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SYNTHESIS, CHARACTERIZATION AND QSAR STUDY OF 2-(5-METHYL-4-PHENYLTHIAZOL-2-YL)-4-OXOTHIAZOLIDINE-5-CARBOXYLIC ACID DERIVATIVES

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ABSTRACT

In this present work, we report a green and eco-friendly procedure for the synthesis of various different derivatives of Schiff bases N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline. These derivatives were synthesised by 5-methyl-4-phenylthiazole-2-carbaldehyde, substituted anilines, and reaction mixture was irradiated with microwave at 20% power to furnish Schiff bases N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline derivatives. The products react with 2-Mercapto-malonic acid, dry dioxane in scientific microwave oven (20%, 140 watts), on cyclocondensation gave different 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid derivatives with good yield. Library of such 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid derivatives has been generated and the structures were exposed to PASS to check probabilities of biological activity. QSAR study of the library was carried out to find the most active molecules.

Key words: cyclocondensation; 2-Mercapto-malonic acid; microwave; Schiff bases

Article History

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1. Introduction:

The 4-oxo-thiazolidine is an important class of heterocyclic compounds had wide spectrum of biological activities. The 4-oxo -thiazolidines occupies significant place in medicinal field.[1] Initially 4-oxothiazolidine are

derivatives having a carbonyl group at 4-posotion are prepared by intermolecular cyclization followed elimination of water. Literature survey tells that 4-oxo-thiozolidinederivatives has shown Anti-HIV,[2] enzyme murB,[3] antimicrobial activity,[4] antituberculosis,[5] antiproliferative agent,[6] CNS activity,[7] cytotoxic agent,[8] anticonvulsant activity,[9] antibacterial activity,[10] analgesic agent [11] antiinflammetry agent,[12] antihypertensive agent, [13] and hypolipidemic agent [14] properties.

The 4-oxo-thiozolidine derivatives has biological potential and essay synthetic protocols attracted the attention of many researchers. [15-17] Organic reaction induced by microwave irradiation are environmentally friendly and proceed with short time. [18-20] M.W. assisted method is termed as e-chemistry because easy, effective, economical and eco-friendly.[21] This method is more significant than conventional methods.[22]

Schiff bases are synthesised by condensation of aldehyde and ketones and amines or anilines. [23] Schiff bases has wide application in biological and medicinal field. [24] QSAR study done by using Pass online is software application used for prediction of 565 possible biological activities of compounds. The biological activity spectrum shows intrinsic properties of compounds based on structure. Pass online tool is used to design drug with high probable activity. [25-29]

Recent literature survey reports successful attempt made for the preparation of 4-oxo-thiozolidine derivatives phthalimido[2-aryl-3-(5'-(4''-pyridyl)-1',3',4'-thiadiazol-2'-yl)-4-oxothiazolidin-5-yl]ethanoates,[30]2-[5-(arylidene)-2-imino-4-oxo-thiazolidin-yl]benzothiazole-6-carboxylic acid, N-(5-methyl-4-oxo-thiazolidin-3-yl)-nicotinamide,[31] 2-(aryl)-3-[2-(benzothiazolylthio)-acetamidyl]-4-oxo-thiazolidines,[32] N-(2-aryl-4-oxothiazolidin-3-yl)-2-(5-(phenoxymethyl)-2-thioxo-1,3,4-oxadiazol-3(2H)-yl)acetamide,[33]4-oxo-thiazolidine derivatives have been obtained by cyclisation of various Schiff's base with thiomalic acid, and N-(2-(4-substituted phenyl)-4-oxothiazolidin-3-yl)isonicotin-amide[34]etc.

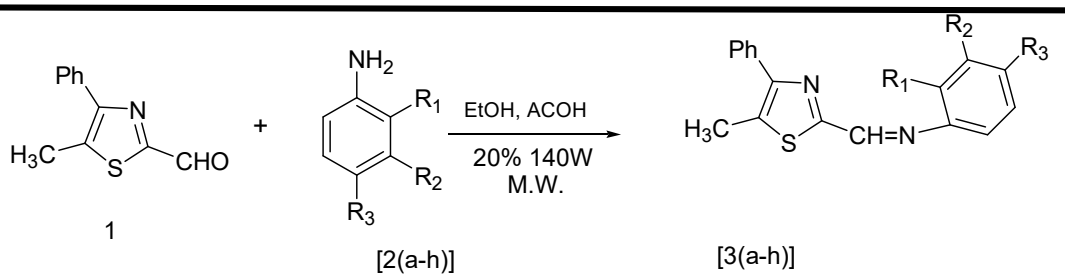
In continuation of this, we had carried out microwave assisted synthesis different of 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid in two steps. In first step formation of Schiff base by reacting 5-Methyl-4-phenyl-thiazole-2-carbaldehyde with different substituted anilines. Second step consists cyclocondensation of different Schiff bases with 2- Mercapto-malonic acid gives desired products using green chemistry.

