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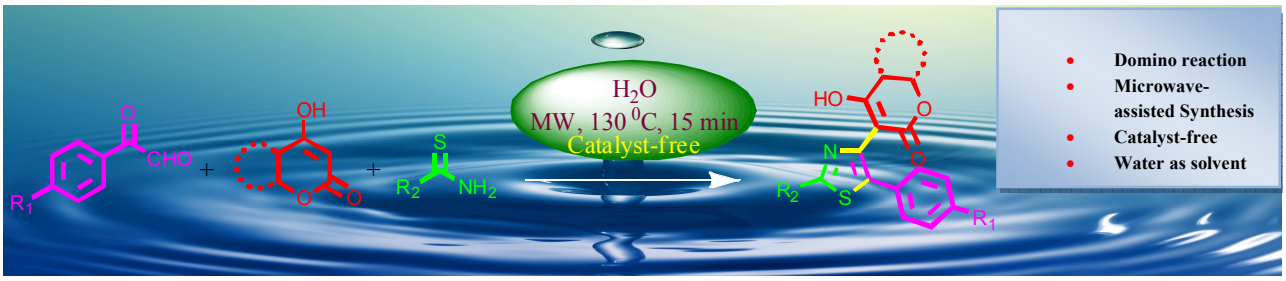
Shaik Karamthulla, Suman Pal, Md. Nasim Khan and Lokman H. Choudhury*



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PAPER

"On-water" synthesis of novel trisubstituted 1, 3-thiazoles via microwave-assisted catalyst-free domino reactions

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A clean, efficient and catalyst free multicomponent domino reaction of arylglyoxals, cyclic 1, 3-dicarbonyls and thioamides in aqueous medium under microwave conditions is reported. A wide variety of trisubstituted thiazoles can be synthesized in good to very good yields using this green protocol. The salient features of this methodology are: catalyst-free reaction, water as reaction medium, short reaction time, good yields, use of microwave heating, and no harmful by-products.

Introduction

Synthesis of chemicals or required products in a selective and environmentally friendly way is an enduring challenge in chemical sciences.[1] Thus in recent times "Green Chemistry" which give us the guidelines for safer and eco-friendly method of chemical synthesis has gained significant attention both from the academia and industries.[2] Water is considered as unique solvent for biochemical reactions and most of the reactions in biological systems take place in water as solvent. Considering its ready availability with negligible cost, non toxic nature, and safety in handling, it is considered as one of the best and green reaction medium in synthesis. The major hurdle for using this excellent solvent in organic synthesis is due to the poor solubility of organic molecules in water. However, after the report of rate acceleration in Diels-Alder reactions[3] and Claisen rearrangements[4] using water as reaction medium and subsequently introduction of "on water concept" by Sharpless et al.[5] the use of water as a reaction medium in organic synthesis has gained more attention.[6] Apart from the solvent the other important parameters for designing a green synthesis is Pot, Atom and Step Economy (PASE) as well as the type of catalyst used and nature of by-products generated etc.[7] In this direction multicomponent domino reactions offer lot of advantages. In multicomponent domino reactions (MDRs) more than two substrates react in one pot under the similar reaction conditions without adding any additional solvent, reagents, catalyst or altering reaction conditions avoiding the isolation and purification of any intermediates.[8] In MDRs two or more bond (usually C-C) are formed in one pot, therefore it saves time, cost, and organic solvents, synthetic steps and proved to be an important tool in recent times for medicinal chemistry and drug discovery process.

Department of Chemistry, Indian Institute of Technology Patna, Patna-800013, India.Tel: +91 612 2552038, Fax: +91 612 227 7383
E-mail: lokman@iitp.ac.in

† Electronic Supplementary Information (ESI) available:: ^{1}H NMR and ^{13}C NMR spectra for all products are available. See DOI:

Use of microwave heating technology for the access of desired products has gained tremendous popularity among the synthetic and medicinal chemists as it reduces reaction times dramatically from several days or hours to minutes.[9] In addition to its advantage in terms of reaction time, it saves energy, cost as well as provides clean products in good to excellent yields. Multicomponent Domino reactions (MDRs) in conjunction with microwave-assisted chemistry offer considerable improvements in selectivity, chemical yield, purity, enhanced reaction rates and manipulative simplicity.[10]Thus we were interested to use MW heating in our newly developed domino reactions.

Thiazoles are five membered heterocycles with N and S heteroatom. They are ubiquitous in natural products,[11] biologically active alkaloids[12] and in pharmaceuticals.[13] Substituted 1,3-thiazoles especially, tethered with aryl or heteroaryl groups (in the 2, 4 and 5 position or di substituted such as 2,4-diaryl, 2,5-diaryl or 4,5-diaryl etc.) are considered as privileged structural motifs and have applications in various fields such as in material science for the preparation of liquid crystals,[14] cosmetics (sunscreens),[15] etc. In addition to these, they also find lot of applications in medicinal chemistry for the access of bioactive lead molecules and drug candidates.[16] A few di- and trisubstituted 1,3-thiazole derivatives with their various pharmacological properties are shown in Fig 1. Febuxostat is a urate lowering drug and inhibitor of xanthine oxidase used for the treatment of hyperuricemia and chronic gout,[17] Fatostatin is a SREBP inhibitor.[18] Similarly, Nizatidine is a useful drug used- for the treatment of peptic ulcer and gastroesophageal reflux disease.[19]Similarly, thiazole moiety is also found in the Vitamin B1 as well as various other bioactive molecules. Thus design and development of novel and eco-friendly methods have lot of scopes.

Substituted thiazoles can be synthesized either by the functionalization of pre existing thioazole moiety,[20] or directly by cyclization of acyclic starting materials.[21] The classical method for the synthesis of thiazoles is the Hantzsch method where α-

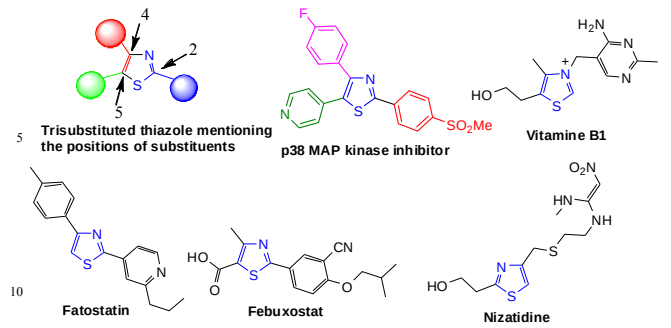
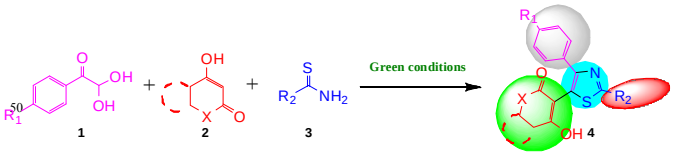


Fig. 1 Representative examples of important substituted thiazoles.

haloketones react with thioamides.[22] Considering the wide spread applications of 1, 3-thiazoles, new methods involving various reagents,[23] using multi-step[24] or multicomponent[25] reactions are also being developed. However, from Green Chemistry point of view most of these new methods have significant limitations, such as tedious work-up procedures, low availability of starting materials, multistep synthesis, harsh reaction conditions, poor yields, long reaction times, and the requirement for an inert atmospheric conditions etc. In addition to these, we realized that very limited methods are available in the literature for the one pot synthesis of trisubstituted 1, 3-thiazole derivatives. Thus, incontinuation of our work for the synthesis of functionalized heterocycles using multicomponent reactions[26] and inspired by the diverse application of aryl tethered thiazoles we were motivated to develop a versatile and benign method for the synthesis of thiazole derivatives (**4**) employing a domino reaction.

