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PEG MEDIATEDMICROWAVE ASSISTED SYNTHESIS OF FUNCTIONALIZED THIAZOLONES

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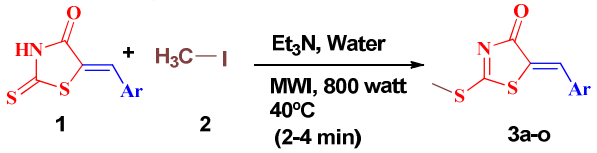
Abstract: A facile and effective synthesis of reported some new series of ((*Z*)-2-((5-(4-fluorobenzylidene)-4-oxo-4, 5-dihydrothiazol-2-yl) amino)-substituted acid in polyethylene glycol under conventional and microwave irradiation method. Nucleophilic Ipso-substitution between amino acid and methylthio-thiazolone was successfully carried out with good yield in less time of reaction using microwave irradiation method.

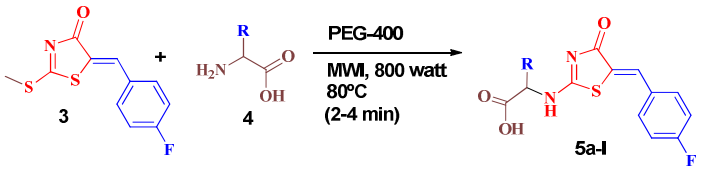
Keyword: PEG, Amino acid, Arylidene rhodanine, Microwave irradiation method.

Introduction:

Thiazolones scaffoldis biologically active and pharmaceutically important compounds with various applications[i-iv]such as anti-microbial,[v-vi] anti-diabetic,[vii] anti-malarial,[viii]anti-fungal,[xiv] anti-inflammatory,[x-xi]anti-tubercular,[xii-xiii] chikungunya virus[xiv-xvi]anti-cancer and anti-leukotriene therapy.[xvii-xviii]For the discovery of new lead structures in drug discovery and progress of our earlier research work[xix]. Using Polyethylene glycol(PEG)[xx], in addition to microwave-assisted.[xi]



Scheme 1: Synthesis of (*Z*)-5-(substituted)-2-(methylthio) thiazol-4(5*H*)-ones **3**



Scheme 2: Synthesis of (*Z*)-2-((5-benzylidene-4-oxo-4, 5-dihydrothiazol-2-yl)amino)propanoic acid(functionalized thiazolones) **5**

The use of microwave energy is one of the green methods to accelerate the organic reactions which may attract many researchers and have a number of advantages such as less time of reaction, cleaner reaction profile, no side product and high yield. Hence, the use of microwave reaction for the synthesis of organic molecules is considered part of green approach protocol.[xxii-xxiii]

In past some synthetic methods for functionalized thiazolones.[xxiv]Thesesynthetic approaches, however, suffer from disadvantages such as using toxic and hazardous solvent and catalyst, low yield,

lack of selectivity, and complicated workup in procedures, use of hazardous chemical compounds and are expensive.To overcomethese difficulties, it is essential to develop a simple and more eco-friendly method for the synthesis of functionalized thiazolones using triethyl amine, water, PEG as green catalyst, solvent (**Scheme 1 & 2**). They have become an increasingly attractive synthetic tool because of their green credentials such as convergence, atom-economy, energy savings, and waste and cost minimization.[xxv]In continuation with our interest as a part of green synthetic protocol.[xxvi-xxx]

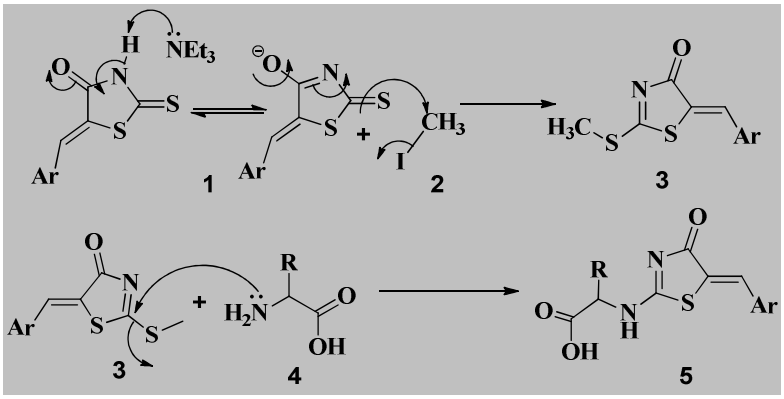


Figure 1. Plausible Mechanism for the synthesis of functionalized thiazolidinones**5**

