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Synthesis and anti-HBV activity of novel 5-substituted pyridin-2(1H)-one derivatives

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Abstract

Four novel 5-substituted pyridine-2(1H)-one derivatives were designed and synthesized by using addition–elimination reactions. The structures of these novelly synthesized compounds were verified by ^{1}H NMR, ESI-MS and single crystal X-ray diffraction. Furthermore, all four compounds (most notably compound **7a**) were found to be highly efficient against hepatitis B virus (HBV) in cultured HepG2 2.2.15 cell, making them promising drug candidates for potential bioactive molecule against hepatitis B.

Keywords: 5-Substituted pyridin-2(1H)-one; Synthesis; Crystal structure; Anti-HBV activity

Chronic hepatitis B virus (HBV) infection is a leading cause of liver cirrhosis and hepatocellular carcinoma and up to 1.2 million people die annually from HBV-related infection [1,2]. HBV is a member of the Hepadnavirus family and the virus particle consists of an outer lipid envelope and an icosahedral nucleocapsid core. The nucleocapsid encloses the viral DNA and a DNA polymerase that has reverse transcriptase activity [3]. Eradication of HBV infection is difficult because stable, covalently closed circular DNA (cccDNA) which is relatively resistant to antiviral immune clearance becomes established in hepatocyte nuclei and integrated into the host genome [1,3]. Currently used drugs for the treatment of HBV infection include pegylated interferon α-2a, lamivudine, and Adefovir dipivoxil [2,4]. However, poor serological response and apparent drug resistance to rapidly mutated virus make current therapy suboptimal. In addition, these drugs are associated with substantial adverse effects. Therefore, there is an urgent need for identification of more effective, better endurable and less resistance-prone antiviral agents with novel structural scaffolds and pharmacological mechanisms.

2-Pyridone is a multiple bioactive small molecule. It is an important pharmacophore that can form hydrogen-bonded structures related to the base-pairing mechanism found in DNA and RNA [5,6]. Our hypothesis is 2-pyridone derivatives would interfere with DNA synthesis, thus inhibiting the replication of DNA viruses, such as HBV. In this study, we synthesized 5-substituted pyridin-2(1H)-one derivatives by a novel reaction route and then screened their anti-HBV activities. Our results, however, showed that all four novelly synthesized compounds demonstrated strong inhibitory effects against HBsAg, HBeAg, and modest inhibitory effects of HBV DNA replication.

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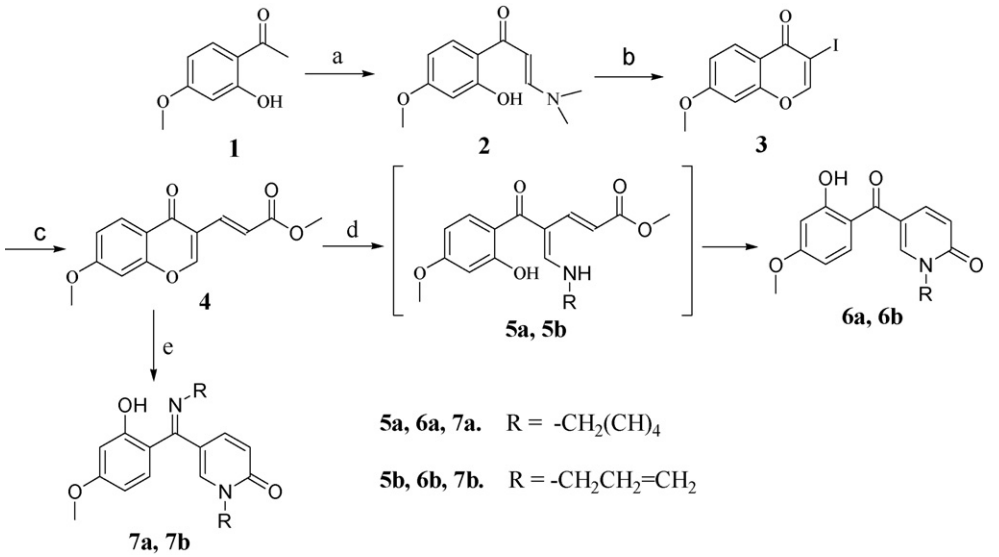

Scheme 1. Synthesis of compounds **6** and **7**.

