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DESIGN, SYNTHESIS AND ANTIMICROBIAL EVALUATION OF NOVEL *5-(3,5-Bis((E)-4-HYDROXY-3-METHOXYSTYRYL)-1H-PYRAZOL-1-YL)PENTANAL* DERIVATIVES OBTAINED *VIA* CURCUMIN

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Abstract: The synthesis of novel heterocyclic compound namely 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (**5**) with the presence of curcumin and hydrazine derivatives and characterized by ^{1}H, ^{13}C NMR spectra, UV-Visible, FT-IR spectroscopy. The compound (**5**) was obtained *via* curcumin and hydrazine derivatives under reflux for few hours using glacial acetic acid as a catalyst. The synthesized compound also tested for antimicrobial activity, investigation of antimicrobial activity of the curcumin based compound (**5**) proved the ability to inhibit Gram-positive and Gram-negative microorganisms with zone of inhibition ranging from 12-22 mm. The microbial studies show the curcumin based heterocyclic compounds, (**5**) have highly effective towards antimicrobial activity.

Keywords: Curcumin, Glutaraldehyde, Hydrazine, Pyrazole, Antibacterial activity.

I. INTRODUCTION

The Curcumin, is a yellow-coloured spice from natural product of turmeric (Curcuma longa L)[1,2]. The major reason for choosing the curcumin to the formation of heterocyclic compound in organic chemistry is it exhibits variety of applications such a pharmacological-activities, act as anti-inflammatory, antioxidant, antimicrobial and anticancer activities[3-5]. Because of the various reason, change curcumin into novel pyrazole derivatives and to develop its biological activity[6,7].The Curcumin based heterocyclic compounds have shown a significant in vitro antimicrobial activity against Gram-positive and Gram-negative bacteria.curcumin (1,7-bis(4-hydroxy-3-methoxy phenyl)- 1,6-heptadiene-3,5-dione) consist of seven-carbon atom with α,β-unsaturated β-diketone connected with two phenyl rings and o-methoxy group[8-10].The phenolic and methylene group in curcumin is important for the antimicrobial activity, the chemical structure of curcumin as shown in Figure 1.

The hydrazine (H_2N-NH_2), the two nitrogen atoms linked with covalent bond, in which one or more hydrogen atoms replaced by hydrocarbon gropus[11].The heterocyclic compounds are exceptionally key role in organic chemistry, in this paper have to synthesized curcumin-based pyrazole compounds using hydrazine derivatives in acidic medium as per in the literature[12].

