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Synthesis and antimicrobial activity of novel pyrazole nucleus containing 4-oxothiazolidine acetate derivatives

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A new series of 4-oxothiazolidin-5-ylidene acetates **4a-r** containing pyrazole moiety have been designed and synthesized by using dimethyl acetylenedicarboxylate (DMAD) and diethyl acetylenedicarboxylate (DEAD) through a facile route involving regioselective heterocyclization. The synthesis has been achieved at ambient temperature in good to excellent yields under catalyst free conditions. The newly synthesized compounds have been examined for *in vitro* antimicrobial activity against some anti-bacterial and fungal strains. The synthesized compounds have been characterized by various spectral techniques including ^{1}H and ^{13}C NMR, IR, mass spectroscopy, and elemental analysis.

Keywords: Pyrazole, 4-Oxo-thiazolidines-2-ylidene, DMAD, DEAD, Antimicrobial activity

Microbial diseases have become a major cause of illness and immune suppression in the past two decades. The treatment of bacterial infections remains a major challenge due to emerging infectious diseases and the rise of multidrug-resistant pathogens. Despite the availability of numerous antibiotics and chemotherapeutic agents, the continuous emergence of antibiotic-resistant bacterial strains highlights the urgent need for new antimicrobial agents[1]. Many existing antimicrobial drugs are toxic and only inhibit bacterial growth rather than eliminating them, leading to disease recurrence and resistance development due to prolonged use[2]. To address this issue, there is a continuous need for new chemotherapeutic agents that can prevent resistance development and ideally reduce treatment duration[3].

The pyrazole ring system is a well-established structural motif in various synthetic analogs, making it a key focus in medicinal chemistry[4]. Researchers have extensively explored pyrazole as a potential pharmacophore due to its significant therapeutic relevance. Pyrazole derivatives have a long-standing role in the pharmaceutical industry[5], serving as key compo nents in biologically active drugs[6]. They exhibit a wide range of pharmacological activities, including antitubercular[7], antitumor[8], anti-inflammatory[9], antihyperglycemic[10], antimicrobial[11], antihypertensive activity[12], antimalarial[13], analgesic and platelet anti-aggregating activity[14]. Simultaneously, derivatives of 4-oxo-thiazolidin-2-ylidene acetate have been relatively less explored. Literature reports reveal that 4-oxo-thiazolidines-2-ylidene acetate derivatives can be synthesized through a thermal and regioselective cyclization reaction. This process involves the reaction of various aromatic aldehyde derivatives with hydrazinecarboxamide and DMAD OR DEAD in ethanol *via* a simple domino approach[15].

Thiazolidines derivatives especially 4-oxothiazolidin-5-ylidene derivatives have gained significant interest due to their broad spectrum of biological activities. This versatile class of compounds exhibits a broad spectrum of biological activities, including antifungal[16], antidiabetic and anti-inflammatory activity[17], antiviral[18], antiproliferative[19], antimicrobial[20], antioxidant, and antitumor activity[21].

In this study, we present the synthesis of a novel series of 4-oxothiazolidin-5-ylidene acetates derivatives incorporating a pyrazole moiety. The structural characterization of the synthesized compounds was confirmed using advanced analytical techniques, including IR, NMR, and mass spectrometry. The newly synthesized target compounds were evaluated *in vitro* for their antibacterial activity against four bacterial strains, including two Gram-negative bacteria (*Enterobacter aerogenes* and *Salmonella typhi*) and two Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus megaterium*), as well as for their antifungal activity against two fungal strains (*Aspergillus flavus* and *Aspergillus niger*).

Experimental Section

All chemicals and solvents were obtained from Sigma Aldrich and Spectrochem Ltd. and used without further purification. Melting points were measured in one-end open capillary tubes using a Digital Auto Melting Point Apparatus. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) were recorded on a BRUKER AVANCE-III spectrometer. Chemical shifts were reported in parts per million (ppm) relative to tetramethylsilane (TMS). Mass spectra were obtained using a Shimadzu GC-MS-QP 2010 mass spectrometer equipped with a direct inlet probe. IR spectra were recorded on an IR Affinity-1S spectrophotometer (SHIMADZU) in the frequency range of 4000-400 cm^{-1} using KBr disc. Elemental analyses were performed using a Perkin Elmer 2400 Elemental Analyzer. TLC was carried out using E. Merck 0.25mm silica gel plates, and spots were visualized under UV light (λ 254–366 nm).

General procedure for the preparation of substituted-2-(1- phenylethylidene) hydrazine, 1a-i

A mixture of phenylhy-drazine (2.0 g, 18.59 mmol) and appropriate acetophenones (18.59 mmol) in ethanol (20 mL) containing 0.05 mL of glacial acetic acid was refluxed for 1 h. The solid that separated out on cooling was filtered and recrystallized from ethanol to afford product with 94-96% yield without the need for any purification as off white solid.

General procedure for the preparation of 1-phenyl-3-substituted-1*H*-pyrazole-4-carbaldehyde, 2a-i

For the Vilsmeier–Haack reaction, the reagent prepared from DMF (10 mL) and $POCl_3$ (1.3 mL, 14.26 mmol), intermediates 1 (11.89 mmol) was added and the reaction mixture stirred at RT for 8 h. After the completion of reaction, it was poured into ice-cold water. The solid that separated on neutralization with $NaHCO_3$ was filtered, washed with water, and recrystallized from ethanol to give the desired product.

General procedure for the preparation of (E)-2-((substituted-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide, 3a-i

To a round bottom flask Pyrazole aldehyde (8.06 mmol) and hydrazine-carbothioamide (8.06 mmol) were added sequentially in 20 mL ethanol. Then resulting reaction mixture was heated at 80°C temperature for 3 h. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into ice-cold water. The obtained solid was dried over a vacuum and washed with hexane.