For designing an efficient and versatile multicomponent reaction, selection of appropriate starting materials is very important. E.g. arylglyoxals are very useful synthetic building block in organic synthesis where two adjacent carbonyl groups (one ketone and one aldehyde group) act as double electrophilic sites for cyclization reactions. Thus considering their interesting reactivities, very recently it is being used in diverse two and multicomponent reactions for the construction of various functionalized heterocycles.[27] Inspired by the recent methods of arylglyoxal based MCRs and in continuation of our work on synthesis of functionalized heterocycles, herein we would like to report a three component reaction of arylglyoxals, cyclic-1, 3-dicarbonyls and thioamides under eco-friendly reaction conditions as shown in Scheme 1.



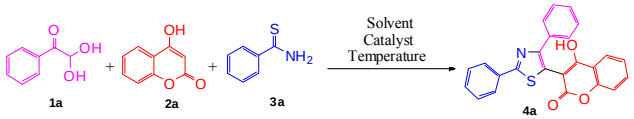
Scheme 1 Synthesis of trisubstituted thiazoles by three component reactions.

Result and discussion

Initially, the reaction of phenylglyoxal monohydrate (1 mmol), 4-hydroxycoumarin (1 mmol), and thiobenzamide (1 mmol) in 5 ml EtOH at room temperature was stirred without any catalyst to synthesize our desired product **4a.** We did not observe our desired product **4a** even after 24 h under these conditions. The same combination at room temperature was next tried in the presence of 20 mol% Et_3N and corresponding desired product **4a** was not observed even in this case. Interestingly, in the presence of 20 mol% of Et_3N and at reflux temperature the same reaction combination in ethanol provided 16% yield of our desired three component product after 20 hours of reaction time. The compound **4a** was fully characterized by usual spectroscopic techniques (IR, ^1H and ^{13}C NMR) as well as by elemental analysis.

Encouraged by this result we attempted to optimize the reaction by changing reaction conditions, temperature, solvents, and using alternative heating technique such as microwave irradiation. The optimization results of this reaction are summarized in Table 1. Performing the same reaction under microwave heating conditions at 120 ^oC in the presence of Et_3N (20 mol %) in ethanol provided 72% yield of the desired product **4a** within 15 minutes. This encouraging result prompted us to check whether Et_3N has any role in this reaction. Therefore, a similar combination of reaction under microwave conditions and in absence of catalyst was performed, and to our surprise we found almost similar yield (70%) of the desired product within 15 minutes (Table 1, entry 6). Thus we realized that this reaction can be performed under catalyst free conditions. Then we focused our attention to optimize the yield by changing various solvents. The reaction in water as solvent and under Microwave conditions at 120 ^oC, provided a better yield than ethanol as solvent. The best yield was found by increasing the reaction temperature to 130 ^oC in water under microwave conditions (Table 1, entry 9). Keeping reaction time 15 minutes and temperature fixed at 130 ^oC, other various organic solvents such as toluene, THF, acetonitrile, DMF were also screened for the same model reaction and in all these cases yields were found less than the entry 9.

Table 1 Optimization of reaction conditions[a]



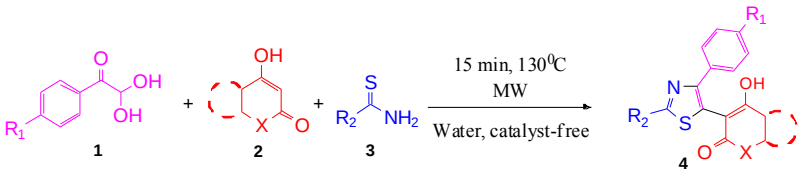
Entry	Solvent	Catalyst (20 mol %)	Temp (^oC)	Time (min/h)	Yield [b](%)	Heating conditions
1	EtOH	----	RT	24[c]	0	
2	EtOH	Et_3N	RT	24[c]	0	
3	EtOH	Et_3N	Reflux	20[c]	16	CH
4	Water	Et_3N	Reflux	20[c]	28	CH
5	EtOH	Et_3N	120	15	72	MWH
6	EtOH	----	120	15	70	MWH
7	EtOH-Water mixture(1:1)	----	120	15	76	MWH
8	Water	----	120	15	82	MWH
9	**Water**	**----**	**130**	**15**	**89**	MWH

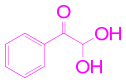
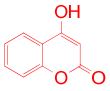
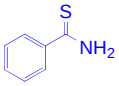
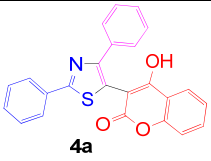
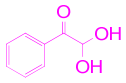
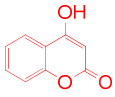
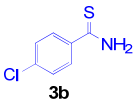
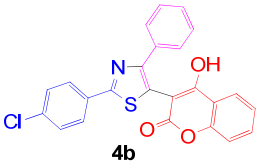
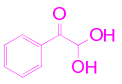
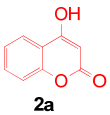
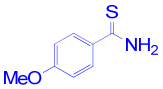
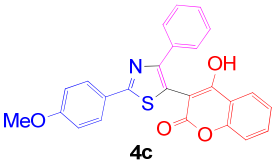
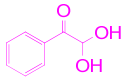
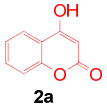
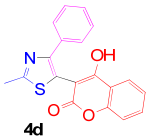
10	Water	----	100	15	78	MWH
11	Water	----	130	20	89	MWH
12	Toluene	----	130	15	32	MWH
13	THF	----	130	15	trace	MWH
14	CH_3CN	----	130	15	60	MWH
15	DMF	----	130	15	43	MWH
16	Neat	----	130	15	71	MWH

