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SYNTHESIS, CHARACTERIZATION AND ANTIBACTERIAL EVALUATION OF NOVEL B- LACTAM AND THIAZOLIDIN-4-ONE DERIVATIVES HAVING THIADIAZINYL RING

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Since ancient times, several heterocyclic scaffolds have been recognized as possessing a wide spectrum of anti-infectious pharmacological properties. The present work aimed to synthesize and to perform antibacterial screening of some novel heterocyclic derivatives of thiadiazinyl β-lactam and thiazolidin-4-one. Cyclization of thiosemicarbazide with cyclohexanone and substituted aromatic aldehydes leads to the formation of Schiff bases, which form thiazolidinone derivatives upon reaction with thioglycolic acid in the presence of a catalytic amount of $ZnCl_2$. Lactam derivatives were synthesized by the cyclization of Schiff bases with chloroacetyl chloride in presence of triethyl amine. The synthesized derivatives ***2a*** *(MIC 25 µg/ml)****,*** *and* ***3f*** *(MIC 25 µg/ml) with 4-OH, 3-OCH3, and o-hydroxy substituents, respectively, exhibit good activity against S. aureus, while compound 2c containing p-nitro substituent was found to be the most active (MIC 12.5 µg/ml) against B. subtilis. In Gram-negative bacterial strains, compound* ***3b (****o-chloro) was extremely potent (MIC 12.5 µg/ml) against P. pneumonia while compound* ***2d*** *containing the p-hydroxy group shows excellent activity (MIC 12.5 µg/ml) against E.coli.*

Keywords: *Thioglycoolic acid, Thiourea, thiosemicarbazide, Cyclohexanone, Substituted Aromatic aldehyde.*

INTRODUCTION

Numerous heterocyclic scaffolds have been recognized as having a wide range of anti-infectious pharmacological characteristics from ancient times. To keep flora and fauna healthy and free from the fear of contracting deadly diseases, the development of innovative heterocyclic derivatives has become appealing, essential, and crucial for medicinal researchers[1-5]. For decades, thiazole, a heterocyclic derivative with nitrogen, and sulfur atom in the ring have been studied as a pharmacophore in heterocyclic medicinal chemistry. Literature revels that altering the substituents of the four- or five-membered β-lactam/thiazole nucleus significantly affects the degree of potential microbial activity[6-10]. β-lactam a cyclic amide moiety synthesized by Hermann Staudinger in 1907 exhibits exclusive medicinal properties and are used as antibacterial, antimicrobial, anti-inflammatory, anticonvulsant, and antitubercular agents[11-18]. They also inhibit enzymes and have a beneficial effect on the central nervous system. Their Antitubercular[19&20], anti-inflammatory[21], anti-tumor[22&23], anti-HIV[24], anti-parkinsonism[25-27], anti-diabetic[28-30], and vasopressin antagonist characteristics have been discovered. Thiazole derivatives have been discovered to be adaptable scaffolds with

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strong antibacterial, antiviral, antidiabetic, diuretic, antioxidant, anti-HIV, analgesic, anti-inflammatory, neuroprotective, and anticancer properties[31].

Azomethine, the condensation product of aromatic aldehydes with various substituent groups, and amines, are the most common, significant, and well-accepted classes of compounds due to their simplicity in converting into various cyclization products and a wide range of anti-microbial activity, chelating property, and stability[32&33]. The newly synthesized compounds' antibacterial potentiality may change as a result of the conversion of azomethine (CH=N) into β-lactam and thiazole ring derivatives. Several biological activities associated with azomethine compounds have been documented in the literature, including antibacterial, antifungal, anti-inflammatory, and anticancer properties[23-36].

As part of our ongoing effort to develop new heterocyclic compounds with distinct activity characteristics, we present this paper as a designing and synthesis of 2-(Un/substitutedphenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one and 3-chloro-4-(Un/substitutedphenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one derivatives.

MATERIALS AND METHODS

Chemistry

Analytical grade cyclohexanone (Merck India), ammonium acetate (Qualigens Fine Chemicals Pvt. Ltd.), chloroform (CDH), chloroacetyl chloride (SD Fine Chem. Limited), dimethyl carbonate (Merck India), methanol (CDH), ethanol (CDH), benzaldehyde (Himedia), thiosemicarbazide (SD Fine Chem. Limited), *p* and *o*-nitro benzaldehyde (Avarice laboratories), *o* and *p*-chloro benzaldehyde (Avarice laboratories), acetaldehyde (SD Fine Chem. Limited), thioglycolic acid (Merck India), dimethylformamide (Merck India), zinc Chloride (CDH), trimethylamine (Qualigens Fine Chemicals Pvt. Ltd.), dioxane (Merck India), vanillin and isovanillin (SD Fine Chem. Limited), salcylaldehyde (Merck India) were used during the synthesis of compounds 1a-h. 2a-h, and 3a-h.

Thermo Scientific (1201DQ) manual melting point apparatus was used to examine the melting point of synthesized compounds and was left uncorrected. To check the purity of synthesized derivatives thin layer chromatographic plates (Merk, 60F-254) were used and visualization was done by I_2 vapors. The values were assessed through R_f values in different solvent conditions (5:2 hexane/ethyl acetate). All the new synthesized compounds were characterized by Proton Nuclear magnetic resonance spectroscopy recorded in deuterated $CDCl_3$ or DMSO. 300 MHz Bruker NMR spectrophotometer was used for these studies by taking TMS as an internal standard. The values were presented in form of chemical shift (δ) given in ppm. For other analytical studies, Jasco FTIR-470 spectrophotometer/ MS-JEOL SX102 Mass spectroscopy were used. For FT-IR studies KBr plates was used in diffuse reflectance methodology. In mass spectroscopy NBA was used as matrix and Xenon / Argon (10mA, 6Kv) was used as the FAB gas. Elemental analysis were performed at CDRI Lucknow, India on Flash Smart Elemental Analyzer (ThermoFischer Scientific-11206100).