Compounds **6** and **7** were synthesized based on the following routes (Scheme 1). The key intermediate **3** was prepared from paeonol through a two-step reaction as previously reported [7]. A subsequent Heck reaction of compound **3** with methyl acrylate yielded compound **4** [8]. To synthesize compounds **6a** and **6b**, compound **4** was heated at reflux with equimolar amounts of amine in methanol for 3 h by an addition–elimination reaction. Compounds **7a** and **7b** (trans-configuration) were produced by the reaction of compound **4** with two equivalent amounts of amine under reflux in methanol for 8 h [9]. To dissect their molecule structures, we obtained the monocrystals of compounds **6b** and **7a** which had been collected at Cambridge Crystallographic Data Centre (CCDC) with CCDC Nos. of 705282 and 705283, respectively. The structures of these two compounds are shown in Fig. 1.

Reagents and conditions: (a) N,N-dimethylformamide dimethylacetal, 90 °C; (b) I_2 in $CHCl_3$; (c) methyl acrylate, CuI, $PdCl_2(PPh_3)_2$, K_2CO_3, DMF/H_2O, 70 °C; (d) methanol, TEA, substituted amine, reflux, 3 h; (e) methanol, TEA, substituted amine, reflux, 8 h.

The addition–elimination process might be a two-step reaction: firstly, furan ring was broken between position O-1 and C-2, followed by generating an enamine transition state (compounds **5**) in alkaline solution; and secondly, a cis-trans transformation at high temperature led to the possibility that the ester carbonyl is attacked by the nitrogen atom. Then leaving of a methanol molecule formed a new substituted 2-pyridone ring.

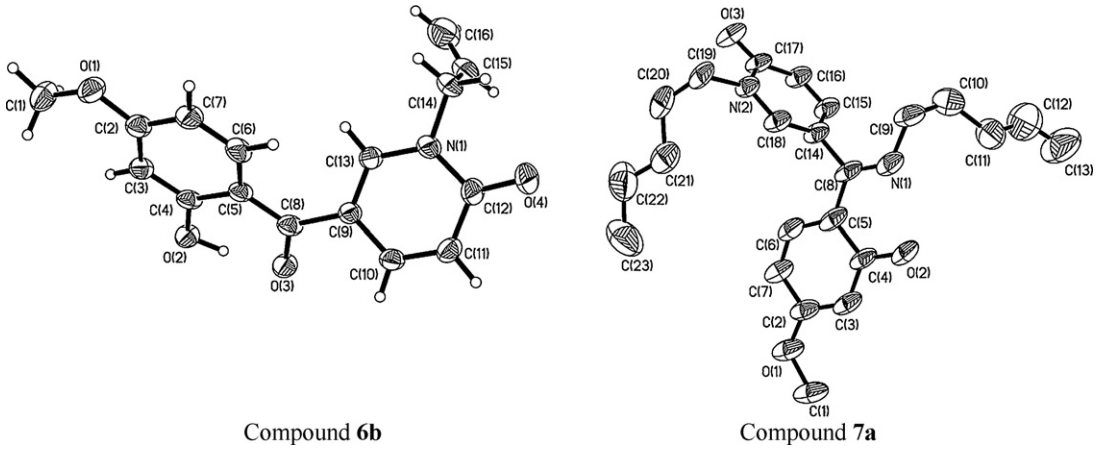

Fig. 1. Crystal structures of compounds **6b** and **7a**.

Table 1
Anti-HBV activity and cytotoxicity of synthesized compounds *in vitro*.

