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Design and synthesis of novel lactam/thiazole derivatives having five membered thiazolyl ring and their antimicrobial activity

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ABSTRACT: In the present communication, we conceived a new synthetic approach for the preparation of novel thiazolyl-lactam/thiazole analogs. The reaction was started through cyclization of ketone with thiourea along with substituted aryl aldehydes to culminate imine derivatives which subsequently cyclized with thioglycolic acid/chloroacetyl chloride to produce final compounds. The structural elucidation of newly synthesized compounds was performed through elemental detections, FT-IR, ^{1}HNMR, and Mass spectrometric techniques. Antimicrobial studies were performed for all synthesized molecules by serial dilution method by tacking the positive (K. pneumonia, S. aureus, B. subtills) and negative (P. aeruginosa and E. coli.) bacterial strains. The in vitro antimicrobial screening results show that the compounds **2e, 3c,** and **3d** containing o-hydroxy, p-chloro, and p-nitro substituent respectively exhibit exceptional activity against *S. aureus* while compounds **2d** and **3f** bearing p-nitro and o-chloro substituent respectively were deemed to be the most competent against *B. subtilis*. Compounds **2d (**p-nitro**)** and **2f** (o-chloro) were found to be most potent against *E. coli*. In gram-negative bacterial strains, compounds **2c (**p-chloro**), 2g** (4-OH,-OCH_3), **3b** (p-hydroxy), **and 3e** (o-hydroxy) were extremely potent against *P. aeruginosa* while compound **2e** containing o-hydroxy group shows excellent activity against *E.coli*.

KEYWORDS: Synthesis; Lactam; Thiazolyl ring; Antimicrobial activity; Thiourea.

1. INTRODUCTION

Infectious diseases are a challenge for chemists, who must concentrate their efforts on producing novel heterocyclic compounds so that fauna and flora can exist without fear of getting life-threatening infections [1]. Heterocyclic scaffolds are found in nature or can be built artificially. For decades, azetidinone, a heterocyclic scaffold having a nitrogen atom in the ring, has been studied as a pharmacophore in medicinal chemistry [2]. Changes in the four-membered -lactam nucleus's substituent have been demonstrated to have a substantial impact on conferring promising microbial activity [3]. B-lactam moiety exhibits outstanding antibacterial [4], antimicrobial [5], anti-inflammatory [6], anticonvulsant [7], and antitubercular effects [8]. They also inhibit enzymes and have a beneficial effect on the central nervous system. Antitubercular [9], anti-inflammatory [10], anti-tumor [11], anti-HIV [12], anti-parkinsonism [13], antidiabetic [14] and vasopressin antagonist characteristics have been discovered.

Thiazole derivatives have been discovered to be adaptable scaffolds with strong pharmacological properties that are frequently used in disease treatment. Thiazoles have different pharmacological properties against different diseased conditions [15-20]. These compounds also have an antifungal, antibacterial, antimalarial, antiproliferative, anti-inflammatory, antiviral, and antipyretic intermediate called Schiff base. Imine or azomethine groups are be found in a variety of natural, natural-derived, and non-natural compounds. Schiff bases also exhibit fluorescence, photoluminescence, potentiometric titration, aggregation and anthelmintic activities [21-23]. As part of our ongoing effort to develop new heterocyclic compounds

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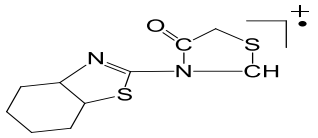
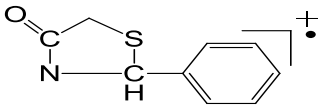
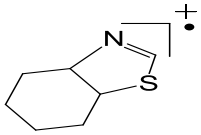
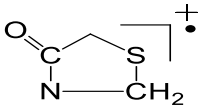
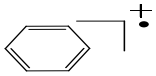
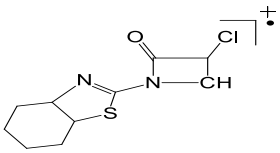
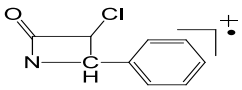
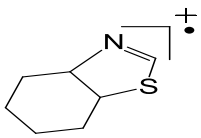
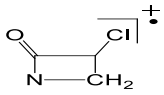
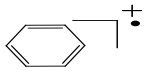
with distinct activity characteristics, we present this paper as a design and synthesis of thiadiazin-3-yl-2-one and thiazol-2-yl-azetidin-2-one/thiazolidine-4-one derivatives.

2. RESULTS AND DISCUSSION

Compounds **1a-h** were synthesized by the reaction of cyclohexanone, substituted Aromatic aldehyde, and thiourea. The characteristic FTIR spectrum of the synthesized compounds exhibits the absorption bands of C-S, and C=N in the range of 899-886 cm^{-1}, and 1662-1634 cm^{-1} respectively, while the absorption band corresponding to C=O str. has disappeared. The signal at ~980 cm^{-1} corresponds to the C=N stretching of the thiazole ring [24]. The singlet at δ 8.89-8.97 ppm is due to -N=CH-C- proton which is also following the proposed structure **1a-h** [24]. The reaction of compounds **1a-h** with thioglycolic acid results in cyclization to yield **2a-h**. The FTIR spectra of synthesized compounds **2a-h** show a new absorption band of C=O in the range of 1650-1698 cm^{-1} [25, 26]. In the ^1H NMR spectrum of compounds **2a-h**, the signal of the two protons (O=C-CH_2-S) appeared as a singlet at δ 2.81-2.94 ppm, the one proton singlet which was present at δ 8.89-8.97 ppm due to -N=CH-C- (**1a-h**) has been shifted to δ 3.32-3.45 ppm (due to –N-CH-S-). The IR and NMR data suggest the formation of 5 membered lactam ring in which the -CH_2 and -CH groups are not attached directly [25, 26].

Table 1: Mass fragmentation pattern of compounds 2a and 3a

Fragments of Compounds 2a	m/z value
	242
	179
	141
	103
	78
Fragments of Compounds 3a	**m/z value**
	244
	181
	141

	104
	78

The novel **3a-h** was synthesized via cyclization of 1**a-h** with CH_2COCl_2. Based on analytical and spectral data (FTIR and ^1H NMR) the molecular structure of the novel synthesized series was characterized. The characteristic FTIR spectrum of the synthesized compounds exhibits new absorption bands of C=O, and C-Cl at ~1660 and 770 cm^{-1} respectively [25, 26]. Proton NMR spectra suggest that the compounds **3a-h** contain two new doublets at δ 3.11-3.21 and 4.17-4.31 ppm due to –C-CH-Cl and –N-CH- of lactam ring respectively, while a singlet of **1a-h** at δ 8.89-8.97 ppm due to -N=CH-C- was absent in **3a-h** [25, 26]**.** The mass fragmentation pattern of compounds **2a** and **3a** has been represented in table 1**.** The IR, NMR, and Mass fragmentation data suggest the formation of 4 membered lactam ring in which the –C-CH-Cl and -N=CH-C- groups are attached directly. All the compounds show an excellent agreement between calculated and experimentally obtained data

The computed optical density value at 600 nm was used to assess the potency of the ten synthesized compounds. A routine antimicrobial susceptibility test (AST) was employed to evaluate the toxicity of the fabricated compounds towards gram-negative (*P. aeruginosa, E. coli, K. pneumonia*) (Figure 2 & 4) and gram-positive (*B. subtilis, S. aureus*) (Figure 1 & 3) bacteria The MIC value of these compounds was found in the range of 12.5 - >100 µg/mL (Table 2). The relation between the physicochemical/biological activity of chemicals and their molecular structure is known as Structure-Activity Relationships (SAR). The thiazole derivative **2f** having p-hydroxy substituent has shown good activity against *S. aureus*. Among all derivatives, compounds **2a, 2b, 2c, 2g**, and **2h** containing phenyl without substituent and p-hydroxy, p-chloro, o-chloro, and 3-OH, 4-OCH_3 group exhibit moderate antibacterial activity while compound **2d** containing p-nitro group shown exceptional antibacterial against *B. subtilis*. Whereas **2c, 2d,** and **2e** exhibit exceptional activity against *P. aeruginos* and *K. pneumonia* while the rest were showing moderate activity towards Gram -ve bacteria.

