ISSN 1070-3632, Russian Journal of General Chemistry, 2019, Vol. 89, No. 10, pp. 2108–2114. © Pleiades Publishing, Ltd., 2019.

Design, Synthesis, Antimicrobial, and Antioxidant Activity of Dimers of Chromene Containing 1,2,3-Triazole Derivatives Bearing an Alkyl Spacer[1]

I. Vani[a] and K. R. S. Prasad[b]*

[a] *Department of Chemistry, GDC, Kukatpally, India*
[b] *Department of Chemistry, K.L.E.F. Vaddeswaram, India*
**e-mail: vaniinavolu@gmail.com*

Received April 20, 2019; revised September 27, 2019; accepted October 3, 2019

Abstract—A new series of chromene based 1,2,3-triazole derivatives has been synthesized by incorporating biologically active heterocyclic rings containing chromene and triazole moieties in one molecular structure. All newly synthesized compounds are characterized by ^{1}H and ^{13}C NMR, mass, and IR spectra. The title compounds are tested for their activity against different bacterial and fungal strains, and antioxidant activity. Several compounds are determined to be potent antimicrobial and antioxidant agents.

Keywords: chromene, 1,2,3-triazole, click chemistry, alkyl spacer, antimicrobial, antioxidant

DOI: 10.1134/S1070363219100190

INTRODUCTION

Chromenes (benzopyran) are important medicinal pharmacophores that make a significant structural component of a big number of natural compounds [1–4]. Synthetic chromene derivatives demonstrate antitumor, antivascular [5], antioxidant, antimicrobial [6, 7], antifungal, and many other types of activities. Lipophilic nature of benzopyran derivatives supports their crossing the cell membranes [8].

Many 1,2,3-triazole derivatives are well known as compounds of high biological activity.

Based on the biological significance of chromene and triazole derivatives and our ongoing efforts in developing newer antimicrobial agents, in the present study we present design and synthesis of a series of novel chromene based 1,2,3-triazole derivatives **7a**–**7l** via copper-catalyzed Huisgen [3+2] cycloaddition reaction. All the synthesized compounds have been tested for their antimicrobial activity.

RESULTS AND DISCUSSION

Synthesis of a series of chromene based 1,2,3-triazole derivatives **7a**–**7l** (Scheme 1) started with the reaction of dihaloalkanes **1** with sodium azide giving diazidoalkanes **2** according to the literature procedure [9]. Propargylation of compound **3** followed by cyclization of thus formed intermediates **4a**–**4d** gave the corresponding cyclized derivatives **5a**–**5d** [10]. Propargylation of the latter compounds led to the corresponding derivatives **6a**–**6d** that were introduced in the copper-catalyzed Huisgen [3+2] cycloaddition reaction with diazidoalkanes **2** giving the target chromene based 1,2,3-triazole derivatives **7a**–**7l**.

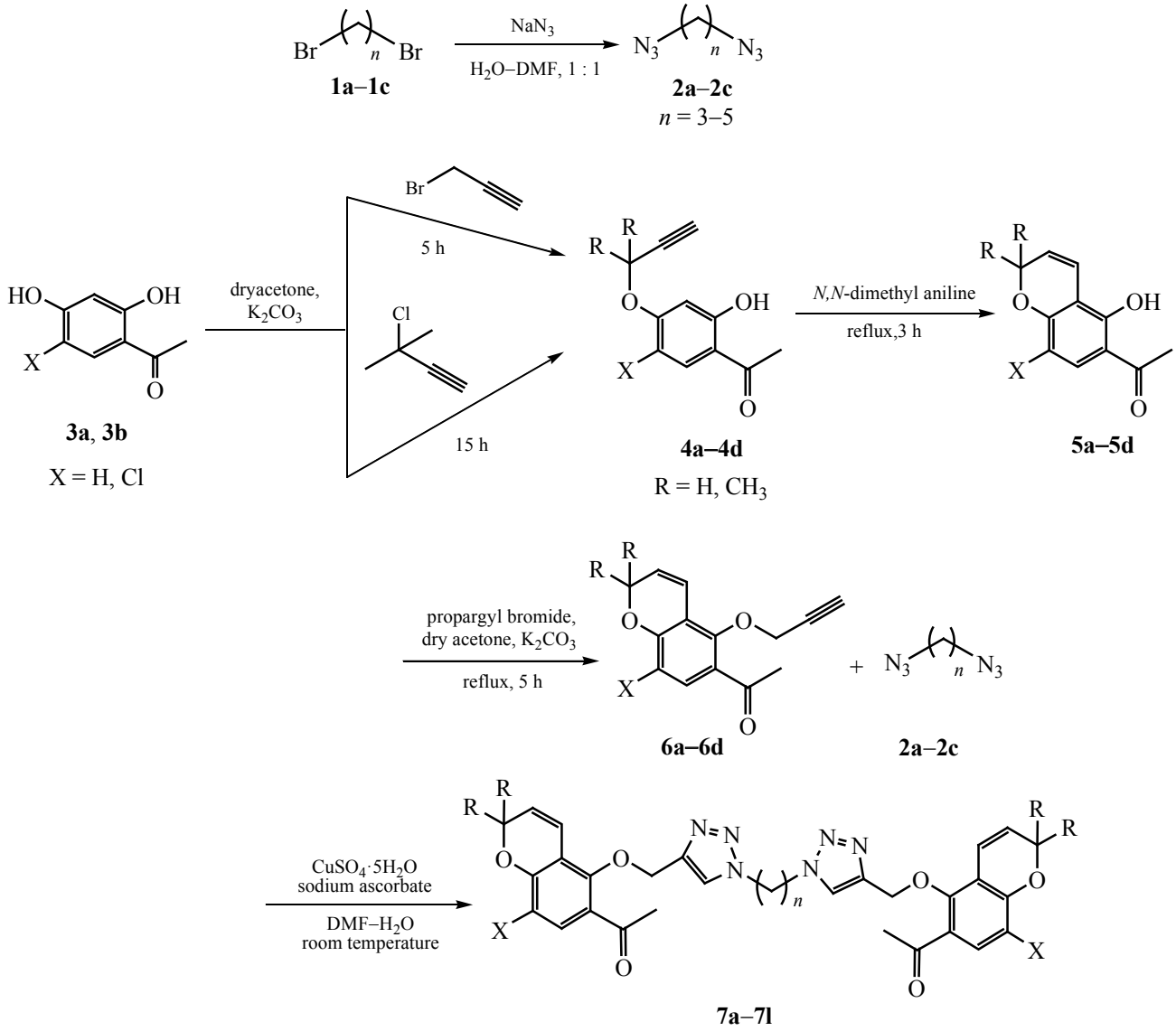
The products **7a**–**7l** were characterized by ^{1}H and ^{13}C NMR, IR, and mass spectra.