Synthesis of 1-(Un/substitutedphenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine: 1a-h

0.1 moles of cyclohexanone, substituted aromatic aldehydes, thiosemicarazide were mixed with 25 ml of dimethyl carbonate (solvent) and NH_4OAc as a catalyst. The mixture was refluxed for 6 hours on a water bath. The progress of the reaction was checked by TLC using a mixture of chloroform and methanol. After accomplishment of the reaction, the residue left was repeatedly washed with cold water. Ethanol was used for recrystallization to get analytically pure samples.

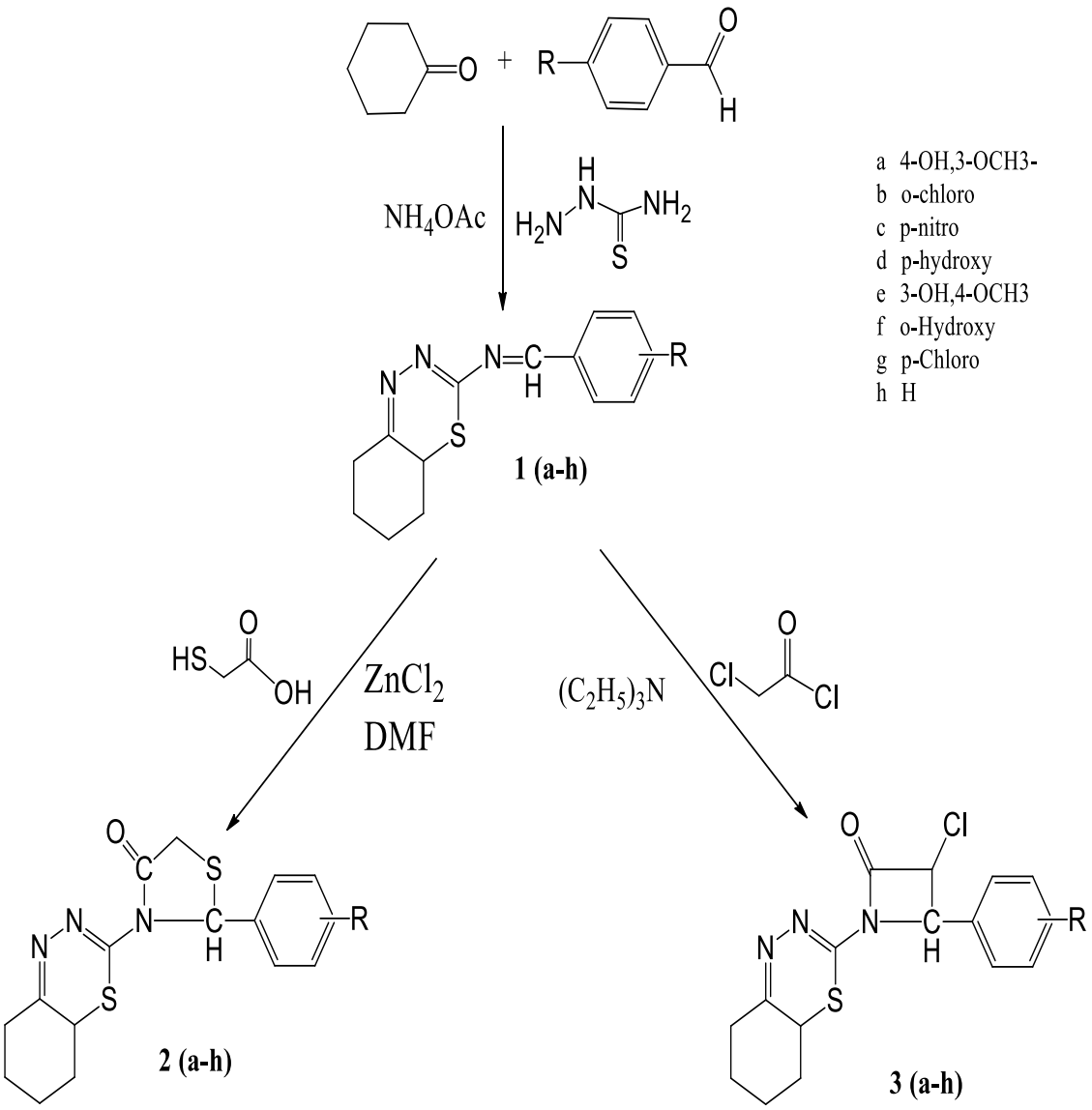
Synthesis of 2-(Un/substitutedphenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one: 2a-h

The final derivatives were synthesized by refluxing (8 hrs) 0.01mole of compounds Ia-h with thioglycolic acid (0.01mole) in DMF

using 0.01gm of zinc-chloride as a catalyst. The reaction mixture was then transferred into the ice-cold water and stirred vigorously. After 15 minutes, the solid compound thus obtained was separated and washed repeatedly with cold water followed by recrystallization from ethanol.

Synthesis of 3-chloro-4-(Un/substitutedphenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one: 3 a-h

The compounds **3 a-h** were synthesized by the reaction of 0.1 moles of Schiff base (1 a-h) with triethylamine (0.01 moles) and chloroacetyl chloride (0.01 mole) in 30 ml of dioxane at 0 ^{o}C under stirring. After keeping at room temperature for 5 hours the reaction mixture was then refluxed for 10 hours on the heating mantle. Excess solvent was removed via distillation and the remaining part was poured into ice-cooled water, the compound thus obtained was recrystallized with ethanol. Scheme 1 represents the synthesis if **1a-h**, **2a-h**, and **3a-h**.



Scheme 1

Spectral data of the synthesized compounds (1 a-h) are given as:-

1-(*p*-hydroxy,m-methoxyphenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine: (1a)

Yield 71 %; mp, 124-125 °C, Anal. Calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85; S, 10.57, found: C, 59.48; H, 5.60; N, 13.82; S, 10.51 %. IR υ_{max} (KBr, cm^{-1}): 873 (CH-S-CH_2, str. thiadiazin ring), 974 (N-N, str. thiadiazin ring), 1170 (O-C, str. 3-OCH_3-phenyl), 1655 (C=N, str.), 2948 (C-H, str. cyclohexane ring), 3061 (C-H, str. Aromatic ring), 3445 (O-H, str. 4-OH-phenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.84 (s, 3H, Ar-OCH_3), 5.4 (brs, 1H, s, changeable-OH), 6.81-7.23 (m, 3H, Aromatic proton), 9.1 (s, 1H, N=CH-C).

