Synthesis of maleimide derivatives via CuAAC click chemistry and biological evaluation of their antitumor activity against cancer cell lines

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ABSTRACT

A new series of maleimide derivatives bearing the 1,2,3-triazole moiety have been synthesized using the CuAAC reaction and evaluated for their cytotoxicity in vitro against human cervical carcinoma hela cell. The characterization of the target compounds was performed using IR, NMR, MS and HRMS. Most of the tested compounds showed potent activity toward the hela cell line. The most promising compound 6c showed excellent cytotoxicity with 16.7 μM of IC_{50} values. These findings might provide an alternative strategy for the development of novel anticancer agent.

Key words: maleimide derivatives, synthesis, antitumor activity, click chemistry

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INTRODUCTION

Cancer is a prevalent, complex and fatal disease and the search for new anticancer agents has been an active area. Many compounds with maleimide, both natural and synthesized, have good anticancer activity [1-6]. Recently, maleimides such as N-methylmaleimide, N-ethylmaleimide and 3-anilino-4-(3-indolyl) maleimide have attracted the interest of many researchers due to their cytotoxicity toward tumor cell lines through the inhibition of human topoisomerase II[7] or protein kinase C-β[8]. According to our previous study[9,10], compounds containing maleimide ring have the cytotoxic potency *in vitro* against various human cancer cell lines.

Many compounds containing 1,2,3-triazole moiety have good biological activities such as anti-inflammatory[11], anticancer[12,13], and antimicrobial activity[14]. The Cu(I)-catalysed azide-alkyne cycloaddition (CuAAC) reaction is a convenient and regiospecific manner to give disubstituted 1,2,3-triazole triazoles[15,16] and it has been widely applied in drug discovery and medicinal chemistry[17-21]. In order to find more potent compounds possessing antitumor activity, we try to design a series of maleimide derivatives linked with 1,2,3-triazole using the CuAAC reaction. In this paper, we describe the synthesis of this type of compounds and their cytotoxic activity *in vitro* against Hela cell line.

EXPERIMENTAL SECTION

The synthetic strategy for the preparation of the maleimide derivatives was illustrated in Scheme 1.
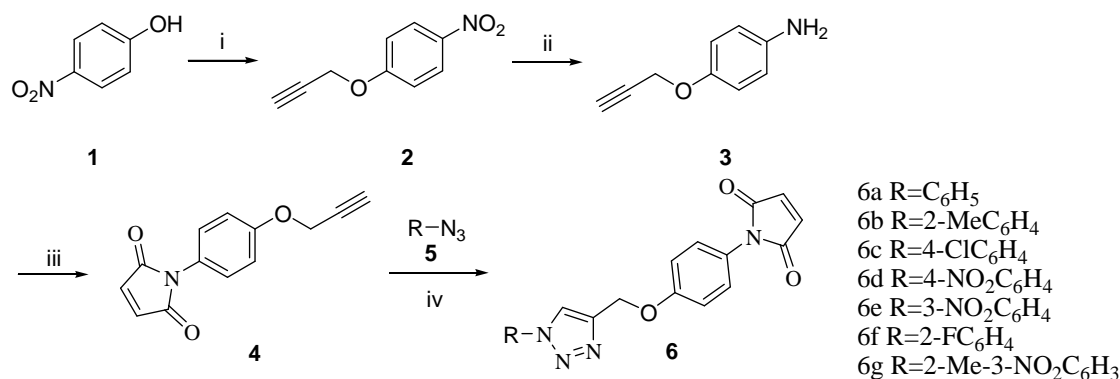
Scheme 1. Synthesis of the target compounds
Reagents and conditions: (i) K₂CO₃, acetone, propargyl bromide, reflux; (ii) Fe, NH₄Cl, C₂H₅OH, reflux; (iii) maleic anhydride, toluene/DMF (4:1), p-toluenesulfonic acid; (iv) C₆H₅COOH, Cu₂O, r.t.