Antibacterial activity. All the newly synthesized compounds were screened *in vitro* for antibacterial activity against Gram positive *Bacillus subtilis* (ATCC 6633) and *Staphylococcus aureus* (ATCC 6538) bacteria, and Gram negative *Escherichia coli* (ATCC 11229) and *Proteus vulgaris* (ATCC 29213) bacteria. Agar well-diffusion method was used to assay the antibacterial activity against test strains on Mueller-Henton agar plates. Gentamicin was used as a standard antibacterial drug (Table 1). The accumulated antibacterial activity data revealed that compounds **7a**, **7d**, **7e** were of the highest antibacterial activity. The other synthesized compounds exhibited moderate zones of inhibition of bacterial cultures.

Antifungal activity. The same compounds were evaluated for their *in vitro* antifungal activity against *Aspergillus niger* (ATCC 9029) and *Candida albicans* (ATCC

[1] Supplementary materials are available for this article at https://doi.org/10.1134/S1070363219100190 and are accessible for authorized users.

Scheme 1. Synthetic route to novel chromene based 1,2,3-triazole derivatives **7a–7l.**



10231) fungal strains. Agar well-diffusion method was used to evaluate the antifungal activity. Fluconazole was used as a standard antifungal drug (Table 1). The compound **7d** demonstrated the highest antifungal activity. Compounds **7a**, **7c**, **7e** exhibited the promising growth inhibitory activity. The rest of the synthesized compounds demonstrated moderate to poor zone of inhibition against fungal strains.

Antioxidant activity. Antioxidant activity of the synthesized compounds was evaluated *in vitro* by the 2,2-diphenyl-1-picrylhydrazyl (DPPH) radical scavenging assay and hydrogen peroxide. The results were compared with the standard ascorbic acid. Most of compounds demonstrated significant inhibitory activity (Table 2). The compounds **7e**, **7f,** 7**o** exhibited strong scavenging effects on the DPPH stable radical and the highest H_2O_2 radical scavenging activity (Table 2).

EXPERIMENTAL

All melting points were determined on a Stuart SMP3 melting-point apparatus and are uncorrected. IR (KBr) spectra were recorded on a Shimadzu FTIR 8400 S spectrophotometer. ^1H and ^{13}C NMR spectra were measured on a Bruker Avance-400 spectrometer using TMS as an internal reference and $CDCl_3$ as a solvent. Mass spectra (EI) were measured on a Finnigan MAT 1020 mass spectrometer. Elemental analyses were carried out on a Karlo Erba 1106 elemental analyzer. All reactions were

Table 1. Antimicrobial activity of the synthesized compounds

Compound	Gram positive bacteria		Gram negative bacteria		Fungal strains	
	B. subtilis	*S. aureus*	*E. coli*	*P. vulgaris*	*A. niger*	*C. albicans*
7a	29	26	32	27	23	19
7b	21	17	19	22	17	16
7c	18	18	22	23	22	18
7d	27	26	28	27	26	27
7e	23	23	23	28	18	22
7f	22	23	24	18	14	18
7g	16	15	20	17	16	16
7h	19	22	24	24	17	12
7i	16	19	19	21	19	14
7j	22	16	17	16	13	16
7k	13	15	17	19	09	12
7l	11	17	16	16	11	16
Gentamicin	33	28	35	31	–	–
Fluconazole	–	–	–	–	35	33

monitored on silica gel percolated TLC plates (Merck 60 F254) and spots were visualized under UV light.

