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Microwave-assisted synthesis of (*E*)-7-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-(3-arylacryloyl)-4-methyl-2*H*-chromen-2-ones and their antimicrobial activity

Abstract: Hybrid compounds are relevant products in the structure-activity relationships analysis. A new series of hybrid compounds containing coumarin, 1,2,3-triazole, and chalcone substructures were synthesized and screened for their antimicrobial activity. The structures of the synthesized compounds have been established on the basis of analytical and spectral data.

Keywords: alkyne; azide; chalcone; click chemistry; 1,3-dipolar cycloaddition; triazole.

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Introduction

Heterocyclic compounds containing nitrogen and oxygen atoms play an important role in agrochemical and pharmaceutical sciences. A large volume of research has been carried out on triazoles and their derivatives, which has proven the pharmacological importance of this heterocyclic system. 1,2,3-Triazole and its derivatives have received considerable attention in the past few decades due to their chemotherapeutical value. For example, (1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol and 2-(1-(2-methylbutyl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol, shown in Figure 1, are potent antimicrobial agents [1]. Other 1,2,3 triazole derivatives exhibit anti-inflammatory, analgesic, local anesthetic, antiallergic, antineoplastic, antimalarial [2], anti-HIV [3], and anticancer activities [4]. 1,2,3-Triazole compounds have also been widely used as synthetic intermediates, dyes, anti corrosive agents, photo stabilizers, photographic materials, and agrochemicals [5].

Coumarins are important oxygen-containing fused heterocycles used in drugs and dyes [6, 7]. The interesting biological activities of coumarins make them attractive targets in organic synthesis. Natural coumarins are known to have antidiabetic activity [8] and are antioxidant, hepato-protective, antimicrobial, antioxidant, anticancer [9], and antiviral agents. Synthetic coumarins are of pharmaceutical importance. The potent antibiotic novobiocin, shown in Figure 1, is a coumarin derivative [10]. These pharmacological properties of coumarin aroused our interest in synthesizing some coumarin derivatives with the aim of testing their microbiological activity. The compounds with the backbone of chalcones have been reported to possess various biological activities such as antimicrobial, anti-inflammatory, analgesic, antiplatelet, antiulcerative, antimalarial, anticancer [11], antiviral, antileishmanial, antioxidant [12], antitubercular [13], antihyperglycemic, and immunomodulatory properties. They show inhibition of chemical mediators release [14], inhibition of leukotriene B4 [15], inhibition of tyrosinase [16], and inhibition of aldose reductase [17]. Other derivatives show estrogenic activities [18]. Licochalcone (Figure 1) exhibits antimalarial activity [19]. Chalcones have also been used as starting materials for the synthesis of various chemicals, including plastics, resins, pesticides, dyes, and pharmaceuticals [20].

Microwave irradiation (MWI) is used for a variety of organic syntheses due to short reaction time, easy workup, and good yields. The microwave oven procedure is now well established in MORE chemistry [21].

Encouraged by the biological importance of coumarins, triazoles, and chalcones, in this report, we describe the synthesis of (*E*)-7-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-[3-arylacryloyl]-4-methyl-2*H*-chromen-2-ones **6** by conventional and MWI methods (Scheme 1). The products were evaluated for antimicrobial activity.

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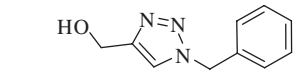
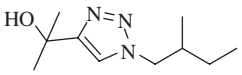
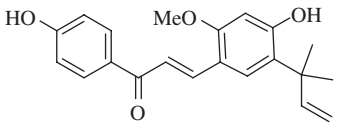


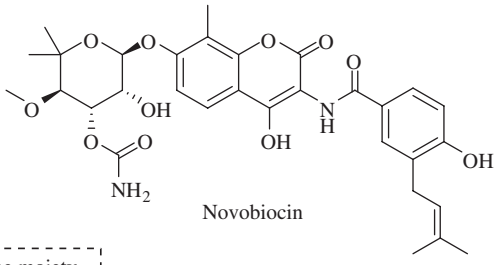
(1-benzyl-1*H*-1,2,3-triazol-4-yl)methanol