Chemistry

All reagents were obtained from commercial sources and used without further purification unless stated. All reactions were detected by thin layer chromatography (TLC). Melting points were determined by YUHUA X-3 melting point apparatus and are uncorrected. IR spectra were recorded on a Bio-rad FTS-40. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker Avance 400 MHz spectrometer operating at 400.13 and 100.61 MHz, respectively. Chemical shifts are expressed as ppm (δ) referenced to DMSO-d_6 with 2.50 for ^{1}H and 39.50 for ^{13}C. Signals are abbreviated as follows: s, singlet; d, doublet; dd, double of doublets; t, triplet; q, quartet; m, multiplet. Coupling constants (J) are expressed in Hertz (Hz). MS (ESI) were recorded on a Bruker Esquire 3000. High-resolution mass spectra (HRMS) were performed on a MicrOTOF-Q II mass spectrometer with an ESI source (Waters, Manchester, UK).

Procedure for the preparation of 1-nitro-4-(prop-2-ynyloxy)benzene (2)

To a solution of 4-nitrophenol (0.1 mol) and anhydrous K_2CO_3 (0.1 mol) in acetone (100 mL), propargyl bromide (0.12 mol) was added dropwise with stirring at room temperature. The reaction mixture was refluxed for 4 h. After cooling to room temperature, the reaction mixture filtered and the filtrate was evaporated *in vacuo*. The residue was purified by recrystallization from ethanol to get **2** as white powder in 92% yield.

Procedure for the preparation of 4-(prop-2-ynyloxy)benzenamine (3)

Iron powder (0.3 mol) and NH₄Cl (0.3 mol) were added to a solution of compound **2** (0.1 mol) in C_2H_5OH (100 mL). The mixture was refluxed for 2h. After cooling to room temperature, the reaction mixture filtered and the filtrate was extracted with CH_2Cl_2 (3 × 50 mL). The combined extracts were successively washed with water, dried over Na_2SO_4 and concentrated *in vacuo* to provide the crude product **3** in 85% yield which could be used in the next step without further purification.

Procedure for the preparation of 1-(4-(prop-2-ynyloxy)phenyl)-1H-pyrrole-2,5-dione (4)

To a solution of compound **3** (0.1 mol) in toluene (80 mL) and DMF (20 mL), maleic anhydride (0.12 mol) was added and the mixture was stirred at room temperature for 2 h. Then *p*-toluenesulfonic acid (0.01 mol) was added and the solution was refluxed for 4 h. After cooling to room temperature, the mixture was poured into 500 mL of ice water and a yellow precipitate was obtained. After filtration, the precipitate was recrystallized from ethanol to afford yellow crystal in 92 % yield. m.p. 121-123 °C. IR (KBr, v_{max}/cm^{-1}): 3281, 3108, 2115, 1715, 1587, 1512, 1461, 1398, 1295, 1266, 1224, 1181, 1153, 1006, 835, 719, 688, 643, 519. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 7.26 (d, J = 9.2 Hz, 2H), 7.17 (s, 2H), 7.08 (d, J = 9.2 Hz, 2H), 4.84 (s, 2H), 3.61 (s, 1H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.6, 157.0, 135.1, 128.8, 125.2, 115.6, 79.5, 78.9, 56.1.

General procedure for the preparation of 5a-g

Compounds **5a-g** were synthesized according to the Lit. [25].

General procedure for the preparation of 6a-g

To a suspension of compound **4** (1 mmol) and compound **5** (1 mmol) in H₂O (2 mL), Cu₂O (1 mol%) and C₆H₅COOH (2 mol%) were added with stirring at room temperature. The reaction was completed within 10~15 min. After filtration, the crude product was purified by column chromatography on silica gel using ethyl acetate/petroleum ether as eluent.