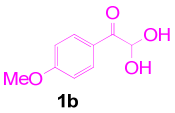
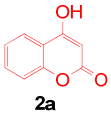
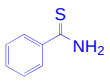
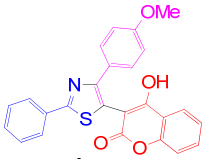
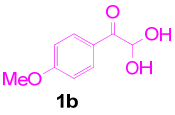
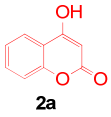
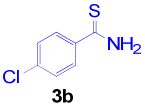
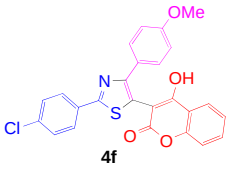
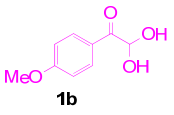
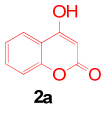
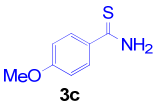
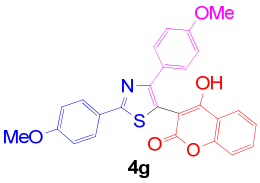
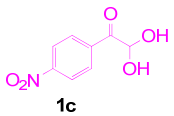
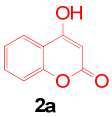
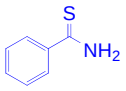
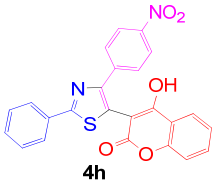
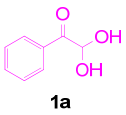
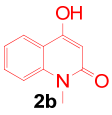
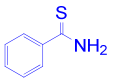
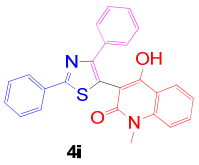
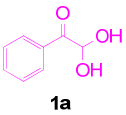
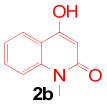
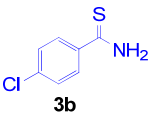
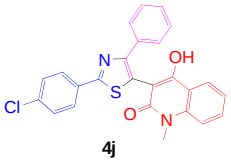
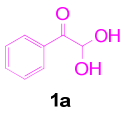
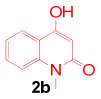
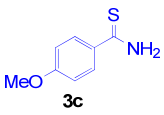
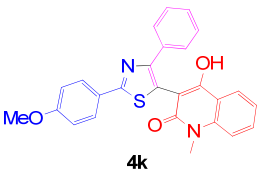
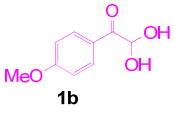
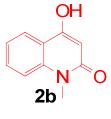
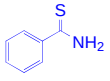
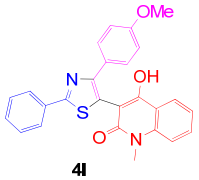
[a]Reaction conditions: phenylglyoxal monohydrate (1 mmol), 4-hydroxycoumarin (1 mmol), and thiobenzamide (1 mmol). [b]Isolated yield, [c]Time in hours. CH-Conventional heating, MWH-Microwave heating

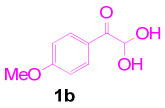
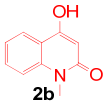
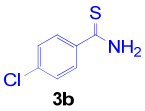
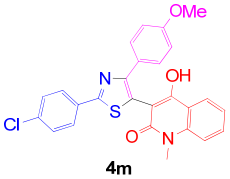
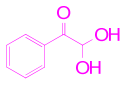
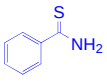
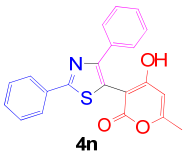
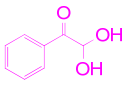
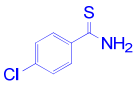
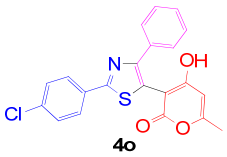
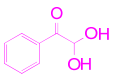
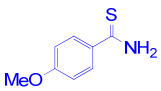
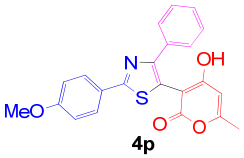
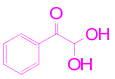
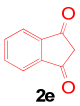
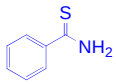
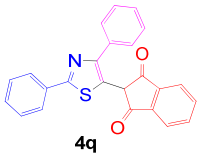
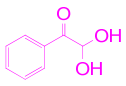
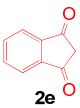
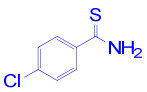
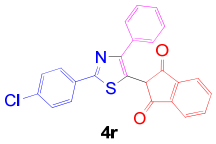
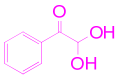
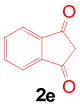
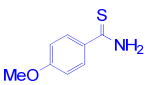
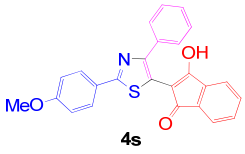
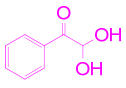
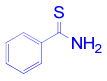
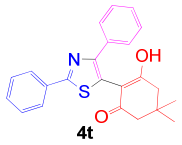
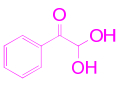
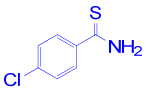
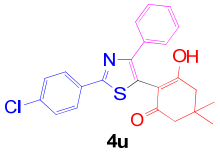
With the optimized reaction conditions in hand, the substrate scope of this domino reaction was investigated. Thiobenzamide bearing different substituent's such as 4-Cl, 4-OMe were found useful for this domino reaction to synthesize diverse thiazole derivatives. Interestingly, aliphatic thioamide such as thioacetamide also provided the corresponding three component product (**4d**) under the similar reactions with moderate yield. Next we have tested the applicability of arylglyoxals tethered with both electron donating as well as withdrawing group in this domino reaction. In all these cases the corresponding thiazole derivatives were obtained in good to very good yields. Similarly, to widen the scope of this method, the cyclic 1,3-dicarbonyls were also varied. Other cyclic 1, 3-dicarbonyls such as 4-hydroxy-1-methylquinolin-2(1H)-one, 4-hydroxy-6-methyl-2-pyrone, indane-1, 3-dione and dimedone also reacted similar to 4-hydroxycoumarin to provide the desired products in good yields and the results are summarized in Table 2. All the products were fully characterized by IR, ^{1}H NMR, ^{13}C NMR and by elemental analysis.

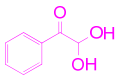
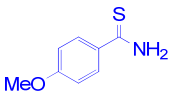
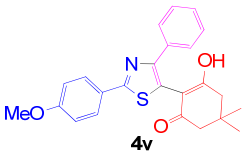
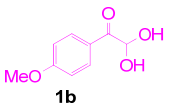
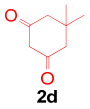
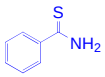
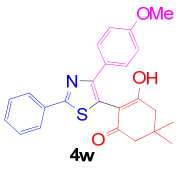
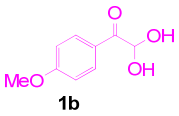
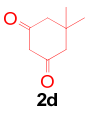
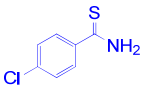
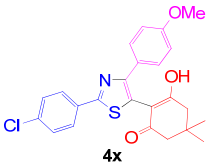
Table 2 Domino Synthesis of 1, 3-thiazoles[a] **4**



