Supplementary Materials

Structural Modification of Epigallocatechin-3-gallate to (2*R*,3*R*)-5,7-dimethoxy-2-(3,4,5-trimethoxyphenyl)chroman-3-yl *L*-valinate in 4 Steps

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NMR spectrometry

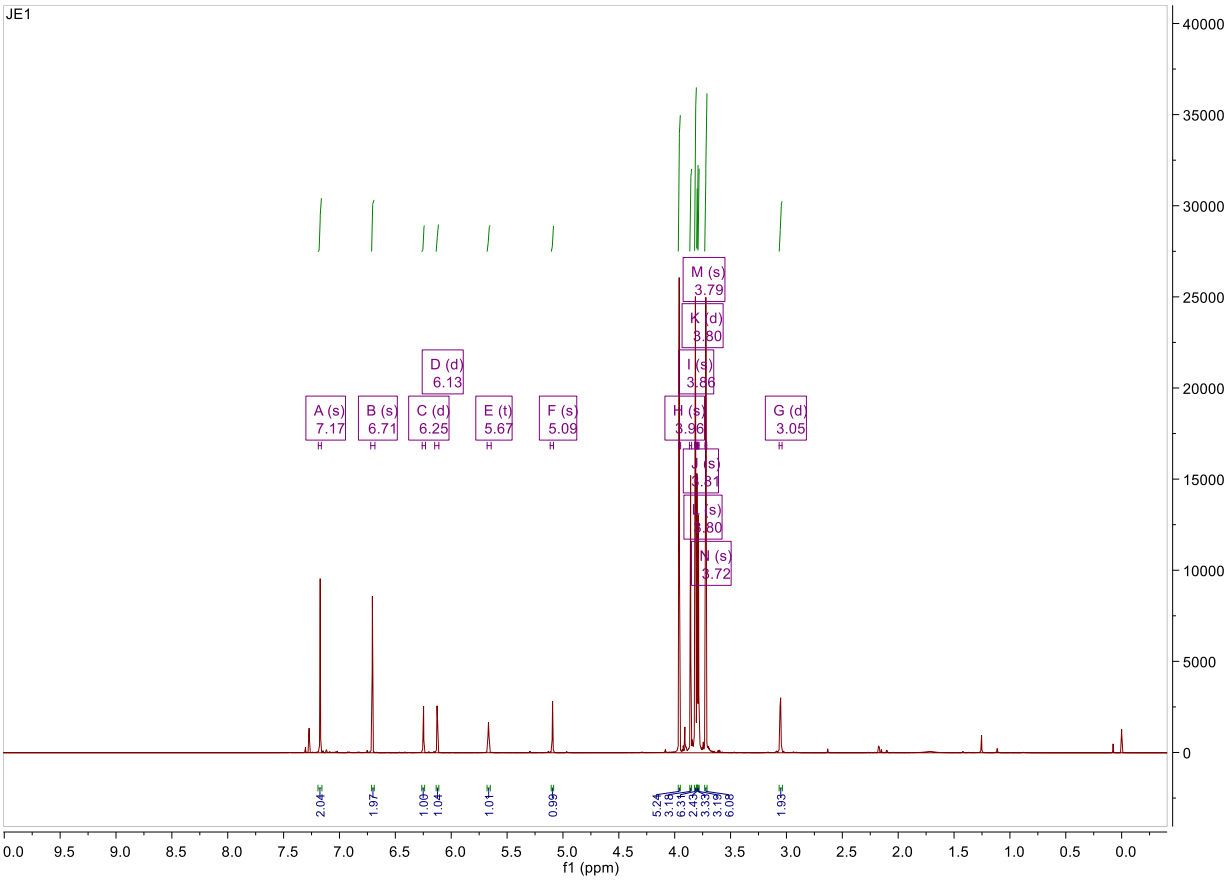


Figure S1. ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **1**. An impurity peak at 3.96 ppm arising from the methylating reagent, dimethyl sulfate.

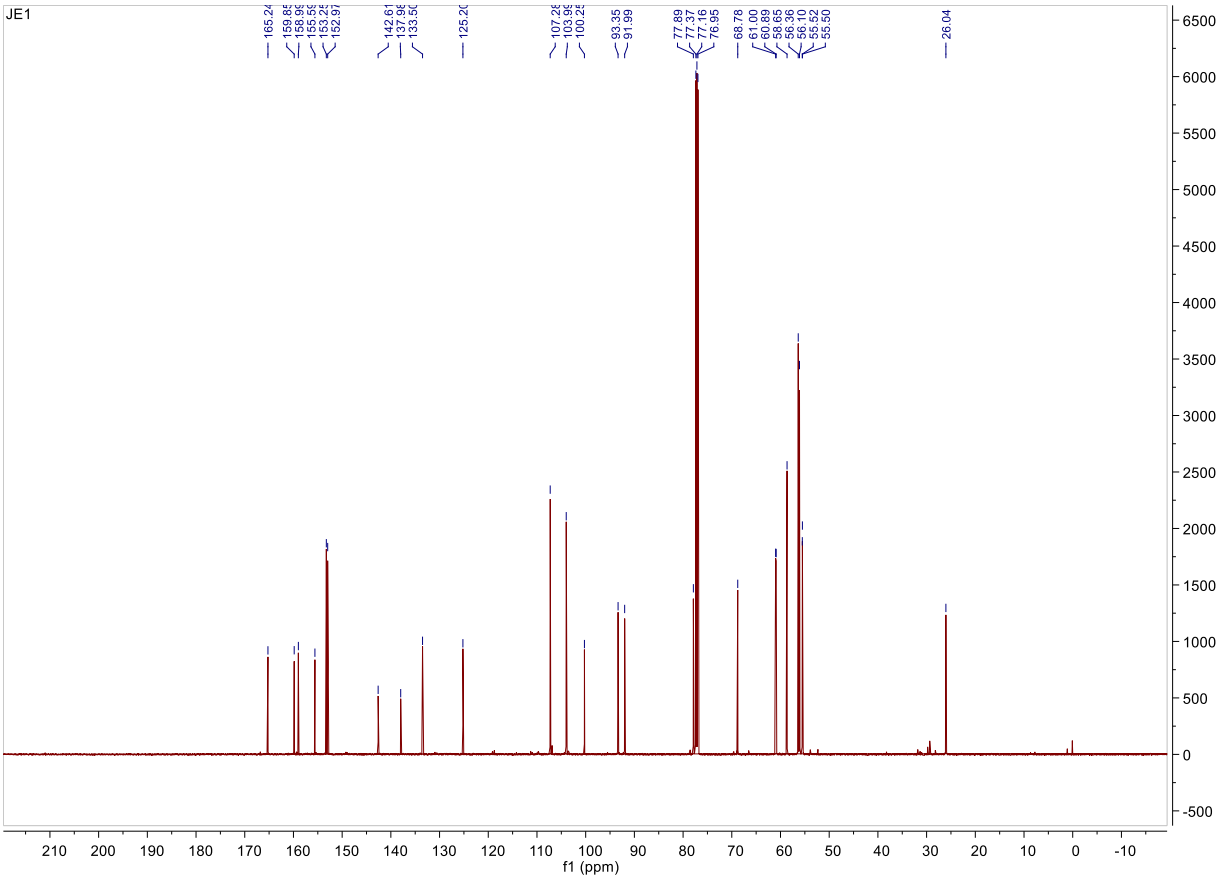


Figure S2. ^{13}C NMR ($CDCl_3$, 150 MHz) spectrum of compound **1**. An impurity peak at 58.65 ppm arising from the methylating reagent, dimethyl sulfate.

