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SYNTHESIS OF CURCUMIN BASED 4,4'-((1E,1'E)-(1-CINNAMYL-1H-PYRAZOLE-3,5-DIYL)BIS(ETHENE-2,1-DIYL))BIS(2-METHOXYPHENOL) DERIVATIVE AND THEIR ANTIBACTERIAL ACTIVITIES

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Abstract: This paper aims to synthesis curcumin based heterocyclic moiety because curcumin extracted from turmeric which is a naturally yellow colored compound has many applications in antibacterial activities. A new series of 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) compound was developed from freshly prepared (E)-((E)-3-phenylallylidene)hydrazine derivative and commercially available curcumin under reflux for certain hours in presence of glacial acetic acid. The structure of the synthesized heterocyclic compound was characterized with the help of various techniques such as ^{1}H, ^{13}C NMR spectra, X-ray analysis, UV-Visible and FT-IR spectroscopy. This curcumin-based pyrazole derivative could also be evaluated for antibacterial activity against gram-positive and gram-negative bacteria with the zone of inhibition ranging between 15-20mm.

Keywords: Curcumin, Cinnamaldehyde, Hydrazine, Pyrazole derivatives, Antibacterial activity.

I. INTRODUCTION

Curcumin is a natural yellow colored product occurred from the rhizome of Curcuma longa[turmeric], soluble in acetone, ethanol and DMS. It has several pharmacological activities and anti-therapeutic assets such as anti-cancer, anti-microbial, anti-bacterial, anti-arthritic, anti-HIV and the treatment of Alzheimer's diseases a kind of neurodegenerative disorder[1,2,3]. Curcumin was first isolated by Vogel in the year of 1842. Curcumin was used by many researchers in the field of organic chemistry, medicinal chemistry, physical chemistry as well as biotechnologists[4,5]. The Curcumin gives remedies to biliary disorders, coughs, diabetes, hepatic disorders, rheumatism and sinusitis and it has broad biological activity as anti-leukemic, anti-tumor and anti-fungal activities[6]. Curcumin act as anti-oxidant and anti-inflammatory properties so it will heal the tissue damages in human body and also treat diabetes mellitus related to chronic hyperglycaemia[7]. Now-a-days the naturally available materials are used to treat many diseases, especially curcumin is one of the nature's gifted products commonly helpful to recover human diseases in ayurvedic and other Indian medicinal therapies[8,9]. Curcumin is also used as a photosensitizer and pH indicator, one of the research papers mentioned the curcumin indicator indicates the fish freshness. Advantageous properties of curcumin are low intestinal absorption, quicker metabolism and high dosages in humans are lesser toxicity upto 12g per day[10,11]. In organic chemistry, the synthesis of curcumin based heterocyclic compound is common because it has many applications. Curcumin plays an important role in chemotherapeutic agent, in modern life breast cancer is one of the common diseases among women, scientist aims to develop curcumin-based drug to reduces human breast cancer cells[12,13]. Curcumin used in textile industry turn as a dye in fabrication, food coloring agent and cosmetics, it gives natural color to the fabrics and also act as antimicrobial property[14]. Due to larger applications of curcumin, it is kept as a key substance to synthesis heterocyclic compounds. Many of the researchers successfully developed heterocyclic moiety in presence of curcumin as an intermediate. The heterocyclic compounds are mostly five membered like pyrazole, pyrrole, imidazole etc[15]., Based on these facts, we aims to synthesis curcumin based heterocyclic compounds called as 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) from natural product of curcumin and synthesized hydrazine derivatives in presence of glacial acetic acid.