Results and discussion:

In continuation of our earlier research work[xix]. The model of reaction were performed as selected green protocols; benzylidine rhodanine **1**(1 mmol), iodo methane **2**(1.2 mmol) in presence of triethyl amine (1.2 mmol), water (3-4mL) at 40°C temperature under the microwave irradiation method programmed at 800 watt. (**Scheme 1**,**Table 1**) excellent yield was obtained in very less time of reaction due to triethyl amine water is best paired emerged catalyst-solvent[xxxi]. Here in we select fluorine substituted aromatic arylidene thiazolones because of for the biological significance, fluorinated compound gave good biological active **Table 1**, entry 3, compound **5c** for the second model reaction as compound **3** (1 mmol), amino acids **4a-l**(1.5 mmol) were screened in different solvent such as water, acetonitrile, ethyl alcohol, methyl alcohol, dichloromethane and acetic acid, PEG-400; amount of (8-10mL). As we can observed good yield was obtained in ethanol and acetonitrile (**Table 2,** entry 1,2), other solvent gave corresponding yield but in PEG best result was (**Table 2**, entry 7) in very less time of reaction, using microwave irradiation method (800 W), at 80ºC temperature. There is no significant yield was obtained under the solvent free reactions (**Table 2**, entry 7). Thus, We decided all examples were tested in PEG-400 under the microwave irradiation method with good to excellent yields (94-98%) could be achieved in short reaction time 2-4 min (**Table 3**). Finally, the structure of compounds were demonstrated by ^{1}H NMR spectra shows one signal for the amine proton at 10.23 ppm and starting reactant of methyl singlet of thio-methyl range at 2.71–2.83 for 3 proton singlet were completely disappear in the final product (see spectral copy ^{1}HNMR).Another one proton singlet at 7.89 this strongly indicates that the compounds have the *Z*-configuration.IR spectrum showed a strong absorption band at 1690-1698 cm^{-1}due to a carbonyl group of amide and 3171-1382 cm^{-1} due to secondary amine.

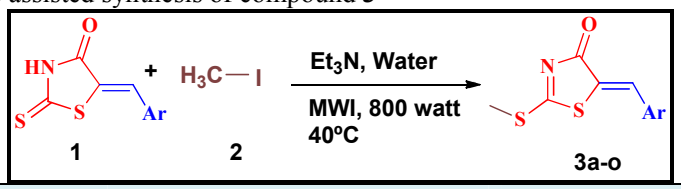
Experimental:

Instruments

The starting arylidene rhodanine is prepared from our earlier research work[xix], aromatic aldehydes, tri-ethylamine, iodomethane and various solvents were commercially available. The major chemicals were purchased from Sigma Aldrich and Avra labs. Microwave reactions were carried out in Micro SYNTH Lab station of Ethusi Milestone. Reaction courses were monitored by thin layer chromatography on silica gel precoated F254 Merck plates. Developed plates were examined with UV

lamps (254 nm). IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and these are uncorrected. ^{1}H NMR spectra were recorded on a 300 and 400MHz Bruker spectrometer and ^{13}C NMR were recorded in solvent DMSO$d_6$at 100 MHz Bruker spectrometer are reported as part per million (ppm) downfield from a tetra methyl silane internal standard. The following abbreviations are used, singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m) and broad (br). Mass spectra were taken with Micromass-II of WATER mass spectrometer.

Table 1. Microwave assisted synthesis of compound **3**



Entry	Compound	Ar	Yield[a] (%)/Time	
			Microwave (min)	M.P. (ºC)
1	3a	- benzyl	90/2	146-147
2	3b	-4-chlorobenzyl	91/3	161-162
3	3c	-4-flurobenzyl	92/3	141-142
4	3d	-4-notrobenzyl	96/2	163-164
5	3e	-4-hydroxybenzyl	88/4	123-124
6	3f	-4-methoxybenzyl	90/3	162-163
7	3g	-4-methylbenzyl	89/3	173-174
8	3h	-3-methoxybenzyl	90/3	164-165
9	3i	-3-methylbenzyl	89/3	176-177
10	3j	-3-flurobenzyl	90/3	144-145
11	3k	-2,4-dichlorobenzyl	90/3	164-165
12	3l	-2,4-dimethoxybenzyl	91/3	173-174
13	3m	-2-chlorobenzyl	90/3	171- 172
14	3n	-2-thiophenyl	88/3	151-152
15	3o	-2-furyl	83/3	161-162