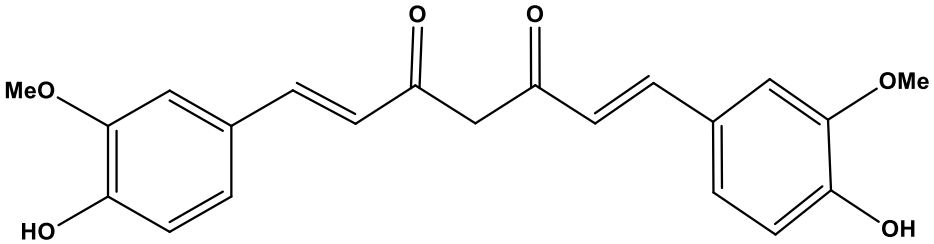


Figure 1: Structure of Curcumin

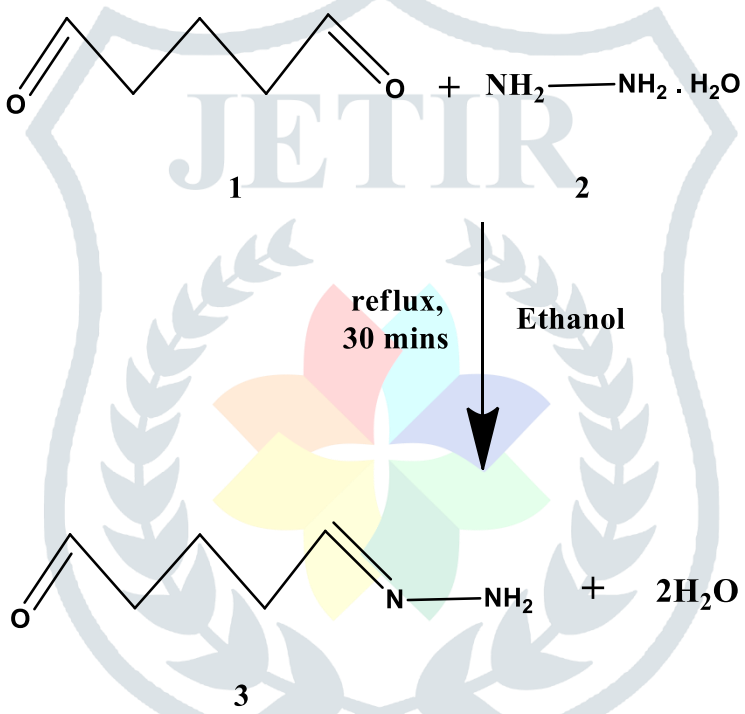
The synthesized curcumin based five membered pyrazole compounds are screened to antimicrobial activities against Gram-positive and Gram-negative bacteria.Curcumin was used by scientist or chemist in the field of organic chemistry, medicinal chemistry to identify the various drug-based compounds. In Asian countries, curcumin is commonly used in ayurvedic to recover any injuries[13,14]. Advanced methods are identified to synthesize curcumin -based compounds to cure cancer diseases in

humans[15,16]. The heterocyclic compounds are mostly five membered like pyrazole, pyrrole, imidazole etc[17]., Based on these facts, we aims to synthesis curcumin based heterocyclic compounds called as5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanalfrom natural product of curcumin and synthesized hydrazine derivatives in presence of glacial acetic acid.

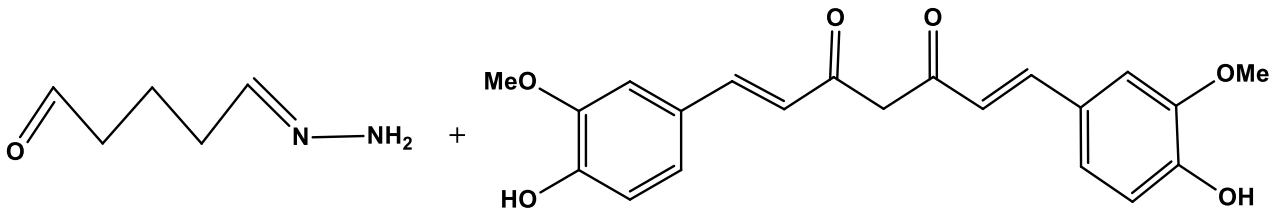
II. RESULTS AND DISCUSSION

In the present paper the novel curcumin based heterocyclic compound **5-5d** were synthesized from newly prepared hydrazine derivative **3-3d** and curcumin **4**. It was refluxed under acidic media as glacial acetic acid, it perform both catalyst and solvent. The reaction took more or less reflux time to finish and the yield of the compounds **5-5d** is moderate. The obtained compounds **5-5d** was purified and confirmed by taking ^{1}H and ^{13}C NMR spectra.

