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# Synthesis, Identification, and Antibacterial Effect Assessment of Some New 1,4-Thiazepines, Derived from Substituted Diphenyl Acrylamides and Diphenyl Dienones

**Saad Salem Jasim[1] Jawdat Hilmi Abdulwahid[2], Shakhawan Beebany[1]*, Bari Lateef Mohammed[3]**

[1]*Chemistry Department, College of Sciences, University of Kirkuk, Kirkuk, Iraq*
[2]*Environmental and Pollution Engineering Department, Technical Engineering College, Northern Technical University of Kirkuk, Kirkuk, Iraq*
[3]*Biology Department, College of Sciences, University of Kirkuk, Kirkuk, Iraq*

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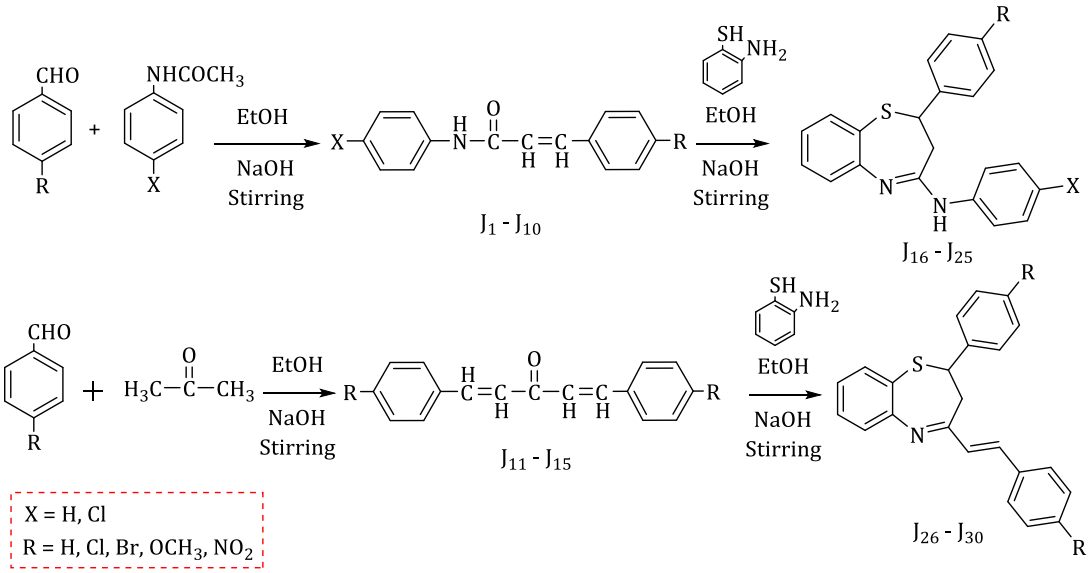
**ABSTRACT**

Some new 1,4-thiazepine derivatives ($J_{16}$-$J_{30}$) have been successfully synthesized through the reaction between each of diphenyl acryl amides ($J_1$-$J_{10}$) and diphenyl dienones ($J_{11}$-$J_{15}$) with ortho-mercapto aniline. The reaction was performed in an alkaline medium using ethanol as a solvent. The diphenyl acryl amides were prepared from the condensation reaction of para-substituted acetanilides with different para benzaldehydes, while para-substituted benzaldehydes were reacted with acetone to produce the diphenyl dienones. All the prepared compounds have been identified, using visible and ultraviolet radiation spectrum, and infrared spectrum. Some of the new synthesized compounds have been diagnosed and confirmed their structures by proton and carbon nuclear magnetic resonance spectrum ($^1$H-NMR and $^{13}$C-NMR, respectively). The purity of prepared compounds was confirmed by relying on thin-layer chromatography (TLC) results. The biological effect of these derivatives was assessed against certain types of gram-positive bacteria (*Streptococcus Pneumonia* and *Staphylococcus Aureus*) and gram-negative bacteria (*Escherichia Coli, Pseudomonas Aeruginosa,* and *Proteus Moralities*). The results showed a high antibacterial effect towards both types of the used bacteria at high concentrations, while the prepared compounds behaved differently at low concentrations. The results indicated that most of new thiazepines revealed a high antibacterial effect towards both types of the tested bacteria at high concentrations (100 mg/mL), while behaved oppositely at low concentrations (10 and 50 mg/mL). This is related to high concentration effect resulting in an increase for inhibition zone diameter. The highest antibacterial effect was observed for compounds ($J_{17}$, $J_{19}$, $J_{21}$, $J_{24}$, $J_{25}$, $J_{26}$, $J_{28}$, and $J_{30}$) at 100 mg/mL. One of the reasons could be the presence of halogenes and nitro groups compared to the other compounds as a result of electron withdrawal groups role.

* Corresponding author: Shakhawan Beebany
✉ E-mail: sh.beebany@uokirkuk.edu.iq

**GRAPHICAL ABSTRACT**




## Introduction

Heterocyclic compounds have been of great interest in the synthesis of many pharmaceutical properties increasing their biological significance such as anesthesia, sedatives, anti-inflammatories, and anti cancer [1], in addition to be used as antifungal, antibacterial [2], and depression treatment [3]. Heterocycles with seven rings containing nitrogen atoms in their composition possess wide pharmaceutical applications such as effective anti-cancer drugs [4].

Thiazepine derivatives are one example of heterocyclic compounds having a good biological activity. It was reported that thiazepines heva been widely applied as antibacterial [5], antifungal [6], antiinflamotry [7], antioxidant, and anticancer [8].

According to the literature, the more recent and common method to synthesis thiazepines is carried out via cyclization reaction for *α,β*-unsaturated carbonyl compounds treated with ortho mercapto aniline in alkaline media [9]. This reaction included 1,4-Michael addition followed by 1,2- cycloaddition to give thiazepine [6]. Thiazepine synthesis reaction has academic interest [7] due to it gives good yield and does not require complicated separation and purification steps. Furthhermore, thiazepine preparation is not complicated reaction and needs to cheap started materials. Thiazepine also enjoys with a high biological activity.

Recently, synthesis of some new chemical compounds including thiazepine unit has been reported in the literature as follow; *N*-propargylic-*β*-enaminothiones submitted to cyclization reaction to synthesize methylene-thiazepines [10] using zinc chloride with chloroform as solvent. Moreover, dibenzoimidazothiazepine compounds [11] were synthesized, when substituted diaryllimidazole treated with orthobromothiol through catalyzed coupling reaction via copper ligand (CuI/o-phen) in alkaline salt ($K_2CO_3$). Likewise, alkylester thiolates were treated with substited phenyl amide in organic alkaline salt (tBuOK) and dichloromethane as solvent to prepare benzothiazepine derivatives [12]. In addition, dipyrimidothiazepine derivatives [13] were prepared by the treatment of substituents of methylpyrimidine with substituted of pyrimidinethiols in the presence of organic base ($Et_3N$) and acetonitrile as solvent.

According to this literature review, there is a lack in synthesis of thiazepine derivaties from substituted acrylamides and phenyl dienones whereas the mentined compounds can be easily prepared from cheap materials. In general, these derivatives are also possess bioactive characterstics (antibacterial and anti-fungal effect among others). Consequently, plan has been made to synthesis substituted acrylamides and phenyl dienones with their transferral to new corresponding thiazepines.

The aim of this research is to synthesize some new 1,4-thiazepine derivatives; from substituted diphenyl acrylamides and diphenyl dienones in addition to the evaluation of their antimicrobial activity against some gram-positive and gram-negative bacteria. Synthesis and biological activity evaluation of new heterocycle compounds are considered as scientific value academically.