General procedure for the preparation of substituted (E)-2-((Z)-2-(((E)-(Substituted-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4a-r

To a stirred solution of (E)-2-((Substituted-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide (1.56 mmol) in MeOH (10 mL) was added DMAD (1.56 mmol) or DEAD (1.56 mmol). The resulting mixture was refluxed for 2-3 h. The reaction was monitored by TLC. After the completion of the reaction, the reaction mixture was poured into ice cold water. The obtained yellow-coloured solid was recrystallization from ethanol.

Ethyl (E)-2-((Z)-2-(((E)-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4a: The general experimental procedure described above afforded **4a**, and the product obtained from (E)-2-((3-(4-methoxy-phenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DEAD. Yield 83%. Yellow solid. m.p.187-188°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.16 bs (1H, -NH), 9.02 s (1H, Pyrazole - H), 8.53 s (1H, -CH=N), 7.93 dd (6H, H_{arom}, J = 8 Hz, 2.4 Hz), 7.14 d (3H, J = 7.5 Hz), 6.64 s (1H, vinyl-CH), 4.25 q (2H, J = 7 Hz, -CH_2), 3.87 s (3H, -OCH_3), 1.26 t (3H, J = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 169.9, 166.6, 162.7, 151.8, 145.9, 140.2, 138.7, 138.4, 131.0, 130.1, 129.8, 124.0, 123.9, 118.7, 116.0, 115.7, 113.8, 61.11, 54.1, 13.3; IR (KBr): 3441.1, 2962.7, 2785.3, 1728.2, 1689.7, 1643.4, 1612.5, 1527.6, 1458.2, 1365.6, 1319.3, 1249.9, 1188.1, 1111.0, 1026.1, 956.7, 856.4, 833.2, 763.8, 740.6, 694.4, 609.5, 555.5, 470.6, 439.7 cm^{-1}; MS: *m/z* 476 [M+1]. Anal. Found: C 60.64; H 4.41; N 14.76. $C_{24}H_{21}N_5O_4S$. Calcd: C 60.62; H 4.45; N, 14.73%.

Methyl (E)-2-((Z)-2-(((E)-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4b: The general experimental procedure described above afforded **4b**, and the product obtained from (E)-2-((3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide and DMAD. Yield 87%. Yellow solid. m.p.175-177°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.17 bs (1H, -NH), 9.02 s (1H, Pyrazole - H), 8.54 s (1H, -CH=N), 7.93 dd (6H, H_{arom}, J = 7.5 Hz, 2.5 Hz), 7.14 d (3H, H_{arom}, J = 7.5 Hz), 6.67 s (1H, vinyl-CH), 3.81 s (6H, -OCH_3 & -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 168.1, 165.3,

162.8, 152.37, 145.9, 140.9, 138.4, 132.3, 130.4, 129.7, 124.7, 123.9, 118.8, 116.5, 114.3, 111.2, 56.0, 54.3; IR (KBr): 3433.4, 3132.5, 3063.0, 1720.5, 1635.6, 1527.6, 1450.5, 1327.0, 1249.9, 1203.6, 1018.4, 956.7, 825.5, 756.1, 686.6, 563.2, 509.2, 447.50 cm^{-1}; MS: *m/z* 460.9 [M+]. Anal. Found: C 59.89; H 4.13; N 15.20. $C_{23}H_{19}N_5O_4S$. Calcd: C 59.86; H 4.15; N 15.18.

Ethyl (E)-2-((Z)-2-(((E)-(3-(3-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4c: The general experimental procedure described above afforded 4c, and the product obtained from (E)-2-((3-(3-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DEAD. Yield 77%. Yellow solid. m.p.198-200°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.36 bs (1H, -NH), 9.06 s (1H, Pyrazole - H), 8.53 s (1H, -CH=N), 7.99 – 7.87 m (5H), H_{arom}) 7.80 – 7.60 m (4H, H_{arom}), 6.63 s (1H, vinyl-CH), 4.26 q (2H, *J* = 7 Hz, -CH_2), 1.26 t (3H, *J* = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 169.9, 166.5, 162.1, 152.3, 145.9, 141.6, 139.9, 138.5, 132.1, 130.2, 128.3, 124.0, 123.7, 119.9, 119.6, 115.8, 114.4, 112.8, 61.1, 14.7; IR (KBr): 3417.9, 3132.5, 3063.0, 2978.1, 1728.2, 1689.7, 1643.4, 1604.8, 1512.2, 1411.9, 1342.5, 1242.2, 1195.9, 1111.0, 1072.4, 1026.1, 956.7, 864.1, 756.1, 717.5, 686.6, 555.5, 516.9 cm^{-1}; MS: *m/z* 524.8 [M+1]. Anal. Found: C 52.61; H 3.49; N 15.21. $C_{23}H_{18}BrN_5O_3S$. Calcd: C 52.68; H 3.46; N 15.24.

Methyl (E)-2-((Z)-2-(((E)-(3-(3-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4d: The general experimental procedure described above afforded 4d, and the product obtained from (E)-2-((3-(3-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DMAD. Yield 78%. Yellow solid. m.p.183-186°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.33 bs (1H,-NH), 9.06 s (1H, Pyrazole - H), 8.54 s (1H, -CH=N), 7.99 – 7.95 m (5H, H_{arom}), 7.86 – 7.66 m (4H, H_{arom}), 6.66 s (1H, vinyl-CH), 3.84 s (3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 168.9, 165.3, 162.1, 153.6, 145.8, 141.5, 139.7, 137.6, 133.3, 130.2, 128.3, 124.2, 123.7, 119.6, 115.0, 113.3, 112.9, 56.7; IR (KBr): 3140.2, 3063.0, 2793.0, 1720.5, 1643.4, 1597.1, 1512.2, 1435.0, 1342.5, 1242.2, 1203.6, 1111.0, 1072.4, 1010.7, 964.4, 902.7, 856.4, 756.1, 717.5, 686.6, 555.5, 516.9 cm^{-1}; MS: *m/z* 510.7 [M+1]. Anal. Found: C 52.69; H 3.48; N 13.39. $C_{22}H_{16}BrN_5O_3S$. Calcd: C 52.68; H 3.46; N 13.36%.

