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Synthesis and structural characterization of novel *O*-substituted phenolic and chalcone derivatives with antioxidant activity

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Abstract

A series of novel 4-*O*-alkyltriazolylphenolic derivatives is first synthesized with good to excellent yields via the click reaction of 3-methoxy-4-*O*-propargylbenzaldehyde or 3-allyl-4-*O*-propargylacetophenone and aromatic azide derivatives. Next, the chalcones are prepared via the Claisen-Schmidt method from 4-*O*-alkylphenylketone derivatives in the presence of the corresponding (hetero)aromatic aldehydes as electrophiles. The structures of the newly synthesized compounds are confirmed from their infrared, nuclear magnetic resonance spectral data, and by elemental analysis. The main advantages of this procedure are the simplicity of the reaction conditions, easily available starting materials, and simple work-up. The antioxidant activity of several of the products is determined using the DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) radical scavenging assay. 4-*O*-propargylvanillin (IC_{50} = 14.54 µg/mL) had moderate antioxidant activity.

Keywords

1,3-dipolar cycloaddition, antioxidant activity, click chemistry, condensation reaction, *O*-alkylation, triazolated derivatives

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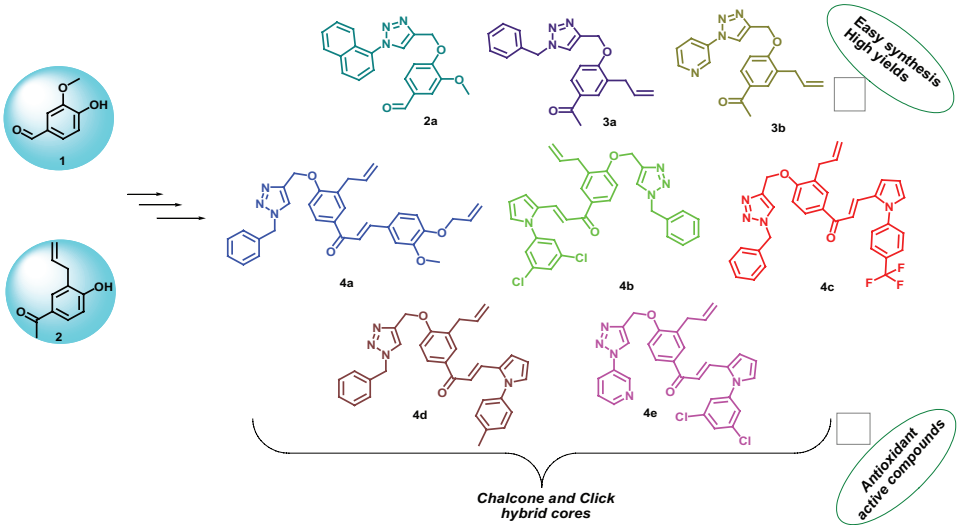
The antioxidant activity of novel 4-*O*-alkyltriazolylphenylaldehydes/ketones, *O*-substituted triazolyl-chalcone derivatives, and vitamin C was determined using DPPH (2,2-diphenyl-1-picryl-hydrazyl-hydrate) radical scavenging assay. Some of these synthesized molecules had moderate antioxidant activities meanwhile other compounds displayed low antioxidant capacity.



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Introduction

Chalcones (1,3-diphenyl-2-propen-1-ones) and their derivatives are an important class of natural products. They are found in a large number of plants and are considered to be precursors or intermediates in flavonoid and isoflavonoid synthetic pathways.[1] Chalcones are also useful compounds in pharmaceutical chemistry. Notably, chalcones and their derivatives have been found to be associated with various biological activities.[2] Our previous research on this class of molecules indicated that many natural and synthetic chalcones exhibit a wide spectrum of biological activities, such as antimalarial,[3] antimicrobial,[4] antifungal,[5] and antitumour activity.[6,7]

Recent work has explored the introduction of an alkyltriazolyl group in the chalcone skeleton at the C-4 position to afford lead compounds for the development of new therapeutic agents. Chalcones substituted with imidazoles,[8] triazoles,[9] amines,[10] and stilbene[11] have been reported to be potential antimalarial compounds. They have also been used as the synthetic intermediates of choice for functionalization of the α,β-position during the total synthesis of natural products such as the tropone-chalcones and heterocyclic derivatives which have attracted considerable interest due to their unique structure and properties.[12] The derivatives of 4-*O*-alkyltriazolylchalcone are known to possess antibacterial[13] and antifungal[14] activities. The interest of researchers in lead molecules containing the 1,2,3-triazole group as chemotherapeutic agents for various types of diseases is growing because they are known to exhibit a wide range of biological activity, such as antibiotic,[15] antifungal,[16] and anticancer properties.[17] Some 1,2,3-triazoles are used as deoxyribose nucleic acid (DNA) cleaving agents[18] and potassium channel activators.[19] Clinically used drugs containing a 1,2,3-triazole moiety include the β-lactam antibiotics tazobactam and cefatrizine, as well as the calcium channel blocker carboxyamidotriazole (Figure 1). Also, they have been widely used as synthetic intermediates and in industrial applications, for example, as dyes, anticorrosive agents, photostabilizers, photographic materials, and agrochemicals.[20] Therefore, the biological importance of the 1,2,3-triazole system as a link between two active molecules is useful to improve their biological properties.

Prompted by these observations on the pharmacological significance of triazole derivatives, and in order to discover new intermediates for the synthesis of antioxidant agents, this research describes the synthesis of new *O*-alkyltriazolylphenylaldehyde/ketone and chalcone derivatives. The preparation of new triazolated compounds as synthetic intermediates, is currently under investigation in our laboratory for the investigation of their potential pharmacological activities.

