethylphenol from 2-hydroxy-4,5-dimethylacetophenone

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Abstract. This study reports the development of a novel substituted hydrazone prepared from 2-hydroxy-4,5-dimethylacetophenone and hydrazine in alkaline medium at controlled conditions which yields as corresponding hydrazone [(E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol]. The structure of synthesized (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol was elucidated by elemental analysis and spectroscopic techniques like infrared spectroscopy, ultraviolet–visible spectroscopy, high-performance liquid chromatography, proton nuclear magnetic resonance and mass spectrum.

Keywords. 2-Hydroxy-4,5-dimethylacetophenone; hydrazone; hydrazine.

1. Introduction

Hydrazone is the product of hydrazine with simple or substituted acetophenone obtained in the alkaline medium. Hydrazones are a class of organic compounds which possess the general structure $R_1R_2C{=}NNH_2$.[1] Hydrazones are aromatic in nature and shows that one aromatic ring linked with a hydrazine group. Hydrazone molecules play a major role in the heterocyclic chemistry.[2–6] The IUPAC name of hydrazone group is (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol, which possesses a conjugate double bond and a delocalized π electron on both the benzene rings.

Hydrazones are related to ketones and aldehydes by the replacement of oxygen with the N-NH_2 functional group.[3,7,8] They containing an azomethine –NHN=CH proton and are synthesized by heating the appropriately substituted hydrazines/hydrazides with aldehydes and ketones in solvents like ethanol, methanol, tetrahydrofuran, butanol, glacial acetic acid.[9,10] These are widely studied molecules owing to their ease of preparation and diverse pharmacological potential. Hydrazones offers various active potential donor sites, i.e. C=O, N–H and NH_2.[11]

The C-atom in hydrazone has both electrophilic and nucleophilic characters and in both the N-atoms are nucleophilic although the amino type nitrogen is more reactive. Due to the electrophilic and nucleophilic properties, hydrazones are widely used in organic synthesis.[1,12]

The hydrazones show a wide range of pharmaceutical activities, such as antimalarial,[1,3,13] antibacterial,[14–16] antidepressant,[16] analgesic agents,[17,18] antifungal,[19–21] antimicrobial,[22–26] and anticonvulsant agents.[27–30]

2. Experimental

2.1 *Materials*

The chemicals: 2-hydroxy-4,5-dimethylacetophenone, hydrazine, methanol, acetic acid, sodium hydroxide, ethyl alcohol, ethyl acetate, n-hexane, methanol, chloroform, DMSO, etc., used in this work were of AR Grade, commercially available and used without further purification.

2.2 *Preparation of 2-hydroxy-4,5-dimethylacetophenone*

The 3,4-dimethylphenylacetate was cooled in ice and anhydrous aluminum chloride was add to it. The

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reaction mixture was heated for 4–5 h. Subsequently, the reaction mixture was cooled to room temperature. The $AlCl_3$ decomposed after adding ice cold water and concentrated HCl. The solid product obtained was filtered and washed with demineralized water until the pH of filtrate was neutral and then dried safely. The purity of the product was checked by Thin Layer Chromatography in solvent ethyl acetate : n-hexane (80:20) and its melting point was 69–73°C, and yield 63%. Reaction Scheme of 3,4-dimethylphenyl acetate is give below Scheme 1 and 1-(2-hydroxy-4,5-dimethylphenyl)ethanone is given below Scheme 2.

2.3 *Preparation of substituted hydrazone: (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol*

The substituted hydrazones were prepared by stirring the equimolar concentration mixture of 2-hydroxy-4,5-dimethylacetophenone (1 mol) and hydrazine hydrate (1 mol) in 150 mL methanol, stirred for 15 min at room temperature and dissolved. The solution was refluxed for 3 h in presence of acetic acid at 65°C, and then the progress of the reaction was checked by TLC [mobile phase:10% ethyl acetate:n-hexane (10:90)]. After the completion of the reaction, the mixture was cooled at room temperature. The pale yellow color compound formed was filtered, washed with chilled methanol and dried at 40–45°C. For purification and improving description, the compound was re-crystallized in methanol. Reaction scheme preparation of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol is given below Scheme 3.