Ethyl (E)-2-((Z)-2-(((E)-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4e: The general experimental procedure described above afforded 4e, and the product obtained from (E)-2-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DEAD. Yield 84%. Yellow solid. m.p.163-164°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.36 bs (1H, -NH), 9.03 s (1H, Pyrazole - H), 8.55 s (1H, -CH=N), 7.97 – 7.94 m (9H, H_{arom}), 6.65 s (1H, vinyl-CH), 4.28 q (2H, *J* = 7 Hz, -CH_2), 1.24 t (3H, *J* = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 169.1, 165.0, 163.3, 150.5, 144.9, 139.0, 138.7, 131.5, 129.6, 128.1, 127.2, 124.7, 123.7, 119.9, 119.3, 115.0, 114.6, 113.7, 113.4, 61.9, 13.9; IR (KBr): 2970.48, 2769.87, 1728.28, 1697.41, 1643.41, 1527.67, 1442.80, 1365.65, 1319.35, 1249.91, 1195.91, 1118.75, 1033.88, 956.72, 856.42, 825.56, 748.41, 686.68, 601.81, 555.52, 501.51, 470.65 cm^{-1}; MS: *m/z* 490.1 [M+]. Anal. Found: C 56.35; H 3.71; N 17.16. $C_{23}H_{18}N_6O_5S$. Calcd: C 56.32; H 3.70; N 17.13%.

Methyl (E)-2-((Z)-2-(((E)-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4f: The general experimental procedure described above afforded 4f, and the product obtained from (E)-2-((3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide and DMAD. Yield 82%. Yellow solid. m.p.152-153°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.58 bs (1H, -NH), 9.04 s (1H, Pyrazole - H), 8.57 s (1H, -CH=N), 8.13 – 7.66 m (9H, H_{arom}), 6.64 s (1H, vinyl-CH), 3.81 s (3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 168.5, 165.9, 162.0, 150.5, 145.9, 139.0, 138.7, 130.4, 129.8, 128.2, 127.7, 124.7, 123.3, 119.9, 119.0, 115.3, 114.8, 113.8, 113.3, 56.9; IR (KBr): 3063.06, 2924.18, 2854.74, 2769.87, 1705.13, 1651.12, 1597.11, 1527.67, 1504.5, 1442.8, 1203.6, 1111.0, 1018.4, 956.7, 856.4, 817.8, 756.1, 686.6, 493.7 cm^{-1}; MS: *m/z* 476.8 [M+1]. Anal. Found: C 55.49; H 3.42; N 17.60. $C_{22}H_{16}N_6O_5S$. Calcd: C 55.46; H 3.38; N17.64%.

Ethyl (E)-2-((Z)-2-(((E)-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4g: The general experimental procedure described above afforded 4g, and the product obtained from (E)-2-((3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DEAD. Yield 81%. Yellow solid. m.p.201-202°C. ^{1}H NMR (500 MHz,

DMSO-d_6): δ 11.24 bs (1H, -NH), 9.04 s (1H, Pyrazole-H), 8.55 s (1H, -CH=N), 7.39 – 7.75 m (9H, H_{arom}), 6.63 s (1H, vinyl-CH), 4.21 q (2H, J = 7 Hz, -CH_2), 1.21 t (3H, J = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 168.1, 165.5, 162.8, 151.7, 145.9, 140.7, 139.9, 138.0, 130.8, 129.7, 127.1, 125.0, 123.8, 119.5, 116.7, 115.8, 114.6, 61.1, 54.2, 13.7; IR (KBr): 3063.06, 2970.48, 2762.16, 1728.28, 1450.52, 1404.22, 1365.65, 1327.07, 1249.91, 1195.91, 1095.60, 1026.16, 964.44, 856.42, 825.56, 756.12, 725.26, 686.68, 601.81, 555.52, 516.94, 470.65 cm^{-1}; MS: *m/z* 480.8 [M+1]. Anal. Found: C 57.57; H 3.75; N 14.62. $C_{23}H_{18}ClN_5O_3S$. Calcd: C 57.56; H 3.78; N 14.59%.

Methyl (E)-2-((Z)-2-(((E)-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4h: The general experimental procedure described above afforded **4h**, and the product obtained from (E)-2-((3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DMAD. Yield 85%. Yellow solid. m.p.194-196°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.23 s (1H, -NH), 9.03 s (1H, Pyrazole – H), 8.55 s (1H, -CH=N), 7.78 – 7.75 m (9H, H_{arom}), 6.64 s (1H, vinyl-CH), 3.08 s (3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 167.5, 165.2, 162.9, 150.6, 145.2, 140.7, 138.4, 137.7, 130.5, 129.4, 127.2, 125.1, 122.9, 1118.0, 115.5, 114.5, 56.7; IR (KBr): 3433.41, 3063.06, 2955.04, 2769.87, 1712.85, 1651.12, 1597.11, 1504.53, 1442.80, 1327.07, 1249.91, 1203.62, 1095.60, 1057.03, 1018.45, 956.72, 902.72, 848.71, 825.56, 756.12, 732.97, 686.6, 555.52, 516.94, 439.78 cm^{-1}; MS: *m/z* 466.9 [M+1]. Anal. Found: C 56.69; H 3.47; N 15.05. $C_{22}H_{16}ClN_5O_3S$. Calcd: C 56.72; H 3.46; N 15.03.

