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Synthesis and biological evaluation of matrine derivatives as anti-hepatocellular cancer agents

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ABSTRACT

We delineate herein the synthesis and anti-cancer effects of 15 matrine derivatives. The in vitro growth inhibitory assays showed that most of the prepared compounds exhibited improved anti-proliferative activities towards cancer cells with IC_{50} 17–109 times lower than that of matrine. Compounds CH6 showed the most potent anti-proliferative activities in the four tested cancer cell lines. Moreover, compound CH6 could induce G1 cell cycle arrest and inhibit cell migration in human hepatocellular cancer cell lines Bel-7402 and HepG2 through up-regulation of P21, P27 and E-cadherin and down-regulation of N-cadherin.

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Hepatocellular cancer (HCC) is the second cause of cancer-related death and more than 50% of the HCC cases occur in China.[1] Currently, chemotherapy is the main treatment for HCC.[2–5] Although the survival of HCC patients has been improved with the emergence of sorafenib[6–14], a kinase inhibitor, there still comes with new issues, such as drug resistance. It is still urgent to develop novel drugs to improve patient outcomes.

Matrine is the main chemical ingredient of Fufang Kushen injection which was approved by Chinese FDA (CFDA) in 1995 as an Adjuvant to treat liver cancer and non small cell lung cancer.[15–20] Owing to its druggable advantages, such as flexibility structure and favorable safety profiles, matrine has been considered as an ideal lead compound for further modification.[21–23]

In the present study, we designed and synthesized 15 matrine derivatives which displayed improved anti-cancer effects than matrine in four tested cancer cell lines. The synthetic route is outlined in Scheme 1. First, treatment of matrine with lithium diisopropylamide (LDA) provided the lithium enolate intermediates. Then lithium enolate intermediates reacted with compounds B which were prepared via a reported medthod[24] to give intermediate products D. Intermediate D could easily convert to product E quantitatively via deprotection at 0 °C with trifluoroacetic acid and methylene chloride (the volume ratio was 1:20). Subsequently, as described[25], cyclodehydration of product E in the presence of poly-phosphonic ester (PPE) at 120 °C in an inert atmosphere of nitrogen gave the desired products (CH1–CH10) with yields ranging from 15% to 25%. While preparing compound CH11, two hydroxyl groups in methyl 2, 5-dihydroxybenzoate needed to be protected. Briefly, the 2-position hydroxyl group was initially protected by methyl ether, following a protection of 5-position hydroxyl group by benzyl group. Interestingly, B11 was successfully obtained via recrystallization with a yield of 60%. Compounds CH12 and CH13 were prepared successfully by removing methyl ether protection of CH7 and CH8 in the condition of 40% HBr/CH_3COOH mixture, respectively. In order to promote the reaction rate, acetic acid was replaced by acetic anhydride or a certain amount of PBr_3 was added to increase the HBr concentration. For the synthesis of compounds CH14–15, prior obtained compounds CH4–5 were oxidized at the nitrogen atom with m-CPBA as an oxidant. All the compounds are characterized (Supplementary information).

All the available matrine derivatives were evaluated for their cytotoxic activities against four human cancer cell lines, including A549 (lung cancer cell), MCF-7 (breast cancer cell), SGC-7901 (gastric cancer cell) and Bel-7402 (hepatocellular cancer cell) using MTT assay.[26] The anti-proliferative activities of 15 matrine derivatives were depicted in Table 1. Most of the derivatives exhibited improved anti-cancer effects with IC_{50} 17–109 times lower than that of matrine. Especially, compounds CH6 showed the most

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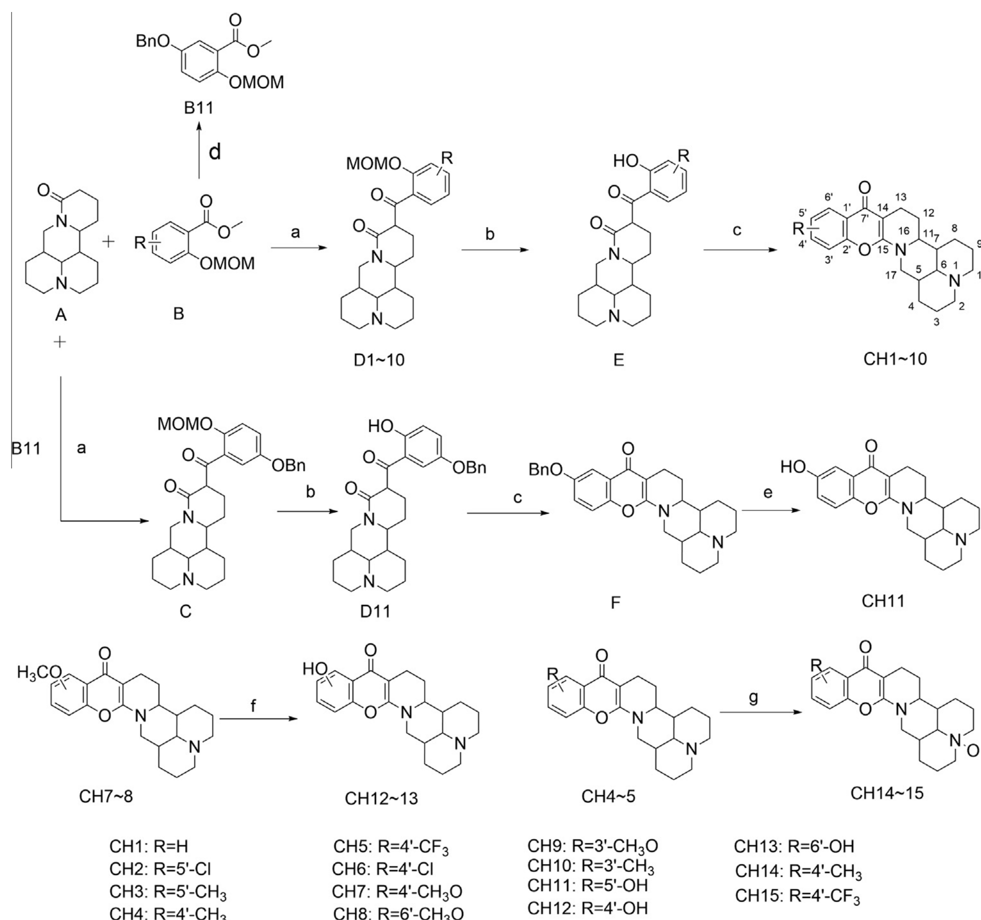