1-(*o*-chlorophenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine: (1b)

Yield 83 %; mp, 114-115 °C, Anal. Calcd. for $C_{14}H_{14}ClN_3S$: C, 57.63; H, 4.84; N, 14.40; S, 10.99, found: C, 57.69; H, 4.80; N, 14.45; S, 10.96 %. IR υ_{max} (KBr, cm^{-1}): 762 (C-Cl bend), 872 (CH-S-CH_2, str. thiadiazin ring), 968 (N-N, str. thiadiazin ring), 1558 (C=C, str. ring skeletal), 1635 (C=N, str.), 2915 (C-H, str. cyclohexane ring), 3078 (C-H, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 7.35-7.75 (m, 4H, Aromatic proton), 9.2 (s, 1H, N=CH-C).

1-(*p*-nitrophenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine: (1c)

Yield 68 %; mp, 90-91 °C, Anal. Calcd. for $C_{14}H_{14}N_4O_2S$: C, 55.61; H, 4.67; N, 18.53; S, 10.61, found: C, 55.65; H, 4.62; N, 18.50; S, 10.67 %. IR υ_{max} (KBr, cm^{-1}): 768 (C-Cl bend), 881 (CH-S-CH_2, str. thiadiazin ring), 968 (N-N, str. thiadiazin ring), 1290 (-N=O, sym. str.), 1564 (C=C, str. ring skeletal), 1585 (N=O str. asym), 1647 (C=N, str.), 2917 (C-H, str. cyclohexane ring), 3089 (C-H, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 7.93-8.46 (m, 4H, Aromatic proton), 9.2 (s, 1H, N=CH-C).

1-(*p*-hydroxyphenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine: (1d)

Yield 69 %; mp, 103-104 °C, Anal. Calcd. for $C_{14}H_{15}N_3OS$: C, 61.51; H, 5.53; N, 15.37; S, 11.73, found: C, 61.47; H, 5.48; N, 15.34; S, 11.68 %. IR υ_{max} (KBr, cm^{-1}): 874 (CH-S-CH_2, str. thiadiazin ring), 966 (N-N, str. thiadiazin ring), 1619 (C=N, str.), 2912 (C-H, str. cyclohexane ring), 3063 (C-H, str. Aromatic ring), 3405 (O-H, str. p-OH-phenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 5.3 (brs, 1H, s, changeable-OH), 6.92-7.34 (m, 4H, Aromatic proton), 9.2 (s, 1H, N=CH-C).

1-(*m*-hydroxy,*p*-methoxyphenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine: (1e)

Yield 62 %; mp, 99 °C, Anal. Calcd. for $C_{15}H_{17}N_3O_2S$: C, 59.38; H, 5.65; N, 13.85; S, 10.57, found: C, 59.30; H, 5.58; N, 13.80; S, 10.51 %. IR υ_{max} (KBr, cm^{-1}): 877 (CH-S-CH_2, str. thiadiazin ring), 974 (N-N, str. thiadiazin ring), 1174 (O-C, str. 4-OCH_3-phenyl) 1658 (C=N, str.), 2951 (C-H, str, cyclohexane ring), 3067 (C-H, str. Aromatic ring), 3448 (O-H, str. 4-OH-yphenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.84 (s, 3H, Ar-OCH_3), 5.4 (brs, 1H, s, changeable-OH), 6.81-7.23 (m, 3H, Aromatic proton), 9.1 (s, 1H, N=CH-C).

1-(*o*-hydroxyphenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine (1f)

Yield 75 %; mp, 111 °C, Anal. Calcd. for $C_{14}H_{15}N_3OS$: C,61.51; H, 5.53; N, 15.37; S, 11.73, found: C, 61.55; H, 5.45; N, 15.39; S, 11.77 %. IR υ_{max} (KBr, cm^{-1}): 886 (CH-S-CH_2, str. thiadiazin ring), 969 (N-N, str. thiadiazin ring), 1630 (C=N, str.), 2930 (C-H, str. cyclohexane ring), 3061 (C-H, str. Aromatic ring), 3420 (O-H, str. o-OH-phenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H,

cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 5.3 (brs, 1H, s, changeable-OH), 6.92-7.34 (m, 4H, Aromatic proton), 9.2 (s, 1H, N=CH-C).

1-(*p*-chlorophenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine: (1g)

Yield 82 %; mp, 108-109 °C, Anal. Calcd. for $C_{14}H_{14}ClN_3S$: C, 57.63; H, 4.84; N, 14.40; S, 10.99, found: C, 57.54; H, 4.79; N, 14.37; S, 10.95 %. IR υ_{max} (KBr, cm^{-1}): 765 (C-Cl, bend), 878 (CH-S-CH_2, str. thiadiazin ring), 968 (N-N, str. thiadiazin ring), 1560 (C=C. str. ring skeletal), 1640 (C=N, str.), 2912 (C-H, str. cyclohexane ring), 3076 (C-H, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 7.35-7.75 (m, 4H, Aromatic proton), 9.2 (s, 1H, N=CH-C).

1-(Phenyl)-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-methanimine (1h)

Yield 68 %; mp, 119 °C, Anal. Calcd. for $C_{14}H_{15}N_3S$: C, 65.34; H, 5.87; N, 16.33; S, 12.46, found: C, 65.31; H, 5.83; N, 16.27; S, 12.38 %. IR υ_{max} (KBr, cm^{-1}): 874 (CH-S-CH_2, str. thiadiazin ring), 966 (N-N, str. thiadiazin ring), 1619 (C=N, str.),), 2912 (C-H, str, cyclohexane ring), 3066 (C-H, str. Aromatic ring. ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 7.35-7.75 (m, 5H, Aromatic proton), 9.2 (s, 1H, N=CH-C).