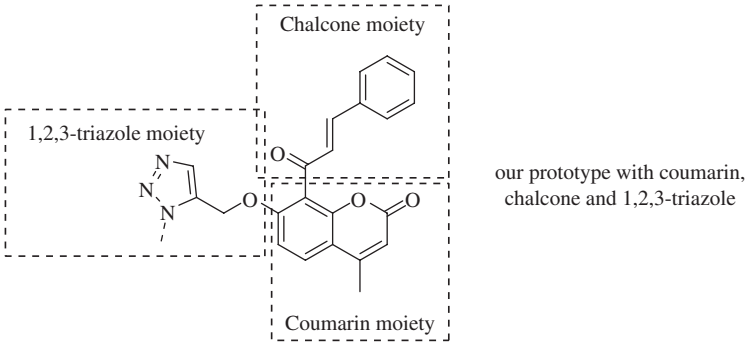
2-(1-(2-methylbutyl)-1*H*-1,2,3-triazol-4-yl)propan-2-ol



licochalcone

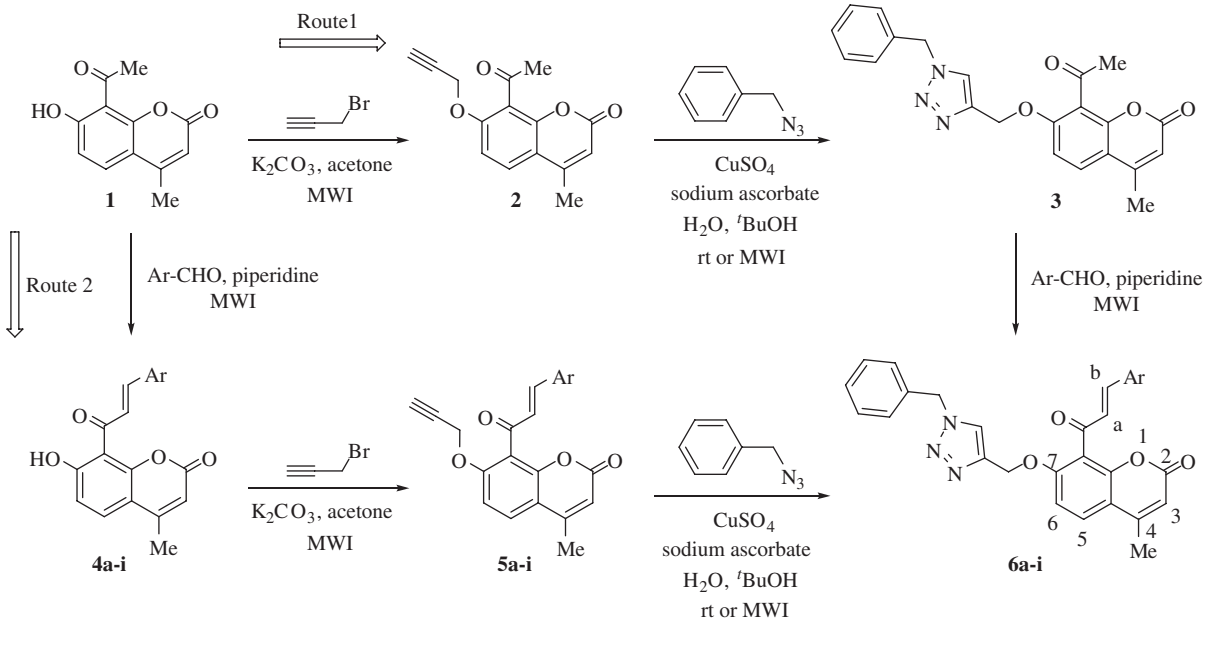


Novobiocin



our prototype with coumarin, chalcone and 1,2,3-triazole

Figure 1 Representative examples of biologically active triazoles, chalcones, and coumarins and a general structure of synthesized coumarin-chalcone-triazole hybrids.



a: Ar = Ph
b: Ar = 4-methoxyphenyl
c: Ar = 3,4-dimethoxyphenyl
d: Ar = 3,4,5-trimethoxyphenyl
e: Ar = 4-fluorophenyl
f: Ar = 4-(dimethylamino)phenyl
g: Ar = 4-isopropylphenyl
h: Ar = 4-chlorophenyl
i: Ar = 4-methylphenyl