Table 2. Antioxidant activity of the synthesized compounds

Compound	Scavenging activity IC_{50}, μM	
	DPPH	H_2O_2
7a	21.75± 1.76	27.88±1.51
7b	23.89±0.68	28.09±0.96
7c	28.71±0.86	26.50±0.40
7d	35.91±0.56	33.85±0.71
7e	16.71±1.72	16.84±0.73
7f	16.46±0.79	19.36±1.97
7g	29.75±1.29	28.59±0.75
7h	43.43±1.03	36.75±0.39
7i	31.12±0.47	38.54±0.72
7j	32.66±0.59	29.90±0.83
7k	21.73±1.73	23.96±1.45
7l	21.84±1.16	21.91±1.00
Ascorbic acid	78.25±3.92	92.48±2.73

Synthesis of compounds 6. To the stirred mixture of a compound **5a**–**5d** (1 mmol) with K_2CO_3 (0.72 g, 2 mmol) in dry acetone (5 mL), was added propargyl bromide (80% in toluene) (0.36 mL, 1.2 mmol). The reaction mixture was refluxed for ca 5 h. After completion of the reaction, acetone was distilled off, and the residue was treated with 25 mL of ice cold water. The precipitate was filtered off and washed with an excess of water to obtain the corresponding pure compound **6a**–**6d**.

Synthesis of compounds 7a–7l. To the well stirred mixture of a compound **6a**–**6d** (1 mmol) and one of 1,3-diazidoalkanes **2a**–**2c** (0.5 mmol) in DMF–H_2O (1 : 1 v/v) (10 mL), were added copper(II)sulphate pentahydrate (0.2 mmol) and sodium ascorbate (0.5 mmol). The mixture was stirred for 18 h at room temperature. Upon completion of the process (as indicated by TLC), the reaction mixture was added to 90 mL of ice cold water. The precipitate was separated, washed twice with brine and purified by silica gel column chromatography to afford the corresponding compound **7a**–**7l** as white solid.

1-[5-(Prop-2-yn-1-yloxy)-2*H*-chromen-6-yl]-ethanone (6a). White solid, yield 95%, mp 86–88°C. IR spectrum, ν, cm^{-1}: 2189 (C≡C), 1637 (C=O). ^1H NMR spectrum, δ, ppm: 7.63 d (1H, J = 8.36 Hz, Ar-H),

6.80–6.85 m (1H, OCH_2CH=CH), 6.50 d (1H, J = 8.36 Hz, Ar-H), 5.81–5.85 m (1H, OCH_2=CH), 4.90 s (2H, OCH_2), 4.71–4.74 d (2H, OCH_2), 2.93 t (1H, OC–H), 2.56 s (3H, $COCH_3$). ^{13}C NMR spectrum, δ_C, ppm: 203.3 (C=O), 160.3, 159.1, 129.5, 124.1, 123.7, 115.1, 110.5, 104.3, 76.7 (C≡C–H), 74.7 (≡C–H), 62.3 (OCH_2), 59.3 (OCH_2), 26.7 ($COCH_3$). MS: m/z : 229 $[M + H]^+$. Found, %: C 73.63; H 5.32. $C_{14}H_{12}O_3$. Calculated, %: C 73.67; H 5.30.

1-[2,2-Dimethyl-5-(prop-2-yn-1-yloxy)-2*H*-chromen-6-yl]ethanone (6b). Light yellow solid, yield 96%, mp 98–99°C. IR spectrum, ν, cm^{-1}: 2195 (C≡C), 1634 (C=O). ^1H NMR spectrum, δ, ppm: 7.55 d (1H, J = 8.14 Hz, Ar-H), 6.83–6.88 m (1H, OCH_2CH=CH), 6.56 d (1H, J = 8.14 Hz, Ar-H), 5.73–5.78 m (1H, OCH_2=CH), 4.74 d (2H, OCH_2), 2.90 t (1H, ≡C–H), 2.58 s (3H, $COCH_3$), 1.56 s (6H, $C(CH_3)_2$). ^{13}C NMR spectrum, δ_C, ppm: 203.1 (C=O), 160.1, 159.3, 129.2, 124.8, 123.4, 114.9, 110.6, 104.2, 76.7 (C≡C–H), 74.8 (≡C–H), 72.1 (OCH_2), 59.2 (OCH_2), 26.7 ($COCH_3$), 30.1 [$(CH_3)_2$]. MS: m/z : 257 $[M + H]^+$. Found, %: C 74.95; H 5.16.25; N 18.77. $C_{16}H_{16}O_3$. Calculated, %: C 74.98; H 5.16.29; N 18.73.

