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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Microwave-assisted synthesis, molecular docking, and biological evaluation of 2-arylidene-2*H*-furo[2,3-*f*]chromen-3(7*H*)-ones as antioxidant and antimicrobial agents

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Abstract An efficient microwave-assisted method of synthesis of some novel 2-arylidene-2*H*-furo[2,3-*f*]chromen-3(7*H*)-ones **6a–j** in excellent yields was described and structural assignment of the products was confirmed on the basis of IR, ^{1}H NMR, ^{13}C NMR, MS, and analytical data. The synthesized compounds were screened for antioxidant activity using 2,2-diphenyl-1-picrylhydrazyl and hydrogen peroxide radicals. The compounds **5d**, **5h**, **6a**, **6e**, and **6j** exhibited better radical scavenging ability. Antimicrobial activity results demonstrated that compounds **5b**, **5e**, **6b**, **6c**, and **6e** showed promising antimicrobial potency. The in silico molecular docking studies were also carried out for the inhibition of cyclooxygenase-II enzyme. These molecular docking results were well complemented to the antioxidant activity studies.

Keywords Chromenone · Aurone · Microwave irradiation · Molecular docking · Antioxidant · Antimicrobial

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Introduction

Free radicals that are reactive oxygen species such as hydroxyl radicals, superoxide radicals, singlet oxygen, hydrogen peroxide radical are constantly formed as a result of normal organ functions or excessive oxidative stress (Yin et al. 2011). Cellular damage arising from these free radicals is one of the fundamental mechanisms underlying a number of human neurodegenerative disorders such as diabetes, cancer, coronary heart diseases, inflammation, and aging (Hangum-balkir and Mckenney 2012; Turkoglu et al. 2007). Antioxidants, such as butylated hydroxytoluene (BHT) and butylated hydroxyanisole, which are commercially available, are currently being used as radical scavengers. However, since suspected actions as promoters of carcinogenesis and other side effects have been reported, their use in food, cosmetic, and pharmaceutical products has been decreasing (Politeo et al. 2007; Tepe et al. 2005; Ku and Mun 2008; Gulcin et al. 2003). Thus, there has been an upsurge of interest in discovery of new and more effective antioxidant agents. On the other hand, infectious diseases caused by microorganisms are one of the main threats to the population of the world. There is an urgent need to search for new antibacterial and antifungal drugs with broad spectrum of activity because of the increasing resistance of microbial pathogens. It is desirable to find drugs with improved potency and wide activity spectrum.

Aurones (2-benzylidenebenzofuran-3(2*H*)-ones) are a class of flavonoids found in yellow pigments of plants (Pare et al. 1991). Natural and synthetic aurones have been shown to possess a broad spectrum of bioactivity including anticancer (Sim et al. 2011; Cheng et al. 2010), antioxidant (Detsi et al. 2009), antiparasitic (Roussaki et al. 2012; Kerboeuf et al. 2008) antiviral, antiparasitic, antifungal, antidiabetic (Boumendjel 2003), and neuroprotective

(Shrestha et al. 2013). 2-Benzylidine-benzofuranone based flavopiridol drug (**A**) is used as selective CDK1 inhibitor (Schoepfer et al. 2002) and Sulfuretin (**B**) is a naturally occuring aurone flavonoid known to possess diverse biological activities, such as anti-nociceptive (Kim et al. 2004), antioxidant (Jung et al. 2003), anti-mutagenic (Park et al. 2004), and antidiabetic (Lee et al. 2008; Song et al. 2010) (Fig. 1). 4′-Chloroaurone (**C**) is a naturally occuring aurone known to possess antioxidant and antibacterial activity (Venkateswarlu et al. 2007) (Fig. 1). In recent years microwave-assisted organic synthesis has gained popularity as an environmental benign technology. Microwave-assisted synthesis leads to significantly reduced reaction times, enhanced conversions and known to be environment friendly (Ashok et al. 2016).

Keeping in view of the therapeutic importance of aurones and furochromenone scaffolds, in order to investigate the combined enhanced effect of these motifs on biological potency, and in continuation of our search on biologically potent molecules, we hereby report the synthesis, characterization, and biological studies of some novel 2-arylidene-2*H*-furo[2,3-*f*]chromen-3(7*H*)-ones under microwave irradiation as well as conventional heating. The new derivatives were screened for antioxidant and antimicrobial activity. The molecular-docking studies of the compounds for better understanding of the drug-receptor interaction were also carried out.

Results and discussion

Chemistry

Traditionally, aurones have been prepared from 2-hydroxychalcones, which were synthesized from 2-hydroxyacetophenones and aromatic benzaldehydes under Claisen–Schmidt conditions, which could undergo oxidative cyclization to furnish aurone ring system. The synthetic route for the 2-arylidene-2*H*-furo[2,3-*f*]chromen-3(7*H*)-ones is illustrated in Scheme 1 and Scheme 2. All these syntheses involve the preliminary preparation of 1-(5-hydroxy-2*H*-chromen-6-yl)ethanone (**3**) starting from resacetophenone (**1**) upon treating with propargyl bromide in presence of anhydrous K_2CO_3 in dry acetone yielded 1-(2-hydroxy-4-(prop-2-yn-1-yloxy)phenyl)ethanone (**2**), was further refluxed in N,N-dimethyl aniline at 180 °C for 3 h gave compound **(3)** (Sreenivas 2011) (Scheme 1). Claisen–Schmidt condensation between 1-(5-hydroxy-2H-chromen-6-yl)ethanone (**3**) and substituted aromatic aldehydes **(4a–j)** in presence of powdered KOH under

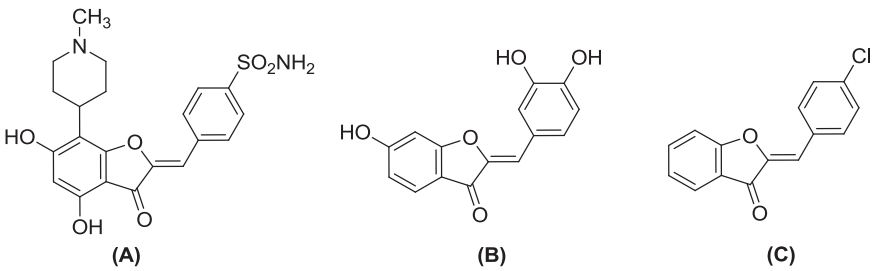
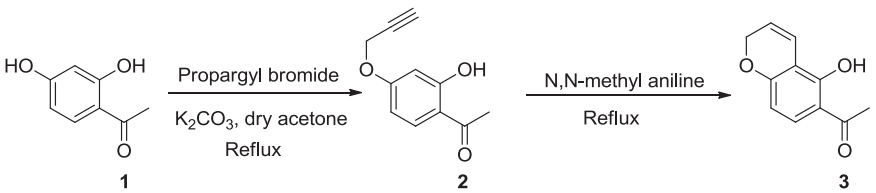
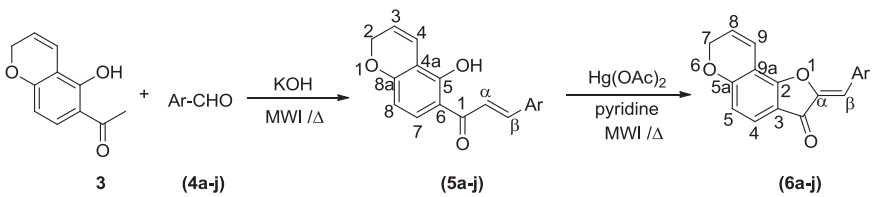


Fig. 1 Biologically significant aurone-based scaffolds



Scheme 1 Synthesis of 1-(5-hydroxy-2*H*-chromen-6-yl) ethanone (**3**)



Scheme 2 Synthesis of 2-arylidene-2*H*-furo[2,3-*f*] chromen-3(7*H*)-ones **(6a–j)**