Spectral data of the synthesized compounds (2 a-h) are given as:

2-(4-hydroxy-3-methoxyphenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one (2a)

Yield 58 %; mp, 163 °C, Anal. Calcd. for $C_{17}H_{19}N_3O_3S_2$: C, 54.09; H, 5.07; N, 11.13; S, 16.99, found: C, 54.01; H, 5.02; N, 11.19; S, 16.94 %. IR υ_{max} (KBr, cm^{-1}): 741 (C-Cl, bend), 1079 (C-S-C, str.), 1571 (C=C, str. ring skeletal), 1683 (C=O, str. tert amide), 2336 (N-N, str.), 3075 (C-H, str. Aromatic ring), 3435 (N-H, str.), 3432 (O-H, str. o-hydroxyphenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.84 (s, 3H, Ar-OCH_3), 3.93 (dd, O=C-CH_2-S-), 5.4 (brs, 1H, s, changeable-OH), 5.95 (s, 1H, -N-CH-S-), 6.83-7.34 (m, 3H, Aromatic proton). Mass M^+: 104, 124, 154, 227, 257.

2-(2-chlorophenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one (2b)

Yield 67 %; mp, 137 °C, Anal. Calcd. for $C_{16}H_{16}ClN_3OS_2$: C, 52.52; H, 4.41; N, 11.48; S, 17.53, found: C, 52.57; H, 4.35; N, 11.42; S, 17.59 %. IR υ_{max} (KBr, cm^{-1}): 739 (C-Cl, bend), 1077 (C-S-C, str.), 1567 (C=C, str. ring skeletal), 1678 (C=O, str. tert amide), 2333 (N-N, str.), 3072 (C-H, str. Aromatic ring), 3431 (N-H, str.), 3434 (O-H, str. o-hydroxyphenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.93 (dd, O=C-CH_2-S-), 5.95 (s, 1H, -N-CH-S-), 7.33-7.64 (m, 4H, Aromatic proton). Mass M^+: 104, 112, 154, 215, 257.

2-(4-nitrophenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one (2c)

Yield 68 %; mp, 136 °C, Anal. Calcd. for $C_{16}H_{16}N_4O_3S_2$: C, 51.05; H, 4.28; N, 14.88; S, 17.04, found: C, 51.09; H, 4.22; N, 14.80; S, 17.01 %. IR υ_{max} (KBr, cm^{-1}): 1081 (CH-S-CH_2, str. thiadiazinyl ring), 1287 (-N=O, str. symmetric), 1572 (C=C, str. ring skeletal), 1681 (C=O, str. thiazolidinone ring), 1741 (-N=O, str. asymmetric), 2334 (N-N, str.), 3074 (C-H, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.93 (dd, O=C-CH_2-S-), 5.95 (s, 1H, -N-CH-S-), 7.53-8.04 (m, 4H, Aromatic proton). Mass M^+: 104, 123, 154, 226, 257.

2-(4-hydroxyphenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one (2d)

Yield 63 %; mp, 140 °C, Anal. Calcd. for $C_{16}H_{17}N_3O_2S_2$: C, 55.31; H, 4.93;N, 12.09; S, 18.46, found: C, 55.37; H, 4.87;N, 12.04; S, 18.43 %. IR υ_{max} (KBr, cm^{-1}): 1078 (CH-S-CH_2, str. thiadiazinyl ring), 1563 (C=C, str. ring skeletal), 1670 (C=O, str. thiazolidinone ring), 2326 (N-N, str.), 3067 (C-H, str. Aromatic ring), 3442 (O-H, str. p-OH-phenyl). ^{1}HNMR

(300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.93 (dd, O=C-CH_2-S-), 5.4 (brs, 1H, s, changeable-OH), 5.95 (s, 1H, -N-CH-S-), 7.03-7.54 (m, 4H, Aromatic proton). Mass M^+: 94, 104, 154, 197, 257.

2-(3-hydroxy-4-methoxyphenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one (2e)

Yield 71 %; mp, 144 °C, Anal. Calcd. Molecular for $C_{17}H_{19}N_3O_3S_2$: C, 54.09; H, 5.07; N, 11.13; S, 16.99, found: C, 54.02; H, 5.00; N, 11.18; S, 16.93 %. IR υ_{max} (KBr, cm^{-1}): 737 (C-Cl, bend), 1073 (C-S-C, str.), 1566 (C=C, str. ring skeletal), 1682 (C=O, str. tert amide), 2337 (N-N, str.), 3076 (C-H, str. Aromatic ring), 3430 (O-H, str. o-hydroxyphenyl), 3435 (N-H, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.84 (s, 3H, Ar-OCH_3), 3.93 (dd, O=C-CH_2-S-), 5.4 (brs, 1H, s, changeable-OH), 5.95 (s, 1H, -N-CH-S-), 6.83-7.34 (m, 3H, Aromatic proton). Mass M^+: 104, 124, 154, 227, 257.

2-(2-hydroxyphenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one (2f)

Yield 62 %; mp, 156 °C, Anal. Calcd. for $C_{16}H_{17}N_3O_2S_2$: C, 55.31; H, 4.93; N, 12.09; S, 18.46, found: C, 55.36; H, 4.88; N, 12.03; S, 18.42 %. IR υ_{max} (KBr, cm^{-1}): 1082 (CH-S-CH_2, str. thiadiazinyl ring), 1568 (C=C, str. ring skeletal), 1674 (C=O, str. thiazolidinone ring), 2329 (N-N, str.), 3071 (C-H, str. Aromatic ring), 3446 (O-H, str. o-OH-phenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.93 (dd, O=C-CH_2-S-), 5.4 (brs, 1H, s, changeable-OH), 5.95 (s, 1H, -N-CH-S-), 7.03-7.54 (m, 4H, Aromatic proton). Mass M^+: 94, 104, 154, 197, 257.