2. Materials and Methods:

The melting points of the compounds were determined in open capillary tubes are uncorrected. The purity of compound was checked on silica gel G plates. FT-IR spectra were recorded on a Shimadzu Miracle 10 ATR spectrometer. ^{1}H NMR spectra were recorded on a Bruker 500 MHz spectrometer with $CDCl_3$ as the solvent and TMS as the internal reference.^{13}C NMR spectra were recorded on Bruker 125 MHz spectrometer with $CDCl_3$ as the solvent. Elemental analysis carried out using CHN elemental analyser. All chemicals were analytical grade.

2.1 Synthesis of Schiff bases N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline

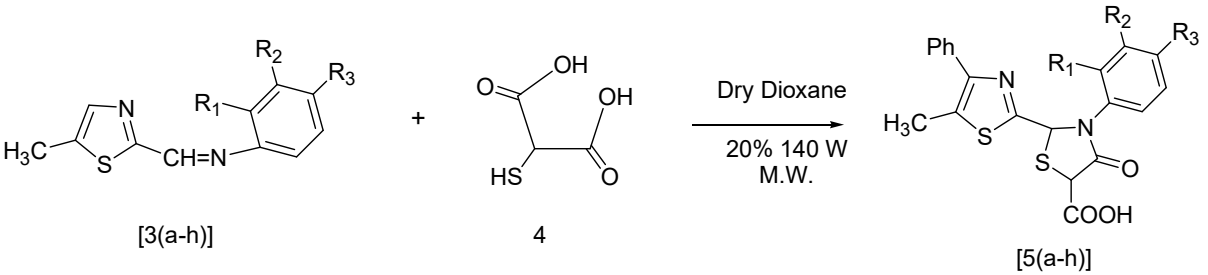
Schiff bases are prepared by mixture of 5-methyl-4-phenylthiazole-2-carbaldehyde (0.02 mol) [1], substituted anilines (0.02 mol) [2(a-h)], 10 ml ethanol and 1 ml acetic acid added in microwave tube. The contents were subjected to 20 % microwave power (140 W) for 3-5 min. The progress of reaction was monitored on TLC (Ethyl acetate: Hexane 1:9). After completion of the reaction, solid product obtained in reaction was poured into crushed ice filtered and recrystallised in methanol gives solid product [3(a-h)] **Scheme-I**.



Scheme I- Synthesis of Schiff bases N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline [3(a-h)] derivatives.

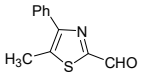
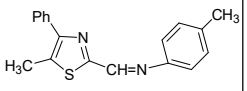
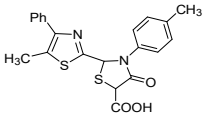
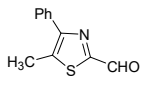
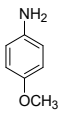
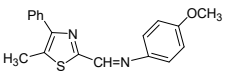
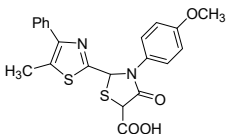
2.2 Synthesis of 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid

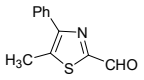
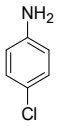
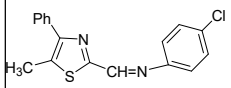
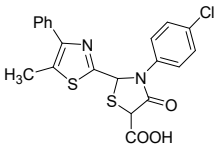
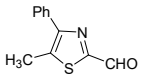
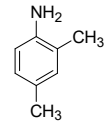
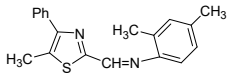
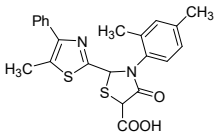
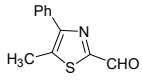
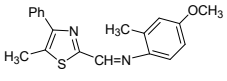
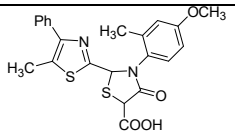
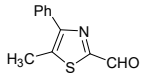
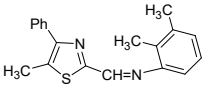
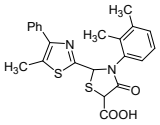
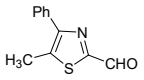
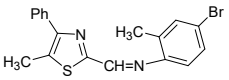
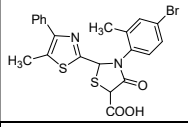
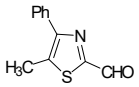
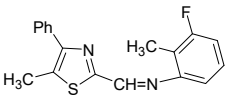
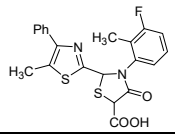
A mixture of (1mmol) of Schiff base N-((5-methyl-4-phenylthiazol-2-yl) methylene) aniline[3(a-h)] and 2- Mercapto-malonic acid (15ml) [4] in 30 ml Dry dioxane was added in small round bottom flask at room temperature then mixture was exposed to microwave power 20% 140W for 3-5 min. The progress was monitored on TLC (Ethyl acetate: Hexane 1:9). The resultant solution was cooled and poured into crushed ice. The separated solid was filtered, recrystallised from ethanol gives solid product [5(a-h)] **Scheme-II summarised in Table -1**.