Results and discussion

Chemistry

The goal of our synthesis was to introduce a propargyl and thus triazole group to 3-methoxy-4-hydroxybenzaldehyde or 3-allyl-4-hydroxyacetophenone derivatives in order to prepare the desired *O*-substituted chalcone moieties and to investigate their antioxidant profiles. *O*-Substituted phenolic and chalcone derivatives are an important class of compounds which are known to possess good biological activities.

The synthetic routes to the desired compounds are outlined in Schemes 1–3. Initially, 4-*O*-substituted phenolic derivatives **1a–c** were used as the starting materials, and were prepared via two precursors **1** and 1-(3-allyl-4-hydroxyphenyl)ethanone (**2**). Compounds **1a–c** were synthesized by a one-pot nucleophilic substitution reaction as described in the literature.[6,21] The acetophenone **1c** was obtained in a good 84% yield (Scheme 1).

Azide derivatives **3–5**, for use in this work for 1,3-dipolar cycloaddition (click reaction) were prepared using previously described methods (Scheme 2).[22–24]

The intermediates, 4-*O*-methyltriazolylphenylaldehyde **2a** and ketones **3a,b**, were prepared in very good yields by the click reaction with aromatic azides **3–5** and the corresponding 4-*O*-propargylphenolic derivatives **1b,c** at ambient temperature in the presence of $CuSO_4 \cdot 5H_2O$ (2 mol%) and (+)-sodium L-ascorbate (5 mol%) in a mixture of *t*-BuOH/H_2O (1:1) (Scheme 2).[25,26] This synthesis of *O*-substituted triazolyl-chalcone derivatives by the click reaction followed the methods recently reported by Anand et al.[27] and Lv et al.[28]

Biologically, pyrroles tend to construct the key structure of porphyrin rings, which act as an active moiety in chlorophyll, vitamin B12, or bile pigments.[29] Pyrrole and its derivatives are widely used as intermediates in synthesis of pharmaceuticals, agrochemicals, dyes, photographic chemicals, perfumes, and other organic compounds. They are also the versatile molecules, which are active against the various diseases as antiviral, anticonvulsant, and antiinflammatory.[29] Otherwise, pyrrole and its derivatives exhibit wide range of biological activities such as anticancer and antioxidant activity.[30] In addition, the pyrrole-containing heterocyclic compounds have attracted attention particularly as antimicrobial agents.[29] These studies confirmed that pyrrole ring is a good pharmacophore group for the design of bioactive molecules.[29,30]

Thus, under these biological interests of pyrrole derivatives, our group recently developed a synthetic methodology of *O*-alkyl substituted heterocyclic-chalcones and evaluated their antioxidant profile.

Compounds **4a–e** were prepared via the Claisen-Schmidt condensation using the appropriate substituted ketones and aldehydes (Scheme 3).[31–34] All the reactions were performed in the presence of both KOH and EtOH. The obtained products were the *trans* chalcones, as was evident from their coupling constants.[6,7] The presence of the 1,2,3–triazole group was indicated by a singlet in the ^{1}H NMR spectra at approximately 7.60 ppm, and signals for the triazolyl C-4 and C-5 atoms at approximately 144 and 132 ppm, respectively, in the ^{13}C NMR spectra.[21,35] The structures of all the target compounds were assigned by elemental mass analysis and by infrared (IR) and nuclear magnetic resonance (NMR) spectroscopy.

Biological studies

The antioxidant activity of compounds **1b, 1c, 2a, 3a, 3b, 4a, 4b, 4c, 4d**, **4e**, and vitamin C (reference antioxidant

