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Bioorganic & Medicinal Chemistry Letters 18 (2008) 1884–1888
Bioorganic & Medicinal Chemistry Letters

New nordihydroguaiaretic acid derivatives as anti-HIV agents

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Received 13 November 2007; revised 1 February 2008; accepted 7 February 2008
Available online 10 February 2008

Abstract—Reaction of nordihydroguaiaretic acid with various alkyl chloride, 1-piperidinecarbonyl chloride, methyl chloroformate, or 1,1′-carbonyldiimidazole under alkaline conditions produced the corresponding phenol ethers, carbamates and carbonates, respectively, in 67–83% yields. Among these derivatives, the nitrogen-containing compounds were converted to the corresponding hydrochloride salts. Having good solubility, these NDGA derivatives were found stable in aqueous solution. These new compounds exerted appealing activity against HIV Tat-regulated transactivation in human epithelial cells. The most potent compound *meso*-2,3-dimethyl-1,4-bis(3,4-[2-(piperdino)ethoxyphenyl])butane tetrakishydrochloride salt (**5b**) showed IC_{50} value of 0.88 μM.
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Nordihydroguaiaretic acid (NDGA, **1** in Fig. 1) is a lignan found in the leaves and twigs of the shrub *Larrea tridentata*. Being a lipoxygenases inhibitor, NDGA can induce cystic nephropathy in the rat.[1] In addition, it shows various bioactivities, including inhibition of protein kinase C,[2] induction of apoptosis,[3] alterations of membrane,[4] elevation of cellular Ca^{2+} level[5] and activation of Ca^{2+} channels in smooth muscle cells,[6] breakdown of pre-formed Alzheimer's β-amyloid fibrils in vitro,[7] anti-oxidation,[8] etc. Although having been banned in some countries (e.g., USA), this natural product is used commercially as a food additive to preserve fats and butter. Recently, the derivatives of the plant lignan NDGA have been used for block of viral replication through the inhibition of viral transcription.[9–16] These compounds can inhibit production of HIV,[9–13] herpes simplex virus,[14,15] and HPV transcripts[16] by deactivation of their Sp1-dependent promoters. Moreover, (tetra-*O*-methyl)nordihydroguaiaretic acid (M_4N, **2**) can function as an anti-HIV proviral transcription inhibitor; this NDGA derivative also causes growth arrest of a variety of transformed human and mouse cells in culture and in mice.[17,18]

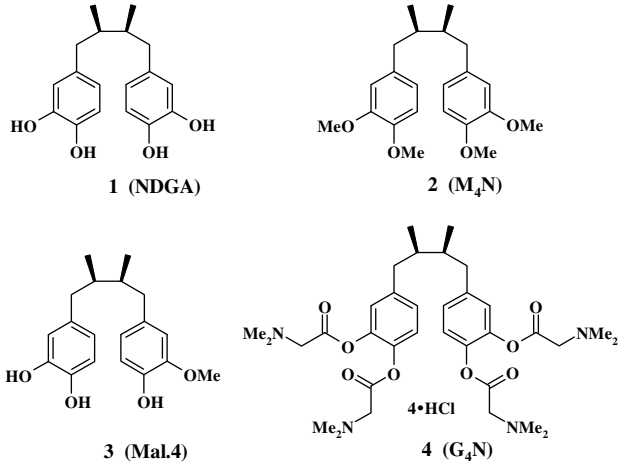

Figure 1. The structures of NDGA derivatives.

We have been focusing on design of NDGA derivatives that can selectively arrest growth and induce apoptosis of cancer cells with minimal toxicity to normal tissues. Huang et al.[12] reported that (3′-*O*-methyl)nordihydroguaiaretic acid (Mal.4, **3**) can directly and specifically interfere wit21h the binding of Sp1 protein to the Sp1 sites of the HIV long terminal repeat. The M_4N (**2**) appears to induce cell cycle arrest in mammalian cell lines[18] and thus inhibits tumor cell growth. Nevertheless, M_4N and other methylated NDGA show poor water solubility, which limits their applicability. To circum-