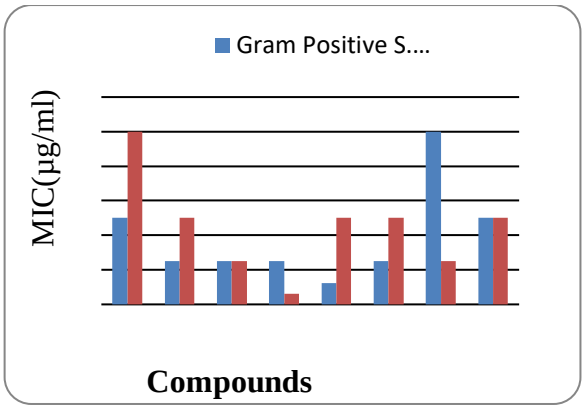


Figure 1. Activity of compounds 2 a-h against Gram Positive Bacteria.

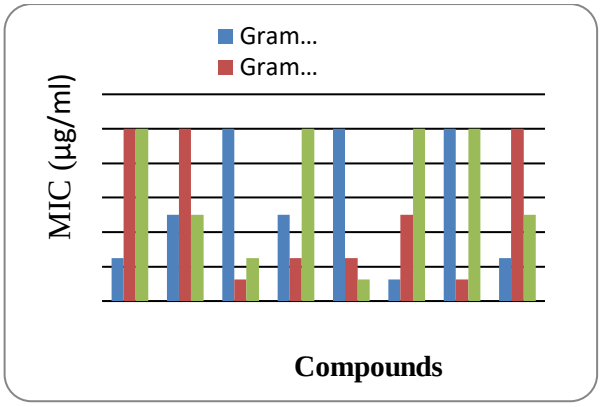


Figure 2. Activity of compounds 2, a-h against Gram Negative Bacteria.

The lactam derivatives **3c, 3d** bearing p-chlorophenyl, p-nitro, and **3f** o-chlorophenyl substituent respectively in the main scaffold exhibit exceptionally good antibacterial activity towards *B. subtilis/S. aureus*. Compounds **3e** and **3f** having o-hydroxy and o-chlorophenyl show excellent and good activity against Gram -ve bacteria *P. aeruginos*. Whereas **3c, 3e,** and **3h** give good MIC values against *K. pneumonia*. The rest derivatives of this category show moderate activity against Gram -ve and Gram +ve bacteria. The structural activity relationship study concludes that the variation in substituent and its position plays an important role in the activity of the fabricated compounds against Gram - ve and Gram +ve bacteria. Scheme 1 represents the effect of various substituents on the activity of the synthesized compounds.

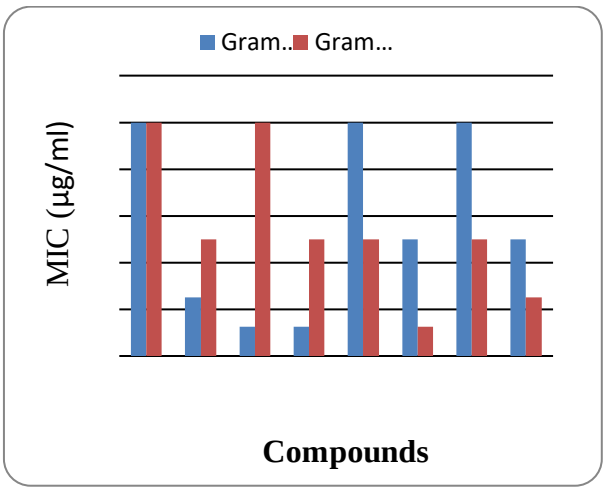


Figure 3. Activity of compounds 3, a-h against Gram Positive Bacteria.

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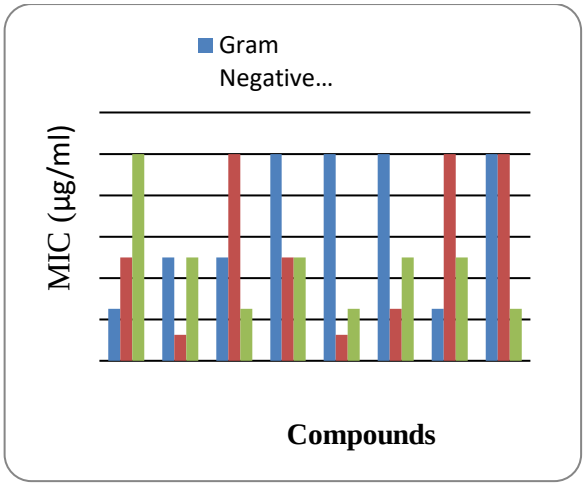


Figure 4. Activity of compounds 3, a-h against Gram Negative Bacteria.

Table 2: Antimicrobial activity: (MIC µg/mL) of compounds 2, a-h and 3, a-h

Compound No.	R with benzene ring	MIC (µg/mL) against Gram +ve Bacteria		MIC (µg/mL) against Gram -ve Bacteria		
		S. aureus	B. subtilis	E. coli	P. aeruginosa	K. pneumonia
2 a	phenyl	**50**	**>100**	25	>100	>100
2 b	*p*-OH- phenyl	25	50	50	>100	50
2 c	*p*-Cl-phenyl	25	25	>100	12.5	25
2 d	*p*-NO_2-phenyl	25	6.25	12.5	25	>100
2 e	*o*-OH-phenyl	12.5	50	>100	25	12.5
2 f	*o*-Cl-phenyl	25	50	12.5	50	>100
2 g	4-OH,3-OCH_3-phenyl	>100	25	>100	12.5	>100
2 h	3-OH,4-OCH_3-phenyl	50	50	25	>100	50
3 a	phenyl	>100	>100	25	50	>100
3 b	*p*-OH-phenyl	25	50	50	12.5	50
3 c	*p*-Cl-phenyl	12.5	>100	50	100	25
3 d	*p*-NO_2-phenyl	12.5	50	100	50	50
3 e	*o*-OH-phenyl	>100	50	>100	12.5	25
3 f	*o*-Cl-phenyl	50	12.5	>100	25	50
3 g	4-OH,3-OCH_3-phenyl	>100	50	25	>100	50
3 h	3-OH,4-OCH_3-phenyl	50	25	>100	>100	25
Control	ciprofloxacin	50	25	----	-----	50