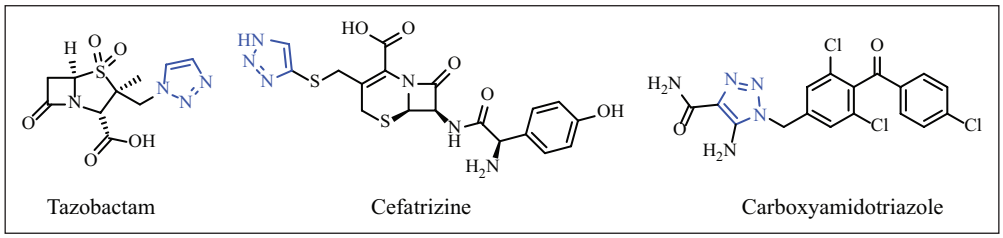
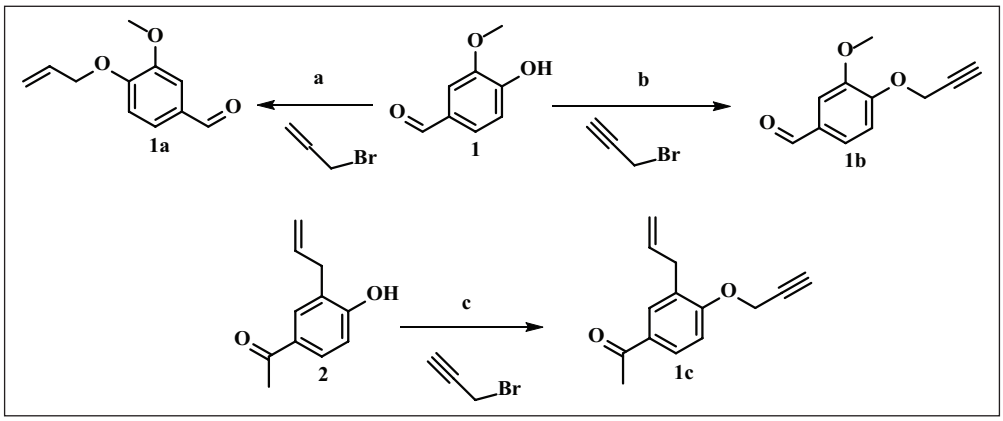
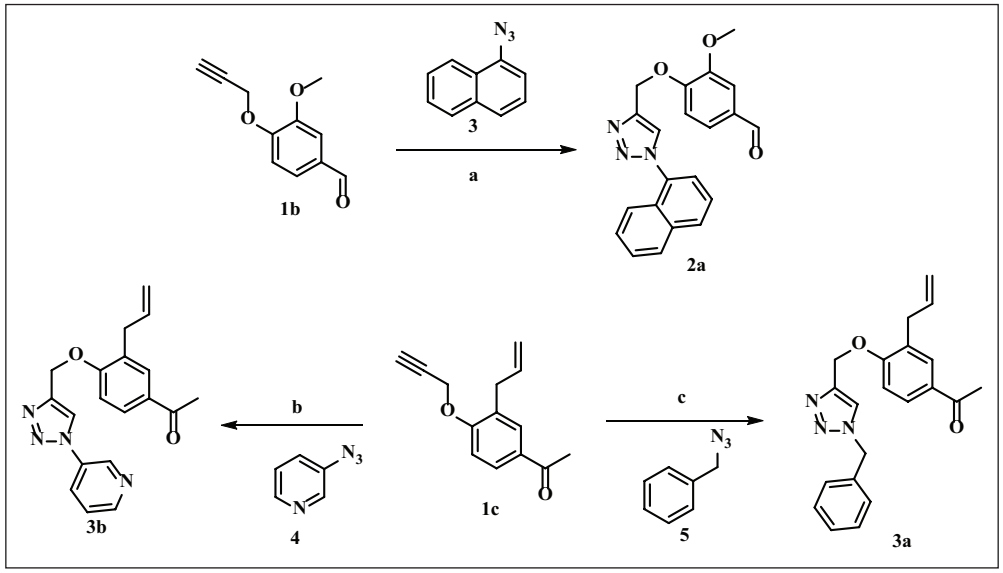


Figure 1. A few biologically active compounds containing 1,2,3-triazole moiety.



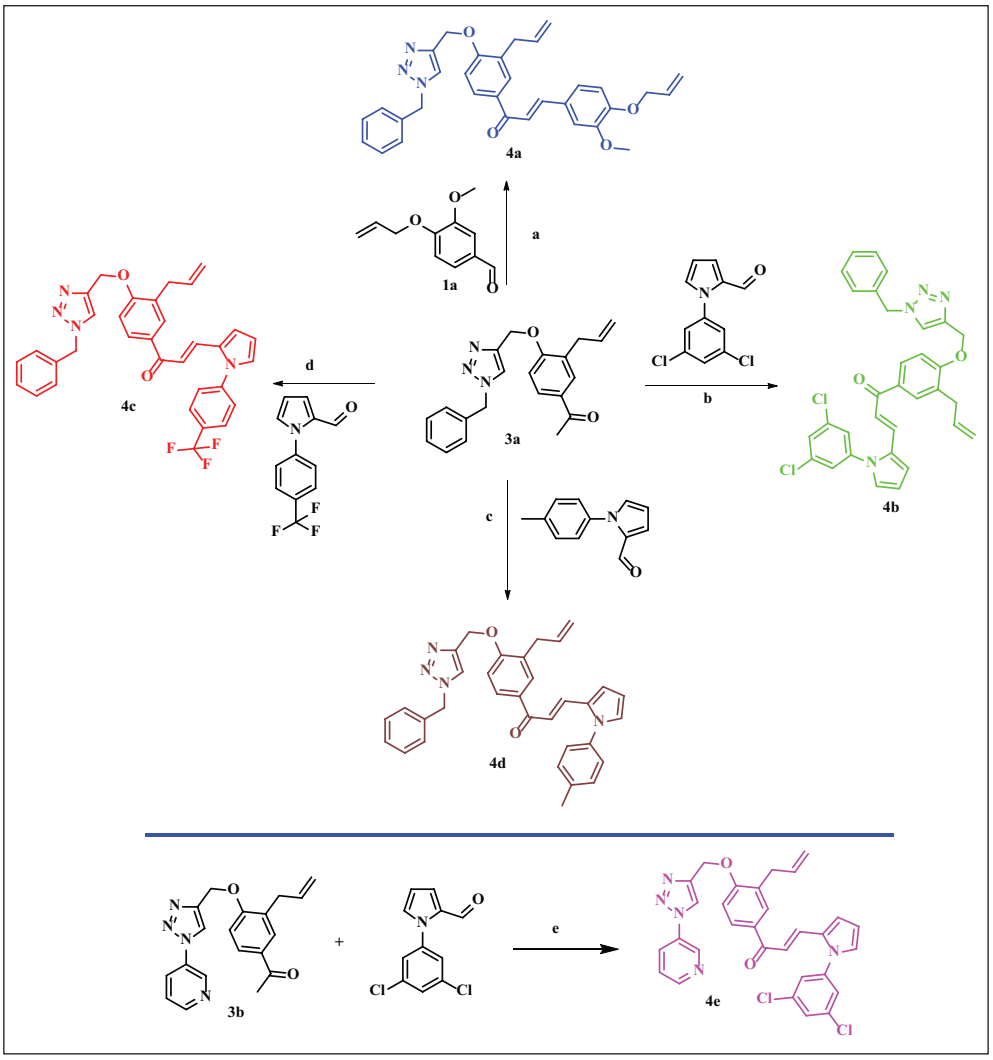
Scheme 1. Synthesis of 4-*O*-substituted phenolic derivatives **1a–c**. (a) K_2CO_3, dry acetone, reflux (65 °C), 20 h, N_2, 81%. (b) K_2CO_3, dry acetone, reflux (65 °C), 16 h, N_2, 92%. (c) K_2CO_3, dry acetone, reflux (69 °C), 16 h, N_2, 84%.