Entry	Reactant **1**	Reactant **2**	Reactant **3**	Time (min)	Product **4**	Yield[b] (%)
1	 **1a**	 **2a**	 **3a**	15	 **4a**	89
2	 **1a**	 **2a**	 **3b**	15	 **4b**	85
3	 **1a**	 **2a**	 **3c**	15	 **4c**	85
4	 **1a**	 **2a**	 **3d**	15	 **4d**	52

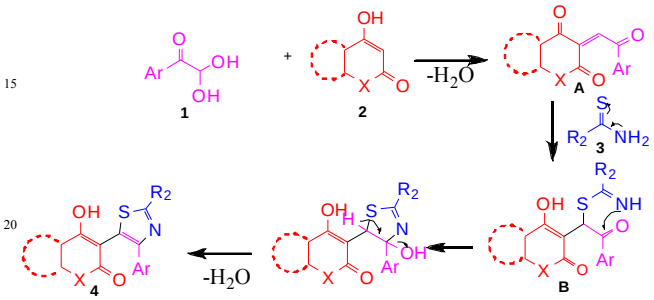
5	 1b	 2a	 3a	15	 4e	82
6	 1b	 2a	 3b	15	 4f	78
7	 1b	 2a	 3c	15	 4g	76
8	 1c	 2a	 3a	15	 4h	63
9	 1a	 2b	 3a	15	 4i	80
10	 1a	 2b	 3b	15	 4j	73
11	 1a	 2b	 3c	15	 4k	74
12	 1b	 2b	 3a	15	 4l	68

13	 1b	 2b	 3b	15	 4m	71
14	 1a	 2c	 3a	15	 4n	73
15	 1a	 2c	 3b	15	 4o	75
16	 1a	 2c	 3c	15	 4p	78
17	 1a	 2e	 3a	15	 4q	67
18	 1a	 2e	 3b	15	 4r	64
19	 1a	 2e	 3c	15	 4s	68
20	 1a	 2d	 3a	15	 4t	80
21	 1a	 2d	 3b	15	 4u	76

22	 1a	 2d	 3c	15	 4v	75
23	 1b	 2d	 3a	15	 4w	70
24	 1b	 2d	 3b	15	 4x	68

[a]Reaction conditions: phenylglyoxal monohydrate or its derivatives (1 mmol), 1, 3-dicarbonyls (1 mmol), and thioamide derivatives (1 mmol), in Water at 130 °C (MW). [b]Isolated yield

On the basis of the above results a plausible reaction mechanism is shown in Scheme 2. Initially Knoevenagel type of reaction takes place between the reactant **1** and **2** to form alkene A**.** Then the thioamide **3** undergoes thia-Michael addition to A affording intermediate **B** which subsequently undergoes cyclization by the loss of water to form desired product **4**.



Scheme 2 Proposed mechanism for the synthesis of **4**.

Conclusion

In summary we have developed a catalyst-free on-water microwave-assisted domino reaction for the efficient synthesis of trisubstituted 1, 3-thiazole derivatives from the readily available starting materials. Considering the importance of thiazole and 4-hydroxycoumarin moiety we expect this type of molecule will have broad application in medicinal chemistry. Further efforts to see the scope and diversity of these MDRs is currently underway and will be reported in due course. The reaction is easy to perform simply by mixing easily available starting materials under microwave irradiation. All the reactions took place within 15 minutes with water as the only benign by-product.

Experimental

General information

All starting materials were purchased from Sigma Aldrich and Alfa Aesar and used without further purification. NMR spectra were recorded on 400 or 500 MHz for ^{1}H and 100 or 125 MHz for ^{13}C in $CDCl_3$ or DMSO-d6, Chemical shift values were reported in δ values (ppm) downfield from tetramethylsilane. Infrared (IR) spectra were recorded on a Shimadzu IR Affinity-1, FTIR spectrometer. Elemental analyses were carried out using either Elementar Vario EL III or Perkin-Elmer 2400 II elemental analyzers. Microwave irradiation was carried out with Initiator 2.5 Microwave Synthesizers from Biotage, Uppsala, Sweden. Melting points were recorded by using SRS EZ-Melt automated melting point apparatus by capillary methods and uncorrected.

General procedure for the synthesis of 1, 3-thiazole analogues (4).

A mixture of arylglyoxal monohydrate **1** (1 mmol), 1, 3-dicarbonyl derivatives **2** (1 mmol), and thioamide derivatives **3** (1 mmol) in 3 mL H_2O was introduced in a 2-5 mL Initiator reaction vial, the mixture was irradiated for 15 minutes at 130 °C and 200 W. The reaction mixture was then cooled to room temperature and the solid was filtered off, and was washed with 95% EtOH to yield the pure products **4**. Some of the products **4n-4p**, **4q, 4r** and **4t** were purified by column chromatography on a silica gel column using EtOAc–hexane mixture as the eluent.

3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-2H-chromen-2-one (4a): Yield: 89%, White solid, mp. 162-164 °C; IR (KBr): 3081, 2943, 1954, 1810, 1673, 1608, 1575, 1550, 1488, 1420, 1340, 1273, 1192, 1093, 1028 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.04 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.94 (d, *J* = 7.5 Hz, 1H, Ar-H), 7.72 (d, *J* = 6.0 Hz, 2H, Ar-H), 7.70 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.56 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.52 (d, *J* = 7.0 Hz, 1H, Ar-H),

7.45 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.41-7.35 (m, 3H, Ar-H), 7.30 (t, *J* = 7.0 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.0, 164.3, 161.6, 154.3, 153.2, 135.3, 133.7, 133.5, 130.9, 129.8, 128.9, 128.5, 127.8, 126.5, 124.8, 124.5, 122.9, 116.9, 116.3, 96.5; Anal. Calcd for $C_{24}H_{15}NO_3S$ (397.45): C, 72.53; H, 3.80; N, 3.52; Found: C, 72.57; H, 3.83; N, 3.58.

3-(2-(4-chlorophenyl)-4-phenylthiazol-5-yl)-4-hydroxy-2H-chromen-2-one (4b): Yield: 85%, Pale Yellow solid, mp. 257-259 °C; IR (KBr): 3083, 2941, 1957, 1811, 1677, 1618, 1573, 1550, 1498, 1423, 1349, 1263, 1196, 1097, 1032 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.06 (dd, *J* = 6.8, 1.6 Hz, 2H, Ar-H), 7.94 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar-H), 7.73-7.68 (m, 3H, Ar-H), 7.62 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.41-7.35 (m, 3H, Ar-H), 7.31 (d, *J* = 7.2 Hz, 1H, Ar-H); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 166.1, 164.7, 161.9, 154.9, 153.7, 135.9, 135.6, 134.2, 132.8, 130.3, 129.4, 129.0, 128.7, 128.3, 125.2, 124.9, 123.8, 117.4, 116.7, 96.8; Anal. Calcd for $C_{24}H_{14}ClNO_3S$ (431.89): C, 66.74; H, 3.27; N, 3.24; Found: C, 66.79; H, 3.29; N, 3.28.

