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"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 media 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

The selective and environmentally friendly synthesis of chemicals or required products is an enduring challenge in chemical sciences.[1] Thus, in recent times, "green chemistry," which provides guidelines for safer and more eco-friendly methods of chemical synthesis has gained significant attention both from academia and industry.[2] Water is considered a 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, its non-toxic nature, and its safety in handling, water is considered one of the best and greenest reaction media in chemical synthesis. The major hurdle for using this excellent solvent in organic synthesis is 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 the reaction medium and the subsequent introduction of the "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, some other important parameters for designing a green synthesis are pot, atom and step economy (PASE) as well as the type of catalyst used and the nature of by-products generated.[7] In this direction, multicomponent domino reactions offer numerous advantages. In multicomponent domino reactions (MDRs) more than two substrates react in one pot under similar reaction conditions without the addition of any additional solvents, reagents, catalyst or altered reaction conditions, avoiding the isolation and purification of any intermediates.[8] In MDRs, two or more bonds (usually C–C) are formed in one pot. Therefore, these reactions save time, cost, organic solvents, and synthetic steps and have proved to be an important tool in recent times for medicinal chemistry and drug discovery processes.

Use of microwave heating technology to access desired products has gained tremendous popularity among 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, microwave heating saves energy and cost as well as providing 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, reaction rate and manipulative simplicity.[10] Thus, we were interested in using MW heating in our newly developed domino reactions.

Thiazoles are five-membered heterocycles with N and S heteroatoms. They are ubiquitous in natural products,[11] biologically active alkaloids[12] and pharmaceuticals.[13] Substituted 1,3-thiazoles, especially tethered with aryl or heteroaryl groups (in the 2, 4 and 5 positions or disubstituted, such as 2,4-diaryl, 2,5-diaryl or 4,5-diaryl) are considered privileged structural

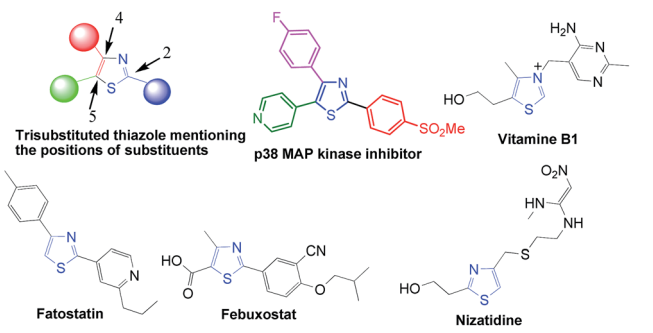

Fig. 1 Representative examples of important substituted thiazoles.

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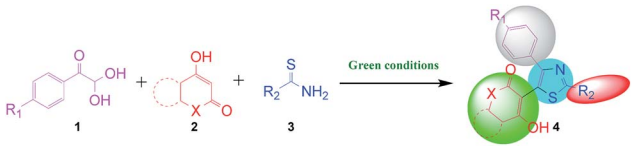
† Electronic supplementary information (ESI) available: ^{1}H NMR and ^{13}C NMR spectra for all products are available. See DOI: 10.1039/c4ra06239f



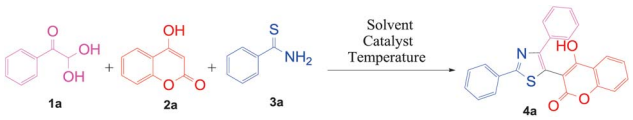
Scheme 1 Synthesis of trisubstituted thiazoles by three component reactions.

motifs and have applications in various fields, such as materials science for the preparation of liquid crystals,[14] cosmetics (sunscreens),[15] *etc.* In addition, they also have numerous applications in medicinal chemistry for the access of bioactive lead molecules and drug candidates.[16] Some 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] and fatostatin is a SREBP inhibitor.[18] Similarly, nizatidine is a useful drug used for the treatment of peptic ulcers and gastroesophageal reflux disease.[19] The thiazole moiety is also found in vitamin B1 as well as various other bioactive molecules. Thus, the design and development of novel and eco-friendly methods for synthesizing such compounds are of great interest.

Substituted thiazoles can be synthesized either by the functionalization of a preexisting thioazole moiety,[20] or directly by the cyclization of acyclic starting materials.[21] The classical method for the synthesis of thiazoles is the Hantzsch method where α-haloketones react with thioamides.[22] Considering the widespread 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 a 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 syntheses, harsh reaction conditions, poor yields, long reaction times, and the requirement for inert atmospheric conditions. In addition, we realized that very limited methods are available in the literature for the one pot synthesis of trisubstituted 1,3-thiazole derivatives. Thus, in continuation of our work on 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.