Ethyl (E)-2-((Z)-2-((E-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4i: The general experimental procedure described above afforded 4i, and the product obtained from (E)-2-((3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide and DEAD. Yield 79%. Yellow solid. m.p.186-188°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.34 bs (1H, -NH), 9.05 s (1H, Pyrazole - H), 8.52 s (1H, -CH=N), 7.89 – 7.53 m (9H, H_{arom}), 6.62 s (1H, vinyl-CH), 4.25 q (2H, J = 7 Hz, -CH_2), 1.27 t (3H, J = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C, ppm: 168.1, 165.5, 162.8, 151.3, 145.9, 140.5, 139.4, 138.0, 130.5, 129.5, 127.7, 125.4, 123.8, 118.2, 116.0, 115.6, 114.8, 61.9, 54.2, 13.3; IR (KBr): 3063.06, 2962.76, 2777.59, 1728.28, 1651.12, 1597.11, 1504.53, 1450.52, 1365.65, 1327.07, 1249.91, 1195.91, 1103.32, 1033.88, 964.44, 856.42, 756.12, 686.68, 555.52, 509.22, 470.65 cm^{-1}; MS: *m/z* 525.4 [M+1]. Anal. Found: C 52.71; H 3.42; N 13.38. $C_{23}H_{18}BrN_5O_3S$. Calcd: C 52.68; H 3.46; N 13.36%.

Methyl (E)-2-((Z)-2-(((E)-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4j: The general experimental procedure described above afforded 4j, and the product obtained from (E)-2-((3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DMAD. Yield 74%. Yellow solid. m.p.183-185°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.35 bs (1H, -NH), 9.06 s (1H, Pyrazole - H), 8.53 s (1H, -CH=N), 7.96 – 7.51 m (9H, H_{arom}), 6.63 s (1H, vinyl-CH), 3.83 s (3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C, ppm: 167.6, 165.5, 162.9, 151.3, 145.9, 140.3, 139.4, 137.0, 130.6, 129.8, 126.5, 124.7, 122.4, 119.6, 116.0, 115.9, 114.8, 56.3; IR (KBr): 3063.0, 2955.0, 2762.1, 1705.1, 1651.1, 1527.6, 1504.5, 1442.8, 1327.0, 1242.2, 1203.6, 1072.4, 1010.7, 956.7, 825.5, 756.1, 686.6, 555.5, 501.5 cm^{-1}; MS: *m/z* 511.3 [M+1]. Anal. Found: C 51.82; H 3.13; N 13.71. $C_{22}H_{16}BrN_5O_3S$. Calcd: C 51.78; H 3.16; N13.72%.

Ethyl (E)-2-((Z)-2-(((E)-(3-(3,4-dichlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4k: The general experimental procedure described above afforded 4k, and the product obtained from (E)-2-((3-(3,4-dichlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl) methylene)hydrazine-1-carbothioamide and DEAD. Yield 86%. Yellow solid. m.p.158-160°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.34 bs (1H, -NH), 9.05 s (1H, Pyrazole - H), 8.56 s (1H, -CH=N), 8.32 d (1H, H_{arom}, J = 2.5 Hz), 8.30 d (1H, H_{arom}, J = 8.8 Hz), 8.09 – 7.64 m (6H, H_{arom}), 6.65 s (1H, vinyl-CH), 4.24 q (2H, H_{arom}, J = 7 Hz, -CH_2), 1.28 t (3H, J = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δ_C, ppm: 168.8, 166.6, 162.8, 150.3, 145.6, 140.8, 139.6, 137.6, 130.2, 128.8, 123.4, 116.6, 118.9, 115.7, 114.3, 113.7, 61.0, 54.2, 13.5; IR (KBr): 3063.0, 2955.0, 2769.8, 1712.8, 1651.1, 1527.6, 1496.8, 1442.8, 1327.0, 1249.9, 1203.6, 1041.6, 964.4, 879.5, 810.1, 748.4, 678.9, 555.5, 493.7, 408.9 cm^{-1}; MS: *m/z* 515.4 [M+1]. Anal. Found: C 53.73; H 3.37; N 13.59. $C_{23}H_{17}Cl_2N_5O_3S$. Calcd: C 53.71; H 3.33; N 13.62%.

Methyl (E)-2-((Z)-2-(((E)-(3-(3,4-dichlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4l: The general experimental procedure described above afforded 4l, and the product obtained from (E)-2-((3-(3,4-dichlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl) methylene)hydrazine-1-carbothioamide and DMAD. Yield 84%. Yellow solid. m.p.141-142°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.54 bs (1H, -NH), 9.05 s (1H, Pyrazole - H), 8.55 s (1H, -CH=N), 8.31 d (1H, H_{arom}, J = 2.5 Hz), 8.29 d (1H, $H_{arom,}$ J = 8.0 Hz), 8.09 – 7.64 m (6H, H_{arom}), 6.66 s (1H, vinyl-CH), 3.89 s (3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 167.7, 165.5, 162.8, 150.0, 145.9, 141.9, 139.9, 137.5, 130.4, 129.7, 123.1, 117.7, 119.9, 115.2, 114.5, 113.6, 56.5; IR (KBr): 3070.78, 2978.19, 2762.16, 1728.28, 1651.12, 1527.67, 1435.09, 1396.5, 1365.65, 1327.0, 1249.9, 1203.6, 1026.1, 964.4, 864.1, 817.8, 748.4, 686.6, 555.5, 501.5, 439.7 cm^{-1}; MS: *m/z* 500 [M+1]. Anal. Found: C 52.84; H 3.06; N 14.02. $C_{22}H_{15}Cl_2N_5O_3S$. Calcd: C 52.81; H 3.02; N 14.00%.