Scheme II- Synthesis of 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid derivatives [5(a-h)]

TABLE-1
PREPARATION OF SUBSTITUTED OXOTHIAZOLIDINE UNDER MICROWAVE IRRADIATION

Comp.	Substrate			Product	Time (min)	M.P. (^{0}C)	Yield (%)
	1	2	3				
5a					4	682-683	84
5b					3	704-705	79

5c					4	701-702	78
5d					5	706-707	86
5e					5	728-730	83
5f					4	706-707	82
5g					4	754-755	85
5h					5	695-696	80

Spectral data of compounds [5(a-h)]

5'-Methyl-4-oxo-4'-phenyl-3-p-tolyl-2,3,4,5-tetrahydro- [2,2'] bithiazolyl-5-carboxylic acid 5(a): IR (KBr) ν_{max}: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) cm^{-1}. H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s, 1H, CH), 2.35(s, 6H, 2× CH_3), 4.35(s, 1H, CH), 6.98 (d, 2H,2×CH), 7.11(d, 2H,2×CH),7.22-7.48(m, 5H, C_6H_5),11.0(s,1H, OH) ppm.^{13}C NMR ($CDCl_3$, 50.32 MHz): δ 166.50(=C<), 152.60(=C<), 128.50(=C<), 56.60(>C<), 7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<), 20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<). Anal. calcd. (%) for $C_{21}H_{18}N_2O_3S_2$: C, 61.44; H, 4.42; N, 6.82; O,11.69; S,15.62. Found (%): C, 61.41; H, 4.48; N, 16.27; O,11.72; S,15.68. M.P. 682^{0}C; mass(M+) 410.

3-(4-Methoxy-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2']bithiazolyl-5-carboxylic acid 5(b): IR (KBr) νmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3)cm^{-1}.H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s, 1H, CH), 2.35(s, 6H, 2× CH_3), 4.35(s,1H,CH),6.98(d,2H,2×CH),7.11(d,2H,2×CH),7.22-7.48(m,5H,C_6H_5),11.0(s,1H,OH),3.73(s,3H)ppm.^{13}C

NMR(CDCl3, 50.32 MHz): δ 166.50(=C<), 152.60(=C<), 128.50(=C<), 56.60(>C<), 7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),
120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00 (=C<),56.00(>C<). Anal. calcd. (%) for $C_{21}H_{18}N_2O_4S_2$: C, 59.14; H, 4.25; N, 6.57; O,15.00; S,15.04. Found (%): C, 59.10; H, 4.29; N,6.55; O,15.01; S,15.04. M.P. 704^0C; mass(M+)426.

3-(4-Chloro-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2']bithiazolyl-5-carboxylic acid 5(c):IR (KBr) νmax: 1440(C-CH3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3), 650(-Cl)cm^{-1}.H^1 NMR (CDCl3, 200.13 MHz): δ 5.92(s, 1H, CH), 2.35(s, 6H, 2×CH_3), 4.35(s,1H,CH),6.98(d,2H,2×CH),
7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH)ppm.^{13}CNMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60 (=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),13 3.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<).Anal.calcd.(%)forC_{20} $H_{15}ClN_2O_3S_2$:C,55.74; H,3.51; Cl,8.23; N, 6.50; O,11.14; S,14.88. Found (%): C, 55.70; H, 3.50; Cl,8.23; N,6.55; O,11.12; S,14.90. M.P. 701^0C; mass(M+1)430.

