Synthesis of paeonol derivatives linked with 1,2,3-triazole moiety by 1,3-dipolar huisgen-cylcoaddition reaction

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Paeonol is a major phenolic component isolated from Moutan Cortex, a traditional Chinese medicine. An efficient synthesis of paeonol derivatives linked to a 1,2,3-triazole moiety using a 1,3-dipolar Huisgen-cycloaddition reaction is described. The paeonol derivatives are regioselectively obtained in good yields under mild conditions using $Cu(OAc)_2{\cdot}H_2O$/sodium ascorbate as a catalyst system, and *t*-BuOH/H_2O (1:1, v/v) as a co-solvent.

Keywords: paeonol, Huisgen cycloaddition, $Cu(OAc)_2{\cdot}H_2O$/sodium ascorbate, ultrasound irradiation

Paeonol (2′-hydroxyl-4′-methoxyacetophenone), the major phenolic component isolated from Moutan Cortex, a traditional Chinese medicine widely used in clinical treatment of inflammatory diseases, has various bioactivities such as antineoplastic activity,[1–4] anti-inflammatory,[5,6] antioxidant,[7] and antithrombotic activities.[8] More recent studies have shown that paeonol could increase levels of cortical cytochrome oxidase and vascular actin and improve behaviour in the rat model of Alzheimer's disease (AD), which indicated that paeonol is a possible therapeutic measure in slowing down the pathogenic processes associated with AD.[9] Efforts to improve the pharmacological and biological activities of paeonol have led to the development of its derivatives by appropriate modification of paeonol as mentioned elsewhere.[10–13]

The 1,2,3-triazole moiety is stable to metabolic degradation and capable of hydrogen bonding, which could be favourable in binding of biomolecular targets as well as in increasing solubility.[14] Moreover, 1,2,3-triazoles are attractive linker units which could connect two pharmacophores for constructing bioactive and functional molecules.[15–17] Compounds containing a 1,2,3-triazole ring show various biological properties, such as anti-HIV,[18] anti-microbial,[19] and anti-allergic activities.[20] A simple, quick and useful approach to introducing the 1,2,3-triazole moiety is using the copper(I)-catalysed azide–alkyne cycloaddition (CuAAC reaction).[21,22]

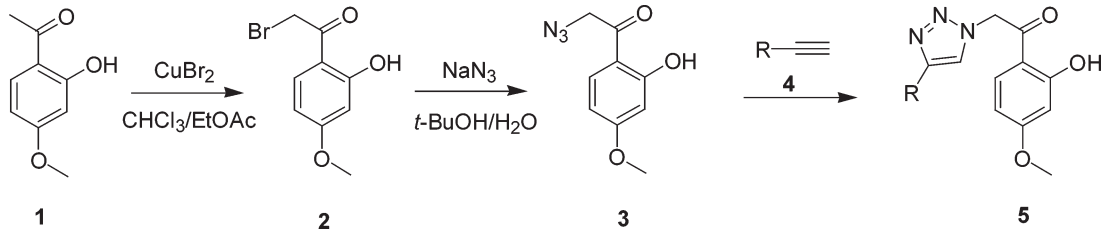
As far as we know, the modification of introducing 1,2,3-triazole groups into paeonol has not been previously reported. In order to maintain the main chemical structure of paeonol, the hydrogen atom in the methyl group of paeonol was replaced by an azide group to form the intermediate, azide-paeonol. The main targets of this work was to find efficient conditions for the 1,3-dipolar cycloaddition reaction between azide-paeonol and terminal alkynes and synthesise a series of paeonol derivatives linked with 1,2,3-moiety. In our previous works,[23,24] we found that ultrasound irradiation could greatly accelerate the CuAAC reaction at room temperature. In the work described here, a series of paeonol derivatives linked with 1,2,3-triazoles were synthesised using the CuAAC reaction between azide-paeonol and terminal alkynes, which could be successively carried out in *t*-BuOH/H_2O (1:1, v/v) using $Cu(OAc)_2{\cdot}H_2O$/sodium ascorbate as the catalyst system under the help of ultrasound irradiation at room temperature.

