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# SYNTHESIS AND CHARACTERIZATION OF NOVEL (E)-3-PHENYL-5-STYRYL-4,5-DIHYDRO-1H-PYRAZOLE-1-CARBOXAMIDE AND 5-(FURAN-2-YL)-3-PHENYL-4,5-DIHYDRO-1H-PYRAZOLE-1-CARBOXAMIDE DERIVATIVES AND EVALUATION OF ITS ANTIMICROBIAL ACTIVITIES

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***Abstract:*** A modular synthetic route that entails the synthesis of distinctive chalcones from aldehydes (Cinnamaldehyde and Furfuraldehyde) and acetophenone precursors in a manner consistent with Claisen-Schmidt condensation. On reaction with semicarbazide hydrochloride, certain substituted (E)-3-phenyl-5-styryl-4,5-dihydro-1H pyrazole-1-carboxamide and 5-(furan-yl)-3-phenyl-4,5-dihydro-1H-Pyrazole-1-carboxamide derivatives were synthesised from properly substituted chalcone. It is a simple, low cost and efficient method to produce 3,5 substituted (phenyl-styryl& phenyl-furan)-1H pyrazole carboxamide derivatives. It was confirmed by UV, FT-IR, XRD, $^{1}H$ and $^{13}C$ NMRs. And the synthesized compounds possess antimicrobial activity, especially antibacterial activity.

**Keywords:**

3,5 substituted (phenyl-styryl& phenyl-furan) carboxamide derivatives, Claisen Schmidt condensation, Substituted chalcones from cinnamaldehyde and Furfuraldehyde, Recrystallization

## I. INTRODUCTION

Pyrazoles are a crucial class of heterocyclic compounds. Pyrazole and its derivatives are regarded as a pharmacologically significant active scaffold with practically all sorts of pharmacological activity. Five-membered nitrogen heterocycles, pyrazoles, and their derivatives serve as a starting point for the synthesis of several classes of bioactive compounds. A π-excess aromatic heterocycle is pyrazole from its structure, position 4 is the preferred site for electrophilic substitution reactions, whereas positions 3 and 5 are the preferred sites for nucleophilic attacks.[2] Conventional preparation methods have been developed to enhance the structural variety of substituted pyrazoles. In addition to the formation of C-N and C-C bonds via cross-coupling reactions of aryl electrophiles with substituted pyrazoles, more promising alternative techniques with quick reaction time and excellent yield have been applied in subsequent synthesis and chemical purification.[3] In the fields of organic chemistry and drug development, pyrazole derivatives have been widely employed as significant synthons.[4] The presence of the pyrazole nucleus in distinctive systems results in diversified programs in exceptional regions consisting of technology, medicine, and agriculture; specifically, they're defined as inhibitors of protein glycation, antibacterial, antifungal, anticancer, antidepressant, anti-inflammatory, anti-tuberculosis, antioxidant, and antiviral agents.[5-18] Due to their intriguing pharmacological properties, pyrazole compounds have recently drawn more attention as biomolecules.[19] In the last few years, the variety of life-threatening infections caused by multi-drug-resistant gram-positive and gram-negative pathogen microorganisms has increased in many nations worldwide.[20,21] A number of antifungal azoles were discovered within the closing three years and have been delivered in scientific practice up until now.[22] The medical community has a severe problem treating infections brought on by these germs, which has prompted researchers to look for new antibacterial drugs. According to the literature, pyrazole compounds also have antibacterial action among their many other pharmacological characteristics.[23, 24]

From the literature survey, it's miles believed that pyrazole carboxamide derivatives have greater efficient bioactivity and it is synthesized via chalcones from two special aldehydes (cinnamaldehyde and furfuraldehyde) by using Claisen Schmidt

condensation and in addition reaction with semicarbazide hydrochloride to form substituted 3,5-substituted-(phenyl-styryl& phenyl-furan) -1H pyrazole carboxamide derivatives.

## EXPERIMENTAL

All of the chemicals were of high reagent grade and were utilised without additional purification. All melting points were measured in uncorrected open capillaries. TMS was used as an internal standard for the $^{1}$HNMR and $^{13}$CNMR spectra, which were recorded on a Bruker 400MHz& 100MHz in DMSO.