Scheme 2. Synthesis of *O*-substituted 4-*O*-methyltriazolylphenylaldehyde **2a** and ketones **3a,b** via the click reaction. (a) $CuSO_4{\cdot}5H_2O$, (+)-Sodium L-ascorbate, *t*-BuOH/H_2O (1:1), room temperature, 16 h, 88%. (b) $CuSO_4{\cdot}5H_2O$, (+)-Sodium L-ascorbate, *t*-BuOH/H_2O (1:1), room temperature, 26 h, 71%. (c) $CuSO_4{\cdot}5H_2O$, (+)-Sodium L-ascorbate, *t*-BuOH/H_2O (1:1), room temperature, 15 h, 86%.

molecule) were determined using the DPPH (2,2-diphenyl -1-picryl-hydrazyl-hydrate) radical scavenging assay (Table 1).

Chemicals are considered to have high or significant antioxidant capacity when their IC_{50} value is below 10 µg/mL, moderate antioxidant capacity for IC_{50} values between 10 and 20 µg/mL and low antioxidant capacity if the IC_{50} value is >20 µg/mL.[36] Thus, compound **1b** (IC_0 = 14.54 µg/mL) has moderate antioxidant activity meanwhile all the other compounds displayed low antioxidant capacity. The recorded IC_{50} values were however below 52 µg/mL. At the highest concentration of 1000 µg/mL, all the compounds displayed more than 70% DPPH scavenging activity, with even more than 90% for compounds **1b** (95.03%), **3a** (91.43%), and **4e** (91.48%) along with vitamin C (98.78%) (Table 1). The fact that the DPPH radical scavenging



Scheme 3. Synthesis of 4-*O*-methyltriazolyl-chalcone derivatives **4a–e**. (a) KOH (aq.) (50%), EtOH, 40 °C, 45 h, N_2, 90%. (b) KOH (aq.) (50%), EtOH, 42 °C, 80 h, N_2, 88%. (c) KOH (aq.) (50%), EtOH, 42 °C, 45 h, N_2, 68%. (d) KOH (aq.) (50%), EtOH, 42 °C, 39 h, N_2, 80%. (e) KOH (aq.) (50%), EtOH, 40 °C, 45 h, N_2, 90%.

Table 1. Antioxidant activity of the prepared compounds and vitamin C as determined by the DPPH radical scavenging assay.

Sample	Inhibition percentage at 1000 µg/mL	IC_{50} values in µg/mL
1b	95.03 ± 1.90	14.54 ± 1.71 A
1c	88.79 ± 3.12	24.74 ± 3.17 B, C
2a	88.75 ± 1.76	36.01 ± 2.45 D
3a	91.43 ± 2.09	20.25 ± 1.09 B
3b	86.85 ± 4.27	42.68 ± 2.98 E
4a	71.24 ± 3.18	45.98 ± 2.39 E, F
4b	85.12 ± 2.09	27.83 ± 2.55 C
4c	85.12 ± 4.87	51.25 ± 3.11 F
4d	89.10 ± 3.63	50.88 ± 2.82 F
4e	91.48 ± 3.26	22.11 ± 1.77 B
Vitamin C	98.78 ± 0.89	12.64 ± 0.91 A

Values are mean ± standard deviation (SD) of six independent experiments; values with the same letter are not significantly different ($p < 0.05$; ANOVA).

capacity of **1b** is closer to that of the reference compound, vitamin C, suggests that this compound can be used as antioxidant agent.

Conclusion

In conclusion, we have developed an efficient method for the synthesis of new *O*-substituted triazolylphenylaldehyde/ketone compounds as interesting intermediates for the preparation of chalcone derivatives in order to explore their antioxidant profiles. Also, this synthesis, which will be the key subject of our further research, offers significant improvements over existing procedures and thus helps to facilitate the synthesis of a variety of *O*-alkyltriazole compounds with potentially high synthetic and biological utilities. Further studies on *O*-substituted phenolic and chalcone derivatives as model intermediates for the synthesis of antioxidant lead compounds are currently under investigation in our laboratory.

Experimental section

General

Melting points were determined using open-glass capillaries on a Gallenkamp 8093/08/224 melting point apparatus which are uncorrected. IR spectra were determined with a Perkin Elmer FT-IR spectrophotometer. Nuclear magnetic

resonance (NMR) spectra were recorded using a Bruker or Varian spectrometers (400 MHz for ^{1}H NMR and 100 MHz for ^{13}C NMR). The chemical shifts are reported in parts per million (ppm) downfield from tetramethylsilane (TMS), which was used as the internal standard. Elemental analyses were recorded on a LECO 932 CHNS elemental analyzer. Thin-layer chromatography (TLC) was carried out using Merck silica gel 60 F-254 plates (layer thickness = 0.25 mm), and all solvents were distilled prior to use.