1-[8-Chloro-5-(prop-2-yn-1-yloxy)-2*H*-chromen-6-yl]ethanone (6c). White solid, yield 92%, mp 75–77°C. IR spectrum, ν, cm^{-1}: 2197 (C≡C), 1639 (C=O). ^1H NMR spectrum, δ, ppm: 7.65 s (1H, Ar-H), 6.71–6.76 m (1H, OCH+CH=CH), 5.80–5.84 m (1H, OCH_2=CH), 4.92 s (2H, OCH_2), 4.79–4.81 d (2H, OCH_2), 2.92 t (1H, ≡C–H), 2.58 s (3H, $COCH_3$). ^{13}C NMR spectrum, δ_C, ppm: 203.2 (C=O), 159.6, 159.4, 129.3, 124.3, 123.9, 118.8, 115.3, 110.4, 76.6 (C≡C–H), 74.8 (≡C–H), 61.9 (OCH_2), 59.2 (OCH_2), 26.8 ($COCH_3$). MS: m/z: 263 $[M + H]^+$. Found, %: C 64.05; H 4.19. $C_{14}H_{11}ClO_3$. Calculated, %: C 64.01; H 4.22.

1-[8-Chloro-2,2-dimethyl-5-(prop-2-yn-1-yloxy)-2*H*-chromen-6-yl]ethanone (6d). White solid, yield 90%, mp 94–96°C. IR spectrum, ν, cm^{-1}: 2195 (C≡C), 1636 (C=O). ^1H NMR spectrum, δ, ppm: 7.72 s (1H, Ar-H), 6.68–6.73 m (1H, OCH_2CH=CH), 5.74–5.79 m (1H, OCH_2=CH), 4.74–4.78 d (2H, OCH_2), 2.91 t (1H, OC–H), 2.59 s (3H, $COCH_3$), 1.55 s [6H, $C(CH_3)_2$]. ^{13}C NMR spectrum, δ_C, ppm: 203.2 (C=O), 159.3, 129.1, 124.9, 123.1, 119.0, 114.9, 110.5, 76.7 (C≡C–H), 74.7 (≡C–H), 72.2 (OCH_2), 59.2 (OCH_2), 26.7 ($COCH_3$), 30.2 [$(CH_3)_2$]. Mass spectrum, m/z : 263 ($[M + H]^+$. Found, %: C 66.07; H 5.24. $C_{16}H_{15}ClO_3$. Calculated, %: C 66.10; H 5.20.

1,1'-[5,5'-({[1,1'-(Propane-1,3-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)]bis(oxy)}bis(2*H*-chromene-6,5-diyl)]diethanone (7a). Yield 92%, mp 107–109°C. IR spectrum, ν, cm^{-1}: 1626 (C=O). ^1H NMR spectrum, δ, ppm: 8.19 s (2H, triazole-H), 7.63 d (2H, J = 8.49 Hz, Ar-H), 6.81–6.85 m (4H, Ar-H), 5.84–5.90 m (2H, OCH_2 =CH), 5.22 s (4H, OCH_2), 4.94 s (4H, OCH_2), 4.44 s (4H, NCH_2), 2.58 s (6H, $COCH_3$), 2.26 t (2H, aliphatic-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 201.3 (C=O), 164.8, 163.7, 141.8, 128.0, 124.8, 123.9, 119.0, 114.7, 109.3, 106.9, 69.2 (OCH_2), 61.4 (OCH_2), 46.5 (NCH_2), 30.2 (CH_2), 26.8 ($COCH_3$). MS: m/z: 582 $[M + H]^+$. Found, %: C 63.95; H 5.21; N 14.44. $C_{31}H_{30}N_6O_6$. Calculated, %: C 63.91; H 5.19; N 14.42.

1,1'-{5,5'-[{1,1'-(Propane-1,3-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)}bis(oxy)]bis(2,2-dimethyl-2*H*-chromene-6,5-diyl)}diethanone (7b). Yield 94%, mp 122–124°C. IR spectrum, ν, cm^{-1}: 1625 (C=O). ^1H NMR spectrum, δ, ppm: 8.21 s (2H, triazole-H), 7.65 d (2H, J = 8.49 Hz, Ar-H), 6.79–6.83 m (4H, Ar-H), 5.82–5.88 m (2H, OCH_2 =CH), 5.21 s (4H, OCH_2), 4.40 s (4H, NCH_2), 2.56 s (6H, $COCH_3$), 2.22 t (2H, aliphatic-CH_2), 1.46 s (12H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 201.1 (C=O), 164.2, 163.8, 141.9, 127.9, 124.8, 123.6, 117.9, 114.0, 109.5, 107.1, 69.9 [$C(CH_3)_2$], 61.4 (OCH_2), 46.6 (NCH_2), 30.2 (CH_2), 29.0 [$(CH_3)_2$], 26.8 ($COCH_3$). MS: m/z: 639 $[M + H]^+$. Found, %: C 65.85; H 6.03; N 13.13. $C_{31}H_{30}N_6O_6$. Calculated, %: C 65.82; H 6.00; N 13.16.