II. EXPERIMENTAL

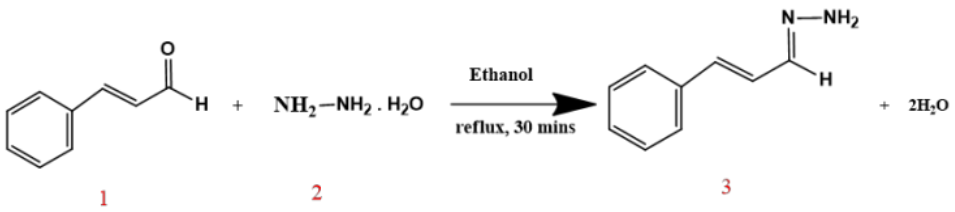
Materials and Methods

Curcumin, Cinnamaldehyde, Hydrazine hydrate were purchased from Nice brand used without any purification and solvent like glacial acetic acid bought from Aldrich company. The ^{1}H NMR and ^{13}C NMR spectra was recorded in Bruker nmr spectra using $CDCl_3$ as a solvent at 400 MHZ and 100 MHZ respectively. The coupling constant (J) is shown in Hz. XRD analysis at 40

KV and 15 mA in continuous scan mode. FT-IR spectra were recorded using Perkin-Elmer machine and Jasco spectrophotometer used to record UV-Vis spectra. The synthesized pyrazole compound tested for antibacterial activities using four bacterial strains.

Synthesis of (E)-((E)-3-phenylallylidene) hydrazine (3)

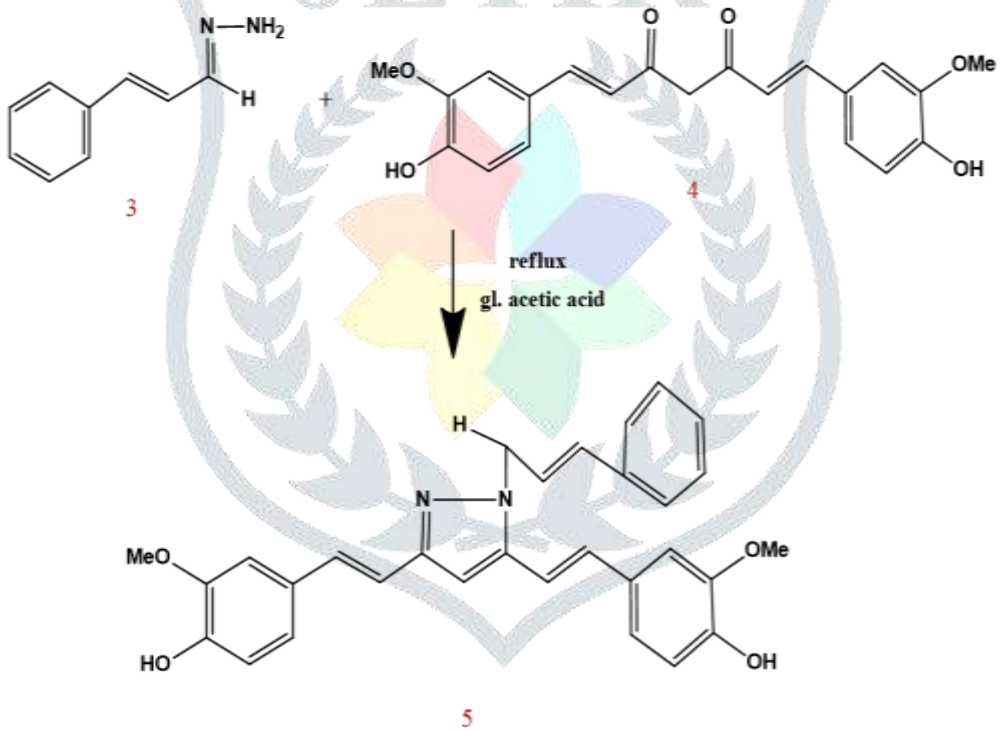
An equivalent mole ratio of cinnamaldehyde **1** and hydrazine hydrate **2** reacts in presence of 30 ml of ethanol as a solvent for 30 mins reflux at room temperature, get a yellow-colored crystal of compound **3** in good yield as shown in scheme 1, roughly washed with ethanol to remove impurities. Other set of hydrazine compounds was synthesized by substituted cinnamaldehyde **1a-1d** [2-chloro cinnamaldehyde, 2-bromo cinnamaldehyde, o-methoxy cinnamaldehyde and 4-methoxy cinnamaldehyde] with hydrazine hydrate **2** to get a (E)-((E)-3-(2-chlorophenyl)allylidene)hydrazine **3a**, (E)-((E)-3-(2-bromophenyl)allylidene)hydrazine **3b**, (E)-((E)-3-(2-methoxyphenyl)allylidene)hydrazine **3c** and (E)-((E)-3-(4-methoxyphenyl)allylidene)hydrazine **3d** respectively.