## Experimental

*Materials*

All the chemicals were used in this research supplied by (BDH, Alfa, GCC, Fluke, Merck, and Aldrich).

*Devices instrument*

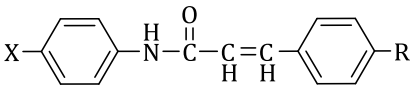
The melting point was measured using Electrothermal melting point apparatus 9300 in open capillary tubes (uncorrected). For the purity of all the prepared compounds, the TLC has been used. The FT-IR spectra have been taken recorded using the FT-IR 8400s Shimadzu spectrophotometer scale 4000-400 $cm^{-1}$. The UV-Vis Spectra have been scanned in ethanol using Shimadzu 800uv in the range of 200-800 nm. For the UV-Visible spectra, ethanol ($10^{-5}$-$10^{-4}$ M, 95 %) was used. $H^1$-NMR and $C^{13}$-NMR spectra were recorded on Varian operating at 400 MHz instrument using DMSO-$d^6$ as a solvent.

*Synthesis methods*

*Synthesis of diphenyl acrylamide derivatives ($J_1$-$J_{10}$) [14]*

Acetanilide and para-cholro acetanilide (0.676 g, 0.005 m and 0.853 g, 0.005 m respectively) was sepearately mixed with different para-substituted benzaldehydes (0.005 m) in ethanol (25 mL) as solvent. After that, sodium hydroxide solution (10 %) was added dropewise to the mixture with constant stirring until it became alkaline. The mixture was stirred for 6-7 hours at the room temperature. The solution was concentrated by evaporating the excess solvent, cooled, and neutralized by adding HCl (10 %). After filtration, the solid product collected and dried. It was crystlalized by ethanol to obtain the interested product. The physical characterstics of prepared derivatives are listed in Table 1.

**Table 1**: Physical properties of the compounds ($J_1$-$J_{10}$)



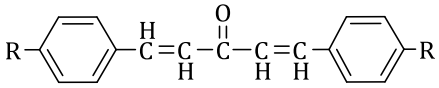

| Compound No. | X | R | M. Wt (g/mole) | M.P. (°C) | Yield % | Colour |
|---|---|---|---|---|---|---|
| $J_1$ | H | H | 233.28 | 119-120 | 60 | Light yellow |
| $J_2$ | H | Cl | 257.72 | 126-128 | 67 | Yellowish white |
| $J_3$ | H | Br | 302.17 | 116-118 | 75 | Yellowish white |
| $J_4$ | H | $OCH_3$ | 253.30 | 121-123 | 65 | White crystal |
| $J_5$ | H | $NO_2$ | 268.27 | 112-113 | 70 | Dark red |
| $J_6$ | Cl | H | 257.72 | 173-175 | 65 | Light orange |
| $J_7$ | Cl | Cl | 292.16 | 183-185 | 68 | Light orange |
| $J_8$ | Cl | Br | 336.61 | 276-277 | 55 | White |
| $J_9$ | Cl | $OCH_3$ | 287.74 | 143-145 | 68 | Yellow |
| $J_{10}$ | Cl | $NO_2$ | 302.71 | 178-179 | 60 | Dark red |

*Synthesis of Diphenyl Dienones derivatives ($J_{11}$-$J_{15}$) [15]*

Some para-substituted benzaldehydes (0.002 m) mixed with acetone (0.058 g, 0.001 m) in ethanol (25 mL), and then NaOH solution (10 %) added to the mixture as drops gradually. After the mixture alkalinity was confirmed by litmus paper, it was stirred for 2 hours at room temperature. The precipitatnt was filtered and washed with a little cold water, and then dried. It was crystallized by

ethanol to obtain the desired product. The physical characterstics of the prepared derivatives are summarized in Table 2.

**Table 2:** Physical properties of $J_{11\text{-}15}$

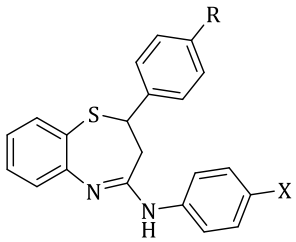


| Compound No. | R | M. Wt (g/mole) | M.P. (°C) | Yield % | Colour |
|---|---|---|---|---|---|
| $J_{11}$ | H | 234.30 | 108-110 | 81 | Yellow |
| $J_{12}$ | Cl | 303.18 | 192-194 | 71 | Light yellow |
| $J_{13}$ | Br | 392.09 | 141-143 | 86 | Light yellow |
| $J_{14}$ | $OCH_3$ | 294.35 | 118-119 | 65 | Greenish yellow |
| $J_{15}$ | $NO_2$ | 324.11 | 133-134 | 75 | Dark yellow |

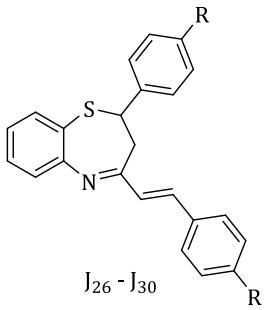
*Synthesis of thiazepine derivatives ($J_{16}$-$J_{30}$) [9]*

The prepared compounds ($J_1$-$J_{15}$) (0.005 m) mixed with (0.6 g, 0.005 m) of 2-aminobenzthiol in ethanol (50 mL), and then sodium hydroxide solution (5 mL, 10 %) was added to the mixture. It was refluxed for 8-10 hours. After cooling, it was filtered and the precipitate was washed three times with water, and then it was dried. The solid product was crystallized from ethanol to give the desired product. The physical characterstics of the prepared derivativeis are indicated in Table 3. Note that the used weights of compounds ($J_1$-$J_{15}$) were (1.166, 1.289, 1.511, 1.267, 1.341, 1.289, 1.461, 1.683, 1.439, 1.514, 1.172, 1.516, 1.960, 1.472, and 1.621) g, respectively.

