In silico design, synthesis and evaluation of 3′-*O*-benzylated analogs of salacinol, a potent α-glucosidase inhibitor from Ayurvedic traditional medicine "*Salacia*"

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Electronic Supplementary Information (ESI)

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Experimantal Section

IR spectra were measured on either a Shimadzu IR-435 grating spectrophotometer or a Shimadzu FTIR-8600PC spectrophotometer. NMR spectra were recorded on a JEOL JNM-ECA 500 (500 MHz ^{1}H, 125 MHz ^{13}C) spectrometer. Low-resolution and high-resolution mass spectra were recorded on a JEOL JMS-HX 100 spectrometer. Optical rotations were determined with a JASCO P-2200 polarimeter. Column chromatography was effected over Fuji Silysia silica gel BW-200.

1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-1-*O*-(*p*-methoxybenzyl)-2-*O*-(*o*-nitrobenzyl)-D-erythritol-4-yl]episulfoniumylidene}-2,3,5-tri-*O*-(*p*-methoxybenzyl)-D-arabinitol Tetrafluoroborate (α-13k and β-13k)

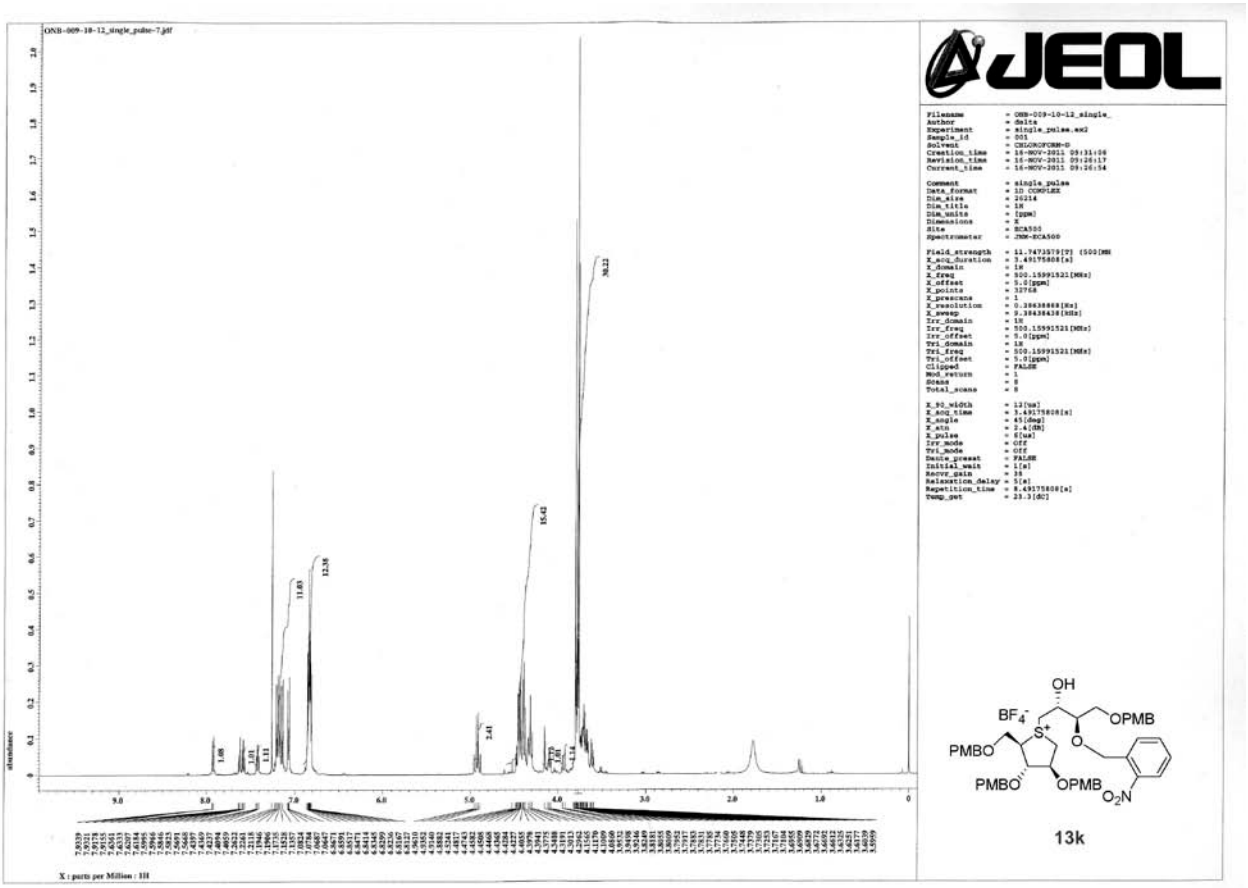
To a mixture of **8k** (100 mg, 0.28 mmol), **9** (118 mg, 0.23 mmol), and dichloromethane (2 ml) was added tetrafluoroboric acid ethyl ether complex [HBF_4·$(C_2H_5)_2O$, 41 μl, 0.3 mmol] at –60 °C, and the reaction mixture was stirred at –60 °C for 1h. After the reaction was quenched by addition of sodium acetate at –60 °C, the resulting suspension was filtered, and inorganic materials were washed with dichloromethane. The combined filtrate and washings were condensed under the reduced pressure to give a pale yellow oil (247 mg), which on column chromatography ($CHCl_3$→$CHCl_3$-MeOH, 100:1→50:1) gave **α-13k** (110 mg, 50%), a *ca*. 3:1 mixture of **α-13k** and the stereoisomer **β-13k** (56 mg, 25%) and a *ca*. 1:1.5 mixture of **α-13k** and **β-13k** (10 mg, 5%).