Scheme 1. Synthesis of (E)-((E)-3-phenylallylidene) hydrazine

Synthesis of 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)(5)

A mixture of (E)-((E)-3-phenylallylidene) hydrazine [0.001m=0.147g] and Curcumin [0.001m=0.368g] was refluxed for 25 -30 hrs in presence of 50 ml of glacial acetic acid, in-between the process of the reaction was checked by TLC using silica gel



Scheme 2. Synthesis of 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)

plates, the product **5** formed in a brown colored powder in moderate yield shown in scheme 2. The compound was dissolved in acetone and DMSO. Other set of curcumin-based pyrazole derivatives (**5a-5d**) are synthesized from **3a-3d** and **4** in presence of glacial acetic acid by refluxing certain hours and the spectroscopic data are attached[16,17].

III. RESULTS AND DISCUSSION

Spectroscopic data of 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 5

^{1}H NMR (400 MHz, DMSO) δ 7.51 – 7.42 (m, 2H), 7.51 – 7.21 (m, 6H), 7.16 – 7.09 (m, 3H), 7.03 (s, 1H), 6.94 (s, 1H), 6.88 (d, *J* = 3.6 Hz, 2H), 6.74 (d, *J* = 5.2 Hz, 2H), 6.61 (s, 1H), 6.25 (s, 1H), 6.21 (s, 1H), 4.99 (s, 1H), 4.64 (s, 1H), 4.31 (s, 1H), 3.91 (s, 1H), 3.83 – 3.79 (m, 6H). ^{13}C NMR (100 MHz, DMSO) δ 151.04 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 143.80 (s), 137.67 (s), 133.04 (s), 131.33 (s), 129.99 (s), 129.30 – 128.98 (m), 128.91 (s), 128.08 (s), 127.69 – 127.47 (m), 127.18 – 126.97 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 105.13 (s), 56.89 – 56.58 (m), 52.10 (s).

Spectroscopic data of 4,4'-((1E,1'E)-(1-((E)-3-(2-chlorophenyl)allyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 5a

^{1}H NMR (400 MHz, DMSO) δ 7.45 – 7.15 (m, 19H), 7.15 – 6.97 (m, 14H), 6.86 (s, 4H), 6.84 – 6.66 (m, 23H), 6.66 (s, 2H), 6.47 (s, 4H), 6.13 (s, 3H), 4.65 (s, 4H), 4.54 (s, 4H), 3.93 – 3.89 (m, 8H), 3.84 – 3.80 (m, 24H). ^{13}C NMR (100 MHz, DMSO) δ 151.04 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 143.80 (s), 134.30 (d, *J* = 10.6 Hz), 133.04 (s), 132.13 (s), 131.22 (s), 130.65 (s), 129.08 (s), 128.91 (s), 128.71 (s), 127.80 (d, *J* = 5.8 Hz), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 105.13 (s), 56.89 – 56.58 (m), 52.10 (s).

Spectroscopic data of 4,4'-((1E,1'E)-(1-((E)-3-(2-bromophenyl)allyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 5b

^{1}H NMR (400 MHz, DMSO) δ 7.37 (d, *J* = 30.7 Hz, 2H), 7.21 (dd, *J* = 20.9, 13.8 Hz, 4H), 7.06 (d, *J* = 12.9 Hz, 2H), 6.90 (t, *J* = 9.3 Hz, 3H), 6.77 (d, *J* = 2.0 Hz, 2H), 6.66 (d, *J* = 5.6 Hz, 2H), 6.25 (s, 1H), 6.12 (s, 1H), 4.64 (d, *J* = 18.7 Hz, 2H), 3.84 – 3.77 (m, 8H). ^{13}C NMR (100 MHz, DMSO) δ 151.04 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 143.80 (s), 138.46 (s), 134.06 (s), 133.04 (s), 130.94 (s), 129.08 (s), 128.91 (s), 128.52 (d, *J* = 0.4 Hz), 128.11 (d, *J* = 11.1 Hz), 127.69 – 127.47 (m), 126.12 (s), 125.39 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 105.13 (s), 56.89 – 56.58 (m), 52.10 (s).