Results and discussion

The title compounds were synthesised in three steps and the synthetic routine is shown in Scheme 1. Paeonol (**1**) was firstly selectively α-brominated by $CuBr_2$ in $CHCl_3$/EtOAc at reflux to form compound **2**,[25] which could be converted to azide-paeonol (**3**)[26] by reacting with sodium azide in DMF at 0 °C. Then **3** was reacted with various kinds of terminal alkynes **4**[27–31] to form the title compounds (**5**). The CuAAC reaction is a key step in the pathway for preparation of the target molecules. The 1,3-dipolar cycloaddition between **3** and propargyl phenyl ether was chosen as a model reaction (Table 1) to optimise the CuAAC reaction conditions. Considering the solubility of the organic reactants and the inorganic copper salt catalyst, *t*-BuOH/H_2O (1:1, v/v) was chosen as the reaction solvent. The model reaction was carried out using compound **3** (0.1 mmol) and propargyl phenyl ether (0.1 mmol) in the presence of 10 mol% Cu(I) in *t*-BuOH/H_2O (3mL, 1:1, v/v) at room temperature.

The following experiments were designed to investigate the acceleration effect of ultrasound on the model reaction. The model reaction was performed using $Cu(OAc)_2{\cdot}H_2O$/sodium ascorbate as the catalyst with a magnetic stirring in the absence of ultrasound irradiation and in the presence of ultrasound irradiation (Table 1). Tracked by TLC, 36 hours was taken to complete the reaction in the absence of ultrasound irradiation in 94% yield at room temperature, whereas only 25 minutes was needed in the presence of ultrasound irradiation in almost the same yield, indicating that the cycloaddition rate was greatly accelerated by ultrasound. The outcome is consistent with the precious work.[23,24]

Different copper catalyst systems (10 mol%) were screened by the model reaction in *t*-BuOH/water (1:1, v/v) under continuous sonication at room temperature. As shown in Table 1, the best catalytic efficiency was observed for $Cu(OAc)_2{\cdot}H_2O$/sodium ascorbate among the tested catalysts. Most notably, the



Scheme 1 Synthetic routine of the title compounds.

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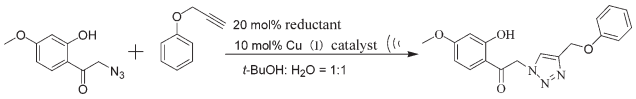
Table 1 Screening of catalysts for the model reaction in *t*-BuOH/H_2O under the ultrasonic irradiation [a]



Copper salts	Reductant	Time/min	Yield/%[b]
$Cu(OAc)_2·H_2O$	Sodium ascorbate	25	95
$Cu(OAc)_2·H_2O$[c]	Sodium ascorbate	36 (h)	94
$CuSO_4·5H_2O$	Sodium ascorbate	40	83
$CuBr_2$	Sodium ascorbate	70	68
$CuCl_2·2H_2O$	Sodium ascorbate	80	67
CuI	–	55	86
CuBr	–	55	71
CuCl	–	55	85

[a] Reaction conditions: 0.1 mmol azide, 0.1 mmol terminal alkyne, 30 °C.
[b] Isolated yield.
[c] In absence of ultrasound irradiation condition.

1,3-dipolar cycloaddition reaction catalysed by $Cu(OAc)_2·H_2O$/sodium ascorbate was completed in 25 minutes in 95% yield (Table 1). In comparison to $Cu(OAc)_2·H_2O$/sodium ascorbate, lower catalytic efficiencies were observed for other catalysts, among which $CuCl_2·2H_2O$/sodium ascorbate showed the lowest (67% yield) in 80 minutes and $CuSO_4·5H_2O$/sodium ascorbate the highest (83% yield). Therefore, $Cu(OAc)_2·H_2O$/sodium ascorbate was chosen as the catalyst.

