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SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF ISOXAZOLYL AZETIDIN-2-ONES AND THIAZOLIDIN-4-ONES

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ABSTRACT

A series of novel isoxazolyl azetidin-2-ones, **4a-h** and thiazolidin-4-ones, **5a-h** were synthesized from (*E*)-3-(methylimino)-*N*-(5-methylisoxazol-3-yl)butanamides, **3a-h**. The four-membered *β*-lactam ring was built by adding choloroacetyl chloride to butanamides, **3a-h** in the presence of triethylamine to give **4a-h**. Cyclocondensation of mercapto acetic acid with, **3a-h** in presence of anhydrous $ZnCl_2$ resulted in the formation of thiazolidin-4-ones, **5a-h**. The newly synthesized compounds, **4a-h** and **5a-h** were confirmed using IR, ^{1}HNMR, ^{13}CNMR and mass spectral data and were evaluated for in *vitro* antibacterial activity. From the results, it is evident that the compounds **4d** and **5d** are showing exceptional antibacterial activity. Insilico ADME studies were performed and the results highlighted the designed compounds are safe to be considered as drug like molecules

Keywords: isoxazolyl thiazolidin-4-ones, isoxazolyl azetidin-2-ones, Schiff's bases, antibacterial activity.

INTRODUCTION

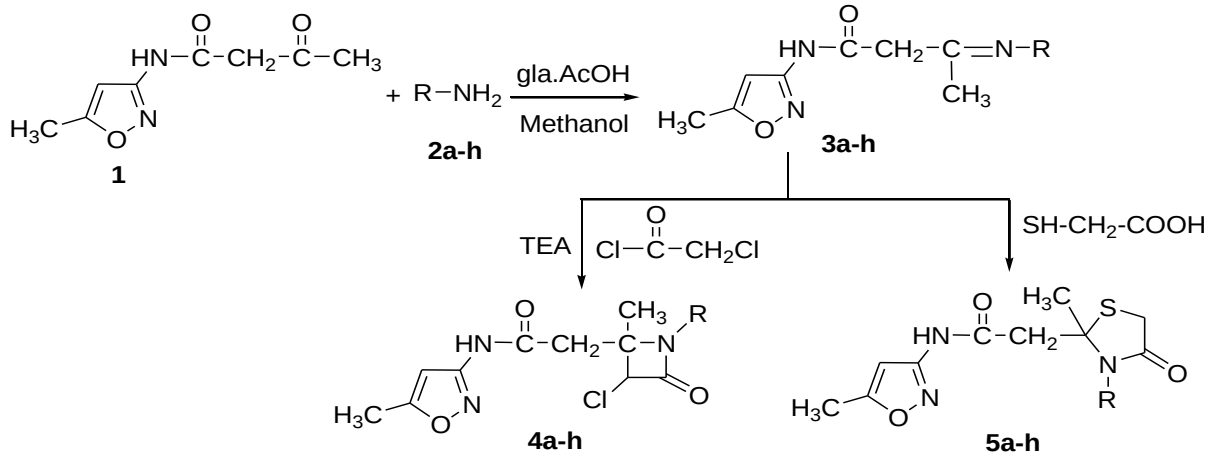
Medicinal chemists have paid much attention for the synthesis of heterocyclic compounds like isoxazoles, thiazolidinones and azetidin-2-ones, mainly due to their broad spectrum of biological activities. Amino isoxazole derivatives constitute an important class of heterocyclics that possesses anticancer[1], antibacterial[2], anticonvulsant[3], analgesic[4], and antifungal activity[5]. Thiazolidin-4-ones is a key pharmacophore in medicinal chemistry and is responsible for broad range of biological activities including antimicrobial[6,7], antioxidant[8], anti-inflammatory[9], analgesic[10], antitumor[11], anticonvulsant[12] and antitubercular[13], on the other hand, it is evident from the literature survey, that the 2-azetidinones are also associated with various pharmacological activities. 3-chloro monocyclic *β*-lactams derivatives having substitutions at 1 and 4 positions displayed antimicrobial[14-16], anti-inflammatory[17], antitubercular[18] and antitumor[19] activities. In view of the broad pharmacological activities of the isoxazoles, thiazolidin-4-ones and azetidin-2-ones, we envisioned the synthesis of hybrids of isoxazoles with thiazolidin-4-ones and azetidin-2-ones. Our quest in search of new biologically active molecules[20-22], herein we report the synthesis and anti bacterial activity of isoxazolyl azetidin-2-ones and thiazolidin-4-ones.

