Proceeding of the Third International & the Fifth Scientific Conference of College of Science - Tikrit University
Int.3, Loc.5, Article ID:2022-P4-10

Purposeful scientific research is a basic pillar for the advancement of Iraq

Synthesis of Novel 4-Thiazolidinones as Antibacterial Agents

Haneen Hadi Abbas , Zeid Hassan Abood
Department of Chemistry, Faculty of Science, University of Kerbala, Kerbala,Iraq
haneen.h@s.uokerbala.edu.iq

ABSTRACT

Amino function of 2-Amino-1,3,4-thiadiazole-5-thiol (1) has been diazotized by hydrochloric acid and sodium nitrite. The generating thiadiazolyldiazonium chloride was directly reacted with sodium phenoxide of salicylaldehyde affording azo copound (2) that containing aldehyde function. Compound (2) has been condensed with aromatic amines (3-nitroaniline, 2-nitroaniline, 4-aminophenol, 3-aminophenol, and 2-aminophenol) utilizing microwave method in ethyl alcohol to give the imine compounds (3a-3e), correspondingly**.** Cyclization reaction of Schiff bases (3a-3e) and α-mercaptoacetic acid usage microwave method in dimethylformamide gave easy thiazolidin-4-one derivatives (4a-4e), respectively. Antibacterial activities of 4-thiazolidinone compounds were tested using Gram-positive and Gram-negative bacteria. The outcomes indicated that thiazolidinone derivatives (4c, 4d, and 4e) possess greater activity against Gram-positive bacteria comparing to standard antibiotic (amoxicillin-clavulanate), whereas derivatives (4c and 4e) appeared bester impact than the control drug athwart Gram-negative germs.

Keywords: Cycloadditions, Thiazolidin-4-ones, Microwave technique, Antibacterial effects.

Introduction

Heterocyclic derivatives, particularly those containing nitrogen, oxygen, and sulfur are the most significant class of chemicals in the agrochemical and pharmaceutical manufacture[1,2], where heterocycles account for around 60% of the medicinal ingredients[3]. Five-membered sulfur, nitrogen, or oxygen heterocycles, such as thiadiazole, are key structural motifs found in a wide range of physiologically active chemicals[4]. Thiadiazole is a heterocyclic molecule with five members[5], the thiadiazole unit functions as a "hydrogen-binding field" and a "two-electrons donor system"[6], presence of sulfur atom lends lipo-solubility for thiadiazole ring, resulting in analogues with increased lipophilicity[7]. A little 1,3,4-thiadiazole scaffold-containing medicinal chemistry medications, acetazolamide and methazolamide, for example are powerful carbonic anhydrase inhibitors[8,9], pharmaceuticals used to treat glaucoma, an eye-related illness that causes optic nerve damage. Sulfamethizole has antimicrobial properties[10]. Azeteta is a phosphorus-containing medication used to treat cancer[11,12]. As a result, 1,3,4-thiadiazole has a variety of pharmacological effects, including anti-inflammatory[13-15], anticonvulsant agents[16].

Thiazolidinones are a type of heterocyclic chemical generated from thiazolidine[17], which is a type of five-membered ring heterocyclic compounds containing nitrogen and sulfur atoms[18]. Because of its intriguing biological effects, this class of chemicals is regarded as extremely essential[19]. Thiazolidinones are found in several isomers, like 5-thiazolidinones, 4-thiazolidinones, and 2-thiazolidinones[20]. Thiazolidinone derivatives have a wide range of pharmacological uses[21], including anti-microbial[22,23], antibacterial[24,25], antioxidant[26], antiviral[27,28], antitubercular[29-31], and anti-inflammatory characteristics[32]. The most important and diversely investigated compounds are 4-thiazolidinones and their derivatives[33]. This family of chemicals is considered extremely essential due to their intriguing biological actions[34] such as anti-inflammatory[35], anticancer[36,37], antioxidant[38,39], antiviral[40,41], antidiabetic[42,43], and anti-microbial agents[44,45].

Materials and Methods

2-amino-1,3,4-thiadiazole-5-thiol was purchased by Sigma Aldrich. Sodium hydroxide, Sodium nitrite, 4-aminophenol, 3-aminophenol, 2-aminophenol, 3-nitroaniline, 2-nitroaniline, Ethyl acetate and dimethyl sulfoxide were provided from (BDH). *N*,*N*-dimethylformamide and iodine by (GCC, Germany). Mercaptoacetic acid was supplied from Fluka. Ethanol (absolute) from J.T.Baker, Netherlands. Diethyl ether and *n*-Hexane from Scharlau, Spain. 2-Hydroxy benzaldehyde supplied by S.D. Fine, India. Hydrochloric acid (Conc.) from Merck, Germany. Domestic microwave oven was used for preparing imines and the target thiazolidinones. Thin layer chromatography was carried out using silica gel 60

F_{254} plate with iodine vapor as a developer. An Electro thermal Stuart SMP 30 capillary melting point apparatus was utilized for measuring melting points and are uncorrected. SHIMADZU FTIR–8400S Infrared Spectrophotometer were used for recording infrared spectra as (KBr) disc. Avance III Bruker, Germany, 400 MHz NMR spectrometer was utilized for collecting ^{1}H NMR and ^{13}C NMR spectra using TMS as an internal reference and DMSO-d_6 as solvent. Perkin Elmer 300A apparatus was used to measure (CHNS) analyses.

Preperation of azo-aldehyde derivative (2)[46]

(3.99 g, 30 mmol) of 2-Amino-5-mercapto-1,3,4-thiadiazole (1) was dissolved in a solution of (15 mL) of hydrochloric acid and (25 mL) of distilled water at 0-5°C. A cold solution of sodium nitrite (2.07 g, 30 mmol) dissolved in (25 mL) of distilled water was added drop wise to this solution with stirring. The resultant mixture was left in ice-chest for 1h after completing addition, then the diazonium salt solution was added very slowly to cold solution of 2-hydroxy benzaldehyde (3.66 g, 30 mmol) dissolved in (25 mL) of (10% w/v) sodium hydroxide with stirring. After completing addition, the solution was left overnight to give orange precipitate which was filtered and washed with distilled water, then recrystallized by ethyl alcohol giving (2) as a orange solid, yield 55%, m.p. 169-171 °C.

preparation of Schiff bases (3a-3e)[47]

A mixture of (0.283 g, 1 mmol) of aldehyde derivative (2) and (1 mmol) of aniline derivatives were dissolved in (1 mL) of ethyl alcohol has been irradiated in microwave oven around (300W) for (10 min). End of reactions was monitored by TLC (*n*-hexane: EtOAc, 1:2). Ethyl alcohol was used to recrystallized crude yields. Some physical properties for preparing compounds were listed in (Table 1).