2-(4-chlorophenyl)-3-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)thiazolidin-4-one (2g)

Yield 67 %; mp, 108 °C, Anal. Calcd. for $C_{16}H_{16}ClN_3OS_2$: C, 52.52; H, 4.41; N, 11.48; S, 17.53, found: C, 52.58; H, 4.36; N, 11.43; S, 17.58 %. IR υ_{max} (KBr, cm^{-1}): 760 (C-Cl, bend), 1076 (CH-S-CH_2, str. thiadiazinyl ring), 1567 (C=C, str. ring skeletal), 1678 (C=O, str. thiazolidinone ring), 2328 (N-N, str.), 3065 (C-H, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.93 (dd, O=C-CH_2-S-), 5.95 (s, 1H, -N-CH-S-), 7.33-7.64 (m, 4H, Aromatic proton). Mass M^+: 104, 112, 154, 215, 257.

Phenyl-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl,thiazolidin-4-one (2h)

Yield 65 %; mp, 132 °C, Anal. Calcd. for $C_{16}H_{17}N_3OS_2$: C, 57.98; H, 5.17; N, 12.68; S, 19.35,found: C, 57.93; H, 5.14; N, 12.64; S, 19.31 %. IR υ_{max} (KBr, cm^{-1}): 1074 3065 (C-H, str. Aromatic ring), 1563 (C=C, str. ring skeletal), 1670 (C=O, str. thiazolidinone ring), 2326 (N-N, str.), (CH-S-CH_2, str. thiadiazinyl ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.93 (dd, O=C-CH_2-S-), 6.03 (s, 1H, -N-CH-S-), 7.36-7.54 (m, 5H, Aromatic proton). Mass M^+: 78, 104, 154, 181, 257.

Characterization data of the novel synthesized lactam derivatives (3 a-h), are given as:

3-chloro-4-(4-hydroxy-3-methoxyphenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one (3a)

Yield 63 %; mp, 141 °C, Anal. Calcd. for $C_{17}H_{18}ClN_3O_3S$: C, 53.75; H, 4.78; N, 11.06; S, 8.44, found: C, 53.71; H, 4.74; N, 11.01; S, 8.49 %. IR υ_{max} (KBr, cm^{-1}): 767 (C-Cl, bend), 1098 (CH-S-CH_2, str. thiadiazin ring), 1173 (O-C, str. 3-OCH_3-phenyl), 1582 (C=C, str. ring skeletal), 1694 (C=O, str. lactam ring), 2346 (N-N, str. thiadiazin ring), 2923(C-H, str. cyclohexane ring), 3095 (C-H, str. Aromatic ring), 3465 (O-H, str. 4-OH-yphenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.82 (s, 3H, Ar-OCH_3), 5.1 (d, 1H, N-CH-, lactam ring), 5.4 (brs, 1H, s, changeable-OH), 5.43 (d, 1H, -HC-CH-Cl, lactam ring), 7.13-7.54 (m, 3H, Aromatic proton). Mass M^+: 103, 124, 154, 195, 255.

3-chloro-4-(2-chlorophenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one (3b)

Yield 84 %; mp, 132 °C, Anal. Calcd. for $C_{16}H_{15}Cl_2N_3OS$: C, 52.18; H, 4.11; N, 11.41; S, 8.71, found: C, 52.22; H, 4.09; N, 11.45; S, 8.78 %. IR υ_{max} (KBr, cm^{-1}): 761 (C-Cl. bend), 1094 (CH-S-CH_2, str. thiadiazin ring), 1572 (C=C, str. ring skeletal), 1693 (C=O, str. lactam ring), 2341 (N-N, str. thiadiazin ring), 2921 (C-H, str. cyclohexane ring), 3093 (C-H, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 5.1 (d, 1H, -N-CH-, lactam ring), 5.45 (d, 1H, -HC-CH-Cl, lactam ring), 6.85-7.14 (m, 4H, Aromatic proton). Mass M^+: 103, 112, 154, 213, 255.

3-chloro-4-(4-nitrophenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one (3c)

Yield 62 %; mp, 169 °C, Anal. Calcd. for $C_{16}H_{15}ClN_4O_3S$: C, 50.73; H, 3.99; N, 14.79; S, 8.46, found: C, 50.78; H, 3.91; N, 14.72; S, 8.41 %. IR υ_{max} (KBr, cm^{-1}): 747 (C-Cl, bend), 1087 (CH-S-CH_2, str. thiadiazin ring), 1366 (-N=O, str. symmetric), 1581 (C=C, str. ring skeletal), 1663 (-N=O, str. asymmetric), 1689 (C=O, str. lactam ring), 2338 (N-N, str. thiadiazin ring), 2912 (C-H, str. cyclohexane ring), 3086 (C-H, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 5.1 (d, 1H, -N-CH-, lactam ring), 5.43 (d, 1H, -HC-CH-Cl, lactam ring), 7.25-7.57 (m, 4H, Aromatic proton). Mass M^+: 130, 123, 154, 224, 255.

3-chloro-4-(4-hydroxyphenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one (3d)

Yield 65 %; mp, 197-198 °C, Anal. Calcd. for $C_{16}H_{16}ClN_3O_2S$: C, 54.93; H, 4.61; 10.13; N, 12.01; S, 9.17, found: C, 54.97; H, 4.55; N, 12.07; S, 9.14 %. IR υ_{max} (KBr, cm^{-1}): 748 (C-Cl, bend), 1088 (CH-S-CH_2, str. thiadiazin ring), 1578 (C=C, str. ring skeletal), 1690 (C=O, str. lactam ring), 2348 (N-N, str. thiadiazin ring), 2918 (C-H, str, cyclohexane ring), 3091 (C-H, str. Aromatic ring), 3449 (O-H, str. p-OH-yphenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 5.1 (d, 1H, -N-CH-, lactam ring), 5.4 (brs, 1H, s, changeable-OH), 5.43 (d, 1H, -HC-CH-Cl, lactam ring), 6.83-7.24 (m, 4H, Aromatic proton). Mass M^+: 94, 103, 154, 194, 255.