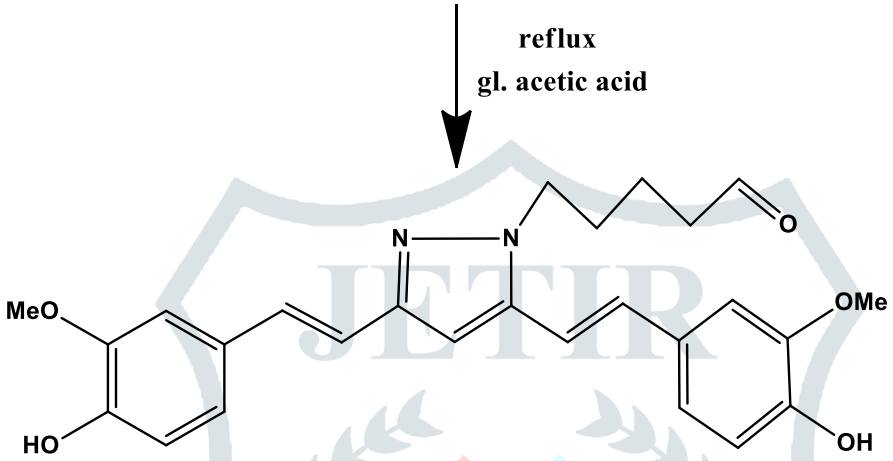
The starting material to prepare compound **5** is hydrazine derivatives. The hydrazine derivative of compound **3** can be prepared by equivalent amount of glutaraldehyde **1** (1 g, 0.01m) and hydrazine hydrate **2** (5 g, 0.01m) refluxed for half an hour to get a compound **3** in colloidal form. After purified with ethanol and followed by evaporation, the precipitate of compound **3** formed in good yield shown in scheme 1. The compound formation was confirmed by ^{1}H and ^{13}C NMR spectra. Then the curcumin-based pyrazole derivative of compound **5** was prepared by (E)-5-hydrazonopentanal **3** and curcumin **4** under reflux for 20-22 hrs in presence of glacial acetic acid (acidic medium) to get a 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal **5** (scheme 2) in moderate yield. Other set of curcumin based heterocyclic compounds **5a-5d** were prepared from various hydrazine derivatives **3a-3d** and curcumin **4** shown in Table 1.



Scheme 1: Synthesis of (E)-5-hydrazonopentanal (3)



3 4



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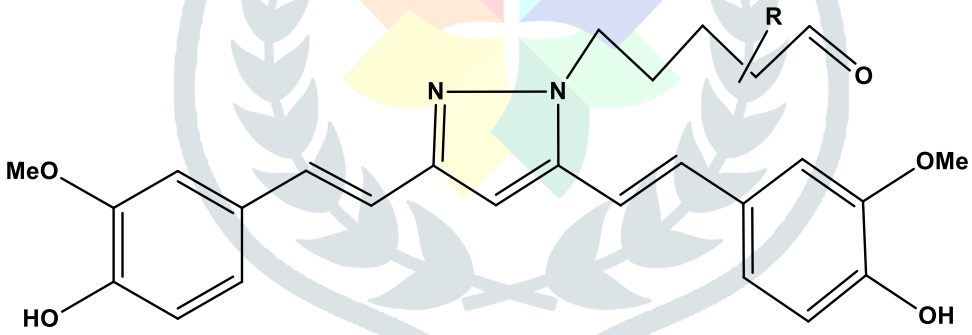
Scheme 2: Synthesis of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (5)



Compound	R	Time (h)	Yield (%)
5a	2-Cl	15	88
5b	2-br	16	85
5c	2-MeO	16	86
5d	4-MeO	18	89

Table 1: Synthesized curcumin based compounds (5a-5d) from curcumin and hydrazine derivatives