4-hydroxy-3-(2-(4-methoxyphenyl)-4-phenylthiazol-5-yl)-2H-chromen-2-one (4c): Yield: 85%, White solid, mp. 173-175 °C; IR (KBr): 2955, 2869, 2578, 1575, 1508, 1486, 1369, 1322, 1260, 1088, 1030 cm^{-1}; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 8.06 (dd, *J* = 6.8, 1.6 Hz, 2H, Ar-H), 7.94 (dd, *J* = 8.0, 1.2 Hz, 1H, Ar-H), 7.73-7.68 (m, 3H, Ar-H), 7.69 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.41-7.35 (m, 3H, Ar-H), 7.31 (d, *J* = 7.2 Hz, 1H, Ar-H), 3.88 (s, 3H, OMe); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 167.4, 164.6, 162.0, 161.9, 154.4, 153.7, 135.8, 134.1, 129.3, 128.8, 128.6, 128.3, 126.8, 125.2, 124.9, 122.1, 117.4, 116.7, 115.6, 97.0, 56.3; Anal. Calcd for $C_{25}H_{17}NO_4S$ (427.47): C, 70.24; H, 4.01; N, 3.28; Found: C, 70.21; H, 4.03; N, 3.32.

4-hydroxy-3-(2-methyl-4-phenylthiazol-5-yl)-2H-chromen-2-one (4d): Yield: 52%, White solid, mp. 211-213 °C; IR (KBr): 3049, 2905, 2869, 1700, 1653, 1609, 1564, 1527, 1496, 1472, 1423, 1336, 1221, 1179, 1157, 1081, 1034 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, *J* = 7.8 Hz, 1H, Ar-H), 7.62 (dd, *J* = 7.0, 1.5 Hz, 1H, Ar-H), 7.61-7.57 (m, 2H, Ar-H), 7.37 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.32 (dt, 1H, *J* = 8.0, 1.0 Hz, ArH), 7.33-7.25 (m, 3H, Ar-H), 2.75 (s, 3H, CH_3); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ = 165.3, 163.4, 161.1, 152.7, 152.1, 134.7, 132.7, 128.1, 127.5, 127.2, 123.9(2C), 121.2, 116.2, 115.7, 96.3, 18.9; Anal. Calcd for $C_{19}H_{13}NO_3S$ (335.38): C, 68.04; H, 3.91; N, 4.18; Found: C, 68.09; H, 3.94; N, 4.22.

4-hydroxy-3-(4-(4-methoxyphenyl)-2-phenylthiazol-5-yl)-2H-chromen-2-one (4e): Yield: 82%, White solid, mp. 236-238 °C; IR (KBr): 3085, 2959, 2837, 1706, 1671, 1610, 1564, 1528, 1500, 1490, 1464, 1415, 1340, 1273, 1253, 1173, 1154, 1099, 1030 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.02 (dd, *J* = 8.1, 1.5 Hz, 2H, Ar-H), 7.94 (dd, *J* = 7.9, 1.3 Hz, 1H, Ar-H), 7.70 (dt, *J* = 8.5, 1.5 Hz, 1H, Ar-H), 7.66 (d, *J* = 8.9 Hz, 2H, Ar-H), 7.56-7.52 (m, 3H, Ar-H), 7.45 (d, *J* = 8.5 Hz, 1H, Ar-H),7.39-7.38 (dt, *J* = 8.0, 0.5 Hz, 1H, Ar-H), 6.93(d, *J* = 9.0 Hz, 2H, Ar-H), 3.73(s, 3H, OMe); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.3, 163.6, 161.0, 158.9, 153.6, 152.7, 133.2, 133.1, 130.3, 129.3, 128.7, 127.3, 125.9, 124.2, 124.0, 120.6, 116.5, 115.7, 113.8, 96.2, 55.0; Anal. Calcd for $C_{25}H_{17}NO_4S$ (427.47): C, 70.24; H, 4.01; N, 3.28; Found: C, 70.21; H, 4.06; N, 3.33.

3-(2-(4-chlorophenyl)-4-(4-methoxyphenyl)thiazol-5-yl)-4-hydroxy-2H-chromen-2-one (4f): Yield: 78%, Pale Yellow solid, mp. 223-225 °C; IR (KBr): 3056, 2975, 2844, 1671, 1609, 1567, 1495, 1456, 1417, 1397, 1340, 1309, 1256, 1232, 1174, 1152, 1091,cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.04 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.94 (dd, *J* = 8.0, 1.5 Hz, 1H, Ar-H), 7.71 (dt, *J* = 8.5, 1.5 Hz, 1H, Ar-H), 7.65 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.60 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.38 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.92 (d, *J* = 8.5 Hz, 2H, Ar-H), 3.73 (s, 3H, OMe); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.9, 163.7, 161.0, 159.0, 153.7, 152.7, 134.8, 133.2, 131.9, 129.3, 128.7, 127.7, 127.2, 124.2, 124.0, 121.2, 116.5, 115.7, 113.8, 96.0, 55.0; Anal. Calcd for $C_{25}H_{16}ClNO_4S$ (461.92): C, 65.00; H, 3.49; N, 3.03; Found: C, 65.02; H, 3.51; N, 3.10.

(4g): Yield: 76%, Pale Yellow solid, mp. 249-251 °C; IR (KBr): 3015, 2903, 2840, 1706, 1675, 1653, 1609, 1569, 1520, 1496, 1459, 1417, 1340, 1304, 1257, 1173, 1153, 1093, 1029 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 7.96-7.93 (m, 3H, Ar-H), 7.70 (dt, *J* = 8.5, 1.5 Hz, 1H, Ar-H), 7.65 (dd, *J* = 7.0, 1.8 Hz, 2H, Ar-H), 7.45 (d, *J* = 8.0 Hz, 1H, Ar-H), 7.39 (dt, *J* = 8.0, 1.0 Hz, 1H, Ar-H), 7.09 (d, *J* = 9.0 Hz, 2H, Ar-H), 6.92 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.84 (s, 3H, OMe), 3.72 (s, 3H, OMe); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 166.2, 163.5, 161.1, 161.0, 158.9, 153.3, 152.7, 133.1, 128.6, 127.6, 127.5, 125.9, 124.2, 123.9, 119.4, 116.4, 115.8, 114.6, 113.7, 96.3, 55.3, 55.0; Anal. Calcd for $C_{26}H_{19}NO_5S$ (457.50): C, 68.26; H, 4.19; N, 3.06; Found: C, 68.29; H, 4.22; N, 3.14.

