Indian Journal of Chemistry
Vol. 65, August 2026, pp. 745-753
DOI: 10.56042/ijc.v65i8.20461

Synthesis and characterisation of new 1,3-thiazepine derivatives and evaluation of their antimicrobial activity

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Received 8 June 2025; accepted (revised) 10 August 2026

This study has achieved the synthesis of new 1,3-thiazepine derivatives (**Z_1-Z_{27}**) from cyclo condensation of thiourea derivatives. A series of new thiourea derivatives (**T_1-T_{33}**) have been synthesised *via* a substitution reaction of potassium thiocyanate with acid chloride produced isothiocyanate derivatives, which have been elaborated to thioureas by a nucleophilic reaction with different primary amines. The structures of the obtained compounds have been established by different spectroscopic methods such as FT-IR and ^{1}H NMR. Compared to conventional methods, the non-conventional protocol offers several advantages, such as a simple procedure, fast reaction rate, mild reaction conditions, and improved yields. More importantly, these novel compounds have been subjected to antimicrobial activity tests against three types of bacteria: *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*. The results indicate that the present series of 1,3-thiazepine derivatives display significant activity against these three types of bacteria.

Keywords: Thiazepines, Thiourea, Antimicrobial activity

Organic synthetic chemistry is now a fast-growing research field in chemistry. Among the various organic compounds, heterocyclic compounds have been associated with various biological activities. Due to bioactivity connected with heterocycle and ease of preparation, several researchers are taking a keen interest in the study of this. N- and S- containing heterocycles, such as thiazepine and its derivatives, exhibit a broad spectrum of biological activity[1-3]. Thiazepines have benzene ring, chloride, and nitro groups, and it is associated with antibacterial[1], antifungal[4], antimicrobial[5], anticonvulsant[6], and anti-breast cancer activity[7], acting as a central nervous system depressant[8]. The 1,3-thiazepine derivatives have been considered of interest due to their biological activity[9,10]. A novel pyrrole [2,1-b] [1,3] benzo thiazepines have been prepared, and they demonstrate activity as antipsychotic agents with serotonin and dopamine antagonist properties[11]. Thiazepine derivatives of different types[1,3-5] were prepared by various methods such as synthesised of methylene-bis-benzofuran [1,5] benzothiazepine[6,12], and 3-(2-substituted phenyl)4-(3-pyridine)-2,3-dihydro-[1,5] benzothiazepine[13,14]. The preparation of [1,4] derivatives are widely reported[15,16] such as some novel pyrido[3,2-f][1,4]thiazepines[17] and pyrazolo [3,4-e][1,4]thiazepine[18]. Various synthetic methods have constructed the 1,3-thiazepine ring systems. An excellent yield of ethyl-2-amino-7-methyl-4-oxo-4,5,6,7-tetrahydro-1,3-thiazepine-5-carboxylate was prepared cyclo condensation of thiourea derivative that, derived from the reaction of diethyl allyl malonate with thiourea. Also, the preparation of 2-amino derivatives of the 7-methyl-4-oxo-4,5,6,7-tetrahydro-1,3-thiazepine-5-carboxylic acid ester from the cyclo condensation of 1-alkyl-3-pent-4-enoyl-thiourea with bromine[19,20].

The thiourea derivatives have been obtained from the reaction of 4-amino-butanol with an isothiocyanate in an acidic solution resulting in the formation of 4-substituted (methyl, benzyl, and propyl)imino-4,5,6,7-tetrahydro-1,3-thiazepine[21,22]. The reaction of 4-bromobutyl isothio-cyanate with aromatic amines has been confirmed as a general method for preparing 2-arylamino-1,3-thiazepine derivatives[23]. The 1,3-thiazepine ring system could be formed from the condensation of thiourea derivatives with 1,4-dibromobutane. Tricyclo derivatives of 1,3-thiazepine were obtained by the above method[24].

This study synthesised some new derivatives of 1,3-thiazepines from thiourea derivatives using NaH

as a reducing agent. These compounds have been evaluated for biological activity *via* antibacterial, and the compounds show significant activity against *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*.

Experimental Section

Chemicals and Materials

Acid chlorides, sodium hydride, potassium thiocyanate, and primary amines were purchased from Sigma-Aldrich's. Silica gel was supplied by Merck Company. Melting points were determined at the SMP30-type melting point apparatus (Stuart, Germany) and were uncorrected. FTIR (KBr disc) spectra were recorded on a Shimadzu FTIR 84005 spectrophotometer between 4000-400 cm^{-1}. ^1H NMR spectra were recorded on a Brucker DMX500 NMR spectrometer operating at 400MHz. The chemical shift values are expressed in ppm relative to TMS as an internal standard. Thin-layer chromatography (TLC) plates were used for analysis, and they were made from silica gel F_{254}, 0.25 thickness coated on aluminium sheets (20×20 cm).

Methods

Method for synthesising thiourea derivatives (T_1-T_{33}) [25,26]

The acid chloride (0.025mol) was dissolved in (20 mL) acetone and added gradually with continuous stirring to a solution of potassium thiocyanate (0.025 mol) in (20 mL) acetone. The reactants were heated by reflux for half an hour with stirring. A primary amine solution (0.025 mol) in (20 mL) of acetone was added gradually at RT. The reactants were left to stir at RT for two hours. The product was acidified with HCl (100 mL, 0.1 N), and the resulting precipitate was filtered and washed with distilled water. The precipitate was crystallised from a mixture of chloroform-ethanol (2:1). The melting point and the product (%) of the prepared compounds ranged from (73-232°C) and (81.2-95.3%), respectively.

N-[(2,4-Dichlorophenyl)carbamothioyl]-4-methoxybenzamide, T_2: Yield (85%), grey solid. T_{mp} 166°C. IR (KBr): 1662 (C=O), 3292 (N-H), 1161 cm^{-1} (C=S); ^1H NMR (400 MHz): δ 3.3 s (3H, OCH_3), 7.3-8.8 m (7H, aromatics), 12.1 s (1H, R_2-NH), 13.5 s (1H, R_1CONH) (Supplementary Figure 1).