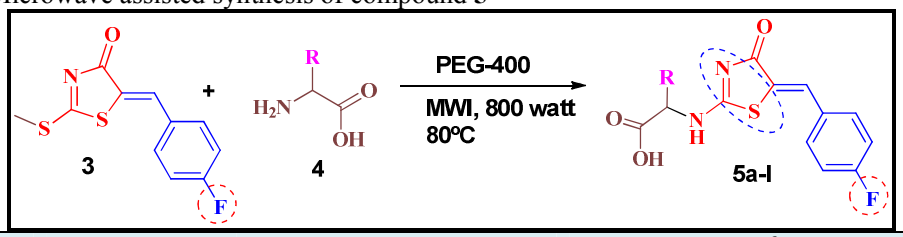
[a]Isolated yield after purification by MeOH-$CHCl_3$.Microwave assisted synthesis: triethylamine, Water, 40-50 ºC,800 w

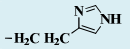
Table 2. Screening of solvents, reaction time and yield for the synthesis of compound**5**[a]

Entry	Solvent	Time (min)	Yield[b] (%)
			Microwave Irradiation
1	CH_3CN	3	89
2	EtOH	3	90
3	MeOH	3	86
4	DCM	4	68
5	CH_3COOH	4	40
6	PEG	2	**98**
7	Neat	4	65

[a]**Reaction condition:** The reaction was carried out; Compound (**3**) (1 mmol), amino acids (**4a-l**) (1.2 mmol) in 8 mL of solvent at 80 ºC ; MWI
[b]**Isolated yield** after purification by recrystallization from aq. Ethanol or MeOH:$CHCl_3$

Table 3. Microwave assisted synthesis of compound **5**



Entry	Compound	R	Yield[a] (%)/Time	
			Microwave (min)	M.P. (ºC)
1	5a	-CH_3	98/2	228-230
2	5b	-$CH(CH_3)_2$	98/3	200-202
3	5c	-$CH(CH_3)CH_2CH_3$	96/3	138-140
4	5d	-CH_2Ph	96/2	168-170
5	5e	-$CH_2CH_2SCH_3$	97/4	154-156
6	5f	-$CH_2CH(CH_3)_2$	98/3	231-233
7	5g	-CH_2OH	94/3	199-201
8	5h	-CH_2SH	94/3	204-206
9	5i	-CH_2COOH	98/3	180-182
10	5j		98/3	190-191
11	5k	-$CH_2C_6H_4OH$	97/3	190-192
12	5l	-$CHOHCH_3$	95/3	168-170

[a]Isolated yield after purification by MeOH-$CHCl_3$.Microwave assisted synthesis: triethyl-amine, PEG, 80ºC,800 w

Synthesis

General method for synthesis of (Z)-5-(benzylidine)-2-(methylthio)thiazol-4(5H)-one (3):

Microwave irradiation method: To a suspension of 5-arylidine rhodanine **1** (1 mmol), methyl iodide **2** (1.2 mmol) and triethyl amine (1.2 mmol) in water (2-4mL) shake well and then placed in Biotage Microwave Synthesizer, mixture of solution was subjected to microwave irradiation (800 W) at 40-50 ºC for 2-4 min, reaction mixture were cool at room temperature and then further well stirred for 1-2 minute. The progress of reaction was monitored by thin layer chromatography (10% chloroform-methyl alcohol). After completion of reaction, the reaction mixture was concentrated in vacuo. The residue was washed with water to afford crude product was recrystallized by ethanol to give yield (83-96%)

Synthesis of (Z)-2-((5-benzylidene-4-oxo-4, 5-dihydrothiazol-2-yl)amino) propanoic acid (functionalized thiazolones) (5):

Conventional Method: In a 100 ml round bottom flask, the compound **3**(1 mmol), amino acids **4a-l**(1.5 mmol) potassium carbonate (1.5 mmol) and PEG-4008mL was added and this mixture were stirred to heat at 40-50º C for 15-18 min. The progress of reaction was monitored by TLC (chloroform: methanol). After completion of reaction, the reaction mixture crushed with ice cold water the solid was obtained and recrystallized from ethanol. If necessary the column chromatography was performed using silica gel (200–300 mesh), eluted with ethyl acetate and petroleum ether (1:1, v/v) to give product **5a;** Yield: 93 %