5'-Methyl-4-oxo-4'-phenyl-3-p-tolyl-2,3,4,5-tetrahydro- [2,2'] bithiazolyl-5-carboxylic acid 5(d): IR (KBr) νmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH3),750(CH_3), 820(CH_3) cm^{-1}. H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s, 1H, CH), 2.35(s,6H,2×CH_3),4.35(s,1H, CH),6.98(d,2H,2×CH), 7.11(d,2H,2×CH),7.227.48(m,5H, C_6H_5),11.0(s,1H, OH),8(s,3H, CH_3),1.0(s,3H, CH_3) ppm.
^{13}CNMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166. 70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C <),128.50(=C<),129.00(=C<),21.2(>C<),12.4(>C<).Anal.calcd.(%)for $C_{22}H_{20}N_2O_3S_2$:C,62.24; H, 4.75; N, 6.60; O,11.31; S,15.11. Found (%): C,62.20; H, 4.72; N,6.64; O,11.33; S,15.12. M.P. 706^0C; mass(M+) 424.

3-(4-Methoxy-2-methyl-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2']bithiazolyl-5-carboxylic acid 5(e):IR (KBr) νmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3),750(CH_3),1240(OCH_3) cm^{-1}. H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s,1H,CH), 2.35(s,6H,2×CH_3),4.35(s,1H,CH),
6.98(d,2H,2×CH),7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH),8(s,3H,CH_3),3.6(s,3H,OCH_3)ppm.^{13}C NMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<), 128.50(=C<),129.00(=C<),12.4(>C<).Anal.calcd.(%)for $C_{22}H_{20}N_2O_4S_2$:C,59.98; H, 4.58; N, 6.36; O,14.56; S,14.56. Found (%): C,59.96; H, 4.60; N,6.34; O,14.54; S,14.57. M.P. 728^0C; mass(M+) 440.

3-(2,3-Dimethyl-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2']bithiazolyl-5-carboxylic acid 5(f): IR (KBr) νmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3),750(CH_3) , 880(CH_3) cm-1.H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s,1H,CH),2.35(s,6H,2×CH_3),4.35(s,1H,CH), 6.98 (d,2H,2×CH), 7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH),8(s,3H,CH_3),2.35(s,3H,CH_3)ppm.^{13}CNMR($CDCl_3$,50.3 2MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=

),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<),14.4(>C<).Anal.calcd.(%)for $C_{22}H_{20}N_2O_3S_2$: C,62.24; H, 4.75; N, 6.60; O,11.31; S,15.11. Found (%): C,62.22; H, 4.77; N,6.61; O,11.30; S,15.11. M.P. 706^{0}C; mass(M+)424.

3-(4-Bromo-2-methyl-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2'] bithiazolyl-5-carboxylic acid 5(g):IR (KBr) νmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH3),750(CH_3) , 1075(Br) cm-1.H^1 NMR ($CDCl_3$, 200.13 MHz): δ 5.92(s,1H,CH), 2.35(s,6H,2×CH_3), 4.35(s,1H,CH), 6.98(d,2H,2×CH),7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH),8(s,3H,CH_3)ppm.^{13}CNMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<).Anal.calcd.(%) for $C_{21}H_{17}BrN_2O_3S_2$: C,51.54; H, 3.50; Br,16.33,N, 5.72; O,9.81; S,13.10. Found (%): C,51.52; H, 3.52; Br,16.32; N,5.73; O,9.80; S,13.11. M.P. 754^{0}C; mass(M+1)489, (M+2) 491.

3-(3-Fluoro-2-methyl-phenyl)-5'-methyl-4-oxo-4'-phenyl-2,3,4,5-tetrahydro-[2,2'] bithiazolyl-5-carboxylic acid 5(h): IR (KBr) νmax: 1440(C-CH_3), 1595(C=C), 1600(C=N), 1690(C=O), 1760(COOH) 3030(Ar-CH), 3300(OH) ,1150(OCH_3),750(CH_3) , 1250(F) cm-1.H^1 NMR ($CDCl_3$, 200.13 MHz): 5.92(s,1H,CH), 2.35(s,6H,2×CH_3), 4.35(s,1H,CH), 6.98(d,2H,2×CH),7.11(d,2H,2×CH),7.227.48(m,5H,C_6H_5),11.0(s,1H,OH),8(s,3H,CH_3)ppm.^{13}CNMR($CDCl_3$,50.32MHz):δ166.50(=C<),152.60(=C<),128.50(=C<),56.60(>C<),7.40(>C<),58.10(>C<),166.70(=C<),137.80(>C=),120.30(=C<),129.4(=C<),133.30(=C<),20.9(>C<),176.00(=C<),136.50(=C<),127.00(=C<),128.50(=C<),129.00(=C<).Anal.calcd.(%)for $C_{21}H_{17}FN_2O_3S_2$: C,58.86; H, 4.00; F,4.43,N, 6.54; O,11.20; S,14.97. Found (%): C,58.54; H, 4.02; F,4.42; N,6.55; O,11.19; S,14.98. M.P. 695^{0}C; mass(M+) 428.