Keywords: Anti-HIV; NDGA; Nordihydroguaiaretic acid; DNA; HIV Tat-regulated transactivation.
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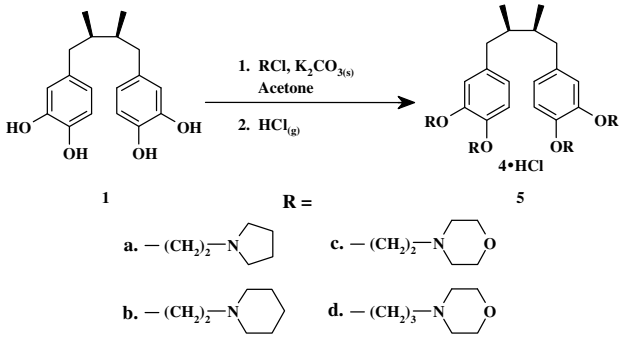
doi:10.1016/j.bmcl.2008.02.018

vent this problem, we designed and synthesized (tetra-*O*-glycyl)nordihydroguaiaretic acid (G_4N, **4**), a water soluble derivative of NDGA.[11] It can act as mutation-insensitive transcription inhibitor to HSV-1.[10,15] The high water solubility associated with G_4N allows it to work efficiently in inhibition of HSV despite its short half-life in aqueous solution. The instability comes from the ester bonds therein, which connect the glycine moieties onto the NDGA main skeleton. Accordingly, we planned to synthesize a new series of NDGA derivatives with appealing anti-HIV activity as well as good water solubility and stability.

Being a potent transcription activator encoded by the human immunodeficiency virus-1 (HIV-1), HIV Tat is required for replication of the deadly virus.[19] Tat-regulated transactivation has since become an attractive strategy for the development of anti-HIV drugs.[20] On the other hand, Berger et al.[21] reported a novel eukaryotic reporter gene, the secreted alkaline phosphatase (SEAP). By adopting these methods, we screened our newly synthesized NDGA derivatives against HIV by using HIV long terminal repeat (LTR) promoter, SEAP, and CMV promoter driven Tat. We found that compound **5b** was able to inhibit of HIV Tat-regulated transactivation in a great extent and represents a new lead of anti-HIV drugs.



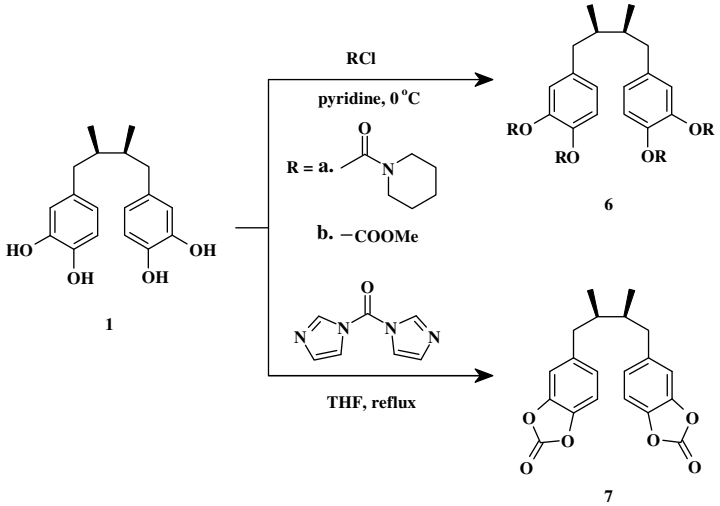
Scheme 1. Synthesis of new NDGA derivatives.

We first treated NDGA (**1**) with an alkyl chloride bearing a hydrocarbon spacer and a nitrogen—containing five- or six-membered ring in the presence of sodium carbonate and acetone (see Scheme 1). These intermediates were then allowed to react with $HCl_{(g)}$ in situ to give tetra-*O*-alkylated NDGAs **5a**–**d** in 67–82% overall yields. Their solubility in aqueous solution was found 379–541 mg/mL.

Furthermore, we prepared NDGA derivatives in the families of carbamate and carbonate as shown in Scheme 2. Treatment of NDGA with 1-piperidinecarbonyl chloride in the presence of pyridine at 0 °C produced the NDGA carbamate **6a** in 72% yield. Under the same conditions, NDGA reacted with methyl chloroformate or 1,1′-carbonyldiimidazole afforded carbonates **6b** and **7**, respectively. The latter product was generated through an intramolecular cyclization process.

These new NDGA derivatives were found stable in aqueous solution; >99% of these compounds remained intact after 28 days (see Fig. 2(b)). In a sharp contrast, >96% G_4N (**4**) decomposed in aqueous solution within 24 h (see Fig. 2(a)).

We used the transactivation assay involving transfection of plasmid constructs[21] to test the effect of synthesized NDGA derivatives on Tat-regulated secreted alkaline phosphatase (SEAP). This protein was produced in COS cells as described previously.[12,13,21] The plasmid constructs included a cytomegalovirus (CMV) promoter driven *tat* gene and an HIV LTR promoter driven reporter gene (i.e., SEAP). A standard SEAP assay in the absence of drug was initially run to find out efficiency of transfection. Our results shown in Figure 3 indicate a nearly 5 times increment in Tat-induced SEAP expression after 60 min in comparison with the control (i.e.,



Scheme 2. Synthesis of new NDGA derivatives.

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