When designing an efficient and versatile multicomponent reaction, the selection of appropriate starting materials is very important. Arylglyoxals are very useful synthetic building blocks in organic synthesis where two adjacent carbonyl groups (one ketone and one aldehyde group) act as double electrophilic sites for cyclization reactions. Considering their interesting reactivities, these compounds have very recently been used in diverse two component 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 the synthesis of functionalized heterocycles, herein we report a three component reaction of arylglyoxals, cyclic-1,3-dicarbonyls and thioamides under eco-friendly reaction conditions as shown in Scheme 1.

Table 1 Optimization of reaction conditions[a]



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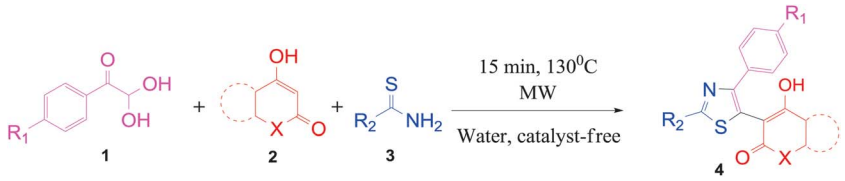
2	EtOH	Et_3N	RT	24[c]	0	
3	EtOH	Et_3N	Reflux	20[c]	16	CH
4	Water	Et_3N	Reflux	20[c]	28	CH
5	EtOH	Et_3N	120	15	72	MWH
6	EtOH	—	120	15	70	MWH
7	EtOH–water mixture (1 : 1)	—	120	15	76	MWH
8	Water	—	120	15	82	MWH
9	Water	—	130	15	89	MWH
10	Water	—	100	15	78	MWH
11	Water	—	130	20	89	MWH
12	Toluene	—	130	15	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.

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



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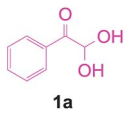
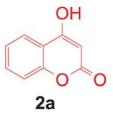
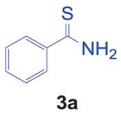
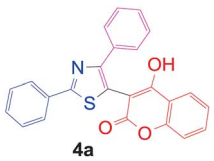
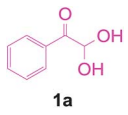
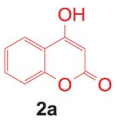
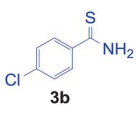
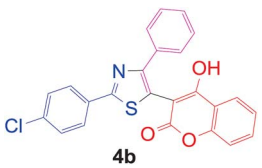
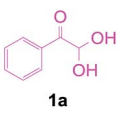
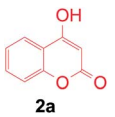
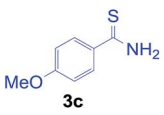
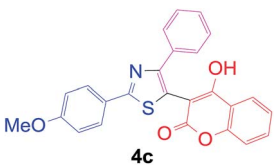
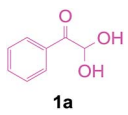
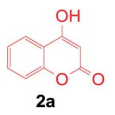
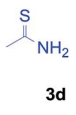
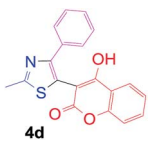
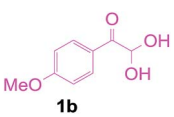
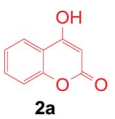
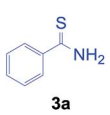
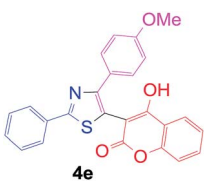
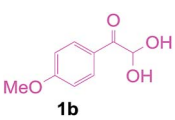
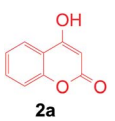
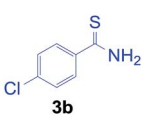
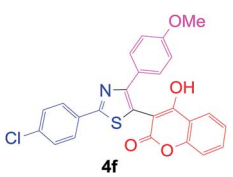
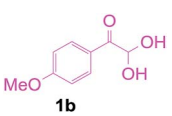
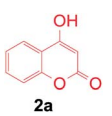
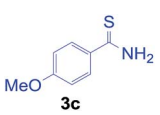
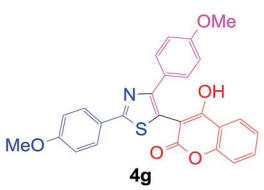
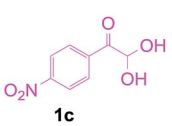
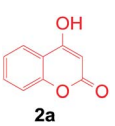
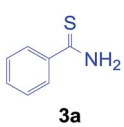
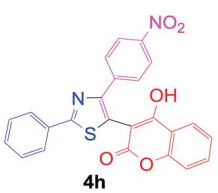
1				15		89
2				15		85
3				15		85
4				15		52
5				15		82
6				15		78
7				15		76
8				15		63