EXPERIMENTAL

Materials and Methods

Cintex melting point apparatus was used to record the melting points and are uncorrected. Merck precoated 60F 254 silica gel plates were used for TLC analysis and visualized under U.V. Light. IR Spectra (KBr Pellet) was recorded on a Perkin-Elmer BX series FT-IR Spectrometer. Proton and Carbon NMR spectra were recorded on a Brucker spectrometer (300 and 75 MHz, respectively) in the dueterated

chloroform solvent with TMS as an internal reference. ESI mass spectra were recorded on an Agilent LC-MSD mass spectrometer. Elemental analyses were performed on a Carlo Erba 106 and Perkin-Elmer model 240 analyzers. All the chemicals were procured from Sigma-Aldrich and are used as such without further purification.



1 **2a-h** **3a-h** **4a-h** **5a-h**

2a: R = -CH_3; **2b:** R = -CH_2-CH_3; **2c:** R = -C_6H_5; **2d:** R = 4-ClC_6H_4-; **2e:** R = 4-$OCH_3C_6H_4$-; **2f:** R = $C_6H_5CH_2$-; **2g:** R = 4-$ClC_6H_4CH_2$-; **2h:** R = 4-$OCH_3C_6H_4CH_2$-

Scheme-1: Synthesis of Isoxazolyl Azetidin-2-Ones and Thiazolidin-4-Ones

General Procedure

Synthesis of 2-(3-chloro-1,2-dimethyl-4-oxoazetidin-2-yl)-N-(5-methylisoxazol-3-yl)acetamides(4a-h)

To a well-stirred solution of compound **(**3, 0.01 mmol) and triethyl amine (0.02 mmol) in dry toluene (10 mL) was added drop wise chloroacetyl chloride (0.02 mmol) at room temperature. The reaction mixture was heated to reflux for 4 h and the separated solid was removed by filtration. The filtrate was concentrated under vacuum, and the residue was subjected to purification by column chromatography eluting with *n*-hexane and ethyl acetate (9:1).

Synthesis of 2-(2,3-dimethyl-4-oxothiazolidin-2-yl)-N-(5-methylisoxazol-3-yl)acetamide (5a-h)

A mixture of compound **3** (0.01 mmol) and mercaptoacetic acid (0.01 mmol) was dissolved in 1,4-dioxane (15 mL) and added 200 mg of anhydrous Zinc Chloride. The resulting solution was heated to reflux for 10-12 h and then cooled to room temperature. The reaction mixture was poured over crushed ice and the residue was extracted with ethyl acetate. The combined organic layer was washed with 10% aq.$NaHCO_3$ solution and dried over anhydrous Na_2SO_4. The solvent was distilled off under vacuum and the product was recrystallized from methanol.

Antibacterial Activity

The cultures were diluted with 0.9% saline and the final volume was made with concentration approximately 105–106 CFU/mL. The synthesized compounds were dissolved in DMSO. For agar disc diffusion method, Luria Bertani media was prepared, autoclaved and poured into sterilized Petri plates and then plates were spread separately with both two Gram positives and two Gram-negative bacterial strains. The synthesized compounds were added to the disc and plates were incubated at 37°C for 24 h. Inhibition Zones were measured (mm) and all experiments were repeated 3 times.

ADME Profiling

In our present study, the ADME properties of the synthesized compounds **(4a-h** and **5a-h)** were determined by using Chemsketch ACD/I-Lab Version 8.0 software and results are summarized in Table-2.

RESULTS AND DISCUSSION

Synthesis of title compounds, **4a-h** and **5a-h** were accomplished as depicted in Scheme-1. Synthesis of isoxazolyl Schiff's bases **3a-h**[23] was achieved by condensation of *N*-(5-methylisoxazol-3-yl)-3-

oxobutanamide[24] **1** with different primary amines, **2a-h**. These Schiff's base derivatives, **3a-h** underwent smooth cycloaddition reaction with chloroacetyl chloride in presence of triethyl amine to give **4a-h**. Isoxazolyl thiazolidin-4-ones were obtained by the cyclocondensation of **3a-h** with mercapto acetic acid in the presence of anhy. $ZnCl_2$ in 1,4-dioxane.