Table 1 Physical data of synthesized compounds **5a-j** and **6a-j**

Compound	Ar	Conventional heating		Microwave irradiation	
		Time (h)	Yield (%)	Time (min)	Yield (%)
5a	phenyl	12	56	4	81
5b	4-bromophenyl	16	62	4	86
5c	2-chlorophenyl	18	64	5	82
5d	4-isopropylphenyl	10	53	6	82
5e	2,4-dichlorophenyl	24	58	7	84
5f	4-methylphenyl	12	60	5	79
5g	4-methoxyphenyl	10	57	7	85
5h	3,4-dimethoxyphenyl	10	64	4	84
5i	2-thiophenyl	12	66	6	87
5j	3-indolyl	12	55	5	80
6a	phenyl	4	65	3	82
6b	4-bromophenyl	4	66	4	85
6c	2-chlorophenyl	5	57	4	81
6d	4-isopropylphenyl	4.5	61	5	84
6e	2,4-dichlorophenyl	5	66	4	88
6f	4-methylphenyl	4	62	5	86
6g	4-methoxyphenyl	4	59	5	84
6h	3,4-dimethoxyphenyl	4.5	67	3	80
6i	2-thiophenyl	4	65	4	81
6j	3-indolyl	5	70	4	84

microwave irradiation for 5–7 min (Scheme 2) gave (*E*)-3-(aryl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones (**5a–j**). These chalcones were then oxidatively cyclized using mercury(II) acetate as the oxidative agent in pyridine under microwave irradiation to furnish the aurone derivatives **6a–j** in excellent yields.

Preliminarily, the synthesis of compounds **5a–j** and **6a–j** was carried out under conventional heating method, but this method suffers from poor yields (40–54%). In order to improve the yields and reduce the reaction time, the synthesis approach was changed to microwave irradiation method. Microwave-assisted synthesis of title compounds **6a–j** is advantageous over conventional method in terms of higher yields in shorter reaction times. Comparison of yields of title compounds in conventional and microwave irradiation methods was demonstrated in Table 1. Formation of 2-arylidene-2*H*-furo[2,3-*f*]chromen-3(7*H*)-ones **6a–j** was confirmed by recording IR, ^{1}H-NMR, ^{13}C-NMR, mass and elemental analyses. IR (Infra red) spectrum of compound **6c** showed absorption band at 1699 cm^{-1} due to α,β unsaturated C=O group. The ^{1}H-NMR (nuclear magnetic resonance) spectrum of **6c** showed a singlet at δ 6.98 corresponds to pyrazole ring proton, a singlet at δ 6.52 due to H_β of α,β unsaturated C=O and a quartet at δ 5.02 was due to O–CH_2 protons. The ^{13}C-NMR spectrum of **6c** showed a peak at δ 181.47 corresponds to C=O and δ 66.56 due to O–CH_2 carbon. Similarly the mass spectrum (MS) was recorded and reported as $[M + H]^+$ values, exhibited the peak at *m/z* 310 for the compound **6c**.

Biological evaluation

Antioxidant activity

The antioxidant activity of synthesized compounds was evaluated using 2,2-diphenyl-1-picrylhydrazyl (DPPH) (Burits and Bucar 2000; Cuendet et al. 1997) and H_2O_2 radical scavenging assays (Ruch et al. 1989). Ascorbic acid and BHT were used as standard antioxidants. DPPH radical scavenging assay results (Table 2) revealed that, compounds **5d**, **5h**, **6e**, and **6j** exhibited strong scavenging ability with potent IC_{50} values of 09.43 ± 1.20, 14.25 ± 0.54, 12.46 ± 1.56, and 08.34 ± 0.40 μg/mL, respectively. These values were lower than the standard drugs ascorbic acid (15.54 ± 0.67 μg/mL) and BHT (17.22 ± 0.21 μg/mL). It can be observed that the precursor chalcone compounds **5d** and **5h** comprised of electron rich isopropyl and dimethoxy substitutions on phenyl ring, respectively, displayed potent free radical scavenging ability. However, up on cyclization, the aurone derivatives **6e** and **6j** having electronegative dichloro atoms and indolyl nucleus, respectively, exhibited promising antioxidant activity.

It can be envisaged that substituent with lone pair of electrons on the aurone scaffold enhanced the radical

Table 2 Antioxidant activity of synthesized compounds **5a-j** and **6a-j**

Compound	Scavenging activity (IC_{50} μg/mL)	
	DPPH	H_2O_2
5a	20.25 ± 0.15	22.24 ± 0.25
5b	18.12 ± 0.54	17.53 ± 0.42
5c	19.56 ± 0.23	21.28 ± 1.24
5d	**09.43 ± 1.20**	16.94 ± 0.11
5e	23.68 ± 0.02	19.75 ± 1.65
5f	24.68 ± 0.34	26.19 ± 0.60
5g	19.65 ± 0.82	21.02 ± 0.24
5h	**14.25 ± 0.54**	**13.46 ± 0.67**
5i	20.10 ± 0.53	23.44 ± 0.29
5j	19.45 ± 0.32	24.07 ± 0.40
6a	19.42 ± 0.38	**11.72 ± 0.46**
6b	17.85 ± 1.37	19.05 ± 0.71
6c	18.62 ± 0.46	18.24 ± 0.49
6d	17.28 ± 0.65	17.52 ± 1.24
6e	**12.46 ± 1.56**	**12.21 ± 0.35**
6f	21.10 ± 0.50	22.18 ± 0.75
6g	22.15 ± 0.43	25.76 ± 0.42
6h	18.67 ± 0.56	23.52 ± 0.24
6i	22.46 ± 0.46	24.55 ± 0.43
6j	**08.34 ± 0.40**	**10.10 ± 0.27**
AA[a]	15.54 ± 0.67	14.65 ± 0.76
BHT[b]	17.22 ± 0.21	16.21 ± 0.14

[a] Ascorbic acid, [b] Butylated hydroxy toluene

scavenging potency. It can be justified by the highest scavenging activity displayed by compound **6j** with indolyl substitution. The remaining compounds showed moderate activity.

The same series was screened for H_2O_2 radical scavenging activity (Table 2). As observed from the results, compound **6j** emerged as the better radical scavenger with potent IC_{50} 10.10 ± 0.27 μg/mL. Compounds **5h**, **6a**, and **6e** exhibited good antioxidant activity with IC_{50} 13.46 ± 0.67, 11.72 ± 0.46, and 12.21 ± 0.35 μg/mL, respectively, with more scavenging potency than the standard drugs ascorbic acid (14.65 ± 0.76 μg/mL) and BHT (16.21 ± 0.14 μg/mL). The rest of the compounds displayed moderate antioxidant activity. From the antioxidant screening, it can be concluded that presence of lone pair of electrons on the aurone nucleus played an important role to exhibit radical scavenging ability.

Antimicrobial activity

Antibacterial activity

The synthesized compounds were screened in vitro for their antibacterial activity against *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 29213) as examples of Gram-positive bacteria and *Escherichia coli* (ATCC 11229), *Proteus vulgaris* (ATCC 29213) as examples of Gram-negative bacteria. Agar well-diffusion method was used to assay the antibacterial activity against test strains on Mueller–Henton agar plates. Gentamicin was employed as standard antibacterial drug. The results obtained as minimum inhibitory concentration (MIC) in μg/mL and measurements are presented in Table 3. Investigation of the antibacterial efficiency of the synthesized compounds revealed that most of the tested compounds displayed variable inhibitory effects on the growth of the tested gram-positive and gram-negative bacterial strains. It is evident from Table 3, compounds **5b** (Ar = 4-bromophenyl) displayed MIC 3.125 μg/mL against gram-positive bacteria and 6.25 μg/mL against gram-negative bacteria, **5e** (Ar = 2,4-dichlorophenyl) exhibited MIC 6.25 μg/mL against most of the bacteria, **6b** showed MIC 1.56 μg/mL against *S.aureus* and 3.125 μg/mL against rest of the bacteria, **6c** (Ar = 2-chlorophenyl) displayed 3.125 μg/mL against most of the bacteria except *E.coli* (6.25 μg/mL) and **6e** with dichloro substitution exhibited 3.125 μg/mL against all the bacteria. It was envisaged from the analysis of antibacterial activity results that electro-negative atoms such as chloro, bromo on phenyl ring were found more potent as compared to control drug gentamicin (1.56 μg/mL).