3. Results and Discussion

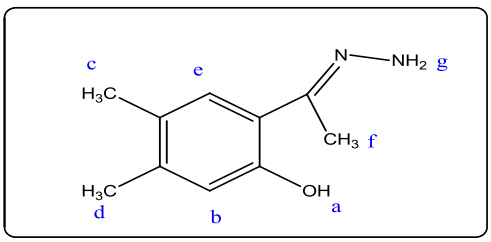
The (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol was analyzed by Infrared spectroscopy, Ultraviolet–visible spectroscopy, Proton nuclear magnetic resonance, Carbon, Hydrogen, Nitrogen, Sulphur elemental analyzer, melting point, purity by high-performance liquid chromatography, water content and mass spectroscopy. Melting points were recorded using Veego Scientific Device (Model: VMP-AD) in open capillaries and were uncorrected. Some physical properties of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol are mentioned in Table 1.

3.1 *Mass analysis: (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol*

The mass spectrum of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol was recorded on Waters Quattro Micro Triple Quad Spectrometer. The mass analysis of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol shows molecular ion peak (M^+/e) correctly corresponding to molecular formula in Table 2 and the mass spectrum is shown in Figure 1.

3.2 *^{1}H NMR analysis: (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol*

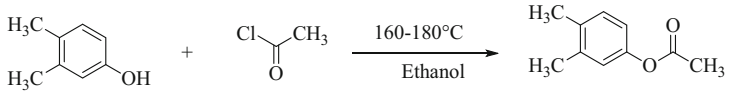
Nuclear resonance spectra of the (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol was recorded in $CDCl_3$ solution and ^{1}H NMR, shown in Figure 2. The relevant data on observed chemical shifts together with their assignments are summarized in Table 3.



Compound Name: (*E*)-2-(1-hydrazonoethyl)-4,5-dimethylphenol

3.3 *Infrared analysis: (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol*

The IR spectra of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol compound was recorded in the region of 4000–600 cm^{-1} using FTIR spectrometer of model Agilent Resolutions Pro by direct sampling method.

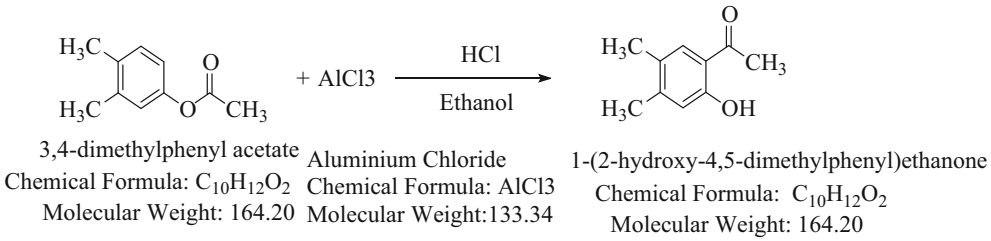


3,4-dimethylphenol
Chemical Formula: $C_8H_{10}O$
Molecular Weight: 122.16

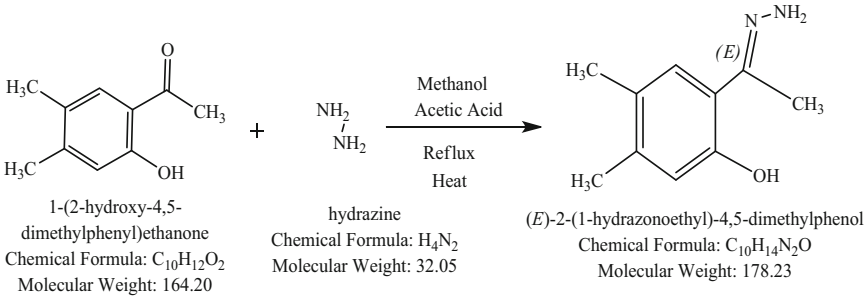
acetyl chloride
Chemical Formula: C_2H_3ClO
Molecular Weight: 78.50

3,4-dimethylphenyl acetate
Chemical Formula: $C_{10}H_{12}O_2$
Molecular Weight: 164.20

Scheme 1. Reaction scheme preparation of 3,4-dimethylphenyl acetate.