### General Procedure

Step I: Synthesis of Chalcones

Equimolar amounts of substituted benzaldehyde(Cinnamaldehyde and Furfuraldehyde) and acetophenone 1 (0.01 mol each) were dissolved in 25 ml of methanol. Equimolar NaOH pellets (0.01mol) were immediately added to this solution, and the reaction mixture was agitated at room temperature for 40 minutes. Extra methanol was once again added, and it was then agitated for the following 40 minutes at a temperature of roughly 40°C. After cooling, it was diluted with cold water. Crystals from the product that had separated out were filtered and gently washed in water till neutral. Through recrystallization with methanol, the resultant chalcone has become purer.

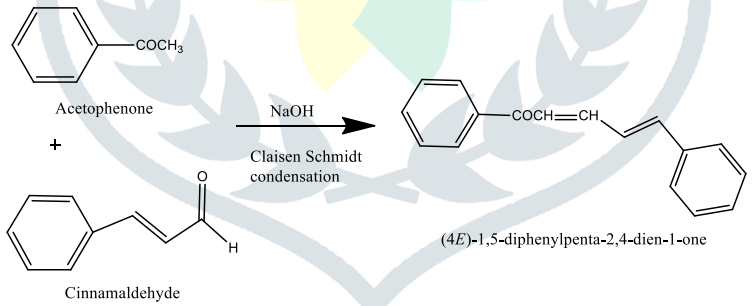
Step II Synthesis of 3,5 substituted (phenyl-styryl& phenyl-furan) -1H -pyrazole carboxamide derivatives

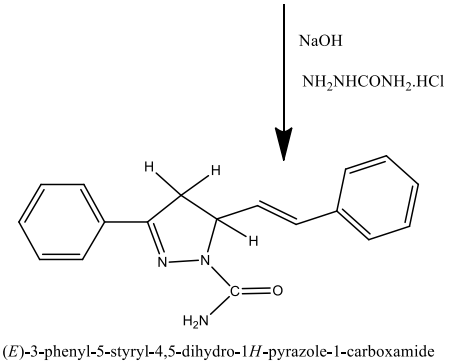
Semicarbazide hydrochloride (0.0085 mol) was dissolved in aqueous sodium hydroxide (0.017 mol). The substituted chalcones solution (0.005 mol) in ethanol (25 ml) was added to this solution, which was then refluxed for 2–5 hours. There was intensive TLC surveillance. When the product had cooled, crushed ice had been added. The solid mass that broke apart was filtered, slowly rinsed in water to stop the reaction, dried, and recrystallized using the right ratio of solvents, such as ethanol and chloroform (8:2).

## RESULTS AND DISCUSSION

The synthesis of chalcones from (Cinnamaldehyde and Furfuraldehyde) and acetophenone was according to the ClaisenSchmidt condensation. The substituted (E)-3-Phenyl-5-styryl-4,5-dihydro-1H-pyrazole-1-carboxamide and 5-(Furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide derivatives were synthesized from these chalcones using semicarbazide hydrochloride. (Scheme I and Scheme II). The primary reactions are the synthesis of intermediate hydrazones and the subsequent addition of N-H on the olefinic bond of the propenone moiety, which results in the end products, which are ring-closed. The signals of the corresponding protons of the final title compounds were confirmed in the nuclear magnetic resonance spectra (1H-NMR) based on their chemical shifts and multiplicities. All of the two synthesized compounds' analytical and spectral data (1H-NMR, 13C-NMR, IR, and UV) were entirely in favour of the suggested structures. Based on the obtained data, relationships between structure and activity suggested that the kind of aryl group substitution connected to the 5-position of the pyrazole nucleus controls the antibacterial action.