The synthesized compounds, **4a-h** and **5a-h** were confirmed by using IR, ^{1}HNMR, ^{13}CNMR and Mass spectral data. Spectral data of all the synthesized compounds are in full agreement with proposed structures. The formation of compounds, **4a-h** was confirmed by newly observed ^{1}HNMR signal at δ 5.20 ppm and it is due to β-lactam -CHCl proton. ^{13}CNMR of compound **4a** displayed -CHCl & -NCO carbon signals at δ 40.2 ppm and δ 168.3 ppm respectively. The observed signal at δ 3.82 ppm as a singlet in ^{1}HNMR of compound **5a** confirms the -SCH_2- of thiazolidine ring and ^{13}CNMR of compound **5a** displayed peaks at δ 33.0 ppm and 170.0 ppm respectively due to the carbon of -SCH_2 and CO of the thiazolidine ring.

Spectroscopic Data for the Derivatives 4(a-h) and 5(a-h)

2-(3-Chloro-1,2-dimethyl-4-oxoazetidin-2-yl)-*N*-(5-methylisoxazol-3-yl)acetamide (4a)

Yield (79%) M.P. 160-162ºC M.F. $C_{11}H_{14}N_3O_3Cl$ Elemental Analysis: Calculated C, 48.63; H, 5.19; N, 15.47; Found C, 48.65; H, 5.18; Cl, N, 15.46. IR (KBr): 3225, 1712, 1672 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.61 (s, 3H, Aze-CH_3), 2.31 (s, 3H, isoxazole-CH_3), 3.02 (s, 3H, *N*-CH_3), 3..61 (s, 2H, CH_2), 5.21 (s, 1H, -CHCl), 6.21 (s, 1H, isoxazole-H), 9.31 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm): 12.1, 20.1, 32.0, 40.2, 58.2, 66.2, 95.0, 158.2,168.3, 168.9, 170.2; ESI-MS: *m/z* 272 $[M + H]^+$.

2-(3-Chloro-1-ethyl-2-methyl-4-oxoazetidin-2-yl)-*N*-(5-methylisoxazol-3-yl)acetamide (4b)

Yield (75%) M.P. 168-169ºC; M.F. $C_{12}H_{16}ClN_3O_3$ Elemental Analysis: Calculated C, 50.44; H, 5.64; N, 14.71; Found C, 50.47; H, 5.62; N, 14.69. IR (KBr): 3251, 1708, 1662 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.20 (t, *J* = 7.2 Hz, 3H, *N*-CH_2-CH_3), 1.60 (s, 3H, Aze-CH_3), 2.28 (s, 3H, isoxazole-CH_3), 3.22 (q, *J* = 7.2 Hz, 2H, *N*-CH_2-CH_3), 3.50 (s, 2H, CH_2), 5.22 (s, 1H, -CHCl), 6.31 (s, 1H, isoxazole-H), 9.21 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm): 12.0, 12.2, 20.2, 40.9, 42.1, 58.9, 66.1, 95.1, 158.0, 169.0, 169.9, 171.2; ESI-MS: *m/z* 286 $[M + H]^+$.

2-(3-Chloro-2-methyl-4-oxo-1-phenylazetidin-2-yl)-*N*-(5-methylisoxazol-3-yl)acetamide (4c)

Yield (76%) M.P. 178-179ºC; M.F. $C_{16}H_{16}ClN_3O_3$ Elemental Analysis: Calculated C, 57.58; H, 4.83; N, 12.59; Found C, 57.57; H, 4.81; N, 12.58 IR (KBr): 3265, 1718, 1675 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.56 (s, 3H, Aze-CH_3), 2.31 (s, 3H, isoxazole-CH_3), 3.61 (s, 2H, CH_2), 5.30 (s, 1H, -CHCl), 6.29 (s, 1H, isoxazole-H), 7.18 (m, 2H, Ar-H), (m, 3H, Ar-H), 9.41 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm):12.0, 20.9, 41.0, 59.0, 66.8, 95.0, 122.1, 122.3, 125.2, 130.0, 130.1, 142.3, 158.6, 168.8, 170.0, 171.1; ESI-MS: m/z 334 $[M + H]^+$.