Preparation of thiazolidin-4-ones (4a-4e)[48]

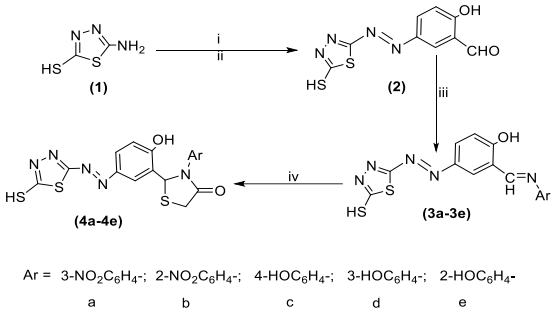
A mixture of compounds (3a-3e) (1 mmol), mercaptoacetic acid (1 mmol) and DMF (1 mL) has been heated in microwave oven around (300W) for (15 min). End of reactions was monitored by TLC (*n*-hexane: EtOAc, 1:2). Recrystallization of crude yields has been carried out using ethyl alcohol. (Table 1) shows some characteristics for the target thiazolidinone compounds.

Antibacterial test

Evaluation of antibacterial effects of the target thiazolidin-4-one derivatives (4a-4e) athwart *Staphylococcus aurous* and *Escherichia coli* bacteria has been done by the agar diffusion method[49] on tryptic soya agar media. The concentration of (20 mg/mL) for each compound has been prepared in (DMSO) as solvent. The activities were presented as inhibition zones for each compound and Amoxicillin-clavulanate has been utilizd as a standard antibiotic (Table 4).

Results and Discussion

Diazotization of 2-Amino-1,3,4-thiadiazole-5-thiol (1) using sodium nitrite and hydrochloric afforded 2-thiadiazolyl diazonium salt that was reacted with phenoxide salt of 2-hydroxybenzaldehyde giving azoaldehyde (2). Carbonyl function in compound (2) was condensed with (3-nitroaniline, 2-nitroaniline, 4-aminophenol, 3-aminophenol, and 2-aminophenol) utilizing microwave ethod in ethyl alcohol yielding Schiff bases (3a-3e) correspondingly, as intermediates. Addition of mercaptoacetic acid to imines (3a-3e) using microwave irradiation in dimethylformamide produced 4-thiazolidinone derivatives (4a-4e), respectively (Scheme 1).



Scheme 1: Thiazolidin-4-ones synthesis, Conditions and reagents (i) Conc. HCl, $NaNO_2$, 0 °C; (ii) Salicylaldehyde, NaOH 10%; (iii) Ar-NH_2, EtOH, MW (300W), (10 min); (iv) Chloroacetic acid, DMF, MW (300W), (15 min).

IR, ^{1}H NMR, and ^{13}C NMR spectral means have been utilized for deducing chemical structures of the target compounds synthesized, in addition of (CHNS) elemental microanalysis measurements.

Infrared of compound (2) showed the absence of peaks around 3394 cm^{-1} and 3275 cm^{-1} assiged to (NH_2) stretching in the initial compound (1), and appearing broad peak around 3128 cm^{-1} for (O-H) stretching, the peak around 1647 cm^{-1} recorded for aldehyde (C=O) stretching, the peak around 1427 cm^{-1} for (N=N) stretching, the stretching of thiazolic (C=N) was overlapped with carbonyl absorption at 1647 cm^{-1}. Infrared of Schiff bases (3a-3e) indicated the absence of peak for aldehydic (C=O) stretching around 1647 cm^{-1}, also absence of absorption for (NH_2) stretching of amines around scope (3400-3250) cm^{-1} and pointing peak around scope (1597-1620) cm^{-1} for stretching of imine function (C=N). Infrared of thiazolidin-4-ones (4a-4e) showed appearing band for (C=O) stretching of thiazolidinone ring around the scope (1701-1627 cm^{-1}), the spectra also appeared (C=N) stretching of thiadiazole around scope (1624-1585 cm^{-1}), whereas imine (C=N) stretching was disappeared (Table 2).

The structures of thiazolidin-4-ones (**4a-4e**) have been proven by ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra in DMSO-d_6 as solvent.

^{1}H NMR of compound (4a) recorded multiple peak for thiazolidinone (CH_2) hydrogens around δ 3.99 ppm, while the signal of (CH) hydrogen for the same ring was recorded as singlet at δ 6.29 ppm[50]. The (Ar-H) signals were recorded around δ 6.88–7.37 ppm.

The singlet signal around δ 9.89 ppm assigned to proton of hydroxyl group (O-H). The sulfhydryl proton (S-H) pointed at δ 13.15 ppm. ^{13}C NMR spectrum of compound (4a) appeared signal around δ 33.85 ppm attributed to (CH_2) carbon of thiazolidinone ring, whereas signal of (CH) carbon in the same ring was pointed at 57.83 ppm. The aromatic carbons of benzene rings were recorded at 116.29 -148.80 ppm, the signal around δ 168.53 ppm recorded for (C-SH) carbon of thiadiazole ring. The signal of carbonyl group carbon of thiazolidinone moiety indicated around δ 171.24 ppm. The signal around 174.71 ppm assigned to (C-N=N) carbon of thiadiazole unit.

^{1}H NMR spectrum of compound (4b) appeared signal of (CH_2) protons of thiazolidinone unit as multiplet around δ 3.90 ppm. The singlet peak at δ 6.48 ppm for (CH) proton of thiazolidinone ring. The signals of aromatic hydrogens as multiplet around δ 7.02–7.44 ppm. The signal of (O-H) proton recorded at δ 9.91 ppm. Thiolic (S-H) hydrogen appeared at δ 13.88 ppm. ^{13}C NMR of derivative (4b) recorded two lines around δ 33.49 ppm and 58.41 ppm assigned to (CH_2) and (CH) carbons of thiazolidinone moiety, correspondingly. The aromatic carbons appeared signals at δ 117.21-155.74 ppm, the (C-SH) carbon of thiadiazole recorded signal at δ 168.56 ppm, the signal of carbonyl group carbon recorded around δ 170.44 ppm, the signal around δ 174.79 ppm attributed to (C-N=N) carbon of thiadiazole moiety.

^{1}H NMR spectrum of compound (4c) showed multiple peak around δ 3.99 ppm assigned to methylene protons of thiazolidinone moiety. The signal of (CH) proton for thiazolidinone unit pointed around δ 6.84 ppm. The multiple signals around δ 6.89–7.32 ppm assigned to (Ar-H) hydrogens. The singlet peaks around δ 9.39 ppm and 9.85 ppm assigned to protons of (O-H) groups. The peak around δ 13.21 ppm attributed to sulfhydryl proton. ^{13}C NMR spectrum of compound (4c) pointed signals of (CH_2) and (CH) carbons of thiazolidinone around δ 33.82 ppm and 57.84 ppm, correspondingly, the signals recorded at the range δ 116.99-155.76 ppm due aromatic carbons, the signal around δ 168.74 ppm for (C-SH) carbon of thiadiazole, the signal of carbonyl carbon of thiazolidinone appered at δ 171.20 ppm, the signal pointed around 174.57 ppm attributed to (C-N=N) carbon of thiadiazole ring.