Microwave irradiation method: In a 100 ml round bottom flask, the compound **3**(1 mmol), amino acids **4a-l**(1.5 mmol) potassium carbonate (1.5 mmol) and PEG-4008mL was added and this mixture subjected to MW irradiation (800 W), at 80ºC temperature for 2-4 min. The progress of reaction was monitored by TLC (chloroform: methanol). After completion of reaction, the reaction mixture crushed with ice cold water the solid was obtained and recrystallized from ethanol. If necessary the column chromatography was performed using silica gel (200–300 mesh), eluted with ethyl acetate and petroleum ether (1:1, v/v) to give product **5a-l**(Yield: 94-98 %).

Spectral characterization data of Compound (3a-3o):

(Z)-5-benzylidene-2-(methylthio) thiazol-4(5H)-one (3a):
Yellow solid; Yield: 90%;M.p.: 146–147 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3027 (CH–Ar) (aryl), 1696 (C=O) (Amide), 1606(C=N), 1590 (C=C), 1160(C-S), 985 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.83 (s, 3H, S–CH_3), 7.44–7.76 (m, 5H, Ar–CH), 7.80–7.96 (s, 1H, =CH).;^{13}C NMR (100 MHz, DMSO-d6): δ162.2 (C2), 166.9 (C4), 132.0 (C5), 151.8 (C6), 125.6-136.3 (C7-C12), 14.6 (C14).;MS (ESI) *m/z*[M+H]$^+$ 236.00.

(Z)-5-(4-chlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (3b):
Yellow solid; Yield: 91%;M.p.: 161–162ºC(Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3020 (CH–Ar), 1716 (C=O), 1583 (C=C), 1465 (C=N), 1155 (C-S), 979 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.81 (s, 3H, S–CH_3), 7.41–7.73 (m, 4H, Ar–CH), 7.83–7.98 (s, 1H, =CH).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C2), 166.9 (C4), 132.3 (C5), 151.6 (C6), 137.9 (C7), 128.5 (C8), 128 (C9), 134.1 (C10), 128 (C11), 128.9 (C12), 14.6 (C14).; MS (ESI) *m/z*[M+H]$^+$271.00.

(Z)-5-(4-fluorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (3c):
Yellow solid; Yield: 88%; M.p.: 141–142 ºC(Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3012 (CH–Ar), 1710 (C=O), 1597 (C=C), 1490 (C=N), 1156 (C-S), 975 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.83 (s, 3H, S–CH_3), 7.44–7.76 (m, 4H, Ar–CH), 7.81–7.95 (s, 1H, =CH).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C2), 166.9 (C4), 132.4 (C5), 151.5 (C6), 130.1 (C7), 130 (C8), 115 (C9), 161.8 (C10), 152 (C11), 130.2 (C12), 14.6 (C14).; MS (ESI) *m/z*[M+H]$^+$254.00.

(Z)-2-(methylthio)-5-(4-nitrobenzylidene)thiazol-4(5H)-one (3d):
Orange solid; Yield: 96%;M.p.: 163–164 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3016 (CH–Ar), 1695 (C=O), 1590 (C=C), 1590 (C=N), 1156(C-S), 971 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.81 (s, 3H, S–CH_3), 7.80–7.95 (s, 1H, =CH), 7.96–8.20 (m, 4H, Ar–CH).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C2), 166.9 (C4), 132.4 (C5), 151.7 (C6), 140.8 (C7), 129 (C8), 123 (C9), 146.8 (C10), 123 (C11), 130 (C12), 14.5 (C14).; MS (ESI) *m/z*[M+H]$^+$281.00.

(Z)-5-(4-hydroxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (3e):
Yellow solid; Yield: 88%;M.p.: 123–124 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3416 (OH), 3005 (CH–Ar), 1690(C=O), 1595 (C=C), 1608 (C=N), 1165 (C-S), 998 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.70–2.78 (s, 3H, S–CH_3), 5.33–5.47 (s, 1H, OH), 7.43–7.75 (m, 4H, Ar–CH), 7.86–7.99 (s, 1H, =CH).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C2), 166.8 (C4), 132.5 (C5), 151.9 (C6), 127.8 (C7), 130 (C8), 115 (C9), 156.8 (C10), 115 (C11), 130 (C12), 14.3 (C14).; MS (ESI) *m/z*[M+H]$^+$252.00.