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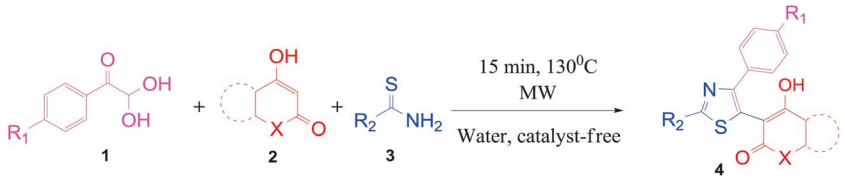

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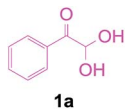
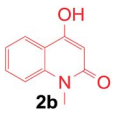
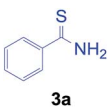
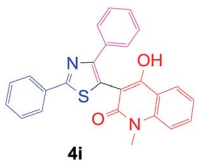
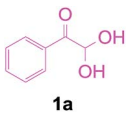
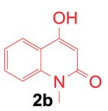
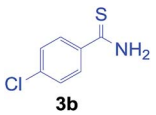
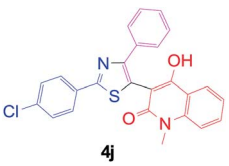
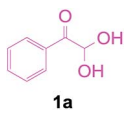
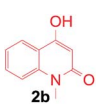
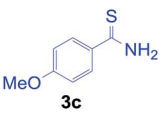
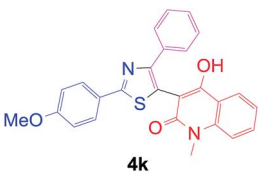
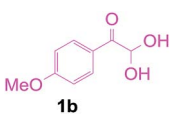
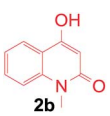
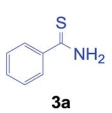
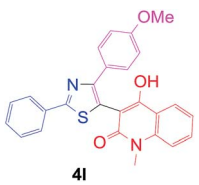
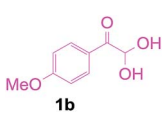
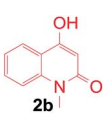
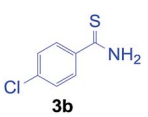
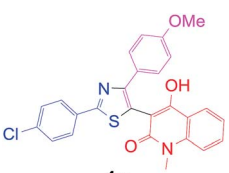
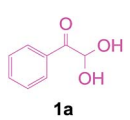
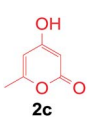
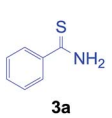
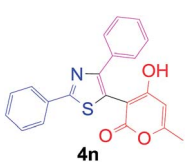
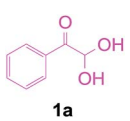
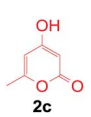
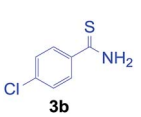
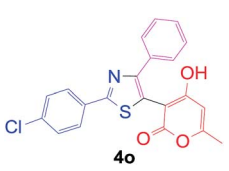
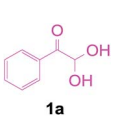
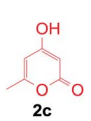
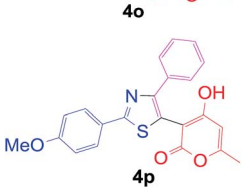
9	 1a	 2b	 3a	15	 4i	80
10	 1a	 2b	 3b	15	 4j	73
11	 1a	 2b	 3c	15	 4k	74
12	 1b	 2b	 3a	15	 4l	68
13	 1b	 2b	 3b	15	 4m	71
14	 1a	 2c	 3a	15	 4n	73
15	 1a	 2c	 3b	15	 4o	75
16	 1a	 2c	 3c	15	 4p	78