^{1}H NMR spectrum of compound (4d) indicated multiplet signal around 3.99 ppm for (CH_2) protons of thiazolidinone ring. The peak of (CH) proton of thiazolidinone ring appeared as singlet around 6.87 ppm. The (Ar-H) hydrogens appeared as multiplet around δ 6.89–7.39 ppm. The signals of (O-H) groups hydrogens appeared at δ 9.30 ppm and 9.81 ppm. Proton of (S-H) recorded at δ 13.31 ppm. ^{13}C NMR spectrum of compound (4d) appeared two signals for (CH_2) and (CH) carbons of thiazolidinone moiety at δ 33.85 ppm and 57.87 ppm, correspondingly, the signals of aromatic carbons pointed around δ 107.19-158.74 ppm. The signal around δ 168.55 ppm for (C-SH) carbon of thiadiazole, the signal around δ 171.26 ppm assigned to carbonyl carbon of thiazolidinone unit, the signal of (C-N=N) carbon of thiadiazole unit recorded around 174.64 ppm.

^{1}H NMR of derivative (4e) appeared the multiplet signal of (CH_2) protons around δ 3.99 ppm, the (CH) hydrogen appeared around δ 6.80 ppm. (Ar-H) hydrogen as multiplet at δ 6.89-7.36 ppm. The hydroxyl groups protons as two signals around δ 9.35 ppm and 10.33 ppm. The peak around 13.33 ppm for (S-H) hydrogen. ^{13}C NMR of derivatives (4e) appeared two lines around δ 33.57 ppm and 58.63 ppm for (CH_2) and (CH) carbons of thiazolidinone unit, respectively. The signals of aromatic carbons recorded around δ 115.35-155.75 ppm, the signal of (C-SH) carbon of thiadiazole ring pointed around δ 168.55 ppm, the signal of (C=O) carbon of thiazolidinone recorded around δ 170.63 ppm, the signal of (C-N=N) carbon for thiadiazole indicated around 174.89 ppm.

Table 1: Some characteristics of derivatives (3a-3e) and (4a-4e)

Compound No.	Color and state	R_f (*n*-hexane/ EtOAc, 1:2)	Mp (^{o}C)	Yield (%)
3a	Yellow solid	0.72	141-143	84
3b	Orange solid	0.63	138-140	61
3c	Dark red solid	0.71	160-162	68
3d	Dark red solid	0.69	169-171	73
3e	Dark red solid	0.62	154-156	76
4a	Dark red solid	0.69	178-180	63
4b	Dark red solid	0.70	183-185	58
4c	Dark brown solid	0.74	227-229	87
4d	Dark brown solid	0.82	229-231	85
4e	Dark brown solid	0.69	226-228	87

Table 2: Infrared information's of derivatives (3a-3e)) and (4a-4e).

Comp. no	Infrared data
3a	3275 (O-H)str, 3120 (thione N-H)str, 3078 (arom. C-H)str, 1604 (imine C=N)str, 1523 (NO_2)as.str, 1485 (arom. C=C)str, 1427 (N=N)str, 1265 (NO_2)s.str, 1053 (thione C=S)str.
3b	3302 (O-H)str, 3113 (thione N-H)str, 3082 (arom. C-H)str, 1620 (imine C=N)str, 1562 (arom. C=C)str, 1500 (NO_2)as.str, 1431 (N=N)str, 1249 (NO_2)s.str, 1099 (thione C=S)str.
3c	3336 and 3279 (O-H)str, 3140 (thione N-H)str, 3028 (arom. C-H)str, 1608 (imine C=N)str, 1554 and 1508 (arom. C=C)str, 1053 (thione C=S)str.
3d	3360 (O-H)str, 3163 (thione N-H)str, 3050 (arom. C-H)str, 1597 (imine C=N)str, 1535 and 1496 (arom. C=C)str, 1427 (N=N)str, 1053 (thione C=S)str.
3e	3236 (O-H)str, 3140 (thione N-H and arom. C-H, overlapped)str, 1608 (imine C=N)str, 1535, 1496 and 1462 (arom. C=C)str, 1431 (N=N)str, 1057 (thione C=S)str.
4a	3325 (O-H)str, 3115 (thione N-H)str, 3059 (arom. C-H)str, 1674 (thiazolidine C=O)str, 1616 (thiadiazole C=N)str, 1523 (NO_2)as.str, 1462 (arom. C=C)str, 1425 (N=N)str, 1269 (NO_2)s.str, 1057 (thione C=S)str.
4b	3124 (O-H and thione N-H, overlapped)str, 3039 (arom. C-H)str, 1643 (thiazolidine C=O)str, 1624 (thiadiazole C=N)str, 1516 (NO_2)as.str, 1462 (arom. C=C)str, 1427 (N=N)str, 1261 (NO_2)s.str, 1060 (thione C=S)str.
4c	3128 (O-H, thione N-H and arom. C-H, overlapped)str, 1701 (thiazolidine C=O)str, 1624 (thiadiazole C=N)str, 1512 and 1450 (arom. C=C)str, 1400 (N=N)str, 1060 (thione C=S)str.
4d	3101 (O-H and thione N-H, overlapped)str, 3070 (arom. C-H)str, 1658 (thiazolidine C=O)str, 1616 (thiadiazole C=N)str, 1516 and 1465 (arom. C=C)str, 1400 (N=N)str, 1049 (thione C=S)str.
4e	3100 (O-H and thione N-H, overlapped)str, 3074 (arom. C-H)str, 1627 (thiazolidine C=O)str, 1585 (thiadiazole C=N)str, 1508 and 1458 (arom. C=C)str, 1053 (thione C=S)str.

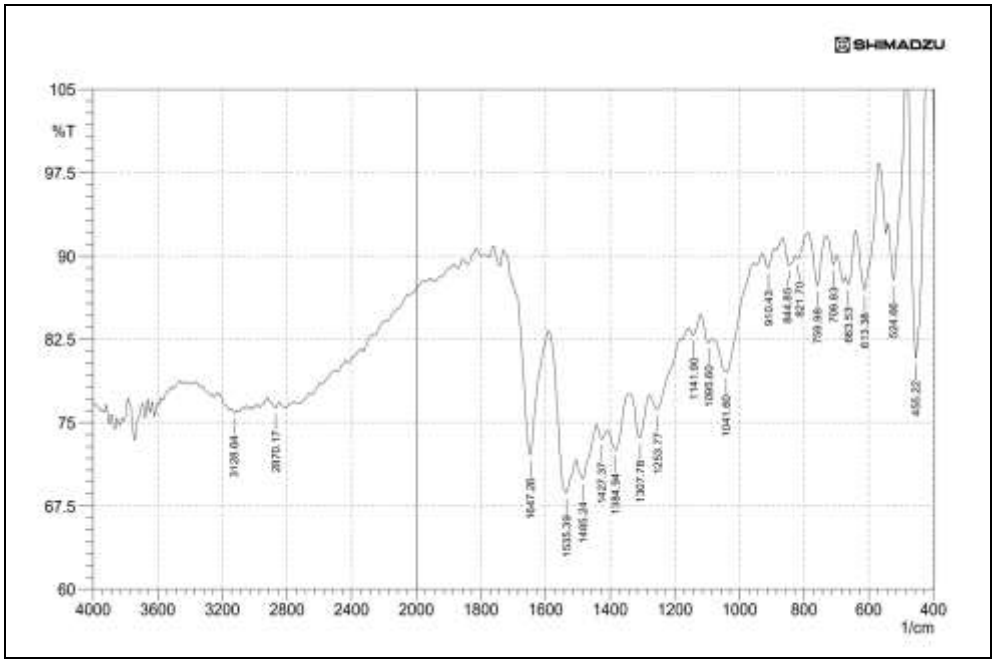


Fig. 1: Infrared of derivative (2)