Structure Activity Relationship of Compounds 2a-h and 3a-h

Gram Positive Bacteria		Gram Negative Bacteria		
S. aureus	B. subtilis	E. coli	P. aeruginosa	K. pneumonia
Comp., Subs, MIC Value	Comp., Subs, MIC Value	Comp., Subs, MIC Value	Comp., Subs, MIC Value	Comp., Subs, MIC Value
2e, *o*-OH-phenyl, 12.5	2d, *p*-NO_2-phenyl, 6.25	2d, *p*-NO_2-phenyl, 12.5	2c, *p*-Cl-phenyl, 12.5	2e, *o*-OH-phenyl, 12.5
2b, *p*-OH- phenyl, 25	2c, *p*-Cl-phenyl, 25	2f, *o*-Cl-phenyl, 12.5	2g, 4-OH,3-OCH_3-phenyl, 12.5	2c, *p*-Cl-phenyl, 25
2c, *p*-Cl-phenyl, 25	2g, 4-OH,3-OCH_3-phenyl, 25	2a, Phenyl, 25	2d, *p*-NO_2-phenyl, 25	2b, *p*-OH- phenyl, 50
2d, *p*-NO_2-phenyl, 25	2b, *p*-OH- phenyl, 50	2h, 3-OH,4-OCH_3-phenyl, 25	2e, *o*-OH-phenyl, 25	2h, 3-OH,4-OCH_3-phenyl, 50
2f, *o*-Cl-phenyl, 25	2e, *o*-OH-phenyl, 50	2b, *p*-OH- phenyl, 50	2f, *o*-Cl-phenyl, 50	2a, Phenyl, >100
2a, Phenyl, 50	2f, *o*-Cl-phenyl, 50	2c, *p*-Cl-phenyl, >100	2a, Phenyl, >100	2d, *p*-NO_2-phenyl, >100
2h, 3-OH,4-OCH_3-phenyl, 50	2h, 3-OH,4-OCH_3-phenyl, 50	2e, *o*-OH-phenyl, >100	2b, *p*-OH- phenyl, >100	2f, *o*-Cl-phenyl, >100
2g, 4-OH,3-OCH_3-phenyl, >100	2a, Phenyl, >100	2g, 4-OH,3-OCH_3-phenyl, >100	2h, 3-OH,4-OCH_3-phenyl, >100	2g, 4-OH,3-OCH_3-phenyl, >100
3c, *p*-Cl-phenyl, 12.5	3f, *o*-Cl-phenyl, 12.5	3a, Phenyl, 25	3b, *p*-OH-phenyl, 12.5	3c, *p*-Cl-phenyl, 25
3d, *p*-NO_2-phenyl, 12.5	3h, 3-OH,4-OCH_3-phenyl, 25	3g, 4-OH,3-OCH_3-phenyl, 25	3e, *o*-OH-phenyl, 12.5	3e, *o*-OH-phenyl, 25
3b, *p*-OH-phenyl, 25	3b, *p*-OH-phenyl, 50	3b, *p*-OH-phenyl, 50	3f, *o*-Cl-phenyl, 25	3h, 3-OH,4-OCH_3-phenyl, 25
3f, *o*-Cl-phenyl, 50	3d, *p*-NO_2-phenyl, 50	3c, *p*-Cl-phenyl, 50	3a, Phenyl, 50	3b, *p*-OH-phenyl, 50
3h, 3-OH,4-OCH_3-phenyl, 50	3e, *o*-OH-phenyl, 50	3d, *p*-NO_2-phenyl, 100	3d, *p*-NO_2-phenyl, 50	3d, *p*-NO_2-phenyl, 50
3a, Phenyl, >100	3g, 4-OH,3-OCH_3-phenyl, 50	3e, *o*-OH-phenyl, >100	3c, *p*-Cl-phenyl, 100	3f, *o*-Cl-phenyl, 50
3e, *o*-OH-phenyl, >100	3a, Phenyl, >100	3h, 3-OH,4-OCH_3-phenyl, >100	3g, 4-OH,3-OCH_3-phenyl, >100	3g, 4-OH,3-OCH_3-phenyl, 50
3g, 4-OH,3-OCH_3-phenyl, >100	3c, *p*-Cl-phenyl, >100	3f, *o*-Cl-phenyl, >100	3h, 3-OH,4-OCH_3-phenyl, >100	3a, Phenyl, >100

Scheme 1

3. CONCLUSIONS

The present communication demonstrates the successful synthesis of novel series of lactam/thiazole derivatives having a five-membered thiazolyl ring. The spectral data of the synthesized compounds meet the standard values. The IR (absorbance band for C=O) and ^{1}HNMR (signal of 2 H) data suggest the formation of a lactam ring. The in vitro antimicrobial screening results show that the compounds **2e, 3c,** and **3d** containing o-hydroxy, p-chloro, and p-nitro substituent respectively exhibit exceptional activity against *S. aureus* while compounds **2d** and **3f** bearing p-nitro and o-chloro substituent respectively were deemed to be the most competent against *B. subtilis*. Against *E. coli* compounds **2d (**p-nitro**)** and **2f** (o-chloro) were found to be most potent. In gram-negative bacterial strains, compounds **2c (**p-chloro**), 2g** (4-OH,-OCH_3), **3b** (p-hydroxy), **and 3e** (o-hydroxy) were extremely potent against *P. aeruginosa* while compound **2e** containing o-hydroxy group shows excellent activity against *E.coli*.

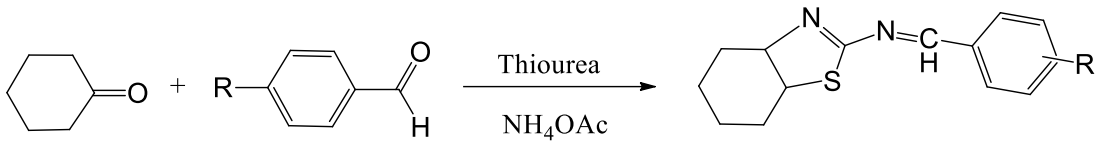
4. MATERIALS AND METHODS

4.1. Chemistry

Open capillaries methodology was used to access the melting point (m.p.) of all the newly synthesized compounds. The purity of synthesized compounds was checked by thin layer chromatographic plates (Merk, 60F-254) using I_2 vapor as a visualizer. All the new synthesized compounds were characterized by proton nuclear magnetic resonance spectroscopy using $CDCl_3$/DMSO as solvent. 300 MHz Bruker NMR spectrophotometer was used for these studies by taking TMS as the internal standard. The chemical shift (δ) values are represented in ppm. For other analytical studies, Jasco FTIR-470 spectrophotometer and MS-JEOL SX102 Mass spectroscopy was used. KBr palates were used to record the IR spectra of synthesized compounds. NBA was used as a matrix and Xenon/Argon (10mA, 6Kv) was used as the FAB gas for the recording of mass spectra.

*4.1.1 Synthesis of (E)substituted-N-benzylidene-4,5,6,7-tetrahydrobenzo[d]thiazol-2-amine (**1 a-h**)*

0.1 mole each of cyclohexanone, substituted aromatic aldehyde, and thiourea was taken in 25 ml dimethyl carbonate (solvent), the reaction mixture was refluxed at 95 ^oC temperature for 6 hrs. using NH_4OAc as a catalyst. The progress of reactions was monitored by thin-layer chromatography using a chloroform-methanol mixture as a developing solvent. After filtration the solid thus obtained was washed with ice-cold water, dried, and finally recrystallized with ethanol.