(Z)-5-(4-methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (3f):
Yellow solid; Yield: 90%;M.p.:162–163 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3008 (CH–Ar), 1705 (C=O), 1578 (C=C), 1458 (C=N), 1160 (C-S), 973 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.82 (s, 3H, S–CH_3), 3.71–2.86 (s, 3H, O–CH_3), 7.43–7.76 (m, 4H, Ar–CH), 7.86–7.96 (s, 1H, =CH).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C2), 166.6 (C4), 132.3 (C5), 152.2 (C6), 127.2 (C7), 130 (C8), 114.3 (C9), 159.3 (C10), 114.7 (C11), 130 (C12), 14.2 (C14), 54.7 (C15).; MS (ESI) *m/z*[M+H]$^+$266.00.

(Z)-5-(4-methylbenzylidene)-2-(methylthio)thiazol-4(5H)-one (3g):
Yellow solid; Yield: 89%;M.p.: 173–174 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3025 (CH–Ar), 1705 (C=O), 1595 (C=C), 1475 (C=N), 1162 (C-S), 978 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.79 (s, 3H,-CH_3), 2.73–2.89 (s, 3H, S–CH_3), 7.51–7.79 (m, 4H, Ar–CH), 7.80–7.91 (s, 1H, =CH).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.2 (C2), 166.9 (C4), 132.2 (C5), 152.7 (C6), 132 (C7), 127.8 (C8), 128.7 (C9), 137.3 (C10), 128.7 (C11), 127.8 (C12), 14 (C14), 20.9 (C15).; MS (ESI) *m/z*[M+H]$^+$250.00.

(Z)-5-(3-methoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (3h):
Yellow solid; Yield: 90%; M.p. 164–165 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3010 (CH–Ar), 1710 (C=O), 1570 (C=C), 1458 (C=N), 1158 (C-S), 975 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.70–2.81 (s, 3H, S–CH_3), 3.70–2.85 (s, 3H, O–CH_3), 7.44–7.76 (m, 4H, Ar–CH), 7.86–7.98 (s, 1H, =CH).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6 (C2), 166.9 (C4), 132.5 (C5), 152.7 (C6), 135 (C7), 113

(C8), 160 (C9), 113 (C10), 128.7 (C11), 120.2 (C12), 13.8 (C14), 55.2 (C15).; MS (ESI) *m/z*$[M+H]^+$266.00.

(Z)-5-(3-methylbenzylidene)-2-(methylthio)thiazol-4(5H)-one (3i):

Yellow solid; Yield: 89%;M.p.: 176–177 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3010 (CH–Ar), 1705 (C=O), 1568 (C=C), 1462(C=N), 1156 (C-S), 975 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.83 (s, 3H, S–$\underline{C}H_3$), 2.30–2.41 (s, 3H, Ar–$\underline{C}H_3$), 7.10–7.40 (m, 3H, Ar–$\underline{C}$H), 7.05–7.16 (s, 1H, Ar–$\underline{C}$H), 7.86–7.98 (s, 1H, =$\underline{C}$H).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.6 (C2), 166.9 (C4), 132.5 (C5), 152.7 (C6), 135 (C7), 125.3 (C8), 138 (C9), 128.2 (C10), 127.9 (C11), 124.8 (C12), 13.8 (C14), 21.6 (C15).; MS (ESI) *m/z*$[M+H]^+$250.00.

(Z)-5-(3-fluorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (3j):

Yellow solid; Yield: 90%;M.p.: 144–145 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3012 (CH–Ar), 1705 (C=O), 1595 (C=C), 1468 (C=N), 1160 (C-S), 976 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.80 (s, 3H, S–$\underline{C}H_3$), 7.51–7.77 (m, 3H, Ar–$\underline{C}$H), 6.93–8.03 (s, 1H, Ar–$\underline{C}$H), 7.80–7.96 (s, 1H, =$\underline{C}$H).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C2), 166.2 (C4), 132.1 (C5), 152 (C6), 135.6 (C7), 113.3 (C8), 162 (C9), 114.2 (C10), 129.9 (C11), 124.2 (C12), 13.9 (C14).; MS (ESI) *m/z*$[M+H]^+$254.00.