Scheme 2. Reaction scheme preparation of 2-hydroxy-4,5-dimethylacetophenone or 1-(2-hydroxy-4,5-dimethylphenyl) ethanone.



Scheme 3. Reaction scheme preparation of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol.

Table 1. Physical properties.

Hydrazone	Molecular formula	Color	Solubility	Melting point (upper and lower range)	yield
(E)-2-(1-hydrazonoethyl) -4,5-dimethylphenol	$C_{10}H_{14}N_2O$	Pale yellow powder	Freely soluble in chloroform Soluble in methanol, ethanol, DMSO, ethyl acetate Insoluble in water	63°C–68°C	76%

Table 2. Mass analysis.

Hydrazone	Molecular formula	Molecular weight	Molecular ion peak (M^+/e)
(E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol	$C_{10}H_{14}N_2O$	178.23	179.2

The IR spectral data along with the possible assignments of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol compound are provided in Table 4, followed by IR spectra performed by IR direct solid method, use of Agilent Resolutions Pro and IR spectrum are shown in Figure 3.

3.4 *UV analysis: (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol*

The UV spectra of the (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol compound in methanol was recorded on SPECORD 50 PLUS-233 H 1409C Spectrophotometer, using a quartz cell of 1 cm optical path where methanol was used as a blank.

The UV spectrum is shown in Figure 4. The spectra shows V (bands maximum in nm) in methanol: 254, 325.

3.5 *Elemental analysis (CHNS): (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol*

Formation of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol was further confirmed by elemental analysis

