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Design, synthesis and RNase A inhibition activity of catechin and epicatechin and nucleobase chimeric molecules

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ABSTRACT

Several novel catechin/epicatechin and nucleobase chimeric molecules **1–6** have been synthesized via azide-alkyne click chemistry. The structures of these hybrids have been confirmed by NMR and mass spectroscopic data. The synthesized molecules were tested for their RNase A inhibition activities. Gel-based assays showed inhibition in micromolar concentrations. The extent of inhibition was found to be dependent upon the nature of base as well as the configuration at C-3 position of catechin.

Proteins belonging to the RNase superfamily are endonucleases that catalyze the degradation of RNA via a two step transphosphorylation-hydrolytic reaction.[1] Although some of these enzymes have purely digestive role, there are others which exhibit potent and unusual biological properties.[2] For example, angiogenin the protein found in the plasma induces new blood vessel formation and thus plays a crucial role in the spreading of primary tumors.[3] Some RNases are neurotoxic and may produce symptoms associated with overproduction of eosinophils.[4] Thus it is implied that inhibition for these enzymes might suppress the biological action of these proteins and hence prove useful for treatment of human diseases and for mechanistic studies. Bovine pancreatic RNase A is a convenient model for development of inhibition because of its well defined active site geometry.[5] The nucleolytic center consisted of multiple subsites that bind the phosphate, the base and the ribose components of its RNA substrate, with the P site stabilizing the phosphate the B site the bases (Fig. 1). At site P_1 cleavage of the phosphodiester occurs. B_1 is the binding site of the base whose 3′ oxygen is involved in the phosphate being hydrolyzed. Besides, there are other subsites P_0, P_2 and B_0 (not shown). Because of the reported RNase activity of natural polyphenols like EGCG,[6] we became interested in synthesizing novel nucleobase-catechin or epicatechin chimeric molecules. The two units are joined by a triazole linker constructed via a click reaction. It is expected that the 5-membered triazole (although planar) may mimic the ribose unit

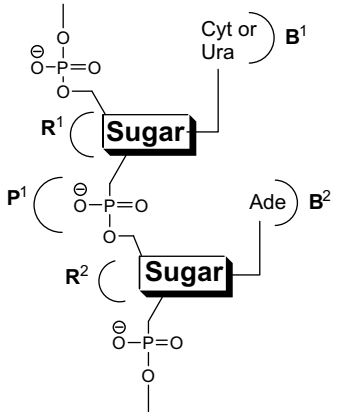

Figure 1. Schematic representation of active site of RNase A with RNA.

while the nucleobase will have binding interactions with the B1-site.

The synthesis of the target molecules require the 3-*O*-propargyl tetrabenzyl catechin or epicatechin which was prepared by propargylation of tetrabenzyl catechin (**TBC**) or epicatechin (**TBEC**). The benzyl ether was chosen as the protecting group because of its deprotection under neutral condition. Acid or base sensitive protecting groups needed to be avoided because of possible racemization at C-2.[7] The other component for the click reaction, namely the azido ethyl nucleobases were prepared using a standard protocol

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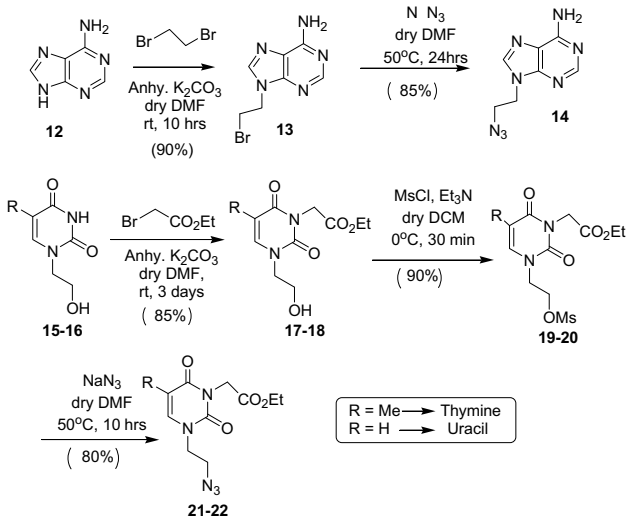


Scheme 1. Synthesis of azido-nucleobases.

