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Inhibition of IGF-1R and lipoxygenase by nordihydroguaiaretic acid (NDGA) analogs

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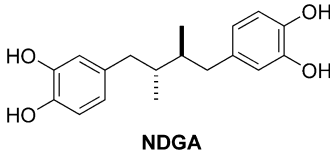
Abstract—Herein, we pursue the hypothesis that the structure of nordihydroguaiaretic acid (NDGA) can be refined for selective potency against the insulin-like growth factor 1 receptor (IGF-1R) as a potential therapeutic target for breast cancer while diminishing its action against other cellular targets. Thus, a set of NDGA analogs (**7a**–**7h**) was prepared and examined for inhibitory potency against IGF-1R kinase and an alternative target, 15-lipoxygenase (15 LOX). The anti-cancer effects of these compounds were determined by their ability to inhibit IGF-1 mediated cell growth of MCF-7 breast cancer cells. The design of the analogs was based upon a cursory Topliss approach in which one of NDGA's aromatic rings was modified with various substituents. Structural modification of one of the two catechol rings of NDGA was found to have little effect upon the inhibitory potency against both kinase activity of the IGF-1R and IGF-1 mediated cell growth of MCF-7 cells. 15-LOX was found to be most sensitive to structural modifications of NDGA. From the limited series of NDGA analogs examined, the compound that exhibited the greatest selectivity for IGF-1 mediated growth compared to 15-LOX inhibition was a cyclic analog **7h** with a framework similar to a natural product isolated from *Larrea divaricata*. The results for **7h** are significant because while NDGA displays biological promiscuity, **7h** exhibits greater specificity toward the breast cancer target IGF-1R with that added benefit of possessing a 10-fold weaker potency against 15-LOX, an enzyme which has a purported tumor suppressing role in breast cancer. With increased specificity and potency, **7h** may serve as a new lead in developing novel therapeutic agents for breast cancer.

Nordihydroguaiaretic acid (NDGA, Fig. 1) is isolated from the resinous extract of the creosote bush *Larrea divaricata*.[1] It has also been reported that NDGA inhibits the growth of tumors, both in vitro and in vivo[2] but relatively high concentrations are required to achieve efficacy in most cases. Preliminary in vivo studies have revealed that NDGA inhibits tumor growth by inhibiting receptor tyrosine kinase (RTK) phosphorylation.[3] NDGA has been shown to inhibit several RTKs overexpressed in certain cancer cells. In a previous study, we noted that NDGA inhibits both the IGF-1R and HER2/neu with moderate potency and impairs subsequent signaling through the anti-apoptotic pathway in breast cancer cell.[3,4] These and other RTKs such as the epidermal growth factor receptor (EGFR) are overexpressed in breast and other cancers and contribute to a poor prognosis.[5–7]



NDGA

Figure 1. Structure of nordihydroguaiaretic acid (NDGA).

However, NDGA is known to directly interact with multiple non-RTK targets, several of which could contribute to its anti-cancer effects. NDGA directly inhibits the interaction of fatty acid synthase (FAS) with the substrate malonyl CoA.[8] NDGA can also directly inhi-