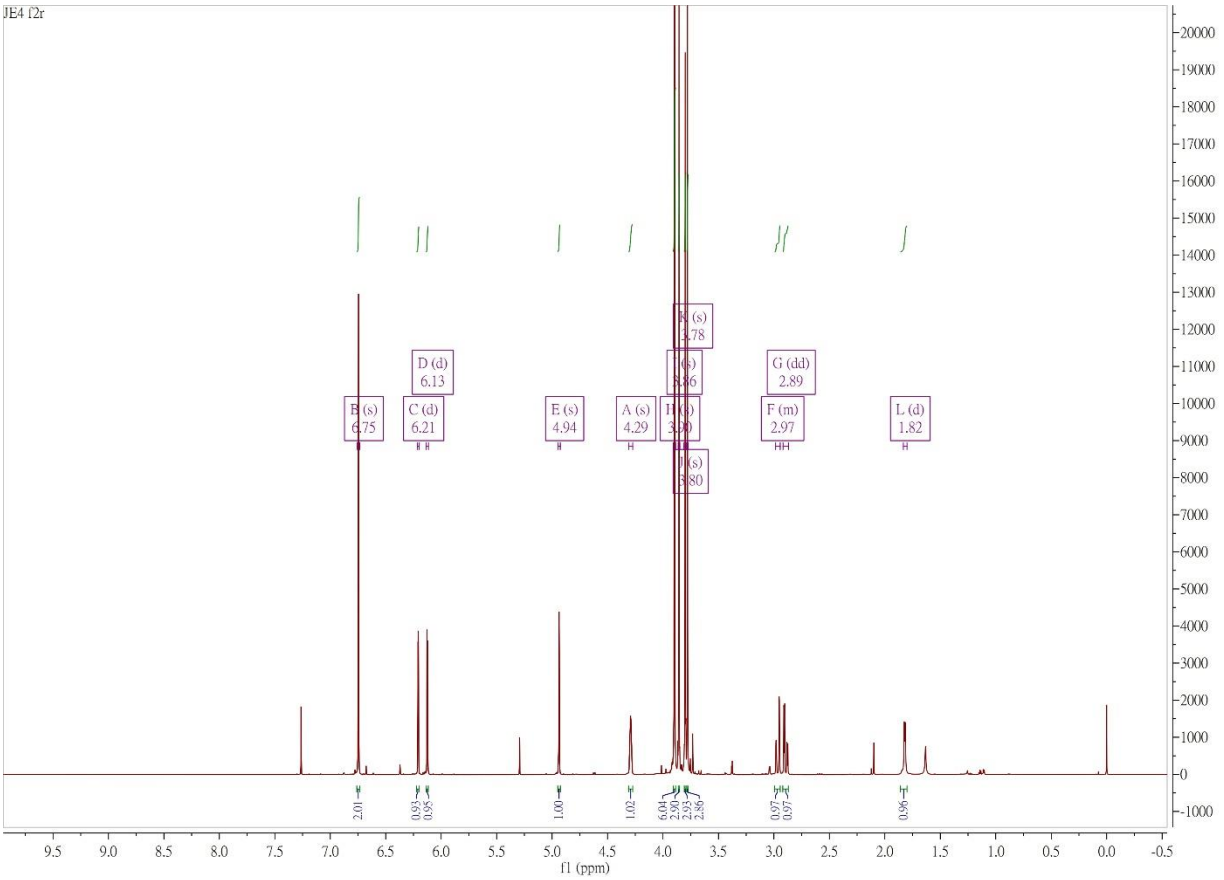


Figure S3. ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **2**.

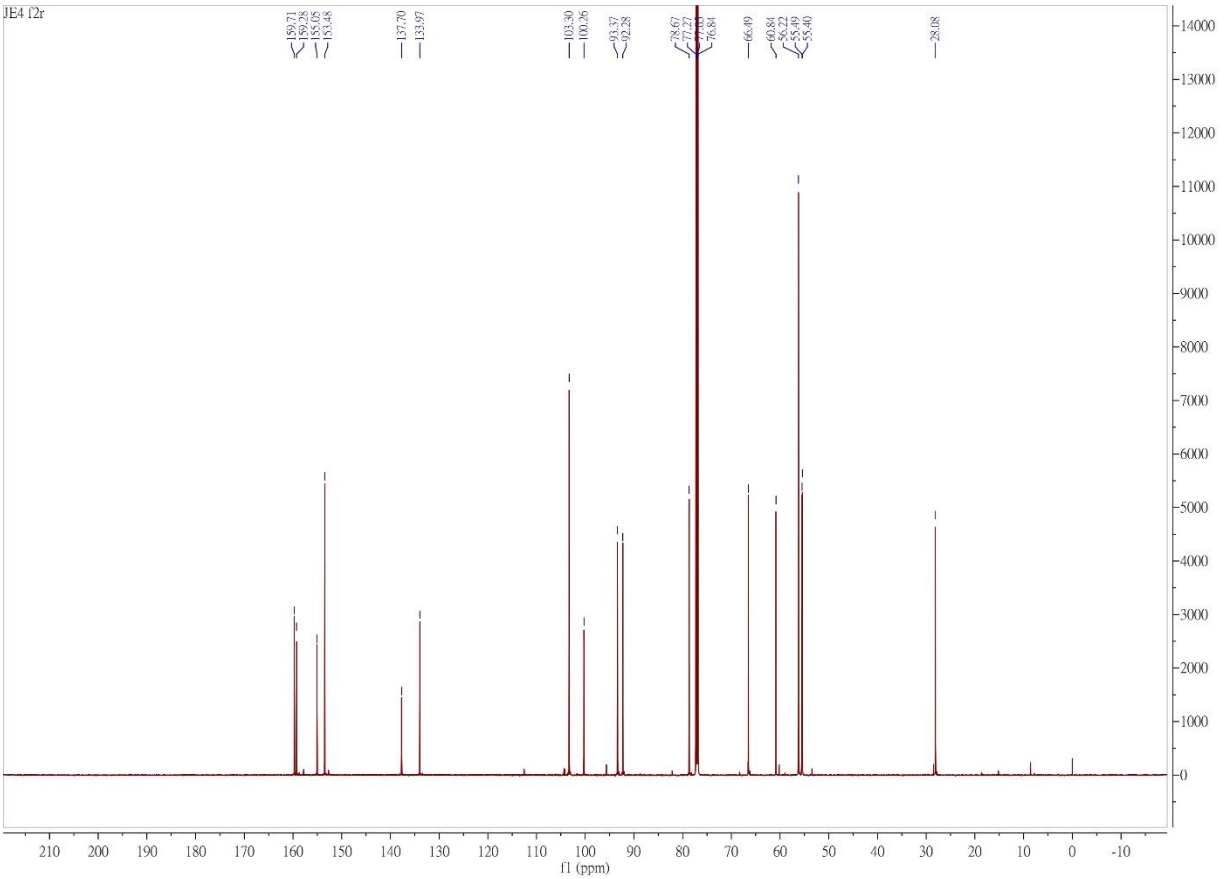


Figure S4. ^{13}C NMR ($CDCl_3$, 150 MHz) spectrum of compound **2**.

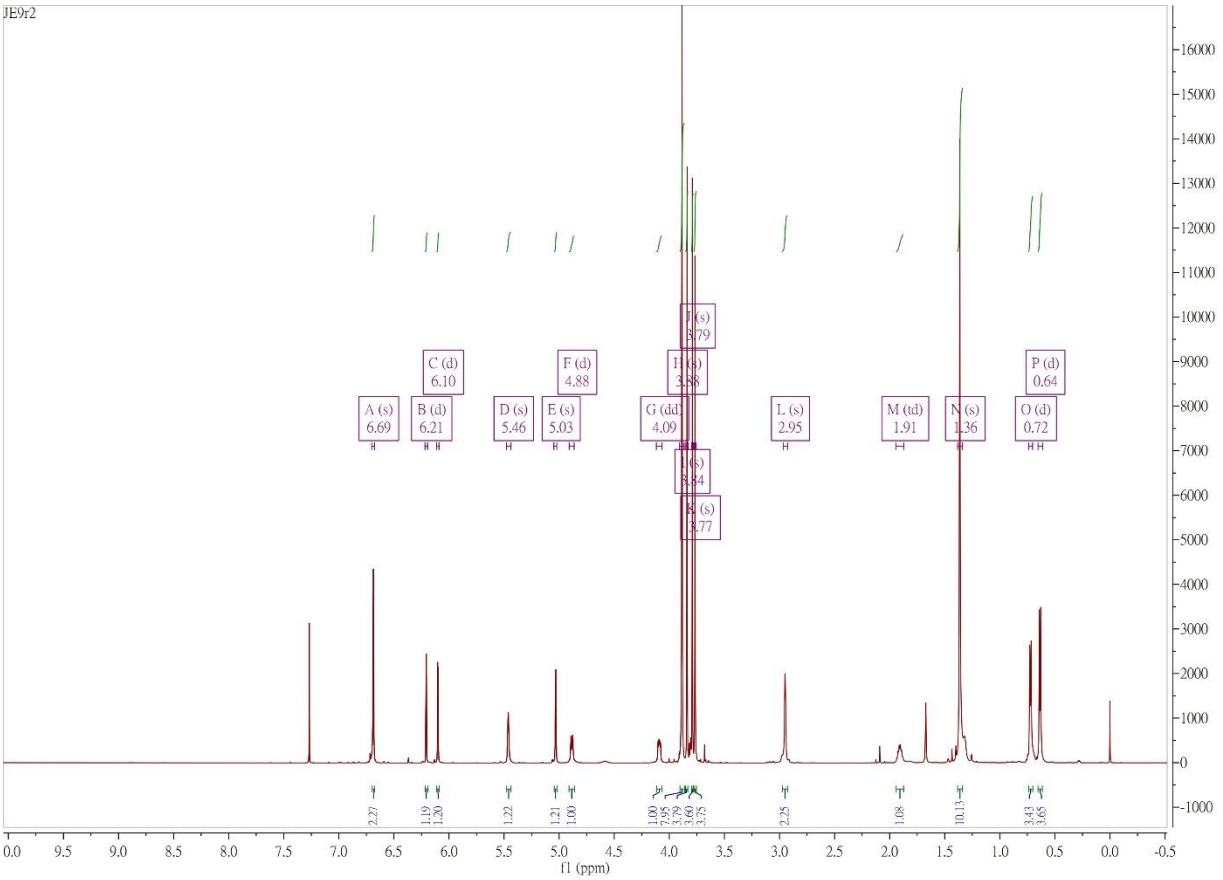


Figure S5. ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **3**.