**Table 3:** Physical characterstics of $J_{16}$-$J_{30}$



$J_{16}$ - $J_{25}$



$J_{26}$ - $J_{30}$

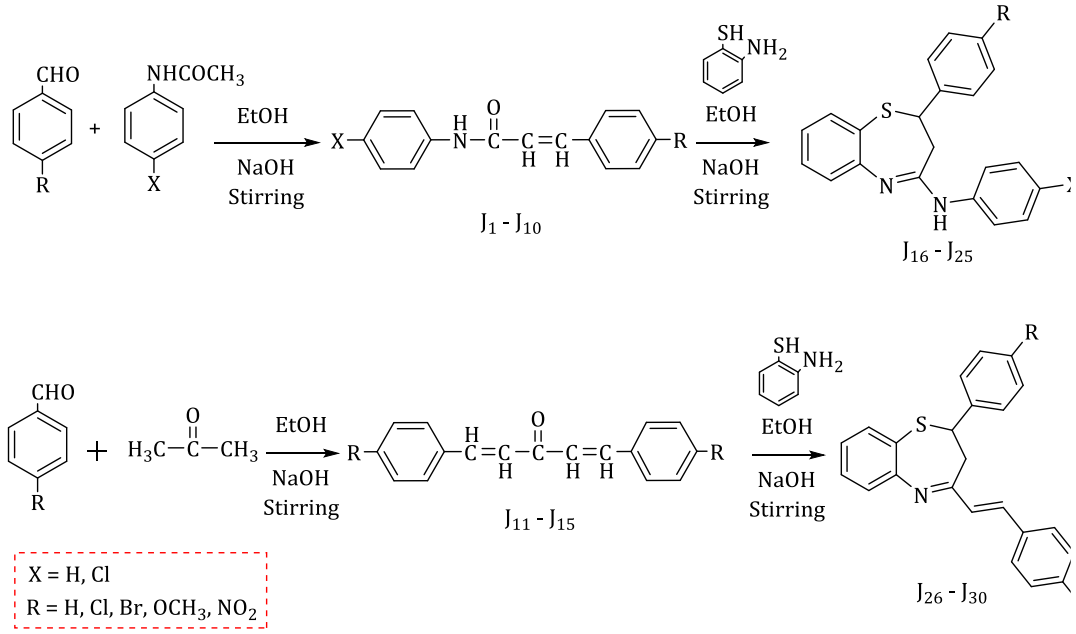
| Compound No. | X | R | M. Wt (g/mole) | M.p (°C) | Yield % | Colour |
|---|---|---|---|---|---|---|
| $J_{16}$ | H | H | 328.10 | 118-121 | 65 | Yellowish white |
| $J_{17}$ | H | Cl | 362.06 | 123-126 | 55 | White |
| $J_{18}$ | H | Br | 407.33 | 180-183 | 60 | White crystal |
| $J_{19}$ | H | $OCH_3$ | 358.46 | 118-121 | 70 | White crystal |
| $J_{20}$ | H | $NO_2$ | 373.43 | 130-132 | 75 | Light orange |
| $J_{21}$ | Cl | H | 362.06 | 184-187 | 65 | Yellow |
| $J_{22}$ | Cl | Cl | 397.32 | 191-193 | 62 | Yellow |
| $J_{23}$ | Cl | Br | 441.77 | 177-179 | 55 | Yellowish white |
| $J_{24}$ | Cl | $OCH_3$ | 392.90 | 189-191 | 63 | Yellow |
| $J_{25}$ | Cl | $NO_2$ | 407.87 | 176-179 | 60 | Light orange |
| $J_{26}$ | - | H | 356.49 | 136-138 | 59 | Light yellow |
| $J_{27}$ | - | Cl | 425.37 | 133-135 | 45 | Light brown |
| $J_{28}$ | - | Br | 514.28 | 186-188 | 57 | Yellowish white |
| $J_{29}$ | - | $OCH_3$ | 416.54 | 124-127 | 55 | Light yellow |
| $J_{30}$ | - | $NO_2$ | 431.15 | 160-162 | 65 | Light orange |

*Biological activity test*

The anti bacterial effect of some prepared products was assessed against gram-positive bacteria (*Streptococcus Pneumonia* and *Staphylococcus Aureus*) and gram-negative bacteria (*Escherichia Coli*, *Pseudomonas Aeruginosa,* and *Proteus Moralities)*. The microbials were separated and dignosed at Biology Laboratories in the Biology Department, Science College in Kirkuk University. The disks have been prepared from Whatman number 1 and maintained for 24 hours with the used compounds (25, 50, and 100) mg/mL. The diameter of inhibition region has been calculated for analysis towards each microbials. Ampicillin and amoxicillin have been utilized as blank and control materials with concentrations (25, 50, and 100) mg/ml. For more information about the procedure see [16,17].

## Results and Discussion

In this work, a new series of 1,4-thiazepine derivatives has been synthesized, as shown in Scheme 1. All the new prepared compounds were characterized by UN-Visible and FT-IR. Some of the new thiazpines have been identified by $^{1}$H-NMR and $^{13}$C-NMR spectra.




**Scheme 1:** Route shows all of the prepared compounds ($J_{1-30}$)

*Characterization of compounds ($J_1$-$J_{15}$)*

According to the UV-Visible scans, spectra were showed an absorbance peak at the range of (218-261 nm) for the (π- π*) transition refering to unsaturated bond group in (HC=CH) and another peak at the range (332-402 nm) for the (n- π*) transition corresponding to carbonyl group attached to unsaturated carbon bond (HC=CHC=O), as presented in Table 4.

The IR spectra of derivativess ($J_1$-$J_{15}$) exhibited disappearance of the carbonyl band for aldehyde derivatives at (1720-1715) cm$^{-1}$ with the appearance of bands at (3303-3288) cm$^{-1}$ referring to the substituted amide (NH). Furthermore, bands at (2887-2804) cm$^{-1}$ and (2998-2921) cm$^{-1}$ were observed corresponding to the symmetric and asymmetric stretching of (C-H) aliphatic, respectively. A strong band also appeared at (1670-1662) cm$^{-1}$ for amide carbonyl group. This refers to evidence for a change occurrence in aldehyde carbonyl group to chalcone. The UV-Visible and IR data are provided in Tables 4 and 5.

**Table 4:** UV-Visible for compounds $J_{1-15}$

| Compound No. | X | R | $\lambda_{max1}$ | $\lambda_{max2}$ |
|---|---|---|---|---|
| $J_1$ | H | H | 227 | 399 |
| $J_2$ | H | Cl | 237 | 392 |
| $J_3$ | H | Br | 261 | 402 |
| $J_4$ | H | $OCH_3$ | 218 | 401 |
| $J_5$ | H | $NO_2$ | 239 | 396 |
| $J_6$ | Cl | Br | 242 | 394 |
| $J_7$ | Cl | Cl | 261 | 393 |
| $J_8$ | Cl | H | 257 | 332 |
| $J_9$ | Cl | $OCH_3$ | 227 | 372 |
| $J_{10}$ | Cl | $NO_2$ | 218 | 390 |
| $J_{11}$ | - | H | 261 | 393 |
| $J_{12}$ | - | Cl | 242 | 401 |
| $J_{13}$ | - | Br | 239 | 385 |
| $J_{14}$ | - | $OCH_3$ | 227 | 401 |
| $J_{15}$ | - | $NO_2$ | 240 | 402 |

**Table 5:** FT-IR spectra data for compounds $J_{1-15}$

| Compound No. | R | IR (KBr) $cm^{-1}$ | | | | | |
|---|---|---|---|---|---|---|---|
| | | υ (C-H) Aromatic | υ (C=O) amide | υ (N-H) | υ (C=C) Aromatic (Sym., Asy.) | υ (C-N) | Other absorptions |
| | X | υ (C-H) Aliphtic (Sym., Asy.) | υ (C=O) *α, β* | | | | |
| $J_1$ | H | 3062 | 1662 | 3296 | 1554<br>1598 | 1261 | - |
| | H | 2856, 2955 | - | | | | |
| $J_2$ | Cl | 3020 | 1662 | 3296 | 1552<br>1598 | 1259 | υ (C-Cl) 754 |
| | H | 2856, 2921 | - | | | | |
| $J_3$ | Br | 3034 | 1662 | 3289 | 1523<br>1597 | 1209 | υ (C-Br) 967 |
| | H | 2829, 2965 | - | | | | |
| $J_4$ | $OCH_3$ | 3070 | 1662 | 3290 | 1552<br>1598 | 1269 | υ (C-O-C)<br>Sym. (1319)<br>Asy. (1498) |
| | | 2831, 2985 | - | | | | |
| $J_5$ | $NO_2$ | 3022 | 1664 | 3288 | 1554<br>1598 | 1261 | υ ($NO_2$)<br>Sym.(1321)<br>Asy.(1492) |
| | | 2856, 2921 | - | | | | |
| $J_6$ | Br | 3054 | 1666 | 3303 | 1568<br>1602 | 1257 | υ (C-Br) 967<br>υ (C-Cl) 824 |
| | Cl | 2870, 2951 | - | | | | |
| $J_7$ | Cl | 3070 | 1670 | 3298 | 1539<br>1602 | 1255 | υ (C-Cl) 831 |
| | Cl | 2860, 2923 | - | | | | |
| $J_8$ | H | 3076 | 1666 | 3303 | 1539<br>1602 | 1255 | υ (C-Cl) 829 |
| | Cl | 2956, 2931 | - | | | | |
| $J_9$ | $OCH_3$ | 3038 | 1664 | 3301 | 1570<br>1593 | 1267 | υ (C-O-C)<br>Sym. (1330)<br>Asy. (1570)<br>υ (C-Cl) 824 |
| | | 2857, 2965 | - | | | | |
| $J_{10}$ | $NO_2$ | 3062 | 1670 | 3301 | 1541<br>1602 | 1257 | υ (C-O-C)<br>Sym.(1331)<br>Asy. (1488)<br>υ (C-Cl) 831 |
| | H | 2856, 2933 | - | | | | |
| $J_{11}$ | H | 3046 | - | - | 1523<br>1597 | - | - |
| | - | 2853, 2975 | 1664 | | | | |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| $J_{12}$ | Cl | 3054 | - | - | 1556<br>1608 | - | υ (C-Cl) 824 |
| | - | 2820, 2941 | 1666 | | | | |
| $J_{13}$ | Br | 3048 | - | - | 1545<br>1593 | - | υ (C-Br) 981 |
| | - | 2804, 2968 | 1643 | | | | |
| $J_{14}$ | $OCH_3$ | 3038 | - | - | 1570<br>1585 | - | υ (C-O-C)<br>Sym. (1330)<br>Asy. (1570) |
| | - | 2887, 2998 | 1649 | | | | |
| $J_{15}$ | $NO_2$ | 3037 | 1655 | - | 1577<br>1588 | - | υ ($NO_2$)<br>Sym. (1324)<br>Asy. (1496) |
| | - | 2875, 2950 | | | | | |