1, a-h

(*E*)-N-benzylidene-4,5,6,7-tetrahydrobenzo[d]thiazol-2-amine (1a)

Yield 69 %; mp, 114 °C, Anal. Calcd. for $C_{14}H_{14}N_2S$: C, 69.39; N, 11.56; S, 13.23, found: C, 69.32; N, 11.51; S, 13.26, %. IR υ_{max} (KBr, cm^{-1}): 886 (C-S-C, str. thiazol ring), 3072 (Ar C-H, str.), 1634 (C=N, str.), 2918 (C-H, str. cyclohexane ring), 971 (C=N, str. thiazol ring). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.38 (m, 8H, cyclohexane ring), 8.89 (N=CH-C), 6.74-7.76 (m, 5H, ArH), 3.98 (d, 2H, cyclohexane ring).

4-(((4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)imino)methyl)phenol (1b)

Yield 76 %; mp, 96-97 °C, Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; N, 6.19; S, 12.41, found: C, 65.01; N, 6.12; S, 12.35 %. IR υ_{max} (KBr, cm^{-1}): 889 (C-S-C, str. thiazol ring), 3075 (Ar C-H, str.), 1642 (C=N, str.), 2923 (C-H, str. cyclohexane ring), 974 (C=N, str. thiazol ring), 3420 (p-OH-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.47 (m, 8H, cyclohexane ring), 8.92 (N=CH-C), 6.73-7.76 (m, 4H, ArH), 4.01 (d, 2H, cyclohexane ring), 4.21 (brs, 1H, s, exchangeable-OH).

N-(4-chlorobenzylidene)-4, 5, 6, 7-tetrahydrobenzo[d]thiazol-2-amine (1c)

Yield 84 %; mp, 129-130 °C, Anal. Calcd. for $C_{14}H_{13}ClN_2S$: C, 60.75; N, 10.12; S, 11.58, found: C, 60.70; N, 10.17; S, 11.52 %. IR υ_{max} (KBr, cm^{-1}): 893 (C-S-C, str. thiazol ring), 3079 (Ar C-H, str.), 1647 (C=N str.), 2932 (C-H, str. cyclohexane ring), 975 (C=N, str. thiazol ring), 770 (C-Cl str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.48 (m, 8H- cyclohexane ring), 8.95 (N=CH-C), 6.76-7.79 (m, 4H, ArH), 4.03 (d, 2H, cyclohexane ring).

N-(4-nitrobenzylidene)-4, 5, 6, 7-tetrahydrobenzo[d]thiazol-2-amine (1d)

Yield 63 %; mp, 122 °C, Anal. Calcd. for $C_{14}H_{13}N_3O_2S$: C, 58.52; N, 14.62; S, 11.16, found: C, 58.46; N, 14.54; S, 11.10 %. IR υ_{max} (KBr, cm^{-1}): 892 (C-S-C, str. thiazol ring), 3074 (Ar C-H str.), 972 (C=N, str. thiazol ring), 2931(C-H, str. cyclohexane ring), 1638 (C=N, str.), 1577 (asym str. N=O), 1298 (sym str. N=O). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.43 (m, 8H- cyclohexane ring), 8.91 (N=CH-C), 6.73-7.76 (m, 4H, ArH), 3.97 (d, 2H, cyclohexane ring).

2-(((4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)imino)methyl)phenol (1e)

Yield 67 %; mp, 102-103 °C, Anal. Calcd. for $C_{14}H_{14}N_2OS$: C, 65.09; N, 10.84; S, 12.41, found: C, 65.01; N, 10.80; S, 12.36 %. IR υ_{max} (KBr, cm^{-1}): 887 (C-S-C, str. thiazol ring), 3073 (Ar C-H str.), 1638 (C=N, str.), 2921(C-H, str. cyclohexane ring), 972 (C=N, str. thiazol ring), 3427 (p-OH-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.43 (m, 8H- cyclohexane ring), 8.91 (N=CH-C), 6.73-7.72 (m, 4H, ArH), 3.96 (d, 2H, cyclohexane ring), 4.19 (brs, 1H, s, exchangeable-OH).

N-(2-chlorobenzylidene)-4,5,6,7-tetrahydrobenzo[d]thiazol-2-amine (1f)

Yield 66 %; mp, 114-115 °C, Anal. Calcd. for $C_{14}H_{13}ClN_2S$: C, 60.75; N, 10.12; S, 11.58, found: C, 60.70; N, 10.07; S, 11.50 %. IR υ_{max} (KBr, cm^{-1}): 897 (C-S-C, str. thiazol ring), 3083 (Ar C-H str.), 1652 (C=N str.), 2938 (C-H, str. cyclohexane ring), 979 (C=N, str. thiazol ring), 781 (C-Cl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.43 (m, 8H- cyclohexane ring), 8.92 (N=CH-C), 6.69-7.72 (m, 4H, ArH), 3.99 (d, 2H, cyclohexane ring).

(*E*)-2-methoxy-4-((4,5,6,7-tetrahydrobenzo[d]thiazol-2-ylimino)methyl)phenol (1g)

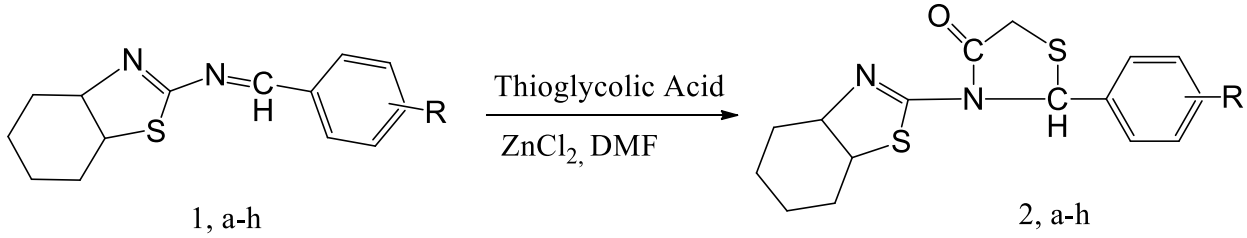
Yield 70 %; mp, 106-107 °C, Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.48; N, 9.71; S, 11.12, found: C, 62.42; N, 9.64; S, 11.08 %. IR υ_{max} (KBr, cm^{-1}): 899 (C-S-C, thiazol ring), 3090 (Ar C-H, str.), 1662 (C=N str.), 2944 (C-H, str. cyclohexane ring), 982 (C=N, str. thiazol ring), 3445 (4-OH-yphenyl, str.), 1170 (3-OCH_3-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.44 (m, 8H- cyclohexane ring), 8.97 (N=CH-C), 6.81-7.71 (m, 3H, ArH), 3.87 (d, 2H, cyclohexane ring), 4.54 (brs, 1H), 3.36 (s, 3H, $ArOCH_3$).