N-[(4-Bromophenyl)carbamothioyl]-4-methoxybenzamide, T_9: Yield: (97.3%), white solid. T_{mp} 194°C. IR (KBr): 1664 (C=O), 3377 (N-H), 1174 cm^{-1} (C=S); ^1H NMR (400 MHz): δ 3.85 s (3H, OCH_3), 7-8 m (8H, aromatics), 11.4 s (1H, R_2-NH), 12.6 s (1H, R_1CONH).

N-(Benzylcarbamothioyl)-4-chlorobenzamide, T_{15}: Yield (85%), dark yellow solid. T_{mp} 96°C. IR (KBr): 1639 (C=O), 3313 (N-H), 1155 cm^{-1} (C=S); ^1H NMR (400 MHz): δ 7.2-8.7 m (7H, aromatics), 11.8 s (1H, R_2NH), 13.1 s (1H, R_1CONH) (Supplementary Figure 2).

N-[(4-Bromophenyl)carbamothioyl]-4-chlorobenzamide, T_{20}: Yield (98%), light yellow solid. T_{mp} 175°C. IR (KBr): 1660 (C=O), 3338 (N-H), 1143 cm^{-1} (C=S); ^1H NMR (400 MHz): δ 7.6-7.9 m (8H, aromatics), 11.7 s (1H, R2NH), 12.4 s (1H, R_2CONH) (Supplementary Figure 3).

3,5-Dinitro-N-(pyrimidin-2-ylcarbamothioyl) benzamide, T_{25}: Yield (93.4%), light yellow solid. T_{mp} 165°C. IR (KBr): 1685 (C=O), 3335 (N-H), 1230 cm^{-1} (C=S); ^1H NMR (400 MHz): δ 6.2 s (1H, R_2NH), 6.6 s (1H, R_1CONH), 6.5 t (1H, H5, Pyrimidine), 8.8 d (2H, H4 and H6, Pyrimidine), 9 s (3H,H_3,H4,H6, dinitrophenyl) (Supplementary Figure 4).

3,5-Dinitro-N-(propylcarbamothioyl)benzamide, T_{27}: Yield (87.5%), yellow solid. T_{mp} 152°C. IR (KBr): 1705 (C=O), 3101 (N-H), 1195 cm^{-1} (C=S); ^1H NMR (400 MHz): δ 0.9 t (3H, CH_3), 1.6 m (2H, CH_3CH_2), 2.8 q (2H, $CSNHCH_2$), 8.2 s (1H, R_2NH), 8.5 s (1H, R_1CONH), 8.8 s (3H,H2,H4,H6, 3,5-dinitrophenyl) (Supplementary Figure 5).

Method for the preparation of thiazepine (Z_1-Z_{26}) [27]

(60%) sodium hydride NaH dispersion in mineral oil (supplied by Aldrich) (0.003 mol) was added to (0.003 mol) solution of thiourea derivatives (**T_1-T_{33}**) in (30 mL) anhydrous DMF with a continuous stirring at RT. At the end of hydrogen liberation, until hydrogen bobbles were ceased, (0.0045 mol) 1,4-dibromobutane was added for 15 minutes. The reactants were left to stir for 6 hours at RT. The solvent (DMF) was evaporated under reduced pressure to give a crude solid product purified by tetrahydrofuran (THF) crystallisation, as displayed in. The physical properties of the prepared compounds included the melting point, and the yield (%) ranged from (75- 234°C), respectively. The physical data are displayed in Table 1.

4-Chloro-N-[(2Z)-3-(pyridin-4-yl)-1,3-thiazepine-2-ylidene]benzamide, Z_{13}: Yield (79%), Light Yellow solid. T_{mp} 177°C. IR (KBr): 1608 (C=N), 1689 cm^{-1}

Table 1 — The physical properties of compounds ($\mathbf{Z_1}$-$\mathbf{Z_{26}}$)

Compd	Mol. Formula	m.p. (°C)	Colour	R_f	Yield (%)
$\mathbf{Z_1}$	$C_{19}H_{20}N_2O_2S$	145	Yellow	0.12	76.3
$\mathbf{Z_2}$	$C_{19}H_{18}C_{l2}N_2O_2S$	229	White	0.27	83
$\mathbf{Z_3}$	$C_{19}H_{22}N_2O_2S$	156	White	0.33	75
$\mathbf{Z_4}$	$C_{16}H_{22}N_2O_2S$	150	Yellow	0.23	78.2
$\mathbf{Z_5}$	$C_{18}H_{19}N_3O_2S$	213.5	White	0.21	69.3
$\mathbf{Z_6}$	$C_{24}H_{26}N_4O_3S$	205	Light Yellow	0.39	81.9
$\mathbf{Z_7}$	$C_{19}H_{19}BrN_2O_2S$	172	Yellow	0.32	81.4
$\mathbf{Z_8}$	$C_{19}H_{19}ClN_2O_2S$	196	White	0.48	76.5
$\mathbf{Z_9}$	$C_{19}H_{19}N_3O_4S$	187	Dark yellow	0.62	81.7
$\mathbf{Z_{10}}$	$C_{18}H_{17}ClN_2OS$	76	Yellow	0.7	72.5
$\mathbf{Z_{11}}$	$C_{18}H_{15}Cl_3N_2OS$	234	White	0.5	80.8
$\mathbf{Z_{12}}$	$C_{16}H_{15}ClN_4OS$	93	Orange	0.22	85
$\mathbf{Z_{13}}$	$C_{17}H_{16}ClN_3OS$	177	Light Yellow	0.46	79
$\mathbf{Z_{14}}$	$C_{23}H_{23}ClN_4O_2S$	213	Yellow	0.24	73
$\mathbf{Z_{15}}$	$C_{18}H_{16}BrClN_2OS$	174	White	0.59	82
$\mathbf{Z_{16}}$	$C_{18}H_{16}Cl_2N_2OS$	84	Yellow	0.77	78.6
$\mathbf{Z_{17}}$	$C_{18}H_{16}ClN_3O_3S$	142	Yellow	0.18	83.4
$\mathbf{Z_{18}}$	$C_{18}H_{16}N_4O_5S$	152	Light Yellow	0.63	77.6
$\mathbf{Z_{19}}$	$C_{16}H_{14}N_6O_5S$	134	Orange	0.68	82
$\mathbf{Z_{20}}$	$C_{19}H_{18}N_4O_5S$	129	Yellow	0.34	75.6
$\mathbf{Z_{21}}$	$C_{15}H_{18}N_4O_5S$	166	Light Yellow	0.36	77
$\mathbf{Z_{22}}$	$C_{17}H_{15}N_5O_5S$	154	Light Nutty	0.35	80
$\mathbf{Z_{23}}$	$C_{18}H_{22}N_4O_5S$	104	Light Nutty	0.52	88
$\mathbf{Z_{24}}$	$C_{19}H_{19}BrN_4O_5S$	146	Nutty	0.29	70.7
$\mathbf{Z_{25}}$	$C_{18}H_{15}ClN_4O_5S$	123	Yellow	0.31	76.4
$\mathbf{Z_{26}}$	$C_{18}H_{15}N_5O_7S$	155	Orange	0.66	86.6