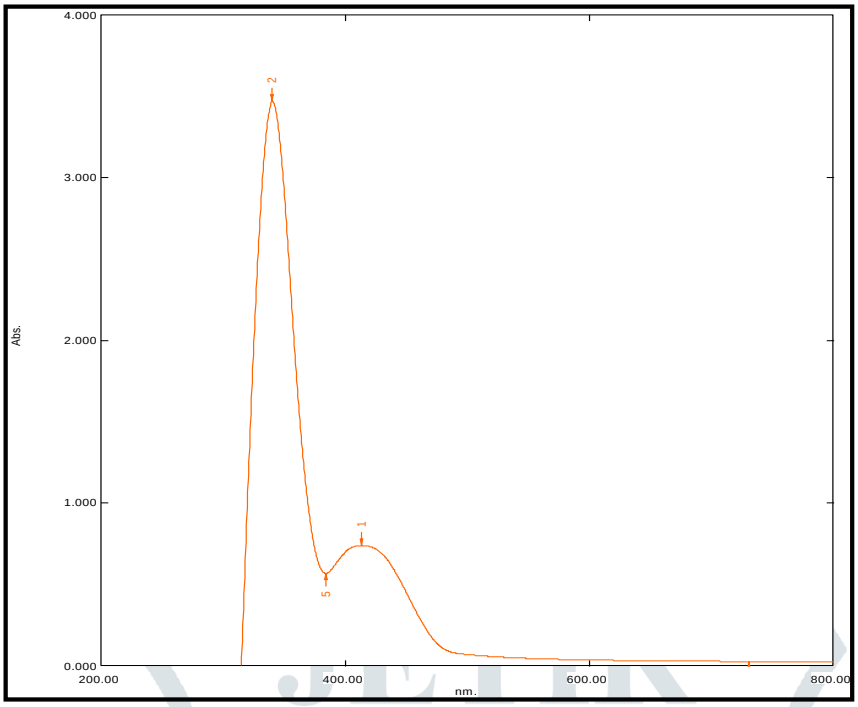


Figure 2: UV-Vis spectrum of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (5)

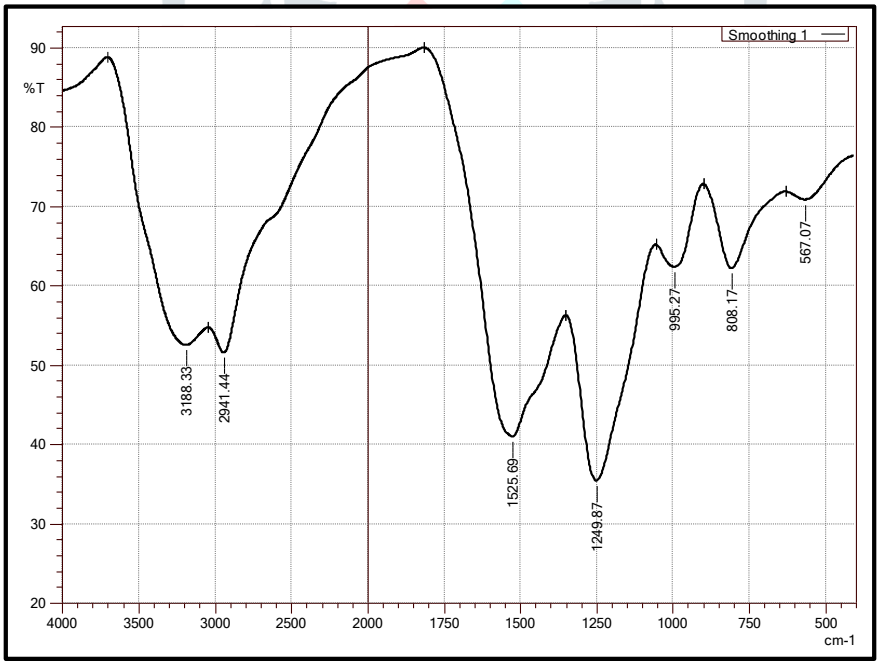


Figure 3: FT-IR spctrum of5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (5)

The ^{1}H NMR spectrum shows the signals at δ 9.65 (s, 1H), 8.58 – 8.53 (m, 2H), 6.77 (dd, *J* = 21.0, 4.3 Hz, 4H), 6.67 (d, *J* = 2.5 Hz, 2H), 6.24 (s, 1H), 4.10 (s, 1H), 4.02 (s, 1H), 3.82 – 3.77 (m, 6H), 2.32 – 2.15 (m, 2H), 1.88 – 1.78 (m, 2H), 1.74 – 1.69 (m, 2H) corresponds to the formation of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal **5**. In^{13}C NMR spectra the signals at δ 198.49 (s), 152.11 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 141.68 (s), 133.04 (s), 128.99 (d, *J* = 16.7 Hz), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 103.36 (s), 56.89 – 56.58 (m), 49.02 (s), 39.82 (s), 26.40 (s), 24.05 (s) confirms the formation of compound **5**. The compound 5 was investigated by spectral analysis of FT-IR spectroscopy, the spectrum as shown in Figure 3. The peaks at ~3188-2941 cm-1 are observed at C-H stretching modes of vibration. The band at ~1525 cm^{-1} have been assigned to C-C stretching vibrations and the peak at ~1249 cm^{-1} are carbonyl group, the absorption in ~1249 cm^{-1} are strongest C-O stretching among the present. The peak at ~808 cm^{-1} are C-N stretching frequency and peak at ~995cm^{-1} are due to C=C bending vibrational frequency. The results in FT-IR spectrum shows the curcumin-based pyrazole compound **5** formed well.The UV spectra results of compound**5**showed the absorbance at 413 nm and shoulder peak at 340 nm in Figure 2. Are decribed the 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal**5** formed well.