2-(3-Chloro-1-(4-chlorophenyl)-2-methyl-4-oxoazetidin-2-yl)-N-(5-methylisoxazol-3-yl) acetamide (4d)

Yield (80%) M.P. 184-186ºC; M.F. $C_{16}H_{15}Cl_2N_3O_3$ Elemental Analysis: Calculated C, 52.19; H, 4.11; N, 11.41; Found C, 52.21; H, 4.10; N, 11.40. IR (KBr): 3230, 1720, 1681 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.58 (s, 3H, Aze-CH_3), 2.34 (s, 3H, isoxazole-CH_3), 3.58 (s, 2H, CH_2), 5.29 (s, 1H, -CHCl), 6.20 (s, 1H, isoxazole-H), 7.21 (d, J = 8.0 Hz, 2H, Ar-H), 7.51 (d, J = 8.0 Hz, 2H, Ar-H), 9.15 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm): 12.2, 21.1, 39.2, 58.5, 66.3, 95.3, 124.3, 128.2, 129.0, 138.3, 159.2, 168.9, 170.0, 171.3; ESI-MS: m/z 368 $[M + H]^+$.

Chloro-1-(4-methoxyphenyl)-2-methyl-4-oxoazetidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (4e)

Yield (79%) M.P. 190-191ºC; M.F. $C_{17}H_{18}ClN_3O_4$ Elemental Analysis: Calculated C, 56.13; H, 4.99; N, 11.55; Found C, 56.12; H, 4.98; N, 11.56. IR (KBr): 3281, 1721, 1679 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.59 (s, 3H, Aze-CH_3), 2.32 (s, 3H, isoxazole-CH_3), 3.52 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3), 5.19 (s, 1H, -CHCl), 6.30 (s, 1H, isoxazole-H), 6.96 (d, J = 8.0 Hz, 2H, Ar-H), 7.18 (d, J = 8.0 Hz, 2H, Ar-H),

9.58 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm):12.0, 21.0, 40.4, 56.4,58.2,66.9, 96.0, 116.2, 124.7, 135.0, 154.1, 158.0, 168.2, 170.0, 171.0; ESI-MS: m/z 364 $[M + H]^+$.

2-(1-Benzyl-3-chloro-2-methyl-4-oxoazetidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (4f)
Yield (75%) M.P. 199-201ºC; M.F. $C_{17}H_{18}ClN_3O_3$ Elemental Analysis: Calculated C, 58.71; H, 5.22; N, 12.08; Found C, 58.70; H, 5.23; N, 12.10. IR (KBr): 3282, 1728, 1669 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.52 (s, 3H, Aze-CH_3), 2.30 (s, 3H, isoxazole-CH_3), 3.49 (s, 2H, CH_2), 4.51 (s, 2H, Ph-CH_2), 5.18 (s, 1H, -CHCl), 6.22 (s, 1H, isoxazole-H), 7.11- 7.30 (m, 5H, Ar-H), 9.81 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm):12.1, 22.0, 40.1, 46.2, 58.7, 66.9, 95.1, 126.0, 127.0, 127.1, 127.9, 128.0, 134.0, 158.1, 169.0, 171.0, 171.2; ESI-MS: m/z 348 $[M + H]^+$.

2-(1-(4-Chlorobenzyl)-3-chloro-2-methyl-4-oxoazetidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (4g)
Yield (78%) M.P. 207-209ºC; M.F. $C_{17}H_{17}Cl_2N_3O_3$ Elemental Analysis: Calculated C, 53.42; H, 4.48; N, 10.99; Found C, 53.45; H, 4.50; N, 10.98. IR (KBr): 3243, 1722, 1659 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.55 (s, 3H, Aze-CH_3), 2.29 (s, 3H, isoxazole-CH_3), 3.52 (s, 2H, CH_2), 4.50 (s, 2H, Ph-CH_2), 5.09 (s, 1H, -CHCl), 6.28 (s, 1H, isoxazole-H), 7.20 (d, J = 8.0 Hz, 2H, Ar-H), 7.30 (d, J = 8.0 Hz, 2H, Ar-H), 9.38 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm): 12.2, 22.2, 41.0, 48.3, 57.9, 67.0, 95.2, 129.8, 131.0, 133.0, 135.1, 158.7, 169.0, 170.2, 171.2; ESI-MS: m/z 382 $[M + H]^+$.