Spectroscopic data of 4,4'-((1E,1'E)-(1-((E)-3-(2-methoxyphenyl)allyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 5c

^{1}H NMR (400 MHz, DMSO) δ 7.47 (s, 2H), 7.45 (s, 2H), 7.46 – 7.15 (m, 11H), 7.46 – 6.97 (m, 23H), 6.96 – 6.86 (m, 12H), 6.86 – 6.69 (m, 21H), 6.67 (s, 4H), 6.39 (s, 4H), 6.09 (s, 3H), 4.62 (d, *J* = 2.4 Hz, 8H), 3.84 – 3.78 (m, 32H), 3.71 – 3.67 (m, 12H). ^{13}C NMR (100 MHz, DMSO) δ 155.95 (s), 151.04 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 143.80 (s), 136.22 (s), 133.04 (d, *J* = 2.3 Hz), 129.28 (s), 129.15 – 128.80 (m), 128.49 (s), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 121.23 (s), 115.91 – 115.70 (m), 113.57 (s), 111.97 – 111.57 (m), 105.13 (s), 56.89 – 56.58 (m), 52.10 (s).

Spectroscopic data of 4,4'-((1E,1'E)-(1-((E)-3-(4-methoxyphenyl)allyl)-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) 5d

^{1}H NMR (400 MHz, DMSO) δ 7.27 – 7.14 (m, 5H), 7.10 (s, 1H), 7.00 – 6.75 (m, 6H), 6.75 – 6.61 (m, 3H), 6.51 (s, 1H), 6.20 (s, 1H), 4.68 (s, 1H), 4.59 (s, 1H), 4.32 – 4.28 (m, 2H), 3.85 – 3.79 (m, 9H). ^{13}C NMR (100 MHz, DMSO) δ 159.03 (s), 151.04 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 143.80 (s), 133.04 (s), 131.33 (s), 130.17 (s), 129.99 (s), 129.08 (s), 128.91 (s), 128.27 – 128.05 (m), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 114.74 – 114.34 (m), 111.97 – 111.57 (m), 105.13 (s), 56.89 – 56.58 (m), 56.04 (s), 52.10 (s).

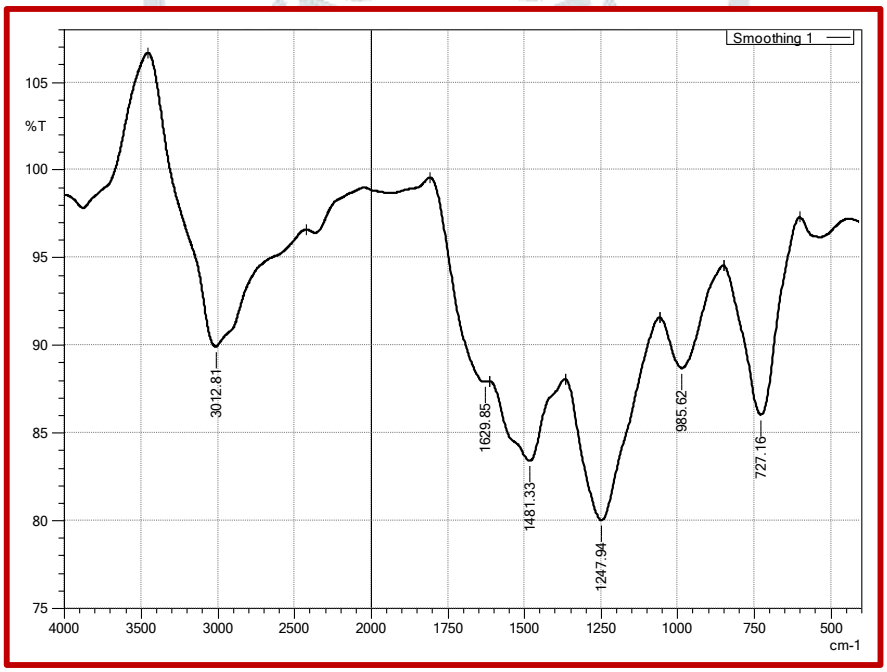


Figure 1. FT-IR spctroscopy of 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)