1,1'-[5,5'-{[1,1'-(Propane-1,3-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)}bis(oxy)bis(8-chloro-2*H*-chromene-6,5-diyl)]diethanone (7c). Yield 96%, mp 118–120°C. IR spectrum, ν, cm^{-1}: 1628 (C=O). ^1H NMR spectrum, δ, ppm: 8.31 s (2H, triazole-H), 7.53 s (2H, Ar-H), 6.73 d (2H, J = 10.19 Hz, OCH_2CH=CH), 5.81–5.87 m (2H, OCH_2 =CH), 5.21 s (4H, OCH_2), 4.93 s (4H, OCH_2), 4.42 s (4H, NCH_2), 2.64 s (6H, $COCH_3$), 2.23 t (2H, aliphatic-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 201.1 (C=O), 164.1, 163.2, 141.8, 127.5, 124.6, 123.3, 119.1, 115.3, 114.9, 106.0, 69.5 [$C(CH_3)_2$], 61.3 (OCH_2), 46.4 (NCH_2), 30.1 (CH_2), 26.8 ($COCH_3$). MS: m/z: 652 $[M + H]^+$. Found, %: C 57.13; H 4.36; N 10.86. $C_{31}H_{28}Cl_2N_6O_6$. Calculated, %: C 57.15; H 4.33; N 10.88.

1,1'-[5,5'-({[1,1'-(Propane-1,3-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl))bis(methylene)]bis(oxy)}bis(8-chloro-2,2-dimethyl-2*H*-chromene-6,5-diyl)]diethanone (7d). Yield 95%, mp 140–142°C. IR spectrum, ν, cm^{-1}: 1631 (C=O). ^1H NMR spectrum, δ, ppm: 8.34 s (2H, triazole-H), 7.52 s (2H, Ar-H), 6.75 d (2H, J = 10.79 Hz, OCH_2CH =CH), 5.81–5.87 m (2H, OCH_2 =CH), 5.22 s

(4H, OCH_2), 4.47 s (4H, NCH_2), 2.61 s (6H, $COCH_3$), 2.23 t (2H, aliphatic-CH_2), 1.49 s (12H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 201.1 (C=O), 164.9, 163.0, 141.7, 127.7, 124.7, 123.0, 117.9, 115.4, 114.2, 106.3, 70.1 ($\underline{C}$–$CH_3)_2$), 61.6 (OCH_2), 46.1 (NCH_2), 30.1 (CH_2), 29.4 (C–$\underline{C}H_3)_2$), 26.7 ($COCH_3$). MS: *m*/*z*: 708 $[M + H]^+$. Found, %: C 59.38; H 5.15; N 10.25. $C_{35}H_{36}Cl_2N_6O_6$. Calculated, %: C 59.41; H 5.13; N 10.02.

1,1'-(5,5'-{[(1,1'-(Butane-1,4-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)]bis(oxy)}bis(2*H*-chromene-6,5-diyl)]diethanone (7e). Yield 95%, mp 114–116°C. IR spectrum, ν, cm^{-1}: 1625 (C=O). ^1H NMR spectrum, δ, ppm: 8.24 s (2H, triazole-H), 7.68 d (2H, *J* = 8.58 Hz, Ar-H), 6.81–6.87 m (4H, Ar-H), 5.90–5.96 m (2H, OCH_2 =C$\underline{H}$), 5.19 s (4H, OCH_2) 4.93 s (4H, OCH_2), 4.35 s (4H, NCH_2), 2.56 s (6H, $COCH_3$), 1.81–1.84 m (4H, aliphatic-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 201.8 (C=O), 164.3, 163.9, 141.9, 128.8, 124.5, 123.2, 119.2, 114.5, 109.6, 107.0, 69.4 (OCH_2), 61.3 (OCH_2), 48.4 (NCH_2), 26.8 (CH_3), 24.6 (CH_2). MS: *m*/*z*: 597 $[M + H]^+$. Found, %: C 64.38; H 14.06; N 14.14. $C_{32}H_{32}N_6O_6$. Calculated, %: C 64.42; H 5.41; N 14.09.

1,1'-[5,5'-({[1,1'-(Butane-1,4-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)]bis(oxy)}bis(2,2-dimethyl-2*H*-chromene-6,5-diyl)]diethanone (7f). Yield 96%, mp 128–130°C. IR spectrum, ν, cm^{-1}: 1627 (C=O). ^1H NMR spectrum, δ, ppm: 8.18 s (2H, triazole-H), 7.70 d (2H, *J* = 8.58 Hz, Ar-H), 6.80 d (2H, *J* = 10.79 Hz, OCH_2CH=C$\underline{H}$), 6.75 d (2H, *J* = 8.58 Hz, Ar-H), 5.89–5.95 m (2H, OCH_2 =C$\underline{H}$), 5.21 s (4H, OCH_2), 4.38 t (4H, NCH_2), 2.53 s (6H, $COCH_3$), 1.79–1.82 m (4H, aliphatic-CH_2), 1.47 s (12H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 201.7 (C=O), 164.45, 163.6, 141.4, 127.7, 124.6, 123.4, 118.1, 114.6, 109.7, 107.1, 71.2 ($\underline{C}CH_3)_2$), 61.5 (OCH_2), 48.5 (NCH_2), 29.1 [$(CH_3)_2$], 26.7 ($COCH_3$), 24.8 (CH_2). MS: *m*/*z*: 597 $[M + H]^+$. Found, %: C 66.27; H 6.20; N 12.84. $C_{36}H_{40}N_6O_6$. Calculated, %: C 66.24; H 6.18; N 12.88.