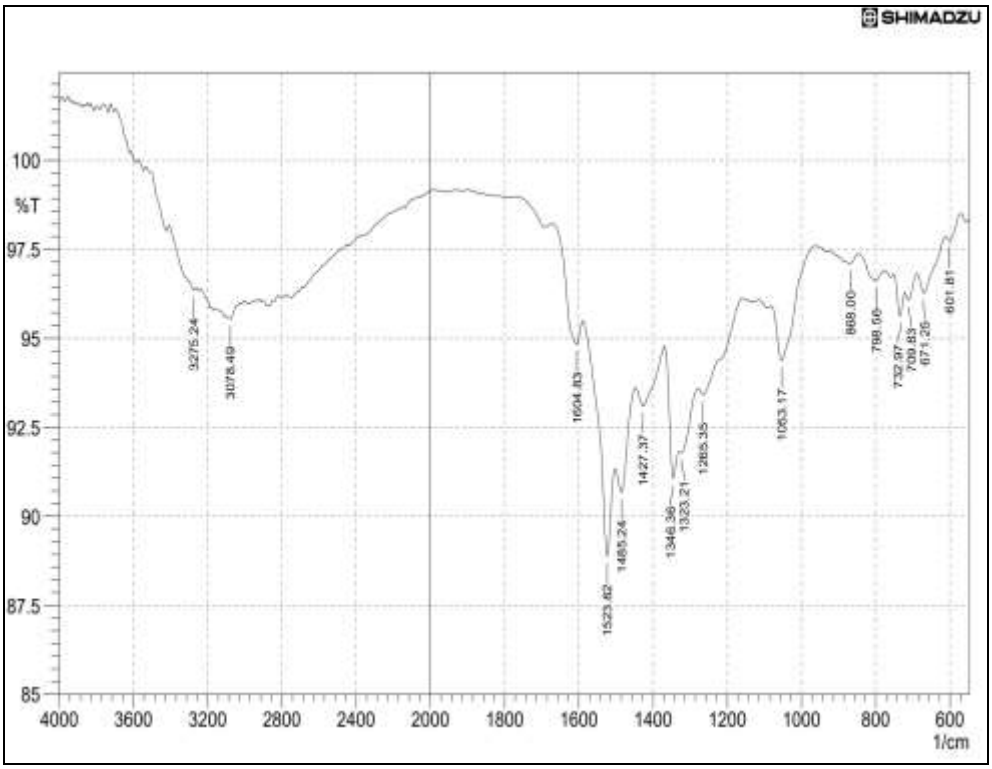


Fig. 2: Infrared of derivative (3a)

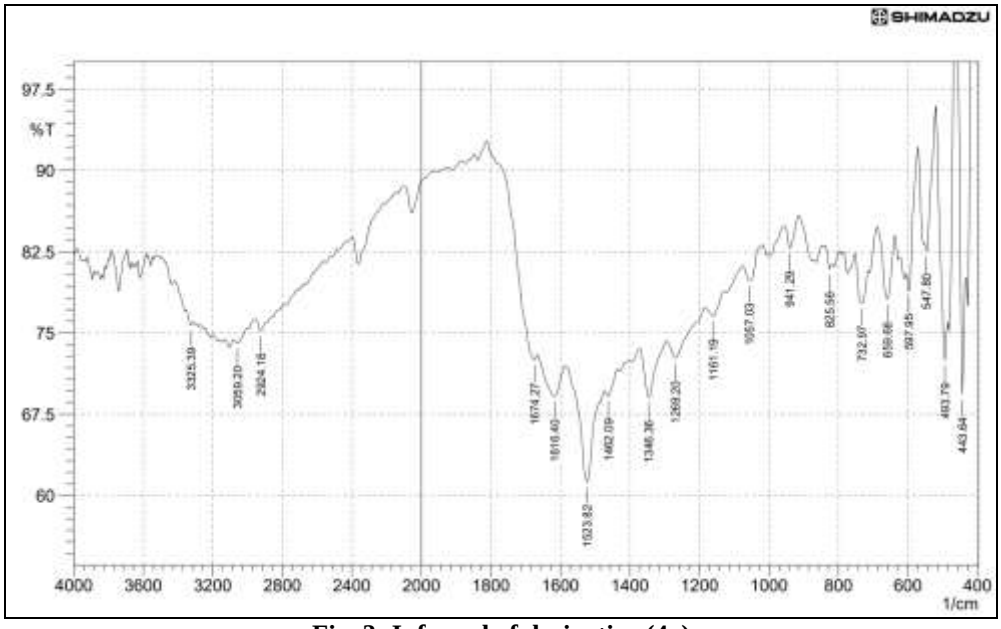


Fig. 3: Infrared of derivative (4a)

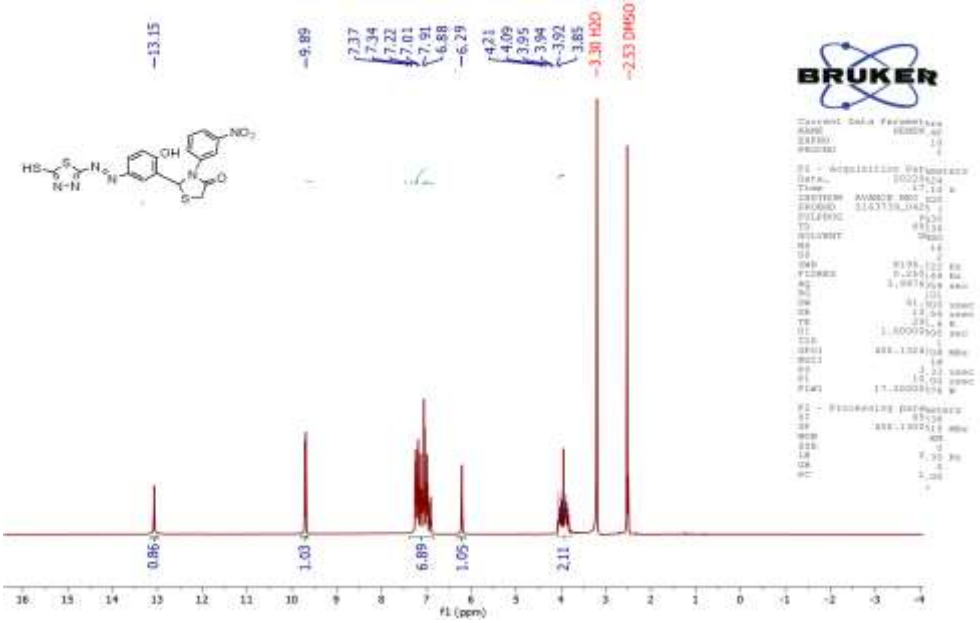


Fig. 4: ^{1}H NMR of derivative (4a)