Ethyl (E)-2-((Z)-2-(((E)-(3-(3,4-dimethoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4m: The general experimental procedure described above afforded 4m, and the product obtained from (E)-2-((3-(3,4-dimethoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl) methylene)hydrazine-1-carbothioamide and DEAD. Yield 77%. Yellow solid. m.p.149-151°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.12 bs (1H, -NH), 9.02 s (1H, Pyrazole - H), 8.51 s (1H, -CH=N), 7.89 – 7.76 m (4H, H_{arom}), 7.74 d (2H, H_{arom}, J = 2.5 Hz), 7.72 d (2H, H_{arom}, J = 8 Hz), 6.58 s (1H, vinyl-CH), 4.18 q (2H, J = 7 Hz, -CH_2), 3.84 s (3H, -CH_3), 1.22 t (3H, J = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 167.7, 165.1, 162.3, 151.3, 145.4, 139.7, 139.5, 137.2, 130.2, 129.8, 127.5, 125.4, 120.3, 119.0, 115.1, 114.5, 54.3, 56.7; IR (KBr): 3433.4, 2962.7, 2777.5, 1728.2, 1643.4, 1527.6, 1465.9, 1365.6, 1319.3, 1242.2, 1195.9, 1026.1, 956.7, 864.1, 833.2, 756.1, 686.6, 624.9, 555.5, 509.2, 416.6 cm^{-1}; MS: *m/z* 506.6 [M+1]. Anal. Found: C 59.43; H 4.54; N 13.86. $C_{25}H_{23}N_5O_5S$. Calcd: C 59.40; H 4.59; N 13.85%.

Methyl (E)-2-((Z)-2-(((E)-(3-(3,4-dimethoxy phenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4n: The general experimental procedure described above afforded 4n, and the product obtained from (E)-2-((3-(3,4-dimethoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide and DMAD. Yield 75%. Yellow solid. m.p.167-168°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.14 bs (1H, -NH), 9.01 s (1H, Pyrazole - H), 8.49 s (1H, -CH=N), 7.88 – 7.76 m (4H, H_{arom}), 7.75 d (2H, H_{arom} , J = 2.5 Hz), 7.74 d (2H, H_{arom}, J = 8 Hz), 6.60 s (1H, vinyl-CH), 3.86 s (3H, H_{arom} , -CH_3), 3.84 s (3H, -OCH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 167.7, 165.1, 162.3, 151.3, 145.4, 139.7, 139.5, 137.2, 130.2, 129.8, 127.5, 125.4, 120.3, 119.0, 115.1, 114.5, 56.7, 54.3; IR (KBr): 3417.98, 3070.78, 2955.04, 2769.87, 1705.13, 1643.41, 1604.83, 1527.67, 1465.95, 1435.09, 1327.07, 1249.91, 1203.62, 1026.16, 956.72, 864.14, 833.28, 756.12, 686.68, 555.52, 393.49 cm^{-1}; MS: *m/z* 492.3 [M+1]. Anal. Found: C 58.66; H 4.29; N 14.21. $C_{24}H_{21}N_5O_5S$. Calcd: C 58.65; H 4.31; N 14.25%.

Ethyl (E)-2-((Z)-2-(((E)-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4o: The general experimental procedure described above afforded 4o, and the product obtained from (E)-2-((3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DEAD. Yield 87%. Yellow solid. m.p.188-190°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.22 s (1H, -NH), 9.02 s (1H, Pyrazole - H), 8.54 s (1H, -CH=N), 7.77 – 7.74 m (9H, H_{arom}), 6.63 s (1H, vinyl-CH), 4.20 q (2H, J = 7 Hz, -CH_2), 1.20 t (3H, J = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 169.9, 165.3, 162.2, 152.5, 145.2, 140.7, 139.5, 138.5, 130.8, 129.5, 127.7, 125.9, 123.8, 118.2, 116.9, 115.6, 114.8, 61.3, 54.2, 13.4; IR (KBr): 3063.0, 2978.1, 2777.5, 1720.5, 1612.5, 1527.6, 1450.5, 1365.6, 1319.3, 1188.1, 1103.3, 1033.8, 956.7, 840.9, 756.1, 694.4, 601.8, 555.5, 509.2, 470.6 cm^{-1}; MS: *m/z* 464.1 [M+1]. Anal. Found: C 59.63; H 3.87; N 15.17. $C_{23}H_{18}FN_5O_3S$. Calcd: C 59.60; H 3.91; N, 15.11%.

Methyl (E)-2-((Z)-2-(((E)-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate, 4p: The general experimental procedure described above afforded 4p, and the product obtained from (E)-2-((3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide and DMAD. Yield 88%. Yellow solid. m.p.193-195°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.21 s (1H, -NH), 9.03 s (1H, Pyrazole - H), 8.56 s (1H, -CH=N), 7.78 – 7.75 m (9H, H_{arom}), 6.62 s (1H, vinyl-CH), 3.80 s (3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 168.0, 165.1, 162.3, 151.3, 145.7, 140.3, 139.6, 138.4, 130.7, 129.4, 127.7, 125.9,

123.8, 117.5, 116.6, 115.5, 113.3, 56.0; IR (KBr): 3356.25, 3147.93, 2955.04, 2777.59, 1944.31, 1712.85, 1651.12, 1604.83, 1527.67, 1450.52, 1334.78, 1211.34, 1057.03, 964.44, 840.99, 748.41, 686.68, 555.52, 509.22, 408.92 cm^{-1}; MS: *m/z* 450.3 [M+1]. Anal. Found: C 58.81; H 3.55; N 15.61. $C_{22}H_{16}FN_5O_3S$. Calcd: C 58.79; H 3.59; N 15.58%.