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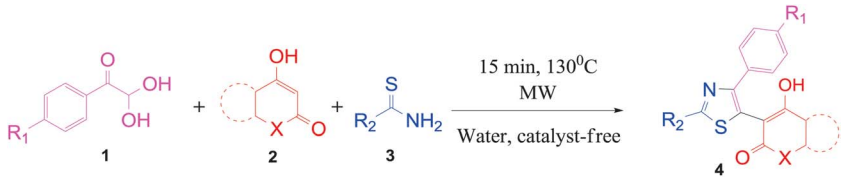
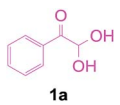
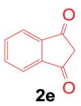
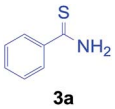
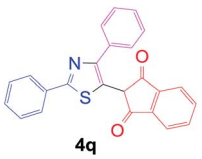
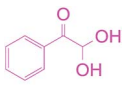
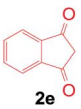
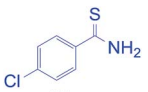
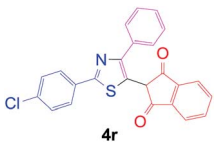
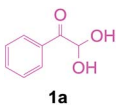
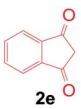
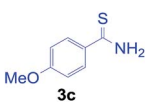
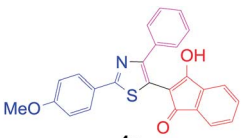
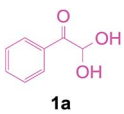
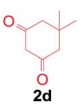
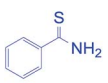
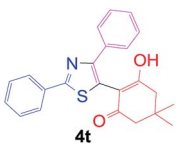
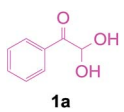
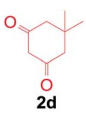
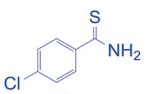
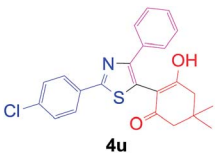
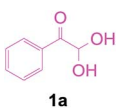
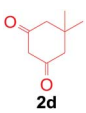
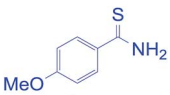
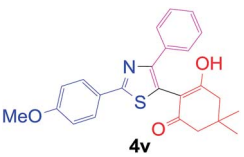
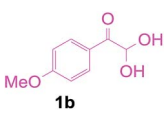
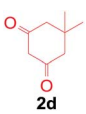
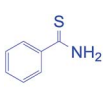
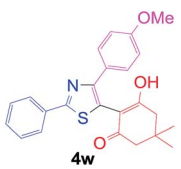
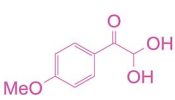
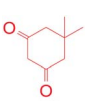
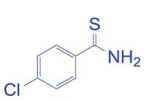
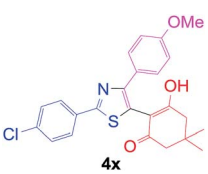


1 2 3 4

Entry	Reactant 1	Reactant 2	Reactant 3	Time (min)	Product 4	Yield[b] (%)
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

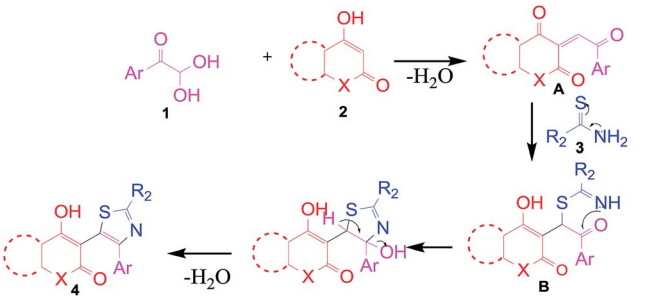
[a] Reaction conditions: phenylglyoxal monohydrate or its derivatives (1 mmol), 1,3-dicarbonyls (1 mmol), and thioamide derivatives (1 mmol), in water at 130 °C (MW). [b] Isolated yield.

