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Synthesis of phosphates and phosphates–acetates hybrids of green tea polyphenol (−)-*epi*gallocatechine-3-gallate (EGCG) and its G ring deoxy analogs as potential anticancer prodrugs

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ABSTRACT

A series of phosphate or phosphate–acetate hybrid modified EGCG or EGCG G ring deoxy analogs were synthesized by a convenient semi-synthesis strategy from the abundant natural compound EGCG.

Green tea, produced from the unfermented dried leaves of the plant *Camellia sinensis*, originated in China and has been consumed by humans for thousands of years. Regular drinking of green tea has been associated with many health benefits.[1,2] Since tea consumption is generally not associated with any toxic effect, the attraction of using green tea extract as potential therapeutic agents is considerable.[3] Polyphenolic catechins constituents are thought to contribute to the biological effects of green tea. A number of catechins have been identified and the major ones are (−)-*epi*catechin (EC), (−)-*epi*catechin gallate (ECG), (−)-*epi*gallocatechin (EGC) and (−)-*epi*gallocatechin gallate (EGCG). EGCG is found to be the most abundant and significant active compound among them.[4,5] It is known that a number of cancer-related proteins are affected by tea polyphenols, in particular by EGCG. However, the exact mechanism of tea-mediated cancer prevention is under active investigations.[6] Several years ago, we proposed that inhibition of proteasome may be a key mechanism in the cancer prevention activity of green tea.[7] Furthermore, it is the gallate ester bond-containing tea polyphenols (e.g., ECG, EGCG) but not the flavan-3-ols (e.g., EC, EGC), which inhibit the proteasomal chymotrypsin-like (β5) activities of the proteasome[8] and are responsible for the cancer prevention activity.

A major challenge in extrapolating the biological activities of green tea polyphenols in vitro to possible effects in vivo is bioavailability. In this respect, it is known that EGCG itself has poor bioavailability.[9] EGCG (Fig. 1) is relatively unstable under neutral or alkaline conditions and could be rapidly degraded, involving deprotonation of hydroxyl groups on the phenol rings. Moreover, the hydroxyl groups of EGCG could be modified through biotransformation reactions, such as methylation, glucuronidation, and sulfate formation, resulting in reduced biological activities in vivo. We have suggested that EGCG peracetate (**1**, Fig. 1) which can be converted to EGCG under cellular conditions by esterases with enhanced bioavailability in vivo can act as a prodrug.[10] Even though it is not an inhibitor of proteasome in cell-free system, **1** is more potent than EGCG at inhibiting the proteasomal chymotrypsin-like activity in human breast cancer MDA-MB-231 cells.[11] More importantly, the enhanced bioactivity also manifested in animal xenograft models.[11,12] This progress has encouraged us to screen other potential EGCG prodrugs in order to enhance and promote more desirable qualities, such as chemical stability, bioavailability and site selectivity.

Phosphate esters of alcohol or phenol functionalities have been used as a prodrug approach. For example, a combretastatin A-4

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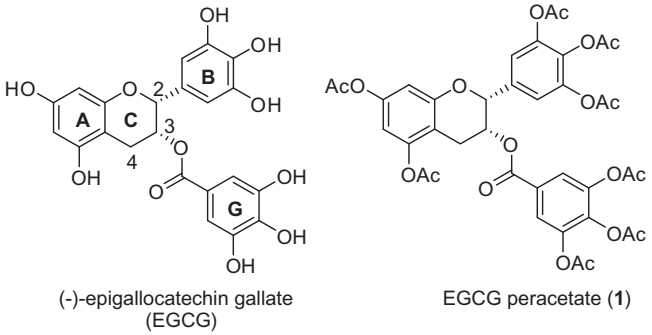
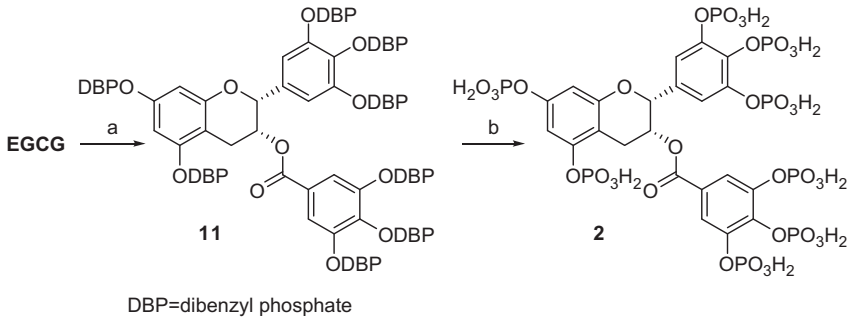


Figure 1. EGCG and EGCG peracetate (**1**).