Scheme 1

Results and discussion

Chemistry

Herein, we wish to report an efficient, practical, and high-yielding method for the synthesis of compounds **6a–i**. The starting material 8-acetyl-7-hydroxy-4-methylcoumarin (**1**) was prepared by acetylation of 7-hydroxy-4-methylcoumarin followed by rearrangement of the resultant 7-acetoxy derivative. The synthesis of the desired products **6a–i** was accomplished by two synthetic strategies shown in Scheme 1. In the first route, compound **2**, prepared by propargylation of **1**, was subjected to the click reaction with benzyl azide using MWI to give compound **3** [22]. Subsequent condensation reactions of **3** with aryl aldehydes in the presence of piperidine under MWI conditions gave compounds **6a–i** in excellent yields. In the second route, the chalcones **4a–i** were synthesized first by the reactions of compound **1** with aryl aldehydes in the presence of piperidine under MWI conditions. Propargylation of chalcones **4a–i** followed by the click reactions of the resultant intermediate products **5a–i** [23] gave the desired products **6a–i**. The optimized click reactions were conducted in *t*-BuOH/water (1:1) in the presence of $CuSO4{\cdot}5H_2O$ and sodium ascorbate under MWI conditions. In both routes, the use of MWI conditions in each particular step proved to be superior in terms of shorter reaction times and yields of products in comparison to the use of conventional conditions. The final steps of the synthesis of products **6a–i** under the two conditions are summarized in Table 1. Structures of all compounds **6a–i** were rigorously characterized by IR, ^{1}H NMR, ^{13}C NMR, and MS (Scheme 1).

Table 1 Comparison of yields of compounds **6a–i** synthesized under conventional and MWI conditions.

Compound	Yield (%)			
	Route 1		Route 2	
	Conventional	MWI	Conventional	MWI
6a	75	94	50	65
6b	80	95	40	58
6c	82	96	40	60
6d	79	96	45	55
6e	75	88	50	60
6f	70	90	40	55
6g	75	85	30	40
6h	74	85	40	55
6i	72	85	50	65

Antimicrobial activity

All compounds **6a–i** show antimicrobial activity (Table 2 and Figure 2). Importantly, derivatives **6c** and **6d** exhibit excellent activities against the selected bacterial strains that are superior to the activities of the reference antibiotic amoxicillin. Compounds **6b**, **6e**, and **6h** display good antibacterial activity, and compounds **6f** and **6g** are moderately active. The coumarin containing triazole derivatives **6a** and **6i** are weakly active in the antibacterial assay. Compounds **6c,d** are also more active against selected fungi that the reference drug mycostatin (Table 2 and Figure 3).

Table 2 Antimicrobial activity of compounds **6a–i**.

Compound	Zone of inhibition (mm)						
	Gram-positive bacteria		Gram-negative bacteria		Fungi		*F. oxysporum*
	S. aureus	*B. subtilis*	*E. coli*	*P. aeruginosa*	*A. niger*	*P. italicum*	
6a	11	08	10	04	08	14	17
6b	28	11	28	09	11	18	23
6c	32	13	31	11	13	21	27
6d	35	15	33	14	16	24	30
6e	27	11	27	10	10	19	24
6f	22	09	23	09	09	17	18
6g	20	08	22	07	08	16	19
6h	25	10	23	08	10	16	20
6i	17	06	14	07	09	17	18
Amoxicillin	30	12	30	10	–	–	–
Mycostatin	–	–	–	–	12	20	25

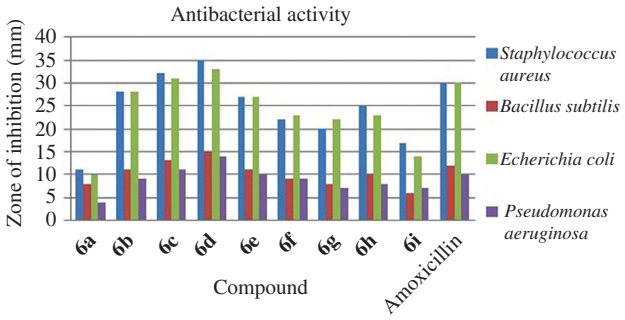


Figure 2 Antibacterial activity of compounds **6a–i**.