α-13k: $[\alpha]_D^{25}$ –13.8 (*c* = 0.94, $CHCl_3$). IR (neat): 3503, 1612, 1585, 1516, 1465, 1346, 1303, 1250, 1177, 1072, 1033 cm^{-1}. ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.61 (1H, dd, *J* = 10.9, 4.0 Hz, H-4′a), 3.674 (1H, dd, *J* = 10.3, 9.2 Hz, H-5a), 3.678 (1H, dd, *J* = 10.9, 4.0 Hz, H-4′b), 3.72 (1H, dd, *J* = 13.8, 3.7 Hz, H-1a), 3.73 (1H, dd, *J* = 10.3, 7.2 Hz, H-5b), 3.70–3.74 (1H, m, H-3′), 3.76 (1H, dd, *J* = 13.0, 6.3 Hz, H-1′a), 3.77/3.81 (each 3H, s, OC*H*$_3$), 3.78 (6H, s, OC*H*$_3$), 3.81 (1H, dd, *J* = 13.0, 3.0 Hz, H-1′b), 3.94 (1H, dd, *J* = 13.8, 1.7 Hz, H-1b), 4.11 (1H, br dd-like, *J* = 9.2, 7.2 Hz, H-4), 4.16 (1H, br dd-like, *J* = *ca*. 2.0, 1.2 Hz, H-3), 4.29–4.33 (1H, m, H-2′), 4.31/4.39 (each 1H, d, *J* = 11.5 Hz, 8H, m, OC*H*$_2$Ar), 4.34 (1H, ddd-like, *J* = *ca*. 3.7, 2.0, 1.7 Hz, H-2), 4.37–4.49 (6H, m, OC*H*$_2$Ar), 4.90/4.95 (each 1H, *J* = 12.9 Hz, OC*H*$_2$Ar), 6.80–6.88 (8H, m, arom.), 7.05–7.24 (8H, m, arom.), 7.43 (1H, ddd, *J* = 7.8, 7.5, 1.4 Hz, arom.), 7.58 (1H, ddd, *J* = 8.3, 7.8, 1.2 Hz, arom.), 7.63 (1H, dd, *J* = 7.5, 1.4 Hz, arom.), 7.93 (1H, dd, *J* = 8.3, 1.2 Hz, arom.). ^{13}C NMR (125 MHz, $CDCl_3$) *δ*: 48.1 (C-1), 50.4 (C-1′), 55.2/55.3 (O*C*H$_3$), 66.2 (C-4), 66.4 (C-5), 68.1 (C-4′), 68.4 (C-2′), 69.5/71.5/71.7/73.1/73.2 (O*C*H$_2$Ar), 80.3 (C-3′), 81.9 (C-3), 82.2 (C-2), 113.8/113.9/114.05/114.07/124.5/128.7/129.6/129.65/129.72/129.7/130.0/133.7 (d, arom.), 127.9/128.0/128.9/133.1/148.0/159.3/159.5/159.7 (s, arom.). FABMS (pos.) *m/z*: 870 $[M–BF_4]^+$.

