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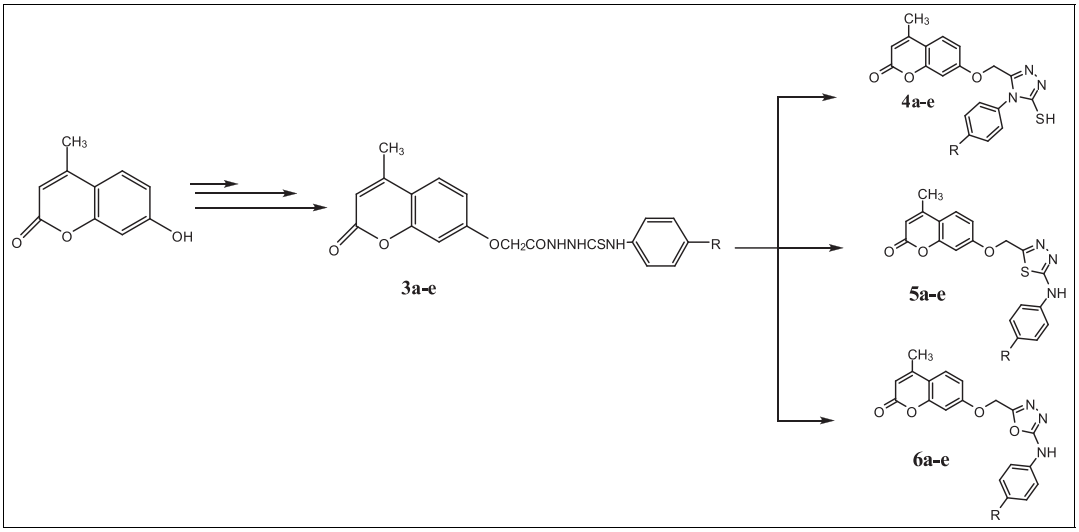

Ethyl-2-(4-methyl-2-oxo-2-coumarin-7-yloxy)acetate **1** has been prepared from 7-hydroxy-4-methyl-2-coumarin, which on further treatment with hydrazine hydrate in boiling ethanol gave the hydrazide compound **2**. The resulting hydrazide was reacted with substituted aryl isothiocyanates to form thiosemicarbazides compounds **3a–e**. 1-(2-(4-Methyl-2-oxo-2-coumarin-7-yloxy)acetyl)-4-aryl thiosemicarbazides **3** underwent cyclization with different reagents under different reaction conditions to furnish coumarin derivatives possessing triazoles **4a–e**, thiadiazoles **5a–e**, and oxadiazoles **6a–e**, respectively. The structures of all the compounds have been assigned by elemental analysis and spectral studies. The synthesized compounds were screened for their antimicrobial analgesic activities. The nonconventional controlled microwave irradiation synthesis is carried out at (200 W) at 70°C. This approach offers a number of advantages in terms of methodology, high-product yield, short reaction time, mild reaction conditions, environmentally benign, and easy workup.

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INTRODUCTION

Synthesis of coumarin derivatives has attracted considerable attention of organic and medicinal chemists owing to their antibacterial and antifungal activities [1]. Coumarin nucleus is widely distributed in natural product, particularly among plant kingdom. Many of such compounds have been reported to possess very interesting pharmacological and physiological activities, such as insecticidal [2], fungicidal [3], antimicrobial, and antioxidant [4] properties. Some coumarin analogs were highly fluorescent in nature and are used as laser dyes [5] in addition to being used in the pharmaceutical industry. Coumarin heterocyclics also find wide application in the dye and photographic industries [6]. A survey of the literature reveals that introduction of either coumarin nucleuses have yielded many biologically active compounds endowed with a wide spectrum of pharmacological activity [7–9]. It has been well established that the presence of 7-hydroxy-4-methyl-2-coumarin moiety is an important structural feature of wide variety of synthetic drugs [10–12]. Additional presence of heterocyclic moieties such as 1,2,4-triazole [13], 1,3,4-thiadiazole [14], or 1,3,4-oxadiazole [15] have a wide range of therapeutic properties. As a result, preparation of novel fused heterocyclic compounds containing triazole, oxadiazole, and thiadiazole on coumarin groups is certainly an advantage for various biological activities. This approach seems to be useful in view of the fact that it may combine the physiological action of the group with the well-known biological activity of the compounds containing triazoles, oxadiazoles, and thiadiazoles on coumarin groups.

Green chemistry was developed to meet the increasing demand for environmentally benign chemical processes.

Microwave irradiation and grinding techniques have an importance in the search for green synthesis because of their use as an efficient alternative heating source for organic reactions. Organic transformations are best driven thermally by microwave-accelerated [16] and grinding-accelerated [17] heating process, which couples directly with the molecules, leading to a rapid rise in temperature to enhance chemical reaction rates faster than conventional heating methods by many folds. The main advantages of microwave-assisted and grinding-assisted organic synthesis are as follows: shorter reaction time, simple experimental procedure, very high yields, clean reaction, eco-friendly, no special apparatus required, nonhazardous, operationally simple, and convenient. The present study describes the synthesis of novel biheterocycles containing coumarin nucleus derivatives and evolution of their *in vitro* antimicrobial activity.