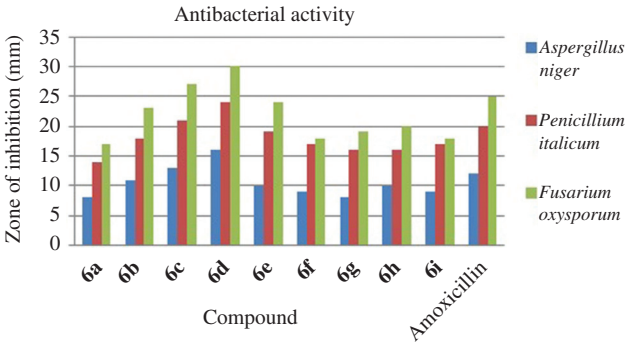


Figure 3 Antifungal activity of compounds **6a–i**.

Conclusions

An efficient microwave synthesis of 1,2,3-triazole derivatives was carried out successfully under mild reaction conditions. All final compounds were investigated for their *in vitro* antimicrobial activity. Compounds **6b**, **6c**, **6d**, **6e**, and **6h** show antimicrobial activity against selected microorganisms compared with the reference drugs.

Experimental

Melting points were determined in open capillaries using an electrical melting point apparatus and are uncorrected. Microwave reactions were carried out in a multi-SYNTH series microwave system (Milestone). The IR spectra were recorded in KBr pellets on a Shimadzu FT-IR-8400s spectrophotometer. The ^{1}H NMR spectra (400 MHz) and ^{13}C NMR spectra (100 MHz) were recorded in $CDCl_3$ on a Bruker DPX 400 spectrophotometer. The high-resolution electron spray ionization mass spectra (ESI-HR-MS) were recorded on a Micromass Q-Tof (ESI-HR-MS) mass spectrometer.

Synthesis of compounds 6a–i from substrates 5a–i

Conventional method A mixture of $CuSO_4 \cdot 5H_2O$ (0.15 mmol), sodium ascorbate (0.15 mmol), benzyl azide (1.5 mmol), and (*E*)-8-(3-(arylacryloyl)-4-methyl-7-(prop-2-yn-1-yloxy)-2*H*-chromen-2-one **5a–i** (1.5 mmol) in *t*-BuOH: H_2O (1:1, 5 mL) was stirred at room temperature for 24 h. After completion of the reaction, as monitored by TLC, the mixture was poured onto ice-cold water (20 mL) and extracted with EtOAc (30 mL). The extract was washed twice with saturated solution of NH_4Cl, twice with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel eluting with hexanes/EtOAc (3:1) to afford compound **6a–i**.

Microwave irradiation The mixture indicated above was subjected to MWI at 180 W for 8–10 min. After completion of the reaction, as monitored by TLC, the mixture was worked up and the product **6a–i** purified as described above.

Synthesis of compounds 6a–i from the substrate 3

Conventional method A mixture of 8-acetyl-7-[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-4-methyl-2*H*-chromen-2-one (**3**, 1 mmol), an aromatic aldehyde (1 mmol), and few drops of piperidine in ethanol (20 mL) was stirred at room temperature for 24 h. Progress of the reaction was monitored by TLC. After completion of the reaction, the mixture was diluted with cold water and acidified with diluted hydrochloric acid. The resulting precipitate was filtered, dried, and crystallized from ethanol to afford pure chalcone **6a–i**.