1,1'-[5,5'-({[1,1'-(Butane-1,4-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl))bis(methylene)]bis(oxy)}bis(8-chloro-2*H*-chromene-6,5-diyl)]diethanone (7g). Yield 94%, mp 138–140°C. IR spectrum, ν, cm^{-1}: 1628 (C=O). ^1H NMR spectrum, δ, ppm: 8.20 s (2H, triazole-H), 7.77 s (2H, Ar-H), 6.83 d (2H, *J* = 10.51, OCH_2 CH=C$\underline{H}$), 5.90–5.95 m (2H, OCH_2 =C$\underline{H}$), 5.19 s (4H, OCH_2), 4.93 s (4H, OCH_2), 4.40 t (4H, NCH_2), 2.54 s (6H, $COCH_3$), 1.76–1.79 m (4H, aliphatic-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 201.5 (C=O), 164.2, 163.3, 141.2, 127.4, 124.3, 123.5, 119.1, 115.3, 114.8, 106.3, 69.7 (OCH_2), 61.4 (OCH_2), 48.5 (NCH_2), 26.8 ($COCH_3$), 24.6 (CH_2). MS: *m*/*z*: 597 $[M + H]^+$. Found, %: C 57.72; H 4.58; N 12.66. $C_{32}H_{30}ClN_6O_6$. Calculated, %: C 57.75; H 4.54; N 12.63.

1,1'-[5,5'-{[1,1'-(Butane-1,4-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)}bis(oxy)bis(2,2-dimethyl-2*H*-chromene-6,5-diyl)]diethanone (7h). Yield 92%, mp 131–133°C. IR spectrum, ν, cm^{-1}: 1630 (C=O). ^1H NMR spectrum, δ, ppm: 8.21 s (2H, triazole-H), 7.64 s (2H, Ar-H), 6.79 d (2H, *J* = 10.79 Hz, OCH_2CH=C$\underline{H}$), 5.90–5.96 m (2H, $OCH_2C\underline{H}$), 5.21 s (4H, OCH_2), 4.38 t (4H, NCH_2), 2.57 s (6H, $COCH_3$), 1.74–1.77 m (4H, aliphatic-CH_2), 1.49 s (12H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 201.4 (C=O), 164.1, 163.2, 141.5, 127.3, 124.4, 123.6, 117.7, 115.4, 114.4, 106.5, 71.6 (OCH_2), 61.4 (OCH_2), 48.6 (NCH_2), 29.4 (CH_3), 26.7 ($COCH_3$), 24.6 (CH_2). MS: *m*/*z*: 722 $[M + H]^+$. Found, %: C 59.95; H 5.33; N 11.61. $C_{36}H_{38}Cl_2N_6O_6$. Calculated, %: C 59.92; H 5.31; N 11.65.

1,1'-[5,5'-{[1,1'-(Pentane-1,5-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)}bis(oxy)bis(2*H*-chromene-6,5-diyl)]diethanone (7i). Yield 95%, mp 125–127°C. IR spectrum, ν, cm^{-1}: 1625 (C=O). ^1H NMR spectrum, δ, ppm: 7.76 d (2H, *J* = 8.39 Hz, Ar-H), 7.62 s (2H, triazole-H), 6.68–6.73 m (4H, Ar-H), 5.88–5.93 m (2H, $OCH_2C\underline{H}$), 5.20 s (4H, OCH_2), 4.89–4.94 m (4H, OCH_2), 4.34–4.39 t, (4H, NCH_2), 2.53 s (6H, $COCH_3$), 1.82–2.02 m (6H, aliphatic-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 201.4 (C=O), 164.5, 161.3, 141.1, 128.0, 124.6, 123.3, 119.3, 114.9, 109.5, 107.5, 70.1 (OCH_2), 61.4 (OCH_2), 47.6 (NCH_2), 29.2 (CH_2), 26.7 ($COCH_3$), 23.6 (CH_2). MS: *m*/*z*: 611 $[M + H]^+$. Found, %: C 64.91; H 5.61; N 15.72. $C_{33}H_{34}N_6O_6$. Calculated, %: C 64.93; H 5.60; N 15.75.