Spectral data of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (5)

^{1}H NMR (400 MHz, DMSO) δ 9.65 (s, 1H), 8.58 – 8.53 (m, 2H), 7.25 (d, *J* = 7.2 Hz, 2H), 7.13 (d, *J* = 15.0 Hz, 2H), 6.77 (dd, *J* = 21.0, 4.3 Hz, 4H), 6.67 (d, *J* = 2.5 Hz, 2H), 6.24 (s, 1H), 4.10 (s, 1H), 4.02 (s, 1H), 3.82 – 3.77 (m, 6H), 2.32 – 2.15 (m, 2H), 1.88 – 1.78 (m, 2H), 1.74 – 1.69 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 198.49 (s), 152.11 (s), 149.68 – 149.46 (m),

148.61 – 148.39 (m), 141.68 (s), 133.04 (s), 128.99 (d, *J* = 16.7 Hz), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 103.36 (s), 56.89 – 56.58 (m), 49.02 (s), 39.82 (s), 26.40 (s), 24.05 (s).

Spectral data of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)-2-chloropentanal (5a)

^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 2H), 8.84 – 8.79 (m, 4H), 7.35 (s, 2H), 7.25 (s, 2H), 7.15 (d, *J* = 9.7 Hz, 4H), 6.83 – 6.72 (m, 8H), 6.67 (d, *J* = 4.8 Hz, 4H), 6.24 (s, 2H), 4.24 (s, 3H), 4.15 (s, 1H), 4.10 (s, 2H), 3.82 – 3.77 (m, 12H), 1.87 (dd, *J* = 52.3, 11.9 Hz, 8H), 1.80 – 1.77 (m, 2H), 1.80 – 1.78 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 194.72 (s), 152.11 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 141.68 (s), 133.04 (s), 128.99 (d, *J* = 16.7 Hz), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 103.36 (s), 64.71 (s), 56.89 – 56.58 (m), 49.18 (s), 34.16 (s), 23.66 (s).

Spectral data of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)-2-bromopentanal (5b)

^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 9.24 – 9.19 (m, 2H), 7.23 (s, 1H), 7.09 (t, *J* = 8.6 Hz, 3H), 6.79 (dd, *J* = 14.0, 8.6 Hz, 4H), 6.67 (d, *J* = 2.1 Hz, 2H), 6.21 (s, 1H), 4.56 (s, 1H), 4.16 (s, 1H), 4.09 (s, 1H), 3.82 – 3.77 (m, 6H), 2.10 (d, *J* = 11.1 Hz, 2H), 1.86 – 1.71 (m, 2H). ^{13}C NMR (100 MHz, DMSO) δ 181.94 (s), 152.11 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 141.68 (s), 133.04 (s), 128.99 (d, *J* = 16.7 Hz), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 103.36 (s), 56.89 – 56.58 (m), 53.98 (s), 49.18 (s), 32.90 (s), 25.39 (s).

Spectral data 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)-2-methoxypentanal (5c)

^{1}H NMR (400 MHz, DMSO) δ 9.72 (s, 1H), 8.49 – 8.44 (m, 2H), 7.28 (d, *J* = 20.1 Hz, 2H), 7.11 (d, *J* = 3.9 Hz, 2H), 6.87 (s, 1H), 6.81 (s, 1H), 6.74 (d, *J* = 1.8 Hz, 2H), 6.67 (d, *J* = 1.3 Hz, 2H), 6.22 (s, 1H), 4.14 – 3.99 (m, 3H), 3.81 – 3.76 (m, 6H), 3.34 – 3.29 (m, 3H), 1.81 (dd, *J* = 21.7, 6.8 Hz, 4H). ^{13}C NMR (100 MHz, DMSO) δ 194.12 (s), 152.11 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 141.68 (s), 133.04 (s), 128.99 (d, *J* = 16.7 Hz), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 103.36 (s), 84.76 (s), 56.89 – 56.58 (m), 56.37 (s), 49.18 (s), 31.27 (s), 24.31 (s).