Antifungal activity

All the title compounds were evaluated for their in vitro antifungal activity against *Aspergillus niger* (ATCC 9029) and *Candida albicans* (ATCC 10231) fungal strains (Table 3). Agar well-diffusion method was used to evaluate the antifungal activity against test strains on PDA plates. Fluconazole was used as standard antifungal drug. Compound **6b** emerged as the promising antifungal agent with MIC 6.25 μg/mL. Compounds **5b** and **6e** were able to induce appreciable promising growth inhibitory activity in the range of MIC 6.25 μg/mL—12.5 μg/mL when compared with standard antifungal agent fluconazole (MIC 3.125 μg/mL). Thus we hypothesized that, compounds with electro-negative groups such as chloro, bromo on phenyl ring were exhibited highest antifungal inhibitory potency.

Molecular docking

In order to gain more insight in to the interactions of the most potent compounds towards antioxidant activity, in silico molecular docking of the title compounds with the cyclooxygenase-II enzyme was carried out. The best poses of the docked compound are shown in the Figs. 2 and 3, and the results are depicted in Table 4. The most potent

Table 3 Antimicrobial activity of synthesized compounds

Compound	Gram-positive bacteria		Gram-negative bacteria		Fungal strains	
	B. subtilis	*S. aureus*	*E. coli*	*P. vulgaris*	*A. niger*	*C. albicans*
5a	12.5	25	12.5	12.5	25	25
5b	3.125	3.125	6.25	6.25	12.5	6.25
5c	6.25	6.25	6.25	12.5	25	25
5d	25	25	12.5	50	50	25
5e	6.25	3.125	6.25	6.25	25	12.5
5f	25	12.5	25	100	50	50
5g	100	50	50	100	>100	>100
5h	50	50	25	50	>100	100
5i	50	25	25	50	50	50
5j	25	25	12.5	25	>100	>100
6a	12.5	6.25	6.25	12.5	>100	>100
6b	3.125	1.56	3.125	3.125	6.25	6.25
6c	3.125	3.125	6.25	3.125	12.5	25
6d	12.5	25	50	25	12.5	12.5
6e	3.125	3.125	3.125	3.125	6.25	12.5
6f	50	12.5	25	25	50	25
6g	50	25	100	50	100	100
6h	25	50	50	25	>100	>100
6i	12.5	25	25	12.5	50	25
6j	12.5	12.5	25	25	50	25
Gentamicin	1.56	1.56	3.125	1.56	–	–
Fluconazole	–	–	–	–	3.125	3.125

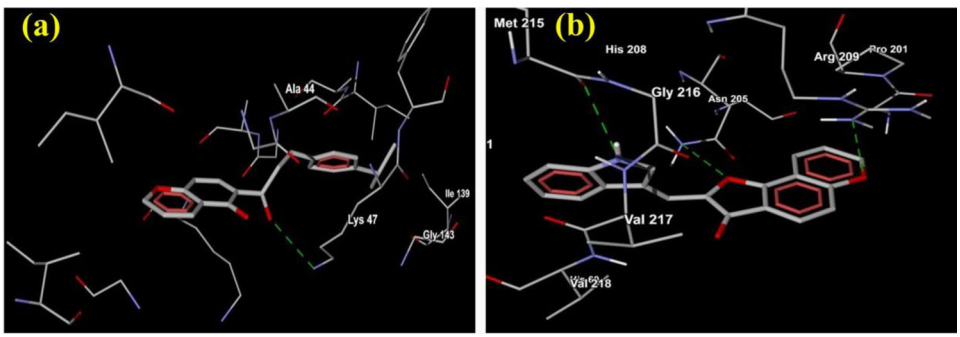


Fig. 2 Best docked pose of compound **5d (a)** and **6j (b)** with 3NM8 (hydrogen bonds are displayed as *green dotted lines*) (color figure online)

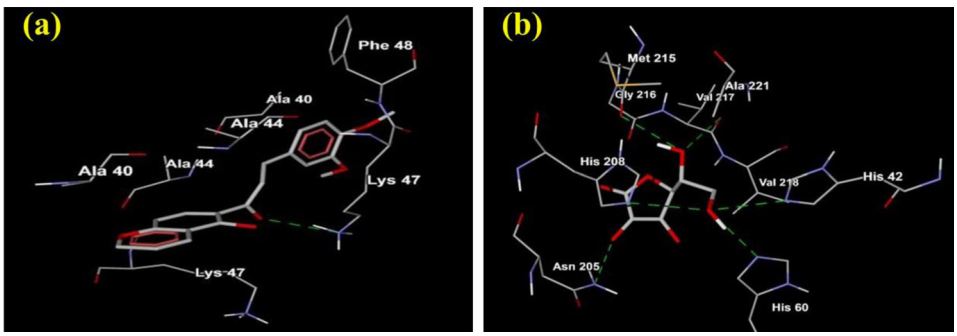


Fig. 3 Best docked pose of compound **5h (a)** and ascorbic acid **(b)** with 3NM8 (hydrogen bonds are displayed as *green dotted lines*) (color figure online)

Table 4 Dock score of synthesized compounds

Compound	MolDock Score	MolDock grid	Rerank score	Torsions	No. of runs	No. of hydrogen bonds	Hydrogen bond energy
5a	−120.478	−119.284	−105.359	4	8	1	−2.5
5b	−127.378	−128.939	−110.459	4	4	1	−2.5
5c	−123.514	−121.877	−106.013	4	1	1	−2.49
5d	−139.102	−141.028	−121.169	5	3	1	−2.4778
5e	−131.528	−133.097	−115.579	4	4	1	−2.498
5f	−121.974	−122.439	−107.599	4	2	0	0
5g	−129.229	−128.667	−109.339	4	7	1	−1.0146
5h	−140.287	−141.714	−121.714	4	7	1	−2.5
5i	−126.777	−126.449	−110.649	4	1	1	−1.218
5j	−124.503	123.506	−88.7356	4	1	0	0
6a	−121.749	−120.542	−103.262	2	2	1	−0.3838
6b	−130.576	−121.003	−106.602	2	5	0	0
6c	−126.339	−124.188	−104.259	2	2	0	0
6d	−137.394	−134.185	−115.04	3	4	0	0
6e	−143.02	−140.311	−118.817	2	5	0	0
6f	−127.094	−125.369	−106.344	2	9	0	0
6g	−132.772	−131.801	−108.901	2	3	0	0
6h	−140.181	−1140.972	−118.882	4	3	0	0
6i	−128.04	−122.115	−107.267	2	5	1	−2.03313
6j	−137.388	−139.885	−106.799	2	1	2	−2.338
Ascorbic acid	−75.7462	−86.9613	−60.8708	2	9	6	−5.193

antioxidant compounds **5d** and **6j** displayed the better MolDock score values −139.102 and −137.388, respectively. The standard drug ascorbic acid exhibited Moldock score of −86.9613. Most of the compounds showed the hydrogen bond interactions with one or more amino acid residues of the active pocket. The amino acids involved interactions with the compounds Met-215, His-208, Gly-216, Asn-205, Arg-209, Pro-201, Val-217, Val-218, Ala-44, Lys-47, Asn-205, His-60, and Val-218.