Compound	TC_{50} (μmol/L)	Anti-HBsAg (μmol/L)		Anti-HBeAg (μmol/L)		DNA replication (μmol/L)	
		IC_{50}	SI	IC_{50}	SI	IC_{50}	SI
6a	79	46	1.72	39	2.03	20	3.95
6b	232	276	0.84	58	4.00	ND	ND
7a	98	29	3.38	5	19.60	30	3.27
7b	20	98	0.20	40	0.50	12	1.67
Adefovir	540	305	1.77	286	1.89	0.517	1400

"TC_{50}" is 50% cytotoxic concentration in HepG2 2.2.15 cells. "IC_{50}" is 50% inhibitory concentration. "SI" is selectivity index (SI: TC_{50}/IC_{50}). "ND" is not determined.

All four novelly synthesized compounds were evaluated for their anti-HBV activities and cytotoxicities in cultured HepG2 2.2.15 cells. Indices included measuring the secretion of HBsAg and HBeAg to cell culture media and replication of HBV DNA. Nucleotide analogue Adefovir was utilized as the positive control. The results are summarized in Table 1 and data demonstrated that four novelly synthesized compounds demonstrated stronger anti-HBV activity than Adefovir; while their cytotoxicity was relatively high (with TC_{50} values of 79, 232, 98 and 20 μmol/L, respectively). Among the four compounds, compound **7a** showed lowest IC_{50} values of anti-HBsAg, anti-HBeAg and DNA replication inhibitory effects (29, 5 and 30 μmol/L, respectively), followed by **6a**, **7b** and **6b**. The difference in their anti-HBV efficacies indicated that when the hydrogen was replaced with pentane at position N-1, the compound would have stronger inhibitory effect against HBV than those in which the hydrogen was replaced with propylene at the same position; moreover, the anti-HBV efficacy would be enhanced by replacement of the benzoyl group with an imino group. The bioassay results also hinted the parent scaffold of four compounds seemed playing an important role in the inhibition of HBV.

In summary, here we report a novel and highly yielding synthesis route for 5-substituted pyridin-2(1H)-one derivatives. The novelly synthesized compounds were verified by structural analyses using single crystal X-ray diffraction. Moreover, these 5-substituted pyridin-2(1H)-one derivatives were shown to be a kind of highly potential bioactive molecule against hepatitis B.

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[9] Yield, physical and spectral data for some synthesized compounds: 1-allyl-5-(2-hydroxy-4-methoxybenzoyl)-pyridin-2(1H)-one **6b**: full yield 89% yellow crystal. M.p.: 131.7–132.6 °C. ^{1}H NMR ($CDCl_3$ 300 MHz): δ 3.87(s, 1H), 4.62(m, 2H), 5.25(m, 2H), 5.92(m, 1H), 6.56(dd, 1H, J_1 = 9 Hz, J_2 = 2.7 Hz), 6.52(d, 1H, J = 2.7 Hz), 6.62(d, 1H, J = 9.6 Hz), 7.46(d, 1H, J = 9 Hz), 7.70(dd, 1H, J_1 = 9.6 Hz, J_2 = 2.7 Hz), 7.86(d, 1H, J = 2.7 Hz), 12.24(s, 1H). ESI-MS (*m/z*): 286.1 [M+1]. (E)-5-((2-hydroxy-4-methoxyphenyl)(pentylimino)methyl)-1-pentylpyridin-2(1H)-one **7a**: full yield 90% yellow crystal. M.p.: 95.8–97.4 °C. ^{1}H NMR ($CDCl_3$ 300 MHz): δ 0.89(m, 6H), 1.34(m, 8H), 1.67(m, 2H), 1.78(m, 2H), 3.39(m, 2H), 3.80(s, 3H), 3.97(m, 2H), 6.19(dd, 1H, J_1 = 9 Hz, J_2 = 2.7 Hz), 6.39(d, 1H, J = 2.7 Hz), 6.66(d, 1H, J = 9.6 Hz), 6.85(d, 1H, J = 9 Hz), 7.22(m, 2H), 16.26(s, 1H). ESI-MS (*m/z*): 385.65 [M+1].