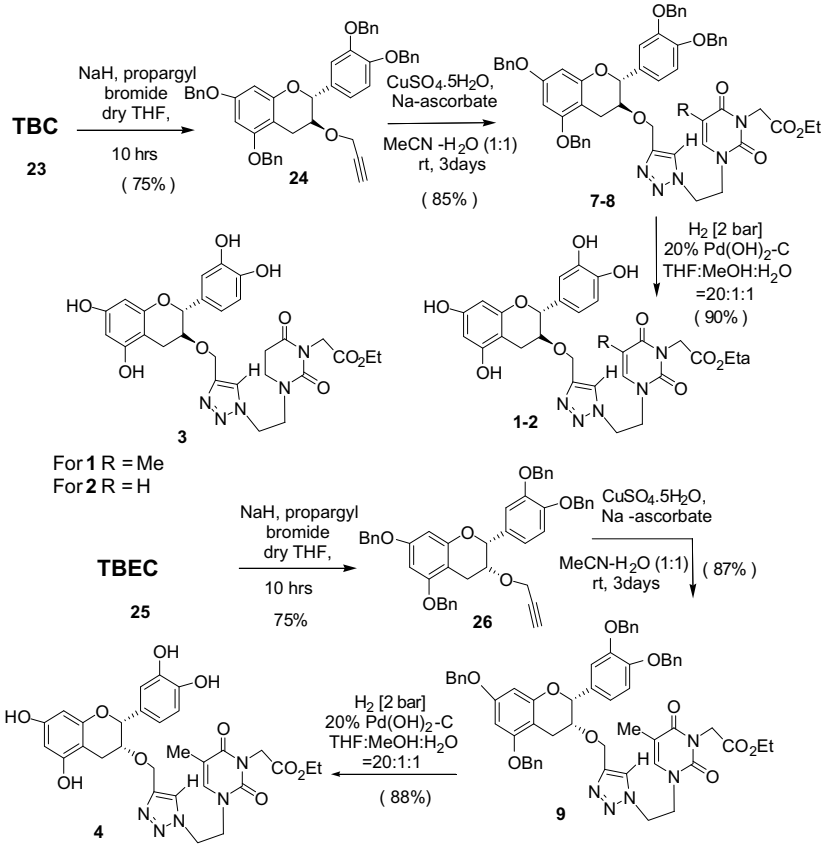
as shown in Scheme 1. The click reaction[8] was performed in presence of Cu (I) made in situ by reduction of $CuSO_4$ with L-ascorbate. The protected chimeric molecules were isolated by pure Si-gel chromatography. Deprotection with H_2 in presence of Pearlman catalyst[9] furnished the final compounds (Schemes 2 and 3). These were all fully characterized by NMR and mass spectral data. The regiochemistry of the cycloaddition was proved to be 1, 3 as revealed by the NOESY spectrum recorded on the catechin adenine chimera. The cross peak observed between the NCH_2 and the olefinic hydrogen confirmed the proposed structure.

Inhibition of RNase A was checked qualitatively by an agarose gel based assay, wherein the degradation of the 28s and 18s rRNA was studied. The ribonuclease A of concentration 0.011 μM was mixed with the synthesized compounds and incubated for 6 hrs at 37 °C. To these preincubated enzyme solutions the RNA (0.22 μg/μl) was added as substrate and the incubation was allowed for a further 15 min. The resulting solution was mixed with 40% sucrose solution (made from RNase free water) and 0.25% bromophenol blue (dissolved in 1× TAE buffer) and loaded onto a 1.1% agarose gel. The bands were visualized under a UV–transilluminator by virtue of the ethidium bromide (final concentration 0.5 μg/mL) present in the gel. Comparison of the gel pattern (Fig. 2) in various lanes indicated that the pyrimidine based chimeric molecules are better inhibitors than the adenine based ones. This was expected as the site B1 has a preference for pyrimidine bases.[10] Between the two adenine based chimeras, the epicatechin based one did not show any inhibition while the catechin did show some inhibition under identical conditions thus showing the importance of the C-3 OH stereochemistry.

