Supplementary Information

O-alkyl derivatives of ferulic and syringic acid as lipophilic antioxidants: Effect of the length of the alkyl chain in the improvement of the thermo-oxidative stability of sunflower oil

Oscar Forero-Doria[1,2], Luis Guzmán[3], Whitney Venturini[4], Felipe Zapata-Gomez[3], Yorley Duarte[5], Lorena Camargo-Ayala[6], Cesar Echeverria[7], Javier Echeverría[1*]

[1]Departamento de Ciencias del Ambiente, Facultad de Química y Biología, Universidad de Santiago de Chile, Santiago, Chile

[2]Departamento de Ciencias Básicas, Facultad de Ciencias, Universidad Santo Tomás, Talca 3460000, Chile

[3]Departamento de Bioquímica Clínica e Inmunohematología, Facultad de Ciencias de la Salud, Universidad de Talca, Talca, Maule, Chile

[4]Departamento de Ciencias Pre-Clinicas, Facultad de Medicina, Universidad Católica del Maule, Talca, Chile

[5]Center for Bioinformatics and Integrative Biology, Facultad de Ciencias de la Vida, Universidad Andrés Bello, Av. República 330, Santiago 8370146, Chile

[6]Laboratorio de Síntesis Orgánica y Actividad Biológica (LSO-Act-Bio), Instituto de Química de Recursos Naturales, Universidad de Talca, Casilla 747, Talca 3460000, Chile

[7]ATACAMA-OMICS, Laboratorio de Biología Molecular y Genómica, Facultad de Medicina, Universidad de Atacama, 1532502, Copiapó, Chile.