4-hydroxy-3-(4-(4-nitrophenyl)-2-phenylthiazol-5-yl)-2H-chromen-2-one (4h): Yield: 63%, Pale Yellow solid, mp. 235-237 °C; IR (KBr): 3072, 2952, 1943, 1831, 1671, 1612, 1535, 1550, 1488, 1452, 1420, 1357, 1340, 1271, 1196, 1073, 1028 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 8.22 (dd, *J* = 6.8, 2.0 Hz, 2H, Ar-H), 8.04 (dd, *J* = 8.2, 2.0 Hz, 2H, Ar-H), 8.0 (dd, *J* = 8.9, 2.0 Hz, 2H, Ar-H), 7.94 (dd, *J* = 8.2, 1.3 Hz, 1H, Ar-H), 7.70 (dt, *J* = 8.2, 1.4 Hz, 1H, Ar-H), 7.57-7.53 (m, 3H, Ar-H), 7.45 (d, *J* = 8.2 Hz, 1H, Ar-H), 7.38 (t, *J* = 6.8 Hz, 1H, Ar-H); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 167.2, 163.7, 160.9, 152.9, 151.5, 146.6, 141.1, 133.4, 132.7, 130.8, 129.4, 128.5, 126.2, 125.9, 124.3, 124.1, 123.9, 116.6, 115.9, 95.6; Anal. Calcd for $C_{24}H_{14}N_2O_5S$ (442.44): C, 65.15; H, 3.19; N, 6.33; Found: C, 65.18; H, 3.21; N, 6.38.

3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-1-methylquinolin-2(1H)-one (4i): Yield: 80%, White solid, mp. 197-199 °C; IR (KBr): 3067, 2937, 2882, 1623, 1576, 1562, 1502, 1419, 1329, 1271, 1216, 1166, 1099, 1044, 983, 919, 873, 753, 700, 666, 536 cm^{-1}; ^{1}H NMR (500 MHz, DMSO-d_6): δ = 10.91 (bs, 1H, OH), 8.03 (dd, *J* = 8.0, 1.5 Hz, 2H, Ar-H), 7.99 (dd, *J* = 8.0, 1.5 Hz,1H, Ar-H), 7.71-7.67 (m, 3H, Ar-H), 7.56-7.53 (m, 4H, Ar-H), 7.31-7.25 (m, 4H, Ar-H), 3.62 (s, 3H, NMe); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.9, 161.4, 159.2, 153.1, 139.5, 135.1, 133.2,

131.9, 130.2, 129.3, 128.2, 127.7, 127.3, 125.9, 124.3, 123.9, 121.6, 115.5, 114.7, 101.8, 29.4; Anal. Calcd for $C_{25}H_{18}N_2O_2S$ (410.49): C, 73.15; H, 4.42; N, 6.82; Found: C, 73.18; H, 4.45; N, 6.89.

3-(2-(4-chlorophenyl)-4-phenylthiazol-5-yl)-4-hydroxy-1-methylquinolin-2(1H)-one (4j): Yield: 73%, Pale Yellow solid, mp. 117-119 °C; IR (KBr): 3058, 2940, 2889, 2627, 1624, 1596, 1501, 1487, 1456, 1398, 1328, 1270, 1224, 1162, 1093, 1042, cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 10.91 (bs, 1H, OH), 8.05-8.03 (td, *J* = 8.5, 2.5 Hz, 2H, Ar-H), 7.68 (dd, *J* = 8.5, 1.0 Hz, 1H, Ar-H), 7.62-7.56 (m, 3H, Ar-H), 7.61 (dd, *J* = 6.5, 2.0 Hz, 2H, Ar-H), 7.55 (d, *J* = 8.5 Hz, 1H, ArH) 7.33-7.24 (m, 4H, Ar-H), 3.62 (s, 3H, NMe); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 164.6, 161.4, 159.3, 153.2, 139.5, 134.9, 134.7, 132.0, 129.3, 128.2, 127.8, 127.6, 127.3, 124.8, 123.9, 121.7, 121.1, 115.5, 114.7, 101.7, 29.4; Anal. Calcd for $C_{25}H_{17}ClN_2O_2S$ (444.93): C, 67.49; H, 3.85; N, 6.30; Found: C, 67.52; H, 3.87; N, 6.37.

4-hydroxy-3-(2-(4-methoxyphenyl)-4-phenylthiazol-5-yl)-1-methylquinolin-2(1H)-one (4k): Yield: 74%, White solid, mp. 272-274 °C; IR (KBr): 3042, 2940, 2841, 1627, 1609, 1569, 1524, 1417, 1330, 1304, 1254, 1207, 1172, 1101, 1027 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 10.84 (bs, 1H, OH), 7.99-7.96 (m, 3H, Ar-H), 7.69-7.68 (m, 3H, Ar-H), 7.54 (d, *J* = 8.5 Hz, 1H, Ar-H), 7.30-7.24 (m, 4H, Ar-H), 7.10 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.84 (s, 3H, OMe), 3.62 (s, 3H, NMe); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.9, 161.4, 160.8, 159.2, 152.8, 139.5, 135.2, 131.9, 128.1, 127.6, 127.5, 127.3, 126.1, 123.8, 123.1, 121.6, 115.5, 114.7, 114.6, 101.9, 55.3, 29.3; Anal. Calcd for $C_{26}H_{20}N_2O_3S$ (440.51): C, 70.89; H, 4.58; N, 6.36; Found: C, 70.92; H, 4.54; N, 6.39

4-hydroxy-3-(4-(4-methoxyphenyl)-2-phenylthiazol-5-yl)-1-methylquinolin-2(1H)-one (4l): Yield: 68%, White solid, mp. 270-272 °C; IR (KBr): 3011, 2951, 2833, 1626, 1580, 1553, 1532, 1494, 1463, 1414, 1330, 1297, 1242, 1166, 1102, 1043, 1028 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.73 (bs, 1H, OH), 8.01-7.98 (m, 3H, Ar-H), 7.68-7.63 (m, 3H, Ar-H), 7.53-7.48 (m, 4H, Ar-H), 7.26 (t, *J* = 7.5 Hz, 1H, Ar-H), 6.84 (d, *J* = 8.7 Hz, 2H, Ar-H), 3.72 (s, 3H, OMe), 3.64 (s, 3H, NMe); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ = 165.7, 161.5, 159.2, 158.7, 152.9, 139.5, 133.3, 131.7, 129.9, 129.1, 128.6, 127.7, 125.8, 123.9, 122.5, 121.5, 115.6, 114.5, 113.5, 101.9, 54.9, 29.3; Anal. Calcd for $C_{26}H_{20}N_2O_3S$ (440.51): C, 70.89; H, 4.58; N, 6.36; Found: C, 70.92; H, 4.55; N, 6.39.