Spectral data of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)-4-methoxypentanal (5d)

^{1}H NMR (400 MHz, DMSO) δ 9.65 (s, 2H), 8.79 – 8.74 (m, 4H), 7.38 – 6.81 (m, 9H), 6.81 (d, *J* = 1.3 Hz, 1H), 6.77 (dd, *J* = 14.4, 4.4 Hz, 8H), 6.72 – 6.56 (m, 4H), 6.32 (s, 2H), 4.40 (s, 2H), 3.95 (s, 2H), 3.82 – 3.76 (m, 14H), 3.40 – 3.35 (m, 6H), 2.68 – 2.51 (m, 4H), 1.76 (d, *J* = 1.2 Hz, 4H). ^{13}C NMR (100 MHz, DMSO) δ 198.63 (s), 151.83 (s), 149.68 – 149.46 (m), 148.61 – 148.39 (m), 140.33 (s), 133.04 (s), 128.99 (d, *J* = 16.7 Hz), 127.69 – 127.47 (m), 126.12 (s), 123.28 – 123.07 (m), 115.91 – 115.70 (m), 111.97 – 111.57 (m), 104.32 (s), 78.23 (s), 56.89 – 56.62 (m), 56.43 (s), 49.09 (s), 36.78 (s), 29.49 (s).

Antimicrobial study of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (5)