Correspondence: javier.echeverriam@usach.cl; Tel.: +56-2-27181154

I. ^{1}H and ^{13}C-NMR spectra

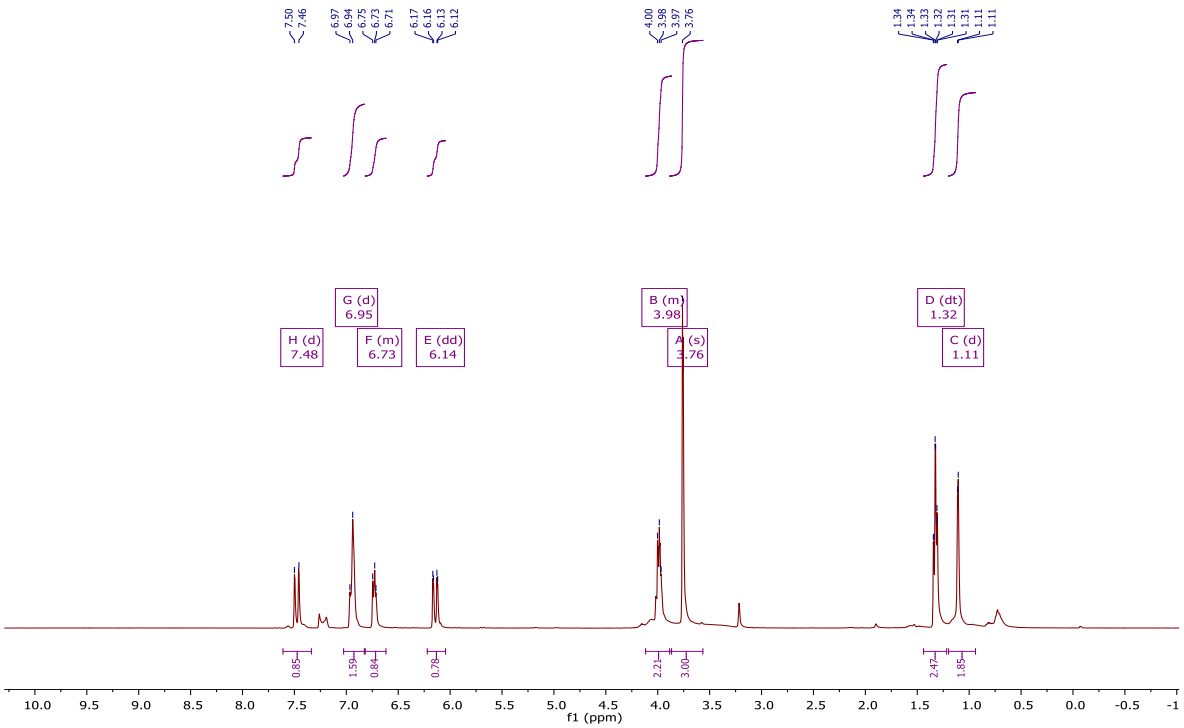

Figure S1. ^{1}H-NMR spectrum of ferulic acid 4-ethyl ether (**3a**).

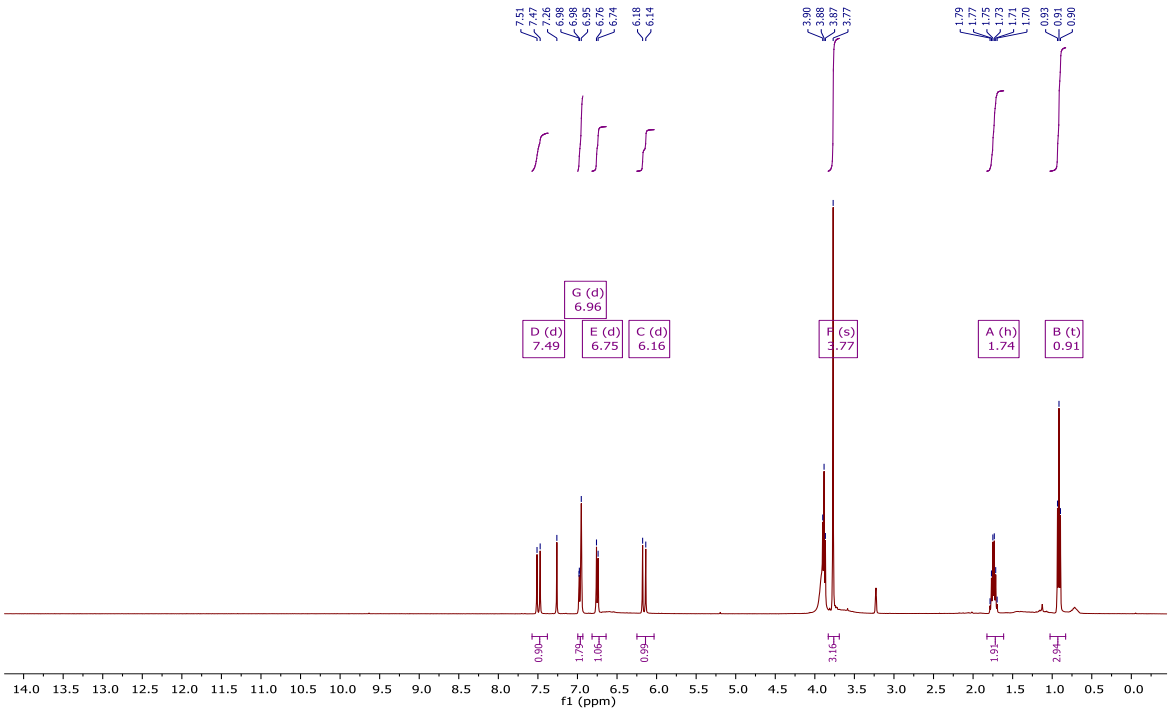

Figure S2. ^{1}H-NMR spectrum of ferulic acid 4-propyl ether (**3b**).