RESULTS AND DISCUSSION

The reaction sequence employed for the synthesis of title compounds is shown in Scheme 1. The key intermediate, ethyl-2-(4-methyl-2-oxo-2-coumarin-7-yloxy)acetate **1** was prepared by the reaction of 7-hydroxy-4-methyl coumarin with ethylchloroacetate in boiling acetone in the presence of anhydrous potassium carbonate. Further, the compound **1** was readily converted into 2-(4-methyl-2-oxo-2H-chromen-4-yloxy)acetohydrazide **2** by treating with hydrazine hydrate. The resulted hydrazide **2** was treated with substituted aryl isothiocyanates to yield hydrazinecarbothiamides **3a–e**. The intramolecular cyclocondensation of hydrazinecarbothiamide **3a–e** in the presence of concentrated H_2SO_4 at RT formed the corresponding thiadiazoles **5a–e** in 65 to 75% yields. The same products are also obtained under microwave irradiation (200 W) at 70°C in 2 min and grindstone synthesis in 6 min with 71–85% and 68–75%, respectively. In this case, microwave irradiation method gives product in less time and better yield.

The carbothiamide **3a–e** in the presence of NaOH in ethanol at RT formed the corresponding triazoles **4a–e** in 60–75% yields. The same products were also obtained by microwave irradiation (200 W) at 70°C in 3 min with a yield of 70–84% and by grindstone synthesis in 6 min and 68–75%, respectively. In this case, microwave irradiation method gives good yield product in less time. Whereas carbothiamide **3a–e** on cyclocondensation in the presence of $NaOH/KI_3$ [17] in ethanol at RT formed the corresponding oxydiazoles **6a–e** in 58–70% yields. The same products have been obtained under microwave irradiation (200 W) at 70°C in 3 min and grindstone synthesis in 6 min with 68–78% and 65–70%, respectively. In this case, microwave irradiation method gives good yields in less time.

With these experimental procedures, we have synthesized a new series of 1,3,4-triazoles, 1,3,4-thiadiazoles, and 1,3,4-oxadiazoles (Scheme 1). The respective yields, times, and physical data of synthesized compounds are summarized in Table 1, and the formation of compounds was confirmed by spectroscopic analysis.

Scheme 1

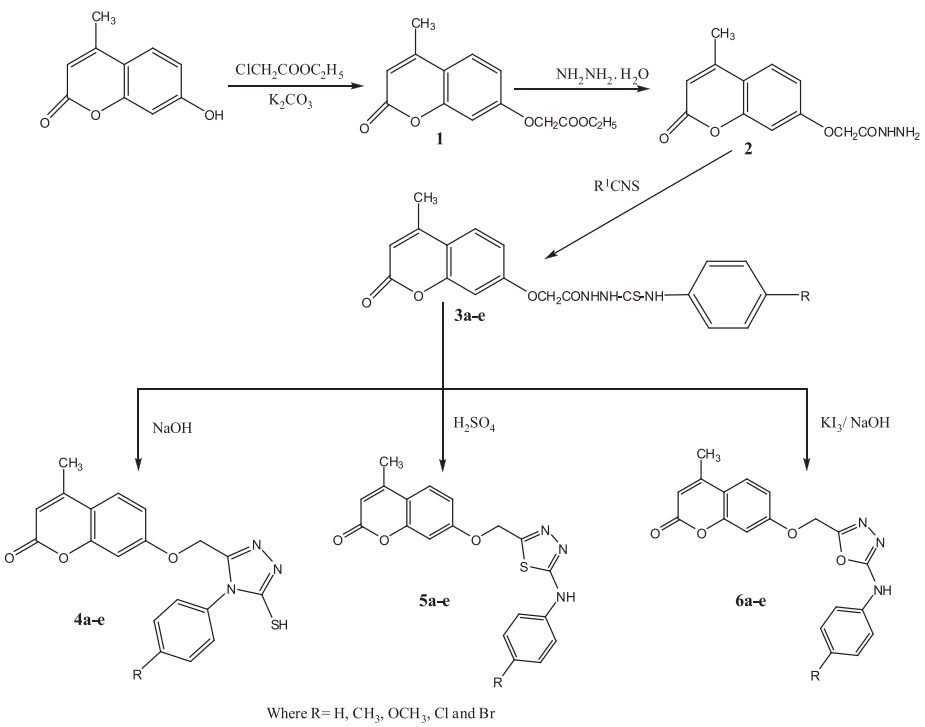

Table 1

Characterization data of the synthesized compounds.[a]

		Conventional		MW		Grinding	
Compound	R	Time (min)	Yield (%)	Time (min)	Yield (%)	Time (min)	Yield (%)
4a	H	120	75	3	80	6	75
4b	CH_3	120	72	3	84	6	75
4c	OCH_3	120	73	3	78	6	78
4d	Cl	120	65	3	70	6	68
4e	Br	120	60	3	71	6	68
5a	H	150	70	2	85	4	75
5b	CH_3	150	75	2	75	4	72
5c	OCH_3	150	72	2	80	4	74
5d	Cl	150	69	2	75	4	70
5e	Br	150	65	2	75	4	68
6a	H	180	68	—	—	5	68
6b	CH_3	180	67	—	—	5	70
6c	OCH_3	180	68	—	—	5	68
6d	Cl	180	60	—	—	5	68
6e	Br	180	58	—	—	5	65

[a]All compounds were characterized by spectral analysis.