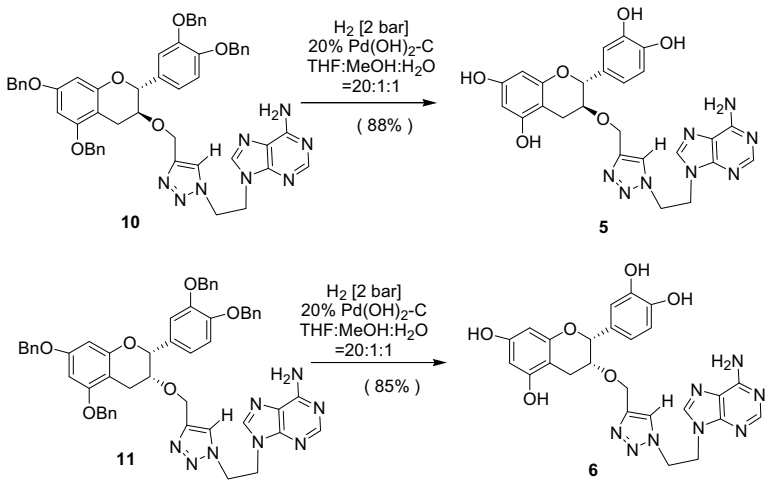
In conclusion, several novel catechin and epicatechin nucleobase chimeric molecules[11] have been synthesized. All the pyrimidine based molecules were found to be potent inhibitors of RNase A and are thus good candidates for further evaluation.

Selected experimental procedure and spectral data. All the ^1H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively.

General procedure for the click reaction. Compounds **7**–**11** were synthesized by this procedure. 3-*O*-propargyl tetrabenzyl catechin or epicatechin (0.13 mmol) and azido-nucleobases **14**, **21**–**22** (0.13 mmol) were dissolved in acetonitrile/H_2O mixture (1:1). Copper sulfate (1 equiv) and sodium ascorbate (2 equiv) were added and the mixture was stirred at room temperature until TLC indicated the disappearance of the starting materials (~24 h). The mix-



Scheme 2. Synthesis of pyrimidine based chimeras via click reaction.



Scheme 3. Synthesis of adenine based chimeras via click reaction.

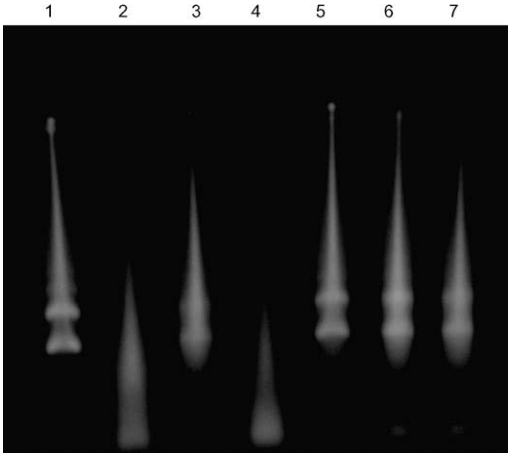


Figure 2. Lane 1: RNA + water + methanol, lane 2: RNA + RNase A + methanol, lane 3: RNA + RNase A + catechin adenine chimera **5** (0.476 mM), lane 4: RNA + RNase A + epicatechin adenine chimera **6** (0.476 mM), lane5: RNA + RNase A + catechin thymine chimera **1** (0.412 mM), lane 6: RNA + RNase A + epicatechin thymine chimera **4** (0.412 mM), lane 7: RNA + RNase A + catechin uracil chimera **2+3** (0.423 mM).

ture was poured into satd aq NH_4Cl solution (1:1, 20 mL) and the product was extracted four times with EtOAc. The organic layer was dried with Na_2SO_4 and filtered, and the solvent was removed under reduced pressure. The residue was purified by flash chromatography.