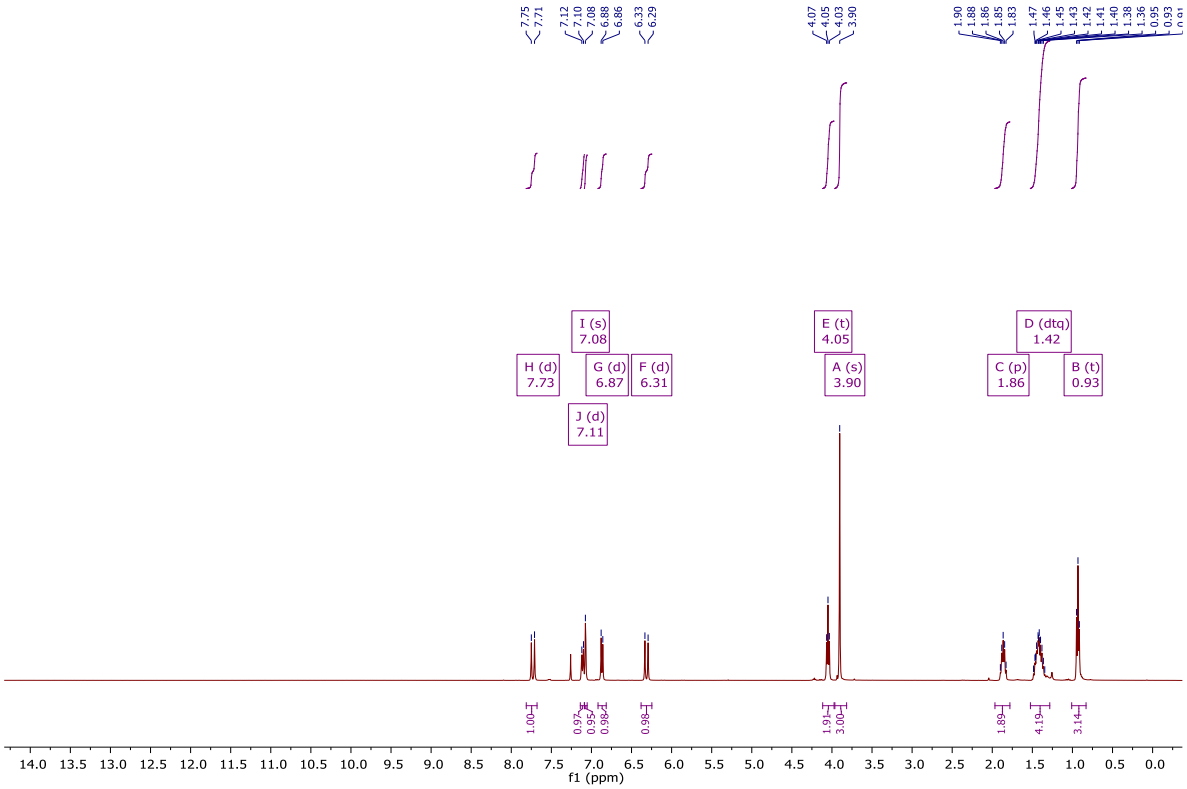

Figure S3. ^{1}H-NMR spectrum of ferulic acid 4-pentyl ether (**3c**).