(C=O); ^{1}H NMR (400 MHz): δ 0.9-2.1 m (4H,-CH_2CH_2-, C5+C6 in cyclic), 3.6 t (2H, N-CH_2 cyclic), 3.7 t (2H, S-CH_2 cyclic), 7.6-7.9 m (8H, aromatic).

3,5-Dinitro-N-[(2Z)-3-(pyrimidin-2-yl)-1,3-thiazepine-2-ylidene]benzamide, $\mathbf{Z_{19}}$: Yield (82%), Orange solid. T_{mp} 134°C. IR (KBr): 1629 (C=N), 1728 cm^{-1}1 (C=O); ^{1}H NMR (400 MHz): δ 1.7-1.9 m (4H, -CH_2CH_2-, C5+C6 in cyclic), 3.4-3.6 t (2H, N-CH_2 cyclic), 4.1-4.4 t (2H, S-CH_2 cyclic), 7.1-9 m (8H, aromatic) (Supplementary Figure 7).

3,5-Dinitro-N-[(2Z)-3-propyl-1,3-thiazepine-2-ylidene]benzamide, $\mathbf{Z_{21}}$: Yield (77%), light yellow solid. T_{mp} 166°C. IR (KBr): 1626 (C=N), 1722 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 0.8 t (3H, CH_3), 1.2-1.9 m (6H, -CH_2CH_2- C5+C6 in cyclic and CH_3CH_2-), 2.7 t (2H, N-CH_2outcyclic), 2.9-3.2 t (2H, N-CH_2 cyclic), 4.4 t (2H, S-CH_2 cyclic), 8.9-9 m (3H, aromatic) (Supplementary Figure 8).

N-[(2Z)-3-(4-Bromophenyl)-1,3-thiazepine-2-ylidene]-4-methoxybenzamide, $\mathbf{Z_7}$

Calcium hydride CaH_2 (0.009 mol, 3 folds excess, added to the proper amount of mineral oil) was added to (0.003 mol) solution of thiourea in (30 mL) anhydrous DMF (dried by sodium sulfate) with continuous stirring at RT. After the liberation of hydrogen, (0.0045 mol) 1,4-dibromobutane was added gradually with stirring for 15 min. The reactants were left to stir overnight. The solvent (DMF) was removed under reduced pressure, and the resulting yellow solid was crystallised from tetrahydrofuran. Yield (81.4%), yellow solid. T_{mp} 172°C. IR (KBr): 1660 (C=N), 1699 cm^{-1} (C=O); ^{1}H NMR (400 MHz): δ 1.2-1.8 m (4H,-CH_2CH_2-, C5+C6 in cyclic), 2.8-3 t (2H, N-CH_2 cyclic), 3.6 t (2H, S-CH_2 cyclic), 6.9-8 m (8H, aromatic) (Supplementary Figure 6).

3,5-Dinitro-N-[(2Z)-3-(pyridin-4-yl)-1,3-thiazepan-2-ylidene]benzamide, $\mathbf{Z_{22}}$

The above compound was prepared using the same general procedure for preparation of thiazepines except that the reaction mixture, which resulted from the addition of 1,4-dibromobutane to the reduced thiourea, was heated by reflux for two hours after removal of the solvent and crystallisation of the resulting residue.

{[(2Z)-3-(4-Bromophenyl)-1,3-thiazepan-2-ylidene]amino}(4-methoxyphenyl) methanol, $\mathbf{Z_{27}}$

Sodium hydride NaH dispersion in mineral oil (60%, 0.009 mol) (3 folds excess) was added to (0.003

mol) solution of thiourea in (30 mL) anhydrous DMF (dried by sodium sulfate) with continuous stirring at RT. After the liberation of hydrogen, (0.0045 mol) 1,4-dibromobutane was added gradually with stirring for 15 min. The reactants were left to stir overnight. The solvent (DMF) was removed under reduced pressure, and the resulting yellow solid was crystallised from chloroform. The structure of the (**Z_{27}**) compound is shown in Fig. 1, and the physical properties are shown in Table 2.

Results and Discussion

In this work[33] new thioureas were prepared starting from the acid chloride of aromatic carboxylic acids, aromatic rings of the acids one substituted with 4-methoxy, 4-chloro, and 3,5-dinitro groups. The nucleophilic substitution reaction of potassium thiocyanate on the acid chloride gave isothiocyanate derivatives, which were elaborated to thioureas by a nucleophilic reaction with different primary amines[25,27]. The primary amines used in this work are aliphatic and aromatic amines (Scheme 1).