General procedure of debenzylation reaction. Compounds **1**–**6** were synthesized by this procedure. Solutions of compounds **7**–**11** (0.041 mmol) in a mixture of THF/MeOH/H_2O (20:1:1) (22 mL) were hydrogenated at 2 bar pressure over 20% $Pd(OH)_2/C$ (5 mg) for 2 h at room temperature. Filtration and concentration afforded a pale brown solid, which was purified by Si-gel (230–400 mesh, N_2 flash) short column chromatography (MeOH–$CHCl_3$) to give pure **1**–**6** (95%) as pale brown amorphous solids.

For **11**. ν_{max} ($CHCl_3$, cm^{-1}): 2930, 1609, 1445, 1262, 1219, 1143,1027; $\delta_{\mathbf{H}}$ ($CDCl_3$): 8.32 (1H, s), 7.46–7.28 (21H, m), 7.24 (1H, m), 7.20 (1H, s), 6.83 (2H, m), 6.40 (1H, s), 6.27 (2H, s), 5.66 (2H, br s), 5.13–5.10 (4H, m), 5.03–4.98 (4H, m), 4.87 (1H, s), 4.54–4.42(5H, m), 3.92 (1H, s), 3.03 (1H, d, J = 16 Hz), 2.80 (1H, dd, J = 17.2, 4.0 Hz), $\delta_{\mathbf{C}}$ ($CDCl_3$): 158.6, 158.0, 155.4, 155.1, 152.5, 149.6, 148.3, 148.2, 145.5, 140.5, 137.1, 137.0, 136.9, 136.8, 132.4, 128.5, 128.4, 128.3, 127.9, 127.8, 127.5, 127.4, 127.3, 127.1, 123.2, 119.8, 114.4, 113.8, 101.3, 94.7, 93.9, 77.8, 72.2, 71.3, 71.2, 70.1, 69.9, 62.4, 48.7, 43.1, 24.7. Mass (ES^+): m/z 893 [MH^+].

For **6**. $\nu_{\mathbf{max}}$ (KBr, cm^{-1}): 3431, 1637, 1385, 1220, 1112, 1078; $\delta_{\mathbf{H}}$ (MeOH-d_4): 8.18 (1H, s), 7.69 (1H, s), 7.23 (1H, s), 7.10 (1H, s), 6.75–6.72 (2H, m), 5.93–5.88 (2H, m), 4.83 (1H, s), 4.76–4.75 (1H, br s), 4.68–4.67 (2H, m), 4.49, 4.38 (2× 1H, AB_q, J = 13.2 Hz), 3.89 (1H, s), 3.35 (1H, s), 2.88 (1H, d, J = 16.8 Hz), 2.72 (1H, dd, J = 13.2, 3.8 Hz); $\delta_{\mathbf{C}}$ (MeOH-d_4): 158.1, 157.9, 157.5, 157.4, 154.1, 150.8, 146.8, 146.0, 142.6, 132.5, 125.3, 119.6, 116.0, 115.6, 115.5, 99.9, 96.5, 95.9, 79.2, 75.0, 63.4, 44.9, 30.8, 25.8. Mass (ES^+): m/z 555 [MNa^+], 533 [MH^+].

For **10**. ν_{max} ($CHCl_3$, cm^{-1}): 2942, 1618, 1445, 1260, 1028; δ_H ($CDCl_3$): 8.26 (1H, s), 7.52–7.28 (22H, m), 6.94 (1H, s), 6.90–6.85 (2H, m), 6.79–6.71 (2H, m), 6.25 (1H, d, J = 2.0 Hz), 6.18 (1H, d, J = 2.0 Hz), 5.14 (2H, s), 5.09 (2H, d, J = 8.0 Hz), 5.05 (2H, s), 5.01 (2H, s), 4.72 (2H, d, J = 7.6 Hz), 4.61 (4H, s), 4.45, 4.23 (2× 1H, AB_q, J = 12.8 Hz), 3.77 (1H, dd, J = 13.2, 8.0 Hz), 3.04 (1H, dd, J = 16.4, 5.6 Hz), 2.62 (1H, dd, J = 16.4, 8.4 Hz); δ_C ($CDCl_3$): 158.7, 157.6, 155.3, 155.1, 152.6, 148.7, 148.6, 145.5, 140.5, 137.1, 137.0, 136.9, 136.8, 132.3, 128.6, 128.5, 128.4, 128.0, 127.9, 127.8, 127.5, 127.3, 127.2, 123.04, 120.6, 114.6, 113.6, 102.0, 94.3, 93.7, 79.4, 62.7, 48.7, 43.3, 25.5. Mass (ES^+): m/z 893 [MH^+].