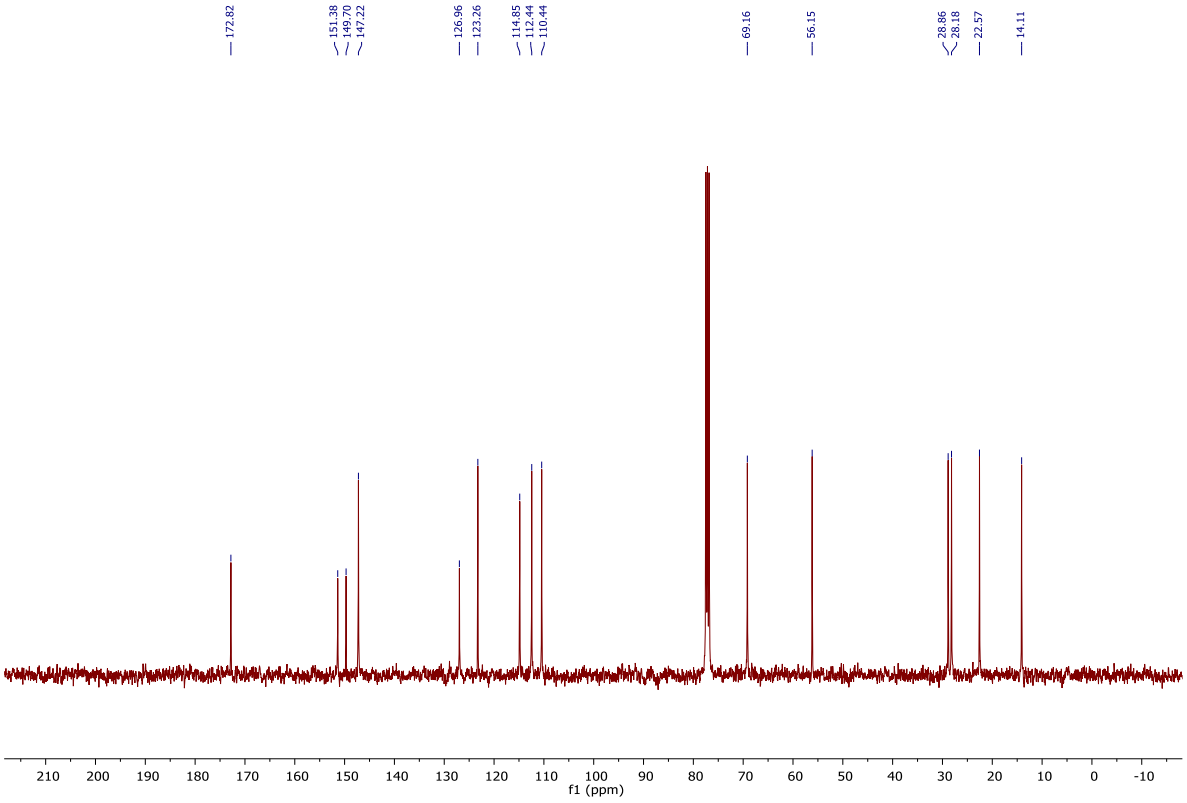

Figure S4. ^{13}C-NMR spectrum of ferulic acid 4-pentyl ether (**3c**).