The $^1$H-NMR spectrum for compound $J_{10}$ clearly shows the protons of benzene rings in the aromatic range region at δ 7.05 to δ 8.21. Furthemore, it gives amide proton in NHCO group at δ 9.43. A significant change is the observation of olefinic proton bands at δ 7.05 to δ 7.07 for HC*=CHCO group and at δ 6.66 to δ 6.68 for HC=C*HCO group, as displayed in Figure 1. This change is good evidence for converting the aldehyde carbrbonyl into chalcone synthesis [14]. Details about the proton signal data are available in Table 6.

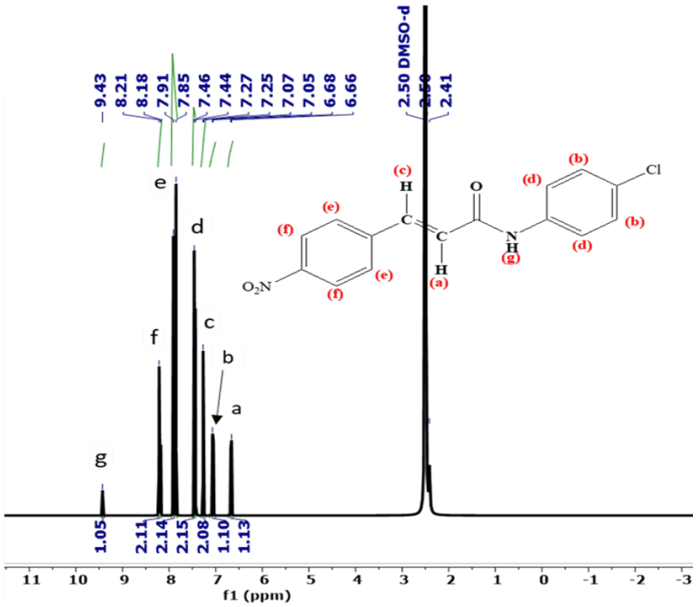
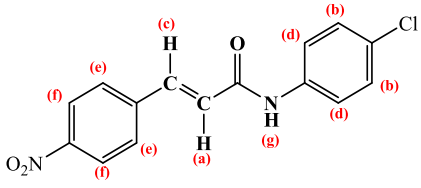



**Figure 1:** $^1$H-NMR spectrum of $J_{10}$

**Table 6:** $^1$H-NMR spectrum data for $J_{10}$

| Compound No. | Compound structure | $^1$H-NMR data of (δ-H) in ppm |
|---|---|---|
| $J_{10}$ |  | δ (6.66-6.68), (d, 1H, olefinic hydrogen) labeled (a); δ (7.05-7.07), (d, 2H, aromatic hydrogen) labeled (b); δ (7.25-7.27), (d, 1H, olefinic hydrogen) labeled (c); δ (7.44-7.46), (d, 2H, aromatic hydrogen) labeled (d); δ (7.85-7.91), (d, 2H, aromatic hydrogen) labeled (e); δ (8.18-8.21), (d, 2H, aromatic hydrogen) labeled (f); δ 9.43, (s, 1H, N-H) labeled (g). δ (2.50) for the solvent (DMSO-$d_6$) |

The $^{13}$C-NMR spectrum for compound $J_{10}$ obviously shows signals of the aromatic carbon atoms at the range of δ 119.42 to δ 146.07. In addition, a carbonl signal band appears at δ 168.74 for amide carbonyl in CONH group. A considerable alteration can be seen at δ 144.02 to δ 114.12 for olefinic carbon signals in *C=CCO and C=C*CO groups, respectively (see Figure 2). This supports the HNMR data and confirms the obtaining of chalcone product [15].

The remaining spectral data are listed in Table 7.

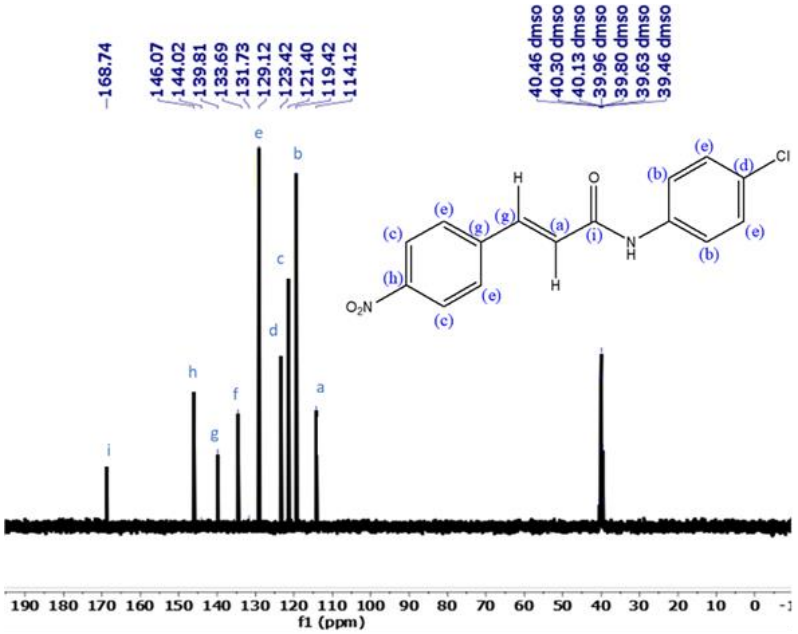
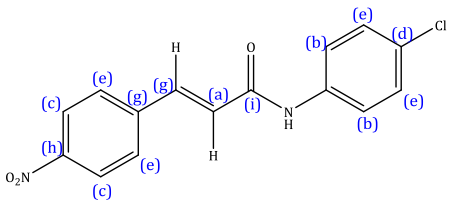



**Figure 2:** $^{13}$C-NMR spectrum of $J_{10}$

**Table 7:** $^{13}$C-NMR spectrum data for $J_{10}$

| Compound No. | Compound structure | $^{13}$C-NMR data of (δ-H) in ppm |
|---|---|---|
| $J_{10}$ |  | δ 144.12 for olefinic carbon labeled (a); δ 119.42 for two aromatic carbons labeled (b); δ 121.40 for two aromatic carbons labeled (c); δ 123.42 for aromatic carbon labeled (d); δ 129.12-131.73 for four aromatic carbons labeled (e); δ 133.69 for aromatic carbon labeled (f); δ 139.81-144.02 for aromatic and olefinic carbons respectively labeled (g); δ 146.07 for aromatic carbon labeled (h); finally δ 168.74 for carbonyl carbon labeled (i). |

*Characterization of 1, 4-Thiazepine compounds ($J_{16}$-$J_{30}$)*

These thiazepines have been synthesized when one mole of chalcones ($J_{1\text{-}15}$) treated with one mole of 2-mercapto aniline using ethanol as a solvent in alkaline medium, see Scheme 1.