(Z)-5-(2,4-dichlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (3k):

Yellow solid; Yield: 90%;M.p.: 164–165 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3020 (CH–Ar), 1690(C=O), 1585(C=C), 1490 (C=N), 1168 (C-S), 965 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.83(s, 3H, S–$\underline{C}H_3$), 7.61–7.86 (d, 2H, Ar–$\underline{C}$H), 7.91–8.00(s, 1H, =$\underline{C}$H), 7.46(s, 1H, =$\underline{C}$H).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C2), 166.7 (C4), 132.4 (C5), 152 (C6), 131.9 (C7), 137.3 (C8), 128 (C9), 124.2 (C10), 126 (C11), 130 (C12), 13.9 (C14).; MS (ESI) *m/z*$[M+H]^+$305.00.

(Z)-5-(2,4-dimethoxybenzylidene)-2-(methylthio)thiazol-4(5H)-one (3l):

Yellow solid; Yield: 91%; M.p.: 173–174 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3011 (CH–Ar), 1690(C=O), 1570 (C=C), 1475 (C=N), 1160 (C-S), 960 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.80 (s, 3H, S–CH_3), 3.70–3.86 (s, 6H, O–$\underline{C}H_3$), 6.53–6.60 (s, 1H, Ar–$\underline{C}$H), 6.70–8.05 (d, 2H, Ar–$\underline{C}$H), 8.13–8.20 (s, 1H, =$\underline{C}$H).; ^{13}C NMR (100 MHz, $CDCl_3$): δ 162.7 (C2), 166.8 (C4), 132.4 (C5), 152 (C6), 107.9 (C7), 142.7 (C8), 97.8 (C9), 160.2 (C10), 105.9 (C11), 130 (C12), 14 (C14).; MS (ESI) *m/z*$[M+H]^+$296.00.

(Z)-5-(2-chlorobenzylidene)-2-(methylthio)thiazol-4(5H)-one (3m):

Yellow solid; Yield: 90%;M.p.: 171–172 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3015 (CH–Ar), 1716(C=O), 1580 (C=C), 1465 (C=N), 1156 (C-S), 976 (C–N).; ^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.81 (s, 3H, S–$\underline{C}H_3$), 7.25–7.45 (m, 4H, Ar–$\underline{C}$H), 7.87–7.99 (s, 1H, C =$\underline{C}$H).;^{13}C NMR (100 MHz, $CDCl_3$): δ 162.3 (C2), 166.4 (C4), 132.2 (C5), 152 (C6), 132.9 (C7), 134 (C8), 128.3 (C9), 129.2 (C10), 125.9 (C11), 127 (C12), 14 (C14).; MS (ESI) *m/z*$[M+H]^+$271.00.

(Z)-2-(methylthio)-5-(thiophen-2-ylmethylene)thiazol-4(5H)-one (3n):

Yellow soli; Yield: 88%; M.p.: 151–152 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3018 (CH–Ar), 1695 (C=O), 1580 (C=C), 1490 (C=N), 1162 (C-S), 972 (C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.71–2.80 (s, 3H, S–$\underline{C}H_3$), 6.90–8.14 (m, 3H, Ar–$\underline{C}$H), 7.81–7.90 (s, 1H, =$\underline{C}$H).;^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3 (C2), 166.3 (C4), 137.4 (C5), 151.8 (C6), 136.8 (C7), 130 (C9), 27.8 (C10), 128.9 (C11), 14 (C13).; MS (ESI) *m/z*$[M+H]^+$242.00.

(Z)-5-(furan-2-ylmethylene)-2-(methylthio)thiazol-4(5H)-one(3o):

Yellow solid; Yield: 83%; M.p.: 161–162 ºC (Lit:[xix]).; FT-IR (KBr, ν, cm^1): 3016 (CH–Ar), 1695 (C=O), 1586(C=C), 1490 (C=N), 1168(C-S), 972(C–N).;^{1}H NMR (400 MHz, $CDCl_3$): ppm = 2.70–2.81 (s, 3H, S–$\underline{C}H_3$), 6.86–8.17 (m, 3H, Ar–$\underline{C}$H), 7.80–7.93 (s, 1H, =$\underline{C}$H).;^{13}C NMR (100 MHz, $CDCl_3$): δ 161.3 (C2), 166.3 (C4), 137.5 (C5), 151.8 (C6), 150.8 (C7), 110 (C9), 112 (C10), 142.9 (C11), 13.9 (C13).; MS (ESI) *m/z*$[M+H]^+$226.00