Compound **3a** shows the characteristic absorption peaks at 3236, 1748, and 1192 cm^{-1} because of N—H, —C═O (ester) and —C═S functionality, respectively. ^{1}H-NMR shows characteristic peaks because of —N—H protons at 9.6 δ (1H, s); 9.4 δ (1H, s); and 10.52 δ (1H, s). The structures of these compounds are also confirmed by their mass spectra. Compound **4a** shows IR absorption peaks at 1560 cm^{-1} because of —C═N functionality [19], and ^{1}H-NMR shows signal at 14.3 δ (1H, s) because of —SH proton [20]. Compound **5a** shows IR absorption peak at 3433 and 2910 cm^{-1} because of —N—H functionality; ^{1}H-NMR shows signal at 10.52 δ (1H, s) because of —N—H proton. The structures of these compounds are also confirmed by mass spectra. In contrast, compound **6a** shows IR absorption peak at 3278 and 1520 cm^{-1} because of —N—H and —C═N functionality. The structures of these compounds are also confirmed by mass spectra.

Antimicrobial activities of synthesized compounds have been tested for their antibacterial activity against *Klebsiella pneumonia* and *Escherichia coli* (recultured) bacterial strains and antifungal activity against *Aspergillus niger*, *Aspergillus fumigates*, and *Aspergillus terrus* by the disk diffusion method [21,22]. Gentamycin and Fluconazole were used as standards for antibacterial and antifungal activities, respectively. The compounds were tested at the concentration of 1000 μg/mL in DMF for both antibacterial and antifungal activity. The zone of inhibition after 24 h of incubation at 37°C in case of antibacterial activity and 72 h in case of antifungal activity was compared with that of standards. The results were tabulated in Table 2.

In antibacterial activity, compounds **4c–e**, **5c–e**, and **6e** showed good activity, and remaining compounds showed moderate activity against *K. pneumonia*; all the compounds showed moderate activity against *E. coli*. In antifungal activity, compounds **5a**, **6c**, and **6e** exhibited good activity against *A. niger;* compounds **4c** and **5e** showed good activity against *A. fumigates*; compounds **5c**, **5d**, and **6d** showed high activity against *A. terrus*, and remaining compounds showed moderate activity against all the test organisms.

EXPERIMENTAL

All the reagents were obtained commercially (SD fine, India) and used with further purification. Melting points were determined by open capillary method. The IR spectra (in KBr pellets) were recorded on a Perkin-Elmer FTIR spectrophotometer. Microwave reactions were carried out in a CATA-2R microwave reactor by irradiation (200 W) at 70°C, intermittently at 30 s. ^{1}H-NMR spectra were recorded in DMSO-d_6 on a Bruker 400 MHz, NMR spectrometer using TMS as an internal standard. The mass spectra were recorded on a fast atom bombardment mass spectra (FABMS) operating at 70 eV. Elemental analysis on a flash EA 1112 Series CHNS was reported. The purity of the compounds was checked by TLC on silica gel plates using a mixture of *n*-hexane and ethyl acetate.

Synthesis of ethyl-2-(4-methyl-2-oxo-2-coumarin-7-yloxy) acetate (1). Take equimolar mixture of 7-hydroxy-4-methyl coumarin (0.01 mol) and ethylchloroacetate (0.01 mol) in around bottom flask. To this, add 6 g of anhydrous potassium carbonate and 25 mL of anhydrous acetone as solvent. Reflux for 10–12 h, filter, and evaporate under low temperature to collect the separated solid as ethyl-2-(4-methyl-2-oxo-2-coumarin-7-yloxy) acetate **1**. Yield: 81%, mp: 88–90°C; elemental analysis: *Anal.* Calcd for $C_{14}H_{14}O_5$: C-64.12 and H-5.38; found: C-64.10 and H-5.35; IR (KBr, cm^{-1}): 2977 (aliphatic C—H strain) and 1753 (C═O); ^{1}H-NMR: δ 1.4 (t, 2H, CH_3), δ 2.1 (s, 3H, CH_3), δ 3.5 (q, 3H, CH_2), δ 4.6 (s, 2H, OCH_2), δ 7.5–6.8 (m, 2H, ArH).