The IR spectra of the 1,4-thiazepine compounds shows strong evidence for obtaining the interested compound with a band at a range of (1620-1640) cm$^{-1}$ for the (C=N) group and gives band for (C-S-C) group at (900-1000) cm$^{-1}$. In addition to the disappearance of both amidic carbonyl and α,β-unsaturated carbonyl groups in chalones ($J_{1\text{-}15}$), this suggests that the cyclization reation of chalcone compounds was successful, as reported in the literature [10]. The UV-Visible and IR data are summarized in Tables 8 and 9, respectively.

**Table 8:** UV-Visible for $J_{16\text{-}30}$

| Compound No. | X | R | $\lambda_{max1}$ | $\lambda_{max2}$ |
|---|---|---|---|---|
| $J_{16}$ | H | H | 245 | 399 |
| $J_{17}$ | H | Cl | 287 | 392 |
| $J_{18}$ | H | Br | 295 | 402 |
| $J_{19}$ | H | $OCH_3$ | 325 | 425 |
| $J_{20}$ | H | $NO_2$ | 339 | 396 |
| $J_{21}$ | Cl | Br | 342 | 394 |
| $J_{22}$ | Cl | Cl | 361 | 393 |
| $J_{23}$ | Cl | H | 257 | 332 |
| $J_{24}$ | Cl | $OCH_3$ | 327 | 372 |
| $J_{25}$ | Cl | $NO_2$ | 318 | 390 |
| $J_{26}$ | - | Br | 339 | 385 |

**Table 9:** FT-IR spectra data for $J_{16\text{-}30}$

| Compound No. | IR (KBr) $cm^{-1}$ | | | | | | |
|---|---|---|---|---|---|---|---|
| | R | υ (C-H) Arom. | υ (N-H) | υ (C=N) | υ (C=C) Arom. (Sym., Asy.) | υ (C-N) | Other absorptions |
| | X | υ (C-H) Aliph. (Sym., Asy.) | | | | υ (C-S) | |
| $J_{16}$ | H | 3120 | 3217 | 1631 | 1554<br>1594 | 1261<br>983 | - |
| | H | 2881, 2987 | | | | | |
| $J_{17}$ | Cl | 3010 | 3286 | 1632 | 1552<br>1598 | 1259<br>980 | υ (C-Cl) 754 |
| | H | 2846, 2951 | | | | | |
| $J_{18}$ | Br | 3024 | 3289 | 1628 | 1523<br>1596 | 1209<br>996 | υ (C-Br) 967 |
| | H | 2819, 2955 | | | | | |
| $J_{19}$ | $OCH_3$ | 3030 | 3293 | 1629 | 1543<br>1591 | 1265<br>972 | υ (C-O-C)<br>Sym.(1319)<br>Asy.(1498) |
| | H | 2831, 2980 | | | | | |
| $J_{20}$ | $NO_2$ | 3021 | 3287 | 1625 | 1574<br>1598 | 1261<br>996 | υ ($NO_2$)<br>Sym.(1321)<br>Asy.(1492) |
| | H | 2853, 2925 | | | | | |
| $J_{21}$ | Br | 3034 | 3313 | 1630 | 1565<br>1602 | 1257<br>1004 | υ (C-Br) 967<br>υ (C-Cl) 824 |
| | Cl | 2872, 2955 | | | | | |
| $J_{22}$ | Cl | 3070 | 3268 | 1632 | 1539<br>1600 | 1255<br>982 | υ (C-Cl) 831 |
| | Cl | 2860, 2923 | | | | | |
| $J_{23}$ | H | 3063 | 3236 | 1629 | 1533<br>1599 | 1294<br>967 | υ (C-Cl) 829 |
| | Cl | 2852, 2951 | | | | | |
| $J_{24}$ | $OCH_3$ | 3045 | 3209 | 1624 | 1572<br>1624 | 1273<br>979 | υ (C-O-C)<br>Sym.(1334)<br>Asy.(1570)<br>υ (C-Cl) 824 |
| | Cl | 2754, 2850 | | | | | |
| $J_{25}$ | $NO_2$ | 3042 | 3241 | 1633 | 1551<br>1612 | 1257<br>980 | υ ($NO_2$)<br>Sym.(1313)<br>Asy.(1488)<br>υ (C-Cl) 831 |
| | Cl | 2816, 2953 | | | | | |
| $J_{26}$ | Br | 3028 | - | 1628 | 1545<br>1593 | -<br>985 | υ (C-Br) 981 |
| | - | 2814, 2968 | | | | | |
| $J_{27}$ | Cl | 3004 | - | 1625 | 1556<br>1608 | -<br>992 | υ (C-Cl) 824 |
| | - | 2840, 2941 | | | | | |
| $J_{28}$ | H | 3056 | - | 1625 | 1523<br>1597 | -<br>1001 | - |
| | - | 2873, 2925 | | | | | |
| $J_{29}$ | $OCH_3$ | 3003 | - | 1624 | 1521<br>1535 | -<br>1039 | υ (C-O-C)<br>Sym.(1317)<br>Asy.(1535) |
| | - | 2891, 2935 | | | | | |
| $J_{30}$ | $NO_2$ | 3050 | - | 1628 | 1575<br>1590 | -<br>1001 | - |
| | - | 2850, 2940 | | | | | |

The $^{1}$H-NMR spectrum for compound $J_{18}$ (Figure 3) exhibits a band for (S-CH) group at δ 4.07 with the disappearance of amidic carbonyl and α,β-unsaturated carbonyl groups compared to the started materials. This reveals an eventuation of electronic alteration in *α,β*-unsaturated carbonyl groups for chalcones [10]. The remaining spectral data are collected in Table 10.