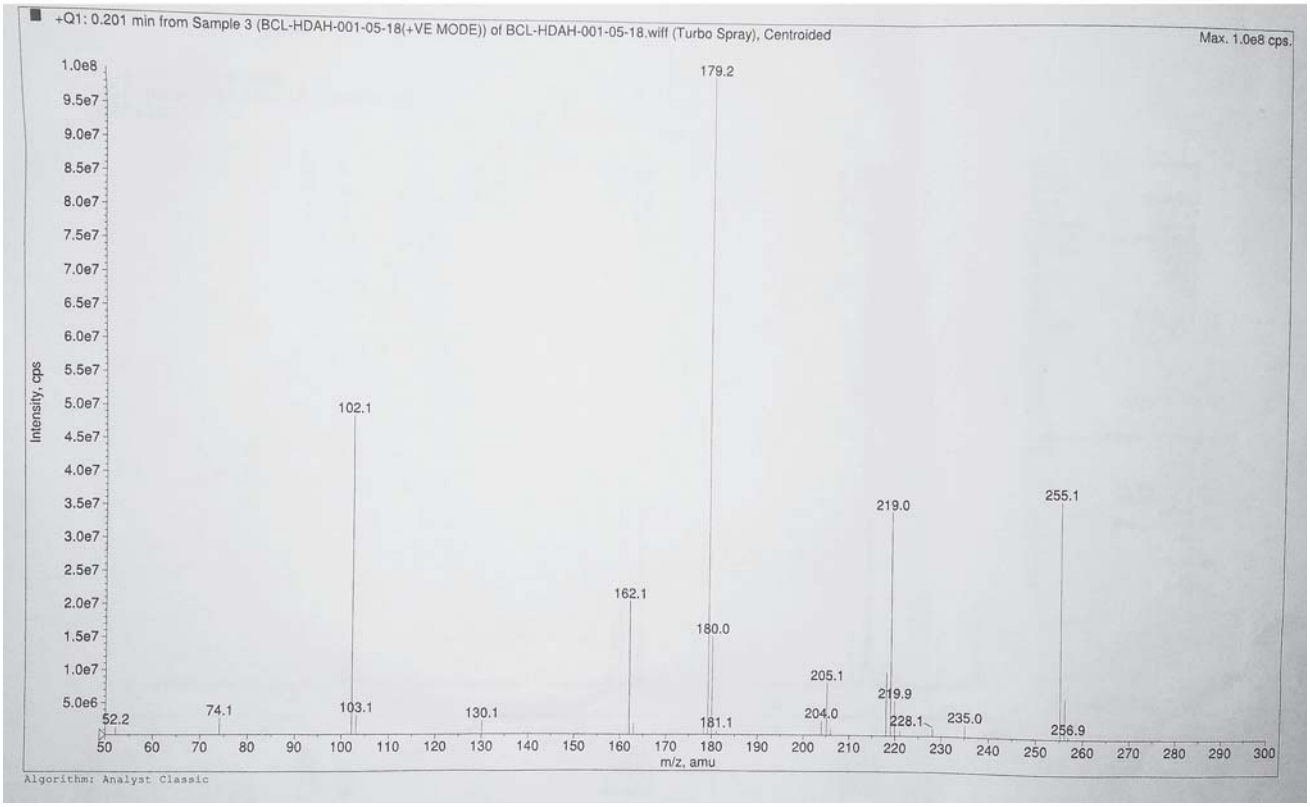


Figure 1. Mass spectrum of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol.