For **5**. ν_{max} (KBr, cm^{-1}): 3428, 1635, 1384, 1222, 1145, 1078; δ_H (MeOH-d_4): 8.34 (1H, s), 8.15 (1H, s),7.76 (1H, s), 7.41 (1H, s), 6.77–6.74 (2H, m), 6.68–6.66 (1H, m), 5.93 (1H, s), 5.85 (1H, *s*), 4.7 (2H, br s), 4.68 (1H, d, J = 7.22 Hz), 4.45 , 4.34 (2× 1H, AB_q, J = 12.8 Hz), 3.77–3.72 (1H, m), 2.84 (1H, dd, J = 16.0 , 5.2 Hz), 2.52 (1H, dd, J = 16.0 , 8.0 Hz); $\delta_{\mathbf{C}}$ (MeOH-d_4): 158.1, 157.7, 157.3, 157.0, 154.0, 150.8, 146.8, 146.3, 146.6, 146.2, 132.5, 125.4, 120.1, 116.3, 115.3, 100.5, 96.5, 95.7, 80.9, 76.7, 63.37, 44.9, 30.9, 26.2. Mass (ES^+): m/z 555 [MNa^+], 533 [MH^+].

For **9**. ν_{max} ($CHCl_3$, cm^{-1}): 2927, 1747, 1705, 1652, 1461, 1377, 1264, 1218, 1146; δ_H ($CDCl_3$):7.48–7.29 (20H, m), 6.97 (1H, s), 6.95–6.91 (2H, m), 6.71 (1H, s), 6.50 (1H, s), 6.27 (2H, s), 5.14 (2H, s), 5.10 (2H, s), 5.03 (2H, s), 5.01 (2H, s), 4.90 (1H, s), 4.67 (2H, s), 4.63–4.47 (2H, m), 4.36 (2H, t, J = 5.6 Hz), 4.27–4.21 (2H, m), 4.03–4.01 (3H, m), 3.04 (1H, d, J = 17.2 Hz), 2.82 (1H, dd, J = 17.2, 4.0 Hz), 1.67 (3H, s), 1.26 (3H, t, J = 7.2 Hz); δ_C ($CDCl_3$): 167.7, 162.8, 158.6, 158.0, 155.4, 150.9, 148.2, 148.1, 145.5, 138.7, 137.1, 137.0, 136.9, 136.8, 132.3, 128.6, 128.5, 128.4, 128.3, 128.0, 127.9, 127.8, 127.6, 127.5, 127.4, 127.2, 123.6, 119.8, 114.2, 113.5, 110.0, 101.3, 94.7, 93.9, 77.8, 72.3, 71.2, 71.1, 70.1, 69.9, 62.3, 61.6, 49.1, 47.6, 42.0, 37.7, 24.8, 14.1, 12.6. Mass (ES^+): m/z 970 [MH^+].