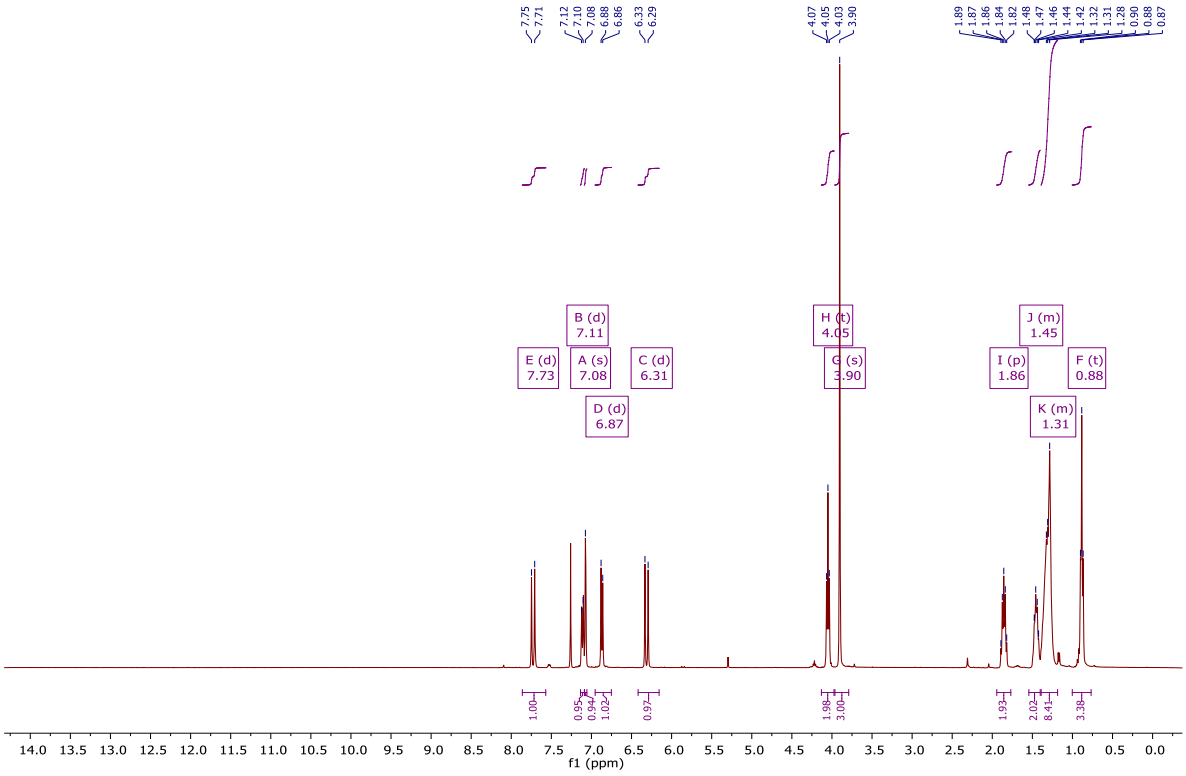

Figure S5. [1]H-NMR spectrum of ferulic acid 4-hexyl ether (**3d**).

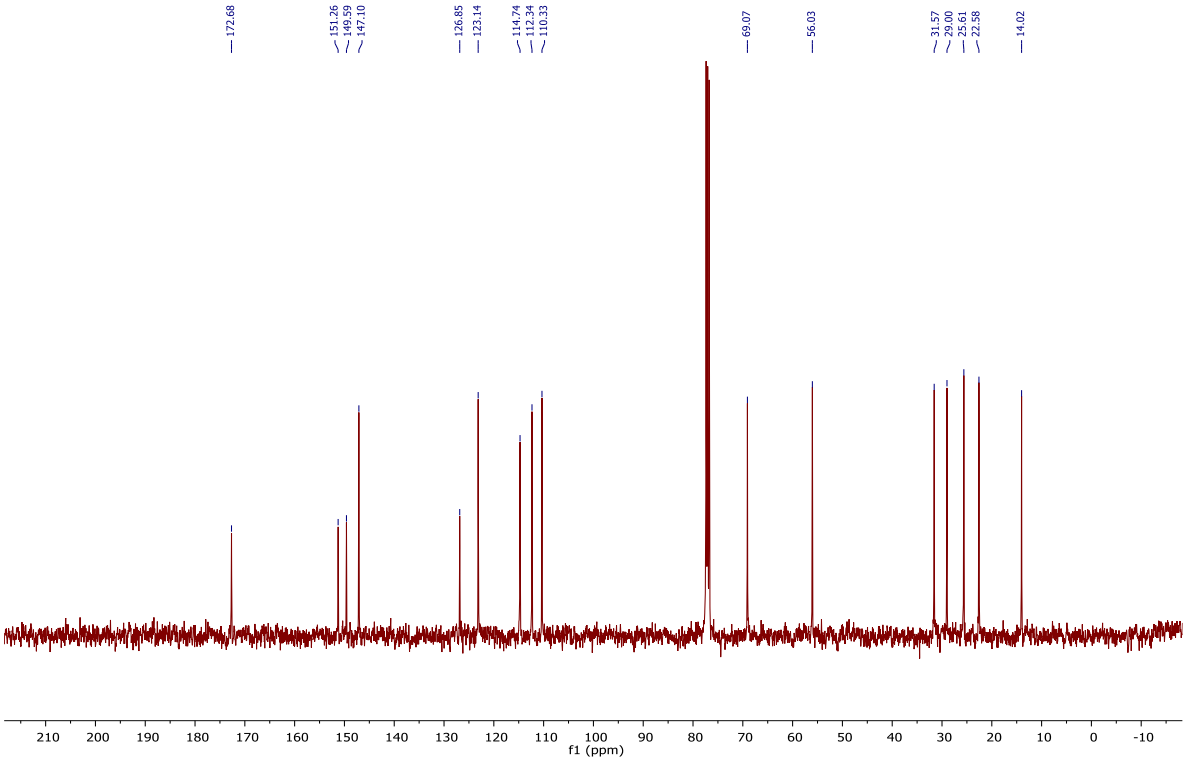

Figure S6. [13]C-NMR spectrum of ferulic acid 4-hexyl ether (**3d**).