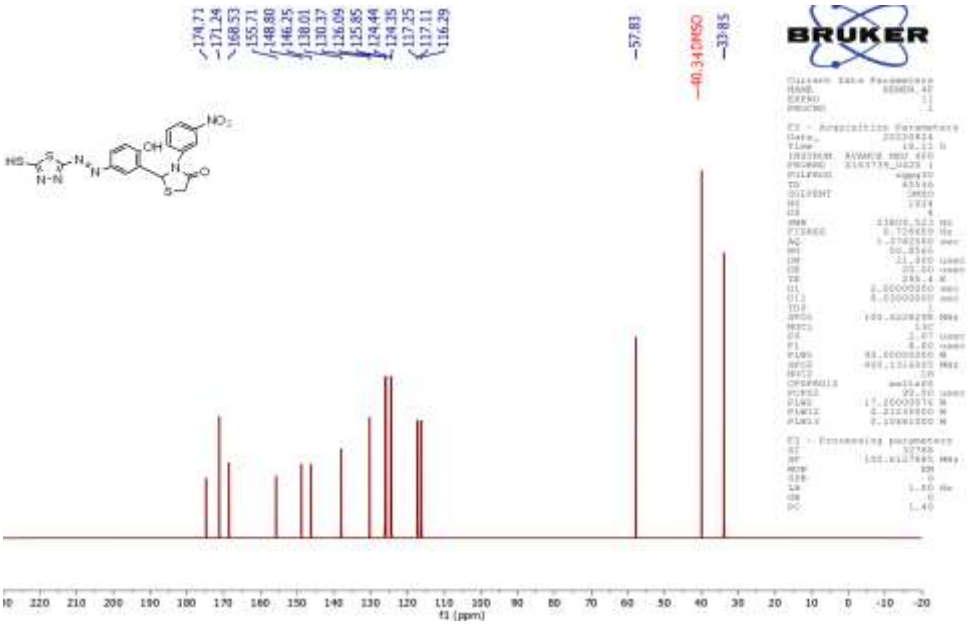


Fig. 5: ^{13}C NMR of derivative (4a)

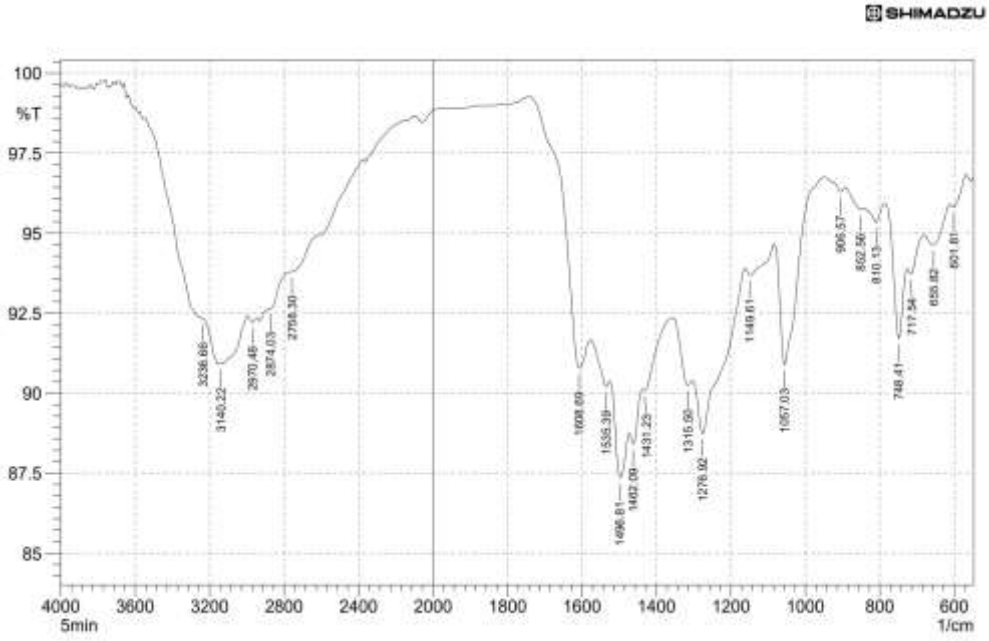


Fig. 6: Infrared of derivative (3e)

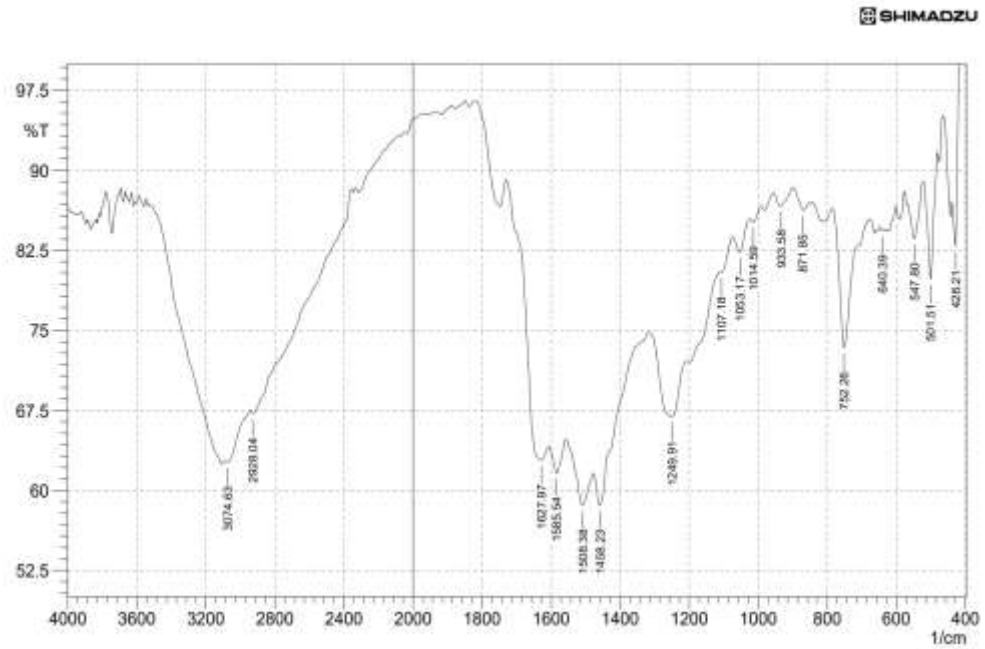


Fig. 7: Infrared of derivative (4e)