The structural characterization of curcumin-based pyrazole compound was investigated by FT-IT spectroscopy, the spectra are shown in Figure 1. It can be seen that the peak appears at ~3012 cm^{-1} is attributed to O-H stretching vibration and the peak arise at ~1629 cm^{-1} corresponds to the C=C stretching vibration of α, β-unsaturated ketone. The peaks at ~1481 and ~1247 cm^{-1} are ascribed to the C-H and C-O bending vibration of alkene. The peaks appeared at ~985 and ~727 cm^{-1} are due to C=C and C=C bending vibration of alkene. The UV-Vis absorption spectra of curcumin-based pyrazole compound are shown in Figure 2. The strong absorption bands appear at ~291 and ~261nm. The shoulder bands at ~320 and ~739nm are due to hydroxyl group and aromatic ring respectively. The XRD analysis was done for curcumin-based pyrazole compound shown in Figure 3, it is a powdered compound [amorphous in nature] so the peaks appear a broad, it was carried out by 40 kV generator in continuous scan mode of

15mA. The scan axis and the scan range are 2 Theta/Theta and 10.0000 - 80.0000 deg. follows a duration time of 7.0000 deg./min and it was shown in Figure 3.

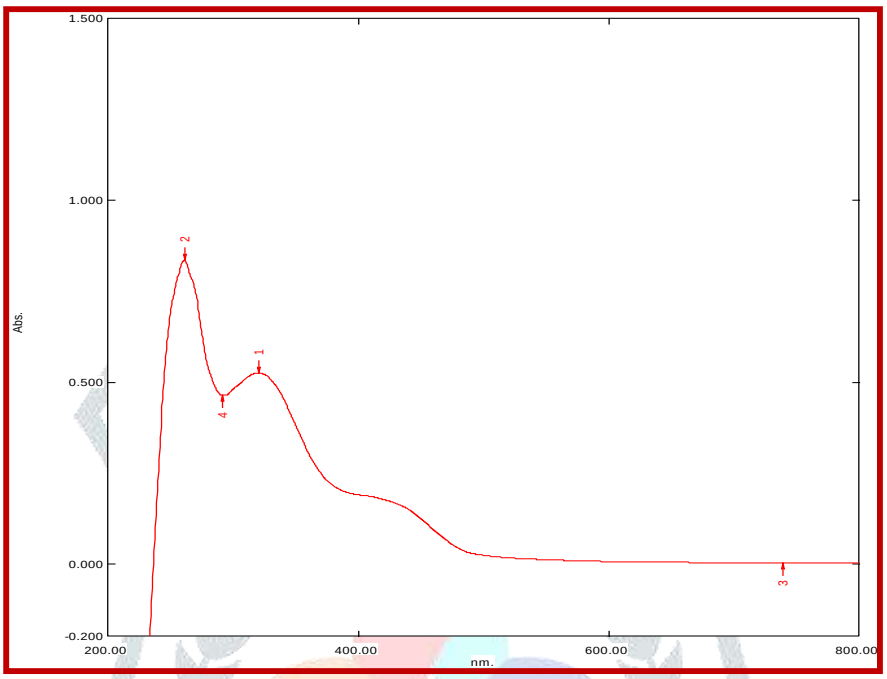


Figure 2. UV-Vis spectroscopy of 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)