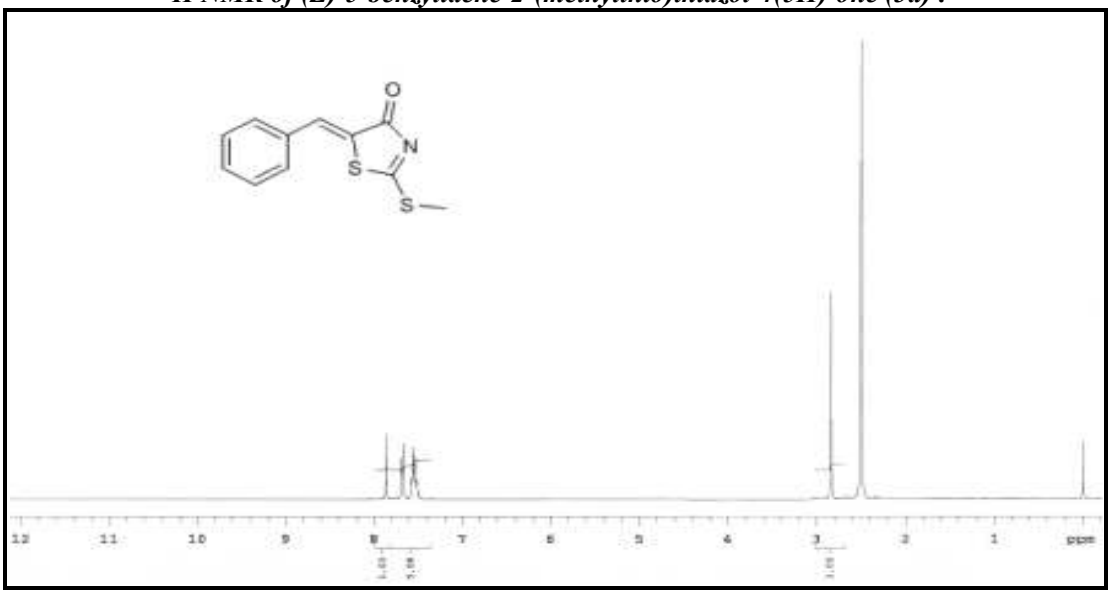
Spectral characterization data of selected Compound 5a:

(Z)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid 5a:

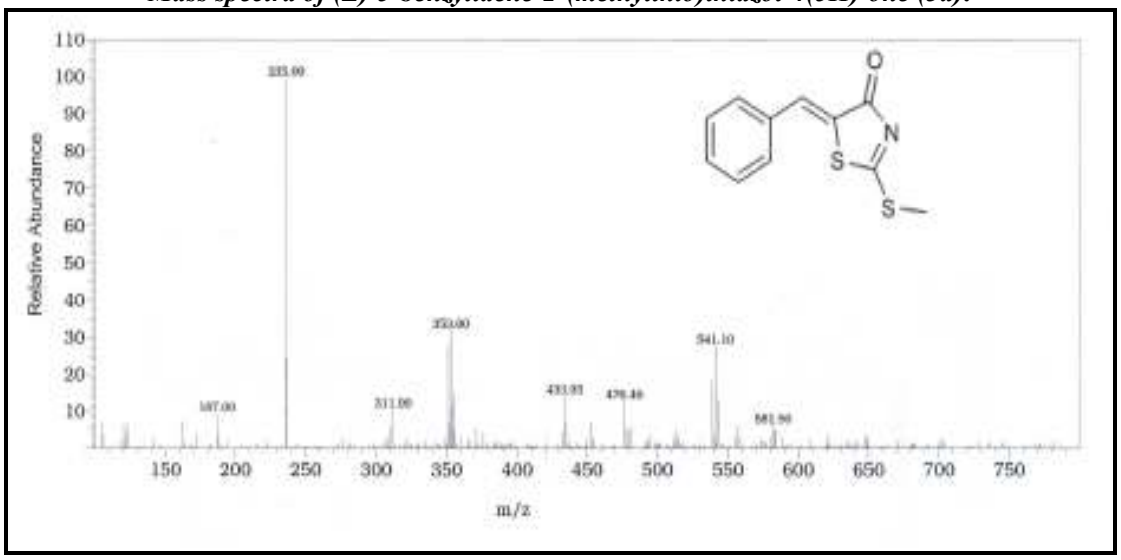
Yellow crystal. Yield: 98%. mp 228–230 ºC(Lit:[xxiv]); ES-MS m/z: 294. IR νmax/cm^{-1}: 3340 (OH), 2968 (CH–Ar),1720 (C=O), 1592 (C=C), 1505 (C=N), 1156 (C-S), 892 (C–N). ^{1}H NMR: δppm = 1.48 (d, 3H, CH_3),4.60–4.80 (q, 1H, CH), 7.36–7.65 (m, 4H, Ar-H), 7.89 (s, 1H, =CH), 10.23 (s, 1H, NH), 12.62 (s, 1H, OH). ^{13}CNMR: δppm = 16.8, 53.6, 115.4, 130.2, 130.6, 132.6, 152.3, 158.3, 167.3, 174.4.