Ethyl (E)-2-((Z)-4-oxo-2-(((E)-(1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)methylene)hydrazono) thiazolidin-5-ylidene)acetate, 4q: The general experimental procedure described above afforded 4q, and the product obtained from (E)-2-((1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide and DEAD. Yield 81%. Yellow solid. m.p.178-179°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.21 s (1H, -NH), 9.02 s (1H, Pyrazole - H), 8.54 s (1H, -CH=N), 7.76 – 7.73 m (9H, H_{arom}), 6.62 s (1H, vinyl-CH), 4.19 q (2H, *J* = 7 Hz, -CH_2), 1.19 t (3H, *J* = 7 Hz, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 168.1, 165.4, 162.3, 153.3, 145.9, 140.7, 139.9, 138.7, 131.3, 130.5, 128.5, 125.2, 123.8, 118.7, 116.6, 115.5, 114.0, 61.7, 54.5, 13.4, 18.5; IR (KBr): 3063.0, 2962.7, 2754.4, 1728.2, 1643.4, 1604.8, 1527.6, 1442.8, 1411.9, 1365.6, 1327.0, 1249.9, 1203.6, 1033.8, 964.4, 864.1, 756.1, 717.5, 555.5, 470.6 cm^{-1}; MS: *m/z* 460.1 [M+1]. Anal. Found: C 62.78; H 4.63; N 15.21. $C_{24}H_{21}N_5O_3S$. Calcd: C 62.73; H 4.61; N, 15.24%.

Methyl (E)-2-((Z)-4-oxo-2-(((E)-(1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)methylene)hydrazono) thiazolidin-5-ylidene)acetate, 4r: The general experimental procedure described above afforded 4r, and the product obtained from (E)-2-((1-phenyl-3-(p-tolyl)-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide and DMAD. Yield 86%. Yellow solid. m.p.210-211°C. ^{1}H NMR (500 MHz, DMSO-d_6): δ 11.23 s (1H, -NH), 9.02 s (1H, Pyrazole - H), 8.54 s (1H, -CH=N), 7.77 – 7.74 m (9H, H_{arom}), 6.63 s (1H, vinyl-CH), 3.81 s (3H, -CH_3); ^{13}C NMR (100 MHz, DMSO-d_6): δC 167.7, 165.8, 162.3, 153.3, 145.8, 140.8, 139.6, 138.4, 131.7, 130.6, 128.5, 125.2, 123.8, 118.6, 116.4, 115.5, 114.0, 56.6, 18.5; IR (KBr): 3425.6, 3063.0, 2924.1, 2854.7, 2754.4, 1728.2, 1643.4, 1604.8, 1535.3, 1442.8, 1327.0, 1249.9, 1203.6, 1049.3, 964.4, 856.4, 756.1, 686.6, 555.5, 393.4 cm^{-1}; MS: *m/z* 446.5 [M+1]. Anal. Found: C 2.03; H 4.33; N 15.75. $C_{23}H_{19}N_5O_3S$. Calcd: C 62.01; H 4.30; N 15.72%.

In vitro antimicrobial activity

The varied pyrazole nucleus containing 4-oxothiazolidine acetate derivatives were tested for their antibacterial activity against Gram-positive and Gram-negative bacterial strains, including *Staphylococcus aureus*, *Bacillus megaterium*, *Enterobacter aerogenes*, and *Pseudomonas aeruginosa*, using the serial broth dilution method at a concentration range of 1000, 500, 250, 125, and 62.5 µg/mL, and were also screened for antifungal activity against two fungal strains, *Aspergillus flavus*, and *Aspergillus niger*, using same method at a concentration range of 1000, 500, 250, 125, and 62.5 µg/mL. The antibiotics used in this study included streptomycin, which is effective against Gram-negative bacteria, ampicillin, which targets Gram-positive bacteria, and nystatin, which exhibits antifungal activity. Antimicrobial activity was evaluated using the serial broth dilution method[23]. Nutrient agar was used as the culture medium. The pure test microbial strains were cultivated in Muller-Hinton broth for 24 hours, with bacterial strains incubated at 37°C and fungal strains at 28°C. Standard antibiotics, including ampicillin, streptomycin, and nystatin, were thawed, weighed, and diluted in DMSO to determine their minimum inhibitory concentration (MIC) against the test strains. Drug stock solutions were also prepared using DMSO as a solvent. To begin the dilution process, 2 mL of Muller-Hinton broth was dispensed into the first tube, while 1 mL was added to all subsequent tubes. The plates and lids were labelled accordingly. The drug was introduced into the first tube to achieve a final concentration of 1000 µg/mL, followed by thorough mixing. 1 mL of this solution was then transferred to the second tube, reducing the concentration to 500 µg/mL. The solution was mixed by pipetting up and down 6–8 times, and 1 mL was further transferred to the third tube containing broth. This serial dilution continued until the concentration reached 62.5 µg/mL, after which 1 mL was discarded from the last tube. Mid-log phase microbial cultures were diluted to match the McFarland 0.5 standard, corresponding to a bacterial cell density of 4×10^5 to 5×10^5 CFU/mL, while fungal cultures were adjusted to 1–5 × 10^5 CFU/mL. 5 µL of each microbial suspension was inoculated from tube 1 to tube 5. The tubes were incubated for 24–48 hours at the optimal temperatures for bacterial and fungal growth. For controls, the positive control contained only the drug solution in broth, while the negative control contained only the

inoculated microorganisms without the drug. Once adequate microbial growth was observed, absorbance measurements were recorded at 600 nm. Antimicrobial activity of each compound **4a-4r** was compared with standard reference and results have been summarized as MIC (average zone of inhibition of two reading in millimeter) in Table 1 and Graphical representation of MIC values comparison of synthesized Pyrazole Nucleus Containing 4-oxothiazolidine acetate derivatives for said bacterial and fungal strain in Fig. 1.

