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A gold-complex initiated functionalization of biologically active polyphenols applied to ^{18}F-labeled chemical probe

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Abstract: (-)-Epigallocatechin gallate (EGCG), a key component of green tea, exerts therapeutic anticancer and antiallergic properties through its binding to the 67-kDa laminin receptor. The functionalization of EGCG is a promising strategy for creating new drug candidates and chemical probes. In our study, we developed a method for effectively modifying the A ring of EGCG through an electrophilic aromatic substitution with amidomethyl 2-alkynylbenzoates initiated with a gold complex. The 2-alkynylbenzoates treated with $(Ph_3P)AuOTf$ under neutral conditions yielded *N*-acylimines. A further electrophilic aromatic substitution resulted in a mixture of EGCG substituted with acylaminomethyl groups at the 6 and 8 positions with a significant amount noted at the 6 position. We then explored the synthesis of ^{18}F-labeled EGCG with a neopentyl labeling group, an

effective labeling group for radiohalogens of not only fluorine-18 but also of astatine-211. To achieve this, we prepared precursors that possessed acid-sensitive protecting groups and base-unstable leaving groups using our established method. Substitution of EGCG with a neopentyl labeling group at either the C6 or C8 position did not affect its anticancer efficacy in U266 cells. Finally, we investigated the preparation of ^{18}F-labeled EGCG. The ^{18}F-fluorination of a mixture of 6- and 8-substituted precursors yielded the corresponding ^{18}F-labeled compounds in 4.5% and 3.0% radiochemical yields (RCYs), respectively. Under acidic conditions, the ^{18}F-labeled 8-substituted compound produced ^{18}F-labeled EGCG in 37% RCY, which heralds the potential of our functionalization approach.

Introduction

(-)-Epigallocatechin gallate (EGCG **1**) is the most abundant catechin in green tea leaves. EGCG **1** exhibits various biological activities such as anticancer and anti-allergic effects.[1] The 67-kDa laminin receptor (67LR) has been identified as a receptor for EGCG that mediates its therapeutic actions.[2] Studies on naturally occurring EGCG-related compounds have suggested that the gallate moiety (D ring) is a crucial pharmacophore for 67LR binding.[3] Furthermore, steps such as combinatorial synthesis and biological evaluation of methylated EGCG have demonstrated that methylation of the hydroxy group at the A and B rings does not significantly reduce its biological activity.[4,5] These results suggest that either the A or B ring of EGCG would be a suitable position for modification with functional groups such as fluorescent dyes or reactive functional groups, and this could be accomplished without compromising the biological activity of EGCG. Indeed, the EGCG

derivatives **3**[6] and **4**[7] possessing a fluorescent dye linked through the A ring are known to be chemical probes for analysis and imaging when using EGCG. However, these chemical probes require a tedious multi-step synthesis to introduce a functional moiety at the A ring. On the other hand, electrophilic substitution allows a site-selective reaction of EGCG at the A ring. Treatment of EGCG with an excess amount of thiol and formaldehyde under acidic conditions provides 6,8-bis(alkylthiomethyl) substituted EGCGs.[8] We have reported the electrophilic substitution of EGCG **1** with 6-azido-6-deoxy-L-idose in the presence of $Sc(OTf)_3$ at 70 ^oC to produce 8-substituted EGCG **2** with an azido group, which does not significantly compromise the anticancer effects of EGCG.[9] The azido-functionalized EGCG is useful as a chemical probe for analyzing EGCG-protein interactions.[10] A direct site-selective modification of EGCG at the A ring could be an efficient and alternative method for the synthesis of biologically active EGCG derivatives. The acidic conditions necessary for these electrophilic substitutions, however, tend to limit the functional groups that could be incorporated. Therefore, the need remains for an effective method that could modify the A ring under mild and neutral conditions.