For **4**. ν_{max} (KBr, cm^{-1}): 3420, 1742, 1640, 1466, 1380, 1232, 1146; δ_H (MeOH-d_4): 7.22 (1H, s), 6.94 (1H, s), 6.89 (1H, s), 6.74 (2H, s), 5.93 (1H, d, J = 2.0 Hz), 5.87 (1H, d, J = 2.0 Hz), 4.83 (1H, s), 4.62 (2H, s), 4.52 (1H, d, J = 12.8 Hz), 4.39 (1H, d, J = 12.8 Hz), 4.18 (2H, q, J = 7.2 Hz), 4.12 (2H, t, J = 5.6 Hz), 3.94 (1H, s), 3.59 (2H, dd, J = 14.0, 7.2 Hz), 2.90 (1H, d, J = 16.0 Hz), 2.73 (1H, dd, J = 16.8 , 4.0 Hz), 1.74 (3H, s), 1.25 (3H, t, J = 7.2 Hz); δ_C (MeOH-d_4): 168.2, 163.5, 156.5, 156.3, 155.9, 151.0,145.2, 144.4, 144.3, 139.9, 130.9, 124.2, 118.1, 114.4, 114.0, 109.0, 98.4, 94.9, 94.3, 77.6, 73.5, 62.0, 61.3, 48.9, 47.8, 41.7, 24.4, 13.0,11.3. Mass (ES^+): m/z 632 [MNa^+], 610 [MH^+].

For **7**. ν_{max} ($CHCl_3$, cm^{-1}): 2922, 1746, 1652, 1460, 1264, 1228, 1145; δ_H **($CDCl_3$):**7.44–7.28 (20H, *m*), 6.98–6.91 (4H, m), 6.49 (1H, s), 6.25 (1H, d, J = 2.0 Hz), 6.19 (1H, d, J = 2.0 Hz), 5.15 (2H, s), 5.11 (2H, d, J = 6.0 Hz), 5.00 (2H, s), 4.96 (2H, s), 4.68–4.67 (1H, m), 4.50–4.42 (2H, m), 4.19 (2H, q, J = 7.2 Hz), 4.11 (2H, t, J = 5.6 Hz), 4.07 (2H, t, J = 6.4 Hz), 3.84–3.82 (1H, m), 3.03 (1H, dd, J = 16.4, 5.6 Hz), 2.67–2.63 (1H, m), 1.69 (3H, s), 1.26 (3H, t, J = 7.2 Hz); δ_C ($CDCl_3$): 167.8, 162.8, 158.7, 157.6, 155.1, 151.0, 148.7, 148.6, 145.5, 138.6, 132.3, 137.0, 136.9, 136.8, 136.7, 128.5, 128.4, 127.9, 127.8, 127. 7, 127.6, 127.5, 127.4, 127.3, 127.2, 123.9, 120.7, 14.5, 113.4, 110.1, 102.0, 94.3, 93.7, 79.5, 74.9, 71.2, 71.1, 70.0, 69.9, 62.6, 61.6, 49.3, 47.8, 42.0, 37.7, 25.7, 14.1, 12.6. Mass (ES^+): m/z 970 [MH^+].

For **1**. ν_{max} (KBr, cm^{-1}): 3426, 1740, 1650, 1462, 1380, 1232, 1145; δ_H (MeOH-d_4): 7.53 (1H, s), 6.98 (1H, *s*), 6.76–6.68 (3H, m), 5.92 (1H, d, J = 2.4 Hz), 5.84 (1H, d, J = 2.4 Hz), 4.67–4.66 (3H, m), 4.61 (2H, *s*), 4.49, 4.41 (2× 1H, AB_q, J = 12.8 Hz), 4.20–4.15 (5H, m), 3.60 (2H, dd, J = 14.0 , 7.2 Hz), 2.85 (1H, dd, J = 16.4 , 5.2 Hz), 2.54 (1H, dd, J = 16.4 , 8.0 Hz), 1.74 (3H, s), 1.26 (3H, t, J = 7.2 Hz); δ_C (MeOH-d_4): 168.2, 163.5, 156.5, 156.1, 155.3, 151.0, 145.3, 144.7, 139.8, 130.9, 127.2, 124.2, 118.4, 114.6, 113.6, 109.0, 98.9, 94.8, 94.0, 79.3, 75.1, 61.8, 61.3, 49.0, 48.0, 41.7, 24.6, 13.0, 11.2. Mass (ES^+): m/z 632 [MNa^+], 610 [MH^+].