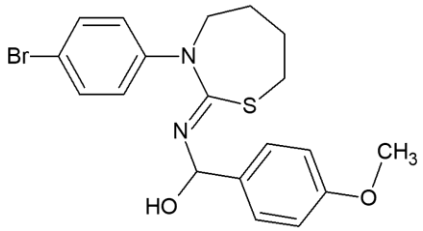
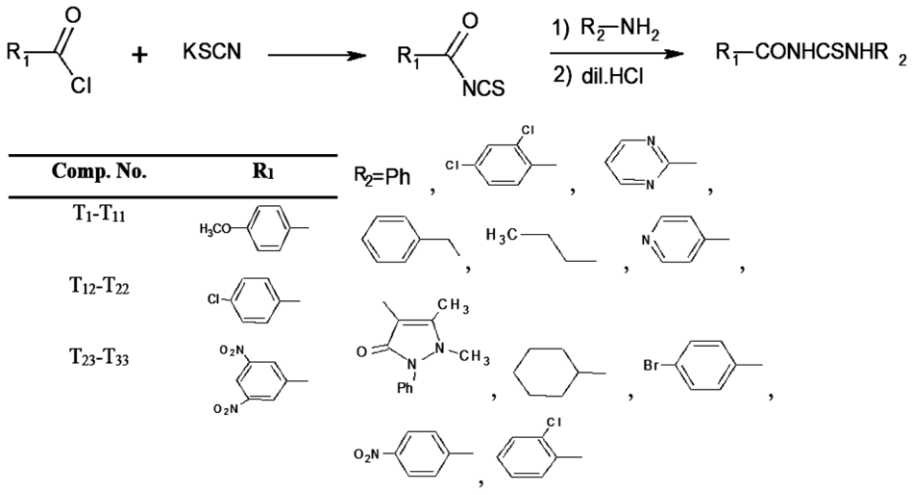


Fig. 1 — The structure of the **Z_{27}** compound

The structure of thiourea derivatives was characterised by using FTIR and ^{1}H NMR (28-31). The characteristic bands observed in infrared spectra of these derivatives are the stretching vibration of the carbonyl group of the amides (C=O), which was noted at (1631-1710 cm^{-1}), and the band for stretching vibration of (N-H) at (3101-3410 cm^{-1}). In some prepared derivatives (**T_1-T_{33}**), the two (N-H) bands were strongly overlapped and appeared approximately in the same region. This may be due to the equivalent effects of the substituents on two nitrogen atoms. The carbon-sulfur double bond stretching vibration (C=S) appeared in the region (1122-1230 cm^{-1})[32,33], as displayed FTIR spectrum in Fig. 2A.

The (N-H) signals for all recorded compounds (**T_2, T_9, T_{15}, T_{20}, T_{25}, T_{27}**) disappeared from the spectra on the addition of D_2O (exchange with D). This confirmed their position and, therefore, the formation of thiourea derivatives. The ^{1}H NMR Spectrum is displayed in Fig. 2B.

Thereafter, 33 new thioureas were prepared starting from the acid chloride of aromatic carboxylic acids, aromatic rings of the acids one substituted with 4-methoxy, 4-chloro, and 3,5-dinitro groups. The nucleophilic substitution reaction of potassium thiocyanate on the acid chloride gave isothiocyanate derivatives, which were elaborated to thioureas by a nucleophilic reaction with different primary amines[25,27]. The primary amines used in this work are aliphatic and aromatic amines (Scheme 2).



Scheme 1 — Prepared derivatives **T_1-T_{33}**

Table 2 — Physical properties of thiazepine (**Z_{27}**)

Mol. Formula	R_f	m.p. (°C)	Colour	Yield (%)
$C_{19}H_{21}BrN_2O_2S$	0.81	298-300	Light Yellow	82