2-(4-Methyl-2-oxo-2H-chromen-4-yloxy)acetohydrazide (2). Hydrazide was prepared by refluxing a mixture of ethyl-2-(4-methyl-2-oxo-2-coumarin-7-yloxy)acetate **1** (0.01 mol) and

Table 2

Antimicrobial activity of the synthesized compounds.

Compound	Concentration (μg/mL) in DMF	Zone of inhibition (mm)[a]				
		Antibacterial activity		Antifungal activity		
		Klebsiella pneumonia	*Escherichia coli*	*Aspergillus niger*	*Aspergillus fumigates*	*Aspergillus terrs*
4a	1000	12	9	11	10	10
4b	1000	12	10	11	10	12
4c	1000	16	11	8	12	8
4d	1000	16	10	8	6	8
4e	1000	16	9	10	6	10
5a	1000	10	8	12	6	11
5b	1000	10	8	10	10	11
5c	1000	15	10	11	10	12
5d	1000	15	10	10	11	12
5e	1000	16	9	8	12	11
6a	1000	13	8	10	9	9
6b	1000	14	8	11	8	9
6c	1000	16	11	12	6	10
6d	1000	14	9	11	9	12
6e	1000	15	10	12	8	11
Control	DMF	6	6	6	6	6
Standard	Gentamycin	18	16	—	—	—
Standard	Fluconazole	—	—	13	12	13

[a]Diameter of well (bore size)—6 mm.

hydrazine hydrate (0.01 mol) solution in ethanol. The reaction mixture was refluxed about 2–3 h on steam bath; after refluxing, the reaction mixture was cooled to RT, and solid separated was 2-(4-methyl-2-oxo-2H-chromen-4-yloxy)acetohydrazide **2** as a colorless solid, re-crystallized from ethanol. Yield: 83%, mp: 190–193°C; elemental analysis: *Anal*. Calcd for $C_{12}H_{12}O_4$: C-58.06, H-4.87, and N-11.29; found: C-58.0, H-4.8, and N-11.30; IR (KBr, cm^{-1}): 3278, 3359 (NH/NH_2), 1748 (C═O), and 1647; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.1 (s, 3H, CH_3), δ 4.6 (s, 2H, OCH_2), δ 6.5–7.3 (m, ArH), δ 9.0 (s, 2H, NH_2).

General procedure for synthesis of hydrazinecarbothioamides compounds (3a–e). A suspension of hydrazide **2** (0.005 mol) in ethanol was treated with appropriate amount of aryl isothiocyanates and refluxed for 3–4 h. The thiosemicarbazides that separated were cooled and re-crystallized from ethanol to give compounds **3a–e** in 70 to 85% yield.

2-(2-(4-Methyl-2-oxo-2H-chromen-7-yloxy)acetyl)-N-phenylhydrazinecarbothioamide (3a). Yield: 85%, mp: 170–172°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{17}O_4S$: C-59.52, H-4.47, and N-10.96; found: C-59.50, H-4.40, and N-10.95; IR (KBr, cm^{-1}): 3308, 3407 (NH), 1748 (C═O), and 1258 (C—S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.42 (s, 3H, —CH_3), δ 4.5 (s, 2H, OCH_2), δ 6.23 (s, 1H, ═CH), δ 6.6–7.73 (m, 8H, Ar—H), δ 9.2 and 12.5 (s, 1H, NH).

2-(2-(4-Methyl-2-oxo-2H-chromen-7-yloxy)acetyl)-N-p-tolylhydrazinecarbothioamide (3b). Yield: 76%, mp: 180–182°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{19}N_3O_4S$: C-60.44, H-4.82, and N-10.57; found: C-60.50, H-4.80, and N-10.55; IR(KBr, cm^{-1}): 3325, 3387 (NH), 1745 (C═O), and 1255 (C═S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.24 (s, 3H, —CH_3), δ 2.42 (s, 3H, —CH_3), δ 4.45 (s, 2H, OCH_2), δ 6.21 (s,1H, ═CH), δ 6.4–7.8 (m, 7H, Ar—H), δ 9.0 and 11.9 (s, 1H, NH).

N-(4-Methoxyphenyl)-2-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetyl)hydrazinecarbothioamide (3c). Yield: 78%, mp: 188–190°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{19}N_3O_5S$: C-58.10, H-4.63, and N-10.16; found: C-58.10, H-4.60, and N-10.15; IR(KBr, cm^{-1}): 3407, 3308 (NH), 1748 (C═O), and 1258 (C—S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.42 (s, 3H, —CH_3), δ 3.85(s, 3H, —OCH_3) δ 4.7 (s, 2H, OCH_2), δ 6.4 (s,1H, ═CH), δ 6.55–7.9 (m, 8H, Ar—H), δ 10.2 and 111.8 (s, 1H, NH).