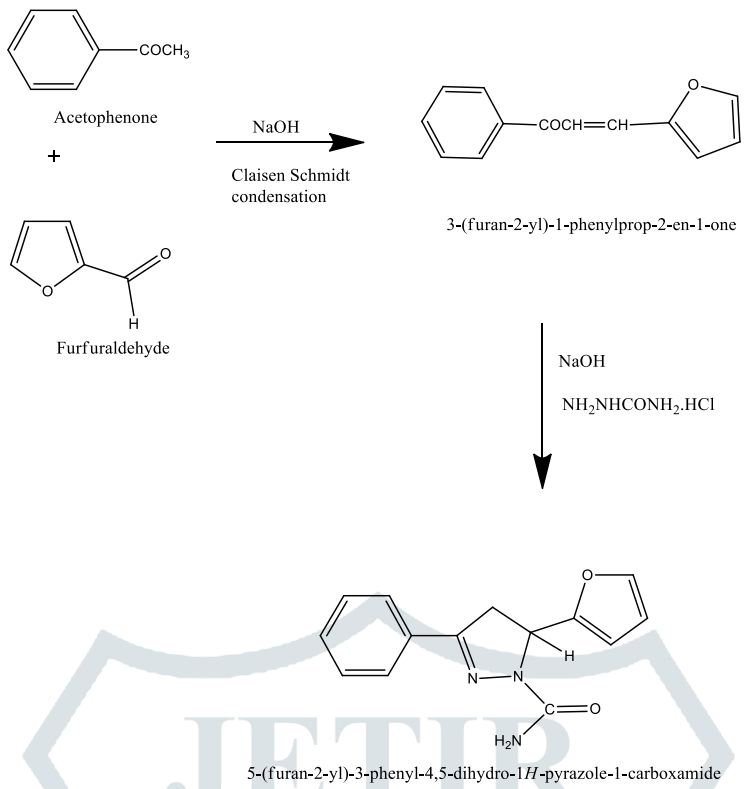
**Scheme I**



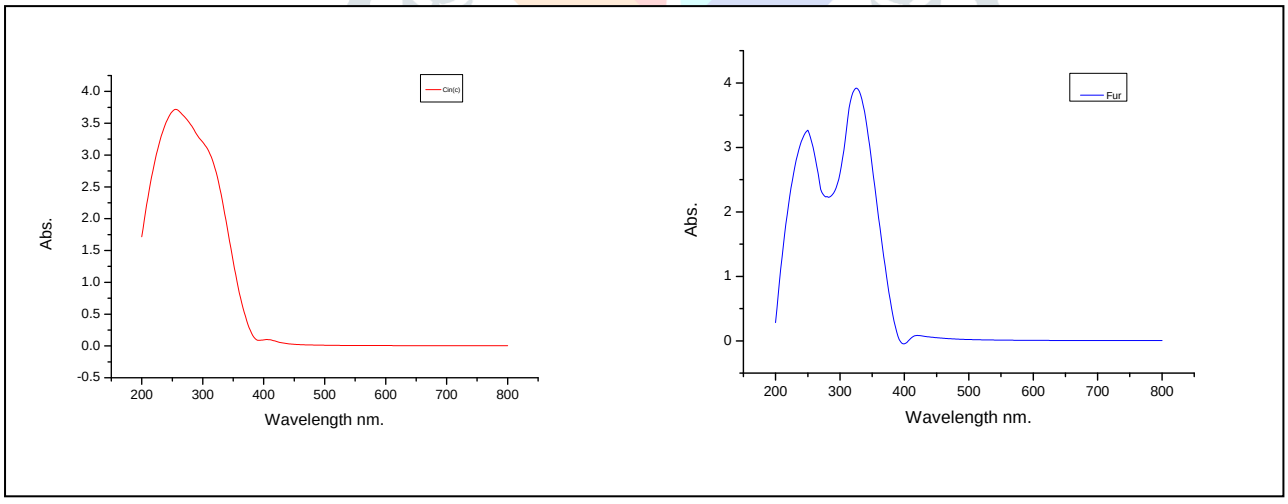




(*E*)-3-phenyl-5-styryl-4,5-dihydro-1*H*-pyrazole-1-carboxamide

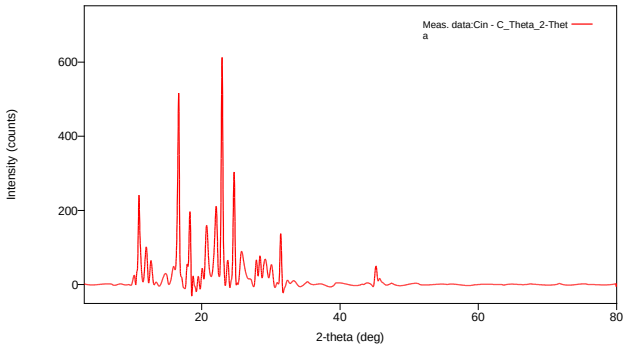
**Scheme II**

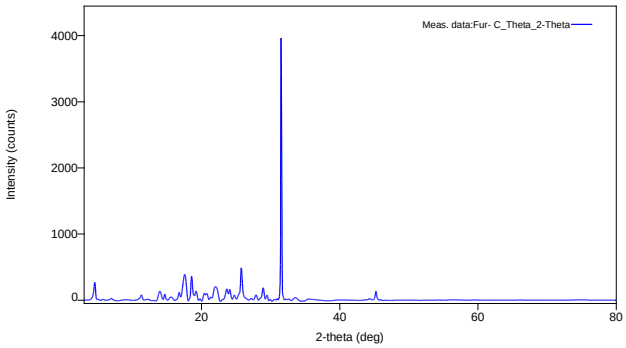


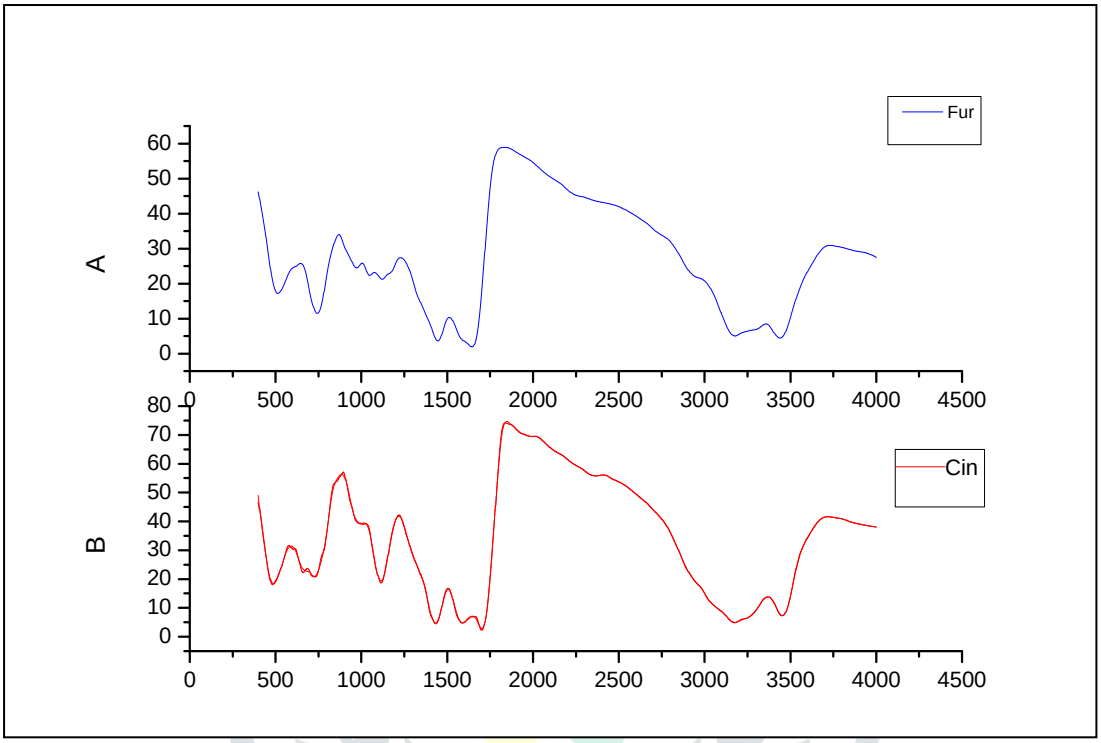

The absorption spectrum for the synthesized (E)-3-phenyl-5-styryl-4,5-dihydro-1H pyrazole-1-carboxamide and 5-(furan-yl)-3-phenyl-4,5-dihydro-1H-Pyrazole-1-carboxamide derivatives was recorded in the range of 200-800nm. The absorption observed at 250nm, which indicates the formation of 3,5 -substituted (phenyl-styryl& phenyl-furan) -1H-pyrazole carboxamide derivatives.