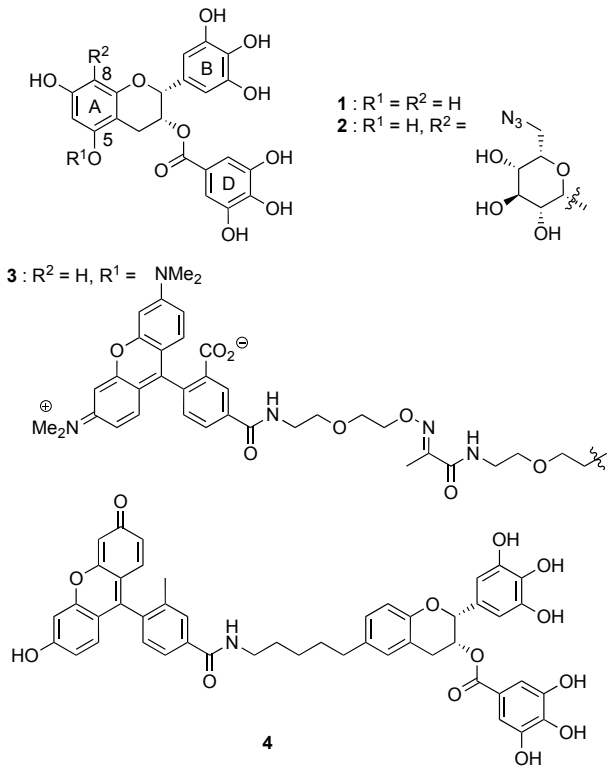
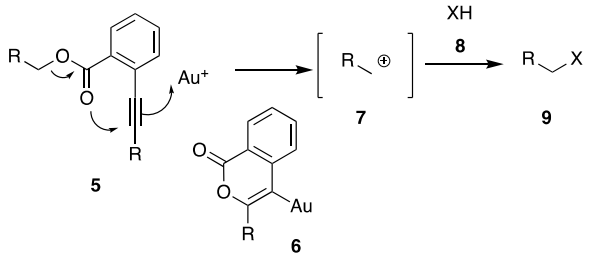


Figure 1. EGCG **1** and the functionalized EGCGs **2**-**4** at the A rings

Ortho-alkynylbenzoate **5** has proven to be an effective alkylating agent in the presence of a gold(I) catalyst under neutral to mildly acidic conditions.[11] This electrophilic coordination of the gold catalyst to a triple bond promotes cyclization to form isocoumarin **6** with an attached Au(I) that generates electrophile **7**, which then couples with nucleophile **8** to produce compound **9**. Asao and co-workers first reported gold-catalyzed O- and N-alkylations of alcohols and sulfonamides using 2-alkynylbenzoates. Yu and co-workers developed glycosyl 2-alkynylbenzoates as glycosyl donors that allow the synthesis of glycosides with acid-sensitive functional groups.[12] Recently, Doi and co-workers reported the preparation of amide/carbamate-linked *N*,*O*-acetals from amidomethyl 2-alkynylbenzoates with bulky amides and alcohols possessing acid-sensitive protecting groups.[13] We hypothesized that amidomethyl 2-alkynylbenzoates would be effective electrophiles for modification of the A ring of EGCG with acidically sensitive functional groups. In this report, we describe a gold

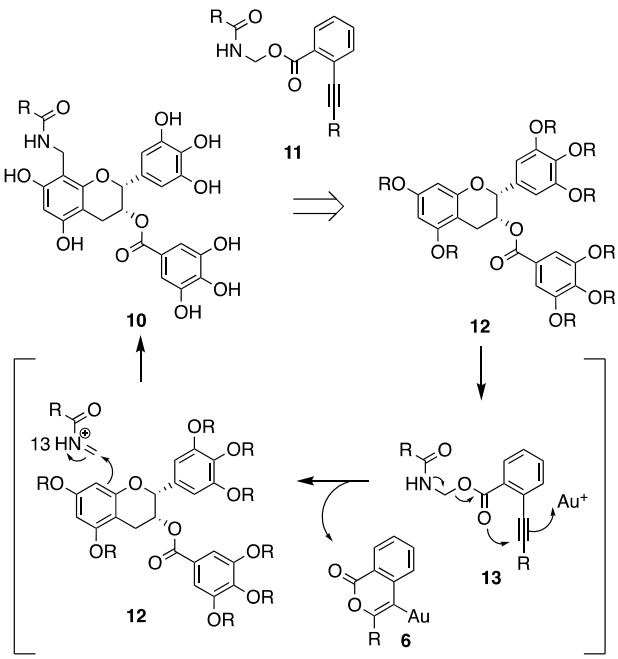
complex-initiated *C*-alkylation of the A ring of EGCG using amidomethyl 2-alkynylbenzoates, and this was followed by application to the synthesis of ^{18}F-labeled EGCG that possesses a neopentyl labeling group.