N-(4-Chlorophenyl)-2-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy)acetyl)hydrazinecarbothioamide (3d). Yield: 75%, mp: 188–190°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{19}N_3O_5S$: C-54.61, H-3.86, and N-10.06; found: C-54.56, H-3.82, and N-10.01; IR (KBr, cm^{-1}): 3308, 3407(NH),1748 (C═O), and 1258 (C—S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.42 (s,3H, —CH_3), δ 4.5 (s, 2H, OCH_2), δ 6.23 (s,1H, ═CH), δ 6.6–7.73 (m, 7H, Ar—H), δ 9.2 and 12.5 (s, 1H, NH).

N-(4-Bromophenyl)-2-(2-(4-methyl-2-oxo-2H-chromen-7-yloxy) acetyl)hydrazinecarbothioamide (3e). Yield: 70%, mp: 175–177°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{16}BrN_3O_4S$: C-49.36, H-3.49, and N-9.09; found: C-49.30, H-3.42, and N-9.00; IR (KBr, cm^{-1}): 3308, 3407(NH), 1648 (C═O), and 1258(C—S); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.41 (s, 3H, CH_3), δ 4.7 (s, 2H, OCH_2), δ 6.4 (s, 1H, ═CH), δ 6.7–7.53 (m, 7H, Ar—H), δ 9.8 and 11.5 (s, 1H, NH).

General procedure for synthesis of triazoles compounds 4.

Method A by conventional method. In 100 mL round bottom flask (RBM), hydrazinecarbothioamides **3a–e** (0.005 mol) was heated under reflux with aqueous NaOH (4%) for 1 h; the clear solution after treatment with activated charcoal was filtered and cooled; the filtrate was acidified with acetic acid and re-crystallized from ethanol.

Method B by MW method. A mixture of hydrazinecarbothioamides **3a–e** (0.005 mol) and 5 mL 2N NaOH solution was taken in 50 mL

Erlenmeyer flask and was subjected to microwave irradiation at (200 W) at 70°C, intermittently at 30-s interval for specified time (Table 1). After the completion of reaction (monitored by TLC), added reaction mixture is cold to RT, treated with crushed ice, and acidified with dilute acetic acid. The product separated was filtration and re-crystallized from ethanol to obtain desired compound **4a–e**.

Method C by grinding method. Hydrazinecarbothioamides **3a–e** (0.005 mol) and NaOH pellets (0.01 mol) were grinded in a mortar with a pestle made of porcelain for 5–10 min at RT. The mixture turns pasty after few minutes of grinding. The reaction was monitored by TLC. After the completion of reaction, resulting slurry was poured into ice cold water and acidified with acetic acid. The crude solid thus separated was collected and re-crystallized from ethanol.

7-((5-Mercapto-4-phenyl-4H-1,2,4-triazol-3-yl)methoxy)-4-methyl-2H-chromen-2-one (4a). Yield: 79%, mp: 124–126°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{15}O_3N_3S$: C-62.45, H-4.14, and N-11.50; found: C-62.40, H-4.10, and N-11.44; IR (KBr, cm^{-1}): 3045, 2923(Ar—H), 1715 (C═O), 1248, 1035, and 845; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.2 (s, 3H, CH_3), δ 4.8 (s, 2H, OCH_2), δ 5.6 (s,1H, C═C—H), δ 6.7–7.7 (m, 8H ArH), δ 14.4 (s, 1H, SH); ES-MS: *m/z* (m + 1): 347.11.

7-((5-Mercapto-4-p-tolyl-4H-1,2,4-triazol-3-yl)methoxy)-4-methyl-2H-chromen-2-one (4b). Yield: 75%, mp: 134–136°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{17}O_3N_3S$: C-63.31, H-4.52, and N-11.07; found: C-63.30, H-4.50, and N-11.04; IR (KBr, cm^{-1}): 3045 (Ar—H), 2923, 2896 (Aliphatic C—H), 1735 (C═O), and 1035 (—C—O); ^{1}H-NMR (300, MHz, DMSO-d_6): δ 2.0 (s, 3H, Ar—CH_3), δ 2.2 (s, 3H, CH_3), δ 4.8 (s, 2H, OCH_2), δ 5.65 (s,1H, C═C—H), δ 6.5–7.7 (m, 7H, ArH), δ 14.2 (s,1H, SH); ES-MS: *m/z* (m + 1): 361.13.

7-((5-Mercapto-4-(4-methoxyphenyl)-4H-1,2,4-triazol-3-yl) methoxy)-4-methyl-2H-chromen-2-one (4c). Yield: 78%, mp: 94–96°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{17}O_4N_3S$: C-60.75, H-4.33, and N-10.63; found: C-60.45, H-4.30, and N-10.44; IR (KBr, cm^{-1}): 3049, 2944 (Ar—H), 2885 (Aliphatic C—H), 1725 (C═O), 1248, 1035, and 845; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.2 (s, 3H, CH_3), δ 3.8 (s, 3H, Ar—OCH_3), δ 4.8 (s, 2H, OCH_2), δ 5.65 (s, 1H, C═C—H), δ 6.5–7.7 (m, 7H, ArH), δ 14.2 (s, 1H, SH); ES-MS: *m/z* (m + 1): 377.12.