2-methoxy-5-(((4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)imino)methyl)phenol (1h)

Yield 78 %; mp, 125-126 °C, Anal. Calcd. for $C_{15}H_{16}N_2O_2S$: C, 62.48; N, 9.71; S, 11.12, found: C, 62.41; N, 9.65; S, 11.06 %. IR υ_{max} (KBr, cm^{-1}): 898 (C-S-C, thiazol ring), 3093 (Ar C-H, str.), 1660 (C=N, str.), 2945 (C-H, str. cyclohexane ring), 984 (C=N, str. thiazol ring), 3447 (3-OH-yphenyl, str.), 1172 (4-OCH_3-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.44 (m, 8H- cyclohexane ring), 8.93 (N=CH-C), 6.83-7.74 (m, 3H, ArH), 3.89 (d, 2H, cyclohexane ring), 4.56 (brs, 1H, s, exchangeable-OH), 3.37 (s, 3H, $ArOCH_3$).

4.1.2. Synthesis of 2-phenyl-3-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2 a-h)

The final derivatives were synthesized by refluxing 0.01 moles of compounds 1a-h with thioglycolic acid (0.01 mole) in DMF at 80 °C temperature for 8 hrs. using 0.01 gm of zinc chloride as a catalyst. The reaction mixture was then transferred into the ice-cold water and stirred vigorously. After one hour, the solid compound thus obtained was separated and washed with cold water. An analytically unblended sample was obtained via recrystallization with ethanol. Characterization data of the compounds thus synthesized are given as:



2-phenyl-3-(4, 5, 6, 7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2a)

Yield 70 %; mp, 167 °C, Anal. Calcd. for $C_{16}H_{16}N_2OS_2$: C, 60.73; N, 8.85; S, 20.27, found: C, 60.69; N, 8.80; S, 20 %. IR υ_{max} (KBr, cm^{-1}): 1650 (C=O, str. thiazolidinone ring), 1068 (CH_2-S-CH, str. thiadiazinyl ring), 3072 (Ar C-H, str.), 1558 (C=C, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.21 (m, 8H- cyclohexane ring), 3.63 (d, 2H, cyclohexane ring), 6.68-7.72 (m, 5H, ArH), 3.32 (s, -N-CHS-, 1H), 2.81 (s, 2H, O=CCH_2-S). Mass M^+: 242, 179, 141, 103, 78.

2-(4-hydroxyphenyl)-3-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2b)

Yield 80 %; mp, 129-130 °C, Anal. Calcd. for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; N, 8.43; S, 19.29, found: C, 57.87; N, 8.46; S, 19.22 %. IR υ_{max} (KBr, cm^{-1}): 1656 (C=O, str. thiazolidinone ring, 1069 (CH_2-S-CH, str. thiadiazinyl ring), 3074 (Ar C-H, str.), 1565 (C=C, str.), 3438 (p-OH-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.24 (m, 8H, cyclohexane ring), 3.65 (d, 2H, cyclohexane ring), 6.63-7.66 (m, 4H, ArH), 3.35 (s, -N-CHS- 1H), 2.83 (s, 2H, O=CCH_2-S), 4.74 (brs, 1H, s, exchangeable-OH). Mass M^+: 242, 194, 141, 103, 94.

2-(4-chlorophenyl)-3-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2c)

Yield 67 %; mp, 148.6 °C, Anal. Calcd. for $C_{16}H_{15}ClN_2OS_2$: C, 54.77; N, 7.98; S, 18.28, found: C, 54.72; N, 7.94; S, 18.21 %. IR υ_{max} (KBr, cm^{-1}): 1652 (C=O, str. thiazolidinone ring), 1069 (CH_2-S-CH, str. thiadiazinyl ring), 3076 (Ar C-H, str.), 1563 (C=C, str.), 760 (C-Cl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.23 (m, 8H- cyclohexane ring), 3.64 (d, 2H, cyclohexane ring), 6.68-7.76 (m, 4H, ArH), 3.36(s, -N-CHS-, 1H), 2.86 (s, 2H, O=CCH_2-S). Mass M^+: 242, 213, 141, 112, 103.

2-(4-nitrophenyl)-3-(4, 5, 6, 7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2d)

Yield 65 %; mp, 153 °C, Anal. Calcd. for $C_{16}H_{15}N_3O_3S_2$: C, 53.17; N, 11.63; S, 17.74, found: C, 53.11; N, 11.68; S, 17.77 %. IR υ_{max} (KBr, cm^{-1}): 1656 (C=O, str. thiazolidinone ring), 1055 (CH_2-S-CH, str. thiadiazinyl ring), 3071 (Ar C-H, str.), 1561 (C=C, str.), 1720 (N=O, asym str.), 1292(N=O, sym str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.21(m, 8H-, cyclohexane ring), 3.62 (d, 2H, cyclohexane ring), 6.68-7.76 (m, 4H, ArH), 3.36 (s, -N-CHS-, 1H), 2.81 (s, 2H, O=CCH_2-S). Mass M^+: 242, 224, 141, 123, 103.

2-(2-hydroxyphenyl)-3-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2e)

Yield 67 %; mp, 137.8 °C, Anal. Calcd. for $C_{16}H_{16}N_2O_2S_2$: C, 57.81; N, 8.43; S, 19.29, found: C, 57.86; N, 8.49; S, 19.21 %. IR υ_{max} (KBr, cm^{-1}): 1658 (C=O, str. thiazolidinone ring), 1071 (CH_2-S-CH, str. thiadiazinyl ring), 3075 (Ar C-H str.), 1570 (C=C, str.), 3447 (o-OH-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.27 (m, 8H-, cyclohexane ring), 3.69(d, 2H, cyclohexane ring), 6.63-7.62 (m, 4H, ArH), 3.37 (s, -N-CHS-, 1H), 2.85 (s, 2H, O=CCH_2-S), 4.75 (brs, 1H, s, exchangeable-OH). Mass M^+: 242, 194, 141, 103, 94.

2-(2-chlorophenyl)-3-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2f)

Yield 68 %; mp, 121-122 °C, Anal. Calcd. for $C_{16}H_{15}ClN_2OS_2$: C, 54.77; H, 4.31; Cl, 10.10; N, 7.98; S, 18.28, found: C, 54.72; H, 4.38; Cl, 10.17; N, 7.98; S, 18.28 %. IR υ_{max} (KBr, cm^{-1}): 1698 (C=O, str. thiazolidinone ring), 1031 (CH_2-S-CH, str. thiadiazinyl ring), 3187 (Ar C-H str.), 1553 (C=C, str.), 768 (C-Cl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.24 (m, 8H- cyclohexane ring), 3.65 (d, 2H, cyclohexane ring), 6.68-7.78 (m, 4H, ArH), 3.37 (s, -N-CHS-, 1H), 2.89 (s, 2H, O=CCH_2-S). Mass M^+: 242, 213, 141, 112, 103.