3-(2-(4-chlorophenyl)-4-(4-methoxyphenyl)thiazol-5-yl)-4-hydroxy-1-methylquinolin-2(1H)-one (4m): Yield: 71%, Pale Yellow solid, mp. 256-258 °C; IR (KBr): 3066, 2950, 2838, 1627, 1611, 1575, 1495, 1456, 1443, 1413, 1328, 1296, 1248, 1179, 1091, 1030 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 10.76 (bs, 1H, OH), 8.24-8.00 (m, 3H, Ar-H), 7.98 -7.62 (m, 3H, Ar-H), 7.57-7.51 (m, 3H, Ar-H), 7.26 (dt, *J* = 7.3, 0.5 Hz, 1H, Ar-H), 6.86-6.83 (m, 2H, Ar-H), 3.72 (s, 3H, OMe), 3.64 (s, 3H, NMe); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ = 164.4, 161.5, 159.3, 158.8, 153.1, 139.5, 134.7, 132.1, 131.8, 129.2, 128.6, 127.5, 127.4, 123.9, 122.9, 121.5, 115.6, 114.5, 113.5, 101.8, 54.9, 29.3; Anal. Calcd for $C_{26}H_{19}ClN_2O_3S$ (474.96): C, 65.75; H, 4.03; N, 5.90; Found: C, 65.78; H, 4.06; N, 5.97.

3-(2,4-diphenylthiazol-5-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4n): Yield: 73%, Yellow solid, mp. 92-94 °C; IR (KBr): 3059, 1671, 1569, 1539, 1489, 1451, 1405, 1361, 1237, 1158, 1118, 1071 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 12.10 (bs, 1H, OH), 7.98 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.68 (d, *J* = 7.6 Hz, 2H, Ar-H), 7.54-7.48 (m, 3H, Ar-H), 7.39 (dt, *J* = 7.6, 7.2 Hz, 2H, Ar-H), 7.31(dt, *J* = 7.6, 6.8 Hz, 1H, Ar-H), 6.12 (s, 1H, Ar-H), 2.25 (s, 3H, Me); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 168.2, 165.7, 163.5, 162.7, 152.9, 135.3, 133.1, 130.3, 129.3, 128.3, 127.8, 127.2, 126.0, 123.2, 99.9, 92.7, 19.6; Anal. Calcd for $C_{21}H_{15}NO_3S$ (361.41): C, 69.79; H, 4.18; N, 3.88; Found: C, 69.83; H, 4.14; N, 3.94.

3-(2-(4-chlorophenyl)-4-phenylthiazol-5-yl)-4-hydroxy-6-methyl-2H-pyran-2-one (4o): Yield: 75%, Pale Yellow solid, mp. 165-167 °C; IR (KBr): 3048, 2931, 2850, 2647, 1689, 1635, 1580, 1564, 1501, 1447, 1405, 1366, 1229, 1179, 1088 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 12.03 (bs, 1H, OH), 8.00 (d, *J* = 8.0 Hz, 2H, Ar-H), 7.67 (d, *J* = 7.5 Hz, 2H, Ar-H), 7.59 (d, *J* = 8.5 Hz, 2H, Ar-H), 7.38 (t, *J* = 7.0 Hz, 2H, Ar-H), 7.33-7.30 (m, 1H, Ar-H), 6.12 (s, 1H, Ar-H), 2.25 (s, 3H, Me); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.2, 164.2, 163.5, 162.6, 152.9, 135.2, 134.8, 131.9, 129.3, 128.3, 127.8, 127.6, 127.2, 123.7, 99.9, 92.5, 19.5; Anal. Calcd for $C_{21}H_{14}ClNO_3S$ (395.86): C, 63.72; H, 3.56; N, 3.54; Found: C, 63.75; H, 3.59; N, 3.58.

4-hydroxy-3-(2-(4-methoxyphenyl)-4-phenylthiazol-5-yl)-6-methyl-2H-pyran-2-one (4p): Yield: 78%, Pale Yellow solid, mp. 186-188 °C; IR (KBr): 3050, 2935, 2870, 2657, 1696, 1654, 1587, 1568, 1572, 1466, 1472, 1356, 1237, 1179, 1088 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 12.03 (bs, 1H, OH), 7.92 (dd, *J* = 7.0, 1.5 Hz, 2H, Ar-H), 7.68 (dd, *J* = 7.0, 1.5 Hz, 2H, Ar-H), 7.39-7.36 (m, 2H, Ar-H), 7.32-7.29 (m, 1H, Ar-H), 7.07 (dd, *J* = 8.5, 1.5 Hz, 2H, Ar-H), 6.12 (s, 1H, Ar-H), 3.80 (s, 3H, OMe), 2.21 (s, 3H, CH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 168.1, 165.6, 163.3, 162.6, 160.9, 152.5, 135.4, 128.2, 127.6, 127.5, 127.2, 125.9, 122.0, 114.6, 99.9, 92.8, 55.3, 19.5; Anal. Calcd for $C_{22}H_{17}NO_4S$ (391.44): C, 67.50; H, 4.38; N, 3.58; Found: C, 67.53; H, 4.34; N, 3.63.

2-(2,4-diphenylthiazol-5-yl)-1H-indene-1,3(2H)-dione (4q): Yield: 67%, Red solid, mp. 76-78 °C; IR (KBr): 3066, 2880, 1708, 1677, 1600, 1560, 1447, 1349, 1292, 1237, 1202, 1151 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.06 (dd, *J* = 5.6, 3.1 Hz, 2H, Ar-H), 7.92 (dd, *J* = 5.5, 3.0 Hz, 4H, Ar-H), 7.83 (d, *J* = 6.9 Hz, 2H, Ar-H), 7.44-7.37 (m, 6H, Ar-H), 4.86 (s, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.5, 166.8, 157.9, 141.6, 136.3, 134.1, 133.4, 130.2, 129.1, 128.9, 128.7, 128.6, 126.6, 124.0, 122.9, 53.6; Anal. Calcd for $C_{24}H_{15}NO_2S$ (381.45): C, 75.57; H, 3.96; N, 3.67; Found: C, 75.61; H, 3.92; N, 6.71.

2-(2-(4-chlorophenyl)-4-phenylthiazol-5-yl)-1H-indene-1,3(2H)-dione (4r): Yield: 64%, Red solid, mp. 77-79 °C; IR (KBr): 3042, 2790, 1710, 1701, 1677, 1600, 1510, 1448, 1359,

1295, 1247, 1206, 1156 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 8.07-8.04 (m, 2H, Ar-H), 7.93-7.80 (m, 6H, Ar-H), 7.42-7.37 (m, 5H, Ar-H), 4.86 (s, 1H, CH); ^{13}C NMR (125 MHz, $CDCl_3$): δ = 196.4, 165.5, 158.1, 141.6, 136.4, 136.2, 133.9, 131.8, 129.2, 129.1, 128.8, 128.7, 127.8, 124.0, 123.2, 53.6; Anal. Calcd for $C_{24}H_{14}ClNO_2S$ (415.89): C, 69.31; H, 3.39; N, 3.37; Found: C, 69.35; H, 3.42; N, 3.42.