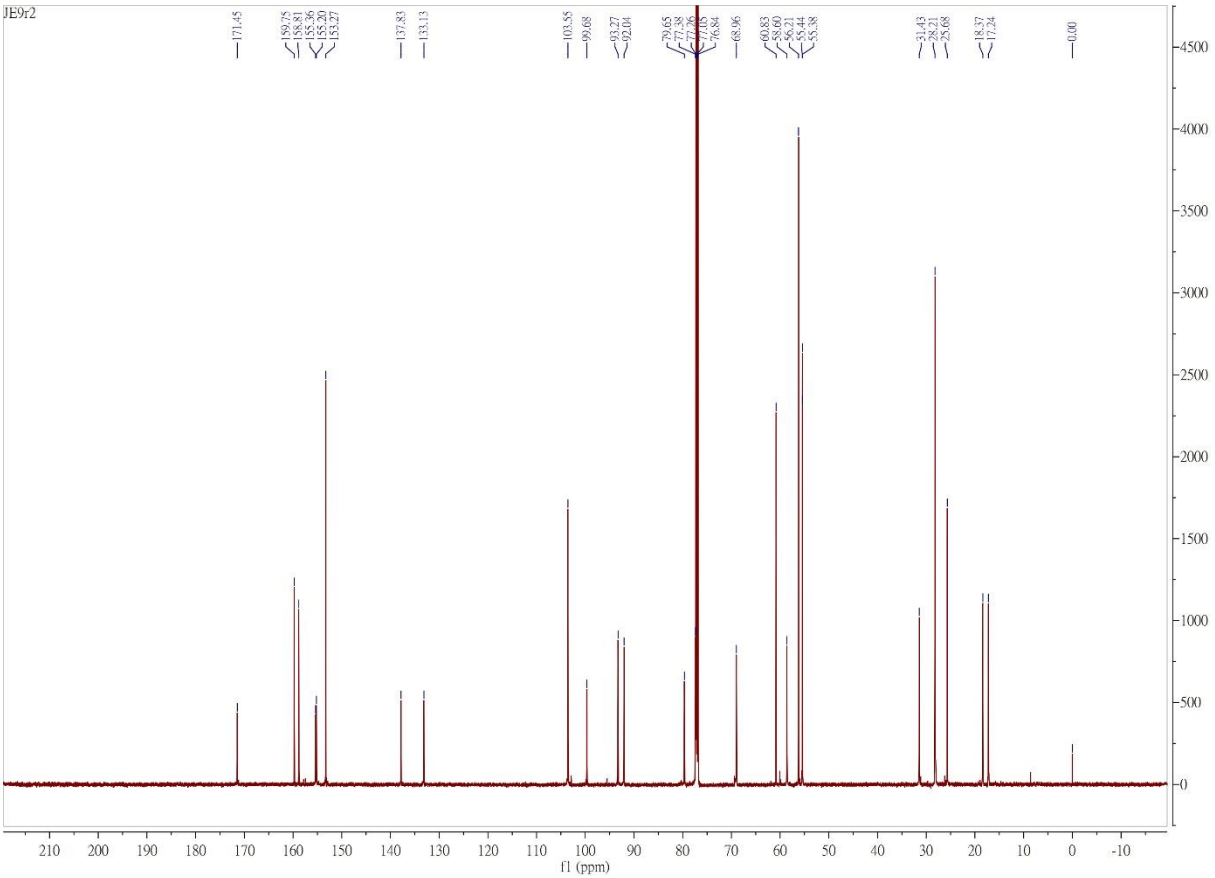


Figure S6. ^{13}C NMR ($CDCl_3$, 150 MHz) spectrum of compound **3**.

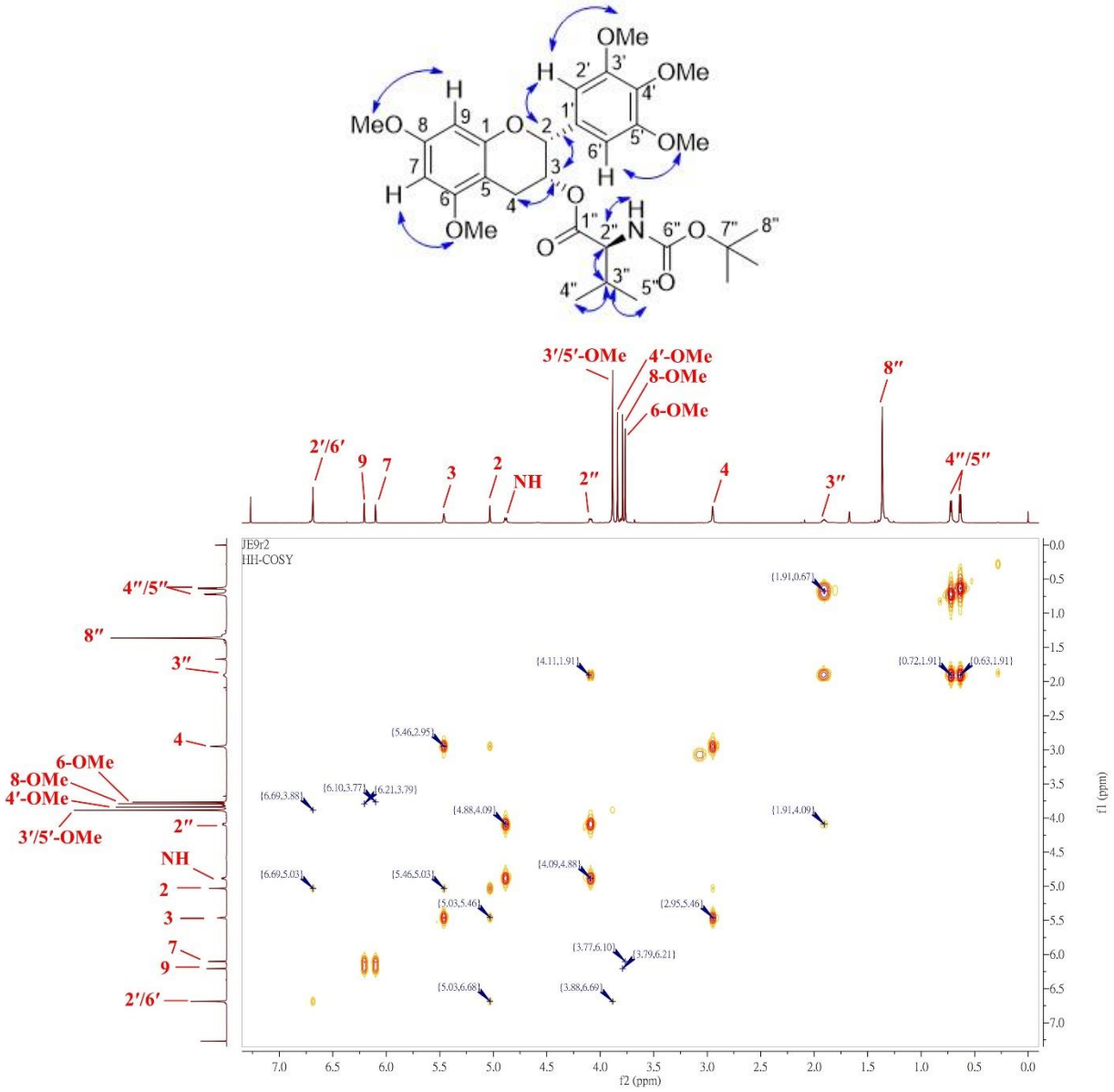


Figure S7. HH-COSY spectrum of compound **3**.