Scheme 1. *Ortho*-alkynylbenzoate **5** as an alkylating agent.

Results and Discussion

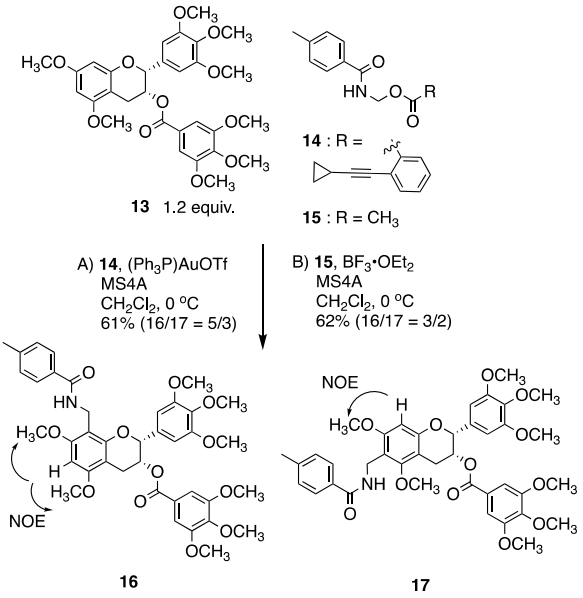
Our approach to the synthesis of EGCG **10** substituted at the C8 position of the A ring is based on an electrophilic substitution of the protected EGCG **12** with amidomethyl 2-alkynylbenzoate **11**. Treatment of the amidomethyl 2-alkynylbenzoate **11** with $(Ph_3P)AuOTf$ generates *N*-acyl imine **13** along with coumarin **6**. *N*-acyl imine **13** reacts with protected EGCG **12** at the electron-rich 8 position of the A ring. This method could be used to directly incorporate acidically and basically sensitive functional groups to EGCG.



Scheme 2. Approach to the synthesis of 8-substituted EGCG **10** based on a gold complex-initiated electrophilic aromatic substitution

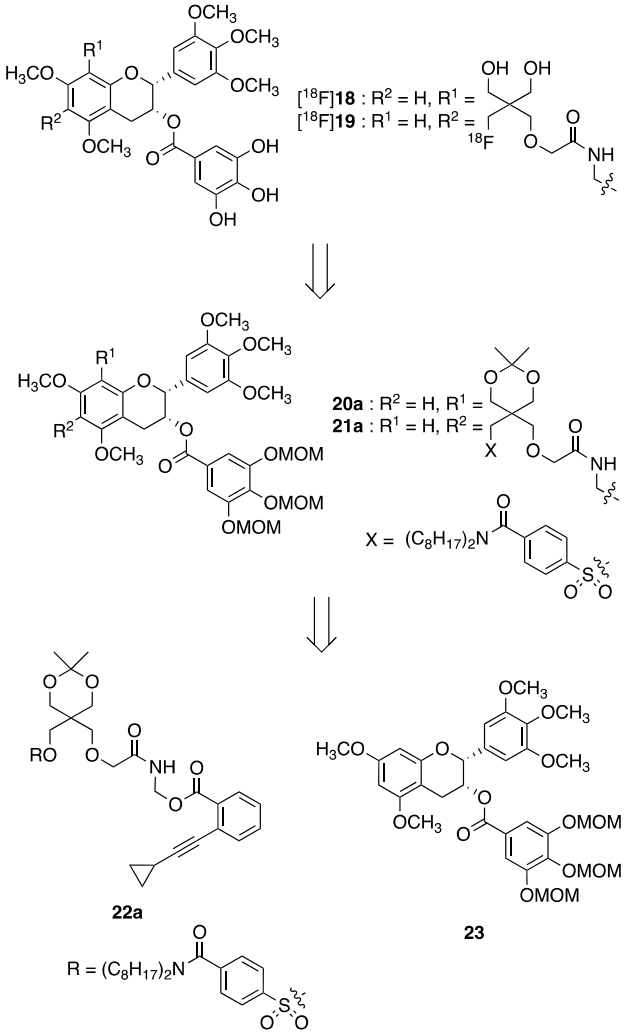
We first examined the electrophilic substitution of *O*-octamethyl EGCG **13**[14] with amidomethyl 2-alkynylbenzoate **14**. A mixture of 2-alkynylbenzoate **14** and 1.2 equivalents of EGCG **13** was treated with 1.0 equivalents of $(Ph_3P)AuOTf$ in dichloromethane at 0 °C, which provided a mixture of 8- and 6-substituted EGCGs **16** and **17** in a 61% yield (**16**/**17** = 5/3). A structural determination of substituted EGCGs **16** and **17** was achieved based on NOESY experiments using each of the products **16** and **17**. The major product **16** showed NOE correlations between a proton of the A ring and two methyl groups. On the other hand, the minor product **17** showed NOE correlations between a proton of the A ring and a methyl group. It should be noted that the generation of a significant amount of 6-substituted EGCG via the electrophilic substitution of protected EGCGs would be a very rare procedure. To estimate the effect that a gold complex-initiated activation of *N*-acyloxymethyl benzamide **14** exerts on site-selectivity of the alkylation of EGCG **13**, an acid-promoted alkylation of EGCG **13** using α-acylaminomethyl acetate **15** was