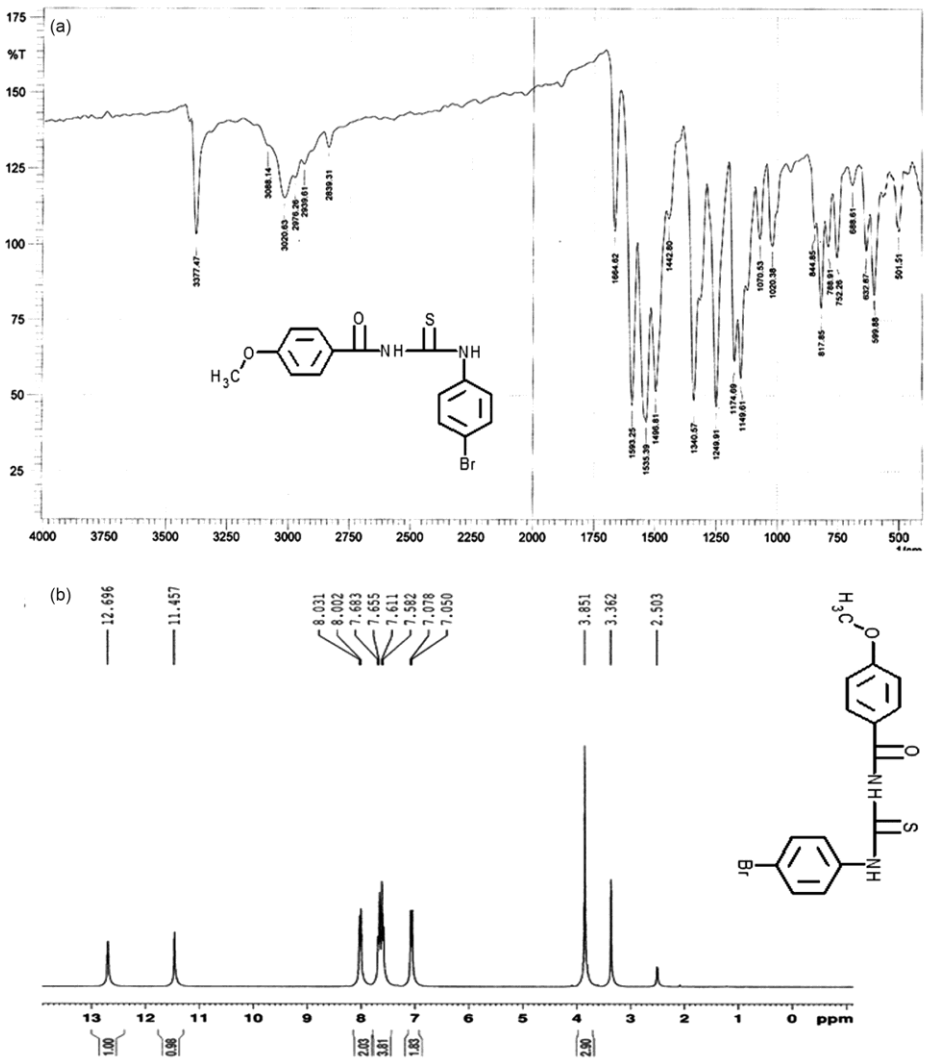
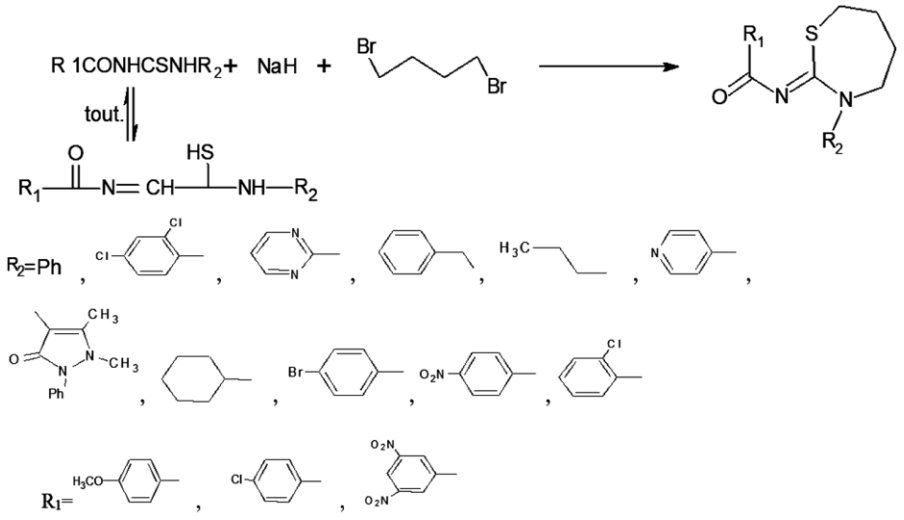


Fig. 2 — (A) FTIR spectrum of T_9 and (B) H^1-NMR of **T_9**



Scheme 2 — Prepared 1,3-thiazepine derivatives

The prepared 1,3-diazepine derivatives resulted from two nucleophilic condensations between two compounds, leading to a 1,3-thiazepine seven-member ring[34]. The reduction of thiourea derivatives using sodium hydride. The resulting thiourea derivative nucleophile attacks the 1,4-dibromobutane at the carbon **1** associated with the liberation of HBr. A second nucleophilic reaction occurs by the nitrogen atom that originated from the primary amine. At the second end of the bromobutane, it resulted in seven-membered rings of 1,3-thiazepine. The resulting thiazepines bear the aryl imino group at position **2**. The 1,3-thiazepines derivatives (**Z_1-Z_{26}**) have resulted from thiourea prepared from three different aryl halides with aliphatic and aromatic primary amines. Therefore, the seven-member ring is essentially substituted at the nitrogen with aliphatic and aromatic groups' variation. In addition to that, the resulting rings are attached to a different aryl imino group at position **2**. The prepared derivatives were identified, and their structures were elucidated using chromatographic and spectroscopic methods[35-37].

The first characteristic band of the prepared compounds (**Z_1- Z_{26}**) (C=N) stretching vibration appeared between (1575-1681 cm^{-1}). The stretching liberation of amide carbonyl groups (C=O) was at (1644-1728 cm^{-1}). The disappearance of (N-H) stretching vibration indicates the consumption of thiourea derivative. The IR data are shown in Fig. 3A and Table 3, as well as the spectral absorption packs of the compound (**Z_{27}**) are shown in Table 4. Some of the prepared 1,3-thiazepine derivatives (**Z_7, Z_{13}, Z_{19}, Z_{21}**) were recorded. The ^{1}H NMR data was shown in Fig. 3B. The spectra confirmed the formation of the compounds and helped the elucidation of their structures.

Table 3 — IR –spectral data of compounds (**Z_1- Z_{26}**)