3. Result and Discussion

In the present work, we Synthesised rapid and efficient various 4-oxo thiazolidines *viz*. 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid derivatives were achieved (Scheme-I and scheme-II) by using microwave method gives good yield. The synthesized compounds were characterized by analysing their H^1NHR & ^{13}C NMR, IR, Mass spectra. It was observed that substituted Schiff bases cyclocondensation with 2-mercaptomalonic acid yields 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid [5(a-h)]. The structures of [5(a-h)] were confirmed by elemental analysis and IR spectra showing an absorption band at 1595 (C=C) and signals at), 6.9-7.1 (d, 2H, =CH),7.2-7.4(m,5H =CH) 11.0 (s, 1H, COOH) in H^1NMR representative of the completion of the reaction and formation of the desired product. Similarly, absorption bands at 1595 (C=C), 1690 (C=O), 1600 (C=N) in IR spectra and signal at 11.0 (s, 1H, OH) in H^1NMR of [5(a-h)] confirmed the structures assigned to 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid [5(a-h)]. The structures assigned to 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid [5(a-h)] were supported by the elemental analysis and IR spectra showing an absorption band at 1690 (C=O), 1595 (C=C).

QSAR Analysis of Activities with PASS:

To obtain the predicted biological activity profile for synthesized compounds the structures of derivatives [5(a-h)] were added to Pass online computer Programme. The predictions of their probabilities active [Pa] and inactive [Pi] for the set of biological activities studied. The subsequent three activities were predicted with highest probability for the series of compounds [5(a-h)]

1. Follicle-stimulating hormone agonist
2. Antiinfertility, female
3. Muramoyltetrapeptide carboxypeptidase inhibitor

Table 2
Predictions Of Biological Activities By Pass Online Programme

Compound	Follicle-stimulating hormone agonist **Pa**	Antiinfertility, female **Pa**	Muramoyltetrapeptide carboxypeptidase inhibitor **Pa**
5-a	**0.916**	**0.724**	**0.684**
5-b	0.904	0.704	0.626
5-c	0.903	0.709	0.626
5-d	0.901	0.693	0.643
5-e	0.886	0.671	0.565
5-f	0.907	0.697	0.664
5-g	0.891	0.660	0.560
5-h	0.886	0.687	0.582

Follicle-stimulating hormone agonist:

The follicle-stimulating hormone receptor (FSHR) is a glycoprotein plays important role in mammalian reproduction and development. Follicle-stimulating hormone agonist is chemical substance which binds to specific hormone receptors stimulates the function of the endocrine glands the biosynthesis of their secreted hormones, or the action of hormones upon their specific sites**.** It helps control the menstrual cycle and stimulates the growth of eggs in the ovaries. The said compounds may acts as drug.

Antiinfertility, female:

Infertility is a disease in which women are unable to get pregnant due to many problems associated with uterus, fallopian tubes and ovulation. These compounds may be used as Antiinfertility agents.

Muramoyltetrapeptide carboxypeptidase inhibitor:

Muramoyltetrapeptide carboxypeptidase is an enzyme also referred as carboxypeptidase IIW belongs to hydrolases. It is involved in peptidoglycan synthesis, catalyzing both decarboxylation and transpeptization. The substance used as thiol blocking agent and stimulated by Ca^{2+} and Mg^{2+} not affected by penicillin. The catalytic activity of the enzyme in the organism is probably inhibited by the compounds under study.

We can conclude that, all compounds have moderately all three activities. Out of [5a-5h] compounds only 5a has highest Pa values for all three activities shown in Table 2.

4. Conclusion:

The synthesis of eight 4-oxo-thiozolidines viz 2-(5-methyl-4-phenylthiazol-2-yl)-4-oxothiazolidine-5-carboxylic acid by microwave assisted method. These synthesized compounds were characterized by IR, ^{1}H NMR,^{13}C NMR, Mass Spectroscopy. All compounds were screened for antimicrobial activities, we found that, all compounds have moderately all three activities such as Antiinfertility in female, Follicle stimulating hormone agonist and Muramoyltetrapeptide carboxypeptidase inhibitor. The compound **5a** found highest all three activities can serve as potent antimicrobial lead for further studies.

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