Here, the XRD was carried out for both synthesised powdered compounds, i.e. (E)-3-phenyl-5-styryl-4,5-dihydro-1H pyrazole-1-carboxamide and 5-(furan-yl)-3-phenyl-4,5-dihydro-1H-Pyrazole-1-carboxamide derivatives. XRD data for the title compounds were examined with an X-ray generator at 40 kV and 15 mA in continuous scan mode. The scan axis and scan range are 2 Theta/Theta and 3.0000-80.0000 deg., keeping the duration time at 7.0000 deg/min. The cluster analysis of the successfully synthesized compounds are shown in the figures below. These figures indicate both the sharp peaks and broad humped peaks combined; if it is completely sharp, it has a crystalline nature; if it is broad, it has an amorphous nature. As a result, the two synthesized substances are semi-crystalline because they have both crystalline and amorphous natures.




The FT-IR spectrum of the synthesized (E)-3-phenyl-5-styryl-4,5-dihydro-1H pyrazole-1-carboxamide and 5-(furan-yl)-3-phenyl-4,5-dihydro-1H-Pyrazole-1-carboxamide derivatives shows the bands at A= 3452.58, 3174.83, 2364.73, 1992.47, 1703.14, 1589.34, 1435.04cm-1 and 1114.86cm$^{-1}$. The peaks at 3452.58, 3174.83 and 2364.73cm$^{-1}$ are due to NH/CH stretching of the formed 1H pyrazole indicated as A. B=3439, 3174.83, 2364.72, 1647.21, 1593.20, 1444.8, 1170.79,1112.93cm$^{-1}$ and 1051cm$^{-1}$. The peaks at 3439, 3174.83 and 2364.72cm$^{-1}$ are due to NH/CH stretching of the formed pyrazole indicated as B.

**$^{1}$H and $^{13}$C NMR:**

The synthesized compounds which represented in Scheme I and Scheme II were confirmed by $^{1}$H and $^{13}$C spectra and its spectral data as follows,

**(E)-3-Phenyl-5-styryl-4,5-dihydro-1H-pyrazole-1-carboxamide derivative:**
$^{1}$H NMR (400 MHz, DMSO) δ 7.41 (t, *J* = 6.0 Hz, 6H), 7.32 – 7.22 (m, 8H), 7.21 (dd, *J* = 4.0, 2.4 Hz, 1H), 7.20 – 7.06 (m, 5H), 6.04 (d, *J* = 8.0 Hz, 2H), 6.01 – 5.73 (m, 2H), 5.48 – 5.32 (m, 2H), 3.62 – 3.57 (m, 1H), 3.13 – 2.98 (m, 2H), 2.15 – 2.10 (m, 4H).
$^{3}$C NMR (100 MHz) δ 153.94, 153.84, 136.75, 134.33, 132.76, 130.75, 129.12, 129.12, 128.76, 128.64, 128.56, 128.56, 127.56, 127.56, 125.81, 125.81, 62.55, 37.62.