examined. A mixture of acetate **15** and 1.2 equivalents of EGCG **13** was treated with BF_3•OEt_2 at –40 to –20 °C to provide a mixture of 8- and 6-subsituted EGCG **16** and **17** in a 62% yield (**16**/**17** = 3/2). The ratio of the 8- and 6-subsutited EGCGs **16** and **17** was comparable to that via a gold complex-initiated reaction. These results indicate that regioselectivity is due to the chemical properties of the acyl iminium cation rather than to the reaction conditions. Previously, Ohmori et al. used theoretical calculations to suggest that the preferential electrophilic substitution at the 8 position of flavan-3-ols with carbocations against at the 6 position would be determined not by differences in the ground-state HOMO orbitals but by variations in the stability of the Wheland cation intermediates.[15] Based on this proposal, we decided that the loss of regioselectivity in electrophilic substitution with the iminium could be due to the fact that deprotonation of the Wheland cation intermediates could become the rate-limiting step.



Scheme 3. Electrophilic substitution of *O*-octamethyl EGCG **13** with *N*-acyloxymethyl benzamide **14** and **15**

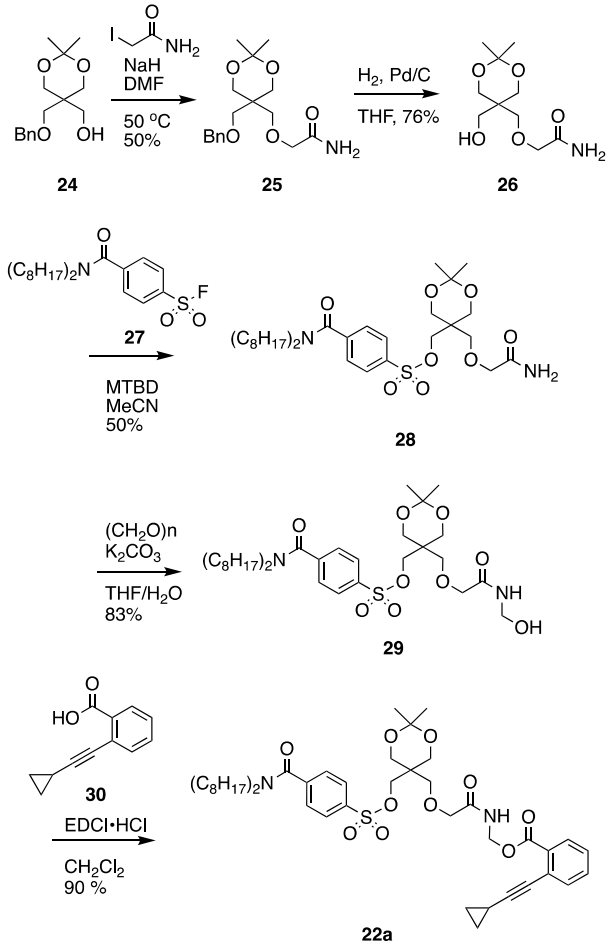
To demonstrate the utility of the method, we planned a synthesis of methylated EGCGs [^{18}F]**18** and [^{18}F]**19** possessing a 2,2-bis(hydroxymethyl)-3-[^{18}F]fluoropropyl group, which is referred to as a neopentyl labeling group (Scheme 4). Fluorine-18 is a positron emitter that is used in positron emission tomography to visualize the location of labeled compounds. The neopentyl labeling group is a hydrophilic labeling group for radiohalogens such as fluoride-18 but also for astatine-211, which is an α-particle emitter.[16-18] The hydrophilicity derived from the hydroxymethyl groups reduces lipophilicity and contributes greatly to the tolerance against in vivo dehalogenation. ^{18}F-labeled EGCG [^{18}F]**18** and [^{18}F]**19** should be effective tools for analysis of the biodistribution of EGCG,[19] and could be prepared from the corresponding precursors **20a** and **21a** that possess (2,2-dimethyl-1,3-dioxan-5-yl)methyl sulfonate. The hydroxy groups of the D ring are protected as acid-labile methoxymethyl ethers, which are removed under the same conditions as propylidene groups. Because radiolabeling is the final step in drug synthesis, it is essential to use reagents that are safe, easy to handle, and adaptable to automated synthesis equipment. For this reason, it is common to use acid-sensitive protecting groups that can be deprotected with an aqueous hydrochloric acid solution. Furthermore, sulfonates, which are essential for nucleophilic fluorination reactions, are unstable under basic conditions. Therefore, The precursors **20a** and **21a** are prepared via electrophilic substitution of EGCG during a gold complex-initiated electrophilic substitution of **23** with *N*-acylaminomethyl benzoate **22a** containing a sulfonyl ester. The coupling reaction proceeds without affecting the acidically and basically sensitive functional groups.



Scheme 4. Strategy for the synthesis of ^{18}F-labeled EGCGs [^{18}F]**18** and [^{18}F]**19**

The preparation of *N*-acylaminomethyl benzoate **22a** is outlined in Scheme 5. Alcohol **24**[20] was prepared from pentaerythritol and treated with sodium hydride in DMF, and was administered following a reaction with α-iodoacetamide at 50 °C to provide primary amide **25** in 50% yield. Hydrogenolysis of benzyl ether **25** in the presence of Pd/C provided alcohol **26** in 76% yield. Alcohol **26** was treated with sulfonyl fluoride **27** in the presence of 7-methyl-1,5,7-triazabicyclo[4.4.0]dec-5-ene (MTBD) in CH_3CN at 0 °C to provide sulfonyl ester **28** in 50% yield. The primary amide **28** was treated with paraformaldehyde under basic conditions to provide *N*-

(hydroxylmethyl)amides **29** in an 83% yield. The sulfonyl ester was not decomposed under the reaction conditions. Alcohol **29** was reacted with *ortho*-alkynylbenzoic acid **30** in the presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI•HCl) in CH_2Cl_2 to provide the linker **22a** in 90% yield.