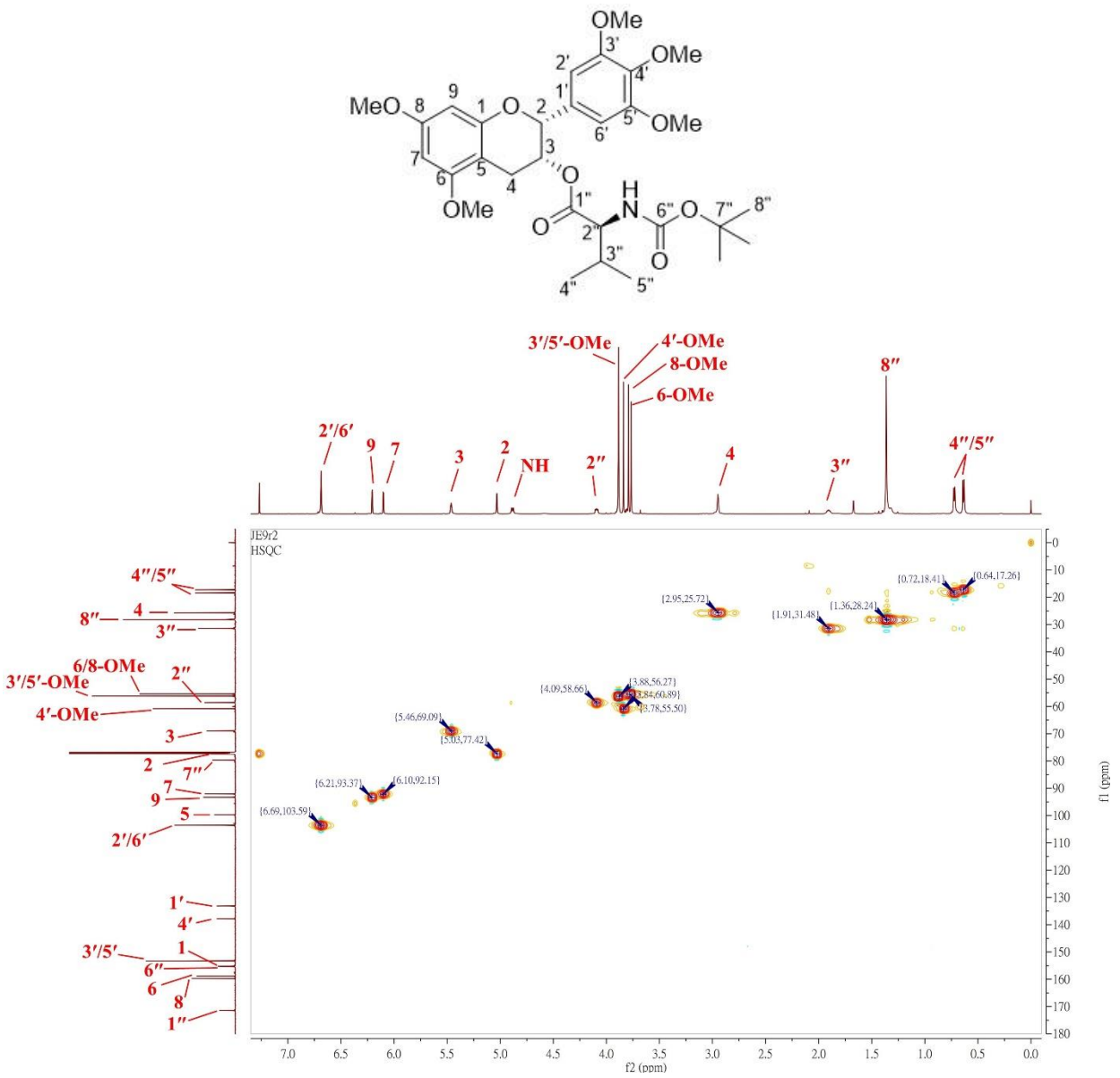


Figure S8. HSQC spectrum of compound **3**.

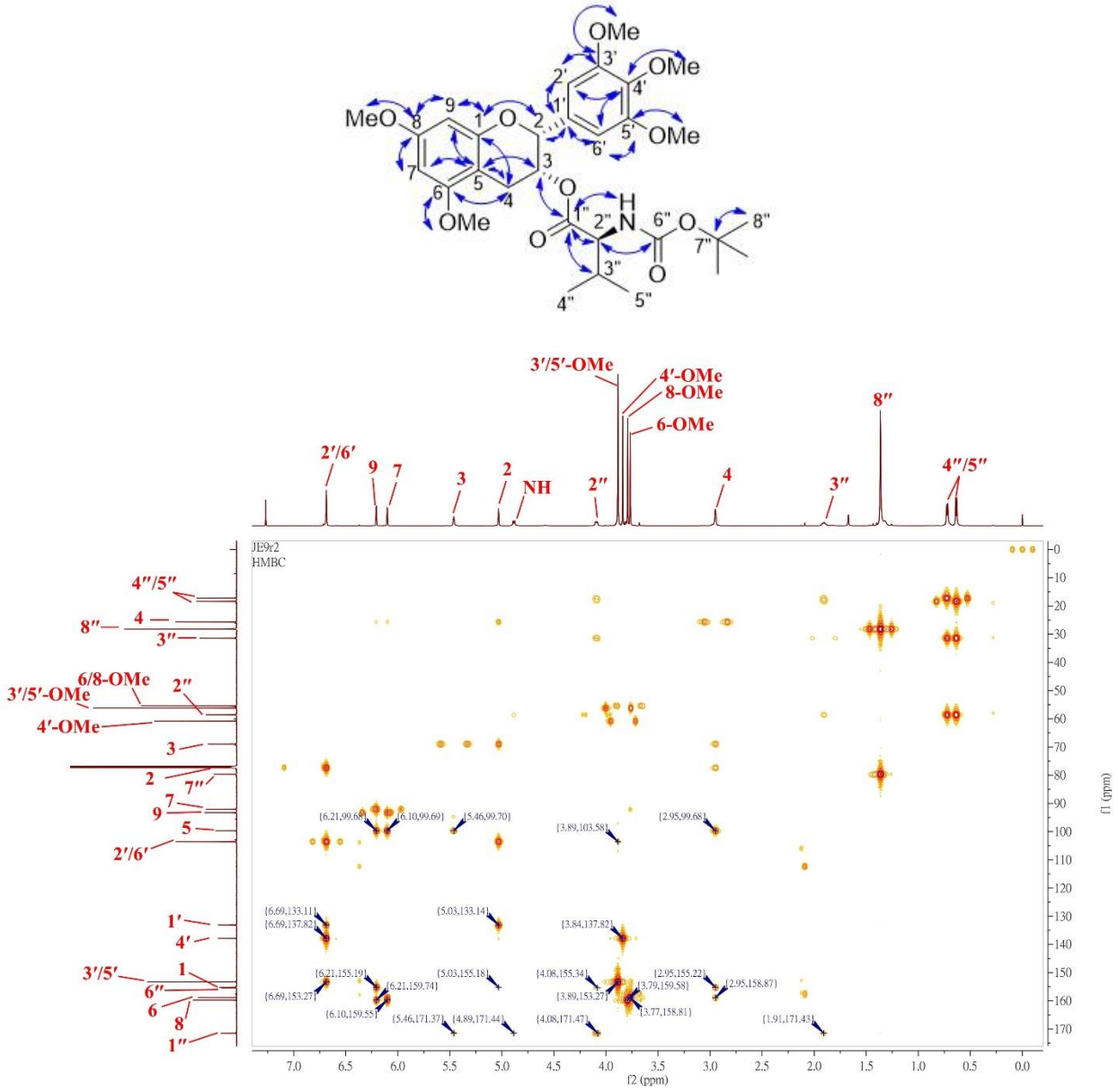


Figure S9. HMBC spectrum of compound **3**.