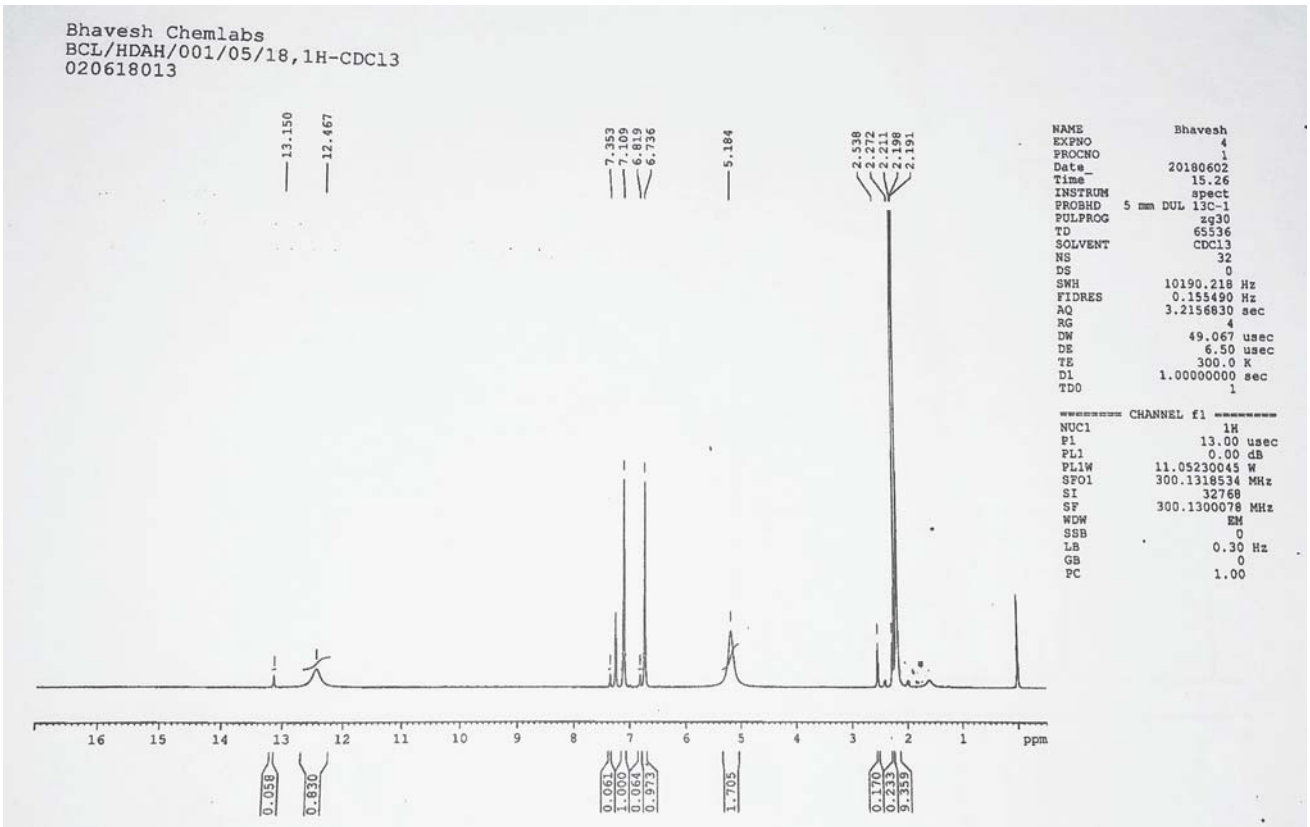


Figure 2. ^{1}H NMR spectrum of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol.

Table 3. ^{1}H NMR analysis.

Assignments	Chemical shift (ppm)	Functional group	No. of proton	Multiplicity
a	12.467	–OH	1	Broad, singlet
b	7.109	–CH	1	Singlet
e	6.736	–CH	1	Singlet
c, d, f	2.191–2.211	$–CH_3$	9	Multiplet
g	5.184	$–NH_2$	2	Broad, singlet

Table 4. IR analysis.

Bond/functional group	Frequency, cm^{-1}
C–O	1230
C=C (aromatic ring)	1447
C–C	1506
N–H	1594
C–H stretch alkenes	2922
C–H stretch aromatics	3050
O–H	3630

which was recorded by Vario MICRO CHNS analyzer. The elemental analysis data of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol is summarized in Table 5.

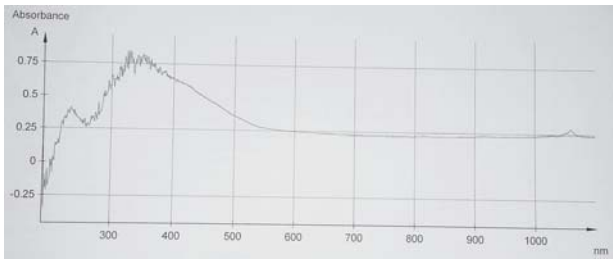


Figure 4. UV spectrum for (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol.

3.6 *Water content: (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol*

The water content of the (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol compound in methanol was