Compd	υ(C=N) cm^{-1}	υ(C=O) cm^{-1}	υ(C=C) Ar cm^{-1}	υ(C-H) Ar cm^{-1}	υ(C-H) Aliphatic cm^{-1}	υ(others) cm^{-1}
Z_1	1654	1699	1599, 1473	3068	2926	–
Z_2	1681	1708	1599, 1479	3088	2968, 2845	υ(C-Cl)759
Z_3	1637	1693	1604, 1477	3020	2937, 2841	–
Z_4	1589	1644	1556, 1464	3061	2968, 2874	–
Z_5	1608	1683	1573, 1452	3000	2922, 2850	υ(C=N)1573
Z_6	1643	1666	1602, 1465	3072	2931, 2839	υ(C=O)1695
Z_7	1660	1699	1595, 1481	3064	2968, 2839	υ(C-Br)603
Z_8	1674	1707	1589, 1481	3066	2980, 2841	υ(C-Cl)734
Z_9	1670	1699	1602, 1435	3080	2972, 2939	υ(C-NO_2)1556,1338
Z_{10}	1637	1687	1600, 1462	3049	2964, 2779	υ(C-Cl)754
Z_{11}	1589	1701	1541, 1477	3138	2928, 2858	υ(C-Cl)752
Z_{12}	1602	1668	1579, 1487	3043	2989, 2943	υ(C-Cl)759
Z_{13}	1608	1689	1515, 1456	3082	2968, 2858	υ(C-Cl)744 υ(C=N)1575
Z_{14}	1643	1697	1581, 1465	3097	2982, 2841	υ(C-Cl)756 υ(C=O)1664
Z_{15}	1672	1701	1591, 1475	3093	2970	υ(C-Cl)763 υ(C-Br)624
Z_{16}	1597	1703	1545, 1487	3080	2931, 2858	υ(C-Cl)746
Z_{17}	1616	1668	1593, 1450	3086	2928	υ(C-Cl)750 υ(C-NO_2)1504,1332
Z_{18}	1626	1724	1545, 1462	3091	2964, 2895	υ(C-NO_2)1545,1350
Z_{19}	1629	1728	1545, 1456	3086	2943	υ(C-NO_2)1545,1350
Z_{20}	1626	1726	1546, 1464	3088	2966	υ(C-NO_2)1546,1350
Z_{21}	1626	1722	1545, 1462	3091	2966	υ(C-NO_2)1545,1352
Z_{22}	1658	1724	1595, 1462	3091	2964, 2940	υ(C-NO_2)1545,1352 υ(C=N)1626
Z_{23}	1626	1726	1546, 1452	3000	2933, 2858	υ(C-NO_2)1500,1348
Z_{24}	1626	1724	1545, 1462	3091	2964, 2920	υ(C-NO_2) 1545,1350 υ(C-Br)646
Z_{25}	1622	1724	1543, 1456	3090	2943, 2920	υ(C-NO_2) 1543,1350 υ(C-Cl)712
Z_{26}	1604	1653	1519, 1465	3109	2976, 2858	υ(C-NO_2)1519,1296

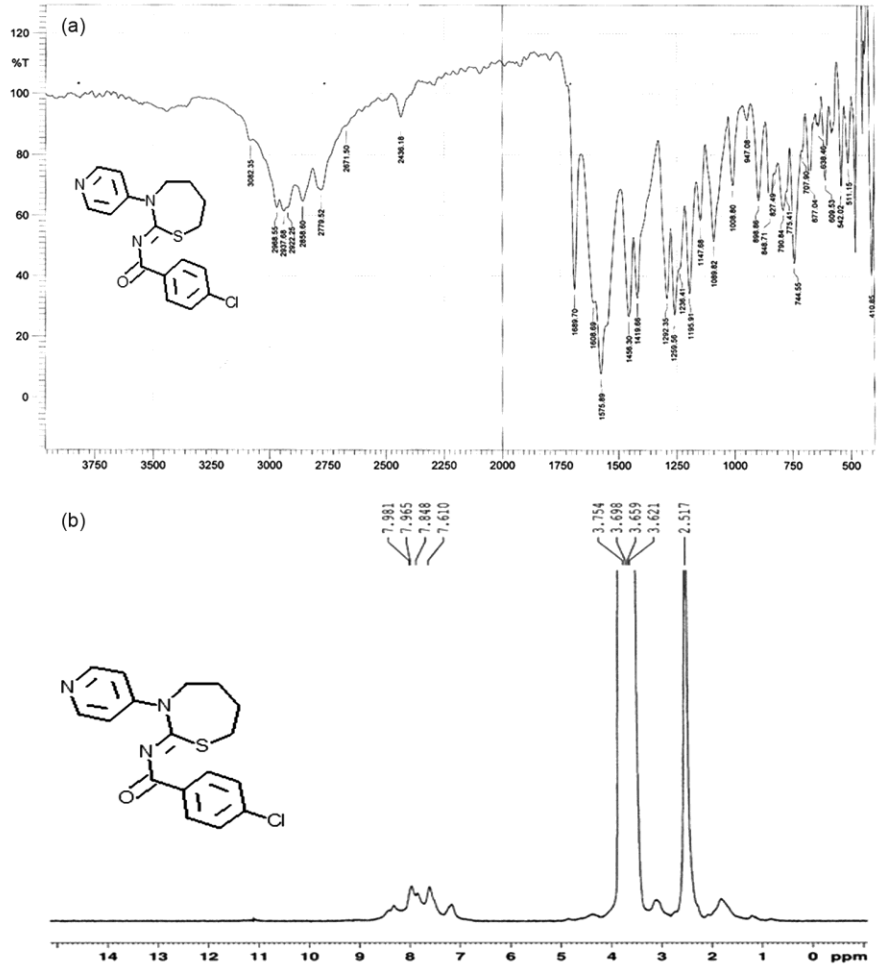


Fig. 3 — (A) FTIR spectrum of $\mathbf{Z_{13}}$ and (B) H^1-NMR of $\mathbf{Z_{13}}$

Table 4 — The spectral absorption packs of the compound ($\mathbf{Z_{27}}$)

Compd	υ(C=N) cm^{-1}	υ(O-H) cm^{-1}	υ(C=C) Ar cm^{-1}	υ(C-H) Ar cm^{-1}	υ(C-H) Aliphatic cm^{-1}	υ(others) cm^{-1}
$\mathbf{Z_{27}}$	1595	3446	1554, 1460	3074	2928, 2852	υ(C-Br) 615

A preliminary study to improve some of the reaction conditions and other parameters finished the following conclusions:

(i) The use of an excess of sodium hydride (at least two folds) reduced the carbonyl group in the thiazepine derivative in preparation ($\mathbf{Z_{27}}$).

(ii) The use of different reducing agents such as calcium hydride, which was added to mineral oil in order to obtain desperation of the hydride on the surface of the oil. Such change resulted in a low conversion of thiourea derivative to 1,3-thiazepine derivative. This might be due to the limited capacity of calcium hydride as a reducing agent. However, using an excess of calcium hydride (three folds) resulted in complete conversion to the desired compounds ($\mathbf{Z_7}$).