2-(4-hydroxy-3-methoxyphenyl)-3-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2g)

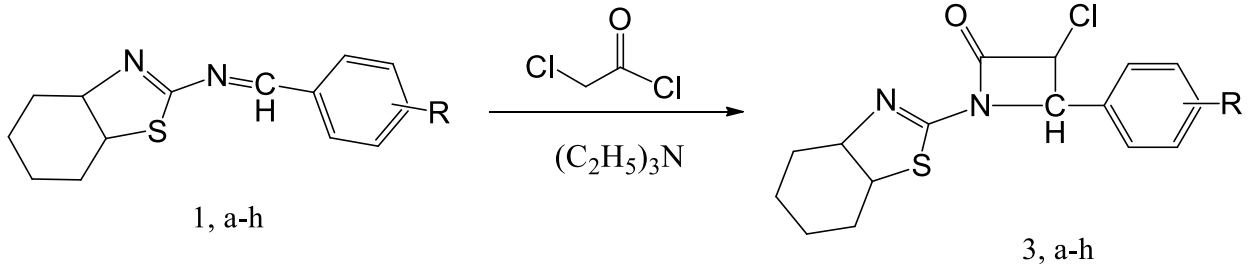
Yield 68 %; mp, 135.8 °C, Anal. Calcd. for $C_{17}H_{18}N_2O_3S_2$: C, 56.33; N, 7.73; S, 17.69, found: C, 56.37; N, 7.79; S, 17.63 %. IR υ_{max} (KBr, cm^{-1}): 1666 (C=O, str. thiazolidinone ring), 1078 (CH_2-S-CH, str. thiadiazinyl ring), 3082 (Ar C-H, str.), 1572 (C=C, str.), 3478 (4-OH-yphenyl, str.), 1174 (3-OCH_3-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.24 (m, 8H- cyclohexane ring), 3.51 (d, 2H, cyclohexane ring), 6.63-7.71 (m, 3H, ArH), 3.43 (s, -N-CHS-, 1H,), 2.92 (s, 2H, O=CCH_2-S), 4.51 (brs, 1H, s, exchangeable-OH), 3.42 (s, 3H, $ArOCH_3$). Mass M^+: 242, 195, 141, 124, 103.

2-(3-hydroxy-4-methoxyphenyl)-3-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)thiazolidin-4-one (2h)

Yield 67 %; mp, 148.6 °C, Anal. Calcd. for $C_{17}H_{18}N_2O_3S_2$: C, 56.33; N, 7.73; S, 17.69 found: C, 56.39; N, 7.73; S, 17.63 %. IR υ_{max} (KBr, cm^{-1}): 1673 (C=O, str. thiazolidinone ring), 1077 (CH_2-S-CH, str. thiadiazinyl ring), 3083 (Ar C-H, str.), 1576 (C=C, str.), 3479 (3-OH-yphenyl, str.), 1176 (4-OCH_3-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 1.28 (m, 8H- cyclohexane ring), 3.58 (d, 2H, cyclohexane ring), 6.68-7.72 (m, 3H, ArH), 3.45 (s, -N-CHS-, 1H), 2.94 (s, 2H, O=CCH_2-S), 4.56 (brs, 1H, s, exchangeable-OH), 3.45 (s ,3H, $ArOCH_3$). Mass M^+: 242, 195, 141, 124, 103.

4.1.3. Synthesis of 3-chloro-4-phenyl-1-(4, 5, 6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)azetidin-2-one (3 a-h)

To synthesize 3a-h, 0.01 moles of 1a-h were taken in 30 ml of dioxane, thereafter 0.02 moles of CH_2COCl_2 and 0.02 moles of $N(C_2H_5)_3$ were added to the reaction mixture under stirring at 0 °C . Thereafter the reaction mixture was kept at 25 °C for 5 hrs. and subsequently refluxed at 90°C temperature for 12 hrs. After evaporation of the additional solvent, the final residue was poured into ice-cold water and ultimately recrystallized with ethanol. The analytical data of the prepared novel derivatives are given as:



1, a-h

3, a-h

3-chloro-4-phenyl-1-(4, 5, 6, 7-tetrahydrobenzo[5,4-d]thiazolyl-2)azetidin-2-one (3a)

Yield 78 %; mp, 119 °C, Anal. Calcd. for $C_{16}H_{15}ClN_2OS$: C, 60.28; N, 8.79; S, 10.06, found: C, 60.38; N, 8.71; S, 10.11 %. IR υ_{max} (KBr, cm^{-1}): 1619 (C=N, str.), 1412 (C-N, str.), 1654 (C=O, str.), 2912(C-H, str. cyclohexane ring), 1571 (C=C. str.), 874 (C-S, str. thiazolyl ring), 3066 (Ar C-H, str.), 966 (HC=N, str. thiazol ring), 768 (C-Cl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 4.31 (d, N-CH, lactam ring), 1.32 (m, 8H-C cyclohexane ring), 1.26 (2H, triplet, cyclohexane ring), 6.78-7.61 (m, 5H, ArH), 3.21 (d, C-CH-Cl, lactam ring). Mass M^+: 244, 181, 141, 104, 78.

3-chloro-4-(4-hydroxyphenyl)-1-(4, 5, 6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)azetidin-2-one (3b)

Yield 65 %; mp, 134-135 °C, Anal. Calcd. for $C_{16}H_{15}ClN_2O_2S$: C, 57.40; N, 8.37; S, 9.58, found: C, 57.47; N, 8.32; S, 9.52 %. IR υ_{max} (KBr, cm^{-1}): 1636 (C=N, str.), 1412 (C-N, str.), 1656 (C=O, str.), 2912 (C-H, str. cyclohexane ring), 1578 (C=C, str.), 875 (C-S-, str. thiazolyl ring), 3066 (Ar C-H, str.), 974 (HC=N, str. thiazol ring), 769 (C-Cl, str,), 3476 (4-OH-yphenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 4.27 (d, N-CH, lactam ring), 1.28 (m, 8H- C cyclohexane ring), 1.26 (2H, triplet, cyclohexane) ring), 6.78-7.60 (m, 4H, ArH), 3.19 (d, C-CH-Cl, lactam ring), 4.37 (brs, 1H, s, exchangeable-OH). Mass M^+: 244, 197, 141, 104, 94.

3-chloro-4-(4-chlorophenyl)-1-(4, 5, 6, 7-tetrahydrobenzo[5,4-d]thiazolyl-2) azetidin-2-one (3c)

Yield 81 %; mp, 112-113 °C, Anal. Calcd. for $C_{17}H_{18}N_2O_3S_2$: C, 54.40; N, 7.93; S, 9.08, found: C, 54.47; N, 7.99; S, 9.02 %. IR υ_{max} (KBr, cm^{-1}): 1725 (C=N, str.), 1347 (C-N, str.), 1589(C=O, str.), 2977 (C-H, str. cyclohexane ring), 1576 (C=C, str.), 877 (C-S-, str. thiazolyl ring), 3027 (Ar C-H, str.), 969 (HC=N, str. thiazol ring), 756 (C-Cl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 4.25 (d, N-CH, lactam ring), 1.29 (m, 8H-C, cyclohexane ring), 1.22 (2H, triplet, cyclohexane) ring), 6.78-7.62 (m, 4H, ArH), 3.17 (C-CH-Cl, lactam ring). Mass M^+: 244, 215, 141, 112, 104.

3-chloro-4-(4-nitrophenyl)-1-(4, 5, 6, 7-tetrahydrobenzo[5,4-d]thiazolyl-2) azetidin-2-one (3d)

Yield 67 %; mp, 136-137 °C, Anal. Calcd. for $C_{16}H_{14}N_3O_3S$: C, 52.82; N, 11.49; S, 8.79, found: C, 52.87; N, 11.51; S, 8.81 %. IR υ_{max} (KBr, cm^{-1}): 1641 (C=N, str.), 1418 (C-N, str.), 1662 (C=O, str.), 2927(C-H, str. cyclohexane ring), 1581 (C=C, str.), 889 (C-S, str. thiazolyl ring), 3086 (Ar C-H, str.), 962 (HC=N, str. thiazol ring), 777 (C-Cl, str.), 158 (N=O, asym str.), 1283 (N=O, sym str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 4.31 (d, N-CH, lactam ring), 1.27 (m, 8H- C, cyclohexane ring), 1.29 (2H, triplet, cyclohexane ring), 6.78-7.68 (m, 4H, ArH), 3.20 (d, C-CH-Cl, lactam ring). Mass M^+: 244, 215, 141, 112, 104.