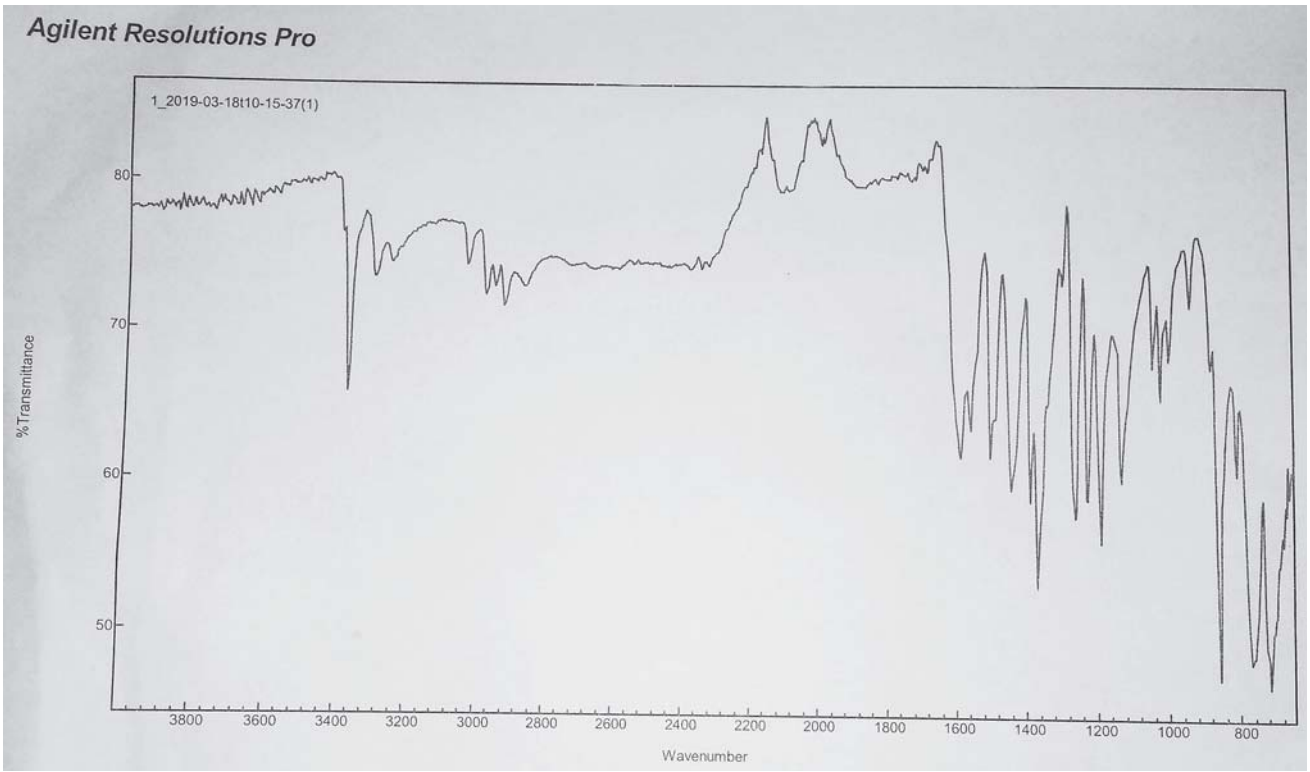


Figure 3. IR spectrum of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol.

Table 5. Carbon, hydrogen, nitrogen, sulphur elemental analyzer.

Hydrazone	Molecular formula	Molecular weight	Elemental data (required/found)		
			Carbon	Hydrogen	Nitrogen
(E)-2-(1-hydrazonoethyl)-4,5-dimethyl phenol	$C_{10}H_{14}N_2O$	178.23	67.16 (67.39)	7.85 (7.92)	15.68 (15.72)

Table 6. Purity, HPLC analysis details.

HPLC system	Shimadzu HPLC	
Column	Phenomenon C18, 100 A, 4.6 mm × 250 mm, 5 μm	
Flow rate	1.0 mL/min	
Wavelength	254 nm	
Column temperature	40°C	
Sampler temperature	25°C	
Injection volume	10 μL	
Run time	32 min	
Gradient		
Time in minutes	Mobile phase A (%)	Mobile phase B (%)
0	90	10
10	25	75
15	20	80
26	90	10
32	90	10
Mobile phase A	1 mL of orthophosphoric acid dissolved in 1000 mL of Milli-Q water	
Mobile phase B	100% Acetonitrile	
Diluent	Methanol	
Sample preparation	10 mg (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol transferred in 10 mL volumetric flask and dissolved in methanol	

recorded using Karl Fischer method and was found to have 0.3% water content.

3.7 *Purity: (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol*

The purity of the (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol compound was analyzed by Shimadzu high-performance liquid chromatography (HPLC) and purity was found to be 98.9% (98.954%) with retention time of 8.697 min using the parameters in Table 6. The purity: HPLC chromatogram for (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol is shown in Figure 5.