2-(1-(4-Methoxybenzyl)-3-chloro-2-methyl-4-oxoazetidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (4h)
Yield (76%) M.P. 215-216ºC; M.F. $C_{18}H_{20}ClN_3O_4$ Elemental Analysis: Calculated C, 57.22; H, 5.34; N, 11.12; Found C, 57.24; H, 5.36; N, 11.13. IR (KBr): 3298, 1712, 1680 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.56 (s, 3H, Aze-CH_3), 2.29 (s, 3H, isoxazole-CH_3), 3.52 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 4.50 (s, 2H, Ph-CH_2), 5.09 (s, 1H, -CHCl), 6.28 (s, 1H, isoxazole-H), 6.78 (d, J = 8.0 Hz, 2H, Ar-H), 7.09 (d, J = 8.0 Hz, 2H, Ar-H), 9.38 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm):12.2, 23.0, 40.7, 48.7, 56.9, 57.9, 67.0, 95.2, 129.8, 131.0, 133.0, 135.1, 158.7, 169.0, 170.2, 171.2; ESI-MS: m/z 378 $[M + H]^+$.

2-(2,3-Dimethyl-4-oxothiazolidin-2-yl)-*N*-(5-methylisoxazol-3-yl)acetamide (5a)
Yield (71%) M.P. 80-81ºC; M.F. $C_{11}H_{15}N_3O_3S$ Elemental Analysis: Calculated C, 49.06; H, 5.61; N, 15.60; Found C, 49.09; H, 5.62; N, 15.62. IR (KBr): 3312, 1701, 1678, 1220 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.62 (s, 3H, CH_3), 2.21 (s, 3H, isoxazole-CH_3), 2.94 (s, 3H, N-CH_3), 3.60 (s, 2H, CH_2), 3.82 (s, 2H, thiazolidine-CH_2), 6.21 (s, 1H, isoxazole-H), 9.08 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm): 11.9, 25.0, 33.0, 35.0, 48.1, 94.1, 63.3, 158.2, 168.0, 170.0, 170.2; ESI-MS: m/z 270$[M + H]^+$.

2-(3-Ethyl-2-methyl-4-oxothiazolidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (5b)
Yield (75%) M.P. 91-93ºC; M.F. $C_{12}H_{17}N_3O_3S$ Elemental Analysis: Calculated C, 50.87; H, 6.05; N, 14.83; Found C, 50.89; H, 6.04; N, 14.81. IR (KBr): 3301, 1705, 1698, 1232 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.21 (t, J = 7.6 Hz, 3H, N-CH_2-CH_3), 1.69 (s, 3H, CH_3), 2.20 (s, 3H, isoxazole-CH_3), 3.22 (q, J = 7.6 Hz, 2H, N-CH_2-CH_3), 3.61 (s, 2H, CH_2), 3.80 (s, 2H, thiazolidine-CH_2), 6.09 (s, 1H, isoxazole-H), 9.41 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm):12.0, 12.0, 26.0, 32.9, 41.0, 48.9, 63.0, 94.9, 157.8, 168.2, 169.8, 170.7; ESI-MS: m/z 284 $[M + H]^+$.

2-(2-Methyl-4-oxo-3-phenylthiazolidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (5c)
Yield (72%) M.P. 108-110ºC; M.F. $C_{16}H_{17}N_3O_3S$ Elemental Analysis: Calculated C, 57.99; H, 5.17; N, 12.68; Found C, 57.98; H, 5.18; N, 12.68. IR (KBr): 3315, 1710,1662, 1280 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.60 (s, 3H, CH_3), 2.31 (s, 3H, isoxazole-CH_3), 3.59 (s, 2H, CH_2), 3.84 (s, 2H, thiazolidine-CH_2), 6.02 (s, 1H, isoxazole-H), 7.30 (m, 5H, Ar-H), 9.05 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm):12.2, 26.8, 33.0, 48.2, 63.8, 94.8, 123.2, 123.3, 126.7, 131.0, 131.1,145.1, 158.3, 168.4, 170.2, 170.9; ESI-MS: m/z: 332 $[M + H]^+$.