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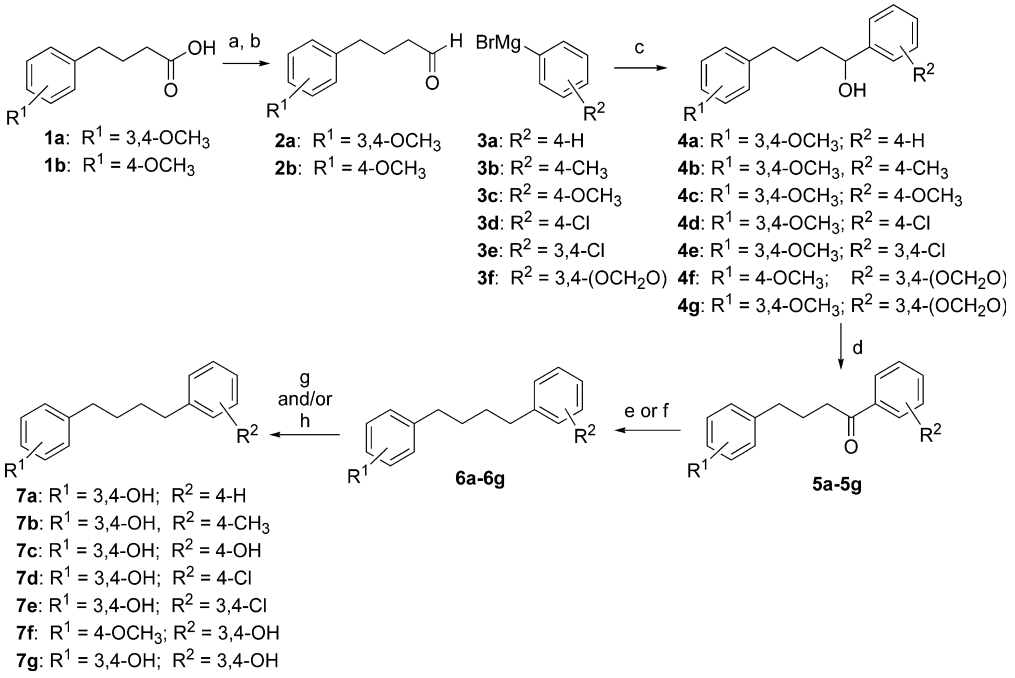
bit 5-α reductase,[9] thereby blocking the conversion of testosterone into the biologically active dihydrotestosterone. Inhibitors of both FAS and 5-α reductase can inhibit growth or induce apoptosis in certain cancer cell lines.[9,10] NDGA's reported antioxidant properties are attributed to its activity as a non-selective inhibitor of lipoxygenases (LOX).[11] The role of LOX isozymes in cancer has been questionable, as the anti-cancer effects of NDGA were originally attributed to reduction of cellular levels of leukotrienes generated from arachidonic acid by 5- and 12-LOX,[12–14] but recent studies suggest that in breast cancer, 15-LOX has a tumor suppressing role.[15]. The multiplicity of NDGA's effects may, in some cases, enhance its anti-tumor actions, but may also antagonize its therapeutic effects or increase the undesirable side effects in non-tumor sites. Therefore, in designing potential therapeutics for breast cancer, compounds capable of inhibiting RTKs such as IGF-1R and HER2/neu but lacking potency against 15-LOX or other targets could prove promising. The development of NDGA analogs with more specific potencies for various cellular targets is expected to result in an enhancement of its anti-cancer properties.

The focus of the present study was to demonstrate that the structure of NDGA could be refined for selective potency against the IGF-1R as a therapeutic target for breast cancer[16] while diminishing its action against 15-LOX. Primarily based upon a cursory Topliss approach,[17,18] our objective was to prepare a small set of NDGA analogs in which the substituents on one of NDGA's aromatic rings were adjusted to explore a range of hydrophobicity, electronics, and steric properties. We also pursued two simplified analogs of NDGA in which the methyl substituents on the bridging butyl chain and one of the hydroxyls of a catechol ring were absent.

The synthesis of NDGA analogs **7a**–**7g** is outlined in Scheme 1. Carboxylic acids **1a** and **1b** were initially reduced to the corresponding alcohols with $LiAlH_4$[19] and subsequently oxidized to the intermediate aldehydes **2a** and **2b** with pyridinium chlorochromate (PCC).[20] Next, treatment with substituted-aryl Grignard reagents (**3a**–**3f**) yielded alcohols[21] **4a**–**4g**, which were oxidized with PCC[20] to yield ketones **5a**–**5g** prior to their complete reduction.

As halogenated aryl rings can undergo dehalogenation under the simple conditions of catalytic hydrogenation to reduce benzylic ketones,[22] the halogen-containing aryl ketones **5d** and **5e** were subjected to adapted Wolff–Kishner conditions employing hydrazine hydrate[23] to generate an initial hydrazone intermediate. Hydrazones were subsequently reduced with KOH[23,24] to yield alkanes **6d** and **6e**. The remaining non-halogen substituted aryl ketones (**5a**–**5c**, **5f**, and **5g**) were reduced by simple catalytic hydrogenation. Next, precursors **6a**–**6e** were demethylated with BBr_3[25] to yield the NDGA analogs **7a**–**7e**. 3,4-Methylenedioxy-protected catechol **6f** was selectively deprotected using PCl_5[26] to yield **7f**. Similar conditions were applied to **6g**, followed by subsequent demethylation with BBr_3 to generate **7g**, the desmethyl analog of NDGA. Both **7a** and **7g** have been reported previously.[27,28]

A cyclic NDGA analog **7h** was prepared as outlined in Scheme 2. Ketone **5a** was reduced with Et_3SiH[29] and TFA, and was expected to proceed through two steps of carbocation formation followed by reduction through



Scheme 1. Reagents and conditions: (a) $LiAlH_4$, CH_2Cl_2, rt, 3.5 h; (b) PCC, CH_2Cl_2, rt, 1 h; (c) Et_2O or THF, −78 °C, then rt, 30 min; (d) PCC, CH_2Cl_2, rt, 1 h; (e) H_2, 10% Pd/C, THF, rt, 1.5 h; (f) $H_2NNH_2.H_2O$ and KOH, 165 °C, 4 h; (g) BBr_3, CH_2Cl_2, −78 °C, then rt, 30 min; (h) PCl_5, PhMe, 160 °C, then H_2O.