(iii) After completing the 1,4-dibromobutane addition, the reactants were heated by reflux in DMF for two hours. After elaboration of the product, the yield was increased by about 10%.

The well-diffusion agar technique was followed to measure the same prepared 1,3-thiazepine antimicrobial activity on three types of bacteria, Staphylococcus aureus Pseudomonas aeruginosa, and *Escherichia coli*[38-42]. The cefotaxime was used as a standard antibiotic. The solvent used for the tested compounds and the standard was DMF. The inhibition zone was measured in mm for four concentrations in ppm (5000, 10000, 20000, and

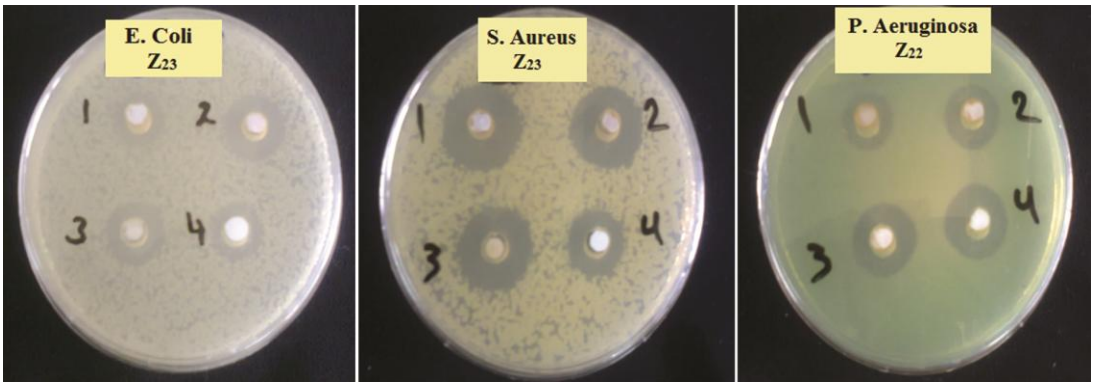


Fig. 4 — Compound (**Z_{23}**) inhibits the growth of bacteria *Escherichia coli* and *Staphylococcus aureus*, and Compound (**Z_{22}**) inhibits the growth of bacteria *Pseudomonas aeruginosa* at four of the effective concentrations 1= 30000ppm, 2= 20000ppm, 3= 10000ppm, 4= 5000ppm

Table 5 — Antimicrobial activity of some synthesized 1,3-thiazepine compounds

Test Compd	*E. coli*				*S. aureus*				*P. aeruginosa*			
	Effective concentration of the compound, ppm											
	30000	20000	10000	5000	30000	20000	10000	5000	30000	20000	10000	5000
	Zone of inhibition, mm											
Z_1	0.9	0.8	0.6	0.6	–	–	–	–	1.45	1.15	1.1	1.1
Z_4	0.55	0.6	0.8	0.8	–	–	–	–	0.9	1	1	1
Z_{12}	0.9	0.9	0.9	1	0.95	0.75	0.65	–	0.95	1.4	1.4	1.45
Z_{16}	0.7	0.7	0.7	0.9	–	–	–	–	1.4	1.1	1.6	1.5
Z_{22}	0.75	0.9	0.75	0.8	1.45	1.4	1.25	1	0.8	0.59	1.05	1.25
Z_{23}	0.8	1.1	0.9	0.9	1.6	1.5	1.4	0.95	1.2	1.55	1.1	1.55
Cefotaxime	1.9	1.7	1.65	0.9	3.25	3.25	2.75	2.65	3.3	3.3	3	2.55

30000), as the data were shown in Fig. 4 and Table 5. The tested compounds (**Z_1, Z_4, Z_{16}**) demonstrated a moderate inhibition against *P. aeruginosa* and *E. coli*. The compounds (**Z_{12}, Z_{22}, Z_{23}**) showed the most significant biological activity against the three bacteria except the compound (**Z_{12}**) in the concentration of 5000 ppm, which did not demonstrate biological activity against *S. aureus*. To conclude, 1,3-thiazepine derivatives were synthesised, characterised, and evaluated for antimicrobial activity. The method employed in this study has several benefits, including a quick reaction rate, a straightforward procedure, moderate reaction conditions, and higher yields. The newly synthesised compounds exhibited significant antibacterial activity against *P. aeruginosa*, *E. coli* and *S. aureus* becteria. However, all of the prepared compounds had varying biological activity against the bacteria examined, indicating that more research is needed by broadening the scope of the bacteria studied and maybe the fungi as well. In addition, the remainder of the produced compounds must be analysed in order to aid their activity and, ultimately, their significance.

Conclusion

To conclude, novel 2-iminohexahydro-1,3-thiazepine derivatives were synthesised, characterised, and evaluated for antimicrobial activity. The newly synthesised compounds exhibited moderate antibacterial activity against *P. aeruginosa*, *E. coli* and *S. aureus*. Compounds (Z_1, Z_4, Z_{16}) showed good activity against *P. aeruginosa* and *E. coli* and compounds (Z_{12}, Z_{22}, Z_{23}) showed good activity against *P. Aeruginosa*, *E. coli* and *S. aureus*.

Supplementary Information

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

Acknowledgements

The authors gratefully acknowledge financial support from Pharmaceutical Chemistry, Pharmaceutical Science, Semmelweis University, Hungary, Budapest, the Institute of Modern Optics, College of Electronic Information and Optical Engineering, Nankai University, Tianjin, China, and Department of

Chemistry, College of Science, Al-Mustansiriya University, Baghdad, Iraq.