2-(3-(4-Chlorophenyl)-2-methyl-4-oxothiazolidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (5d)
Yield (70%) M.P. 99-100ºC; M.F. $C_{16}H_{16}ClN_3O_3S$ Elemental Analysis: Calculated C, 52.53; H, 4.41; N, 11.49; Found C, 52.56; H, 4.40; N, 11.47. IR (KBr): 3298, 1712, 1678, 1238 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.62 (s, 3H, CH_3), 2.33 (s, 3H, isoxazole-CH_3), 3.60 (s, 2H, CH_2), 3.90 (s, 2H, thiazolidine-CH_2), 6.12 (s, 1H, isoxazole-H), 7.18-7.32 (m, 4H, Ar-H), 8.91 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm):12.1, 26.9, 33.0, 48.8, 63.0, 95.2, 128.1, 128.2, 124.0, 138.0, 158.9, 169.1, 170.0, 171.0; ESI-MS: m/z 366 $[M + H]^+$.

2-(3-(4-Methoxyphenyl)-2-methyl-4-oxothiazolidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (5e)
Yield (71%) M.P. 114-115ºC; M.F. $C_{17}H_{19}N_3O_4S$ Elemental Analysis: Calculated C, 56.50; H, 5.30; N, 11.63; Found 56.52; H, 5.31; N, 11.61. IR (KBr): 3329, 1722, 1697, 1245 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.65 (s, 3H, CH_3), 2.33 (s, 3H, isoxazole-CH_3), 3.62 (s, 2H, CH_2), 3.80 (s, 3H, OCH_3), 3.90 (s, 2H, thiazolidine-CH_2), 6.05 (s, 1H, isoxazole-H), 6.78-6.92 (m, 4H, Ar-H), 9.25 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm): 12.0, 26.7, 33.0, 48.7, 64.0, 56.8, 94.6, 113.2, 121.2, 135.1, 157.3, 158.3, 169.2, 170.4, 171.2; ESI-MS: m/z 362 $[M + H]^+$.

2-(3-Benzyl-2-methyl-4-oxothiazolidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (5f)
Yield (69%) M.P. 122-123ºC; M.F. $C_{17}H_{19}N_3O_3S$ Elemental Analysis: Calculated C, 59.11; H, 5.54; N, 12.17; Found C, 59.13; H, 5.55; N, 12.16. IR (KBr): 3309, 1718, 1661, 1218 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.66 (s, 3H, CH_3), 2.30 (s, 3H, isoxazole-CH_3), 3.61 (s, 2H, CH_2), 3.96 (s, 2H, thiazolidine-CH_2), 4.52 (s, 2H, Ph-CH_2), 6.19 (s, 1H, isoxazole-H), 7.18-7.32 (m, 5H, Ar-H), 9.51 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm):12.3, 26.7, 33.0, 46.1, 48.2, 64.0, 94.6, 126.8, 127.0, 128.0, 128.8, 128.3, 140.3, 158.3, 169.8, 170.0, 171.1; ESI-MS: m/z 346 $[M + H]^+$.

2-(3-(4-Chlorobenzyl)-2-methyl-4-oxothiazolidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (5g)
Yield (69%) M.P. 128-129ºC; M.F. $C_{17}H_{18}ClN_3O_3S$ Elemental Analysis: Calculated C, 53.75; H, 4.78; N, 11.06; Found 53.78; H, 4.79; N, 11.08. IR (KBr): 3311, 1703, 1679, 1227 cm^{-1}: ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.68 (s, 3H, CH_3), 2.28 (s, 3H, isoxazole-CH_3), 3.60 (s, 2H, CH_2), 4.01 (s, 2H, thiazolidine-CH_2), 4.51 (s, 2H, Ph-CH_2), 6.25 (s, 1H, isoxazole-H), 6.72 (d, 2H, J = 8.0 Hz, Ar-H), 6.99 (d, 2H, J = 8.0 Hz, Ar-H), 9.14 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm): 12.2, 27.0, 33.0, 46.0, 48.0, 63.9, 95.0, 126.8, 128.0, 134.3, 135.3, 158.0, 169.0, 170.2, 171.0; ESI-MS: m/z 380 $[M + H]^+$.