3-hydroxy-2-(2-(4-methoxyphenyl)-4-phenylthiazol-5-yl)-1H-inden-1-one (4s): Yield: 68%, Red solid, mp. 82-84 °C; IR (KBr): 3066, 2999, 2748, 1709, 1658, 1601, 1555, 1516, 1488, 1449, 1414, 1362, 1305, 1257, 1215, 1177, 1075, 1025, 1005 cm^{-1}; ^1H NMR (500 MHz, DMSO-d_6): δ = 7.93 (d, *J* = 9.0 Hz, 2H, Ar-H), 7.74 (d, *J* = 7.0 Hz, 2H, Ar-H), 7.45-7.43 (m, 4H, Ar-H), 7.36 (t, *J* = 7.5 Hz, 2H, Ar-H), 7.28 (t, *J* = 7.0 Hz, 1H, Ar-H), 7.08 (d, *J* = 9.0 Hz, 2H, Ar-H), 3.83 (s, 3H, OMe); ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.1, 160.8, 151.6, 135.6, 131.7, 128.1, 127.6, 127.5, 127.4, 125.8, 122.7, 120.6, 120.1, 114.6, 101.5, 55.3; Anal. Calcd for $C_{25}H_{17}NO_3S$ (411.47): C, 72.97; H, 4.16; N, 3.40; Found: C, 72.92; H, 4.12; N, 3.43.

2-(2,4-diphenylthiazol-5-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (4t): Yield: 80%, White solid, mp. 204-206 °C; IR (KBr): 3062, 2959, 2867, 1637, 1575, 1486, 1360, 1260, 1177, 1146, 1118, 1072, 1018, cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.38 (bs, 1H, OH), 7.95 (dd, *J* = 8.0, 1.6 Hz, 2H, Ar-H), 7.59 (d, *J* = 7.2 Hz, 2H, Ar-H), 7.52-7.50 (m, 3H, Ar-H), 7.38 (d, *J* = 7.2 Hz, 1H, Ar-H), 7.36 (d, *J* = 6.4 Hz, 1H, Ar-H), 7.31 (d, *J* = 7.2 Hz, 1H, Ar-H), 2.38 (s, 4H, $2CH_2$), 1.06 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ = 165.1, 152.3, 135.5, 133.3, 129.8, 129.0, 127.9, 127.4, 127.3, 125.8, 124.8, 105.7, 46.7, 31.4, 28.0; Anal. Calcd for $C_{23}H_{21}NO_2S$ (375.48): C, 73.57; H, 5.64; N, 3.73; Found: C, 73.54; H, 5.67; N, 3.79.

2-(2-(4-chlorophenyl)-4-phenylthiazol-5-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (4u): Yield: 76%, White solid, mp. 206-208 °C; IR (KBr): 3081, 3004, 2834, 1673, 1608, 1569, 1517, 1486, 1467, 1417, 1343, 1305, 1177, 1098, 1029 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.42 (bs, 1H, OH), 7.98 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.66 (dd, *J* = 8.4, 1.2 Hz, 2H, Ar-H), 7.58 (d, *J* = 8.8 Hz, 2H, Ar-H), 7.37 (t, *J* = 7.6 Hz, 1H, Ar-H), 7.33-7.31 (m, 1H, Ar-H), 7.30 (d, *J* = 7.2 Hz, 1H, Ar-H), 2.39 (s, 4H, $2CH_2$), 1.06 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.6, 153.4, 136.2, 135.4, 133.0, 130.2, 129.0, 128.5, 128.4, 128.3, 126.5, 106.4, 32.4, 28.9; Anal. Calcd for $C_{23}H_{20}ClNO_2S$ (409.93): C, 67.39; H, 4.92; N, 3.42; Found: C, 67.42; H, 4.95; N, 3.46.

3-hydroxy-2-(2-(4-methoxyphenyl)-4-phenylthiazol-5-yl)-5,5-dimethylcyclohex-2-enone (4v): Yield: 75%, Yellow solid, mp. 149-151 °C; IR (KBr): 2958, 2885, 2613, 1607, 1576, 1517, 1499, 1458, 1368, 1323, 1254, 1174, 1108, 1030 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 11.35 (bs, 1H, OH), 7.90-7.87 (m, 2H, Ar-H), 7.66-7.64 (m, 2H, Ar-H), 7.38-7.34 (m, 2H, Ar-H), 7.31-7.27 (m, 1H, Ar-H), 7.07 (dd, *J* = 7.2, 2.0 Hz, 2H, Ar-H), 3.83 (s, 3H, OCH_3), 2.39 (s, 4H, $2CH_2$), 1.06 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.9, 161.6, 152.8, 136.5, 128.9, 128.3, 127.0, 124.8, 115.5, 106.6, 56.2, 32.4, 28.9; Anal. Calcd for $C_{24}H_{23}NO_3S$ (405.51): C, 71.09; H, 5.72; N, 3.45; Found: C, 71.13; H, 5.78; N, 3.48.

3-hydroxy-2-(4-(4-methoxyphenyl)-2-phenylthiazol-5-yl)-5,5-dimethylcyclohex-2-enone (4w): Yield: 70%, Yellow solid, mp. 219-221 °C; IR (KBr): 3056, 2959, 2836, 1653, 1609, 1583, 1490, 1373, 1299, 1247, 1173, 1109, 1075, 1029 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.95-7.92 (m, 2H, Ar-H), 7.63(dd, *J* = 6.8, 2.0 Hz, 2H, Ar-H), 7.49-7.43 (m, 3H, Ar-H), 6.88 (m, 2H, Ar-H), 3.78 (s, 3H, OMe), 2.38 (s, 4H, $2CH_2$), 1.10 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ = 169.9, 164.9, 158.6, 152.1, 133.4, 129.5, 128.8, 128.6, 128.1, 125.7, 123.0, 113.2, 105.9, 54.9, 46.7, 31.4, 28.1 Anal. Calcd for $C_{24}H_{23}NO_3S$ (405.51): C, 71.09; H, 5.72; N, 3.45; Found: C, 71.14; H, 5.78; N, 3.49.

2-(2-(4-chlorophenyl)-4-(4-methoxyphenyl)thiazol-5-yl)-3-hydroxy-5,5-dimethylcyclohex-2-enone (4x):
Yield: 68%, Pale Yellow solid, mp. 222-224 °C; IR (KBr): 3066, 2955, 2831, 2642, 1609, 1575, 1492, 1398, 1365, 1344, 1245, 1173, 1145, 1085, 1037 cm^{-1}; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.93 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.61(d, *J* = 8.7 Hz, 2H, Ar-H), 7.47 (d, *J* = 8.4 Hz, 2H, Ar-H), 6.87 (d, *J* = 8.6 Hz, 2H, Ar-H), 3.78 (s, 3H, OMe), 2.38 (s, 4H, $2CH_2$), 1.10 (s, 6H, $2CH_3$); ^{13}C NMR (100 MHz, DMSO-d_6 + $CDCl_3$): δ = 163.6, 158.6, 152.3, 134.5, 132.1, 128.9, 128.6, 128.0, 127.1, 123.5, 113.2, 105.8, 54.8, 46.7, 31.3, 28.1; Anal. Calcd for $C_{24}H_{22}ClNO_3S$ (439.95): C, 65.52; H, 5.04; N, 3.18; Found: C, 65.54; H, 5.07; N, 3.23.

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