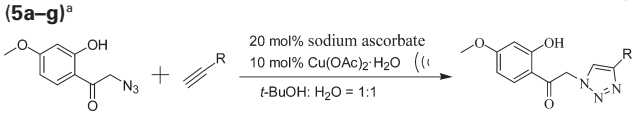
Under the optimised reaction conditions mentioned above, more paeonol derivatives linked with 1,2,3-triazoles ring were synthesised by using various substituted terminal alkynes. As can be seen from Table 2, in all cases, a series of new paeonol derivatives linked with 1,2,3-triazoles moiety were obtained in good yields.

In summary, a highly efficient synthesis of paeonol derivatives linked with 1,2,3-triazole in *t*-BuOH/H_2O was developed by using $Cu(OAc)_2·H_2O$/sodium ascorbate as the catalyst system with the help of ultrasound irradiation.

Experimental

All the chemicals were obtained from Tianjin Kermel Chemical Reagent Co., Ltd. and used as received. All melting points were determined on a YUHUA X-3 melting point apparatus and are reported uncorrected. Sonication was performed in a Kunshan KQ-250B ultrasonic cleaner with a frequency of 40 kHz and a power 150 W. The reaction flasks were located in the maximum energy area in the cleaner, and the temperature of the reaction solution was controlled at 30 °C by the addition or removal of the bath water. IR spectra were recorded on a Bio-rad FTS-40. ^{1}H, ^{13}C spectra were recorded on a Bruker Avance 400 MHz spectrometer operating at 400.13 and 100.61 MHz, respectively. NMR spectra were recorded in $CDCl_3$ or DMSO-d_6 at room temperature (20 ± 2 °C). ^{1}H and ^{13}C chemical shifts are quoted in parts per million downfield from TMS. ESI MS were recorded on a Bruker Esquire 3000. High-resolution mass spectra (HR MS) were performed on a MicrOTOF-Q II mass spectrometer with an ESI source (Waters, Manchester, UK).

Table 2 Paeonol derivatives linked with 1,2,3-triazole moiety (**5a–g**)[a]



Entry	R	Yield/%[b]
5a	4-ClC_6H_5.O.CH_2.	85
5b	3-$CH_3C_6H_5$.O.CH_2.	86
5c	C_3H_5.	69
5d	4-$CH_3CH_2CH_2C_6H_5$.	89
5e	4-$CH_3CH_2C_6H_5$.	89
5f	3-$NH_2C_6H_5$.	88
5g	4-$CH_3C_6H_5$.	88

[a] Reaction conditions: 0.3 mmol azide, 0.3 mmol terminal alkyne, 30 °C.
[b] Isolated yields.

*Synthesis of the target molecules (**5a–g**); general procedure*

Substituted terminal alkyne (0.3 mmol) and **3** (0.3 mmol) were suspended in *t*-BuOH/H_2O (3 mL, 1:1, v/v) in a 10 mL round-bottomed flask followed by $Cu(OAc)_2·H_2O$ (10 mol%) and sodium ascorbate (20 mol%). The mixture was sonicated in a laboratory ultrasonic cleaning bath. After completion of the reaction, as indicated by TLC, the reaction mixture was diluted with 10 mL water, and the precipitate was collected and washed with cold water and saturated ammonium chloride as a grey solid. The crude product was purified by column chromatography on silica gel using ethyl acetate /petroleum ether (2:1, v/v) as eluent.

1-(2-Hydroxy-4-methoxyphenyl)-2-{4-[(4-chlorophenoxy)methyl]-1H-1,2,3-triazol-1-yl}ethan-1-one (**5a**): White solid, m.p. 156–158 °C, IR (KBr, ν_{max}): 2939, 2845, 1631, 1578, 1509, 1202, 1132, 823, 807, 777 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 3.87 (s, 3H, CH_3), 5.23 (s, 2H, CH_2), 5.80 (s, 2H, CH_2), 6.47 (d, J = 2.0 Hz, 1H, ArH), 6.52 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H, ArH), 6.92 (d, J = 12 Hz, 2H, ArH), 7.23 (d, J = 12 Hz, 2H, ArH), 7.64 (d, J = 8.0 Hz, 1H, ArH), 7.78 (s, 1H, CH), 11.90 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 54.3, 55.8, 62.2, 101.2, 108.9, 111.1, 116.1, 124.8, 126.2, 129.4, 130.3, 144.2, 156.8, 165.8, 167.2, 192.9. ESI MS *m/z*: 374 [M + H]$^+$. HR MS *m/z*: 374.0904 [M + H]$^+$, (Calcd for $C_{18}H_{17}ClN_3O_4$ 374.0908).