All the azide derivates **3**–**5** were synthesized according to a previously reported method.[22–24]

*General procedure for the synthesis of 4-allyloxy-3-methoxybenzaldehyde (**1a**)*

To vanillin (**1**) (1.95 g, 12.82 mmol) in dry acetone (25 mL) was added K_2CO_3 (1.77 g, 12.82 mmol) followed by allyl bromide (1.12 mL, 1.55 g, 12.82 mmol). The reaction mixture was refluxed for 20 h at 65 °C under a nitrogen atmosphere. The progress of the reaction was monitored by TLC. On completion of the reaction, the solvent was removed under reduced pressure and the residue was diluted in cold water (50 mL). The aqueous mixture was extracted with EtOAc (3 × 100 mL) and the combined extract was dried over anhydrous Na_2SO_4. After evaporation of the solvent and purification by column chromatography on silica gel eluting with hexane-EtOAc of increasing polarity, product **1a**[6] was obtained as a colorless oil (2.00 g, yield 81% in hexane-EtOAc 85:15).

*General procedure for the synthesis of 3-methoxy-4-O-propargylbenzaldehyde (**1b**) and 3-allyl-4-O-propargylacetophenone (**1c**)*

To a stirring mixture of vanillin (**1**) (2.030 g, 13.34 mmol) or 1-(3-allyl-4-hydroxy)ethanone (**2**) (2.030 g, 11.52 mmol) and anhydrous K_2CO_3 (3.180 g, 23.01 mmol, 2.00 equiv.) in dry acetone (20 mL), propargyl bromide (1.30 mL, 1.800 g, 12.10 mmol) was slowly added at ambient temperature. The reaction mixture was refluxed (65–69 °C) for 16 h under a nitrogen atmosphere. After completion of the reaction, the solvent was evaporated under reduced pressure and the residue was diluted with water (40 mL). The aqueous mixture was extracted with EtOAc (3 × 70 mL) and the extract was dried over anhydrous Na_2SO_4. After evaporation of the solvent under reduced pressure, the crude product was purified by column chromatography on silica gel eluting with hexane-EtOAc of increasing polarity to give product **1b** (2.3 g, 92% in hexane-EtOAc 17:3) or **1c** (2.1 g, 84% in hexane-EtOAc 47:3), respectively.

3-Methoxy-4-prop-2-ynyloxy-benzaldehyde *(**1b**)*:. White solid; m.p. 85–87 °C (lit.9 86 °C); yield 92%,;R_f = 0.40; (hexane-EtOAc 4:1 v/v); ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.87 (s, 1H), 7.47 (br d, J = 8.2 Hz, 1H), 7.44 (br s, 1H), 7.15 (d, J = 8.2 Hz, 1H), 4.86 (d, J = 1.8 Hz, 2H), 3.94 (s, 3H), 2.58 (t, J = 1.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 152.3, 150.2, 131.1, 126.3, 112.8, 109.7, 77.7, 76.9, 56.8, 56.2.

1-(3-allyl-4-propargyloxyphenyl)ethanone *(**1c**)*: White solid; m.p. 47–48 °C; yield 84%; R_f = 0.19; (hexane-EtOAc 9:1 v/v); IR ($CHCl_3$): 3962, 3502, 3293, 3078, 2920, 2579, 2122, 2039, 1846, 1682, 1639, 1600,1496, 1454, 1424, 1360, 1318, 1267, 1190, 1132,1077, 1023, 979, 924, 814, 682, 657, 595, 579 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.85 (dd, J = 8.6, 2.0 Hz, 1H), 7.80 (d, J = 2.0 Hz, 1H), 7.00 (d, J = 8.6 Hz, 1H), 6.06–5.86 (m, 1H), 5.10–5.06 (m, 2H), 4.78 (d, J = 2.1 Hz, 2H), 3.42 (br d, J = 6.6 Hz, 2H), 2.55–2.54 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 159.1, 135.9, 130.8, 130.4, 129.4, 128.6, 116.2, 111.1, 78.0, 76.0, 56.0, 34.2, 26.4; Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.48; H, 6.59; found: C, 78.52; H, 6.62%.

3-Azidopyridine *(**4**)*

(2.00 g, 21.2 mmol) was dissolved in a solution of conc. H_2SO_4 (2.4 mL) and H_2O (14 mL). The resulting solution was cooled to 0 °C, and a solution of $NaNO_2$ (1.76 g, 25.6 mmol) in H_2O (10 mL) was added dropwise with stirring. The solution was stirred at this temperature for a further 15 min, whereupon a solution of NaN_3 (2.34 g, 36.0 mmol) in H_2O (8 mL) was added with vigorous stirring. The mixture was stirred for 1 h at 0 °C, then overnight at room temperature. The reaction mixture was basified with freshly saturated Na_2CO_3 solution and extracted with CH_2Cl_2 (3 × 30 mL). The combined extracts were washed with H_2O (50 mL), dried over $MgSO_4$, and the solvent removed in vacuo to provide 3-azidopyridine (**4**) (1.92 g, 75%), which was used in the next step without additional purification.[23]

General procedure for the synthesis of the 4-O-methyltriazolylphenylaldehyde/ketone derivatives **2a**, *and* **3a–b**

A mixture of 3-methoxy-4-*O*-propargylbenzaldehyde (**1b**) or 3-allyl-4-*O*-propargylacetophenone (**1c**) (0.582 g, 3.06 mmol, 1.00 equiv.), azide derivative **3** or **4**, **5**, (0.625 g, 3.69 mmol, 1.10 equiv.), $CuSO_4{\cdot}5H_2O$ (0.267 g, 1.07 mmol, 0.35 equiv.) and sodium ascorbate (0.133 g, 0.67 mmol, 0.20 equiv.) was charged with freshly prepared solution of *t*-BuOH/H_2O (1:1; 10 mL). The heterogeneous mixture was stirred vigorously for 15–26 h at room temperature. The progress of reaction was monitored by TLC, using a mixture of hexane-EtOAc 7:3. After completion of the reaction, the mixture was poured into brine or NH_4Cl solution and extracted with EtOAc (3 × 40 mL). The organic layer was washed with cold water, dried over anhydrous Na_2SO_4, filtered and evaporated under reduced pressure to afford a crude product. This was purified by column chromatography on silica gel using hexane-EtOAc mixture of increasing gradient to give **2a**, **3a**, or **3b**.