2-(3-(4-Methoxybenzyl)-2-methyl-4-oxothiazolidin-2-yl)-*N*-(5-methylisoxazol-3-yl) acetamide (5h)
Yield (78%) M.P. 115-116ºC; M.F. $C_{18}H_{21}N_3O_4S$ Elemental Analysis: Calculated C, 57.58; H, 5.64; N, 11.19; Found C, 57.57; H, 5.65; N, 11.21. IR (KBr): 3301, 1703, 1699, 1225 cm^{-1}; ^{1}HNMR (300 MHz, $CDCl_3$ δ ppm): 1.65 (s, 3H, CH_3), 2.30 (s, 3H, isoxazole-CH_3), 3.65 (s, 2H, CH_2), 3.79 (s, 3H, OCH_3) 3.99 (s, 2H, thiazolidine-CH_2), 4.54 (s, 2H, Ph-CH_2), 6.19 (s, 1H, isoxazole-H), 6.62 (d, 2H, J = 8.0 Hz, Ar-H), 7.02 (d, 2H, J = 8.0 Hz, Ar-H), 9.51 (s, 1H, NH); ^{13}CNMR (75 MHz, $CDCl_3$ δ ppm): 12.2, 27.0, 33.0, 46.4, 48.0, 57.0, 63.9, 95.0, 116.2, 128.0, 130.2, 154.0, 158.0, 169.0, 170.2, 171.0; ESI-MS: *m/z* 376 $[M + H]^+$.

Antibacterial Activity

The synthesized compounds, **4a–h** and **5a–h** were tested for antibacterial activity against Gram-positive organisms *Staphylococcus aureus* (MTCC 96), *Bacillus subtilis* (MTCC 121) and two Gram-negative organisms *Escherichia coli* (MTCC 43) and *Klebsiella pneumoniae* (MTCC 530). The compounds were tested in concentrations of 10μg/mL and 20μg/mL and the zones of inhibition were measured (mm) with *Gatifloxacin* as the standard drug. The results are presented in Table-1 and all the tested compounds **(4a-h** and **5a-h)** showed good to excellent antibacterial activity. The results indicate that the compounds **4a-h** are more potent than compounds **5a-h** in the series and this may be attributed to the presence of the *β*-lactam ring. *N*-alkyl substituted (*N*-methyl and *N*-ethyl) compounds **4a, 4b, 5a** and **5b** are less potent

when compared to all other compounds. Among the tested compounds, compounds **4d** and **5d** found to be the most effective against strains at higher concentration (20 µg/mL), with zone of inhibition (ZOI) values for **4d** are 24±0.22, 27±0.37, 21±0.19, 22±0.17 respectively against MTCC 96, MTCC 121, MTCC 43 and MTCC 530 strains, followed by compound **5d** with ZOI values of 23±0.31, 24±0.24, 20±0.29, 20±0.17 (Table-1). Rest of the compounds exhibited moderate to good antibacterial activity against different bacterial stains and are not selective. The enhanced activity of **4d** and **5d** may be attributed to the chloro substituent on the benzene ring.