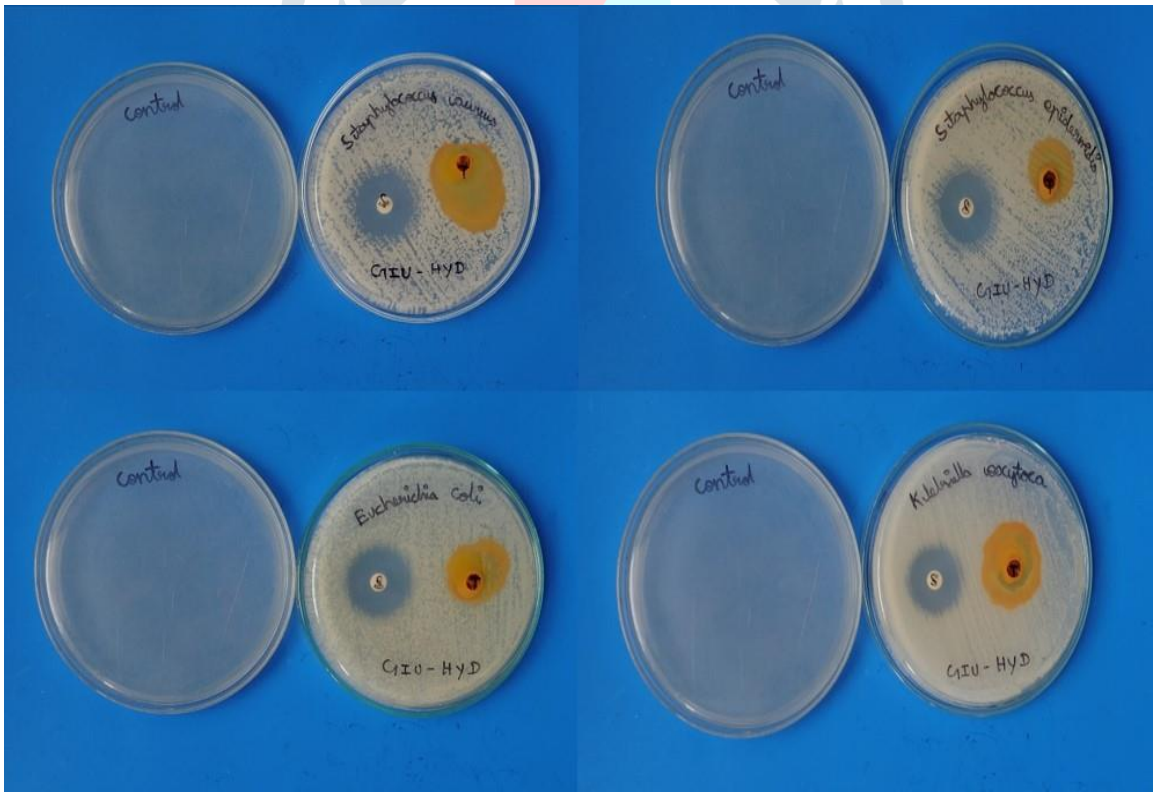


Figure 4. Bacterial strains of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (5)

The synthesized compound **5** were screened for antimicrobial activity against gram-positive and gram-negative bacteria. Acetone (20ml) was used as a standard drug for antimicrobial activity. The antimicrobial testing was reported in Table:2 and the results revealed that the compound **5** was active in four bacterial strains with control (Standard disk). In gram-positive, Staphylococcus aureus showed the highest activity of 22mm as compared to Staphylococcus epidermidis 12mm in zone of inhibition. Likewise in gram-negative, Klebsiella oxytoca the cone of inhibition is 18mm then compared to Escherichia coli of 15mm. The results shows that the compound **5** is active in four bacterial strains such as *Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella oxytoca and Escherichia coli* respectively in Figure 4.

Concentration: 20mg/ml of Acetone				
Sample	Gram positive or negative bacteria	Organisms	Standard disk (ak)	Zone of inhibition
5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal	Gram positive	Staphylococcus aureus	18mm	22mm
		Staphylococcus epidermidis	18mm	12mm
	Gram negative	Escherichia coli	18mm	15mm
		Klebsiella oxytoca	18mm	18mm

Table 2: Antimicrobial activity of curcumin-based compound 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (5)

III. EXPERIMENTAL SECTION

All the chemicals were purchased from Sigma-Aldrich company used without further purification. Both hydrazine derivative **3** and curcumin-based reactions **5-5d** were monitored by TLC using silica gel plates.The ^{1}H NMR and ^{13}C NMR spectra were recorded by Bruker NMR SPECTRA at 400 MHZand 100 MHZ respectively. In NMR analysis the compounds were analyses usingDMSOas a solvent, TMS as internal standard and the coupling constant (J) is shown in Hz. For FT-IR analysis of compound **5** Perkin-Elmer machine was used and Jasco spectrophotometer to record UV spectra.

Synthesis of (E)-5-hydrazonopentanal (3)

In a round bottom flask, add glutaraldehyde **1** (1 g, 0.01m) and hydrazine hydrate **2** (5 g, 0.01m) under reflux for 30 minutes in presence of ethanol. The (E)-5-hydrazonopentanal formed with good yield as shown in Scheme 1. Likewise, the other hydrazine derivatives **3a-3d** was synthesized from **1a-1d** and **2** as shown in Table3. The synthesized hydrazine derivative **3** were confirmed by ^{1}H, ^{13}C NMR spectrum. ^{1}H NMR (400 MHz, DMSO) δ 9.65 (s, 3H), 6.95 (s, 3H), 5.99 – 5.94 (m, 6H), 2.33 – 2.12 (m, 12H), 1.91 – 1.86 (m, 5H). ^{13}C NMR (100 MHz, DMSO) δ 198.49 (s), 144.01 (s), 38.77 (s), 28.97 (s), 22.60 (s).

Aldehyde	Hydrazine hydrate	Product
2-chloro glutaraldehyde **1a**	**2**	(E)-2-chloro-5-hydrazonopentanal **3a**
2-bromo glutaraldehyde **1b**	**2**	(E)-2-bromo-5-hydrazonopentanal **3b**
2-methoxy glutaraldehyde **1c**	**2**	(E)-5-hydrazono-2-methoxypentanal **3c**
4-methoxy glutaraldehyde **1d**	**2**	(E)-5-hydrazono-4-methoxypentanal **3d**

Table 3: Synthesis of hydrazine derivatives (3a-3d) from substituted glutaraldehyde (1a-1d) and hydrazine hydrate 2