Microwave irradiation The mixture described above was placed in a Teflon vial with a screw cap and subjected to MWI at 100 W for 5–6 min. Progress of the reaction was monitored by TLC. Workup and purification of the product **6a–i** were conducted as described above.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-cinnamoyl-4-methyl-2*H*-chromen-2-one (6a) Pale yellow solid; mp 175–177°C; IR: 3034 (Ar-H), 1728 (C=O of chalcone), 1598 (C=C), 1453 (N=N), 1169 (C-N), 1089 cm^{-1} (Ar-O); ^{1}H NMR: δ 2.41 (s, 3H, CH_3), 5.32 (s, 2H, N-CH_2), 5.38 (s, 2H, O-CH_2), 6.15 (s, 1H, H_3), 6.97 (d, 1H, H_α, J = 16 Hz), 7.13–7.15 (m, 2H, Ar-H), 7.17 (d, 1H, H_6, J = 9 Hz), 7.22–7.47 (m, 10H, H_β, triazole H, Ar-H), 7.62 (d, 1H, H_5, J = 9 Hz); ^{13}C-NMR: δ 18.7, 54.2 (N-CH_2), 63.2 (O-CH_2), 109.4, 113.0, 114.6, 122.9, 125.6, 126.5, 127.9, 128.0, 128.03, 128.6, 128.81, 128.82, 128.9, 129.1, 130.9, 134.2, 134.3, 146.4, 151.9, 157.6, 159.8, 191.7 (C=O, chalcone). ESI-HR-MS. Calcd for $C_{29}H_{23}N_3O_4Na$ [M+Na]$^+$: m/z 500.1586. Found: m/z 500.1588.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-[3-(4-methoxyphenyl)acryloyl]-4-methyl-2*H*-chromen-2-one (6b) Pale yellow solid; mp 205–207°C; IR: 3038 (Ar-H), 1731 (C=O of chalcone), 1600 (C=C), 1459 (N=N), 1173 (C-N), and 1097 cm^{-1} (Ar-O). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm): 2.41 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 5.32 (s, 2H, N-CH_2), 5.39 (s, 2H, O-CH_2), 6.15 (s, 1H, H_3), 6.83–7.31 (m, 11H, H_α, Ar-H, H_β), 7.41 (d, 1H, H_6, J = 9 Hz), 7.45 (s, 1H, triazole H), 7.61 (d, 1H, H_5, J = 9 Hz); ^{13}C-NMR: δ 18.7, 54.2, 55.4, 63.2, 109.4, 113.0, 114.4, 115.2, 122.8, 123.0, 125.9, 126.3,127.0, 127.9, 128.8, 129.0, 130.2, 130.43, 146.5, 151.3, 156.0, 157.6, 159.9, 161.9, 166.4, 191.6. ESI-HR-MS. Calcd for $C_{30}H_{25}N_3O_5Na$ [M+Na]$^+$: m/z 530.1692. Found: m/z 530.1694.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-[3-(3,4-dimethoxyphenyl)acryloyl]-4-methyl-2*H*-chromen-2-one (6c) Pale yellow solid; mp 217–219°C; IR: 3040 (Ar-H), 1732 (C=O of chalcone), 1605