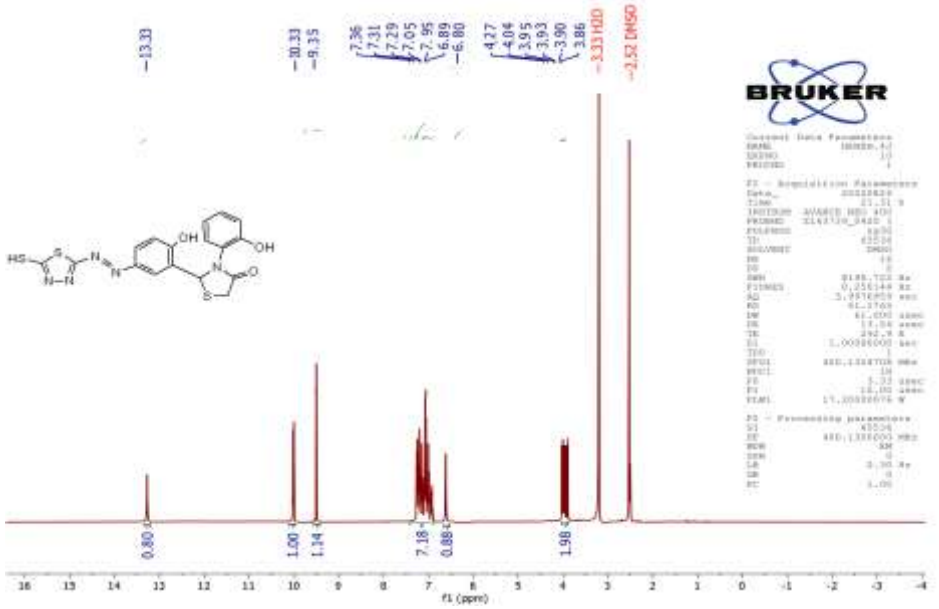


Fig. 8: ^{1}H NMR of derivative (4e)

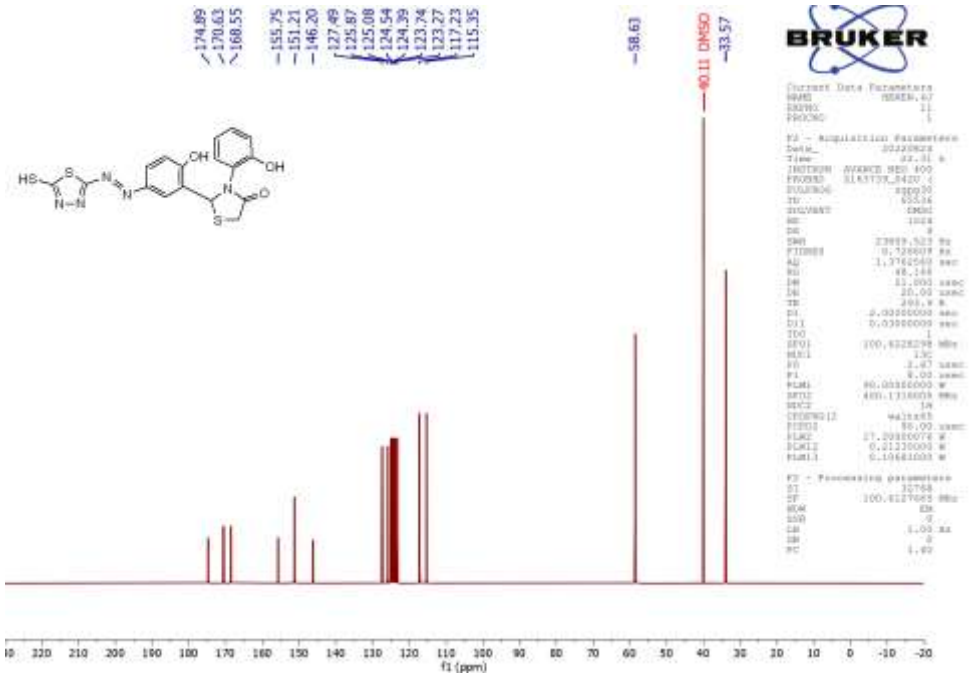


Fig. 9: ^{13}C NMR of derivative (4e)

The (CHNS) elemental microanalysis measurements between calculated and observed values. of the final compounds showed good agreement

Table 3: (CHNS) Elemental analysis of thiazolidine compounds (4a-4e)

Product	Calculated %				Observed %			
	C	H	N	S	C	H	N	S
4a	44.34	2.63	18.25	20.89	44.28	2. 49	18.10	20.96
4b	44.34	2.63	18.25	20.89	44.21	2.52	18.13	2103
4c	47.32	3.04	16.23	22.29	47.45	3.16	16.24	.2241
4d	47.32	3.04	16.23	22.29	47.39	3.13	16.32	22.38
4e	47.32	3.04	16.23	22.29	47.43	2.97	16.15	22.24

Antibacterial activities

The desired thiazolidinone compounds (4a-4e) were screened for their antibacterial activity athwart two kinds of Gram positive and Gram negative bacteria using agar diffusion method[49] on tryptic soya agar media. The solvent used is (DMSO) using concentration (20 mg/ mL) for the test compounds. The thiazolidin-4-one compounds (4c, 4d, and 4e) showed greater activity athwart *Staphylococcus aurous* than reference drug, on the other hand, (4c and 4e) derivatives pointed larger activity than the reference antibiotic athwart *Escherichia coli* as indicated in Table 4.

Table 4: The activities against bacteria of thiazolidin-4-ones (4a-4e)

Entry	*Staphylococcus aurous*	*Escherichia coli*
4a	0	0
4b	17	14
4c	22	22
4d	26	17
4e	28	22
[DMSO]	0	0
[Amoxicillin-Clavulanate]	18	18

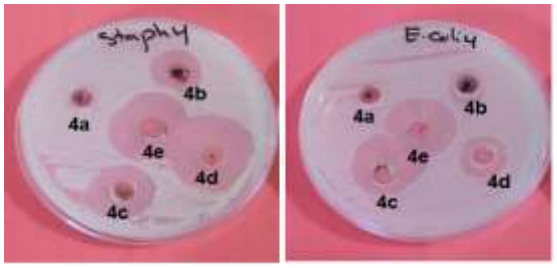


Fig. 10: Antibacterial photographs of 4-thiazolidinone derivatives (4a-4e) against *Gram positive and Gram negative bacteria.*

Conclusion

The preliminary antibacterial test of the prepared thiazolidin-4-ones showed promising antibacterial results against both kinds of bacteria. Most compounds appeared activity better than that of standard antibiotic.

Acknowledgement

We present our deep thanks for University of Basra to record ^{1}H NMR and ^{13}C NMR spectra, also great thanks to personnel at central laboratory, University of Tehran, Iran for measuring elemental microanalysis for the final thiazolidinone compounds.