7-((4-(4-Chlorophenyl)-5-mercapto-4H-1,2,4-triazol-3-yl) methoxy)-4-methyl-2H-chromen-2-one (4d). Yield: 84%, mp: 90–92°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{14}O_3N_3SCl$: C-57.07, H-3.53, and N-10.51; found: C-57.00, H-3.50, and N-10.50; IR (KBr, cm^{-1}): 3049, 2944 (Ar—H), 2885 (Aliphatic C—H), 1696 (C═O), 1248, 1035, and 845 (C—Cl); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.2 (s, 3H, CH_3), δ 4.8 (s, 2H, OCH_2), δ 5.65 (s, 1H, C═C—H), δ 6.5–7.7 (m, 8H, ArH), δ 14.2 (s, 1H, SH); ES-MS: *m/z* (m + 1): 381.08.

7-((4-(4-Bromophenyl)-5-mercapto-4H-1,2,4-triazol-3-yl) methoxy)-4-methyl-2H-chromen-2-one (4e). Yield: 89%, mp: 120–122°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{14}O_3N_3SBr$: C-51.36, H-3.18, and N-9.46; found: C-51.30, H-3.10, and N-9.42; IR (KBr, cm^{-1}): 3049, 2944 (Ar—H), 2885 (Aliphatic C—H), 1696 (C═O),1248, 1035, and 845 (C—Cl); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.2 (s, 3H, CH_3), δ 4.8 (s, 2H, OCH_2), δ 5.65 (s, 1H, C═C—H), δ 6.5–7.7 (m, 8H, ArH), δ 14.2; ES-MS: *m/z* (m + 1): 425.02.

General procedure for synthesis of thiadiazoles compounds 5.

Method A by conventional method. A mixture of hydrazinecarbothioamides **3a–e** (0.005 mol) was added gradually to concentrated H_2SO_4 (3 mL) in about 10 min; the reaction mixture then heated at 80–90°C for 2 h in an oil bath. After the completion of reaction, monitored by TLC, the slurry was poured into ice cold water. The crude solid thus separated was collected and re-crystallized from ethanol to give compounds **5a–e**.

Method B by MW method. A mixture of hydrazinecarbothioamides **3a–e** (0.005 mol) and catalytic amount of silica sulphuric acid [18] was taken in 50 mL Erlenmeyer flask and was subjected to microwave irradiation at 200 W at 70°C, intermittently at 15-s interval for specified time (Table 1). After the completion of reaction (monitor by TLC), added reaction mixture is cold to RT and treated with crushed ice. The product was extracted with ether (3 × 25 mL); combined ether layer is washed with brine and cold water and dried over anhydrous Na_2SO_4. The solid obtained after evaporation of ether is re-crystallized from ethanol to give desired product **5a–e**.

Method C by grinding method. Hydrazinecarbothioamides **3a–e** (0.005 mol) and silica sulphuric acid (0.005 mol) was grinded in a mortar with a pestle made of porcelain for 5–10 min at RT. The mixture turns pasty after few minutes of grinding. The reaction was monitored by TLC. After the completion of reaction, resulting slurry was poured into ice cold water. The crude solid thus separated was collected and re-crystallized from ethanol to give compounds **5a–e**.

4-Methyl-7-((5-(phenylamino)-1,3,4-thiadiazol-2-yl)methoxy)-2H-chromen-2-one (5a). Yield: 92%, mp: 184–186°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{15}O_3N_3S$: C-62.45, H-4.14, and N-11.50; found: C-62.10, H-4.10, and N-11.40; IR (KBr, cm^{-1}): 3428, 3409 (NH), 3022 (Ar—H), and 1714 (C═O); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.6–7.5 (m, ArH), δ 4.8 (s, 2H, OCH_2), δ 2.0 (s, 3H, CH_3); ES-MS: *m/z* (m + 1): 365.08.

4-Methyl-7-((5-(p-tolylamino)-1,3,4-thiadiazol-2-yl)methoxy)-2H-chromen-2-one (5b). Yield: 82%, mp: 146–148°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{17}O_3N_3S$: C-63.31, H-4.52, and N-11.07; found: C-63.30, H-4.50, and N-11.10; IR (KBr, cm^{-1}): 3409 (NH), 3020 (Aromatic CH), 2984, and 1714 (C═O); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.6–7.5 (m, 7H, ArH), δ 4.8 (s, 2H, OCH_2), δ 2.0 (s, 3H, CH_3), δ 1.8 (s, 3H, CH_3); ES-MS: *m/z* (m + 1): 379.23.

7-((5-(4-Methoxyphenylamino)-1,3,4-thiadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (5c). Yield: 68%, mp: 122–124°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{17}O_4N_3S$: C-60.75, H-4.33, and N-10.63; found: C-60.70, H-4.30, and N-10.60; IR (KBr, cm^{-1}): 3385 (NH), 3045, 2922 (Aromatic CH), 1714 (C═O), 1248, 1172, 1036, 827, 731, and 565; ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.5–7.6 (m, 7H, ArH), δ 4.8 (s, 2H, OCH_2), δ 3.28 (s, 3H, OCH_3), δ 1.8 (s, 3H, CH_3); ES-MS: *m/z* (m + 1): 395.09.