1,1'-[5,5'-{[1,1'-(Pentane-1,5-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)}bis(oxy)bis(2,2-dimethyl-2*H*-chromene-6,5-diyl)]diethanone (7j). Yield 96%, mp 120–122°C. IR spectrum, ν, cm^{-1}: 1627 (C=O). ^1H NMR spectrum, δ, ppm: 7.75 d (2H, *J* = 8.39 Hz, Ar-H), 7.64 s (2H, triazole-H), 6.65–6.70 m, (4H, Ar-H), 5.83–5.88 m (2H, $OCH_2C\underline{H}$), 5.27 s (4H, OCH_2), 4.89–4.92 m (4H, OCH_2), 4.37 t (4H, NCH_2), 2.53 s (6H, $COCH_3$), 1.82–2.02 m (6H, aliphatic-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 201.8 (C=O), 164.4, 161.2, 141.3, 127.6, 124.5, 123.5, 117.8, 114.6, 109.6, 107.7, 71.3 ($CCH_3)_2$, 61.6 (OCH_2), 48.0 (NCH_2), 29.1 (CH_2), 28.9 [$(CH_3)_2$], 26.8 ($COCH_3$), 23.4 (CH_2). MS:

m/*z*: 611 $[M + H]^+$. Found, %: C 64.93; H 5.62; N 15.72. $C_{33}H_{34}N_6O_6$. Calculated, %: C 64.90; H 5.65; N 15.70.

1,1'-[5,5'-{[1,1'-(Pentane-1,5-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)}bis(oxy)bis(8-chloro-2H-chromene-6,5-diyl)]diethanone (7k). Yield 90%, mp 148-150°C. IR spectrum, ν, cm^{-1}: 1629 (C=O). ^1H NMR spectrum, δ, ppm: 7.82 s (2H, Ar-H), 7.65 s (2H, triazole-H), 6.59 d (2H, *J* = 10.51, $OCH_2CH{=}C\underline{H}$), 5.86–5.91 m (2H, $OCH_2C\underline{H}$), 5.21 s (4H, OCH_2), 4.38 t (4H, NCH_2), 2.52 s (6H, $COCH_3$), 1.80–1.99 m (6H, aliphatic-CH_2). ^{13}C NMR spectrum, δ_C, ppm: 201.9 (C=O), 164.1, 161.1, 141.2, 127.6, 124.7, 123.5, 119.7, 115.1, 114.9, 107.1, 69.9 (OCH_2), 61.8 (OCH_2), 48.1 (NCH_2), 29.3 (CH_2), 26.8 ($COCH_3$), 24.3 (CH_2). MS: *m*/*z*: 679 $[M + H]^+$. Found, %: C 58.36; H 4.73; N 12.35. $C_{33}H_{32}Cl_2N_6O_6$. Calculated, %: C 58.33; H 4.75; N 12.37.

1,1'-[5,5'-{[1,1'-(Pentane-1,5-diyl)bis(1*H*-1,2,3-triazole-4,1-diyl)]bis(methylene)}bis(oxy)bis(8-chloro-2,2-dimethyl-2*H*-chromene-6,5-diyl)]diethanone (7l). Yield 93%, mp 110–112°C. IR spectrum, ν, cm^{-1}: 1627 (C=O). ^1H NMR spectrum, δ, ppm: 7.87 s (2H, Ar-H), 7.68 s (2H, triazole-H), 6.63 d (2H, *J* = 10.34 Hz, $OCH_2{-}C{=}C\underline{H}$), 5.88–5.93 m (2H, $OCH_2{-}C\underline{H}$), 5.23 s (4H, OCH_2), 4.45 t (4H, NCH_2), 2.55 s (6H, $COCH_3$), 1.87–2.04 m (6H, aliphatic-CH_2), 1.47 s (12H, CH_3). ^{13}C NMR spectrum, δ_C, ppm: 201.5 (C=O), 164.1, 161.2, 141.4, 127.5, 124.7, 123.3, 117.7, 115.2, 114.5, 107.1, 71.8 (OCH_2), 61.6 (OCH_2), 47.7 (NCH_2), 29.3 [$(CH_3)_2$], 29.1 (CH_2), 26.8 ($COCH_3$), 23.5 (CH_2). MS: *m*/*z*: 736 $[M + H]^+$. Found, %: C 60.44; H 5.45; N 11.39. $C_{37}H_{40}Cl_2N_6O_6$. Calculated, %: C 60.41; H 5.48; N 11.42.

Antimicrobial assay. All the new compounds were evaluated for antimicrobial activity against four bacterial and two fungal cultures (100 μg/mL) by the well diffusion method [11]. Simultaneously, the standard antibiotic, gentamicin for antibacterial activity, fluconazole for antifungal activity were tested against the pathogens. The well diffusion method was carried out on nutrient agar medium (0.5% Peptone, 0.5% NaCl and 0.3% Beef extract, Himedia, Mumbai), which was autoclaved at 121°C/15 lbs, after which medium was cooled to 40°C and poured into petri dishes (Borosil, S-Line). After solidification of the content, petri dishes were sterilized by overnight incubation. The medium was cultured with actively grown (0.1 mL) selected bacterial culture with 10^8 cfu/mL by spread plate technique. After few minutes wells were created on cultured medium with the help of sterile well borer (5 mm) and selected dilutions of synthesized derivatives with selected concentrations were inoculated and incubated at 37°C for 24 h for bacteria and at 28°C for 48 h for fungi. The antimicrobial activity was evaluated by the zone of inhibition (mm) around the well.