The compound **5d** showed a hydrogen bond interaction between O atom of keto group with Lys-47 (*green dotted lines*) (Fig. 2a). Compound **6j** formed three hydrogen bonds, two hydrogen bonds between O atoms of aurone ring moiety with Asn-205, Arg-209, and one hydrogen bond between N atom of indole nucleus with Met-215 (*green dotted lines*) (Fig. 2b). Compounds **5h** and **6e** exhibited relatively less binding affinity with dock score values of −141.714 and −140.311. Compound **5h** formed one hydrogen bond between O atom of keto group with Lys-47 (Fig. 3a). Ascorbic acid showed six hydrogen bonds, O atom of hydroxyl group bonded with Asn-205. The O atom of methylene group formed three hydrogen bonds with His-42, His-60, His-208, and another O atom of methylene group formed two hydrogen bonds with Gly-216, Val-217 (Fig. 3b). These in silico findings are well supported by results of antioxidant activity.

Experimental

Chemistry

All melting points were recorded on Stuart SMP3 melting-point apparatus and are uncorrected. The IR spectra ῡ in cm^{-1} (KBr) were recorded on Shimadzu FTIR 8400S spectrometer. All the microwave irradiation experiments were performed in a CEM Discover Microwave System and reaction temperatures were monitored by an equipped IR sensor. The ^{1}H NMR and ^{13}C NMR spectra were run on Bruker Avance-400 spectrometer at 400 and 100 MHz, respectively, using tetramethylsilane as an internal reference and DMSO-d6 as solvent. The mass spectra were recorded on Finnigan MAT 1020 mass spectrometer; in *m/z*. Elemental analyses were recorded on a Karlo Erba 1106 elemental analyzer. All the reactions were monitored on silica gel percolated TLC plates of Merck 60 F254 and spots were visualized with UV light.

General procedure for the synthesis of compounds (5a–j)

Conventional method

To a stirred solution of 1-(5-hydroxy-2*H*-chromen-6-yl)-ethanone (**3**) (0.1 g, 0.52 mmol), KOH (1.04 mmol) in

ethanol (20 mL), was added substituted aromatic aldehydes **(4a–j)** (0.52 mmol) and refluxed for 10–24 h. Progress of the reaction was monitored by TLC (EtOAc:hexane 1:5 v/v). After completion of the reaction, reaction mixture was poured into ice cold water and neutralized with 10% dil. HCl solution. The solid was filtered and recrystallized from ethanol to get the pure compound.

Microwave irradiation method

To a mixture of 1-(5-hydroxy-2H-chromen-6-yl)-ethanone (**3**) (0.1 g, 0.52 mmol) and substituted aromatic aldehydes **(4a–j)** (0.52 mmol) in ethanol (5 mL), powdered KOH (1.04 mmol) was added and subjected to microwave irradiation at 180 W for 4–7 min. Progress of the reaction was monitored by TLC (EtOAc:hexane 1:5 v/v). After completion of the reaction, reaction mixture was poured into ice cold water and neutralized with 10% dil. HCl solution. The solid was filtered and recrystallized from ethanol to get the pure compound.

(E)-1-(5-hydroxy-2H-chromen-6-yl)-3-phenylprop-2-en-1-one **(5a)** Pale yellow solid; yield (91%); m.p.: 102–103 °C; IR (KBr) (cm^{-1}): 3056 (OH), 2927 (H–C=), 1636 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.61 (s, 1H, OH), 7.88 (d, 1H, $J = 15.48$ Hz, H_β), 7.71 (d, 1H, $J = 8.87$ Hz, Ar–H), 7.64 (m, 2H, Ar–H), 7.55 (d, 1H, $J = 15.48$ Hz, Hα), 7.42 (t, 3H, Ar–H), 6.82 (d, 1H, $J = 10.19$ Hz, Ar–CH = C), 6.37 (d, 1H, $J = 8.87$ Hz, Ar–H), 5.72 (m, 1H, Ar–C = CH), 4.91 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 192.1 (C=O), 160.2 (C_{8a}), 159.7 (C_5), 144.3 (C_β), 134.3 ($C_{1'}$), 132.2 ($C_{4'}$), 130.7 (C_7), 129.0, 128.8 ($C_{2'}$, $C_{3'}$), 120.7 (C_3), 120.5 (C_4), 116.8 (C_α), 113.9 (C_6), 109.4 (C_{4a}), 107.5 (C_8), 65.8 (OCH_2); LC-MS (*m/z*): 279 $(M + H)^+$. Elemental analysis ($C_{18}H_{14}O_3$): calcd. C, 77.68; H, 5.07. found: C, 77.90; H, 4.83%

(E)-3-(4-bromophenyl)-1-(5-hydroxy-2H-chromen-6-yl) prop-2-en-1-one **(5b)** Yellow solid; yield (88%); m.p.: 170–172 °C; IR (KBr) (cm^{-1}): 3058 (OH), 2934 (H–C=), 1635 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.74 (Broad-s, 1H, OH), 8.20 (d, 1H, $J =$ 8.92 Hz, Ar–H), 8.07 (d, 1H, $J = 15.40$ Hz, H_β), 7.88 (d, 2H, $J = 8.55$ Hz, Ar–H), 7.79 (d, 1H, $J = 15.40$ Hz, Hα), 7.67 (d, 2H, $J = 8.43$ Hz, Ar–H), 6.69 (d, 1H, $J = 10.14$ Hz, Ar–CH=C), 6.42 (d, 1H, $J = 8.80$ Hz, Ar–H), 5.86 (m, 1H, Ar–C=CH), 4.92 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 190.1 (C=O); 160.2 (C_{8a}), 157.0 (C_5), 138.8 (C_β), 132.9 ($C_{1'}$), 132.3 ($C_{4'}$), 131.9 (C_7), 131.4, 129.0 ($C_{2'}$, $C_{3'}$), 127.7 (C_3), 122.1 (C_4), 117.5 (C_α), 115.4 (C_6), 110.6 (C_{4a}), 107.9 (C_8), 66.0 (OCH_2); LC-MS (*m/z*): 357 $(M + H)^+$. Elemental analysis ($C_{18}H_{13}BrO_3$): calcd. C, 60.52; H, 3.67. found: C, 60.31; H, 3.98%.

(E)-3-(2-chlorophenyl)-1-(5-hydroxy-2H-chromen-6-yl) prop-2-en-1-one **(5c)** Pale yellow solid; yield (89%); m.p. 118–120 °C; IR (KBr) (cm^{-1}): 3062 (OH), 2938 (H–C=), 1636 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.62 (s, 1H, OH), 8.26 (dd, 1H, Ar–H), 8.21 (d, 1H, $J = 8.92$ Hz, Ar–H), 8.14 (d, 1H, $J = 15.40$ Hz, H_β), 8.05 (d, 1H, $J = 15.40$ Hz, Hα), 7.58 (m, 1H, Ar–H), 7.48 (m, 2H, Ar–H), 6.69 (d, 1H, $J = 10.14$ Hz, Ar–CH=C), 6.45 (d, 1H, $J = 8.92$ Hz, Ar–H), 5.87 (m, 1H, Ar–C=CH), 4.93 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 191.6 (C=O), 160.4 (C_{8a}), 159.7 (C_5), 138.6 (C_β), 134.4 ($C_{1'}$), 132.4, 132.0 ($C_{4'}$, $C_{5'}$), 131.9 ($C_{6'}$), 129.9 ($C_{2'}$), 128.6 (C_7), 127.5 ($C_{3'}$), 123.4 (C_3), 120.6 (C_4), 116.7 (C_α), 113.9 (C_6), 109.4 (C_{4a}), 107.6 (C_8), 65.8 (OCH_2); LC-MS (*m/z*): 313 $(M + H)^+$. Elemental analysis ($C_{18}H_{13}ClO_3$): calcd. C, 69.13; H, 4.19. found: C, 69.33; H, 4.41%.