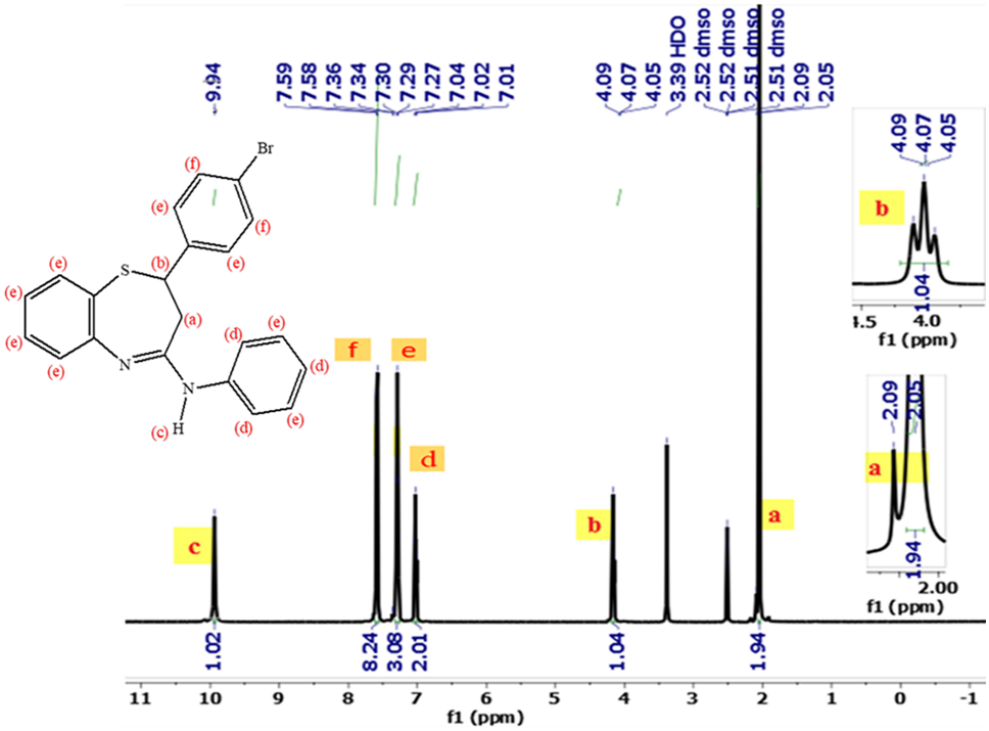
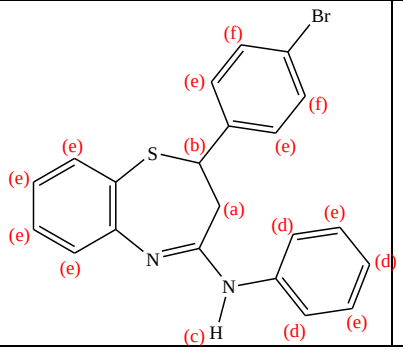



**Figure 3:** $^{1}$HNMR spectrum of $J_{18}$

**Table 10:** $^{1}$H-NMR spectrum data for $J_{18}$

| Compound No. | Compound structure | $^{1}$H-NMR data of (δ-H) in ppm |
|---|---|---|
| $J_{18}$ |  | δ (2.05), (d, 2H, CH2 in thiazepine ring) labeled (a); δ (4.07) δ, (t, 1H, CH-S in thiazepine ring) labeled (b); δ (9.94), (s, 1H, NH) labeled (c); δ (7.01-7.27), (3H, labeled (d)); δ (7.29-7.30), (8H, labeled (e)) and δ (7.34-7.59), (2H, labeled (f). |

The $^{13}$C-NMR spectrum of $J_{18}$ gives obvious evidence of preparation the interested product with a carbon bands at δ 57.58 for C-S group and at δ 57.58 for C-S group. Furthermore, it reveals the disappearance of two bands for carbonyl and olefinic carbons groups in the started material, as demonstrated in Figure 4. This confirms the cyclization reaction of chalcone to obtain the thiazpines [10]. The remaining spectral data are collected in Table 11.

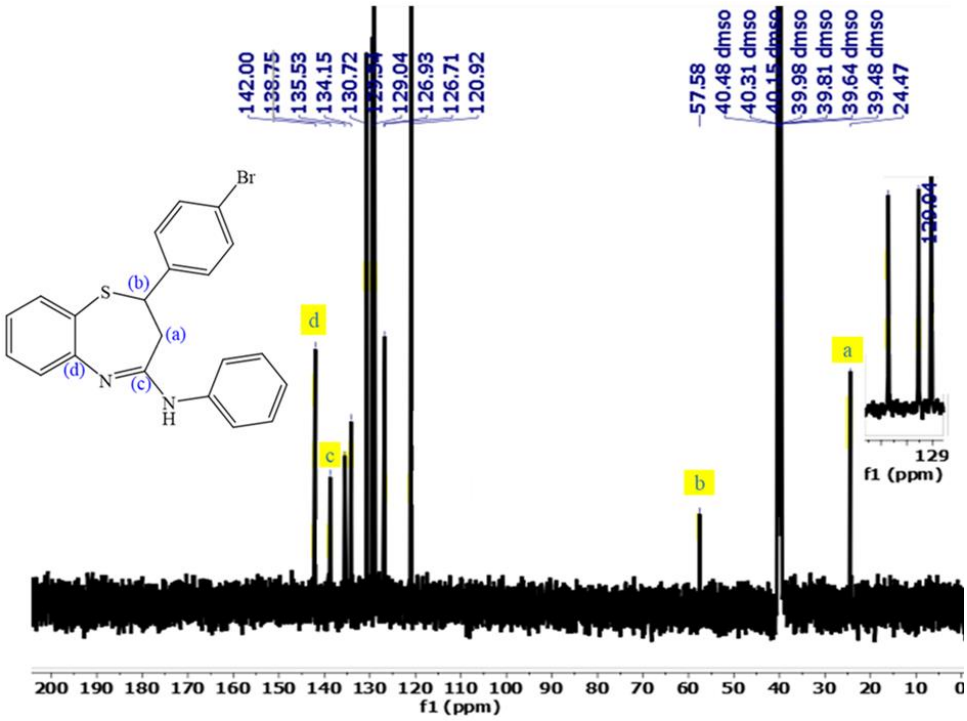
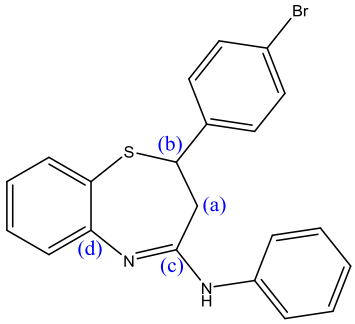



**Figure 4:** $^{13}$CNMR spectrum of $J_{18}$

**Table 11:** $^{13}$C-NMR spectrum data for $J_{18}$

| Compound No. | Compound structure | $^{13}$C-NMR data of (δ-C) in ppm |
|---|---|---|
| $J_{18}$ |  | δ 24.47 for carbon (in benzothiazepine ring) labelled (a); δ 57.58 for carbon (in benzothiazepine ring) labelled (b); δ 138.71 for carbon (in benzothiazepine ring- N=C-N) labelled (c); δ 142.00 for the fusion carbon that binds to nitrogen atom labelled (d); the bands in rang δ 120.92-135.53 due to the other aromatic carbons. |

Compared this synthesized procedure with the previous published works [10-13], it is noted that this method can be easily used to prepare thiazepines from α,□-unsaturated compunds and it is cheap and high slective reaction. Furthermore, it gives good yield and more safer than using bases like $K_2CO_3$ and tBuOK as well as solvents like chloroform, 1,2-dichloroethane, acetonitrile dimethyl sulfoxide, ether, tetrahydrofuran, and toluene. Furthermore, in this method, final products do not require to purification for complete identification of the products structure. Thus, it is easy, cheap, and more safe procedure without complicated steps for final products purification.

*Evaluation of biological efficacy of some prepared compounds*

The antibacterial effect of the compounds ($J_{16}$-$J_{30}$) were evaluated toward two types of gram-positive bacteria (*Streptococcus Pneumonia* and *Staphylococcus Aureus*) and gram-negative bacteria (*Escherichia Coli, Pseudomonas Aeruginosa*, and *Proteus Moralities*). The results indicated that most of new thiazepines revealed a high antibacterial effect towards both types of the tested bacteria at high concentrations (100

mg/mL), while behaved oppositely at low concentrations (10 and 50 mg/mL). This is due to high concentration effect leading to increase inhibition zone diameter. The highest inhibition zone diameter was for compounds ($J_{17}$, $J_{19}$, $J_{21}$, $J_{24}$, $J_{25}$, $J_{26}$, $J_{28}$, and $J_{30}$) at 100 mg/mL. This relates to the presence of halogenes and nitro groups compared to the other compounds due to the role of electron withdrawal groups [18]. The results of antibacterial effect are given in Table 12 and Figures 7-10.