(C=C), 1463 (N=N), 1175 (C-N), and 1097 cm^{-1} (Ar-O). ^1H NMR: δ 2.42 (s, 3H, -CH_3), 3.81 (s, 3H, OCH_3), 3.98 (s, 3H, OCH_3), 5.32 (s, 2H, N-CH_2), 5.39 (s, 2H, N-CH_2), 6.15 (s, 1H, H_3), 6.82–6.91 (m, 2H, H_α, Ar-H), 7.13–7.39 (m, 9H, H_6, Ar-H, H_β), 7.47 (s, 1H, triazole H), 7.62 (d, 1H, H_5, *J* = 9 Hz); ^{13}C-NMR: δ 18.7, 54.3, 56.4, 57.5, 63.2, 109.3, 113.7, 114.1, 115.6, 122.1, 123.9, 125.2, 126.6, 127.1, 127.7, 128.5, 129.0, 130.2, 130.48, 146.4, 151.3, 151.9, 152.6, 156.2, 157.6, 159.9, 161.9, 166.4, 191.6. ESI-HR-MS. Calcd for $C_{31}H_{27}N_3O_6Na$ $[M+Na]^+$: *m/z* 560.1797. Found: *m/z* 560.1794.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-4-methyl-8-[3-(3,4,5-trimethoxyphenyl) acryloyl]-2*H*-chromen-2-one (6d) Pale yellow solid, mp: 221–223°C; IR: 3040 (Ar-H), 1731 (C=O of chalcone), 1602 (C=C), 1460 (N=N), 1171 (C-N), and 1095 cm^{-1} (Ar-O); ^1H NMR: δ 2.42 (s, 3H, CH_3), 3.82 (s, 9H, 3× OCH_3), 5.32 (s, 2H, N-CH_2), 5.40 (s, 2H, O-CH_2), 6.16 (s, 1H, H_3), 6.88 (d, 1H, H_α, *J* = 16 Hz), 7.17–7.35 (m, 9H, H_6, Ar-H, H_β), 7.47 (s, 1H, triazole H), 7.62 (d, 1H, H_5, *J* = 9 Hz); ^{13}C-NMR: δ 18.7, 54.2, 56.0, 56.2, 61.0, 63.2, 105.6, 109.4, 113.1, 114.5, 123.0, 126.4, 127.4,127.9, 128.0, 128.8, 129.0, 129.1, 129.7, 134.1, 146.5, 151.4, 151.8, 153.4, 153.5, 157.6, 191.6. ESI-HR-MS. Calcd for $C_{32}H_{29}N_3O_7Na$ $[M+Na]^+$: 590.1903. Found: *m/z* 530.1900.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-[3-(4-fluorophenyl)acryloyl]-4-methyl-2*H*-chromen-2-one (6e) Pale yellow solid, mp: 185–187°C; IR: 3039 (Ar-H), 1731 (C=O of chalcone), 1600 (C=C), 1460 (N=N), 1173 (C-N), and 1097 cm^{-1} (Ar-O). ^1H NMR: δ 2.41 (s, 3H, CH_3), 5.32 (s, 2H, N-CH_2), 5.38 (s, 2H, O-CH_2), 6.17 (s, 1H, H_3), 6.88 (d, 1H, H_α, *J* = 16 Hz), 6.95–6.98 (m, 2H, Ar-H), 7.04 (d, 1H, H_6, *J* = 9 Hz), 7.07–7.44 (m, 8H, H_β, Ar-H), 7.47 (s, 1H, triazole H), 7.62 (d, 1H, H_5, *J* = 9 Hz); ^{13}C-NMR: δ 18.7, 54.2, 63.2, 109.4, 113.0, 114.6, 116.0, 116.2, 126.4, 126.5,127.9, 128.0, 128.1, 128.7, 128.8, 129.12, 129.19, 130.5, 130.56, 130.6, 134.2, 145.1, 151.4, 152.0, 157.7, 191.7; ESI-HR-MS. Calcd for $C_{29}H_{22}FN_3O_4Na$ $[M+Na]^+$: *m/z* 518.1492. Found: *m/z* 518.1490.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-[3-(4-dimethylaminophenyl)acryloyl]-4-methyl-2*H*-chromen-2-one (6f) Pale yellow solid; mp 198–200°C IR: 3038 (Ar-H), 1732 (C=O of chalcone), 1600 (C=C), 1459 (N=N), 1172 (C-N), and 1097 cm^{-1} (Ar-O); ^1H NMR: δ 2.41 (s, 3H, CH_3), 2.54 (s, 6H, 2× CH_3), 5.31 (s, 2H, N-CH_2), 5.52 (s, 2H, O-CH_2), 6.16 (s, 1H, H_3), 6.63–7.31 (m, 11H, H_α, Ar-H, H_β), 7.40 (d, 1H, H_6, *J* = 9 Hz), 7.47 (s, 1H, triazole H), 7.74 (d, 1H, H_5, *J* = 9 Hz); ^{13}C-NMR: δ 18.7, 32.4, 54.3, 63.2, 109.3, 111.0, 111.7, 112.9, 114.4, 120.0, 122.1, 122.8, 124.8, 126.4, 128.0, 128.1, 128.9, 129.0, 133.4, 152.0, 154.5, 156.9, 159.7, 162.3, 166.5 199.2. ESI-HR-MS. Calcd for $C_{31}H_{28}N_4O_4Na$ $[M+Na]^+$: *m/z* 543.2008. Found: *m/z* 543.2010.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-[3-(4-isopropylphenyl)acryloyl]-4-methyl-2*H*-chromen-2-one (6g) Pale yellow solid; mp 165–167°C IR: 3035 (Ar-H), 1729 (C=O of chalcone), 1598 (C=C), 1448 (N=N), 1163 (C-N), and 1088 cm^{-1} (Ar-O); ^1H NMR: δ 1.2 (s, 6H, $(CH_3)_2$), 2.41 (s, 3H, CH_3), 2.6 (m, 1H, $CH(Me)_2$), 5.32 (s, 2H, N-CH_2), 5.38 (s, 2H, O-CH_2), 6.14 (s, 1H, H_3), 6.95 (d, 1H, H_α, *J* = 16 Hz), 7.12–7.14 (m, 2H, Ar-H), 7.17 (d, 1H, H_6, *J* = 9 Hz), 7.24–7.44 (m, 8H, H_β, Ar-H), 7.47 (s, 1H, triazole H), 7.62 (d, 1H, H_5, *J* = 9 Hz); ^{13}C-NMR: δ 18.7, 23.8, 32.4, 54.2, 63.2, 109.2, 113.0, 114.4, 122.7, 126.5, 128.1, 128.3, 128.6, 128.80, 128.82, 128.9, 129.1, 130.9, 134.2, 134.3, 143.6, 146.4, 150.4, 151.4 153.6, 159.8, 191.7. ESI-HR-MS. Calcd for $C_{32}H_{29}N_3O_4Na$ $[M+Na]^+$: *m/z* 542.2055. Found: *m/z* 542.2051.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-8-[3-(2-chlorophenyl)acryloyl]-4-methyl-2*H*-chromen-2-one (6h) Pale yellow solid; mp 183–185°C IR: 3028 (Ar-H), 1731 (C=O of chalcone), 1600 (C=C), 1459 (N=N), 1170 (C-N), and 1097 cm^{-1} (Ar-O); ^1H NMR: δ 2.41 (s, 3H, CH_3), 5.32 (s, 2H, N-CH_2), 5.38 (s, 2H, O-CH_2), 6.15 (s, 1H, H_3), 6.88 (d, 1H, H_α, *J* = 16 Hz), 6.95–6.98 (m, 2H, Ar-H), 7.04 (d, 1H, H_6, *J* = 9 Hz), 7.07–7.44 (m, 8H, H_β, Ar-H), 7.47 (s, 1H, triazole H), 7.62 (d, 1H, H_5, *J* = 9 Hz); ^{13}C-NMR: δ 18.7, 54.3, 63.2, 109.3, 113.0, 114.5, 126.8, 127.0, 127.2, 128.0, 128.3, 128.8, 129.1, 129.2, 129.5, 130.1, 130.2, 131.5, 134.2, 135.1, 141.6, 142.1, 151.7, 151.9, 157.7, 159.8, 191.6; ESI-HR-MS. Calcd for $C_{29}H_{22}ClN_3O_4Na$ $[M+Na]^+$: *m/z* 534.1196. Found: 534.1192.