3-Methoxy-4-[{1-(naphthalen-1-yl)-1H-1,2,3-triazol-4-yl} methoxy]benzaldehyde *(**2a**)*: Colorless solid; m.p. 127–128 °C; yield 88%; R_f = 0.22; (hexane-EtOAc 7:3 v/v); IR ($CHCl_3$): 3143, 3060, 2939, 2834, 1681, 1587, 1508, 1465, 1425, 1388, 1339, 1267, 1235, 1159, 1136, 1043, 1019,

999, 951, 864, 802, 773, 731, 701, 643, 591, 571 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.86 (s, 1H), 8.07 (s, 1H), 8.03–7.86 (m, 2H), 7.77–7.38 (m, 7H), 7.33 (s, 1H), 5.53 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 190.9, 153.0, 150.0, 143.2, 134.1, 133.5, 130.9, 130.8, 128.6, 128.5, 128.0, 127.1, 126.7, 125.9, 125.0, 123.6, 122.2, 112.8, 109.4, 63.0, 56.0; Anal. Calcd for $C_{21}H_{17}N_3O_3$: C, 70.18; H, 4.77; N, 11.69; found: C, 70.51; H, 4.67; N, 11.42%.

1-[3-allyl-4-{(1-Benzyl-1H-1,2,3-triazol-4-yl)methoxy}phenyl]ethanone (**3a**): White solid; m.p. 100–102 °C; yield 86%; R_f = 0.41; (hexane-EtOAc 2:3 v/v); IR ($CHCl_3$): 3137, 3064, 2913, 2846, 1673, 1599, 1498, 1425, 1358, 1263, 1131, 1002, 816, 736 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (d, *J* = 8.6 Hz, 1H), 7.78 (s, 1H), 7.50 (s, 1H), 7.39–7.37 (m, 3H), 7.32–7.24 (m, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 5.96–5.86 (m, 1H), 5.54 (s, 2H), 5.27 (s, 2H), 5.00 (br s, 1H), 4.97 (br d, *J* = 8.4 Hz, 1H), 3.37 (d, *J* = 6.5 Hz, 2H), 2.54 (s, 3H).^{13}C NMR (100 MHz, $CDCl_3$): δ 197.0, 159.8, 144.2, 136.1, 134.4, 130.6, 130.3, 129.2, 129.0 (2C), 128.9 (2C), 128.8, 128.1, 122.6, 116.1, 110.9, 62.4, 54.3, 34.4, 26.4; Anal. Calcd for $C_{21}H_{21}N_3O_2$: C, 72.60; H, 6.09; N, 12.10; found: C, 72.65; H, 5.79; N, 11.95%.

1-[3-allyl-4-{(1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl) methoxy}phenyl]ethanone (**3b**): White solid; m.p. 97–98 °C; yield 71%; R_f = 0.22; (hexane-EtOAc 2:3 v/v); IR ($CHCl_3$): 3417, 3137, 3076, 3008, 1673, 1598, 1498, 1359, 1263, 1248, 1130, 1018, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.99 (br s, 1H), 8.68 (d, *J* = 4.6 Hz, 1H), 8.13 (br s, 1H), 8.11–8.10 (m, 1H), 7.82 (dd, *J* = 8.6, 2.1 Hz, 1H), 7.76 (d, *J* = 2.1 Hz, 1H), 7.48 (dd, *J* = 8.2, 4.6 Hz, 1H), 7.04 (d, *J* = 8.6 Hz, 1H), 5.94 (ddt, *J* = 16.8, 10.7, 6.6 Hz, 1H), 5.36 (s, 2H), 5.06–5.03 (m, 1H), 5.01 (dd, *J* = 10.7, 1.5 Hz, 1H), 3.39 (d, *J* = 6.6 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 197.2, 159.8, 150.4, 145.3, 141.8, 136.2, 133.7, 130.9, 130.7, 129.3, 129.2, 128.4, 124.5, 121.1, 116.4, 111.1, 62.3, 34.5, 26.6; Anal. Calcd for $C_{19}H_{18}N_4O_2$: C, 68.25; H, 5.43; N, 16.76; found: C, 68.58; H, 5.44; N, 16.33%.

General procedure for the synthesis of 4-O-methyltriazolyl-chalcone derivatives **4a–e**

A solution of KOH (0.5 g, 7.24 mmol) in H_2O (5 mL) was slowly added dropwise to a mixture of substituted aryl/heteroaryl-carbaldehyde (2 mmol) and 3-allyl-4-*O*-methyl-triazolyl-acetophenone (2 mmol) dissolved in EtOH (10–20 mL). The reaction mixture was stirred at 40–42 °C for 39–80 h, under a nitrogen atmosphere and monitored by TLC. The precipitate formed was filtered, dried and purified by silica gel column chromatography using a mixture hexane-EtOAc to provide **4a**–**e**, respectively.