3-chloro-4-(3-hydroxy-4-methoxyphenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one (3e)

Yield 68 %; mp, 107 °C, Anal. Calcd. for $C_{17}H_{18}ClN_3O_3S$: C, 53.75; H, 4.78; N, 11.06; S, 8.44, found: C, 53.71; H, 4.72; N, 11.02; S, 8.37 %. IR υ_{max} (KBr, cm^{-1}): 769 (C-Cl bend), 1097 (CH-S-CH_2, str. thiadiazin ring), 1171 (O-C, str. 4-OCH_3-phenyl), 1580 (C=C, str. ring skeletal), 1691 (C=O, str. lactam ring), 2345 (N-N, str. thiadiazin ring), 2929 (C-H, str, cyclohexane ring), 3092 (C-H, str. Aromatic ring), 3462 (O-H, str. 3-OH-yphenyl),. ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 3.82 (s, 3H, Ar-OCH_3), 5.1 (d, 1H, -N-CH-, lactam ring), 5.4 (brs, 1H, s, changeable-OH), 5.43 (d, 1H, -HC-CH-Cl, lactam ring), 7.13-7.54 (m, 3H, Aromatic proton). Mass M^+: 103, 124, 154, 195, 255.

3-chloro-4-(2-hydroxyphenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one (3f)

Yield 68 %; mp, 153 °C, Anal. Calcd. for $C_{16}H_{16}ClN_3O_2S$: C, 54.93 ; H, 4.61; N, 12.01; S, 9.17, found: C, 54.90 ; H, 4.52; N, 12.07; S, 9.12 %. IR υ_{max} (KBr, cm^{-1}): 752 (C-Cl, bend), 1089 (CH-S-CH_2, str. thiadiazin ring), 1577 (C=C, str. ring skeletal), 1693 (C=O, str. lactam ring), 2349 (N-N, str. thiadiazin ring), 2922 (C-H, str. cyclohexane ring), 3093 (C-H, str. Aromatic ring), 3455 (O-H, str. o-OH-phenyl). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 5.1 (d, 1H, -N-CH-, lactam ring), 5.4 (brs, 1H, s, changeable-OH), 5.43 (d, 1H, -HC-CH-Cl, lactam ring), 6.83-7.24 (m, 4H, Aromatic proton). Mass M^+: 94, 103, 154, 194, 255.

3-chloro-4-(4-chlorophenyl)-1-(5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one (3g)

Yield 83 %; mp, 107-108 °C, Anal. Calcd. for $C_{16}H_{15}Cl_2N_3OS$: C, 52.18; H, 4.11; N, 4.34; S, 8.71, found: C, 52.23; H, 4.07; N, 4.38; S, 8.75 %. IR υ_{max} (KBr, cm^{-1}): 755 (C-Cl, bend), 1089 (CH-S-CH_2, str. thiadiazin ring), 1577 (C=C, str. ring skeletal), 1688(C=O, str. lactam ring), 2339 (N-N, str. thiadiazin ring), 2916 (C-H, str. cyclohexane ring), 3085 (C-S, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 5.1 (d, 1H, -N-CH-, lactam ring), 5.45 (d, 1H, -HC-CH-Cl, lactam ring), 6.85-7.14 (m, 4H, Aromatic proton). Mass M^+: 103, 112. 154, 213, 255.

Phenyl-5,6,7,8-tetrahydro-4aH-benzo[-e][1,3,4]thiadiazin-3-yl)azetidin-2-one: (3h)

Yield 75 %; mp, 144-145 °C, Anal. Calcd. for $C_{16}H_{16}ClN_3OS$: C, 57.56; H, 4.83; N, 12.59; S, 9.61, found: C,57.51; H, 4.77; N, 12.52; S, 9.58 %. IR υ_{max} (KBr, cm^{-1}): 745 (C-Cl, bend), 1080 (CH-S-CH_2, str. thiadiazin ring), 1575 (C=C, str. ring skeletal), 1685 (C=O, str. lactam ring), 2338 (N-N, str. thiadiazin ring), 2912 (C-H, str. cyclohexane ring), 3064 (C-H, str. Aromatic ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.32 (m, 6H, cyclohexane ring), 2.1 (m, 2H, cyclohexane ring), 2.8 (t, 1H, cyclohexane ring), 5.1 (d, 1H, -N-CH-, lactam ring), 5.43 (d, 1H, -HC-CH-Cl, lactam ring), 7.13-7.57 (m, 5H, Aromatic proton). Mass M^+: 78, 103, 154, 179, 255.

In vitro anti-bacterial susceptibility test (AST)

The newly designed heterocyclic derivatives of β-lactam and thiazole were screened for their bacterial activity against different bacterial species viz., Escherichia coli, Staphylococcus aureus, Bacillus subtilis, and K. pneumonia in vitro. The pure isolates of the test bacterial species were obtained from the Department of Microbiology KGMU Lucknow. A reported methodology was used to confirm the identity of the working strains by gram staining and colony morphology. To evaluate the antibacterial activity, the culture was prepared by mixing 1 ml of anti-bacterial growth containing broth and 20 ml of plane luria-bertani medium. From the prepared mixture, 1.0 ml of the culture was taken in six different sterile tubes while one sterile tube contains 1.8 ml of culture. Subsequently, 0.2 ml of sample solution (2 a-h and 3 a-h) in EtOH (1 mg/ml) was inoculated in the tube containing 1.8 ml of culture. From this tube, 1 ml of culture was taken out and transferred into the second tube. Then again 1 ml of the culture was taken out from the second tube and transferred into the third tube; in this manner concentration of the sample in each successive tube was reduced to half. One control tube containing ciprofloxacin was prepared at last. All the prepared tube samples were incubated for 24 hours at 37 ° C. Bacterial growth for every conical tube was checked after 24 hrs by computing the absorbance value at 600 nm. The plot of compound concentration and absorbance value was used to obtain the MIC (corresponding to the drop in optical density) of the particular derivative. The MIC value of these derivatives was found between 12.5 to 100 µg/ml.