(*E*)-7-[(1-Benzyl-1*H*-1,2,3-triazol-4-yl)methoxy]-4-methyl-8-[3-(*p*-tolyl)acryloyl]-2*H*-chromen-2-one (6i) Pale yellow solid; mp 170–172°C; IR: 3038 (Ar-H), 1731 (C=O of chalcone), 1600 (C=C), 1459 (N=N), 1173 (C-N), and 1095 cm^{-1} (Ar-O); ^1H NMR: δ 2.41 (s, 3H, CH_3), 2.62 (s, 3H, Ar-CH_3), 5.32 (s, 2H, N-CH_2), 5.38 (s, 2H, O-CH_2), 6.15 (s, 1H, H_3), 6.85 (d, 1H, H_α, *J* = 16 Hz), 7.05–7.36 (m, 10H, Ar-H, H_β), 7.41 (d, 1H, H_6, *J* = 9 Hz), 7.45 (s, 1H, triazole H), 7.61 (d, 1H, H_5, *J* = 9 Hz); ^{13}C-NMR: δ 18.7, 29.7, 54.2, 63.2, 109.3, 113.0, 114.4, 122.9, 125.9, 126.3, 126.9, 127.9, 128.0, 128.4, 128.7, 129.0, 130.4, 143.7, 146.4, 151.3, 151.8, 156.0, 157.6, 159.4, 161.9, 191.6. ESI-HR-MS. Calcd for $C_{30}H_{25}N_3O_4Na$ $[M+Na]^+$: *m/z* 514.1742. Found: *m/z* 514.1725.

Biological activities

All synthesized compounds were screened for their antimicrobial activity against two strains of Gram-positive bacteria (*Staphylococcus aureus* and *Bacillus subtilis*), two strains of Gram-negative bacteria (*Echerichia coli* and *Pseudomonas aeruginosa*), as well as three strains of fungi (*Aspergillus niger*, *Penicillium italicum*, and *Fusarium oxysporum*). Standard antibiotic drugs *amoxicillin* for bacteria and *mycostatin* for fungi were used at a concentration of 50 μg/mL for comparison. The biological activities of these compounds were evaluated by the filter paper disc method [18] for 50 μg/mL solutions in DMF. The inhibition zones of microbial growth surrounding the filter paper disc (5 mm) were measured in millimeters at the end of an incubation period of 3 days at 37°C for *E. coli* and at 28°C for other bacteria and fungi; DMF alone showed no inhibition zone.

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