(E)-1-(3-allyl-4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy) phenyl)-3-(4-(allyloxy)-3-methoxyphenyl)prop-2-en-1-one (**4a**): Yellow solid; m.p. 115–117 °C; yield 90%; R_f = 0.58; (hexane-EtOAc 3:2 v/v); IR ($CHCl_3$): 3137, 3070, 2937, 1653, 1598, 1509, 1463, 1423, 1310, 1255, 1165, 1135, 1032, 997, 923, 804, 725, 554 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 8.03 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.97 (d, *J* = 2.2 Hz, 1H), 7.85 (d, *J* = 15.6 Hz, 1H), 7.64 (s, 1H), 7.54–7.50 (m, 1H), 7.50–7.45 (m, 3H), 7.45–7.34 (m, 2H), 7.32–7.23 (m, 2H), 7.17 (d, *J* = 8.6 Hz, 1H), 7.01 (d, *J* = 8.3 Hz, 1H), 6.20 (ddd, *J* = 20.4, 10.6, 5.4 Hz, 1H), 6.05 (ddt, *J* = 18.2, 9.5, 6.6 Hz, 1H), 5.65 (s, 2H), 5.54 (dd, *J* = 20.4, 1.1 Hz, 1H), 5.43 (dd, *J* = 10.6, 1.1 Hz, 1H), 5.40 (s, 2H), 5.12 (br d, *J* = 0.9 Hz, 1H), 5.10–5.08 (m, 1H), 4.78 (d, *J* = 5.4 Hz, 2H), 4.06 (s, 3H), 3.51 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.9, 159.6, 150.3, 149.6, 144.2, 144.1, 136.2, 134.4, 132.8, 131.6, 130.6, 129.2 (2C), 129.1, 128.9, 128.8, 128.3, 128.1 (2C), 122.7, 122.6, 120.0, 118.4, 116.0, 113.0, 111.1, 110.7, 69.8, 62.4, 56.1, 54.3, 34.4; Anal. Calcd for $C_{32}H_{31}N_3O_4$: C, 73.68; H, 5.99; N, 8.06; found: C, 73.44; H, 5.93; N, 7.74%.

(E)-1-(3-allyl-4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy) phenyl)-3-(1-(3,5-dichlorophenyl)-1H-pyrrol-2-yl)prop-2-en-1-one (**4b**): Pale brown solid; m.p. 128–130 °C; yield 88%; R_f = 0.26; (hexane-EtOAc 7:3 v/v); IR ($CHCl_3$): 3476, 3069, 1650, 1600, 1589, 1573, 1497, 1464, 1433, 1354, 1320, 1272, 1252, 1136, 1049, 1003, 917, 858, 807, 725, 681, 575 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.83 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.76 (d, *J* = 2.2 Hz, 1H), 7.52 (d, *J* = 15.3 Hz, 1H), 7.50 (br s, 1H), 7.43 (br t, *J* = 1.8 Hz, 1H), 7.38–7.37 (m, 1H), 7.36 (d, *J* = 1.8 Hz, 2H), 7.31–7.24 (m, 4H), 7.21 (d, *J* = 15.3 Hz, 1H), 7.03 (d, *J* = 8.6 Hz, 1H), 6.98–6.92 (m, 2H), 6.41–6.38 (m, 1H), 5.91 (ddt, *J* = 17.5, 11.0, 6.6 Hz, 1H), 5.53 (s, 2H), 5.27 (s, 2H), 4.99 (br s, 1H), 4.98–4.94 (m, 1H), 3.37 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.4, 159.8, 144.5, 141.0, 136.4, 136.0 (2C), 134.7, 131.7, 130.9, 130.7, 129.4 (2C), 129.3, 129.1, 128.9 (2C), 128.6, 128.3, 127.2, 125.3, 122.8, 118.9 (2C), 116.2 (2C), 113.9, 111.7, 111.3, 62.6, 54.5, 34.7; Anal. Calcd for $C_{32}H_{26}Cl_2N_4O_2$: C, 67.49; H, 4.60; N, 9.84; found: C, 67.35; H, 4.63; N, 9.61%.

(E)-1-(3-allyl-4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy) phenyl)-3-(1-(4-(trifluoromethyl)phenyl)-1H-pyrrol-2-yl) prop-2-en-1-one (**4c**): Pale yellow solid; m.p. 140–142 °C; yield 80%; R_f = 0.17; (hexane-EtOAc 7:3 v/v); IR ($CHCl_3$): 3098, 3068, 2936, 1650, 1600, 1536, 1498, 1454, 1357, 1326, 1299, 1249, 1170, 1129, 1067, 1036, 1003, 918, 888, 850, 818, 728, 629, 604, 460 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.82 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.78 (d, *J* = 2.2 Hz, 1H), 7.76 (d, *J* = 3.6 Hz, 2H), 7.58 (d, *J* = 15.4 Hz, 1H), 7.50 (s, 1H), 7.46 (d, *J* = 8.4 Hz, 2H), 7.39–7.35 (m, 3H), 7.28 (br d, *J* = 2.5 Hz, 1H), 7.24 (d, *J* = 15.4 Hz, 1H), 7.03 (d, *J* = 3.6 Hz, 2H), 7.02 (d, *J* = 8.6 Hz, 1H), 6.98 (dd, *J* = 3.7, 1.4 Hz, 1H), 6.43 (dd, *J* = 3.7, 3.1 Hz, 1H), 5.96–5.85 (m, 1H), 5.54 (s, 2H), 5.27 (s, 2H), 4.99 (br s, 1H), 4.98–4.94 (m, 1H), 3.37 (d, *J* = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.0, 159.6, 144.2, 141.9, 136.1, 134.4, 131.8, 131.5, 130.7, 130.4 (2C), 129.2 (2C), 129.1, 128.9, 128.7, 128.1 (2C), 126.9, 126.8, 126.6 (2C), 126.5 (q, *J* = 272.7 Hz, CF_3), 125.1, 122.5, 118.3, 116.0, 113.5, 111.4, 111.1, 62.4, 54.3, 34.4; ^{19}F NMR (376 MHz, $CDCl_3$): δ −62.88 (s, 3F, CF_3); Anal. Calcd for $C_{33}H_{27}F_3N_4O_2$: C, 69.71; H, 4.79; N, 9.85; found: C, 69.32; H, 4.69; N, 9.51%.