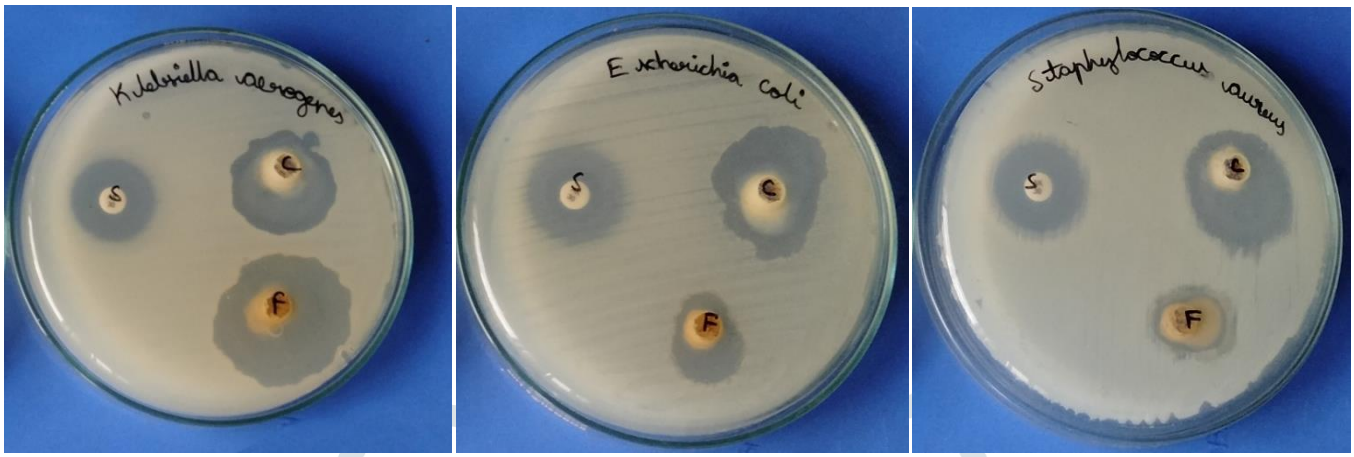
**5-(Furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide derivative:**
$^{1}$H NMR (400 MHz, DMSO) δ 7.48 (d, *J* = 1.8 Hz, 2H), 7.47 – 7.42 (m, 15H), 7.38 (dd, *J* = 7.3, 1.7 Hz, 11H), 7.25 (dd, *J* = 7.5, 1.5 Hz, 5H), 6.20 (t, *J* = 7.5 Hz, 6H), 5.99 (dd, *J* = 7.5, 1.5 Hz, 6H), 5.43 (t, *J* = 9.0 Hz, 6H), 5.33 (s, 6H), 4.97 (s, 6H), 3.15 (dd, *J* = 12.4, 9.0 Hz, 6H), 2.98 (dd, *J* = 12.4, 9.0 Hz, 6H).
$^{13}$C NMR (100 MHz) δ 154.51, 152.92, 149.38, 140.56, 132.76, 128.64, 128.56, 128.56, 125.81, 125.81, 110.96, 94.02, 68.28, 35.3

**Antimicrobial activity**

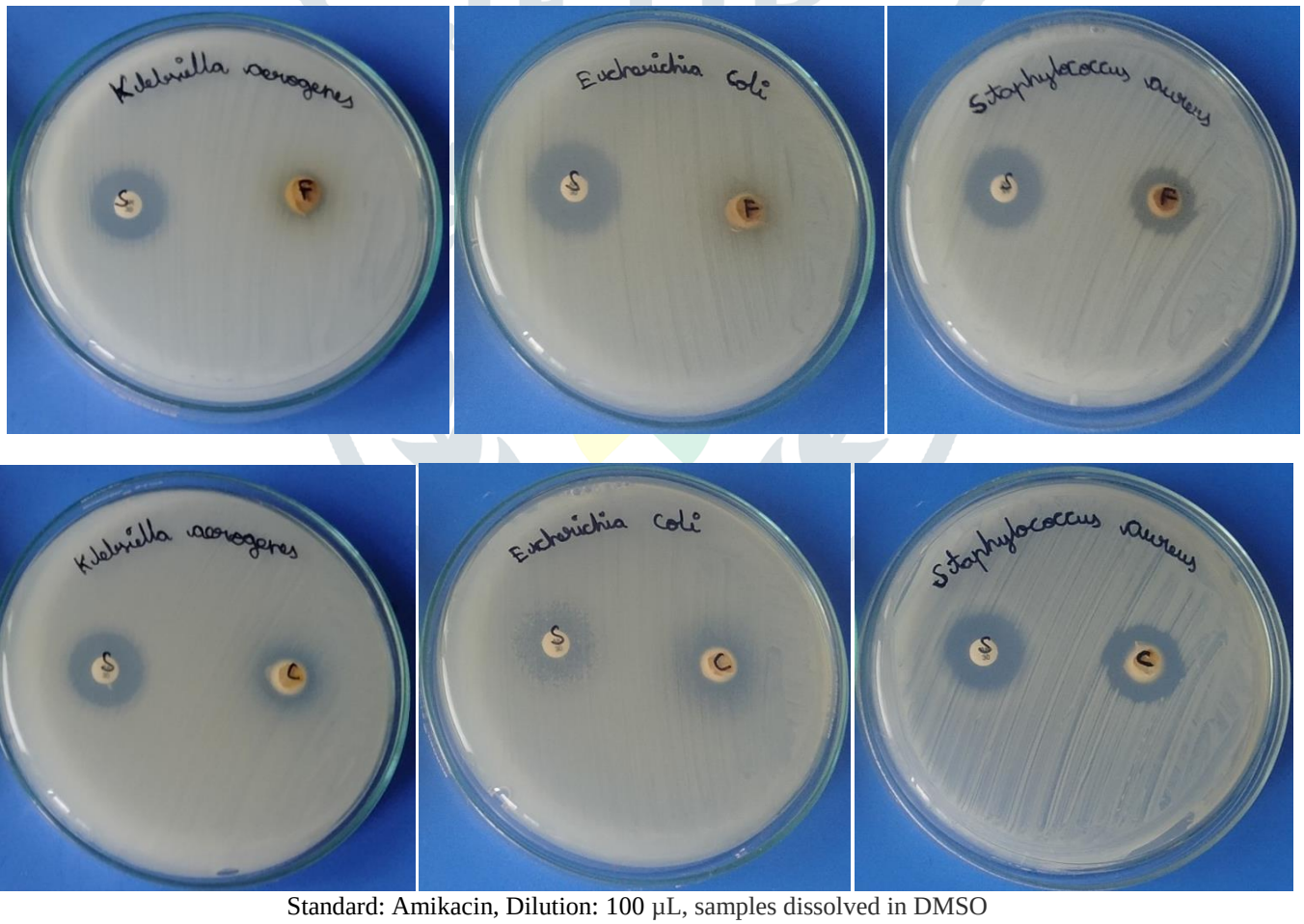
The two synthetic compounds were effective against several species, including Klebsiella aerogenes, Escherichia coli and Staphylococcus aureus. Here the Agar disk diffusion assay is utilized because of its nature of flexible, cost-effective and more accurate method for determining gram positive and gram negative bacteria. The two synthesized compounds were dissolved in both DMSO & Ethanol using Amikacin as a standard drug with 100µL dilution and its zone of inhibition are depicted in figures.