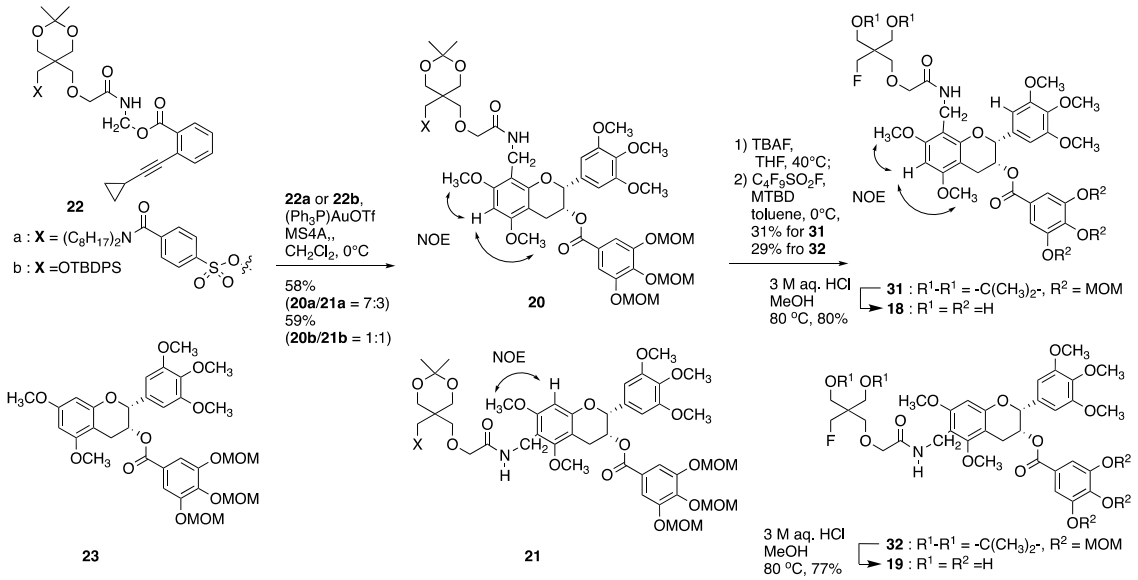


Scheme 5. Preparation of the sulfonate **22a**.

We first examined the coupling of EGCG with *tert*-butyldiphenylsilyl (TBDPS) ether **22b**. *Ortho*-alkynylbenzoate **22b** and 1.1 equivalents of EGCG **23** were treated with 1.0 equivalents of $(Ph_3P)AuOTf$ in dichloromethane in the presence of MS4A at 0 °C. The gold-mediated *C*-acylation of EGCG **23** with (*N*-acylamino)methyl benzoate **22b** proceeded under the proposed reaction

conditions without affecting the acid-labile acetal to provide a mixture of the 8- and 6-subsituted EGCGs **20b** and **21b** in 59% yield. (**20b**/**21b** = 1/1). The ratio was determined via the ^{1}H NMR spectra of a mixture of the products based on the ^{1}H NMR spectra of each isomer, which was separated via HPLC. Structural determination of the 8-subsituted EGCGs **20b** was achieved based on 1D and 2D NMR experiments involving NOE correlations between a proton of the A ring and two methyl groups. Finally, *ortho*-alkynylbenzoate **22a** was reacted with 1.1 equivalents of EGCG **23** under the established conditions to provide a mixture of the 8- and 6-subsituted EGCGs **20a** and **21a** in a 58% yield. (**20a**/**21a** = 7/3). The ratio was determined via the ^{1}H NMR spectra of a mixture of the products based on the ^{1}H NMR spectra of each isomer. The mixture was further purified via HPLC for structural determination, which provided the 8- and 6-subsituted EGCGs **20a** and **21a** in 29% and 12% yields.

We next examined the synthesis of the 6 and 8-substituted fluorides **18** and **19** as authentic samples from the mixture of **20b** and **21b**. A mixture of the 8-and 6-isomers **20b** and **21b** was treated with tetrabutylammonium fluoride (TBAF) in THF. Subsequent treatment of the resulting alcohol with nonafluorobutanesulfonyl fluoride in the presence of MTBD in toluene at 0 ^{o}C provided the corresponding sulfonate in situ, which subsequently underwent fluorination with the released fluoride at the same temperature to provide the 8- and 6-isomers **31** and **32** in 31% and 29% yields, respectively.[21] Structural determination of each of the isomers **31** and **32** was temporally achieved by comparing the ^{1}H NMR spectra of **31** and **32** with those of **20b** and **21b**. Finally, removal of all protecting groups from the hydroxy groups of isomers **31** and **32** under acidic conditions provided the 8 and 6-substituted EGCGs **18** and **19** in 80% and 77% yields, respectively. The structure of the 8-isomer **18** was confirmed by its NOESY spectrum that involved NOE correlations between a proton of the A ring and two methyl groups.



Scheme 6. Preparation of sulfonates **20a** and **21a** as well as fluorides **18** and **19**.