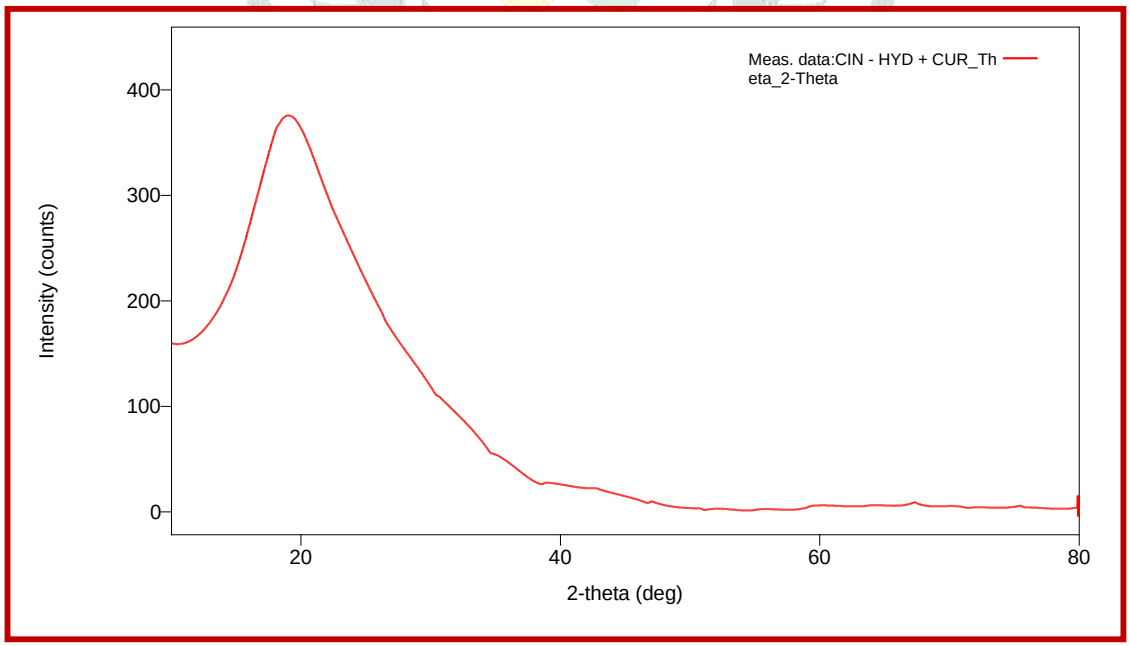


Figure 3. XRD analysis of 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)

Anti-microbial activities

The antimicrobial activity was executed on four types of bacteria strains: *Escherichia coli*, *Klebsiella oxytoca*, *Staphylococcus aureus*, *Staphylococcus epidermidis* using a standard disk. The results of curcumin-based compound are shown in Table 1. The results show that compound has gram-positive bacteria such as Staphylococcus aureus, Staphylococcus epidermidis and gram-negative bacteria as Escherichia coli, Klebsiella oxytoca with zone of inhibition ranges from 15 to 20mm on dilution of 100 µL. All the bacterial stains are shown in Figure 4. In glass plates, curcumin-based compound dissolves in acetone solution. Based on details the 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) has good antibacterial activity.

Table 1. Antimicrobial activity results of curcumin-based compound 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)

Sample	Gram positive or negative bacteria	Organisms	Standard disk (ak)	Zone of inhibition	Dilution
4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol)	Gram positive	Staphylococcus aureus	12mm	18mm	100 µL
		Staphylococcus epidermidis	12mm	16mm	100 µL
	Gram negative	Escherichia coli	12mm	15mm	100 µL
		Klebsiella oxytoca	12mm	20mm	100 µL

Figure 4. Bacterial strains of Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli and Klebsiella oxytoca

IV. CONCLUSION

In this paper, we have synthesized a new series of curcumin-based pyrazole derivative in presence of hydrazine and cinnamaldehyde with moderate yield and evaluated their antibacterial activities against Gram-positive and Gram-negative bacteria. The synthesized compound effectively inhibits Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli and Klebsiella oxytoca with zone of inhibition ranging from 15 to 20 mm. The formation of curcumin based heterocylic compounds was confirmed by the results of ^{1}H NMR, ^{13}C NMR spectra, FT-IR region, UV-Vis region and antimicrobial studies. All the studies is confirmed that the 4,4'-((1E,1'E)-(1-cinnamyl-1H-pyrazole-3,5-diyl)bis(ethene-2,1-diyl))bis(2-methoxyphenol) compound formation formed well.

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