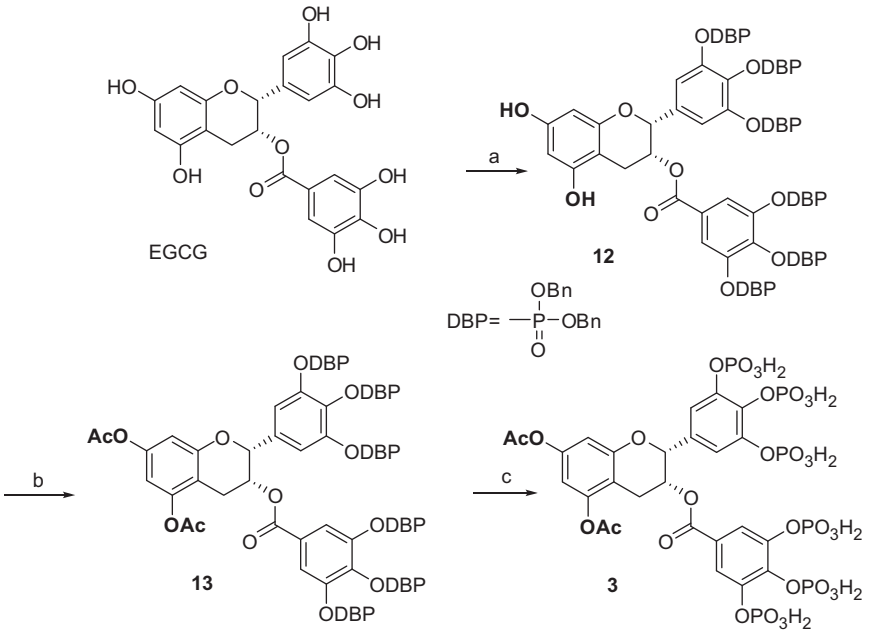
phosphate prodrug is now undergoing phase 1 clinical trial with the potential for combination with other conventional antitumour drugs and radiotherapy.[13–15] The phosphate salt itself is inactive but there is rapid phosphate hydrolysis in vivo to produce combretastatin A-4.[15] Another example is the successful development of Amifostine as the first broad-spectrum cytoprotective agent, on the basis of higher concentration and activity of alkaline phosphatase (which dephosphorylates phosphate esters) in normal cell.[16] An intriguing possibility is to use the cyclic phosphate prodrug approach to direct the parent drug selectively to the liver by taking advantage of the cytochrome P-450 catalyzed oxidation predominantly in hepatocytes.[17–19] Such liver-targeted drug delivery approach has been applied to a collection of nucleosides.[19]

These considerations have prompted us to examine the potential of phosphates or phosphate–acetate hybrids of EGCG and analogs as prodrugs.

A challenge in EGCG chemistry is to differentiate the reactivity of the eight phenolic OH groups. When EGCG was treated with excess dibenzyl phosphite with carbon tetrachloride (CCl_4) together with DMAP/DIPEA in CH_3CN at −10 °C, EGCG was converted to the corresponding dibenzyl phosphate ester **11** (38% yield) with all eight OH phosphorylated (Scheme 1). The phosphorylation was believed to occur through the intermediate dibenzyl chlorophosphate which was generated in situ from the reaction of dibenzyl phosphite with CCl_4.[20] The ^{31}P NMR of **11** showed the expected six signals in the relative intensity ratios of 1:1:1:2:1:2 for the phosphate groups in A, B and G rings. The ^{1}H NMR of **11** also showed the aromatic protons to be well separated and easily assigned to those in A (δ 6.94 and 6.61), B (7.79) and G (7.52) rings. Their chemical shifts are all shifted downfield about 0.8 ppm compared with the same protons in EGCG due to the electron



Scheme 1. Reagents and conditions: (a) Dibenzyl phosphite (8.5 equiv), CCl_4 (40 equiv), DMAP (0.8 equiv), DIPEA (16 equiv), MeCN, 0 °C, 2 h; (b) Pd/C, H_2, THF/MeOH, 4 h.



Scheme 2. Reagents and conditions: (a) Dibenzyl phosphate (6 equiv), CCl_4 (30 equiv), DMAP (0.6 equiv), DIPEA (12 equiv), MeCN, 0 °C, 1 h; (b) DMAP (2.1 equiv), Ac_2O (2.1 equiv), MeCN, 5 min; (c) Pd/C, H_2, THF/MeOH, 4 h.