(E)-1-(5-hydroxy-2H-chromen-6-yl)-3-(4-isopropylphenyl) prop-2-en-1-one **(5d)** Yellow solid; yield (94%); m.p.: 72–74 °C; IR (KBr) (cm^{-1}): 3053 (OH), 2959 (H–C=), 1636 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.86 (s, 1H, OH), 8.19 (d, 1H, $J = 9.06$ Hz, Ar–H), 7.94 (s, 1H, $J = 15.48$ Hz, H_β), 7.82 (t, 3H, Ar–H), 7.34 (d, 2H, $J = 8.12$ Hz, Ar–H), 6.70 (d, 1H, $J = 10.19$ Hz, Ar–CH=C), 6.44 (d, 1H, $J = 8.87$ Hz, Ar–H), 5.86 (m, 1H, Ar–C=CH), 4.92 (q, 2H, OCH_2), 2.94 (m, 1H, CH), 1.22 (d, 6H, $J = 6.98$ Hz, $2 \times CH_3$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 191.8 (C=O), 159.9 (C_{8a}), 159.4 (C_5), 151.4 (C_β), 144.2 ($C_{1'}$), 131.9 ($C_{4'}$), 131.8 (C_7), 128.9, 126.5 ($C_{2'}$, $C_{3'}$), 120.3 (C_3), 119.4 (C_4), 116.5 (C_α), 113.7 (C_6), 109.1 (C_{4a}), 107.2 (C_8), 65.5 (OCH_2), 33.0 (CH), 23.2 (2 C, $2 \times CH_3$); LC-MS (*m/z*): 321 $(M + H)^+$. Elemental analysis ($C_{21}H_{20}O_3$): calcd. C, 78.73; H, 6.29. found: C, 78.52; H, 6.50%.

(E)-3-(2,4-dichlorophenyl)-1-(5-hydroxy-2H-chromen-6-yl) prop-2-en-1-one **(5e)** Yellow solid; yield (86%); m.p.: 128–130 °C; IR (KBr) (cm^{-1}): 3068 (OH), 2946 (H–C=), 1633 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.57 (s, 1H, OH), 8.28 (d, 1H, $J = 8.49$ Hz, Ar–H), 8.20 (d, 1H, $J = 8.87$ Hz, Ar–H), 8.05 (s, 2H, Ar–H), 7.75 (s, 1H, Ar–H), 7.75 (d, 1H, $J = 8.49$ Hz, Ar–H), 6.68 (d, 1H, $J = 10.00$ Hz, Ar–CH=C), 6.44 (d, 1H, $J = 8.68$ Hz, Ar–H), 5.87 (m, 1H, Ar–C=CH), 4.92 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 191.5 (C=O), 160.6 (C_{8a}), 159.7 (C_5), 137.4 (C_β), 135.8, 135.2 (2C, $C_{1'}$, $C_{2'}$), 132.5 (Ar–C), 131.0 (C_7), 129.9, 129.5, 127.9 (3C, Ar–C), 124.1 (C_3), 120.8 (C_4), 116.7 (C_α), 114.0 (C_6), 109.4 (C_{4a}), 107.8 (C_8), 65.9 (OCH_2); LC-MS (*m/z*): 347 $(M + H)^+$. Elemental analysis ($C_{18}H_{12}Cl_2O_3$): calcd. C, 62.27; H, 3.48. found: C, 62.49; H, 3.66%.

(E)-1-(5-hydroxy-2H-chromen-6-yl)-3-(p-tolyl)prop-2-en-1-one **(5f)** Wine red solid; yield (93%); m.p.: 116–118 °C; IR (KBr) (cm^{-1}): 3072 (OH), 2955 (H–C=), 1636 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.86 (s, 1H, OH), 8.18 (d, 1H, $J = 8.87$ Hz, Ar–H), 7.93 (s, 1H, $J = 15.48$ Hz, H_β), 7.80 (m, 3H, Ar–H), 7.27 (d, 2H, $J = 7.93$ Hz, Ar–H), 6.68 (d, 1H, $J = 10.19$ Hz, Ar–CH=C), 6.42 (d, 1H, $J = 8.87$ Hz, Ar-H), 5.85 (m, 1H, Ar–C=CH), 4.90 (q, 2H, OCH_2), 2.34 (s, 3H, Ar–CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 192.2 (C=O), 160.2 (C_{8a}), 159.7 (C_5), 144.5 (C_β), 141.0 ($C_{4'}$), 132.2 ($C_{1'}$), 131.7 (C_7), 129.5, 129.1 ($C_{2'}$, $C_{3'}$), 120.6 (C_3), 119.6 (C_4), 116.8 (C_α), 114.0 (C_6), 109.5 (C_{4a}), 107.6 (C_8), 65.8 (OCH_2), 21.0 (Ar–CH_3); LC-MS (*m/z*): 293 $(M + H)^+$. Elemental analysis ($C_{19}H_{16}O_3$): calcd. C, 78.06; H, 5.52. found: C, 78.24; H, 5.31%.

(E)-1-(5-hydroxy-2H-chromen-6-yl)-3-(4-methoxyphenyl) prop-2-en-1-one **(5g)** Orange solid; yield (91%); m.p.: 112–114 °C; IR (KBr) (cm^{-1}): 3063 (OH), 2943 (H–C=), 1635 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.98 (s, 1H, OH), 8.16 (d, 1H, $J = 8.87$ Hz, Ar–H), 7.85 (m, 4H, Ar–H), 7.02 (d, 2H, $J = 8.87$ Hz, Ar–H), 6.70 (d, 1H, $J = 10.19$ Hz, Ar–CH=C), 6.42 (d, 1H, $J = 8.68$ Hz, Ar–H), 5.85 (m, 1H, Ar–C=CH), 4.90 (q, 2H, OCH_2), 3.83 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 192.0 (C=O), 161.5 (C_{8a}), 160.0 (C_5), 159.7 ($C_{4'}$), 144.4 (C_β), 131.9 ($C_{1'}$), 131.0 (Ar–C), 127.0 (C_7), 120.3 (C_3), 117.9 (C_4), 116.9 (C_α), 114.3 (Ar–C), 114.0 (C_6), 109.4 (C_{4a}), 107.4 (C_8), 65.7 (OCH_2), 55.2 (OCH_3); LC-MS (*m/z*): 309 $(M + H)^+$. Elemental analysis ($C_{19}H_{16}O_4$): calcd. C, 74.01; H, 5.23. found: C, 74.20; H, 5.01%.

(E)-3-(3,4-dimethoxyphenyl)-1-(5-hydroxy-2H-chromen-6-yl)prop-2-en-1-one **(5h)** Orange solid; yield (91%); m.p.: 88–90 °C; IR (KBr) (cm^{-1}): 3060 (OH), 2939 (H–C=), 1632 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.85 (s, 1H, OH), 8.05 (d, 1H, $J = 8.87$ Hz, Ar–H), 7.83 (d, 1H, $J = 15.49$ Hz, H_β), 7.18 (m, 3H, Ar–H), 6.84 (d, 1H, $J = 8.72$ Hz, Ar–H), 6.71 (d, 1H, $J = 10.19$ Hz, Ar–CH=C), 6.45 (d, 1H, $J = 8.87$ Hz, Ar–H), 5.85 (m, 1H, Ar–C=CH), 4.91 (q, 2H, OCH_2), 3.86, 3.82 (s, 6H, $(OCH_3)_2$); ^{13}C-NMR (DMSO-d_6) δ p.p.m.: 192.1 (C=O), 160.0 (C_{8a}), 159.7 (C_5), 151.5, 148.9 ($C_{3'}$, $C_{4'}$), 144.9 (C_β), 132.1 ($C_{1'}$), 132.0 (C_7), 127.2 (C_3), 120.5 (C_4), 118.0 (Ar–C), 116.9 (C_α), 114.0 (C_6), 110.8, 110.7 (Ar–C), 109.4 (C_{4a}), 107.3 (C_8), 65.7 (OCH_2), 55.7, 55.5 (2C,OCH_3); LC-MS (*m/z*): 339 $(M + H)^+$. Elemental analysis ($C_{20}H_{18}O_5$): calcd. C, 70.99; H, 5.36. found: C, 70.78; H, 5.57%.