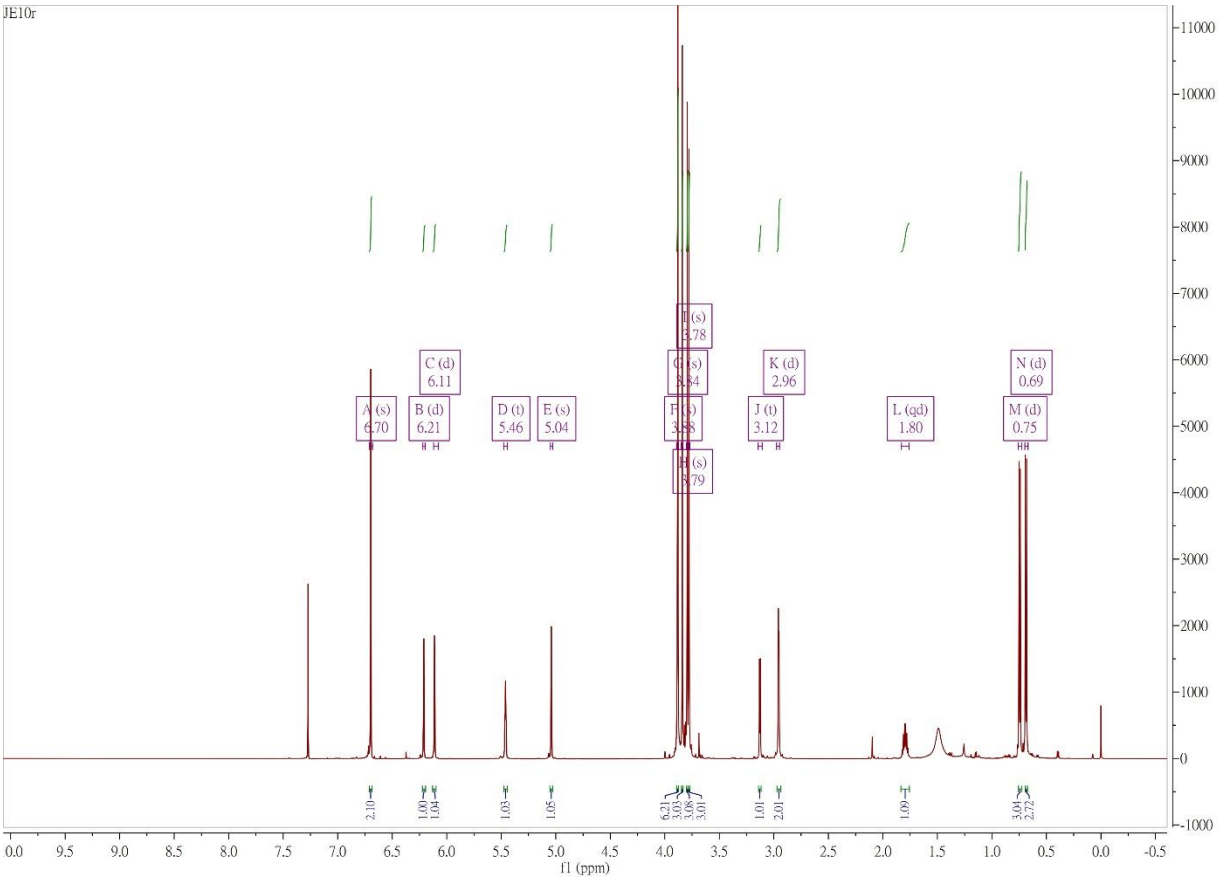


Figure S10. ^{1}H NMR ($CDCl_3$, 600 MHz) spectrum of compound **4**.

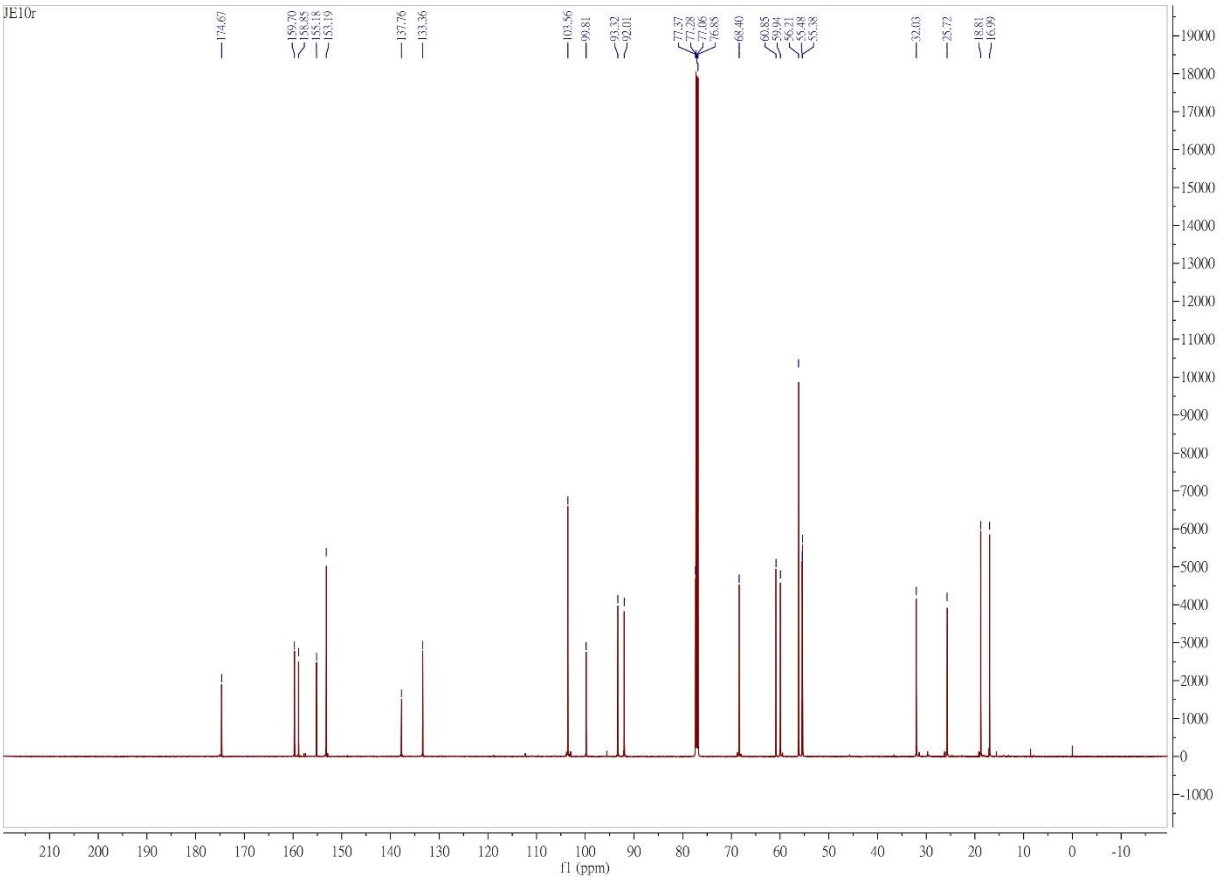


Figure S11. ^{13}C NMR ($CDCl_3$, 150 MHz) spectrum of compound **4**.

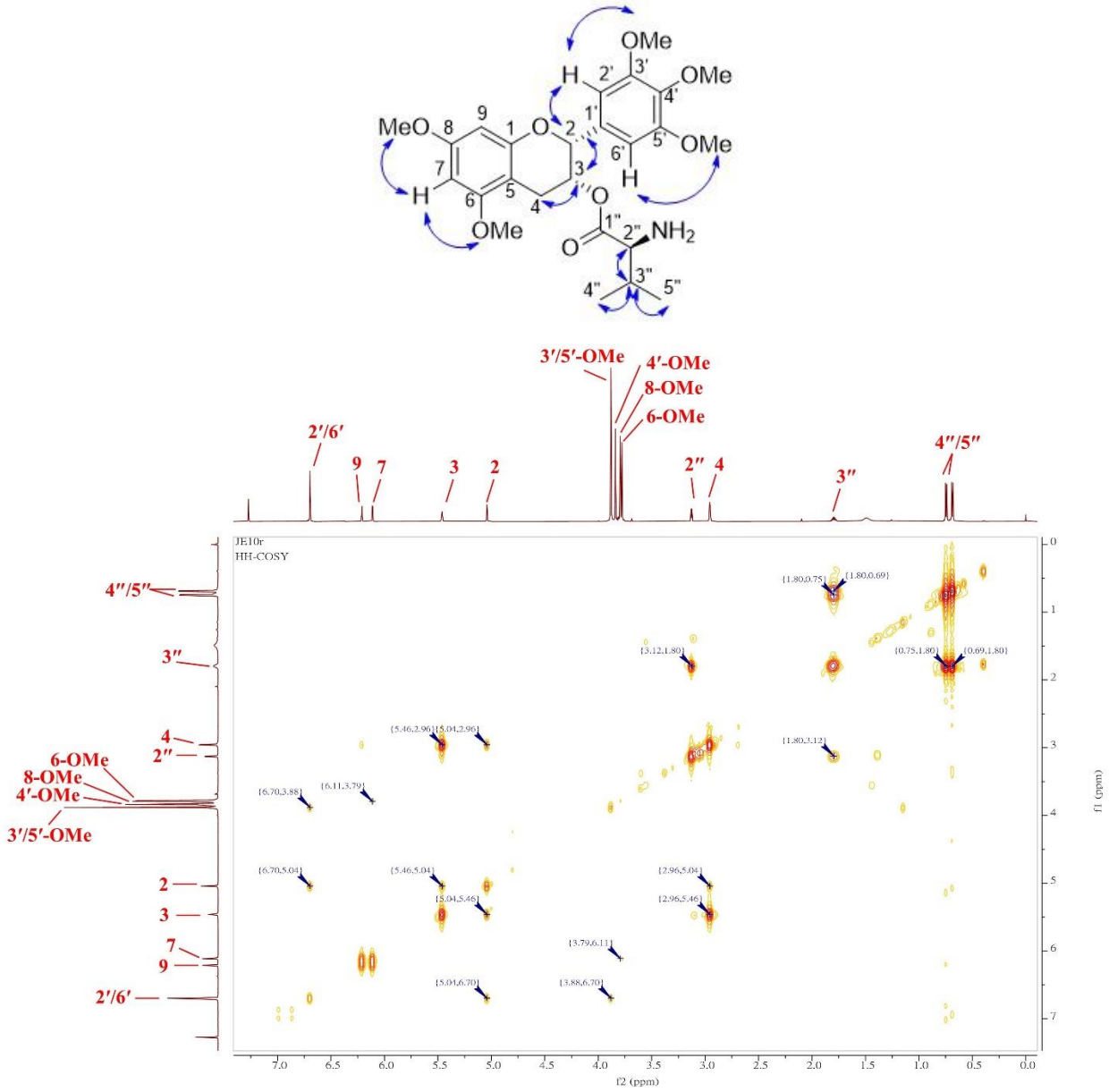


Figure S12. HH-COSY spectrum of compound **4**.