Results and discussion

Initially, a mixture of phenylglyoxal monohydrate (1 mmol), 4-hydroxycoumarin (1 mmol), and thiobenzamide (1 mmol) in 5 mL EtOH was stirred at room temperature without any catalyst to synthesize the desired product **4a**. We did not observe the formation of the desired product **4a** even after 24 h under these conditions. The same combination at room temperature was next reacted in the presence of 20 mol% Et_3N and the corresponding desired product **4a** was not observed even in this case. Interestingly, in the presence of 20 mol% Et_3N at reflux temperature, the same combination of reagents in ethanol afforded a 16% yield of our desired three component product after 20 hours of reaction time. Compound **4a** was fully characterized by standard 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 the reaction conditions, temperature, and solvents, and using alternative heating techniques, 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 °C in the presence of Et_3N (20 mol%) in ethanol afforded a 72% yield of the desired product **4a** within 15 minutes. This encouraging result prompted us to determine whether Et_3N has any role in this reaction. Therefore, a similar combination of reagents was reacted under microwave conditions and in the absence of catalyst, and to our surprise, we obtained a 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. We then focused our attention to optimizing the yield by changing the solvent. The reaction using water as the solvent and under microwave conditions at 120 °C afforded a higher yield than the reaction using ethanol as the solvent. The highest yield was obtained by increasing the reaction temperature to 130 °C in water under microwave conditions (Table 1, entry 9). Keeping the reaction time at 15 minutes and the temperature fixed at 130 °C, other organic solvents such as toluene, THF, acetonitrile, and DMF were also screened for the same model reaction, and in all cases, the yields obtained were lower than that of entry 9.

With the optimized reaction conditions in hand, the substrate scope of this domino reaction was investigated. Thiobenzamides bearing different substituents, such as 4-Cl and 4-OMe were found to be useful in this domino reaction to synthesize diverse thiazole derivatives. Interestingly, aliphatic thioamides such as thioacetamide also provided the corresponding three component products (**4d**) under similar conditions with moderate yields. Next, we tested the applicability of arylglyoxals tethered with both electron donating as well as electron withdrawing groups in this domino reaction. In all 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(1*H*)-one, 4-hydroxy-6-methyl-2-pyrone, indane-1,3-dione and dimedone also reacted similarly 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, ^1H NMR, ^{13}C NMR and by elemental analysis.



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

On the basis of the above results a plausible reaction mechanism is shown in Scheme 2. Initially, a Knoevenagel-type reaction takes place between reactants **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**.

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 readily available starting materials. Considering the importance of the thiazole and 4-hydroxycoumarin moieties, we expect this type of molecule will have broad applications in medicinal chemistry. Further efforts to determine the scope and diversity of these MDRs are currently underway and will be reported in due course. The reaction can be easily performed simply by mixing readily 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 at 400 or 500 MHz for ^1H 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 an Initiator 2.5 Microwave Synthesizer from Biotage, Uppsala, Sweden. Melting points were recorded using an SRS EZ-Melt automated melting point apparatus by the capillary method and are uncorrected.

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

A mixture of arylglyoxal monohydrate **1** (1 mmol), 1,3-dicarbonyl derivative **2** (1 mmol), and thioamide derivative **3** (1 mmol) in 3 mL H_2O was introduced into 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 and washed with 95% EtOH to yield the pure product **4**. Products **4n–4p**, **4q**, **4r** and **4t** were purified by column chromatography on a silica gel column using an EtOAc–hexane mixture as the eluent.

3-(2,4-Diphenylthiazol-5-yl)-4-hydroxy-2*H*-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}; ^1H 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-2*H*-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}; ^1H 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, 3*H*, 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)-2*H*-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}; ^1H 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)-2*H*-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}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.86 (d, J = 7.8 Hz, 1H, Ar-H), 7.62 (d, 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)-2*H*-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}; ^1H NMR (500 MHz, DMSO-d_6): δ = 8.02 (d, 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-2*H*-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}; ^1H 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%.

3-(2,4-Bis(4-methoxyphenyl)thiazol-5-yl)-4-hydroxy-2*H*-chromen-2-one (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}; ^1H 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)-2*H*-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}; ^1H 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(1*H*)-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}; ^1H NMR (500 MHz, DMSO-d_6): $\delta = 10.91$ (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(1*H*)-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): $\delta = 10.91$ (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): $\delta = 164.6$, 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(1*H*)-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): $\delta = 10.84$ (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(1*H*)-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): $\delta = 10.73$ (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 + $CDCl_3$): $\delta = 165.7$, 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(1*H*)-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): $\delta = 10.76$ (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 + $CDCl_3$): $\delta = 164.4$, 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-2*H*-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): $\delta = 12.10$ (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): $\delta = 168.2$, 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-2*H*-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): $\delta = 12.03$ (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-2*H*-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): $\delta = 12.03$ (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): $\delta = 168.1$, 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)-1*H*-indene-1,3(2*H*)-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, $CDCl_3$): $\delta = 8.06$ (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, $CDCl_3$): $\delta = 196.5$, 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)-1*H*-indene-1,3(2*H*)-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)-1*H*-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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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}; ^{1}H 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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