Scheme 1. Synthetic routes of matrine derivatives. Reaction conditions: (a) LDA, 0 °C to 25 °C, 3 h; (b) TFA/DCM (v:v = 1:20), 8 h; (c) PPE, N_2, reflux, 8 h; (d) BnBr, K_2CO_3, 15 °C, 3 h; (e) H_2 balloon, 3% Pd/C, 12 h; (f) CH12: 40% HBr/Acetic anhydride, reflux, 48 h; CH13: 40% HBr/CH_3COOH, PBr_3, reflux, 48 h; (g) m-CPBA, 0 °C, 3 h.

Table 1
The anti-proliferative activities of matrine derivatives CH1-15

Compd	IC_{50} (μM)			
	SGC-7901	MCF-7	A549	Bel-7402
CH1	>100	>100	>100	>100
CH2	45.25 ± 4.83	48.22 ± 1.66	56.99 ± 6.73	36.17 ± 2.35
CH3	40.45 ± 3.97	57.15 ± 5.13	97.24 ± 9.24	36.96 ± 2.04
CH4	46.75 ± 3.99	48.56 ± 5.33	52.91 ± 6.90	30.29 ± 1.29
CH5	34.90 ± 4.36	30.73 ± 0.71	41.2 ± 4.24	31.45 ± 2.64
CH6	28.94 ± 3.76	28.06 ± 2.90	36.03 ± 2.07	25.23 ± 2.46
CH7	67.15 ± 4.13	77.43 ± 3.61	97.63 ± 7.55	47.98 ± 4.37
CH8	81.71 ± 9.02	74.13 ± 5.42	93.55 ± 10.17	69.45 ± 4.59
CH9	81.59 ± 4.33	75.43 ± 7.79	96.47 ± 7.97	71.87 ± 6.72
CH10	51.46 ± 8.20	52.85 ± 30.52	73.25 ± 6.63	40.74 ± 2.86
CH11	>100	>100	>100	>100
CH12	>100	>100	>100	>100
CH13	>100	>100	>100	>100
CH14	57.14 ± 8.26	53.27 ± 5.17	73.78 ± 2.51	49.29 ± 7.94
CH15	79.09 ± 6.30	73.78 ± 5.71	113.78 ± 11.92	66.01 ± 7.07
Matrine	1380 ± 116	2497 ± 208	3923 ± 243	2057 ± 192

Note: IC_{50} values are taken as a mean from 3 experiments. Mean ± SD.

potent anti-cancer effects. The IC_{50} of CH6 were 25–36 μM which was about 48–109 times lower than that of matrine, respectively. Interestingly, most of the derivatives displayed greater cytotoxicity against human hepatocellular cancer cell line Bel-7402 than the other three human cancer cell lines. Thus, we subsequently studied the anti-cancer mechanism of compound CH6 on hepatocellular cancer cells.

To evaluate the anti-proliferative activity of compound CH6 on hepatocellular cancer cells, MTT assay was performed in Bel-7402 and HepG2 cells. The results demonstrated that compound CH6 could inhibit the proliferation of hepatocellular cancer cells in a time- and dose-dependent manner (Fig. 1).

To determine whether the cytotoxicity of compound CH6 against Bel-7402 and HepG2 cells involved cell cycle arrest, we tested the effects of CH6 on cell cycle distribution for 24 h. The results indicated that compound CH6 induced G1 cell cycle arrest in Bel-7402 and HepG2 cells in a dose-dependent manner (Fig. 2A). The percentage of G1 phase in Bel-7402 cells increased from 49% to 67% (10 μM, $p < 0.05$) and 79% (20 μM, $p < 0.05$), respectively (Fig. 2B, left). Consistently, the percentage of G1 phase in HepG2 cells increased from 48% to 54% (10 μM, $p < 0.05$) and 65% (20 μM, $p < 0.01$), respectively (Fig. 2B, right).

Migration and invasion are the main manifestations of tumor progression.[27] To test whether compound CH6 could inhibit cancer cell migration, wound healing assays were conducted in Bel-7402 and HepG2 cells for 48 h. The results indicated that under CH6 treatment, cancer cell migration was inhibited (Fig. 3A). CH6 decreased the percentage of cell migration from 60% (control) to 75% (10 μM, $p < 0.01$) and 85% (20 μM, $p < 0.01$) in Bel-7402 cells and from 58% (control) to 80% (10 μM, $p < 0.01$) and 83% (20 μM, $p < 0.01$) in HepG2 cells, respectively (Fig. 3B).

To further dissect the molecular mechanism of CH6 induced G1 cell cycle arrest and migration inhibition, western blot assays were conducted as described[28] to detect regulators involved in cell cycle and migration regulation. The results demonstrated that upon

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