Result and Discussion

The synthetic pathways employed for the synthesis of the tested compounds are presented in Scheme 1. The synthesis reaction was carried out in four steps. In the first step, substituted 2-(1-phenylethylidene) hydrazine **1a- 1i** were synthesized by refluxing phenylhydrazine and acetophenones in ethanol with glacial acetic acid for 1 hour, followed by filtration and recrystallization to obtain the product in 94–96% yield. In the second step, 1-phenyl-3-substituted-1H-pyrazole-4-carbaldehyde **2a-2i** were synthesized in high yield from substituted 2-(1-phenylethylidene)hydrazine *via* the Vilsmeier–Haack reaction using $POCl_3$–DMF[22]. The obtained solid was filtered, washed, and recrystallized from ethanol. Subsequently, eight different substituted pyrazole aldehydes (2a-e) were refluxed with hydrazinecarbothioamide in ethanol for 3 hours, yielding (E)-2-((substituted-1H-pyrazol-4-yl)methylene) hydrazine-1-carbothioamide **3a-3i**. Finally, the target compounds, substituted (E)-2-((Z)-2-(((E)-(substituted-1H-pyrazol-4-yl)methylene)hydrazono)-4-oxothiazolidin-5-ylidene)acetate **4a-4r**, were obtained by refluxing (E)-2-((substituted-1H-pyrazol-4-yl) methylene)hydrazine-1-carbothioamide **3a-3i** with DMAD and DEAD in methanol for 3 hours. The obtained yellow solid was recrystallized from ethanol.

The ^{1}H NMR spectrum confirms that the number of protons and their chemical shifts align with the proposed structures **4a-4i**. The spectrum of the synthesized compounds in DMSO-d_6 exhibited a singlet signal in the range of δ 11.36–11.17 ppm, corresponding to the -NH protons of the thiazolidine ring. Another singlet signal, observed in the region of δ 9.06–9.02 ppm, is characteristic of the pyrazole ring. Additionally, the presence of azomethine (CH=N) was detected at δ 8.54–8.53 ppm, while the vinyl-CH appeared in the range of δ 6.67–6.62 ppm. The methoxy group showed a signal at δ 3.84 ppm, whereas the ethoxy group displayed a triplet pattern

Table 1 — Antimicrobial activity of synthesized compounds **4a-r**

Compd	Minimum inhibition concentration (MIC) µg/mL					
	Antibacterial activity				Antifungal activity	
	Gram-positive bacteria		Gram-negative bacteria			
	S.aureus	*B. megaterium*	*E. aerogenes*	*P.aeruginosa*	*A. flavus*	*A. niger*
4a	62.5	62.5	62.5	62.5	62.5	62.5
4b	125	125	500	500	1000	1000
4c	1000	1000	1000	1000	250	250
4d	1000	1000	1000	1000	62.5	62.5
4e	62.5	62.5	125	125	1000	1000
4f	250	250	250	250	250	250
4g	1000	1000	250	250	250	250
4h	1000	1000	1000	1000	1000	1000
4i	1000	1000	1000	1000	1000	1000
4j	1000	1000	1000	1000	1000	1000
4k	62.5	62.5	250	250	1000	1000
4l	100	100	1000	1000	1000	1000
4m	250	250	62.5	62.5	1000	1000
4n	1000	1000	250	250	250	250
4o	1000	1000	1000	1000	1000	1000
4p	125	125	125	125	62.5	62.5
4q	250	250	62.5	62.5	1000	1000
4r	62.5	62.5	250	250	125	125
Streptomycin	–	–	50	50	–	–
Ampicillin	100	100	–	–	–	–
Nystatin	–	–	–	–	100	100

MIC – Minimum inhibitory concentration

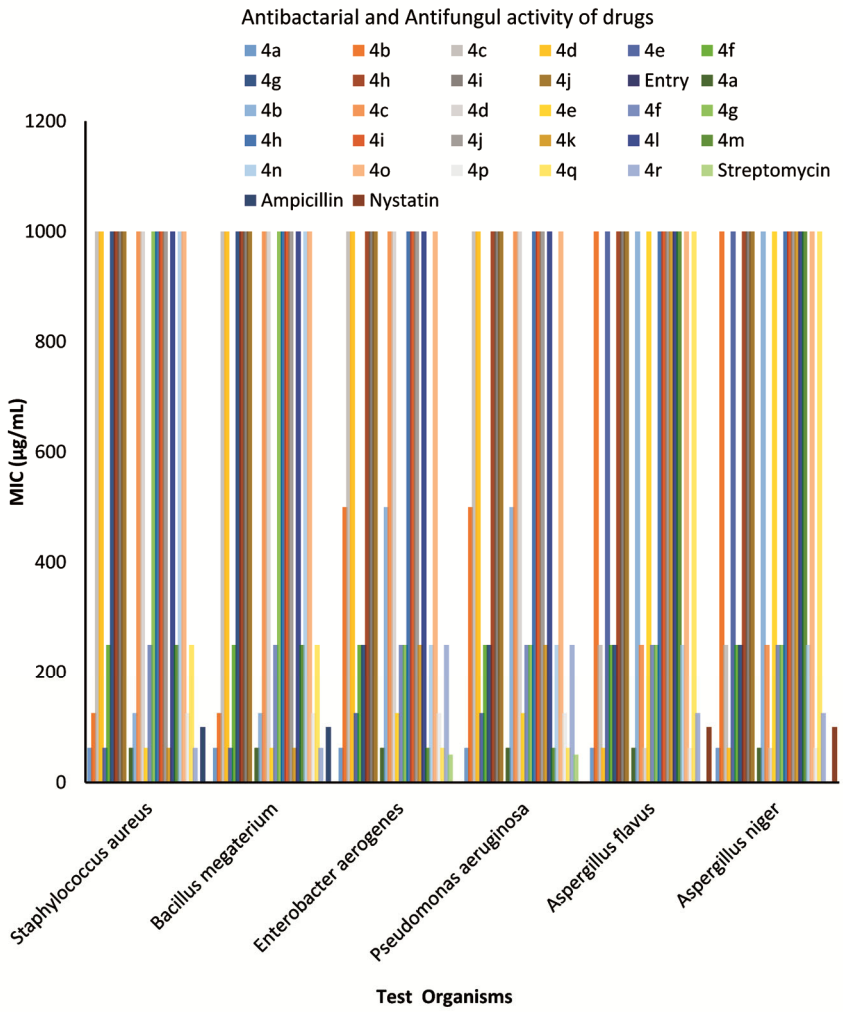
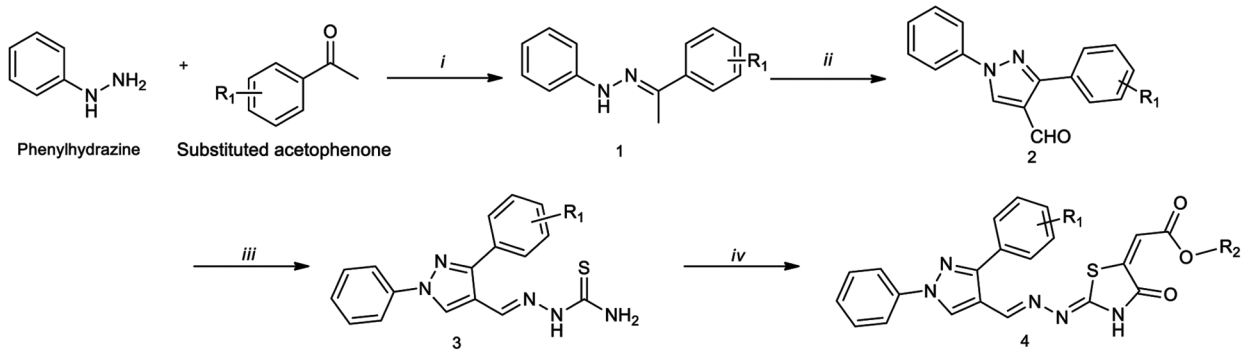