3-chloro-4-(2-hydroxyphenyl)-1-(4, 5, 6, 7-tetrahydrobenzo[5,4-d]thiazolyl-2)azetidin-2-one (3e)

Yield 68 %; mp, 155 °C, Anal. Calcd. for $C_{16}H_{15}ClN_2O_2S$: C, 57.40; N, 8.37; S, 9.58, found: C, 57.47; N, 8.31; S, 9.51 %. IR υ_{max} (KBr, cm^{-1}): 1640 (C=N, str.), 1415 (C-N. str.), 1657 (C=O, str.), 2915 (C-H, str, cyclohexane ring), 1582 (C=C, str.), 878 (C-S, str. thiazolyl ring), 3070 (Ar C-H, str.), 974 (HC=N, str. thiazol ring), 765 (C-Cl, str.), 3476 (OH-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 4.23 (d, N-CH, lactam ring), 1.29 (m, 8H- C cyclohexane ring), 1.28 (2H, triplet, cyclohexane ring), 6.78-7.65 (m, 4H, ArH), 3.16 (d, C-CH-Cl, lactam ring), 4.33 (brs, 1H, s, exchangeable-OH). Mass M^+: 244, 226, 141, 123, 104.

3-chloro-4-(2-chlorophenyl)-1-(4, 5, 6, 7-tetrahydrobenzo[5,4-d]thiazolyl-2)azetidin-2-one (3f)

Yield 79 %; mp, 122 °C, Anal. Calcd. for $C_{16}H_{14}Cl_2N_2OS$: C, 54.40; N, 7.93; S, 9.08, found: C,54.48; N, 7.99; S, 9.02 %. IR υ_{max} (KBr, cm^{-1}): 1632 (C=N, str.), 1415 (C-N, str.), 1662(C=O, str.), 2932(C-H, str. cyclohexane ring), 1576 (C=C, str.), 870 (C-S, str. thiazolyl ring), 3071 (Ar C-H, str.), 974 (HC=N, str. thiazol ring), 774 (C-Cl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 4.26 (d, N-CH, lactam ring), 1.23 (m, 8H-C cyclohexane ring), 1.21 (2H, triplet, cyclohexane) ring), 6.77-7.69 (m, 4H, ArH), 3.12 (d, C-CH-Cl, lactam ring). Mass M^+: 244, 215, 141, 112, 104.

3-chloro-4-(4-hydroxy-3-methoxyphenyl)-1-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)azetidin-2-one (3 g)

Yield 66 %; mp, 142-143 °C, Anal. Calcd. for $C_{17}H_{17}ClN_2O_3S$: C, 55.96; N, 7.68; S, 8.79, found: C, 55.91; N, 7.62; S, 8.74 %. IR υ_{max} (KBr, cm^{-1}): 1634 (C=N, str.), 1415 (C-N, str.), 1662 (C=O, str.), 2939 (C-H, str, cyclohexane ring), 1577 (C=C, str.), 874 (C-S, str. thiazolyl ring), 3075 (Ar C-H, str.), 978 (HC=N, str. thiazol ring), 779 (C-Cl, str.), 3468 (4-OH-yphenyl, str.), 1179 (3-OCH_3-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 4.24 (d, N-CH, lactam ring), 1.25 (m, 8H- C cyclohexane ring), 1.24 (2H, triplet, cyclohexane ring), 6.73-7.68 (m, 4H, ArH), 3.16 (d, C-CH-Cl, lactam ring), 4.44 (brs, 1H, s, exchangeable-OH), 3.36 (s, 3H, $ArOCH_3$). Mass M^+: 244, 227, 141, 124, 104.

3-chloro-4-(3-hydroxy-4-methoxyphenyl)-1-(4,5,6,7-tetrahydrobenzo[5,4-d]thiazolyl-2)azetidin-2-one (3 h)

Yield 61 %; mp, 105-106 °C, Anal. Calcd. for $C_{17}H_{17}ClN_2O_3S$: C, 55.96; N, 7.68; S, 8.79, found: C, 55.98; N, 7.61; S, 8.71 %. IR υ_{max} (KBr, cm^{-1}): 1640 (C=N, str.), 1415(C-N, str.) ,1666 (C=O, str.), 2941 (C-H, str, cyclohexane ring), 1579 (C=C, str.), 878 (C-S, str. thiazolyl ring), 3082 (Ar C-H, str.), 980 (HC=N, str. thiazol ring), 779 (C-Cl, str.), 3471 (3-OH-yphenyl, str.), 1183(4-OCH_3-phenyl, str.). ^{1}HNMR (300 MHz) (DMSO/$CDCl_3$) δ (ppm): 4.17 (d, N-CH, lactam ring), 1.20 (m, 8H- C cyclohexane ring), 1.19 (2H, triplet, cyclohexane ring), 6.78-7.69 (m, 4H, ArH), 3.11 (d, C-CH-Cl, lactam ring), 4.30 (brs, 1H, s, exchangeable-OH), 3.31(s, 3H, $ArOCH_3$). Mass M^+: 244, 227, 141, 124, 104.

4.2. In vitro anti-microbial susceptibility test (AST)

A routine antimicrobial susceptibility test (AST) was employed to evaluate the toxicity of the fabricated compounds toward the gram-negative (*P. aeruginosa, E. coli, K. pneumonia*) and gram-positive (*B. subtilis, S. aureus*) bacteria. The pure isolates of the test microbial species were obtained from the Department of Microbiology KGMU Lucknow. A reported Mueller-Hinton serial dilution methodology was used to confirm the identity of the working strains by gram staining and colony morphology [27, 28].

The variable concentrations of the synthesized compound **(2, a-h** and **3, a-h**) were used to grow the test microbial species in numerous identical sets of LB media. Growth was estimated, by recording the absorbance value after 24 hours at 600 nm for all the test microbial species. Minimum inhibitory concentration (MIC) values of the synthesized compounds against the pathogenic gram-negative and gram-positive bacteria were obtained from the plot of optical density versus compound concentrations. Bacterial growth was done by incubating LB media (10 ml) containing *P. aeruginosa, E. coli, B. subtilis, K. pneumonia,* and *Staphylococcus aureus,* for 8 hrs at 37°C in a conical tube. 100 µl of the above bacterial suspension with 10 ml of LB media was then transferred to each conical tube having test compounds of varying concentration (1200, 600, 300, 150, 75, 37.5, 18.75, 9.38, 4.69, 2.34, 1.17, 0.59, and 0.30 µg ml^{-1}). The control experiment was performed, in a conical tube containing ciprofloxacin and LB media (10 ml), by adding 100 µl of the bacterial suspension. 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 compound.