7-((5-(4-Chlorophenylamino)-1,3,4-thiadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (5d). Yield: 87%, mp: 218–220°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{14}O_3N_3SCl$: C-57.07, H-3.53, and N-10.51; found: C-57.05, H-3.50, and N-10.25; IR (KBr, cm^{-1}): 3385 (NH), 3045, 2922 (Aromatic CH), 1714 (C═O); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.5–7.6 (m, 7H, ArH), δ 4.8 (s, 2H, OCH_2), δ 1.8 (s, 3H, CH_3); ES-MS: *m/z* (m + 1): 399.04.

7-((5-(4-Bromophenylamino)-1,3,4-thiadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (5e). Yield: 80%, mp: 184–186°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{14}O_3N_3SBr$: C-51.36, H-3.18, and N-9.46; found: C-51.10, H-3.10, and N-9.50; IR (KBr, cm^{-1}): 3385 (NH), 3045, 3048 (Aromatic CH), 1714 (C═O), 1248, 1172, 1036, 827,731, and 565; ^{1}H-NMR

(300 MHz, DMSO-d_6): δ 6.5–7.6 (m,7H, ArH), δ 4.8 (s, 2H, OCH_2), δ 3.28 (s, 3H, OCH_3), δ 1.8 (s, 3H, CH_3); ES-MS: *m/z* (m + 1): 445.98.

General procedure for synthesis of oxadiazoles compounds 6.

Method A by conventional method. To a suspension of hydrazinecarbothioamides **3a–e** in ethanol (40 mL) was added to aqueous NaOH (1.5 mL) to a clear solution thus obtained. I_2 in KI (5%) was added gradually with shaking till the color of I_2 persisted at RT about 25–30°C. The contents were refluxed for 3–4 h. The separated solid was collected and re-crystallized from ethanol.

Method C by grinding method. Hydrazinecarbothioamides **3a–e** (0.005 mol), catalytic amount of NaOH pellet, and aqueous KI_3 (3 mL) were grinded in a mortar with a pestle made of porcelain for 5–10 min at RT. The mixture turns pasty after few minutes of grinding. The reaction was monitored by TLC. After the completion of reaction, resulting slurry was poured into ice cold water. The crude solid thus separated was collected and re-crystallized from ethanol.

4-Methyl-7-((5-(phenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-2H-chromen-2-one (6a). Yield: 76%, mp: 202–204°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{15}O_4N_3$: C-65.32, H-4.33, and N-12.03; found: C-65.20, H-4.25, and N-12.00; IR (KBr, cm^{-1}): 3355 (NH), 3040 (Aromatic CH), and 1682 (C═O); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.0 (s, 3H, CH_3), δ 5.0 (s, 2H, OCH_2), δ 6.0–7.5 (m, ArH), δ 9.8 (s, 1H, NH); ES-MS: *m/z* (m + 1): 349.11.

4-Methyl-7-((5-(p-tolylamino)-1,3,4-oxadiazol-2-yl)methoxy)-2H-chromen-2-one (6b). Yield: 85%, mp: 170–172°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{17}N_3O_4$: C-66.11, H-4.72, and N-11.56; found: C-66.05, H-4.70, and N-11.35; IR (KBr, cm^{-1}): 3316 (NH), 3035 (Aromatic CH), and 1675 (C═O); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 1.8 (s, 3H, Ar—CH_3), δ 2.2 (s, 3H, CH_3), δ 5.2 (s, 2H, OCH_2), δ 6.0–7.8 (m, ArH), δ 9.5 (s, 1H, NH); ES-MS: *m/z* (m + 1): 363.24.

7-((5-(4-Methoxyphenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (6c). Yield: 85%, mp: 130–132°C; elemental analysis: *Anal*. Calcd for $C_{20}H_{17}N_3O_5$: C-63.32, H-4.52, and N-11.08; found: C-63.20, H-4.35, and N-11.04; IR (KBr, cm^{-1}): 3402 (NH), 3025 (Aromatic CH), and 1690 (C═O); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 2.2 (s, 3H, CH_3), δ 2.8 (s, 3H, OCH_3) δ 5.2 (s, 2H, OCH_2), δ 6.0–7.8 (m, ArH), δ 9.5 (s, 1H, NH); ES-MS: *m/z* (m + 1): 379.02.

7-((5-(4-Chlorophenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (6d). Yield: 74%, mp: 212–214°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{14}ClN_3O_4$: C-59.46, H-3.68, and N-10.95; found: C-59.20, H-3.20, and N-10.30; IR (KBr, cm^{-1}): 3316 (NH), 3015 (Aromatic CH), and 1682 (C═O); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.0–7.5 (m, ArH), δ 5.0 (s, 2H, OCH_2), δ 9.8 (s, 1H, NH), δ 2.0 (s, 3H, CH_3); ES-MS: *m/z* (m + 1): 383.56.