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1-(4-((1-phenyl-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-pyrrole-2,5-dione (6a)
Yellow solid (95% yield). m.p. 153-155 °C. IR (KBr, v_{max}/cm^{-1}): 3089, 1708, 1597, 1513, 1399, 1296, 1241, 1162, 1032, 842, 759, 686. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.02 (s, 1H), 7.95 (s, 2H), 7.62 (s, 2H), 7.52 (s, 1H), 7.30 (s, 2H), 7.23 (s, 2H), 7.18 (s, 2H), 5.32 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.6, 157.8, 144.1, 137.0, 135.0, 130.3, 129.2, 128.8, 125.0, 123.4, 120.6, 115.4, 61.7. MS (ESI) 347 [M+1]$^+$. HRMS (ESI) calcd for [C$_{19}$H$_{14}$N$_4$NaO$_3^+$]: 369.0964; found: 369.0958.

1-(4-((1-(o-tolyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-pyrrole-2,5-dione (6b)
Yellow solid (93% yield). m.p. 159-161 °C. IR (KBr, v_{max}/cm^{-1}): 3144, 2928, 1716, 1514, 1412, 1249, 1158, 1046, 831, 757, 689. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.66 (s, 1H), 7.50-7.42 (m, 4H), 7.28 (d, J = 8.8 Hz, 2H), 7.20 (d, J = 8.8 Hz, 2H), 7.16 (s, 2H), 5.29 (s, 2H), 2.16 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.6, 157.9, 143.1, 136.7, 135.1, 133.5, 131.8, 130.3, 128.8, 127.5, 126.8, 126.5, 125.0, 115.5, 61.7, 17.9. MS (ESI) 361 [M+1]$^+$. HRMS (ESI) calcd for [C$_{20}$H$_{16}$N$_4$NaO$_3^+$]: 383.1120; found: 383.1115.

1-(4-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-pyrrole-2,5-dione (6c)
Yellow solid (95% yield). m.p. 220-222 °C. IR (KBr, v_{max}/cm^{-1}): 3091, 2924, 1707, 1516, 1417, 1295, 1235, 1174, 1153, 1027, 830, 686. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.03 (s, 1H), 7.98 (d, J = 8.8 Hz, 2H), 7.69 (d, J = 8.8 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.8 Hz, 4H), 5.29 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.6, 157.8, 144.3, 135.8, 135.1, 133.5, 130.3, 128.8, 125.0, 123.5, 122.3, 115.5, 61.7. MS (ESI) 381 [M+1]$^+$. HRMS (ESI) calcd for [C$_{19}$H$_{13}$ClN$_4$NaO$_3^+$]: 403.0574; found: 403.0568.

1-(4-((1-(4-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-pyrrole-2,5-dione (6d)
Yellow solid (97% yield). m.p. 200-202 °C. IR (KBr, v_{max}/cm^{-1}): 3128, 3098, 1708, 1598, 1513, 1395, 1343, 1252, 1233, 1176, 1145, 1043, 856, 833, 686. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.22 (s, 1H), 8.47 (d, J = 8.8 Hz, 2H), 8.26 (d, J = 9.2 Hz, 2H), 7.27 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 10.4 Hz, 4H), 5.33 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.6, 157.7, 147.2, 144.9, 141.2, 135.1, 128.8, 126.0, 125.1, 123.8, 121.2, 115.5, 61.6. MS (ESI) 392 [M+1]$^+$. HRMS (ESI) calcd for [C$_{19}$H$_{13}$N$_5$NaO$_5^+$]: 414.0814; found: 414.0809.

1-(4-((1-(3-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-pyrrole-2,5-dione (6e)
Yellow solid (93% yield). m.p. 189-191 °C. IR (KBr, v_{max}/cm^{-1}): 3125, 3096, 1712, 1536, 1514, 1411, 1351, 1241, 1179, 1151, 1015, 831, 735, 690. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 9.24 (s, 1H), 8.77 (s, 1H), 8.44 (d, J = 8.0 Hz, 1H), 8.35 (d, J = 8.0 Hz, 1H), 7.92 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 8.4 Hz, 2H), 7.19 (d, J = 9.2 Hz, 2H), 7.17 (s, 2H), 5.32 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.6, 157.7, 149.0, 144.6, 137.6, 135.1, 132.0, 128.8, 126.6, 125.1, 123.9, 123.7, 115.5, 115.3, 61.7. MS (ESI) 392 [M+1]$^+$. HRMS (ESI) calcd for [C$_{19}$H$_{13}$N$_5$NaO$_5^+$]: 414.0814; found: 414.0809.