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REFERENCES

[1] Bensalah D, Mnasri A, Chakchouk-Mtibaa A, Mansour L, Mellouli L, Hamdi N. Synthesis and antioxidant properties of some new thiazolyl coumarin derivatives. Green chem Let and rev. 2020; 13(2): 155-163. [CrossRef]

[2] Yet L, Gribble GW, Joule JA. Five-Membered Ring Systems with More than one N Atom, In Progress in Heterocyclic Chemistry., The Netherlands, 2020. [CrossRef]
[3] Dhingra AK, Dash BR, Mittal SK. Synthesis, antimicrobial and anti-inflammatory activities of some novel 5-substituted imidazolone analogs. Chin Chem Lett. 2016; 27(5): 707–710. [CrossRef]
[4] Santana TI, De Oliveira Barbosa M, De Moraes Gomes PAT, Da Cruz CAN, Da Silva TG, Leite ACL. Synthesis, anticancer activity and mechanism of action of new thiazole derivatives. Eur J Med Chem. 2018; 144: 874–886. [CrossRef]
[5] Shehab WS, Mouneir SM. Design synthesis antimicrobial activity and anticancer screening of some new 1, 3-thiazolidin-4-ones derivatives. Eur J Chem. 2015; 6: 157–162. [CrossRef]
[6] Khatik GL, Datusalia AK, Ahsan W, Kaur P, Vyas M, Mittal A, Nayak SK. A retrospect study on thiazole derivatives as the potential antidiabetic agents in drug discovery and developments. Curr Drug Discov Technol. 2018; 15: 163–177. [CrossRef]
[7] Siva Sankar P, Divya K, Dinneswara Reddy G, Padmavati V, Zyryanov GV. Synthesis characterization and antimicrobial activity of azetidinone and thiazolidinone derivatives. AIP Conf Proc. 2019; 2063: 040047. [CrossRef]
[8] Karczmarzyk Z, Swatko-Ossor M, Wysocki W. New Application of 1,2,4-Triazole Derivatives as Antitubercular Agents. Structure, In Vitro Screening and Docking Studies. Molecules 2020; 25(24): 6033. [CrossRef]
[9] Alghamdi S, Almehmadi MM, Asif M. Antimicrobial Activity of N-(3-Chloro-2-aryl-4-oxoazetidin-1-yl)-4-nitro benzamide Derivatives. Indian J Heterocyclic Chem 2022; 32: 91–95. [CrossRef]
[10] Roouf Bhat A, Arshad M, Ju Lee E, Pokharel S, Choi I, Athar F. Synthesis, characterization, and anti-amoebic activity of N-(pyrimidin-2-yl)benzenesulfonamide derivatives. Chem Biodivers. 2013; 10(12): 2267-2277. [CrossRef]
[11] Singh IP, Gupta S, Kumar S. Thiazole compounds as antiviral agents: An update. Med Chem. 2020; 16: 4–23. [CrossRef]
[12] Dale N. Biological insights from the direct measurement of purine release. Biochem Pharmacol. 2021; 187: 114-416. [CrossRef]
[13] Shehab WS, El-Farargy AF, Abdelhamid AO, Aziz MA. Synthesis and biological application of pyranopyrimidine derivatives catalyzed by efficient nanoparticles and their nucleoside analogues. Synth Commun. 2019; 49: 3560–3572. [CrossRef]
[14] AbdEl-Azim MHM, Aziz MA, Mouneir SM, El-Farargy AF, Shehab WS. Ecofriendly synthesis of pyrano[2,3-d]pyrimidine derivatives and related heterocycles with anti-inflammatory activities. Arch Pharm. 2020; 353: 2000084. [CrossRef]
[15] Abdel-Mohsen HT, Abood A, Flanagan KJ, Meindl A, Senge M, El Diwani OHI. Synthesis, crystal structure, and ADME prediction studies of novel imidazopyrimidines as antibacterial and cytotoxic agents. Arch Pharm. 2020; 353: 1900271. [CrossRef]
[16] Agarwal N. Synthetic and therapeutic potential of 4-thiazolidinone and its analogs. Curr Chem Lett. 2021;119-138. [CrossRef]
[17] Mishra I, Mishra R, Mujwar S, Chandra P, Sachan N. A retrospect on antimicrobial potential of thiazole scaffold. J Heterocyclic Chem. 2020; 57: 2304-2329. [CrossRef]
[18] Vaidya A, Pathak D, Shah K. 1,3,4-oxadiazole and its derivatives: A review on recent progress in anticancer activities. Chem Biol Drug Des. 2021; 97: 572–591. [CrossRef]
[19] Singh PP, Bansal S, Rawat K, Rajasekhar Pullabhotla VSR. Synthesis of novel 1,4-bis-isoxazol/pyrazole and phenylpyrazole scaffolds by efficient green protocol and evaluation of biological properties thereof. Res J Chem Environ. 2021; 25(5): 48-61.
[20] Aziz MA, Shehab WS, Al-Karmalawy AA, El-Farargy AF, Abdellattif MH. Design Synthesis Biological Evaluation 2D-QSAR Modeling and Molecular Docking Studies of Novel 1H-3-Indolyl Derivatives as Significant Antioxidants. Int J Mol Sci. 2021; 22: 10396. [CrossRef]
[21] Jitendra NB, Mahale RG, Rajput SS, Dhanraj SS. Design, synthesis and biological evaluation of heterocyclic methyl substituted pyridine Schiff base transition metal complexes. SN Applied Sci. 2021; 3:197. [CrossRef]
[22] Consiglio G, Failla S, Finnocchiaro P. Aggregation/ deaggregation in Schif base zinc(II) complexes. Dalton Trans. 2012; 41: 387–395. [CrossRef]
[23] Ashassi-Sarkhabi H, Shabani B. The efect of some Schif base on the corrosion of aluminium in hydrochloric acid solution. Appl Surf Sci. 2006; 252: 4039–4047. [CrossRef]
[24] Bensalah D, Mnasri A, Chakchouk-Mtibaa A, Mansour L, Mellouli L, Hamdi N. Synthesis and antioxidant properties of some new thiazolyl coumarin derivatives, Green Chem Lett Rev. 2020; 13(2); 155-163. [CrossRef]

[25] Bhatt A, Srivastava K, Kant R, Lakhmani D. Synthesis of novel β-lactam and thiazolidinone compounds derived from 4-methyl-1H-isochromen-1-one and their antibacterial activity. Chem Bio Lett. 2019; 6(2): 46–54.
[26] Bishnoi A, Srivastava K, Singh S, Tripathi CM. Facile synthesis of 3-(1-(4'-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl) biphenyl-4-yl)-5-oxo-2-phenyl-1H-imidazol-4(5H)-ylidene)indolin-2-ones: β-Lactam derivatives as antimicrobes. Eur J Chem. 2011; 2(3): 359-364. [CrossRef]
[27] Kishore KB, Prasoona G, Brahmeshwari G. Synthesis and antimicrobial activity of naphtho-[1,2-e][1,3]oxazines linked Benzimidazole. Ind J Chem. 2017; 56B: 1185-1192.
[28] Evren AE, Yurttas L, Gencer H. Synthesis of New Thiazole Derivatives Bearing Thiazolidin-4(5H)-One Structure and Evaluation of Their Antimicrobial Activity. Braz J Pharm Sci. 2022; 58: el9248. [CrossRef]