Table-1: Antibacterial Activity of Synthesized Compounds 4a-h and 5a-h

Compound	Zone of Inhibition (mm±SD)[a]							
	Gram positive bacteria				Gram negative bacteria			
	S.aureus (MTCC 96)		*B. subtilis (MTCC 121)*		*E. coli (MTCC 43)*		*K. pneumonia (MTCC 530)*	
	10µg/mL	20µg/mL	10µg/mL	20µg/mL	10µg/mL	20µg/mL	10µg/mL	20µg/mL
4a	9±0.21	20±0.37	9±0.39	21±0.31	9±0.19	17±0.29	8±0.34	19±0.22
4b	10±0.32	22±0.26	10±0.28	23±0.28	10±0.21	20±0.31	10±0.26	20±0.36
4c	11±0.26	23±0.24	12±0.24	25±0.42	11±0.39	20±0.22	11±0.34	21±0.21
4d	13±0.34	24±0.22	12±0.26	27±0.37	12±0.28	21±0.19	12±0.21	22±0.17
4e	10±0.27	23±0.38	11±0.37	24±0.29	11±0.31	21±0.16	11±0.19	22±0.34
4f	12±0.19	23±0.21	12±0.41	25±0.25	11±0.24	21±0.27	12±0.26	22±0.21
4g	13±0.28	25±0.24	12±0.29	26±0.34	11±0.19	22±0.71	12±0.31	22±0.18
4h	11±0.31	22±0.23	11±0.27	25±0.19	10±0.27	21±0.35	11±0.42	20±0.25
5a	8±0.29	16±0.28	7±0.19	17±0.42	7±0.25	15±0.31	6±0.35	15±0.23
5b	8±0.26	18±0.39	9±0.31	20±0.17	8±0.17	18±0.29	9±0.31	18±0.21
5c	9±0.19	21±0.40	10±0.29	23±0.35	10±0.34	19±0.21	11±0.24	20±0.34
5d	11±0.35	23±0.31	11±0.27	24±0.24	10±0.23	20±0.29	12±0.29	20±0.17
5e	10±0.28	21±0.29	10±0.32	21±0.31	9±0.17	11±0.31	11±0.23	19±0.22
5f	8±0.25	16±0.17	8±0.36	17±0.19	8±0.23	15±0.37	7±0.34	15±0.39
5g	9±0.27	20±0.24	9±0.21	20±0.19	9±0.22	20±0.27	8±0.27	20±0.27
5h	8±0.22	17±0.21	8±0.40	18±0.31	8±0.18	16±0.19	8±0.33	16±0.42
Gatifloxacin	18	28	17	30	17	25	18	26

[a]Mean value of 3 trials

ADME Profiling

The results indicate that all the test compounds obey and are within the range of ADME parameters[25,26]. The most potent compounds **4d** showed excellent absorption of 82.97% and **5d** showed 72.80% of absorption.

Table-2: Insilico prediction of ADME properties of synthesized compounds 4a-h and 5a-h

Compound	Lipinski Type Properties							
	% ABS[a]	MV[b]	MWt[c]	HBA[d]	HBD[e]	RotB[f]	TPSA[g]	mlogp[h]
4a	82.97	198.2	271.7	6	1	3	75.44	1.31
4b	82.97	214.4	285.73	6	1	4	75.44	1.58
4c	82.97	241.2	333.77	6	1	4	75.44	2.21
4d	82.97	252.1	368.21	6	1	4	75.44	2.72
4e	79.78	263.0	363.79	7	1	5	84.67	2.32
4f	82.97	257.4	347.8	6	1	5	75.44	2.18
4g	82.97	268.3	382.24	6	1	5	75.44	2.68
4h	79.78	279.2	377.82	7	1	6	84.67	2.29
5a	74.24	205.0	269.32	6	1	3	100.74	0.25
5b	74.24	225.5	283.35	6	1	4	100.74	0.54
5c	74.24	249.1	331.39	6	1	4	100.74	1.19
5d	74.24	261.1	365.83	6	1	4	100.74	1.71
5e	71.06	273.1	361.42	7	1	5	109.97	1.31

5f	74.24	263.3	345.42	6	1	5	100.74	1.17
5g	74.24	275.2	379.86	6	1	5	100.74	1.67
5h	71.06	287.3	375.44	7	1	6	109.97	1.28

[a]Percentage of absorption (%ABS = 109- 0.349TPSA), [b]Molecular volume,
[c]Molecular weight ≤ 500, [d]Hydrogen bond acceptor ≤10, [e]Hydrogen bond donar ≤5
[f]Rotatable bonds ≤10, [g]Topological polar surface area ≤140 $^{\circ}A^2$,
[h]Partition coefficient between *n*-Octanol and Water ≤5

CONCLUSION

In conclusion, we have prepared the isoxazolyl azetidin-2-ones **(4a-h)** and isoxazolyl thiazolidin-4-ones **(5a-h)** and the compounds were evaluated for their antibacterial activity. Compounds **4d,** and **5d** have shown excellent antibacterial activity, and they can be exploited as potential bactericides after detailed study.

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