NMR and Mass Copy of some sellected compound:

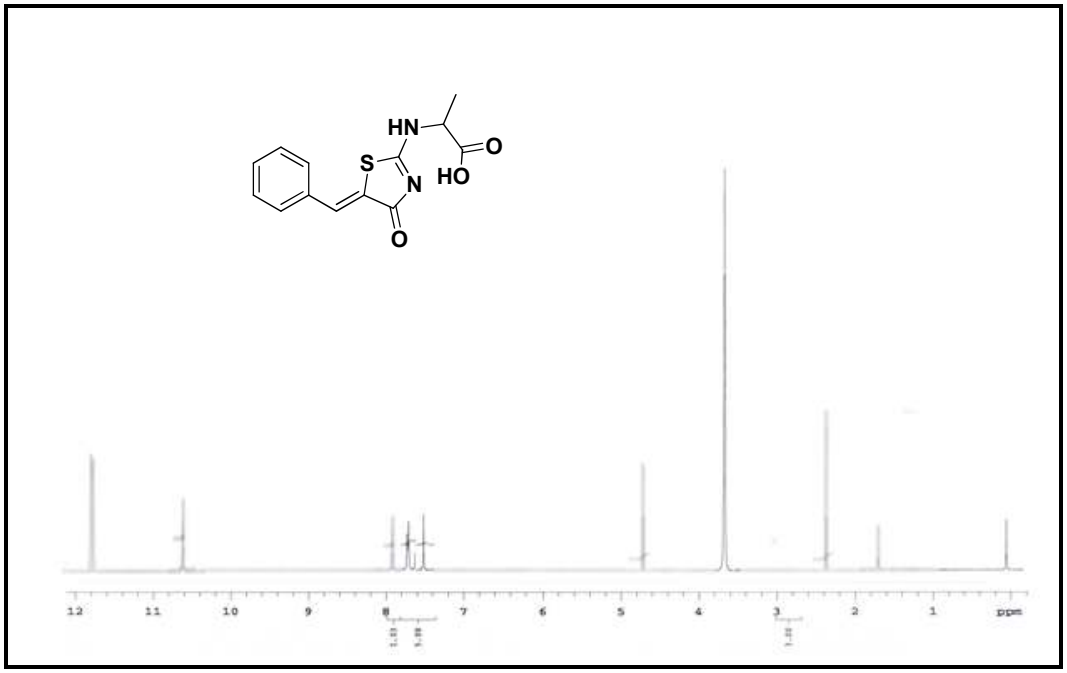
^{1}H NMR of (Z)-5-benzylidene-2-(methylthio)thiazol-4(5H)-one (3a) :



Mass spectra of (Z)-5-benzylidene-2-(methylthio)thiazol-4(5H)-one (3a):



[1]HNMR Spectra of (Z)-2-((5-(4-fluorobenzylidene)-4-oxo-4,5-dihydrothiazol-2-yl)amino)propanoic acid (5a):



Conclusions:

In conclusion, we have successfully developed an eco-friendly protocol for the synthesis of a series of *2-((5-(4-fluorobenzylidene)-4-oxo-4, 5-dihydrothiazol-2-yl)amino) acid derivatives***5a-l**. The mild reaction conditions, good to excellent yields, easy workup, and easily available starting. Notable advantages for the present protocol include short reaction time, cleaner reaction profile and easy isolation of product by microwave irradiation technique using greener solvent.

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