RESULTS AND DISCUSSION

The starting thiadiazin-3-imines (**1a-h**) were synthesized by a multicomponent condensation reaction of cyclohexanone, substituted aromatic aldehydes, and thiosemicarazide. FTIR spectra of the synthesized compounds exhibit absorption bands of C-S (thiadiazin ring), C=N, and N-N in the range of 886-873 cm^{-1}, 1658-1640 cm^{-1} and 970 cm^{-1} respectively, while the absorption bands corresponding to C=O stretching disappeared. The singlet at δ ~9.2 ppm is due to H-C=N proton which is also in accordance with the proposed structure **1a-h**. The $ZnCl_2$ catalyzed reaction of compounds **1a-h** with thioglycolic acid results in cyclization to yield **2a-h**. FTIR spectra of synthesized compounds **2a-h** show a new absorption band of C=O in the range of 1683-1670 cm^{-1}. The ^{1}H NMR spectrum of compounds 2a-h exhibit doublet of doublets for two proton (O=C-CH_2-S-) at δ 3.93 ppm, while the one proton singlet (-N-CH-S-) that appeared at δ ~9.2 ppm in compound 1a-h has been shifted to δ 5.95 ppm. IR and NMR data suggest the formation of 5 membered lactam ring in which the -CH_2 and -

CH groups are not attached directly. The cyclization of Schiff bases with chloroacetyl chloride in presence of triethyl amine results in lactam derivatives (**3a-h**). FTIR spectra of the synthesized compounds exhibits new absorption bands of C=O, and C-Cl at ~ 1690 and 755 cm^{-1} respectively. Proton NMR spectra suggest that the compounds **3a-h** contain two new doublets at δ ~ 4.4 and 3.2 ppm corresponding to N-CH and C-CH-Cl respectively, while a singlet at δ ~8.85 ppm was absent in **3a-h.** The IR and NMR data suggest the formation of 4 membered lactam ring in which the –C-CH-Cl and –N-CH groups are attached directly. All compounds show an excellent agreement between calculated and experimentally obtained elemental analysis data.

A routine antibacterial susceptibility test (AST) was employed to evaluate the toxicity of the synthesized compounds towards gram-negative (*P. aeruginosa, E. coli, K. pneumonia*) and gram-positive (*B. subtilis, S. aureus*) bacteria (Figure 1 & 2). We have taken ciprofloxacin as a control drug as it is effective against both Gram positive and Gram negative bacterial strains under consideration, inferring abroad spectrum activity against different kinds of microbial pathogens, irrespective of the difference in their cell wall structure.

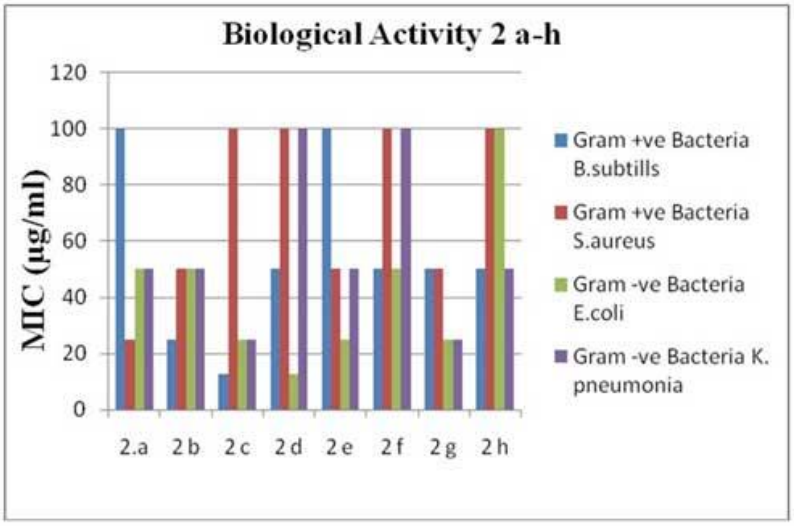


Fig. 1: Comparison of antibacterial activity of compounds 2a-h against Gram negative and Gram positive bacteria.

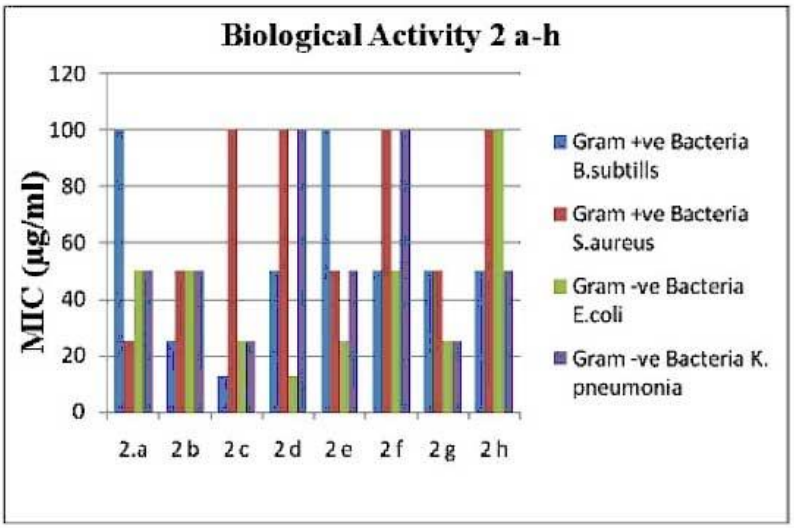


Fig. 2: Comparison of antibacterial activity of compounds 3a-h against Gram negative and Gram positive bacteria.