For **8**. ν_{max} ($CHCl_3$, cm^{-1}): 2926, 1741, 1670, 1451, 1262, 1219, 1027; δ_H ($CDCl_3$): 7.45–7.28 (20H, m), 6.97 (1H, d, J = 4.8 Hz), 6.93 (1H, m), 6.60 (1H, d, J = 8.0 Hz), 6.25 (1H, s), 6.19 (1H, s), 5.44 (1H, d, J = 7.6 Hz), 5.15 (2H, s), 5.11 (2H, d, J = 5.2 Hz), 5.02 (2H, s), 5.00 (2H, s), 4.73 (1H, d, J = 8.0 Hz), 4.63 (2H, s), 4.52–4.46 (2H, m), 4.18 (2H, q, J = 7.2 Hz), 4.12–4.04 (3H, m), 3.86–3.81 (2H, m); 3.05 (1H, dd, J = 16.4 , 5.2 Hz), 2.63 (1H, dd, J = 16.4 , 8.4 Hz), 1.26 (3H, t, J = 7.2 Hz); δ_C ($CDCl_3$): 167.6, 161.8, 158.7, 157.6, 155.1, 151.0, 148.7, 148.6, 145.6, 142.6, 137.0, 136.9, 136.8, 136.7, 132.3, 128.6, 128.5, 128.4, 127.9, 127.8, 127.5, 127.4, 127.3, 123.9, 120.7, 114.5, 113.5, 101.9, 101.6, 94.3, 93.7, 79.5, 74.9, 71.3, 71.1, 70.0, 69.9, 62.6, 61.7, 49.6, 47.7, 41.7, 25.8, 14.1. Mass (ES+): m/z 956 [MH+].

For **3**. ν_{max} (KBr, cm^{-1}): 3406, 1745, 1658, 1503, 1420, 1360, 1342, 1225, 1122; δ_H (MeOH-d_4): 7.57 (1H, s), 6.78–6.74 (3H, m), 5.92 (1H, d, J = 1.6 Hz), 5.84 (1H, d, J = 1.6 Hz), 4.60–4.56 (3H, m), 4.50 (1H, d, J = 12.8 Hz), 4.43 (1H, dd, J = 12.4, 4.4 Hz), 4.22–4.11 (3H, m), 3.85–3.77 (3H, m), 3.21 (2H, t, J = 6.4 Hz), 2.84 (1H, dd, J = 16.0, 5.6 Hz), 2.62 (2H, t, J = 6.4 Hz), 2.54 (1H, dd, J = 16.0, 7.6 Hz), 1.23 (3H, t, J = 7.2 Hz); δ_C (MeOH-d_4): 168.1, 163.0, 156.5, 156.2, 155.4, 145.3, 144.8, 144.0, 130.9, 124.1, 118.5, 114.6, 113.7, 100.2, 94.8, 94.0, 79.3, 75.0, 61.8, 61.3, 61.1, 49.4, 48.1, 47.7, 41.3, 30.5, 24.7, 13.0. Mass (ES^+): m/z 598 [MH^+].

For **2**. ν_{max} (KBr, cm^{-1}):3406, 1740, 1652, 1458, 1284, 1226, 1143, 1060, 1025; δ_H (MeOH-d_4):7.54 (1H, s), 7.12 (1H, d, J = 8.0 Hz), 6.71–6.69 (3H, m), 5.92 (1H, d, J = 1.6 Hz), 5.84 (1H, d, J = 1.6 Hz), 5.53(1H, d, J = 8.0 Hz), 4.67 (2H, d, J = 6.8 Hz), 4.60–4.56 (3H, m), 4.50 (1H, d, J = 12.4 Hz), 4.43 (1H, dd, J = 12.4, 4.0 Hz), 4.21 (2H, q, J = 7.6 Hz), 3.85–3.77 (3H, m), 2.84 (1H, dd, J = 16.4, 5.6 Hz), 2.54 (1H, dd, J = 16.4, 8.0 Hz), 1.23 (3H, t, J = 7.2 Hz); Mass (ES^+): m/z 596 [MH^+].

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