(E)-1-(5-hydroxy-2H-chromen-6-yl)-3-(thiophen-2-yl)prop-2-en-1-one **(5i)** Yellow solid; yield (87%); m.p.: 101–102 °C; IR (KBr) (cm^{-1}): 3075 (OH), 2965 (H–C=), 1639 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 13.64 (s, 1H, OH), 8.00 (d, 1H, $J = 15.10$ Hz, H_β), 7.68 (d, 1H, $J = 8.87$ Hz, Ar–H), 7.38 (m, 3H, Ar–H), 7.10 (m, 1H, Ar–H), 6.83 (d, 1H, $J = 10.19$ Hz, Ar–CH=C), 6.37 (d, 1H, $J = 8.87$ Hz, Ar–H), 5.73 (m, 1H, Ar–C=CH), 4.92 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 192.1 (C=O), 160.2 (C_{8a}), 159.6 (C_5), 141.0 ($C_{1'}$), 139.2 (C_β), 132.8 ($C_{4'}$), 130.1 (C_7), 129.9, 129.3 (2C, Ar–C), 128.0 (C_α), 124.1 (C_3), 120.8 (C_4), 113.6 (C_6), 109.6 (C_{4a}), 107.5 (C_8), 65.2 (OCH_2); LC-MS (*m/z*): 285 $(M + H)^+$. Elemental analysis ($C_{16}H_{12}O_3S$): calcd. C, 67.59; H, 4.25. found: C, 67.78; H, 4.56%.

(E)-1-(5-hydroxy-2H-chromen-6-yl)-3-(1H-indol-3-yl) prop-2-en-1-one **(5j)** Red solid; yield (89%); m.p.: 178–180 °C; IR (KBr) (cm^{-1}): 3075 (OH), 3049 (NH), 2965 (H–C=), 1631 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 11.58 (s, 1H, OH), 8.10 (d, 1H, $J = 15.10$ Hz, H_β), 7.91 (m, 1H, Ar–H), 7.78 (m, 3H, Ar–H), 7.49 (d, 1H, $J = 15.10$ Hz, H_α), 7.42 (m, 1H, Ar–H), 7.18 (m, 2H, Ar–H), 6.70 (d, 1H, $J = 10.19$ Hz, Ar–CH=C), 6.32 (d, 1H, $J = 8.68$ Hz, Ar–H), 5.69 (m, 1H, Ar–C=CH), 4.83 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 192.3 (C=O), 160.7 (C_{8a}), 160.2 (C_5), 138.4 (C_β), 137.2, 130.5 (2C, Ar–C), 130.3 (C_7), 128.4 (C_α), 125.3 (C_3), 123.6, 121.9 (2C, Ar–C), 120.7 (C_4), 118.9, 118.5, 115.7 (3C, Ar–C), 114.7 (C_6), 111.9 (C_{4a}), 107.4 (C_8), 103.9 (Ar–C), 66.1 (OCH_2); LC-MS (*m/z*): 318 $(M + H)^+$. Elemental analysis ($C_{20}H_{15}NO_3$): calcd. C, 75.70; H, 4.76; N, 4.41. found: C, 75.39; H, 4.97; N, 4.61%.

General procedure for the synthesis of compounds (6a–j)

Conventional method

To a well stirred solution of (*E*)-3-(aryl)-1-(5-hydroxy-2*H*-chromen-6-yl)prop-2-en-1-ones (**5a–j**) (0.5 mmol) in pyridine (20 mL), $Hg(OAc)_2$ (0.5 mmol) was added and the reaction mixture was refluxed for 4–5 h. After completion of the reaction, the cooled mixture was poured into ice cold water and acidified with HCl aqueous solution (30%, v/v). The precipitate was extracted with CH_2Cl_2 and dried over Mg_2SO_4. After CH_2Cl_2 was evaporated, the residue was recrystallized from ethanol to give compounds **6a–j**.

Microwave irradiation method

A mixture of (*E*)-3-(aryl)-1-(5-hydroxy-2*H*-chromen-6-yl) prop-2-en-1-ones (**5a–j**) (0.5 mmol) and $Hg(OAc)_2$ (0.5 mmol) in pyridine (5 mL) was subjected to microwave irradiation at 180 W for 3–5 min. After completion of the reaction, the cooled mixture was poured into ice cold water

and acidified with HCl aqueous solution (30%, v/v). The precipitate was extracted with CH_2Cl_2 and dried over Mg_2SO_4. After CH_2Cl_2 was evaporated, the residue was recrystallized from ethanol to give compounds **6a–j**.

(Z)-2-benzylidene-2H-furo[2,3-f]chromen-3(7H)-one **(6a)** Pale yellow solid; yield (81%); m.p.: 138–140 °C; IR (KBr) (cm^{-1}): 2960 (H–C=), 1687 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 7.88 (d, 2H, J = 8.30 Hz, Ar–H), 7.55 (d, 1H, J = 8.49 Hz, Ar–H), 7.43 (m, 3H, Ar–H), 6.81 (m, 2H, H_β, Ar–CH=C), 6.61 (d, 1H, J = 8.49 Hz, Ar–H), 5.88 (m, 1H, Ar–C=CH), 5.02 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.4 (C=O), 161.4 (C_{5a}), 160.9 (C_2), 147.1 (C_α), 131.8 ($C_{1'}$), 131.2 (2C, Ar–C), 129.7 (Ar–C), 128.9 (2C, Ar–C), 124.8 (C_4), 123.2 (C_8), 115.3 (C_9), 114.4 (C_3), 112.5 (C_β), 111.2 (C_5), 106.7 (C_{9a}), 66.3 (OCH_2); LC-MS (*m/z*): 277 $(M + H)^+$. Elemental analysis ($C_{18}H_{12}O_3$): calcd. C, 78.25; H, 4.38; found: C, 78.48; H, 4.16%.

(Z)-2-(4-bromobenzylidene)-2H-furo[2,3-f]chromen-3(7H)-one **(6b)** Pale yellow solid; yield (78%); m.p.: 237–240 °C; IR (KBr) (cm^{-1}): 2959 (H–C=), 1688 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 7.92 (d, 2H, J = 8.53 Hz, Ar–H), 7.70 (d, 2H, J = 8.53 Hz, Ar–H), 7.56 (d, 1H, J = 8.28 Hz, Ar–H), 6.87 (m, 2H, Ar–CH=C, H_β), 6.70 (d, 1H, J = 8.28 Hz, Ar–H), 6.07 (m, 1H, Ar–C=CH), 5.04 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.9 (C=O), 161.8 (C_{5a}), 161.1 (C_2), 147.7 (C_α), 131.9 ($C_{1'}$), 131.1 (2C, Ar–C), 128.8 (Ar–C), 129.3 (2C, Ar–C), 124.9 (C_4), 123.6 (C_8), 116.0 (C_9), 115.2 (C_3), 114.1 (C_β), 111.7 (C_5), 106.9 (C_{9a}), 66.3 (OCH_2); LC-MS (*m/z*): 355 $(M + H)^+$. Elemental analysis ($C_{18}H_{11}BrO_3$): calcd. C, 60.87; H, 3.12. found: C, 60.66; H, 3.30%.

(Z)-2-(2-chlorobenzylidene)-2H-furo[2,3-f]chromen-3(7H)-one **(6c)** Pale yellow solid; yield (80%); m.p.: 176–179 °C; IR (KBr) (cm^{-1}): 2959 (H–C=), 1699 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 8.29 (dd, 1H, Ar–H), 7.50 (m, 4H, Ar–H), 6.98 (s, 1H, H_β), 6.78 (dd, 1H, Ar–CH=C), 6.68 (d, 1H, J = 8.28 Hz, Ar–H), 6.03 (m, 1H, Ar–C=CH), 5.02 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.4 (C=O), 161.6 (C_{5a}), 161.3 (C_2), 148.1 (C_α), 134.3, 131.9, 131.2, 129.9, 129.3, 128.0 (6C, Ar–C), 125.2 (C_4), 123.5 (C_8), 115.3 (C_9), 114.1 (C_β), 112.8 (C_3), 106.8 (C_5), 105.1 (C_{9a}), 66.5 (OCH_2); LC-MS (*m/z*): 310 $(M + H)^+$. Elemental analysis ($C_{18}H_{11}ClO_3$): calcd. C, 69.58; H, 3.57. found: C, 69.76; H, 3.37%.