References

1 Struga M, Kossakowski J, Koziol AE, Kedzierska E, Fidecka S, Colla P L, Ibba C, Collu G, Sanna G, Secci B & Loddo R, *Eur J Med Chem*, 44, (2009) 4960.
2 Li Z-H, Li T-J, Liu J-Q & Wang X-S, *Tetrahedron*, 76 (2020) 130915.
3 Petrova K Y & Kim D, *Russian J Org Chem*, 55 (2019) 142.
4 Khan A J, Baseer M A, Dhole J & Shah S, *J Pharm Sci Res (IJPSR)*, 2 (2011) 2619.
5 Wang L, Zhang P, Zhang X, Zhang Y, Li Y & Wang Y, *Eur J Med Chem*, 44 (2009) 2815.
6 Garg N, Chandra T, Jain A B & Kumar A, *Eur J Med Chem*, 45 (2010) 1529.
7 Ameta K, Rathore N S & Kumar B, *J Serbian Chem Soc*, 77 (2012) 725.
8 Nikalje A P & Vyawahare D, *African J Pure App Chem*, 5 (2011) 422.
9 Pitchai M, Sankar U, Venkateshappa S S, Akunuri A, Rampulla R, Mathur A & Gupta A, *J Heterocyc Chem*, 58 (2020) 558.
10 Umirov M, Eshimbetov A, Ashurov J, Turgunov K & Khodjaniyazov K, *Eur J Chem*, 14 (2023) 9-15.
11 Campiani G, Nacci V, Bechelli S, Ciani SM, Garofalo A, Fiorini I, Wikstrom H, Boer P D, Liao Y, Tepper P G, Cagnotto A & Mennini T, *J Med Chem*, 41 (1998) 3763-72.
12 Nazeri MT, Ahmadi M, Ghasemi M, Shaabani A & Notash B, *Org Biomol Chem*, 21 (2023) 4095.
13 Yadav J, Pawar AP, Nagare YK, Iype E, Rangan K, Ohshita J, Kumar D & Kumar I, *J Org Chem*, 85 (2020)14094.
14 Devi A P, Ameta K L, Alshehri S, Almalki A H, Haque S, Sayyed R Z, *J King Saud Uni Sci*, 35 (2023) 102528.
15 Cheng B, Li Y, Wang T, Zhang X, Li H, He Y, Li Y & Zhai H, *J Org Chem*, 85 (2020) 6794.
16 Yilmaz E S & Zora M, *Syn Comm*, 51 (2021) 709.
17 May L & Müller T J, *Molecules*, 25 (2020) 2180.
18 Mahale G D, Kumar A, Singh D, Ramaswamy A & Waghmode S B, *J Serbian Chem Soc*, 73 (2008) 385.
19 Szakonyi Z, Zupkó I, Sillanpää R & Fülöp F, *Molecules*, 19 (2014) 15918.
20 Kruithof A, Ploeger M L, Janssen E, Helliwell M, De Kanter F J J, Ruijter E & Orru R V A, *Molecules*, 17 (2012) 1675.
21 Kelgokmen Y & Zora M, *Org Biomol Chem*, 17 (2019) 2529.
22 Vairoletti F, Medeiros A, Fontán P, Meléndrez J, Tabárez C, Salinas G, Franco J, Comini M A, Saldana J, Jancik V, Mahler G & Saiz C, *Med Chem Comm*, 10 (2019) 1481.
23 Ahmed M M S & Farghaly T A, *Lett Org Chem*, 15 (2018) 183.
24 Kelgokmen Y & Zora M, *J Org Chem*, 83 (2018) 8376.
25 Kaur N, *Phosph Sulf Silicon Rel Ele*, 194 (2019) 186.
26 Vatankhah E, Akbarzadeh M, Jabbari A, Saadat K & Shiri A, *Poly Aromatic Comp*, 43 (2023) 288.
27 Gudisela MR, Srinivasu N, Mulakayala C, Bommu P, Rao M V B & Mulakayala N, *Bioorg Med Chem Lett*, 27 (2017) 4140.
28 Peudru F, Lohier J-F, Gulea M & Reboul V, *Phosp Sulfur Sil Related Ele*, 191 (2016) 220.
29 Wu L, Yang X, Peng Q & Sun G, *Eur J Med Chem*, 127 (2017) 599.
30 Kelgokmen Y & Zora M, *J Org Chem*, 83 (2018) 8376.
31 Pitchai M, Ulaganathan S, Venkateshappa SS, Akunuri A, Rampulla R, Mathur A & Gupta A, *J Hetero Chem*, 58 (2021) 558.
32 Niu X, Yang B, Li Y, Fang S, Huang Z, Xie C & Ma C, *Org Biomol Chem*, 11 (2013) 4102.
33 Takallou A, Al-Shidhani S, Anwar M U & Al-Harrasi A, *Synthesis*, 55 (2023) 489.
34 Xiang J, Zhang Z, Mu Y, Xu X, Guo S, Liu Y, Russo D P, Zhu H, Yan B & Bai X, *ACS Comb Sci*, 18 (2016) 230.
35 Mouradzadegun A, Elahi S & Ghanbarzadeh P, *Phosph Sulfur Sil Rel Ele*, 190 (2015) 2031.
36 Tayde D & Lande M, *Chem Rev Lett*, 4 (2021) 30.
37 Elmaati T M A & El-Taweel F M, *J Chinese Chem Soc*, 50 (2003) 413.
38 Mohamed S M A & Thoraya A F, *Lett Org Chem*, 15 (2018) 183.
39 Shi F, Zeng X-N, Cao X-D, Zhang S, Jiang B, Zheng W-F & Tu S-J, *Bioorg Med Chem Lett*, 22 (2012) 743.
40 Hernández S, Moreno I, SanMartin R, Herrero M T & Domínguez E, *Org Biomol Chem*, 9 (2011) 2251.
41 Preet S & Cannoo D S, *J Chinese Chem Soc*, 64 (2017) 296.
42 Dar P A, Dar N A, Rather E & Shah W A, *Mater Today Comm*, 35 (2023) 106206.