Antioxidant activity. DPPH radical scavenging activity. Hydrogen atom or electron donating capability of the synthesized compounds was evaluated by bleaching of the purple methanol solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) [12]. To 4 mL of 0.004% (w/v) methanol solution of DPPH, 1 mL of the test compounds (5, 10, 25, 50 and 100 μg/mL) in methanol was added. After 30 min of incubation at room temperature, the absorbance was measured against blank at 517 nm. The percent inhibition of DPPH free radical formation was calculated by the equation:

$$\text{Scavenging} = [(A_{\text{control}} - A_{\text{sample}})/A_{\text{blank}}]\times 100\%. \quad (1)$$

All tests were carried out in triplicates.

Hydrogen peroxide scavenging activity. H_2O_2 Scavenging ability of the compounds was determined according to the method [13]. A solution of H_2O_2 (40 mM) was prepared in phosphate buffer (pH 7.4). The test compounds at 5, 10, 25, 50, and 100 μg/mL in 3.4 mL of phosphate buffer were added to H_2O_2 solution (0.6 mL, 40 mM). Absorbance value of the reaction mixture was recorded at 230 nm. Percent of scavenging of H_2O_2 was calculated using Eq. (1).

CONCLUSIONS

Simple and efficient method of synthesis of novel chromene based 1,2,3-triazole derivatives is developed. The newly synthesized compounds are evaluated for antimicrobial and antioxidant activity. Antimicrobial screening of the tested compounds indicates the products **7a**, **7d**, **7e** as the most antibacterial active and compound **7d** exhibits the highest antifungal activity. Several compounds were determined as potent antioxidant agents. Thus, the synthesized compounds can be considered as lead compounds for further development of more potent antimicrobial and antioxidant drug agents.

FUNDING

The authors are grateful to the KL University for providing laboratory facilities and IICT, Hyderabad for providing analytical facilities.

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Pratap, R. and Ram, V.J., *Chem. Rev.,* 2014, vol. 114, p. 10476. https://doi.org/10.1021/cr500075s
2. Ellis, G.P., and Lockhart, I.M.*, Chromenes, Chromanones, and Chromones: The Chemistry of Heterocyclic Compounds, Vol. 31*, Ellis, G.P., Ed., New York: Wiley-VCH, 2007, p. 1. https://doi.org/10.1002/9780470187012.ch1
3. Batista, J.M., Jr, Lopes, A.A., and Ambrósio, D.L., *Biol. Pharm. Bull.,* 2008, vol. 31, p. 538. https://doi.org/10.1248/bpb.31.538
4. Thomas, N. and Zachariah, S.M., *Asian J. Pharm. Clin. Res.,* 2013, vol. 6, p. 11.
5. Henriette, G., Lorraine, L., Bettina, H., Clemence, D., Kelly, D., and Irenej, K., *Mol. Cancer. Ther.,* 2004, vol. 3, p. 1375.
6. Chetan, B.S., Nimesh, M.S., Manish, P.P., and Ranjan, G.P., *J. Serb. Chem. Soc.,* 2012, vol. 77, p. 1.
7. Milan, M., Mirjana, M., Desanka, B., Sanja, M., Neda, N., and Vladimir, M., *Int. J. Mol. Sci.,* 2011, vol. 12, p. 2822. https://doi.org/10.3390/ijms12052822
8. Nicolaou, K.C., Pfefferkorn, J.A., Roecker, A.J., Cao, G.Q., Barluenga, S., and Mitchell, H.J., *J. Am. Chem. Soc.,* 2000, vol. 122, p. 9939. https://doi.org/10.1021/ja002033k
9. Wang, C., Salmon, L., Li, Q., Igartua, M.E., Moya, S., Cigan-da, R., Ruiz, J., and Astruc, D., *Inorg. Chem.,* 2016, vol. 55, p. 6776. https://doi.org/10.1021/acs.inorgchem.6b01092
10. Wang, L,, Chen, G., Lu, X., Wang, S., Han, S., Li, Y., Ping, G., Jiang, X., Li, H., and Yang, J., *Eur. J. Med. Chem.,* 2015, vol. 89, p. 88. https://doi.org/10.1016/j.ejmech.2014.10.036
11. Sen, A. and Batra, A., *Int. J. Curr. Pharm. Res.,* 2012, vol. 4, p. 67.
12. Burits, M. and Bucar, F., *Phytother. Res.,* 2000, vol. 14, p. 323. https://doi.org/10.1002/1099-1573(200008)14:5<323::AID-PTR621>3.0.CO;2-Q
13. Ruch, R.J., Cheng, S.J., and Klaunig, J.E., *Carcinogenesis,* 1989, vol. 10, p. 1003.