7-((5-(4-Bromophenylamino)-1,3,4-oxadiazol-2-yl)methoxy)-4-methyl-2H-chromen-2-one (6e). Yield: 78%, mp: 208–210°C; elemental analysis: *Anal*. Calcd for $C_{19}H_{14}BrN_3O_4$: C-53.29, H-3.30, and N-9.81; found: C-53.20, H-3.30, and N-9.80; IR (KBr, cm^{-1}): 3316 (NH), 3040 (Aromatic CH), and 1732 (C═O); ^{1}H-NMR (300 MHz, DMSO-d_6): δ 6.0–7.5 (m, ArH), δ 5.0 (s, 2H, OCH_2), δ 9.8 (s, 1H, NH), δ 2.0 (s, 3H, CH_3); ES-MS: *m/z* (m + 1): 427.02.

REFERENCES AND NOTES

[1] (a)Curir, P.; Galeotti, F.; Dolci, M.; Barile, E.; Lanzotti, V. J Nat Prod 2007, 10, 1668; (b)Soroush, S.; Yoki, M.; Kiyoshi, H.; Ronald, G. M.; Sansei, N.; Mohsen, D. Bioorg Med Chem 1999, 7, 1933.

[2] Tada, Y.; Shikishima, Y.; Takaishi, Y.; Shibata, H.; Higuti, T.; Honda, G.; Ito, M.; Takeda, Y.; Kodzhimatov, O. K.; Ashurmetov, O.; Ohmoto, Y. Phyto chem 2002, 6, 649.

[3] Epifano, F.; Pelucchini, C.; Curini, M. Nat Prod Comm 2009, 12, 1755.

[4] Nazari, Z. E.; Iranshahi, M. Phytother Res 2011, 3, 315.

[5] Collins, C. B.; Taylor, K. N.; Lee, F. W. Opt Commun 1978, 26, 101.

[6] Wang, Z. S.; Hara, K.; Yasufumi, D.; Chiaki, K.; Akira, S.; Suga, S.; Arakawa, H.; Sugihara, H. J Phys Chem B 2005, 109, 3907.

[7] Donnelly, A. C.; Mays, J. R.; Burlison, J. A.; Nelson, J. T.; Vielhauer, G.; Holzbeierlein, J.; Blagg, B. S. J Org Chem 2008, 73, 8901.

[8] Devji, T.; Reddy, C.; Woo, C.; Awale, S.; Kadota, S.; Carrico-Moniz, D. Bioorg Med Chem Lett 2011, 21, 5770.

[9] Ngo, N. T.; Nguyen, V. T.; Vo, H. V.; Vang, O.; Duus, F.; Ho, T. D.; Pham, H. D.; Nguyen, L. H. Chem Pharm Bull 2010, 58, 1487.

[10] Yogesh, K. T.; Shvetambari, T.; Hanumantharao, G. R.; Rajinder, K. G. Sci Pharm 2008, 76, 395.

[11] Johansson, I.; Ingelman-Sundberg, M. Toxicol Sci 2011, 120, 1.

[12] Patel, K. C.; Patel, H. D. e-J Chem 2011, 8(1), 113.

[13] Karthikeyan, M. S.; Holla B. S. Monatsh Chem 2008, 139, 691.

[14] Chapleo, C. B.; Myers, P. L.; Smith, A. C.; Tulloch, I. F.; Turner, S.; Walter, D. S. J Med Chem 1987, 30, 951.

[15] Elias, M.; Stefano, A.; Roberto, C.; Sara, V.; Maria, C. C.; Maria, L. S.; Rita, M.; Matilde, Y.; Giosue, C.; Laura, C.; Peter, M.; Simona, D. J Med Chem 2011, 54, 6394.

[16] Lidstrom, P.; Tierney, J.; Wathey, B.; Westman, J. Tetrahedron 2001, 57, 9225.

[17] Mogilaiah, K.; Shiva Kumar, K.; Kumar swamy, J.; Vinay Chandra, A. Ind J Chem 2010, 49B, 840.

[18] Modarresi-Alam, A. L.; Nasrollahzadeh, M.; Khamooshi, F. Arkivoc 2007, xvi, 23.

[19] Mihaela, M.; Valerio, S.; Lenuta, P.; Marcel, P.; Jacques, D.; Cristian, P. Molecules 2009, 14, 2621.

[20] Holla, B. S.; Prassana, C. S.; Boja, P.; Rao, K. S.; Shridhra, K. Ind J Chem 2006, 45B, 2071.

[21] Creaven, S. B.; Egan, D. A.; Kavanagh, K.; McCann, M.; Noble, A.; Thati, B.; Walsh, M. Inorg Chimica Acta 2006, 359, 3976.

[22] Chen, W.-Q.; Song, Z.-J.; Xu, H.-H. Bioorg Med Chem Lett 2012, 5819.