(E)-1-(3-allyl-4-((1-benzyl-1H-1,2,3-triazol-4-yl)methoxy) phenyl)-3-(1-(p-tolyl)-1H-pyrrol-2-yl)prop-2-en-1-one (**4d**): Pale yellow solid; m.p. 100–101 °C; yield 68%; R_f = 0.57; (hexane-EtOAc 13:7 v/v); IR ($CHCl_3$): 3132, 3065, 2975, 2923, 2874, 1648, 1600, 1586, 1516, 1498, 1455, 1359, 1326, 1309, 1248, 1136, 1038, 1003, 917, 824, 728, 629, 606, 570, 465 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (dd, J = 8.5, 1.9 Hz, 1H), 7.74 (d, J = 1.9 Hz, 1H), 7.59 (d, J = 15.4 Hz, 1H), 7.49 (br s, 1H), 7.38–7.35 (dd, J = 5.5, 4.1 Hz, 3H), 7.29–7.25 (br t, J = 6.3 Hz, 4H), 7.20 (d, J = 8.2 Hz, 2H), 7.15 (d, J = 15.4 Hz, 1H), 7.00 (d, J = 8.5 Hz, 2H), 6.93 (br d, J = 3.2 Hz, 1H), 6.38–6.35 (m, 1H), 5.96–5.84 (m, 1H), 5.53 (s, 2H), 5.26 (s, 2H), 4.99 (br s, 1H), 4.97–4.94 (m, 1H), 3.36 (d, J = 6.5 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3, 159.4, 144.3, 138.1, 136.5, 136.2, 134.4, 132.7, 131.8, 130.8, 130.4, 130.0 (2C), 129.2 (2C), 128.9, 128.8, 128.6, 128.1 (2C), 127.5, 126.3 (2C), 122.5, 117.4, 115.9, 112.9, 111.0, 110.5, 62.4, 54.3, 34.4, 21.1; Anal. Calcd for $C_{33}H_{30}N_4O_2$: C, 77.02; H, 5.88; N, 10.89; found: C, 77.41; H, 5.78; N, 10.82%.

(E)-1-(3-allyl-4-((1-(pyridin-3-yl)-1H-1,2,3-triazol-4-yl) methoxy)phenyl)-3-(1-(3,5-dichlorophenyl)-1H-pyrrol-2-yl)prop-2-en-1-one (**4e**): Yellow solid; m.p. 160–162 °C; yield 90%; R_f = 0.33; (hexane-EtOAc 3:2 v/v); IR ($CHCl_3$): 3126, 1586, 1460, 1401, 1351, 1250, 1124, 1046, 806 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 9.01 (d, J = 2.4 Hz, 1H), 8.76–8.69 (m, 1H), 8.14 (ddd, J = 8.3, 2.4, 1.5 Hz, 1H), 8.10 (br s, 1H), 7.86 (dd, J = 8.6, 2.1 Hz, 1H), 7.79 (d, J = 2.1 Hz, 1H), 7.52 (d, J = 15.4 Hz, 1H), 7.50 (br t, J = 3.9 Hz, 2H), 7.43 (br t, J = 1.8 Hz, 1H), 7.25 (d, J = 1.8 Hz, 1H), 7.20 (d, J = 15.4 Hz, 1H), 7.08 (d, J = 8.6 Hz, 1H), 6.98–6.92 (m, 2H), 6.41–6.37 (m, 1H), 5.99 (ddt, J = 16.7, 10.3, 6.4 Hz, 1H), 5.40 (br s, 2H), 5.09–5.05 (m, 1H), 5.03 (br d, J = 1.6 Hz, 1H), 3.45 (d, J = 6.4 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 188.3, 159.6, 150.4, 145.4, 141.8, 140.9, 136.3, 136.0 (2C), 133.8, 131.9, 131.8, 130.9, 130.8, 129.3, 129.0, 128.6, 128.4, 127.2, 125.3, 124.5, 121.0, 118.8 (2C), 116.4, 113.9, 111.7, 111.2, 62.4, 34.7; Anal. Calcd for $C_{30}H_{23}Cl_2N_5O_2$: C, 64.76; H, 4.17; N, 12.59; found: C, 63.90; H, 4.37; N, 12.12%.

Biological studies

Evaluation of the antioxidant activity: DPPH radical scavenging assay. The free radical scavenging activity of the compounds was evaluated as described by Mensor et al.[37] Briefly, the test samples were dissolved in pure dimethylsulfoxide (DMSO, Sigma-Aldrich, St Quentin Fallavier, France) and mixed with a DPPH (Sigma) solution (0.3 mM) in EtOH. Various concentrations (1, 5, 10, 50, 100, 250, 500, and 1000 µg/mL) of each sample were tested. After 30 min at room temperature, the absorbance was measured at 517 nm and converted into percentage of antioxidant activity. Ascorbic acid (vitamin C) was used as a standard control. Each assay was repeated thrice in duplicate and the results recorded as the mean of the six experiments (Table 1). The inhibition ratio (%) was calculated as follows: % inhibition = [(Absorbance of control − Absorbance of test sample)/Absorbance of control] × 100. The IC_{50} value is the concentration of a sample required to scavenge 50% of the DPPH free radical and was calculated from a calibration curve by linear regression.[38] One-way analysis of variance (ANOVA) at the 95% confidence level was used for statistical analysis.

Declaration of conflicting interests

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Supplemental material

Supplemental material for this article is available online.

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