NMR data for the minor stereoisomer **β-13k** extracted from the spectrum of a mixture of a *ca*. 1:1.5 mixture: ^{1}H NMR (500 MHz, $CDCl_3$) *δ*: 3.57–3.84 (8H, m, H-1a, H-1′a, H-1′b, H-3′, H-4′a, H-4′b, H-5a and H-5b), 3.75/3.76/3.79/3.80 (each 3H, s, OC*H*$_3$), 4.01 (1H, br d, *J* = 14.6 Hz, H-1b), 4.08–4.12 (m, H-4), 4.14 (1H, br s-like, H-3), 4.21–4.53 (8H, m, OC*H*$_2$Ar), 4.32–4.38 (2H, m, H-2 and H-2′), 4.92/4.94 (each 1H, d, *J* = 13.2 Hz, OC*H*$_2$Ar), 6.77–6.88 (8H, m, arom.), 7.06–7.24 (8H, m, arom.), 7.41 (1H, td-like, *J* = *ca*. 7.8, 1.2 Hz, arom.), 7.55 (1H, td-like, *J* = 8.0, 1.2 Hz, arom.), 7.64 (1H, br d-like, *J* = *ca*. 8.0 Hz, arom.), 7.96 (1H, dd, *J* = 8.0, 1.2 Hz, arom.). ^{13}C-NMR (125 MHz, $CDCl_3$) *δ*: 41.8 (C-1′), 44.3 (C-1), 55.2 (O*C*H$_3$), 61.9 (C-4), 64.6 (C-5), 67.1 (C-2′), 68.1 (C-4′), 69.5/71.8/72.9/73.2 (OC*H*$_2$Ar), 80.7 (C-3′), 82.4 (C-2), 83.8 (C-3), 113.8/113.9/114.0/114.1/127.9/128.2/129.3/129.5/129.7/129.8/130.0 (d, arom.), 127.8/128.3/130.2/137.2/138.2/159.2/159.3/159.7/159.76/159.81 (s, arom.).

1,4-Dideoxy-1,4-{(*R*)-[4-deoxy-2-*O*-(*o*-nitrobenzyl)-D-erythritol-4-yl]episulfoniumylidene}-D-arabinitol Chloride (7k)