1-(2-Hydroxy-4-methoxyphenyl)-2-{4-[(3-methylphenoxy)methyl]-1H-1,2,3-triazol-1-yl}ethan-1-one (**5b**): White solid, m.p. 116–118 °C, IR (KBr, ν_{max}): 2946, 2920, 2843, 1638, 1625, 1583, 1504, 1205, 1132, 831, 801, 748 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.33 (s, 3H, CH_3), 3.87 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 5.79 (s, 2H, CH_2), 6.47 (d, J = 2.4 Hz, 1H, ArH), 6.52 (d, J = 8.0 Hz, 1H, ArH), 6.79 (t, J = 8.0 Hz, 3H, ArH), 7.16 (t, J = 8.0 Hz, 1H, ArH), 7.64 (d, J = 8.0 Hz, 1H, ArH), 7.78 (s, 1H, CH), 11.92 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 54.3, 55.8, 61.9, 101.2, 108.8, 111.1, 111.6, 115.6, 122.1, 129.3, 130.4, 139.6, 158.2, 165.7, 167.2, 193.1. ESI MS *m/z*: 354 [M + H]$^+$. HR MS *m/z*: 354.1462 [M + H]$^+$, (Calcd for $C_{19}H_{20}N_3O_4$ 354.1454).

2-(4-Cyclopropyl-1H-1,2,3-triazol-1-y)-1-(2-hydroxy-4-methoxyphenyl)-ethan-1-one (**5c**): White solid, m.p. 148–150 °C, IR (KBr, ν_{max}): 2951, 2826, 2850, 1643, 1623, 1572, 1518, 1185, 819 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.89 (m, 2H, CH_2), 0.95 (m, 2H, CH_2), 1.96 (m, 1H, CH), 3.87 (s, 3H, CH_3), 5.72 (s, 2H, CH_2), 6.46 (d, J = 2.4 Hz, 1H, ArH), 6.51 (dd, J_1 = 2.4 Hz, J_2 = 8.0 Hz, 1H, ArH), 7.40 (s, 1H, CH) 7.64 (d, J = 8.0 Hz, 1H, ArH), 11.96 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 6.7, 7.8, 54.2, 55.7, 101.2, 108.8, 111.2, 121.7, 130.5, 150.6, 165.7, 167.1, 193.5. ESI MS *m/z*: 274 [M + H]$^+$. HR MS *m/z*: 274.1190 [M + H]$^+$, (Calcd for $C_{14}H_{16}N_3O_3$ 274.1192).

1-(2-Hydroxy-4-methoxyphenyl)-2-[4-(4-propylphenyl)-1H-1,2,3-triazol-1-yl]ethan-1-one (**5d**): White solid, m.p. 163–164 °C, IR (KBr, ν_{max}): 2950, 2867, 2843, 1633, 1581, 1507, 1464, 1213, 829, 813 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.94 (t, J = 6.0 Hz, 3H, CH_3), 1.64 (m, 2H, CH_2), 2.60 (t, J = 8.0 Hz, 2H, CH_2), 3.87 (s, 3H, CH_3), 5.82 (s, 2H, CH_2), 6.47 (d, J = 8.0 Hz, 1H, ArH), 6.52 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H, ArH), 7.24 (s, 1H, CH), 7.26 (s, 1H, CH), 7.67 (d, J = 8.0 Hz, 1H, ArH), 7.76 (d, J = 8.0 Hz, 2H, ArH), 7.89 (s, 1H, CH), 11.97 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 13.8, 24.4, 37.8, 54.3, 55.7, 101.2, 108.8, 111.2, 121.2, 125.7, 127.8, 128.9, 130.4, 142.9, 148.3, 165.8, 167.2, 193.2. ESI MS *m/z*: 352 [M + H]$^+$. HR MS *m/z*: 352.1662 [M + H]$^+$, (Calcd for $C_{20}H_{22}N_3O_3$ 352.1661).