**C**- (E)-3-Phenyl-5-styryl-4,5-dihydro-1H-pyrazole-1-carboxamide derivative,

**F**- 5-(Furan-2-yl)-3-phenyl-4,5-dihydro-1H-pyrazole-1-carboxamide derivative




Standard: Amikacin, Dilution: 100 µL, samples dissolved in ethanol




Standard: Amikacin, Dilution: 100 µL, samples dissolved in DMSO

| ORGANISMS | STANDARD DISC | USING DMSO | USING ETHANOL |
|---|---|---|---|
| KLEBSIELLA AEROGENES (GRAM-NEGATIVE BACTERIA) | AK – 15MM | 12 MM | 18 MM |
| ESCHERICHIA COLI (GRAM-NEGATIVE BACTERIA) | AK – 15MM | 10 MM | 17 MM |
| STAPHYLOCOCCUS AUREUS (GRAM-POSITIVE BACTERIA) | AK – 15MM | 15 MM | 20 MM |

**(E)-3-PHENYL-5-STYRYL-4,5-DIHYDRO-1H-PYRAZOLE-1-CARBOXAMIDE DERIVATIVE**

| ORGANISMS | STANDARD DISC | USING DMSO | USING ETHANOL |
|---|---|---|---|
| KLEBSIELLA AEROGENES (GRAM- NEGATIVE BACTERIA) | AK – 15MM | NIL | 22 MM |
| ESCHERICHIA COLI (GRAM-NEGATIVE BACTERIA) | AK – 15MM | NIL | 10 MM |
| STAPHYLOCOCCUS AUREUS (GRAM-POSITIVE BACTERIA) | AK – 15MM | 10 MM | 10 MM |

**5-(FURAN-2-YL)-3-PHENYL-4,5-DIHYDRO-1H-PYRAZOLE-1-CARBOXAMIDE DERIVATIVE**

## CONCLUSION:

The synthesis of novel 3,5 substituted (phenyl-styryl& phenyl-furan) -1H-pyrazole carboxamide derivatives, a new heterocyclic compounds were synthesized. A good yield of 3,5 substituted -(phenyl-styryl& phenyl-furan) -1H pyrazole carboxamide derivatives were achieved, and verified by UV, FT-IR, XRD methods and $^{1}H$&$^{13}C$ spectroscopy. Additionally, disc diffusion testing in an agar plate using antibacterial activity demonstrates the potency of the synthesised compounds against Escherichia coli (gram-negative), Klebsiella aerogenes (gram-negative) and Staphylococcus aureus (gram-positive).

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