Fig. 1 — Graphical representation of MIC values: Comparison of synthesized pyrazole nucleus containing 4-oxothiazolidine acetate derivatives for said bacterial and fungal strain

for three protons at δ 1.28–1.22 ppm and a quartet pattern for two protons at δ 4.28–4.23 ppm. The aromatic protons appeared as a multiplet in the range of δ 7.97–7.02 ppm.

The ^{13}C NMR (100 MHz, DMSO-d_6) spectrum confirms that the number of carbons and their chemical shifts correspond to the proposed structure. A signal at δ 61.11 ppm and δ 13.39 ppm was observed, which can be assigned to the –OCH_2 and CH_3 groups of the ethyl ester, respectively. The methyl ester carbon appeared at δ 54.3 ppm, while the aromatic carbons resonated in the range of δ 108.7–160.5 ppm. The carbonyl groups were detected at δ 169.93 ppm (ester) and δ 166.64 ppm (thiazolidinone C=O). The vinylic –CH signal appeared at δ 115.74 ppm, whereas the imide CH=N carbon was observed at δ 138.40 ppm, and the imide N-C=H carbon at δ 130.18 ppm. The thiazolidinone carbons resonated at δ 145.94 ppm and δ 140.22 ppm, respectively.

Antimicrobial screening of newly synthesized compounds is summarized in Table 1. The compounds were diluted at concentrations of 1000, 500, 250, 125, and 62.5 µg/mL. The antibiotics used in the study were streptomycin, ampicillin, and nystatin. Streptomycin was effective against Gram-negative bacteria, while ampicillin targeted Gram-positive bacteria. Nystatin was used for its antifungal properties. The test cultures used for antimicrobial evaluation included both bacterial and fungal strains. The Gram-negative bacteria tested were *Enterobacter aerogenes* and *Pseudomonas aeruginosa*. The Gram-positive bacteria included *Staphylococcus aureus* and *Bacillus megaterium*. Additionally, the fungal strains used were *Aspergillus flavus* and *Aspergillus niger*. The



Reagents and Conditions: *i*: Acetic acid (2-3 drops), Ethanol (10 vol), 78° C, Reflux, 1h; *ii*: $POCl_3$ (1.2 equiv), DMF (10 ml), rt, 8h; *iii*: $NH_2NHCSNH_2$ (1.0 equiv), Ethanol (20 vol), Reflux, 3h; *iv*: DMAD or DEAD (1.0 equiv), Methanol (10 vol), Reflux, 2-3h.

Scheme 1 — Synthetic pathway for the synthesis of compounds **1-4**

antimicrobial screening revealed that all the newly synthesized compounds exhibited moderate activity against the four tested bacteria and two fungi. Among them, compounds **4a** and **4f** demonstrated the highest effectiveness against both Gram-positive and Gram-negative bacteria, as well as fungi. Additionally, compounds **4a**, **4b**, **4e**, **4f**, and **4g** displayed broad-spectrum activity, effectively inhibiting the growth of both Gram-positive and Gram-negative bacteria. In contrast, compounds **4c**, **4d**, and **4p** specifically exhibited antifungal properties, showing activity only against fungi.

Conclusion

In conclusion, a series of pyrazole nucleus-containing 4-oxothiazolidine acetate derivatives were synthesized through facile synthetic method with good yields. The structures of the newly synthesized compounds were confirmed through spectral analysis and elemental analysis. These compounds were evaluated for their antimicrobial activity using the serial broth dilution method. A comparison of the antimicrobial results of the synthesized compounds **4a-4r** with reference standard drugs has revealed the antimicrobial activities of pyrazole nucleus-containing 4-oxothiazolidine acetate derivatives. The antimicrobial screening suggests that all the newly synthesized compounds showed moderate activity against the tested four bacteria and two fungi. The remarkable biological activities and the ease of synthesis make these compounds promising candidates for the development of antimicrobial agents.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Supplementary Information

Supplementary information is available in the website https://nopr.niscpr.res.in/handle/123456789/58776.

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