**Table 12:** Antibacterial activity of the prepared compounds ($J_{16}$-$J_{30}$) and control antibiotic

| Compound No. | Staphylococcus Aureus (conc. mg/mL) | | | Streptococcus Pneumonia (conc. mg/mL) | | | Escherichia Coli (conc. mg/mL) | | | Pseudandrous Aeruginosa (conc. mg/mL) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 25 | 50 | 100 | 25 | 50 | 100 | 25 | 50 | 100 | 25 | 50 | 100 |
| $J_{16}$ | 1 | 1 | 2 | 0 | 1 | 4 | 1 | 1 | 2 | 1 | 2 | 2 |
| $J_{17}$ | 0 | 2 | 3 | 1 | 1 | 3 | 0 | 2 | 3 | 0 | 2 | 3 |
| $J_{18}$ | 0 | 1 | 2 | 0 | 2 | 2 | 0 | 2 | 4 | 0 | 1 | 2 |
| $J_{19}$ | 2 | 3 | 4 | 0 | 1 | 2 | 1 | 2 | 4 | 1 | 2 | 4 |
| $J_{20}$ | 2 | 3 | 3 | 2 | 3 | 4 | 1 | 1 | 2 | 1 | 2 | 2 |
| $J_{21}$ | 2 | 2 | 4 | 1 | 2 | 3 | 2 | 2 | 4 | 2 | 3 | 4 |
| $J_{22}$ | 0 | 1 | 2 | 3 | 3 | 4 | 0 | 1 | 2 | 0 | 1 | 2 |
| $J_{23}$ | 1 | 1 | 2 | 0 | 1 | 1 | 2 | 2 | 3 | 2 | 3 | 4 |
| $J_{24}$ | 0 | 1 | 2 | 2 | 3 | 3 | 0 | 2 | 3 | 0 | 2 | 3 |
| $J_{25}$ | 1 | 3 | 3 | 0 | 1 | 2 | 1 | 3 | 3 | 1 | 3 | 4 |
| $J_{26}$ | 1 | 2 | 4 | 2 | 2 | 5 | 1 | 2 | 4 | 1 | 2 | 4 |
| $J_{27}$ | 1 | 2 | 2 | 1 | 2 | 2 | 1 | 1 | 2 | 1 | 2 | 3 |
| $J_{28}$ | 2 | 2 | 3 | 1 | 3 | 4 | 1 | 2 | 3 | 2 | 2 | 3 |
| $J_{29}$ | 0 | 2 | 3 | 0 | 2 | 2 | 0 | 2 | 2 | 0 | 1 | 2 |
| $J_{30}$ | 2 | 3 | 4 | 0 | 1 | 1 | 1 | 2 | 4 | 2 | 3 | 4 |
| Ampicillin | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Amoxicillin | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Blank disk | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |

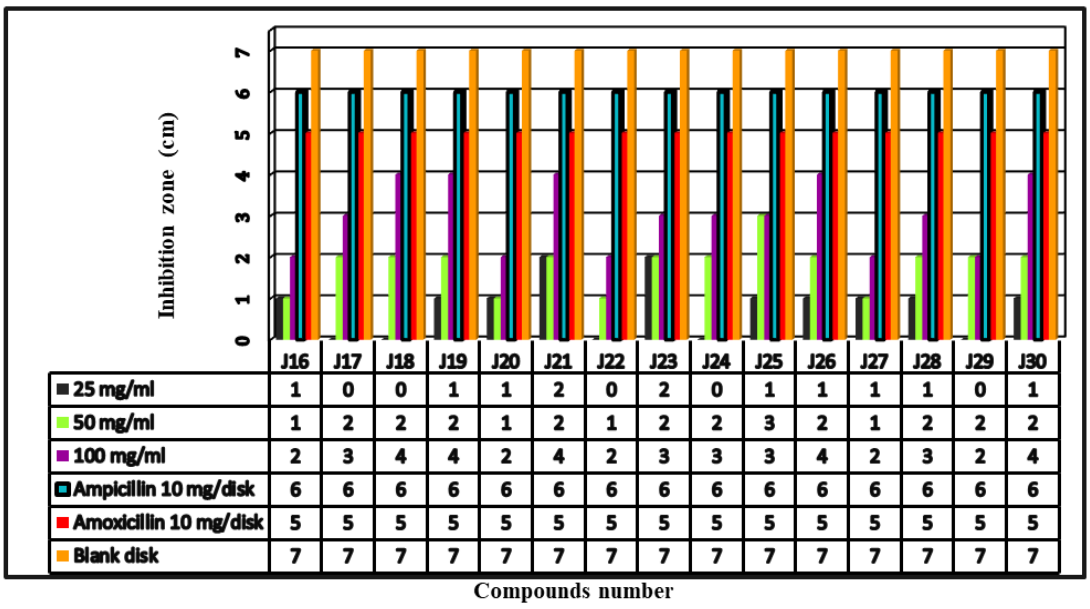
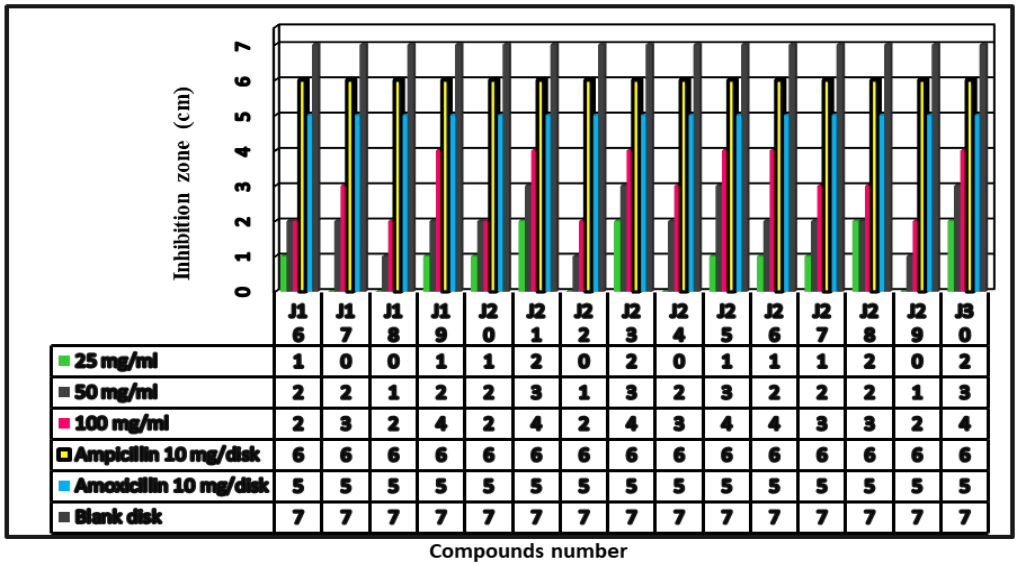
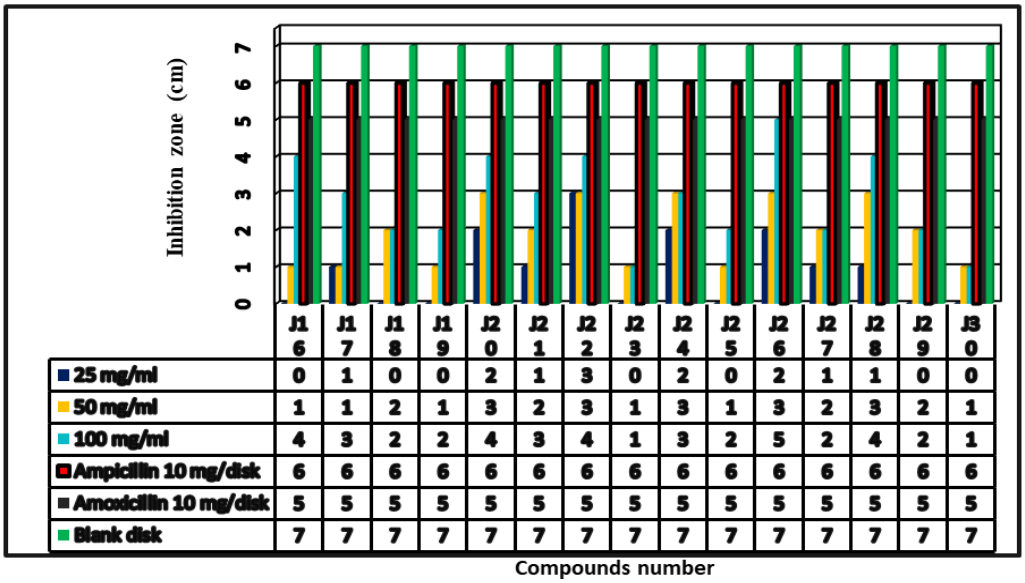