(Z)-2-(4-isopropylbenzylidene)-2H-furo[2,3-f]chromen-3(7H)-one **(6d)** Pale yellow solid; yield (83%); m.p.: 196–198 °C; IR (KBr) (cm^{-1}): 2961 (H–C=), 1696 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 7.90 (d, 2H, J = 8.03 Hz, Ar–H), 7.53 (d, 1H, J = 8.28 Hz, Ar–H), 7.38 (d, 2H, J = 8.03 Hz, Ar–H), 6.83 (m, 2H, Ar–CH=C, H_β), 6.67 (d, 1H, J = 8.28 Hz, Ar–H), 6.06 (m, 1H, Ar–C = CH), 5.03 (s, 2H, OCH_2), 2.94 (m, 1H, CH), 1.23 (d, 6H, J = 6.77 Hz, 2 × CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.4 (C=O), 161.3 (C_{5a}), 160.8 (C_2), 150.6 ($C_{4'}$), 146.8 (C_α), 131.4 (2C, Ar–C), 129.4 ($C_{1'}$), 127.0 (2C, Ar–C), 124.8 (C_4), 123.2 (C_8), 115.3 (C_9), 114.6 (C_3), 112.4 (C_β), 111.5 (C_5), 106.7 (C_{9a}), 66.3 (OCH_2), 33.3 (CH), 23.5 (2C, 2×CH_3); LC-MS (*m/z*): 319 $(M + H)^+$. Elemental analysis $C_{21}H_{18}O_3$: calcd. C, 79.22; H, 5.70. found: C, 79.43; H, 5.44%.

(Z)-2-(2,4-dichlorobenzylidene)-2H-furo[2,3-f]chromen-3(7H)-one **(6e)** Pale yellow solid; yield (75%); m.p.: 253–256 °C; IR (KBr) (cm^{-1}): 2957 (H–C=), 1697 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 8.34 (d, 1H, J = 8.53 Hz, Ar–H), 7.82 (d, 1H, Ar–H), 7.60 (m, 2H, Ar–H), 6.95 (s, 1H, H_β), 6.85 (d, 1H, J = 10.29 Hz, Ar–CH=C), 6.72 (d, 1H, J = 8.53 Hz, Ar–H), 6.08 (m, 1H, Ar–C=CH), 5.06 (s, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.6 (C=O), 161.7 (C_{5a}), 161.4 (C_2), 148.2 (C_α), 134.4 ($C_{2'}$), 132.0, 131.3, 130.0, 129.4, 128.1 (5C, Ar–C), 125.3 (C_4), 123.6 (C_8), 115.3 (C_9), 114.2 (C_3), 112.9 (C_β), 106.9 (C_{9a}), 105.2 (C_5), 66.6 (OCH_2); LC-MS (*m/z*): 345 $(M + H)^+$. Elemental analysis ($C_{18}H_{10}Cl_2O_3$): calcd. C, 62.63; H, 2.92. found: C, 62.81; H, 2.71%.

(Z)-2-(4-methylbenzylidene)-2H-furo[2,3-f]chromen-3(7H)-one **(6f)** Pale yellow solid; yield (83%); m.p.: 194–196 °C; IR (KBr) (cm^{-1}): 2961 (H–C=), 1697 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 7.88 (d, 2H, J = 8.19 Hz, Ar–H), 7.55 (d, 1H, J = 8.31 Hz, Ar–H), 7.33 (d, 2H, J = 8.06 Hz, Ar–H), 7.27 (d, 1H, J = 8.06 Hz, Ar–H), 6.84 (s, 1H, H_β), 6.70 (dd, 1H, Ar–CH=C), 6.08 (m, 1H, Ar–C=CH), 5.04 (q, 2H, OCH_2), 2.37 (s, 3H, Ar–CH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.4 (C=O), 161.3 (C_{5a}), 160.8 (C_2), 146.6 (C_α), 139.9 ($C_{4'}$), 131.2 (2C, Ar–C), 129.6 (2C, Ar–C), 129.0 (Ar–C), 124.8 (C_4), 123.3 (C_8), 115.4 (C_9), 114.6 (C_3), 112.4 (C_β), 111.5 (C_5), 106.7 (C_{9a}), 66.3 (OCH_2), 21.0 (Ar–CH_3); LC-MS (*m/z*): 291 $(M + H)^+$. Elemental analysis ($C_{19}H_{14}O_3$): calcd. C, 78.61; H, 4.86. found: C, 78.82; H, 4.62%.

(Z)-2-(4-methoxybenzylidene)-2H-furo[2,3-f]chromen-3(7H)-one **(6g)** Pale yellow solid; yield (82%); m.p.: 120–122 °C; IR (KBr) (cm^{-1}): 2960 (H–C=), 1691 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 7.86 (d, 2H, J = 7.36 Hz, Ar–H), 7.49 (d, 1H, J = 7.93 Hz, Ar–H), 7.01 (d, 2H, J = 7.55 Hz, Ar–H), 6.80 (m, 2H,

Ar–CH=C, H_β), 6.62 (d, 1H, $J = 7.93$ Hz, Ar–H), 5.96 (d, 1H, $J = 9.06$ Hz, Ar–C=CH), 5.04 (s, 2H, OCH_2), 3.87 (s, 3H, OCH_3); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.2 (C=O), 161.1 (C_{5a}), 160.6 ($C_{4'}$), 160.5 (C_2), 145.9 (C_α), 133.2 (2C, Ar–H), 124.7 (C_4), 124.6 (C_8), 124.3 ($C_{1'}$), 123.2 (C_9), 115.4 (C_3), 114.5 (2C, Ar–C), 113.8 (C_β), 112.3 (C_5), 106.7 (C_{9a}), 66.3 (OCH_2), 55.2 (OCH_3); LC-MS (*m/z*): 307 $(M + H)^+$. Elemental analysis ($C_{19}H_{14}O_4$): calcd. C, 74.50; H, 4.61. found: C, 74.72; H, 4.39%.

(Z)-2-(3,4-dimethoxybenzylidene)-2H-furo[2,3-f]chromen-3(7H)-one **(6h)** Pale yellow solid; yield (81%); m.p.: 96–98 °C; IR (KBr) (cm^{-1}): 2951 (H–C=), 1687 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 8.18 (d, 1H, $J = 9.00$ Hz, Ar–H), 7.81 (m, 2H, Ar–H), 7.55 (s, 1H, H_β), 7.01 (d, 1H, $J = 8.39$ Hz, Ar–H), 6.68 (d, 1H, $J = 10.07$ Hz, Ar–CH=C), 6.41 (d, 1H, $J = 8.85$ Hz, Ar–H), 5.84 (m, 1H, Ar–C=CH), 4.90 (s, 2H, OCH_2), 3.86, 3.81 (s, 6H, $(CH_3)_2$); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.1 (C=O), 160.9 (C_{5a}), 160.8, 160.7 ($C_{3'}$, $C_{4'}$), 160.3 (C_2), 144.7 (C_α), 127.4 (C_4), 126.2 (C_8), 124.3, 124.0 (2C, Ar–C), 124.0 (C_9), 114.5 (C_3), 113.8 (C_β), 112.5 (Ar–C), 112.3 (C_5), 111.5 (Ar–C), 105.4 (C_{9a}), 65.9 (OCH_2), 55.1 (2C, 2×OCH_3); LC-MS (*m/z*): 337 $(M + H)^+$. Elemental analysis ($C_{20}H_{16}O_5$): calcd. C, 71.42; H, 4.79. found: C, 71.65; H, 4.60%.