Sulfonium tetrafluoroborate **α-13k** (88 mg, 0.092 mmol) was treated in a mixture of 80% aqueous TFA (2 ml) and chloroform (1 ml) at room temperature for 6 h. After the reaction mixture was condensed at reduced pressure, the residue was washed with chloroform to give a colorless oil (43.5 mg), which was then stirred with ion exchange resin IRA-400J (2 g) in methanol (2 ml) at room temperature for 4 h. The resins were filtered off, and washed with methanol. The combined filtrate and washings were condensed to give a colorless oil (39 mg), which on column chromatography ($CHCl_3$→$CHCl_3$-MeOH, 50:1 → 10:1) gave title sulfonium salt **7k** (31.3 mg, 80%) as a colorless oil. $[\alpha]_D^{25}$ +2.1 (*c* = 1.12, CH_3OH). IR (neat): 3287, 1612, 1578, 1524, 1404, 1346, 1308, 1261, 1200, 1173, 1076, 1026 cm^{-1}. ^1H NMR (500 MHz, CD_3OD) *δ*: 3.60 (1H, ddd-like, *J* = 5.8, 4.0, 4.0 Hz, H-3'), 3.74 (1H, dd, *J* = 12.3, 4.0 Hz, H-4'a), 3.75 (1H, dd, *J* = 12.9, 9.2 Hz, H-1'a), 3.82 (1H, dd, *J* = 12.9, 3.0 Hz, H-1a), 3.848 (1H, dd-like, *J* = 12.9, 1.7 Hz, H-1b), 3.852 (1H, dd-like, *J* = 12.9, 3.2 Hz, H-1'b), 3.87 (1H, dd, *J* = 