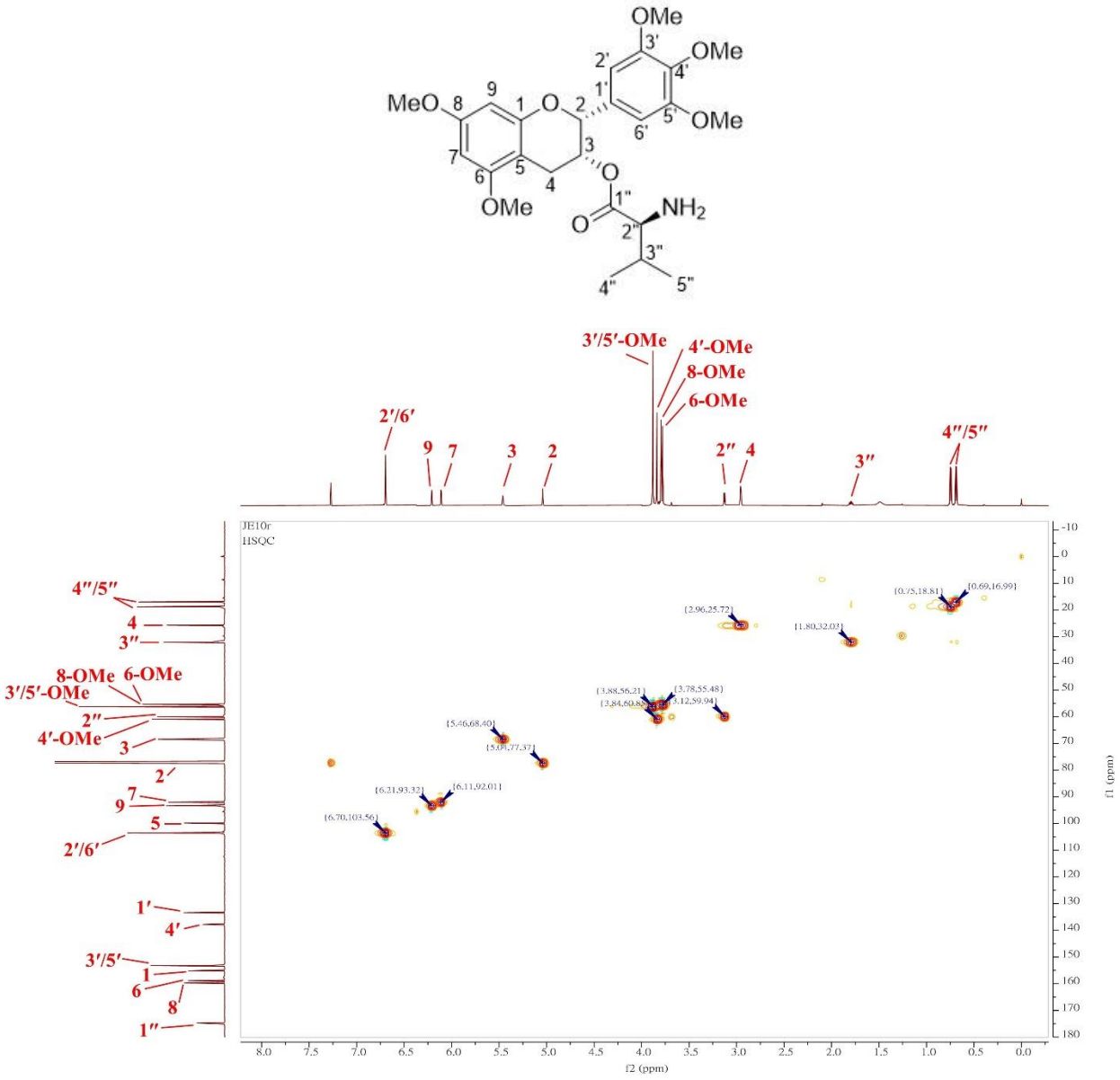


Figure S13. HSQC spectrum of compound **4**.

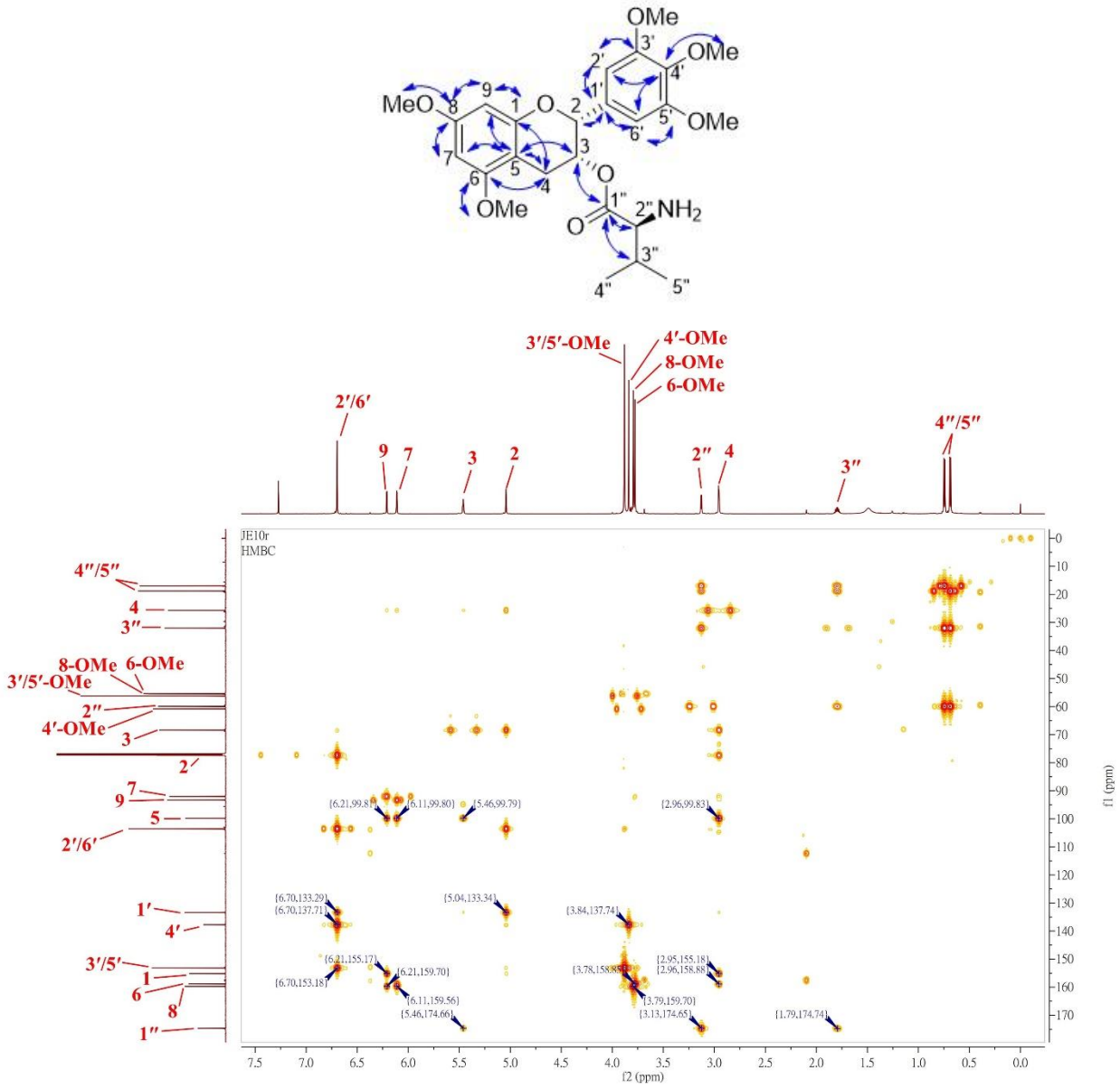
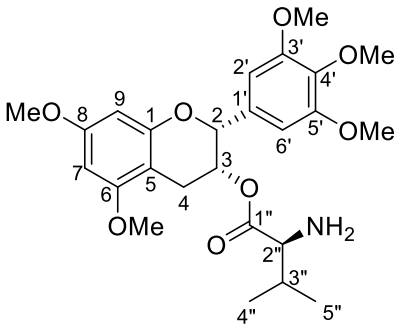


Figure S14. HMBC spectrum of compound **4**.

Table S1. Assignment of ^{1}H and ^{13}C NMR chemical shifts of **4**.