References

1 Mercuri G., Giambastiani G. and Rossin A., Thiazole- and Thiadiazole-Based Metal–Organic Frameworks and Coordination Polymers for Luminescent Applications, *Inorganics*, **7(12)**,144 **(2019)**

2. Younis O., Ahmed F.Al-Hossainy. Mostafa Sayed .Adel M.Kamal El-dean and Mahmoud S.Tolba ., Synthesis and intriguing single-component white-light emission from oxadiazole or thiadiazole integrated with coumarin luminescent core, *Journal of Photochemistry and Photobiology A: Chemistry*, **431**, 113992 **(2022)**

3. El-Masry R.M. Alkadry H.H. Taher T.Z and Sahar M. Abou-Ser., Comparative Study of the Synthetic Approaches and Biological Activities of the Bioisosteres of 1, 3, 4-Oxadiazoles and 1, 3, 4-Thiadiazoles over the Past Decade, *Molecules*, **27(9)**, 2709 **(2022)**

4. Desai K.R. and Patel B.R., Various Synthetic Strategies and Therapeutic Potential of Thiadiazole, Oxadiazole, Isoxazole and Isothiazole Derivatives, in N-Heterocycles, Springer, 221-274 **(2022)**

5. Atmaram U.A. and Roopan S.M., Biological activity of oxadiazole and thiadiazole derivatives, *Applied Microbiology and Biotechnology*, **106(9)**, 3489-3505 **(2022)**

6. Khaldan A., Ayoub Khaldan, Soukaina Bouamrane, Reda El-mernissi, Marwa Alaqarbeh, Halima Hajji, Nada Alsakhen, Hamid Maghat, Mohammed Aziz Ajana, Abdelouahid Sbai, Mohammed Bouachrine and Tahar Lakhlifi., Computational study of quinoline-based thiadiazole compounds as potential antileishmanial inhibitors, *New Journal of Chemistry*, **46**, 17554-17576 **(2022)**

7. Gholivand K. MohammadFaraghi, NasrinFallah, AbouzarBabaei, Foroogh Pirastehfar ,Michal Dusek, Vaclav Eigner and Fatemeh Salimi., Therapeutic potential of phospho-thiadiazole derivatives as anti-glioblastoma agents: synthesis, biological assessment and computational study, *Bioorganic Chemistry*,**129**, 106123 **(2022)**

8. Kumar R. Kumar A, Ram S, Angeli A, Bonardi A , Nocentini A, Gratteri P, Claudiu T. Supuran and Pawan K.Sharma., Novel benzenesulfonamide -bearing pyrazoles and 1, 2, 4-thiadiazoles as selective carbonic anhydrase inhibitors, *Archiv der Pharmazie*, **355(1)**, 2100241 **(2022)**

9. Supuran C.T., Anti-obesity carbonic anhydrase inhibitors: challenges and opportunities, *Journal of Enzyme Inhibition and Medicinal Chemistry*, **37(1)**, 2478-2488 **(2022)**

10. Anthwal T., Singh H. and Nain S., 1,3,4-Thiadiazole Scaffold: Anti-Microbial Agents, *Pharmaceutical Chemistry Journal*, **55(12)**, 1345-1358 **(2022)**

11. Oubella A. Byadi S, Bimoussa A, Fawzi M, Auhmani A., Podlipnik C., Morjani H., Riahi A, Robert A., Youssef A.., Novel isoxazoline-linked 1, 3, 4-thiadiazole hybrids as anticancer agents: Design, synthesis, biological evaluation, molecular docking, and molecular dynamics simulation, *Archiv der Pharmazie*, **355(9)** 2200066 **(2022)**

12. Pham E.C., Pham, Em C.; Truong, Tuyen Ngoc; Dong, Nguyen Hanh; Vo, Duy Duc; Hong Do, Tuoi

Thi, Synthesis of a series of novel 2-amino-5-substituted 1, 3, 4-oxadiazole and 1, 3, 4-thiadiazole derivatives as potential anticancer, antifungal and antibacterial agents, *Medicinal Chemistry*, **18(5)**, 558-573 **(2022)**

13. Pund A.A, Shaikh M.A, Chandak B.G ,Bhosal V.N and ., Pyridine-1, 3, 4-Thiadiazole-Schiff Base Derivatives, as Antioxidant and Antimitotic Agent: Synthesis and in Silico ADME Studies, *Polycyclic Aromatic Compounds*, **15(7),**1-16 **(2022)**

14. Hemanth K., Lakshmanan K. and Rajagopal K., A REVIEW ON BIOLOGICAL ACTIVITIES: 1, 3, 4-THIADIAZOLE AND ITS DERIVATIVES, Journal of Pharmaceutical, Chemical and Biological Sciences,**3(3),** 329- 345**(2015).**

15. Abu-Hashem A.A. and Al-Hussain S.A., Design, synthesis of new 1, 2, 4-triazole/1, 3, 4-thiadiazole with spiroindoline, imidazo [4, 5-b] quinoxaline and thieno [2, 3-d] pyrimidine from isatin derivatives as anticancer agents, Molecules, **27(3)**, 835 **(2022)**

16. Kandemir L, Kandemir, Levent, Karakuş, Sevgi, Özbaş, Suna, Rollas, Sevim and Akbuğa, Julide ., Synthesis, structure elucidation and cytotoxic activities of 2, 5-disubstituted-1, 3, 4-thiadiazole and l, 2, 4-triazole-3-thione derivatives, *Journal of Research in Pharmacy*,**26(2)**,324 **(2022)**

17. Aqlan F.M., Al-Bogamia S.A, Alqahtani N.F,Younus F and A.Khan W., Thiazolidinone: A structural motif of great synthetic and biological importance, *Journal of Molecular Structure*, **1250**, 131771 **(2022)**

18. Finiuk N, Holota S, Klyuchivska O, Kozytskiy A, Karpenkoe O, Manko N, Ivasechko R, Stoika R and Lesyk R ., Novel hybrid pyrrolidinedione-thiazolidinones as potential anticancer agents: Synthesis and biological evaluation, *European Journal of Medicinal Chemistry*, **238**, 114422 **(2022)**

19. Fayed E.A, Salih A, Amaar Y and Bayomi A., Design, synthesis, in silico studies, in vivo and in vitro assessment of pyridones and thiazolidinones as anti-inflammatory, antipyretic and ulcerogenic hits. *Journal of Molecular Structure*, **1260**, 132839 **(2022)**

20. Campos J.C, otcherlakota R, Sravan V and Kumbhar R., Synthesis and Biological Evaluation of Novel 2-imino-4-thiazolidinones as Potential Antitumor Agents for Glioblastoma, *Medicinal Chemistry*, **18(4)**, 452-462 **(2022)**

21. Almasirad A, Ghadimi M, Mirahmadi S, Kodakan P.A, Jahani R, Nazari M, Rezaee E, Azizian H, Rabizadeh M, Tabatabai S.A and Mehrdad Faiz ., Design, synthesis, and preliminary pharmacological evaluation of novel thiazolidinone derivatives as potential benzodiazepine agonists, *Molecular Diversity*, **26(2)**, 769-780 **(2022)**

22. Mohamed F.A, Elkhabiry, Shaban; Ismail, Ismail A.; Attia, Attia O.., Synthesis, Application and Antimicrobial Activity of New Acid Dyes Based on 3-Amino-2-thioxo-4-thiazolidinone Nucleus on Wool and Silk Fabrics, *Current Organic Synthesis*, **19(1)**, 166-176 **(2022)**

23. Verma M. and Verma P.K., Synthesis, characterization, antimicrobial and anticancer evaluation of pyrimidines Clubbed with thiazolidinone, *Journal of Medicinal pharmaceutica and allied sciences*, **2320**, 210**(2022)**