12.3, 4.0 Hz, H-4'b), 3.92 (1H, dd, *J* = 10.1, 8.4 Hz, H-5a), 4.01 (1H, br dd-like, *J* = 8.4, 5.2 Hz, H-4), 4.04 (1H, dd, *J* = 10.1, 5.2 Hz, H-5b), 4.29 (1H, ddd, *J* = 9.2, 5.8, 3.2 Hz, H-2'), 4.37 (1H, br d-like, *J* = *ca.* 1.5 Hz, H-3), 4.61 (1H, ddd-like, *J* = *ca*. 3.0, 1.7, 1.5 Hz, H-2), 5.01/5.08 (each 1H, d, *J* = 11.5 Hz, O*CH*$_2$Ar), 7.53 (1H, ddd, *J* = 8.3, 7.8, 1.2 Hz, arom.), 7.69 (1H, td, *J* = 7.8, 1.2 Hz, arom.), 7.81 (1H, dd, *J* = 7.8, 1.2 Hz, arom.), 8.01 (1H, dd, *J* = 8.3, 1.2 Hz, arom.). ^{13}C NMR (125 MHz, CD_3OD) *δ*: 51.6 (C-1′), 52.2 (C-1), 60.7 (C-4′), 61.0 (C-5), 68.7 (C-2′), 70.3 (O*C*H$_2$Ar), 73.6 (C-4), 79.4 (C-2), 79.6 (C-3), 84.1 (C-3′), 125.6/129.8/131.1/134.6 (d, arom.), 135.0/149.4 (s, arom.). FABMS *m/z*: 390, $[M–Cl]^+$ (pos.), HRFABMS *m/z*: 390.1214 ($C_{16}H_{24}O_8NS$ requires 390.1223).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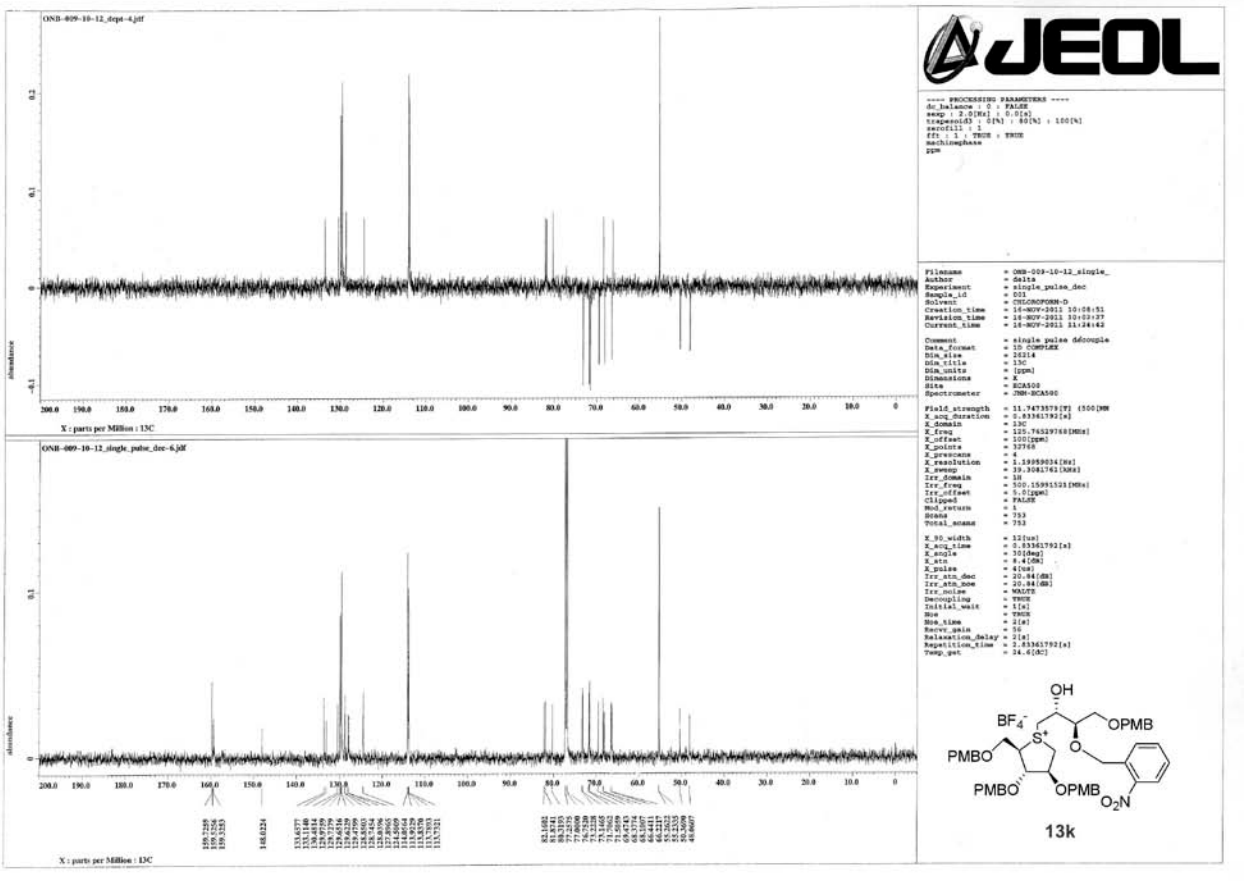
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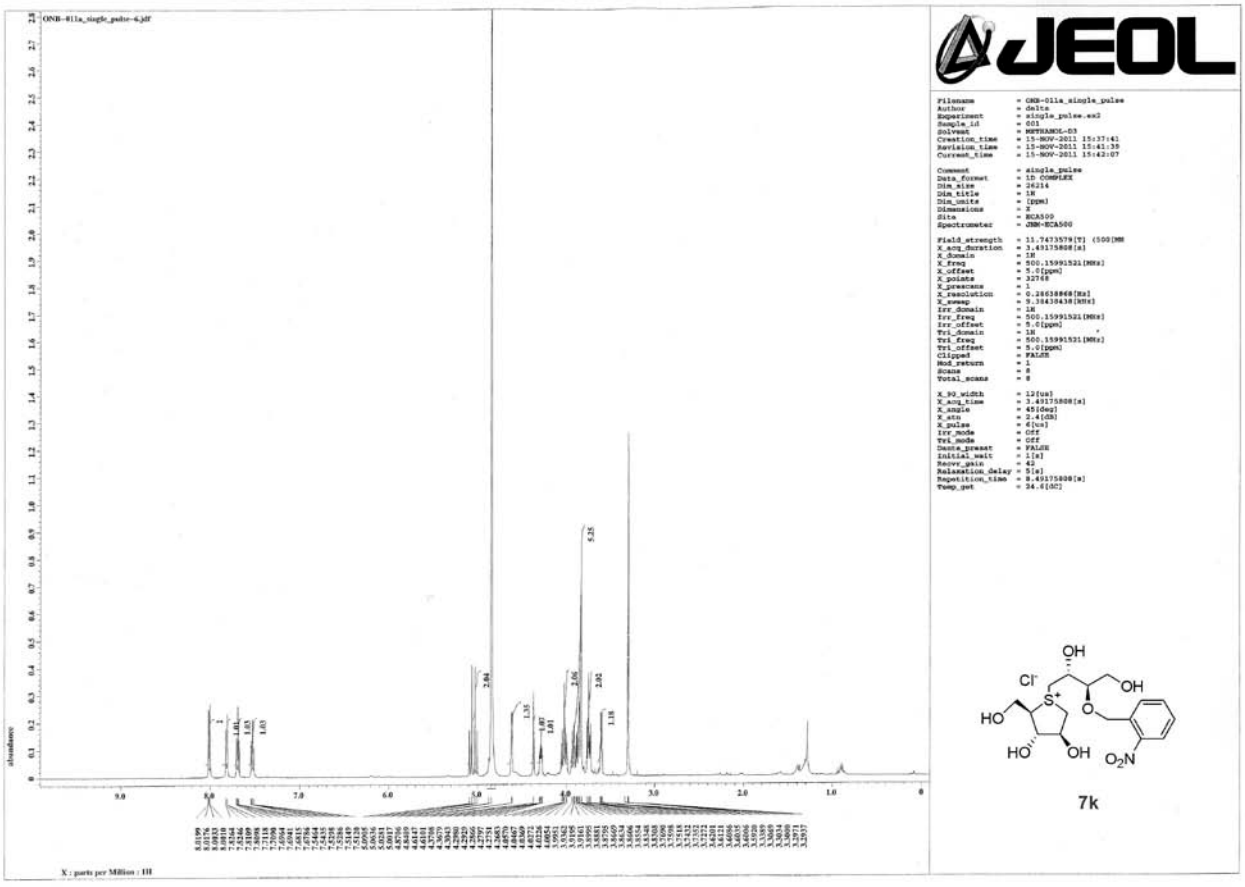
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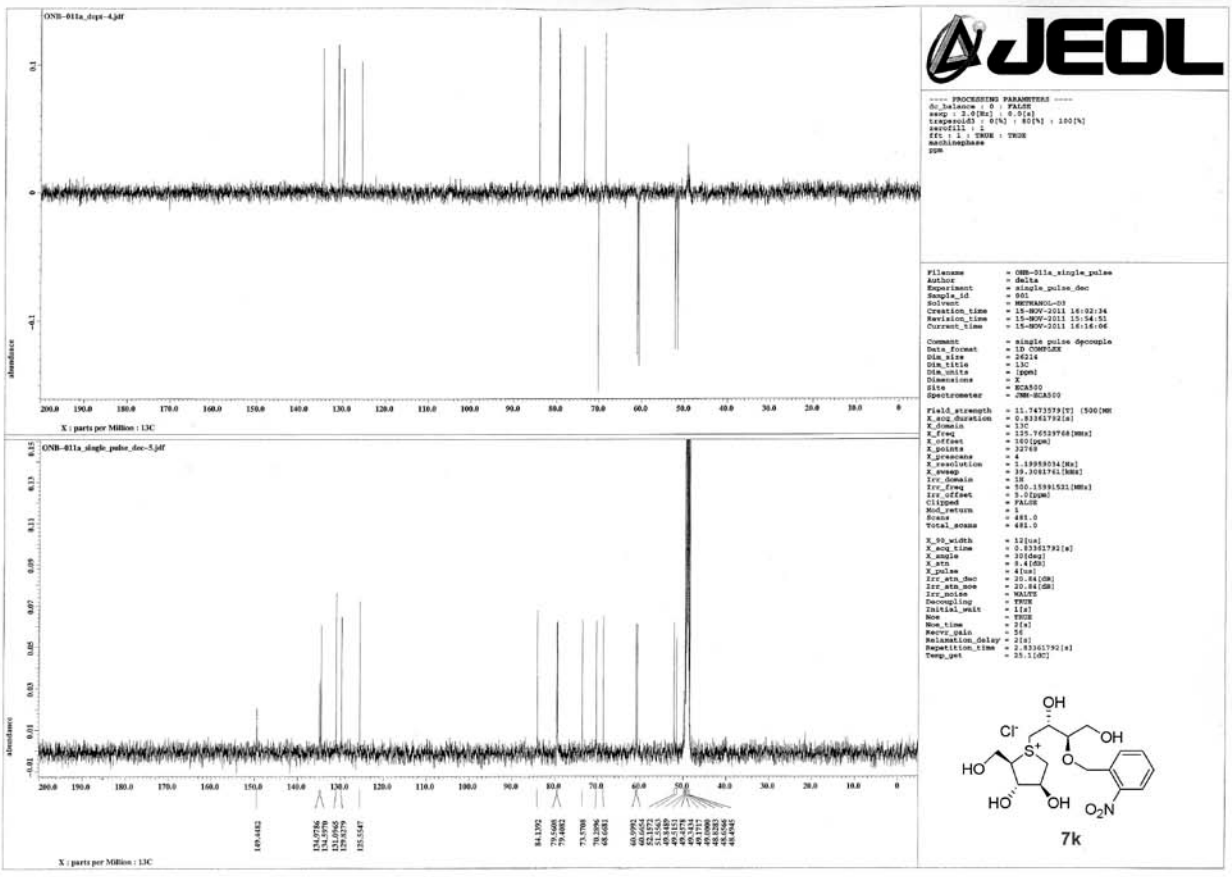
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Enzyme Inhibition Assays: Rat small intestinal brush border membrane vesicles were prepared[1] and its suspension in 0.1 M maleate buffer (pH 6.0) was used as small intestinal α-glucosidase of maltase, sucrase, and isomaltase. A test compound was dissolved in dimethylsulfoxide (DMSO), and the resulting solution was diluted with 0.1 M maleate buffer to prepare the test compound solution (concentration of DMSO: 10%). A substrate solution in maleate buffer (maltose, 74 mM, sucrose, 74 mM, isomaltose, 7.4 mM, 50 μL), a test compound solution (25 μL), and an enzyme solution (25 μL) were mixed and incubated at 37 °C for 30 min. After incubation, the solution was immediately heated by boiling water for 2 min to stop the reaction, and was mixed with water (150 μL). Glucose concentration was determined by the glucose-oxidase method. Final concentration of DMSO in the test solution was 2.5 % and no influence of DMSO was detected on the inhibitory activity.

Reference

1. M. Kessler, O. Acuto, C. Storelli, H. Murer, M. Muller, and G. Semenza, *Biochim. Biophys. Acta*, 1978, **506**, 136.