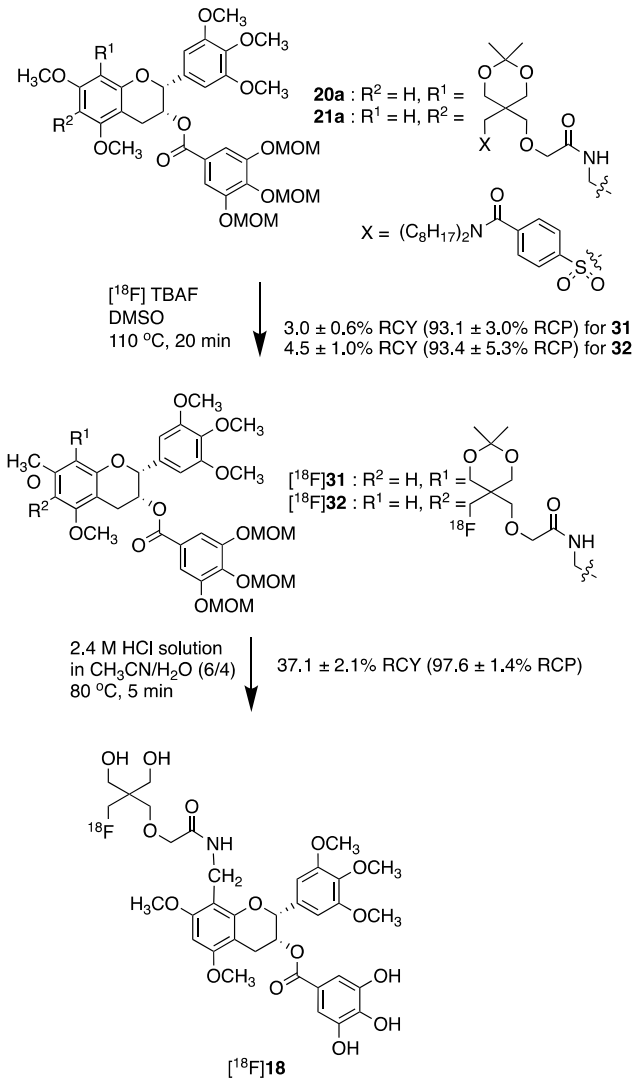
We next investigated the anti-cancer effect of fluorinated EGCGs **18** and **19** in U266 cells (a human multiple myeloma cell line).[22] (-)-EGCG **1** was used as a positive control. The cytotoxicity of EGCG against U266 cells is mediated with 67LR. The U266 cells were incubated with **18** and **19** and (-)-EGCG **1** (0, 5.0, 10, 25, or 50 μM) for 120 h at 37 °C. The relative number of viable cells was estimated using an ATPlite assay. The IC_{50} cytotoxicity values of 8- and 6-subsituted EGCGs **18** and **19** against U266 cells were similar to that of natural (-)-EGCG **1**. These results indicate that linking the neopentyl labeling group at the 6 or 8 position of the A ring does not interfere with the biological function of EGCG.

Table 1. The anti-cancer effect of fluorinated EGCGs **18** and **19** and of EGCG **1** in U266 cells

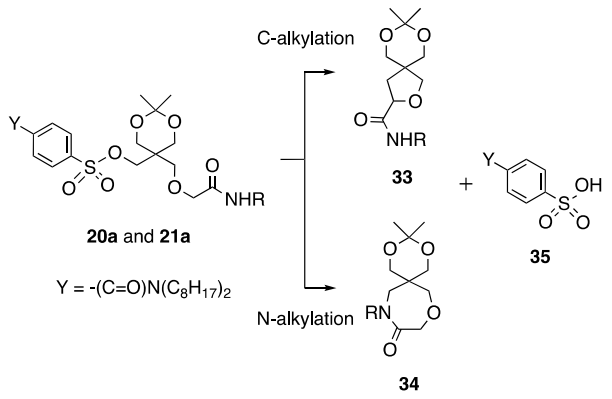
Entry	Sub	IC_{50} [μM]
1	**18**	18
2	**19**	21
3	EGCG **1**	18