1-(4-((1-(2-fluorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-pyrrole-2,5-dione (6f)
Yellow solid (92% yield). m.p. 183-185 °C. IR (KBr, v_{max}/cm^{-1}): 3089, 1709, 1683, 1558, 1513, 1400, 1241, 1164, 1021, 846, 761, 686. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.79 (s, 1H), 7.87 (t, J = 8.0 Hz, 1H), 7.64-7.59 (m, 2H), 7.46 (t, J = 8.0 Hz, 1H), 7.27 (d, J = 9.2 Hz, 2H), 7.19 (d, J = 9.2 Hz, 2H), 7.17 (s, 2H), 5.30 (s, 2H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.6, 157.8, 154.3 (d, J_{C-F} = 249.1 Hz), 143.6, 135.1, 131.8 (d, J_{C-F} = 7.9 Hz), 128.8, 126.7 (d, J_{C-F} = 4.1 Hz), 126.5, 126.0 (d, J_{C-F} = 3.7 Hz), 125.2 (d, J_{C-F} = 11.0 Hz), 125.0, 117.6 (d, J_{C-F} = 19.3 Hz), 115.5, 61.5. MS (ESI) 365 [M+1]$^+$. HRMS (ESI) calcd for [C$_{19}$H$_{13}$FN$_4$NaO$_3^+$]: 387.0869; found: 387.0864.

1-(4-((1-(2-methyl-5-nitrophenyl)-1H-1,2,3-triazol-4-yl)methoxy)phenyl)-1H-pyrrole-2,5-dione (6g)
Yellow solid (96% yield). m.p. 188-190 °C. IR (KBr, v_{max}/cm^{-1}): 2924, 2853, 1706, 1523, 1507, 1349, 1235, 1152, 1018, 900, 833, 738, 689. ^{1}H NMR (DMSO-d_6, 400 MHz) δ: 8.81 (s, 1H), 8.38-8.36 (m, 2H), 7.81 (d, J = 9.2 Hz, 1H), 7.28 (d, J = 9.2 Hz, 2H), 7.19 (d, J = 9.2 Hz, 2H), 7.17 (s, 2H), 5.32 (s, 2H), 2.32 (s, 3H). ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 170.6, 157.8, 146.6, 143.5, 141.9, 136.9, 135.1, 133.3, 128.8, 127.0, 125.1, 124.8, 121.6, 115.5, 61.7, 18.5. MS (ESI) 406 [M+1]$^+$. HRMS (ESI) calcd for [C$_{20}$H$_{15}$N$_5$NaO$_5^+$]: 428.0971; found: 428.0965.

Biological Assay
The cytotoxicity of the test compounds were evaluated with hela cell by the MTT method *in vitro*. The cells were seeded in 96-well plate at the concentration of 4000 cells per well in RPMI 1640 medium. After cultured for 24 h at 37 °C in 5% CO$_2$ atmosphere, cells were incubated with various concentrations of tested compounds for 24 h. MTT was added at a final concentration of 0.5 mg/ml and after 4 h incubation 100 μl of DMSO was added to each well. The optical density was measured at 490 nm. The IC$_{50}$ values were calculated according to Logit method after getting the inhibitory rate.

RESULTS AND DISCUSSION

Chemistry
In the synthetic strategy illustrated in **Scheme 1**, the key intermediate **4** was synthesized from 4-nitrophenol through a three-step procedure[22]. The reaction of commercially available 4-nitrophenol with propargyl bromide in acetone provided intermediate **2** in high yield, which was reduced using iron powder in the presence of ammonium chloride to afford intermediate **3**. Then, **3** and maleic anhydride cyclized to obtain the key intermediate **4**. Finally, the target compounds **6a-6g** were synthesized by the CuAAC reaction.