24. Yang X.C., LiZhang P, Kumar K and HeZhoua C., Discovery of unique thiazolidinone-conjugated coumarins as novel broad spectrum antibacterial agents, *European Journal of Medicinal Chemistry*, **232**, 114192 **(2022)**

25. Sampada P., Kavita G. and Renuka M., SYNTHESIS OF SOME NEW NOVEL THIAZOLIDINONE FROM CHALCONE AND THEIR ANTI-MICROBIAL ACTIVITY,

26. Ganavi D., et al., In vitro and in silico studies of fluorinated 2,3-disubstituted thiazolidinone-pyrazoles as potential α-amylase inhibitors and antioxidant agents, *Archiv der Pharmazie*, **355(3)**, 2100342 **(2022)**

27. Sujatha K., Thirupaiah B. and Vedula R.R., An Efficient One Pot Multicomponent Synthesis of Coumarino Pyrazolyl Thiazolidinones, *Polycyclic Aromatic Compounds*, **42(4)**, 1404-1412 **(2022)**

28. Allaka T.R., Katari N.K. and Jonnalagadda S.B., Synthesis of antiviral drugs by using carbon–carbon and carbon–heteroatom bond formation under greener conditions, *Physical Sciences Reviews*, **(2022)**

29. Hebade M.J., et al., DTP/SiO2 Assisted Synthesis of New Benzimidazole-Thiazole Conjugates Targeting Antitubercular and Antioxidant Activities, *Polycyclic Aromatic Compounds*, 1-22 **(2022)**

30. Othman D.I., et al., Novel 2-arylthiazolidin-4-one-thiazole hybrids with potent activity against Mycobacterium tuberculosis, *Bioorganic Chemistry*, **(124)**, 105809 **(2022)**

31. Desai N., et al., Synthesis and Biological Importance of Pyrazole, Pyrazoline, and Indazole as Antibacterial, Antifungal, Antitubercular, Anticancer, and Anti-inflammatory Agents, in N-Heterocycles, Springer, 143-189 **(2022)**

32. Archna, et al., Exploration of Antioxidant, Anti-inflammatory and Anticancer Potential of Substituted 4-Thiazolidinone Derivatives: Synthesis, Biological Evaluation and Docking Studies, *Polycyclic Aromatic Compounds*,1-22 **(2022)**

33. Morja M.I. and Chikhalia K.H., Iron-catalyzed intermolecular cross-dehydrogenative C (sp3)–H/C (sp)–H coupling of pyrimidine bearing 4-thiazolidinones with terminal alkynes, *Molecular Diversity*, 1-9 **(2022)**

34. Chauhan P.M., et al., Copper catalyzed decarboxylative coupling between coumarin 3-carboxylic acid and 4-thiazolidinones, *Tetrahedron Letters*, **(91)**, 153538 **(2022)**

35. Singh J., et al., 2, 5-Disubstituted-4-Thiazolidinones: Synthesis, Anti-Inflammatory, Free Radical Scavenging Potentials and Structural Insights

through Molecular Docking, *Letters in Organic Chemistry*, **18(12)**, 957-968 **(2021)**
36. Bhagat D.S., et al., An insight into synthesis and anticancer potential of thiazole and 4-thiazolidinone containing motifs, *Current Organic Chemistry*, **25(7)**, 819-841 **(2021)**
37. Hebishy A.M., et al., Novel bis (thiazolidin-4-ones) linked to aliphatic or aromatic spacers: Synthesis, characterization, and anticancer evaluation, *Journal of Sulfur Chemistry*, **42(2)**, 149-166 **(2021)**
38. Fekri L.Z., Fe3O4@ SiO2-Propyl Covalent Dapsone- Copper Complex: Synthesis, Characterization and Application for the Synthesis of New Derivatives of Azo-Linked Thiazolidinones and their Solvatochromism Evaluation, *Current Nanoscience*, **18(1)**, 128-138 **(2022)**
39. Szychowski K.A., et al., 4-thiazolidinone-based derivatives rosiglitazone and pioglitazone affect the expression of antioxidant enzymes in different human cell lines, *Biomedicine & Pharmacotherapy*, **(139)**, 111684 **(2021)**
40. Evren A.E., Yurttaş L. and Gencer H.K., Synthesis of New Thiazole Derivatives Bearing Thiazolidin-4 (5H)-One Structure and Evaluation of Their Antimicrobial Activity, *Brazilian Journal of Pharmaceutical Sciences*, **(58) (2022)**
41. Buzun K., et al., Synthesis and anticancer activity evaluation of 5-[2-chloro-3-(4-nitrophenyl)-2-propenylidene]-4-thiazolidinones, *Molecules*, **26(10)**, 3057 **(2021)**
42. Gummidi L., et al., Multicomponent reaction for the synthesis of new 1, 3, 4-thiadiazole-thiazolidine-4-one molecular hybrids as promising antidiabetic agents through α-glucosidase and α-amylase inhibition, *Bioorganic Chemistry*, **(115)**, 105210 **(2021)**
43. Khan S.A., et al., Mercaptobenzimidazole-Based 1, 3-Thaizolidin-4-ones as Antidiabetic Agents: Synthesis, In Vitro α-Glucosidase Inhibition Activity, and Molecular Docking Studies, *ACS omega*, **(2022)**
44. Haroun M., et al., Exploration of the antimicrobial effects of benzothiazolylthiazolidin-4-one and in silico mechanistic investigation, *Molecules*, **26(13)**, 4061 **(2021)**
45. Kousaxidis A., et al., Non-acidic bifunctional benzothiazole-based thiazolidinones with antimicrobial and aldose reductase inhibitory activity as a promising therapeutic strategy for sepsis, *Medicinal Chemistry Research*, **30(10)**, 1837-1848 **(2021)**
46. Acton Q. A., Azo Compounds: Advances in Research and Application, Scholarly Paper Edition, Atlanta **(2011)**
47. Galván A. F., de la Cruz F.N., Cruz F., Martíneza M., Gomeza C.V., Alcaraz Y., Domínguez J.M., Delgado F. and Vázquez M., Heterogeneous Catalysis with Basic Compounds to Achieve the Synthesis and C–N Cleavage of Azetidin-2-ones under MicrowaveIrradiation, *Synth*esis, **51**, A-M **(2019)**
48. Bolognese A., Correale G., Manfra M., Lavecchia A., Novellino E. and Barone V., Thiazolidin-4-one formation. Mechanistic and synthetic aspects ofthe reaction of imines and mercaptoacetic acid under microwave and conventional heating. *Org. Biomol.*, **2**, 2809-2813 **(2004)**
49. Egorove N. S., Antibiotics Scientific Approach, Mir. Publishers, Moscow, **(1985)**
50. Mirzaei-Mosbat M. and Ghorbani-Vaghei R., Condensation–cyclization reaction for one-pot synthesis of 1,3-thiazolidin-4-one derivatives by poly(*p*-phenylenediamine) grafted on LDHs as a catalyst with green tool, *Journal of Sulfur Chemistry*, **42(1)**, 1-13 **(2021)**.