Finally, we used automated synthesizers to examine the synthesis of ^{18}F-labeled EGCG [^{18}F]**18** (Scheme 7). A mixture of precursors **20a** and **21a** was treated with [^{18}F]tetrabutylammonium fluoride in dimethyl sulfoxide (DMSO) at 110 °C for 20 min. Purification of the reaction mixture by semi-preparative HPLC provided the ^{18}F-fluorinated products [^{18}F]**31** and [^{18}F]**32** in 4.5 ± 1.0% and 3.0 ± 0.6% radiochemical yields (RCYs, based on [^{18}F]fluoride anions) with 93.4 ± 5.3% and 93.1 ± 3.0% radiochemical purity (RCP), respectively (n = 4). An HPLC analysis of the reaction mixture based on UV absorption at 254 nm indicated that most of the precursors **20a** and **21a** were consumed. To estimate the side reactions that reduced the RCY of ^{18}F-fluorinated products [^{18}F]**31** and [^{18}F]**32**, the reaction mixture was purified via solid-phase extraction and subjected to HPLC-MS analysis. Positive high-resolution electrospray ionization mass spectrometry (HRMS) data showed that the reaction mixture involved two main side-products, **I** and **II**, with the molecular formulae $C_{44}H_{57}NO_{18}$ and $C_{31}H_{41}NO_{11}$, respectively. These results suggest that product **I** could be a result of the elimination of 4-(dioctylcarbomoyl)benzenesulfonic acid (**35**) from the precursors **20a** and **21a**, and the side-products **II** would have been generated by the hydrolysis of gallate in product **I**. We estimated that heated basic ^{18}F-fluorination conditions could promote undesired intramolecular *C*- or

N-alkylations in precursors **20a** and **21a** to provide the 5- or 7-membered cyclic products **33** or **34** via intramolecular *C*- or *N*-alkylations to release either sulfonic acid **35** or the corresponding salt (Scheme 8). Next, deprotection of the ^{18}F-fluorinated product [^{18}F]**30** was examined. The ^{18}F-fluorinated product [^{18}F]**31** was treated in 2.4 M of HCl in CH_3CN/H_2O (4/6) at 80 °C for 5 min. The reaction mixture was diluted with water and then loaded onto an Oasis HLB Short cartridge (Waters). After the cartridge was washed with water, it was rinsed with ethanol to provide the ^{18}F-labeled EGCG [^{18}F]**18** in 37.1 ± 2.1% RCY (based on [^{18}F]**31**) with 97.6 ± 1.4% RCP, as determined via radio-HPLC (n = 3).



Scheme 7. The synthesis of ^{18}F-labeled EGCG [^{18}F]**18** from precursors **20a** and **21a**.



Scheme 8. Expected side-reaction of **20a** and **21a** during ^{18}F-fluorination.

In conclusion, we successfully developed a method for the direct modification of EGCG via a gold complex-initiated electrophilic aromatic substitution with an *N*-(2-alkynylbezoyloxyl)methyl amide. This amide generated *N*-acyl imine in the presence of $(Ph_3P)AuOTf$ and provided a mixture of *N*-acylaminomethyl-substituted EGCG at the 6 and 8 positions. This unique selectivity could be due to the nature of *N*-acyl imine as an electrophile. Using the proposed method, we needed only a single step to prepare EGCGs **20a** and **21a** possessing a {5-sulfonyloxymethyl-(2,2-dimethyl-1,3-dioxan-5-yl)}methyl group from the *O*-protected EGCG. ^{18}F-Fluorination of sulfonates **20a** and **21a** provided ^{18}F-labeled-EGCG **31** and **32**. After separation of the isomers, removal of the *O*-protecting group of [^{18}F]**31** provided ^{18}F-labeled EGCG [^{18}F]**18** with a neopentyl labeling group. It should be noted that this is the first report of the synthesis of ^{18}F-labeled EGCG without a significant loss of its binding affinity to 67LR. We currently are focusing our efforts on improving the radiochemical yield of ^{18}F-labeled EGCG via evaluation of its biological distribution.

Acknowledgments

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Keywords: 18F-fluorination • PET tracers • acetonitrile • Solid-phase extraction • amyloid-β

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