In above strategy, the key step is the CuAAC reaction, and its reaction conditions were optimized using a model reaction of **4** and azidobenzene **5a** (**Table 1**).

First, we chose the classic Cu(Ⅰ) salts as catalytic system and the reaction occured in the absence or presence of ultrasound irradiation (**Entry 1-4**). It was found that the yield had no obvious difference but the reaction time was much shorter in the presence of ultrasound. This indicated that the cycloaddition reaction was greatly accelerated under the condition of ultrasound. Then we used Cu(Ⅱ)salt/sodium ascorbate as catalytic system[15] (**Entry 5-8**) and found that the yield and reaction time were not better than Cu(Ⅰ) salts system. But the direct use of Cu (I) salts was restricted because of their thermo-dynamic instability. Finally, we used Cu_2O/C_6H_5COOH system[23] as the catalyst. The result (**Entry 9, 10**) showed that the yield and reaction time were superior to all of the other reactions. However, the data of **Entry 9** and **10** indicated that the ultrasound irradiation did not show the superiority. In view of the above experimental results and Cu_2O is one of the most stable and cheapest Cu(I) sources, we selected Cu_2O/C_6H_5COOH system, room temperature and water, the 'green' solvent as the final reaction condition.

Table 1 Screening of catalysts for the model reaction [a]

Entry	Catalyst system	Times (min) [b]	Yield (%) [c]
1	CuCl	8 (h)	88
2	CuCl [d]	100	82
3	CuBr [d]	100	87
4	CuI [d]	100	85
5	$CuSO_4 \cdot 5H_2O$/Sodium ascorbate	8 (h)	72
6	$CuSO_4 \cdot 5H_2O$/Sodium ascorbate [d]	120	80
7	$Cu(OAc)_2 \cdot H_2O$/Sodium ascorbate [d]	120	83
8	$CuCl_2 \cdot 2H_2O$/Sodium ascorbate [d]	120	76
9	Cu_2O / C_6H_5COOH	15	95
10	Cu_2O / C_6H_5COOH [d]	15	94

[a]   *Reaction conditions: **4** (1 mmol), **5a** (1 mmol), Solvent: H_2O (2 mL), at room temperature.*
[b]   *Complete reaction time.*
[c]   *Isolated yield.*
[d]   *In the presence of ultrasound irradiation condition.*

Biological Activity
Compounds **4** and **6a-g** were evaluated for their cytotoxicity *in vitro* against hela cell line by using the MTT method [24] with doxorubicin as the positive control. The results are reported in Table **2**.

Table 2 *In vitro* cytotoxic activity of target compounds against the hela cell line

Compd.	$IC_{50}/(\mu M)$*
4	88.1
6a	>100
6b	>100
6c	16.7
6d	>100
6e	43.7
6f	55.6
6g	22.5
Doxorubicin	3.7

**The IC_{50} values were calculated according to the Logit method after getting the inhibitory rate and were the averages of three experiments.*

The data indicated that most of the newly synthesized compounds showed potent antitumor activity. The activity of **6a-g** varied according to the substituents on the phenyl ring. Compounds that had no substituent on the phenyl ring or had a strong electron-withdrawing group on the para site of the phenyl ring showed almost no activity(**6a,6d**). Compound **6c**, with a weak electron withdrawing group on the para site of the phenyl ring, exhibited the best activity (IC_{50} =16.7 μmol/L) among all the test compounds. Although the activity of the test was lower than the positive control doxorubicin, it still provided a new structure type that had potent antitumor activity. Furthermore,

other research could be carried out on the basis of the above result. The work is in progress.

CONCLUSION

The present study describes the synthesis of maleimide derivatives bearing the 1,2,3-triazole moiety. The cytotoxic activity of these compounds was evaluated against hela cell. Some of them exhibit potent cytotoxicity and the most promising compound is **6c**. These findings might provide an alternative strategy for finding new drugs against cancer cell lines. Some relate research is underway.

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