**Figure 7:** Shows biological activity of Staphylococcus Aureus



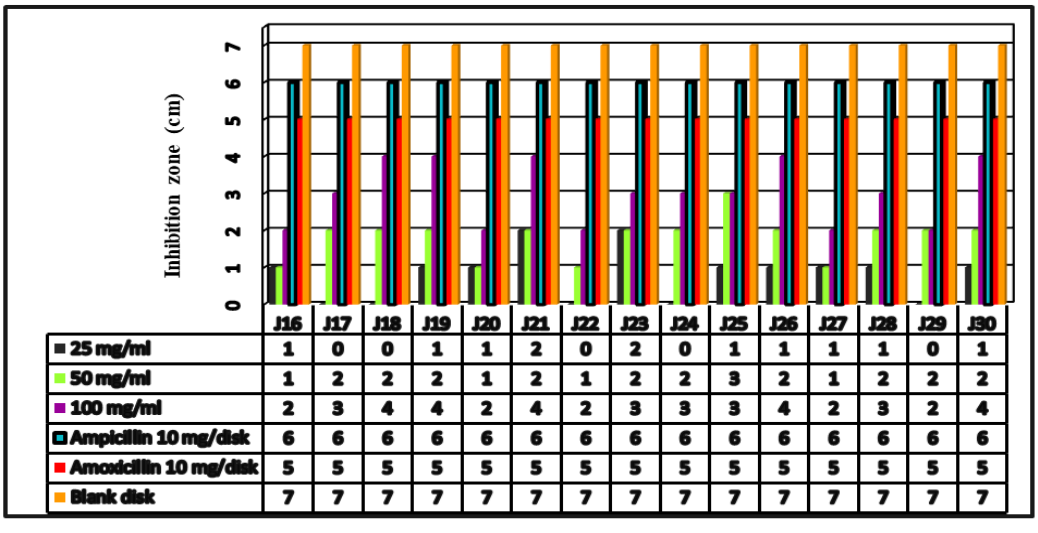

| | J16 | J17 | J18 | J19 | J20 | J21 | J22 | J23 | J24 | J25 | J26 | J27 | J28 | J29 | J30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 mg/ml | 1 | 0 | 0 | 1 | 1 | 2 | 0 | 2 | 0 | 1 | 1 | 1 | 2 | 0 | 2 |
| 50 mg/ml | 2 | 2 | 1 | 2 | 2 | 3 | 1 | 3 | 2 | 3 | 2 | 2 | 2 | 1 | 3 |
| 100 mg/ml | 2 | 3 | 2 | 4 | 2 | 4 | 2 | 4 | 3 | 4 | 4 | 3 | 3 | 2 | 4 |
| Ampicillin 10 mg/disk | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Amoxicillin 10 mg/disk | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Blank disk | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |

**Figure 8:** Sows Biological activity of Pseudandrous aeruginosa




| | J16 | J17 | J18 | J19 | J20 | J21 | J22 | J23 | J24 | J25 | J26 | J27 | J28 | J29 | J30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 mg/ml | 0 | 1 | 0 | 0 | 2 | 1 | 3 | 0 | 2 | 0 | 2 | 1 | 1 | 0 | 0 |
| 50 mg/ml | 1 | 1 | 2 | 1 | 3 | 2 | 3 | 1 | 3 | 1 | 3 | 2 | 3 | 2 | 1 |
| 100 mg/ml | 4 | 3 | 2 | 2 | 4 | 3 | 4 | 1 | 3 | 2 | 5 | 2 | 4 | 2 | 1 |
| Ampicillin 10 mg/disk | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Amoxicillin 10 mg/disk | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Blank disk | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |

**Figure 9:** shows biological activity of *Streptococcus pneumonia*




| | J16 | J17 | J18 | J19 | J20 | J21 | J22 | J23 | J24 | J25 | J26 | J27 | J28 | J29 | J30 |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 25 mg/ml | 1 | 0 | 0 | 1 | 1 | 2 | 0 | 2 | 0 | 1 | 1 | 1 | 1 | 0 | 1 |
| 50 mg/ml | 1 | 2 | 2 | 2 | 1 | 2 | 1 | 2 | 2 | 3 | 2 | 1 | 2 | 2 | 2 |
| 100 mg/ml | 2 | 3 | 4 | 4 | 2 | 4 | 2 | 3 | 3 | 3 | 4 | 2 | 3 | 2 | 4 |
| Ampicillin 10 mg/disk | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 | 6 |
| Amoxicillin 10 mg/disk | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 | 5 |
| Blank disk | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 | 7 |

**Figure 10:** Shows biological activity of Escherichia coli

## Conclusion

Some new thiazepine derivatives were successfully synthesized by cyclization reaction of some prepared chalcones with ortho-mercapto aniline. The results of identifications for the new synthesized compounds were identical to their structure. The majority of new thiazepines showed good biological activity against both types of tested bacteria at high concentration (50 and 100) mg/mL compared to the low concentration 10 mg/mL because of the high concentration effect. However, the highest antibacterial effect was observed by thiazepine compounds ($J_{17}$, $J_{19}$, $J_{21}$, $J_{24}$, $J_{25}$, $J_{26}$, $J_{28}$, and $J_{30}$) at 100 mg/mL. This may associated with the role of electron withdrawal groups (Cl, Br, and $NO_2$). Thus, the biological aciviy of heterocyclic compounds subsitutited by halogen and nirtro groups should be considered.

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## Authors' contributions

All authors contributed to data analysis, drafting, and revising the article and agreed to be responsible for all the aspects of this work.

## ORCID

*Saad Salem Jasim*
https://orcid.org/0000-0003-3893-8769
*Jawdat Hilmi Abdulwahid*
https://orcid.org/0000-0002-2359-4732
*Shakhawan Beebany*
https://orcid.org/0000-0002-8231-5481
*Bari Lateef Mohammed*
https://orcid.org/0000-0002-2031-3747

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