^{1}H Chemical Shift	^{13}C Chemical Shift	**Assignment**
-	174.67	1″
-	159.70	8
-	158.85	6
-	155.18	1
-	153.19 (2C)	3′/5′
-	137.76	4′
-	133.36	1′
6.70	103.56 (2C)	2′/6′
-	99.81	5
6.21	93.32	9
6.11	92.01	7
5.04	77.37	2
5.46	68.40	3
3.84	60.85	4′-OMe
3.12	59.94	2″
3.88	56.21 (2C)	3′/5′-OMe
3.79	55.48	8-OMe
3.78	55.38	6-OMe
1.80	32.03	3″
2.96	25.72	4
0.75	18.81	4″/5″
0.69	16.99	4″/5″

IR spectrometry

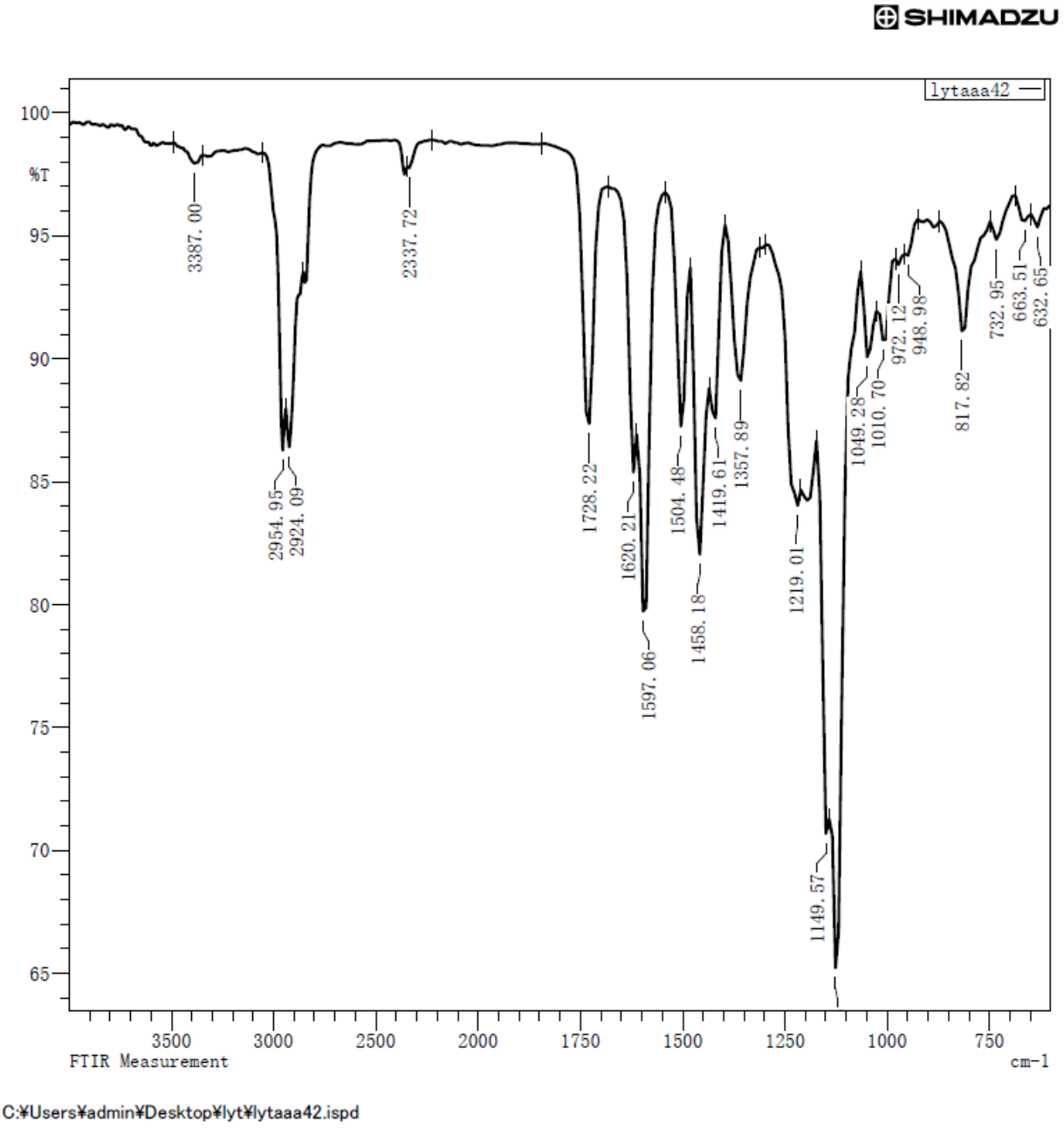
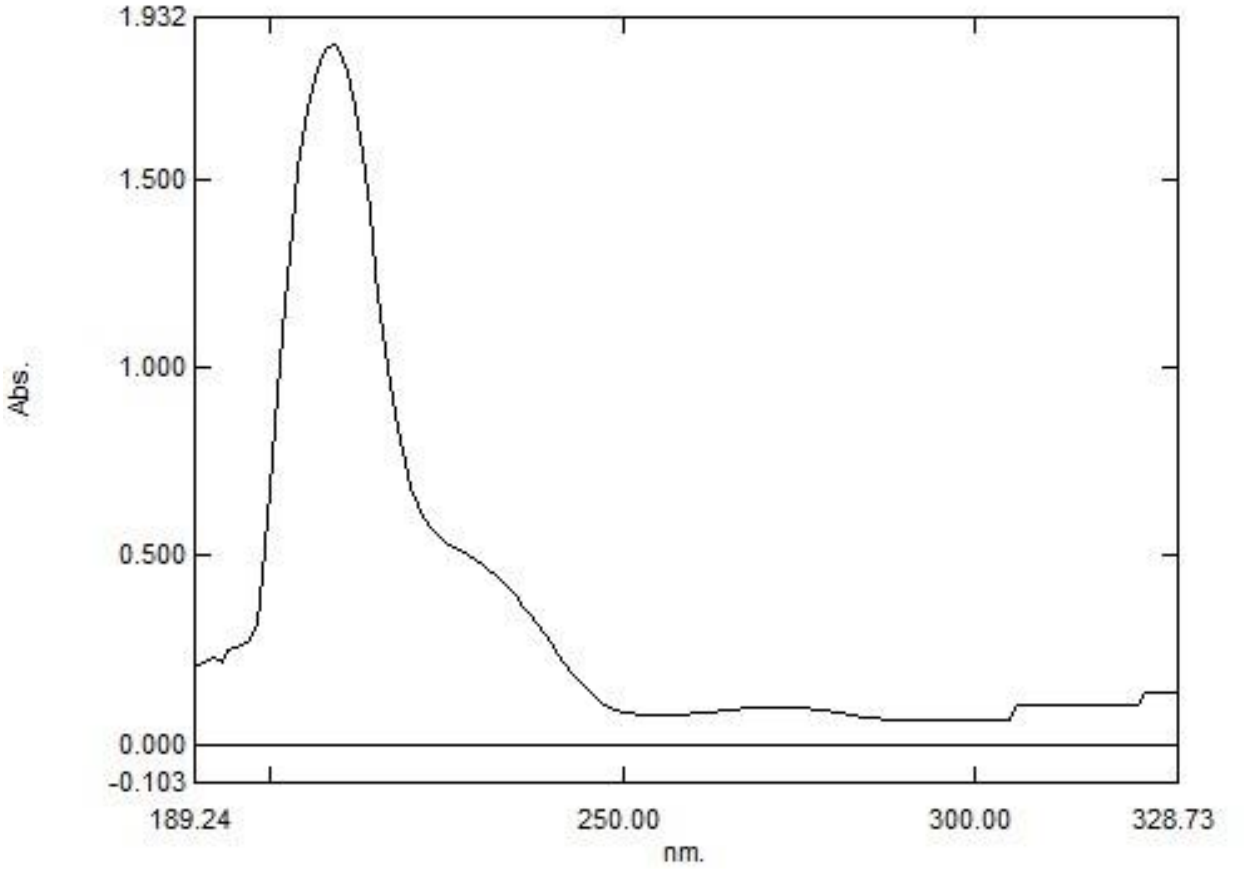


Figure S15. FTIR spectrum of compound **4**.

UV spectrometry



NO.	wavelength nm.	Abs.
1	209.00	1.862
2	229.00	0.489

Figure S16. UV spectrum of compound **4**.