Synthesis of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal (5)

The magnetic stirrer equipped with condenser, in a round bottom flask 0.368 g, 0.001m of curcumin was dissolved in glacial acetic acid (20 ml) and 1.14 g, 0.01m of (E)-5-hydrazonopentanal was added to it. The solution was refluxed for 20 hrs and the reaction was monitored by TLC. After the reaction complete, the mixture was evaporated and redissolved in 100 ml of ethyl acetate. The ethyl acetate layer was washed with saturated solution of $NaHCO_3$ and NaCl, dried over Na_2SO_4. The product **5** was purified by pet ether:ethyl acetate mixture (6:4) as shown in Scheme 2.

Synthesis of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)-2-chloropentanal (5a)

The magnetic stirrer equipped with condenser, in a round bottom flask 0.368 g, 0.001m of curcumin was dissolved in glacial acetic acid (20 ml) and 1.48 g, 0.01m of (E)-2-chloro-5-hydrazonopentanal **3a** was added to it. The solution was refluxed for 15 hrs and the reaction was monitored by TLC. After the reaction complete, the mixture was evaporated and redissolved in 100 ml of ethyl acetate. The ethyl acetate layer was washed with saturated solution of $NaHCO_3$ and NaCl, dried over Na_2SO_4. The product **5a** was purified by pet ether:ethyl acetate mixture (6:4).

Synthesis of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)-2-bromopentanal (5b)

The magnetic stirrer equipped with condenser, in a round bottom flask 0.368 g, 0.001m of curcumin was dissolved in glacial acetic acid (20 ml) and 1.93 g, 0.01m of (E)-2-bromo-5-hydrazonopentanal **3b** was added to it. The solution was refluxed for 16 hrs and the reaction was monitored by TLC. After the reaction complete, the mixture was evaporated and redissolved in 100 ml of ethyl acetate. The ethyl acetate layer was washed with saturated solution of $NaHCO_3$ and NaCl, dried over Na_2SO_4. The product **5b** was purified by pet ether:ethyl acetate mixture (6:4).

Synthesis of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)-2-methoxypentanal (5c)

The magnetic stirrer equipped with condenser, in a round bottom flask 0.368 g, 0.001m of curcumin was dissolved in glacial acetic acid (20 ml) and 1.44 g, 0.01m of (E)-5-hydrazono-2-methoxypentanal **3c** was added to it. The solution was refluxed for 16 hrs and the reaction was monitored by TLC. After the reaction complete, the mixture was evaporated and redissolved in 100 ml of ethyl acetate. The ethyl acetate layer was washed with saturated solution of $NaHCO_3$ and NaCl, dried over Na_2SO_4. The product **5c** was purified by pet ether:ethyl acetate mixture (6:4).

Synthesis of 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)-4-methoxypentanal (5d)

The magnetic stirrer equipped with condenser, in a round bottom flask 0.368 g, 0.001m of curcumin was dissolved in glacial acetic acid (20 ml) and 1.44 g, 0.01m of (E)-5-hydrazono-4-methoxypentanal **3d** was added to it. The solution was refluxed for 18 hrs and the reaction was monitored by TLC. After the reaction complete, the mixture was evaporated and

redissolved in 100 ml of ethyl acetate. The ethyl acetate layer was washed with saturated solution of $NaHCO_3$ and NaCl, dried over Na_2SO_4. The product **5d** was purified by pet ether:ethyl acetate mixture (6:4).

IV. CONCLUSION

From this review we have synthesized novel curcumin based heterocyclic compounds **5-5d** from hydrazine derivative and curcumin with good yield was proved by spectral data. The newly synthesized compound **5** has shows a remarkable biological activity against gram-positive and gram-negative bacteria. It inhibits Staphylococcus aureus, Staphylococcus epidermidis, Escherichia coli and Klebsiella oxytocawith zone of inhibition ranging from 12 to 22 mm. All the studies revealed that the curcumin based 5-(3,5-bis((E)-4-hydroxy-3-methoxystyryl)-1H-pyrazol-1-yl)pentanal compound **5** formed well.

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