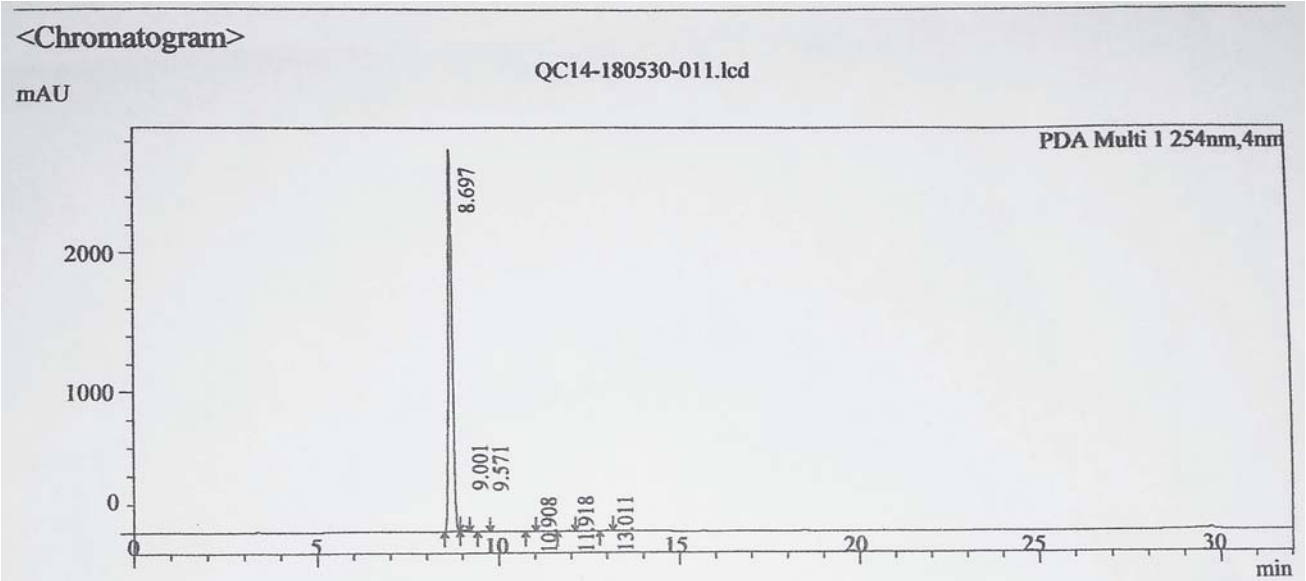
3.8 *Theoretical evaluation of mutagenicity study: (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol and raw material used in preparation*

The evaluation of mutagenicity is carried out as per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) "assessment and control of DNA reactive (mutagenic) impurities in pharmaceuticals to limit potential carcinogenic risk M7 (R1)" by using the software Toxicity Estimation Software Tool (TEST) version 4.2.1.

TEST estimats the toxicity values using several different advanced quantitative structure–activity relationship models (QSAR). The following structure was evaluated using "consensus method" and predicted mutagenicity was estimated by taking an average of the predicted toxicities. Theoretical evaluation of mutagenicity by T.E.S.T. software is shown in Table 7.

4. Conclusion

This study describes the synthesis of (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol derivative from 2-hydroxy-4,5-dimethylacetophenone. The structure of the synthesized hydrazone compound was well



<Peak Table>

QC14-180530-011.lcd

PDA Ch1 254nm

Peak#	Ret. Time	Area	Area%	Height
1	8.697	19960712	98.954	2742540
2	9.001	43695	0.217	3372
3	9.571	35585	0.176	4293
4	10.908	21527	0.107	3045
5	11.918	56673	0.281	5962
6	13.011	53495	0.265	7266
Total		20171687	100.000	2766478

Figure 5. Purity: HPLC chromatogram for (E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol.

Table 7. Theoretical evaluation of mutagenicity by T.E.S.T. software.

Chemical name	Mutagenicity (positive/negative)
(E)-2-(1-hydrazonoethyl)-4,5-dimethylphenol	Mutagenicity positive
1-(2-Hydroxy-4,5-dimethylphenyl)ethanone	Mutagenicity negative
Hydrazine	Mutagenicity negative
3,4-Dimethylphenylacetate	Mutagenicity negative
3,4-Dimethylphenol	Mutagenicity negative
Acetyl chloride	Mutagenicity negative

characterized by melting point, elemental analyses (CHNS), IR, UV, HPLC, ^{1}H NMR and mass spectral studies.

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