Mass spectrometry

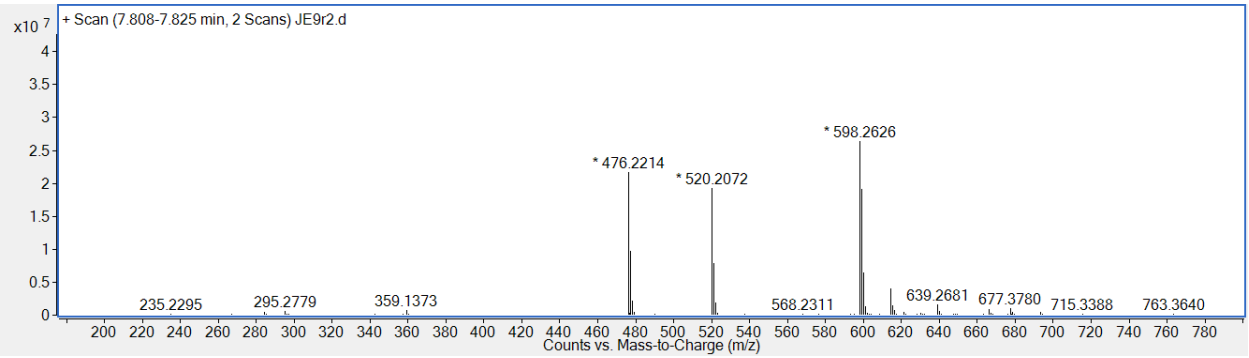


Figure S17. Mass spectrum of compound **3**. The spectrum was recorded in positive ionization mode (ESI).

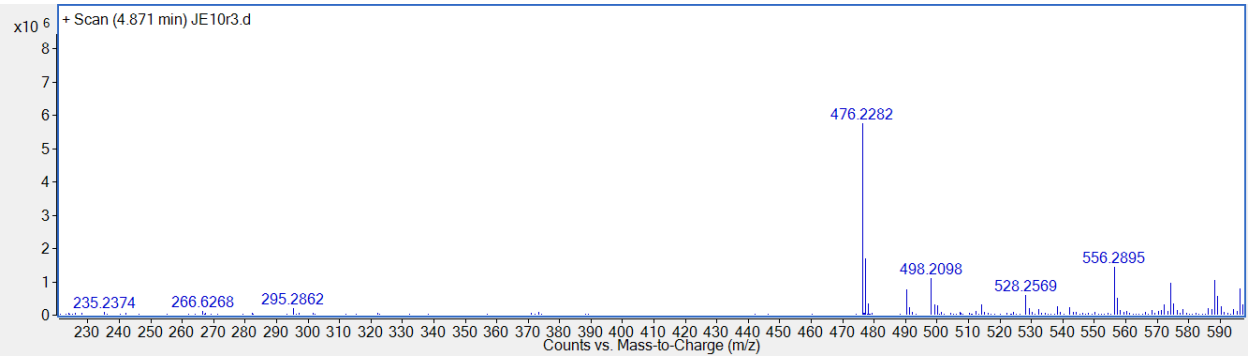


Figure S18. Mass spectrum of compound **4**. The spectrum was recorded in positive ionization mode (ESI).

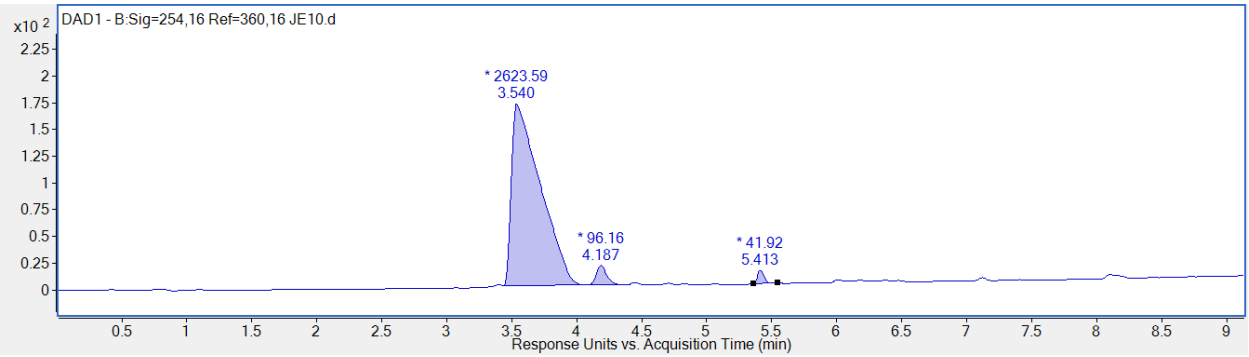


Figure S19. UPLC-UV chromatogram of compound **4** (purity > 95%) at 254 nm.

Table S2. Physicochemical properties of EGCG and derivatives **1** and **4** calculated by SwissADME [1]

Compound	MW	iLogP	HBA	HBD	TPSA[2]	nRtB	Lipinski's rule violations
EGCG	458.37	1.53	11	8	197.37	4	2
1	570.58	4.95	11	0	109.37	12	2
4	475.53	4.19	9	1	107.70	10	0

MW: Molecular weight. iLogP: n-Octanol/Water Partition Coefficient. nRtB: Number of rotatable bond. HBA: Number of hydrogen-bond acceptor. HBD: Number of hydrogen-bond donor. TPSA: Topological surface area [2]

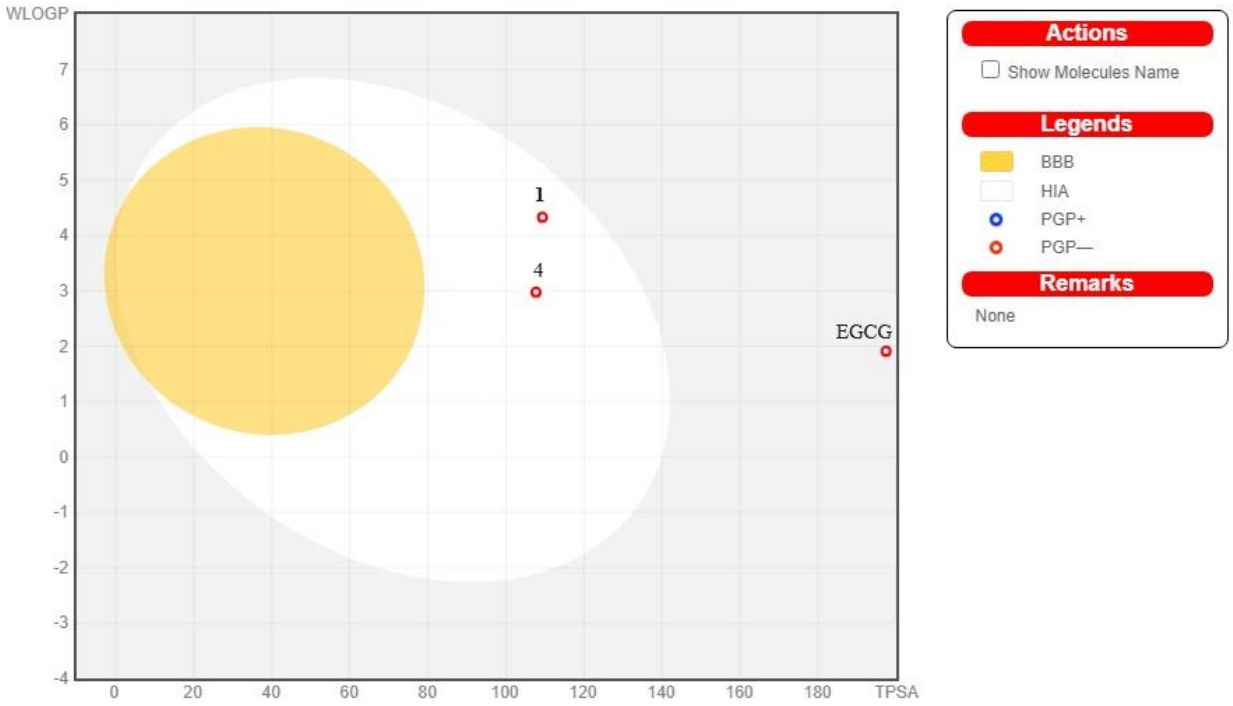


Figure S20. BOILED-Egg graph resuming the predicted properties for EGCG and derivatives **1** and **4**.

The overall predicted pharmacokinetic properties were resumed in the BOILED-Egg graph [3] as reported in Figure S20. The white area indicated the molecules with high probability to be absorbed by the GI tract, while the yellow area indicated the molecules with high probability to passively permeate through the blood-brain barrier. The blue dot represents the molecule which is predicted to be effluxed from CNS by P-glycoprotein. The red dot represents the molecule which is predicted not to be effluxed from CNS by P-glycoprotein.

References

1. Daina, A.; Michielin, O.; Zoete, V. SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules. *Sci. Rep.* **2017**, *7*, 42717. https://doi.org/10.1038/srep42717

2. Ertl, P.; Rohde, B.; Selzer, P. Fast Calculation of Molecular Polar Surface Area as a Sum of Fragment-Based Contributions and Its Application to the Prediction of Drug Transport Properties. *J. Med. Chem.* **2000**, *43*, 3714-3717, https://doi.org/10.1021/jm000942e.

3. Daina, A.; Zoete, V.A. Boiled-egg to predict gastrointestinal absorption and brain penetration of small molecules. *ChemMedChem* **2016**, *11*, 1117–1121. https://doi.org/10.1002/cmdc.201600182