(Z)-2-(thiophen-2-ylmethylene)-2H-furo[2,3-f]chromen-3(7H)-one **(6i)** Pale yellow solid; yield (82%); m.p.: 142–144 °C; IR (KBr) (cm^{-1}): 2953 (H–C=), 1686 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 8.26 (d, 1H, $J = 7.78$ Hz, Ar–H), 7.55 (dd, 1H, Ar–H), 7.50 (d, 1H, $J = 8.28$ Hz, Ar–H), 7.43 (m, 1H, Ar–H), 6.95 (s, 1H, H_β), 6.75 (d, 1H, $J = 10.03$ Hz, Ar–CH=C), 6.35 (d, 1H, $J = 8.28$ Hz, Ar–H), 6.00 (m, 1H, Ar–C=CH), 4.99 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 183.9 (C=O), 154.9 (C_{5a}), 150.5 (C_2), 147.9 (C_α), 136.7, 131.5, 131.1, 128.6 (4 C, Ar–C), 127.3 (C_4), 123.2 (C_8), 121.6 (C_9), 121.0 (C_3), 117.8 (C_β), 113.5 (C_5), 107.3 (C_{9a}), 65.9 (OCH_2); LC-MS (*m/z*): 283 $(M + H)^+$. Elemental analysis ($C_{16}H_{10}O_3S$): calcd. C, 68.07; H, 3.57. found: C, 68.29; H, 3.36%.

(Z)-2-((1H-indol-3-yl)methylene)-2H-furo[2,3-f]chromen-3(7H)-one **(6j)** Red solid; yield (79%); m.p.: 253–256 °C; IR (KBr) (cm^{-1}): 2965 (H–C=), 1692 (α,β-unsaturated C=O); ^{1}H-NMR (400 MHz, DMSO-d_6) δ p.p.m.: 9.87 {s, 1H, NH), 7.97 (d, 2H, $J = 8.69$ Hz, Ar–H), 7.52 (d, 1H, $J = 8.39$ Hz, Ar–H), 7.07 (m, 2H, Ar–H), 7.02 (m, 1H, Ar–H), 6.87 (d, 1H, $J = 10.80$ Hz, Ar–CH=C), 6.83 (s, 1H, H_β), 6.67 (d, 1H, $J = 8.54$ Hz, Ar–H), 6.05 (m, 1H, Ar–C=CH), 5.03 (q, 2H, OCH_2); ^{13}C-NMR (100 MHz, DMSO-d_6) δ p.p.m.: 181.8 (C=O), 156.2 (C_{5a}), 152.4 (C_2), 145.3 (C_α), 137.1, 129.1 (2 C, Ar–C), 128.3 (C_4), 125.8 (C_8), 122.8, 121.1 (2 C, Ar–C), 121.0 (C_9), 120.1 (C_3), 119.5 (C_β), 119.1, 118.4, 115.0 (3 C, Ar–C), 114.1 (C_5), 109.1 (C_{9a}), 104.1 (Ar–C), 66.1 (OCH_2); LC-MS (*m/z*): 316 $(M + H)^+$. Elemental analysis ($C_{20}H_{13}NO_3$): calcd. C, 76.18; H, 4.16; N, 4.44. found: C, 76.37; H, 4.37; N, 4.20%.

Biological assay

DPPH radical scavenging activity

The hydrogen atom or electron donation ability of the compounds was measured from the bleaching of the purple colored methanol solution of DPPH. The spectrophotometric assay uses the stable radical DPPH as a reagent. 1 mL of various concentrations of the test compounds (5, 10, 25, 50, and 100 µg/mL) in methanol was added to 4 mL of 0.004% (w/v) methanol solution of DPPH. After a 30 min incubation period at room temperature, the absorbance was read against blank at 517 nm. The percent of inhibition of free radical production from DPPH was calculated by the following equation.

$$\% \text{ of scavenging} = \left[\left(A_{\text{control}} - A_{\text{sample}}\right)/A_{\text{blank}}\right] \times 100$$
$$\% \text{ of scavenging} = [(\text{A control} - \text{A sample})/\text{A blank}] \times 100 \quad (1)$$

where A_{control} is the absorbance of the control reaction (containing all reagents except the test compound) and A_{sample} is the absorbance of the test compound. Tests were carried at in triplicate.

Hydrogen peroxide (H_2O_2) scavenging activity

The H_2O_2 scavenging ability of the compounds was determined according to the method of Ruch et al., A solution of H_2O_2 (40 mM) was prepared in phosphate buffer (pH 7.4). 5, 10, 25, 50, and 100 µg/mL concentrations of the test compounds in 3.4 mL phosphate buffer were added to H_2O_2 solution (0.6 mL, 40 mM). The absorbance value of the reaction mixture was recorded at 230 nm. The percent of scavenging of H_2O_2 was calculated using Eq. (1).

Antimicrobial activity

The in vitro antimicrobial studies were carried out by agar well-diffusion method against test organisms (Chung et al. 1990; Azoro 2002). Nutrient broth (NB) plates were swabbed with 24 h old broth culture (100 mL) of test bacteria. Using the sterile cork borer, wells (6 mm) were made into each petriplate. The different concentrations of test

samples dissolved in DMSO were added into the wells by using sterile pipettes. Simultaneously, the standard antibiotics, gentamicin for antibacterial activity, fluconazole for antifungal activity were tested against the pathogens. The plates were incubated at 37 °C for 24 h for bacteria and at 28 °C for 48 h for fungi. After appropriate incubation, the diameter of zone of inhibition of each well was measured. Duplicates were maintained and the average values were calculated for eventual antibacterial activity. Broth dilution test was used to determine MIC of the above mentioned samples (Janovska et al. 2003; Bishnu et al. 2009). Freshly prepared NB was used as diluents. The 24 h old culture of the test bacteria *B. subtilis*, *S. aureus, E. coli,* and *P. vulgaris* and the test fungi *A. niger* and *C. albicans* were diluted 100 folds in NB (100 mL bacterial cultures in10 mL NB). Increasing concentrations of the test samples were added to the test tubes containing the bacterial and fungal cultures. All the tubes were incubated at 37 °C for 24 h for bacteria and at 28 °C for 48 h for fungi. The tubes were examined for visible turbidity and using NB as control. The lowest concentration that inhibited visible growth of the tested organisms was recorded as MIC.

Molecular docking

Molecular docking was performed on crystal structure of tyrosinase from B. megaterium (PDB code: 3NM8) and imported into MVD.4.0 (Kalgutkar et al. 1998). All water molecules and co-factors were deleted. Then they were exported as mol2 files and docked by using MVD. We used the template docking available in MVD and evaluated MolDock score, Rerank score, and protein–ligand interaction score from MolDock and MolDock [GRID] options. Ascorbic acid was selected as reference compound for the template. It was used the default settings, including a grid resolution of 0.30 Å, the MolDock optimizer as a search algorithm, and the number of runs was set to 10. A population size of 50, maximum iteration of 2000, scaling factor of 0.50, crossover rate of 0.90 was set. The maximum number of poses to generate was increased to 10 from a default value of 5.

Conclusions

In summary, we synthesized a new series of compounds **5a–j** and **6a–j** under conventional and microwave irradiation methods. In microwave irradiation method, reactions were completed in short reaction time, mild reaction conditions, high yields and convenient operation. All the titled compounds have been screened for antioxidant activity using DPPH and H_2O_2 radical scavenging assays. The compounds **5d**, **5h**, **6e**, and **6j** were most potent with DPPH radical and the compounds **5h**, **6a**, **6e**, and **6j** were exhibited better radical scavenging ability with H_2O_2 radical. Antimicrobial activity screening revealed that compounds **5b**, **5e**, **6b**, **6c**, and **6e** displayed better microbial inhibition. The binding mode of the synthesized compounds with protein active site was predicted using molecular docking. Compounds **5d**, **5h**, and **6j** showed promising dock score values with more number of hydrogen bonding interactions. These in silico findings are well supported by results of antioxidant activity.

Supplementary materials

Spectral data of compounds **5a–j** and **6a–j**; ^{1}H NMR, ^{13}C NMR and mass spectra of representative synthesized derivatives are provided in supplementary materials.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no competing interests.

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