2-[4-(4-Ethylphenyl)-1H-1,2,3-triazol-1-yl]-1-(2-hydroxy-4-methoxyphenyl)ethan-1-one (**5e**): White solid, m.p. 168–170 °C, IR (KBr, ν_{max}): 2934, 2843, 1622, 1566, 1500, 1460, 1199, 847, 813 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.24 (t, J = 8.0 Hz, 3H, CH_3), 2.66 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 2H, CH_2), 2.60 (t, J = 8.0 Hz, 2H, CH_2), 3.87 (s, 3H, CH_3), 5.81 (s, 2H, CH_2), 6.47 (d, J = 2.4 Hz, 1H, ArH), 6.52 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H, ArH), 7.26 (s, 1H, CH), 7.28 (s, 1H, CH), 7.67 (d, J = 8.0 Hz, 1H, ArH), 7.77 (d, J = 8.0 Hz, 2H, ArH), 7.89 (s, 1H, CH), 11.97 (s, 1H, OH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 28.6, 54.3, 55.7, 101.2, 108.8, 111.2, 121.2, 125.8, 127.8, 128.3, 130.4, 144.5, 148.3, 165.8, 167.2, 193.2. ESI MS *m/z*: 338 [M + H]$^+$. HR MS *m/z*: 338.1500 [M + H]$^+$, (Calcd for $C_{19}H_{20}N_3O_3$ 338.1505).

1-(2-Hydroxy-4-methoxyphenyl)-2-[4-(3-aminophenyl)-1H-1,2,3-triazol-1-yl]ethan-1-one (**5f**): White solid, m.p. 130–132 °C, IR (KBr, ν_{max}): 2939, 1624, 1588, 1571, 1509, 1460, 1200, 843, 814 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.82 (s, 3H, CH_3), 5.21 (s, 2H, NH_2), 6.02 (s, 2H, NH_2), 6.51 (m, 2H, ArH), 6.58 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H, ArH), 6.92 (d, J = 8.0 Hz, 1H, ArH), 7.04 (m, 2H, ArH), 7.87 (d, J = 8.0 Hz, 1H, ArH), 8.33 (s, 1H, CH), 11.57 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 56.1, 57.3, 101.5, 108.0, 110.9, 113.4, 113.6, 114.0, 123.2, 129.8, 131.7, 132.5, 147.3, 149.5, 163.1, 166.2, 193.5. ESI MS *m/z*: 325 [M + H]$^+$. HR MS *m/z*: 325.1297 [M + H]$^+$, (Calcd for $C_{17}H_{17}N_4O_3$ 325.1301).

1-(2-Hydroxy-4-methoxyphenyl)-2-[4-(4-methylphenyl)-1H-1,2,3-triazol-1-yl]ethan-1-one (**5g**): White solid, m.p. 180–182 °C, IR (KBr, ν_{max}): 2939, 2843, 1624, 1578, 1498, 1201, 845, 808 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.32 (s, 3H, CH_3), 3.82 (s, 3H, CH_3), 6.04 (s, 2H, CH_2), 6.54 (d, J = 4.0 Hz, 1H, ArH), 6.58 (dd, J_1 = 4.0 Hz, J_2 = 8.0 Hz, 1H, ArH), 7.24 (d, J = 8.0 Hz, 2H, CH), 7.72 (d, J = 8.0 Hz, 2H, CH), 7.87 (d, J = 8.0 Hz, 1H, ArH), 8.45 (s, 1H, CH), 11.97 (s, 1H, OH). ^{13}C NMR (100 MHz, DMSO-d_6): δ = 21.3, 56.1, 57.4, 101.5, 108.0, 113.6, 123.2, 125.5, 128.5, 129.9, 132.5, 137.5, 146.7, 163.2, 166.2, 193.4. ESI MS *m/z*: 324 [M + H]$^+$. HR MS *m/z*: 324.1337 [M + H]$^+$, (Calcd for $C_{18}H_{18}N_3O_3$ 324.1348).

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