The MIC value of highly active compounds was found as low as 12.5 µg/ml (Table 1), Thiazolidinone derivative **2c** having *p*-nitro-phenyl shows an excellent MIC value of 12.5 µg/ml against *B. subtilis*. Interestingly, when the nitro group was replaced by 3-hydroxy-4-methoxy (**2e**) MIC value decreased twofold against *B. subtilis*. Among all (**2a-h**) derivatives, compounds **2b, 2d, 2f, 2g**, and 2**h** containing *o*- chloro, *p*-hydroxy, *o*-hydroxy, *p*-chloro, and phenyl group respectively show moderate antibacterial activity while the antibacterial activity of compound **2a** (4-hydroxy-3-methoxy) was completely lost against *B. subtillis.* All **2a-h** derivatives exhibit moderate activity against *S. aureus.* Only one derivative **2d** containing *p*-hydroxy group shows an exceptionally strong MIC value of 12.5 µg/ml against *E. coli*. However, the antibacterial activity of compounds **2c (***p*-nitro**)**, and **2g (***p*-chloro**)** is two times as compared to **2d** against *E. coli.* Moderate activity is shown by all **2a-h** derivatives against *K. pneumonia*. The derivatives of β- lactam series **3a-h** bearing *o*-chloro-phenyl group were found the most active derivative of the series with a MIC value of 12.5 µg/ml against *K. pneumonia*. Interestingly, the change in the position of R group from ortho to para, reduces the antibacterial activity to two folds against the same microbe. However a phenyl without any substituent exhibit the same activity as *p*-chloro- substituted phenyl. Other substituents with R= 3-hydroxy-4-methoxy, *p*-nitro, *p/o*-hydroxy, and 4-hydroxy-3methoxy exhibit moderate activity against K. pneumonia. The compound **3e** having MIC >100 µg/ml could not cause the inhibition of the multiplication of *E. coli.* Only four compounds **3a, 3b, 3f,** and **3h** with R= 4-hydroxy,3-methoxy. *o*-chloro, *o*-hydroxy, and unsubstituted phenyl show moderate MIC value against *E. coli.* This demonstrates that the different groups attached to the scaffold show a significant effect on antimicrobial activity. It predicts that electronic factor (electronegativity of the attached group) play a significant role to alter antibacterial activity of the synthesized compounds.

Table 1 : Antibacterial activity of synthesized (2 a-h and 3 a-h) compounds against Gram negative and Gram positive bacteria.

Compound No.	R group with benzene ring	MIC (µg/ml) against Gram +ve Bacteria		MIC (µg/ml) against Gram -ve Bacteria	
		B. subtills	S. aureus	E.coli	K. pneumonia
2 a	*4*-OH,3-OCH_3-phenyl	100	25	50	50
2 b	*o*-Chloro-phenyl	25	50	50	50
2 c	*p*-nitro-phenyl	12.5	100	25	25
2 d	*p*-Hydroxy-phenyl	50	>100	12.5	100
2 e	3-OH,4-OCH_3-phenyl	100	50	25	50
2 f	*o*-Hydroxy-phenyl	50	100	50	>100
2 g	*p*-Chloro--phenyl	50	50	25	25
2 h	phenyl	50	>100	>100	50
3 a	*4*-OH,3-OCH_3-phenyl	25	50	50	100
3 b	*o*-Chloro-phenyl	50	100	100	12.5
3 c	*p*-nitro-phenyl	50	100	25	50
3 d	*p*-Hydroxy-phenyl	100	100	25	100
3 e	3-OH,4-OCH_3-phenyl	>100	50	>100	50
3 f	*o*-Hydroxy-phenyl	50	25	100	50
3 g	*p*-Chloro--phenyl	>100	50	25	25
3 h	phenyl	50	50	100	25
Control	Ciprofloxacin	50	50	25	50

Conclusions

The present communication demonstrates the design and synthesis of novel heterocyclic derivatives of series **2a-h** and **3a-h** from non-expensive reagents using simple conditions. The one-step multiple component reaction forms Schiff base attached through a six-membered ring has been directly transformed into heterocycles derivatives of thiazolidinone and β- lactams using suitable cyclizing agents. The in vitro antibacterial screening results show that the compounds **2a,** and **3f** containing 4-OH,3-OCH_3, and *o*-hydroxy substituent respectively exhibit good activity against *S. aureus* while compound **2c** bearing *p*-nitro substituent was deemed to be the most effective against *B. subtilis*. In Gram-negative bacterial strains, compound **3b (***o*-chloro) was extremely potent against *P. pneumonia* while compound **2d** containing the *p*-hydroxy group shows excellent activity against *E.coli*.

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Conflicts of interest/Competing interests

None of the authors has any potential or actual conflict of interest to disclose in relation to the published article.

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التشييد والتوصيف والتقييم المضاد للبكتيريا لمشتقات بيتا – لكتام و الثيازوليدون الجديدة التي تحتوي على حلقة ثياديازينيل

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تم التعرف منذ القدم على العديد من الوحدات الاساسية الفعالة ذات التراكيب الغير متجانسة الحلقة و التى تمتلك مجموعة واسعة من الخصائص الدوائية المضادة للعدوى. يهدف العمل الحالي إلى تشييد و اختبار الفاعلية المضادة للبكتيريا لبعض المشتقات الحلقية غير المتجانسة الجديدة من ثياديازينيل مع بيتا–لكتام و الثيازوليدون. يؤدي تفاعل ثيوسيميكاربازيد مع سيكلوهكسانون والألدهيدات العطرية إلى تكوين قواعد شيف، والتي تُكوّن مشتقات ثيازوليدينون الحلقية عند التفاعل مع حمض الثيوجليكوليك في وجود كمية محفزة من كلوريد الخارصين. و قد تم تشييد مشتقات اللاكتام عن طريق تفاعل قواعد شيف مع كلوروأسيتيل الكلوريد في وجود امين ثلاثي الايثيل. اظهر المركبين a٢ و f٣ فاعلية مضادة للمكورات العنقودية الذهبية بمقدار (٢٥ ميكروجرام/مل)، يحتوي هذين المركبين على مجموعات ٤–هيدروكسى، ٤–ميثوكسى و ٢–هيدروكسى على التوالى، بينما اظهر المركب c٢ و الذى يحتوى على مجموعة ٤– نيترو فااعلية اكثر تجاه العصوية الرقيقة (١٢,٥ ميكروجرام/مل). بينما اظهر الاختبار المضاد للسلالات البكتيرية السالبة لصبغة جرام ، ان المركب b٣ و الذى يحتوى على مجموعة ٢–هيدروكسى فعال للغاية (١٢,٥ ميكروجرام/مل) ضد بكتيريا الالتهاب الرئوي. بينما اظهر المركب d٢ المحتوي على مجموعة ٤– هيدروكسى نشاطًا ممتازًا (١٢,٥ ميكروجرام/مل) ضد الإشريكية القولونية.