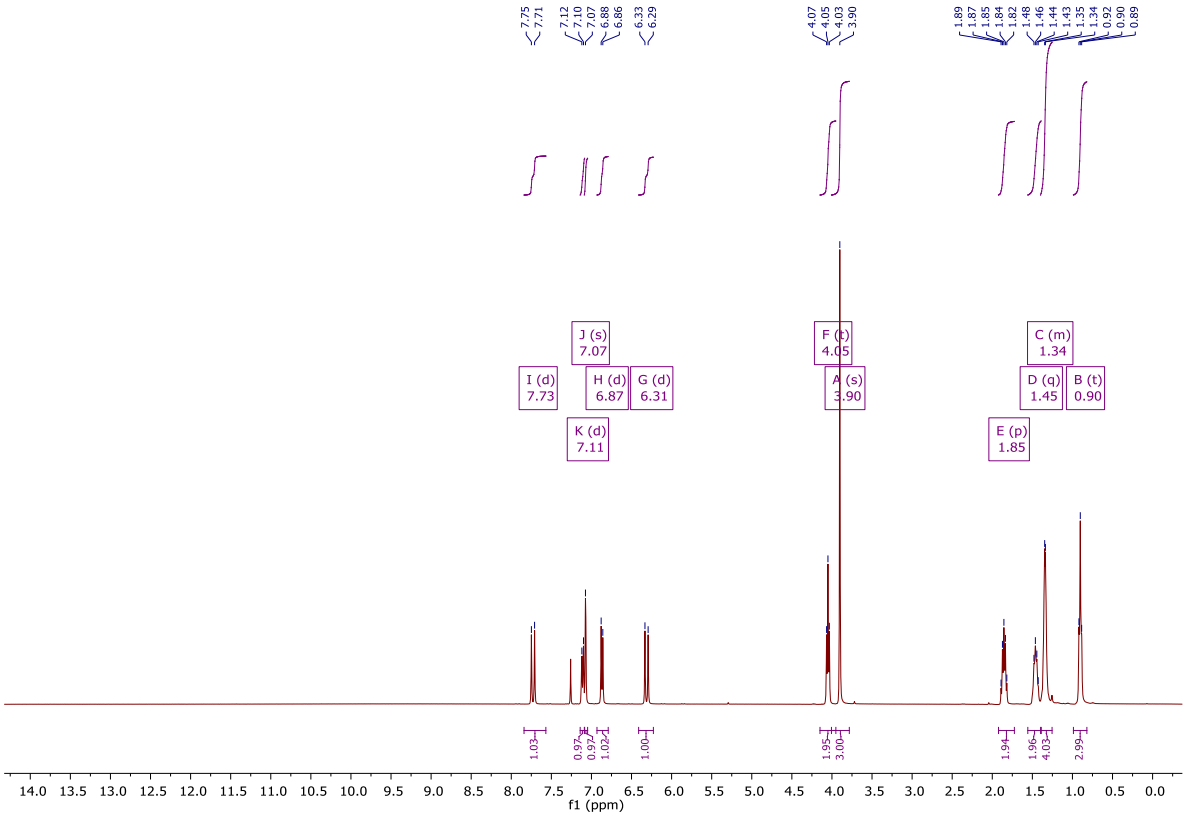

Figure S7. ^{1}H-NMR spectrum of ferulic acid 4-octyl ether (**3e**).

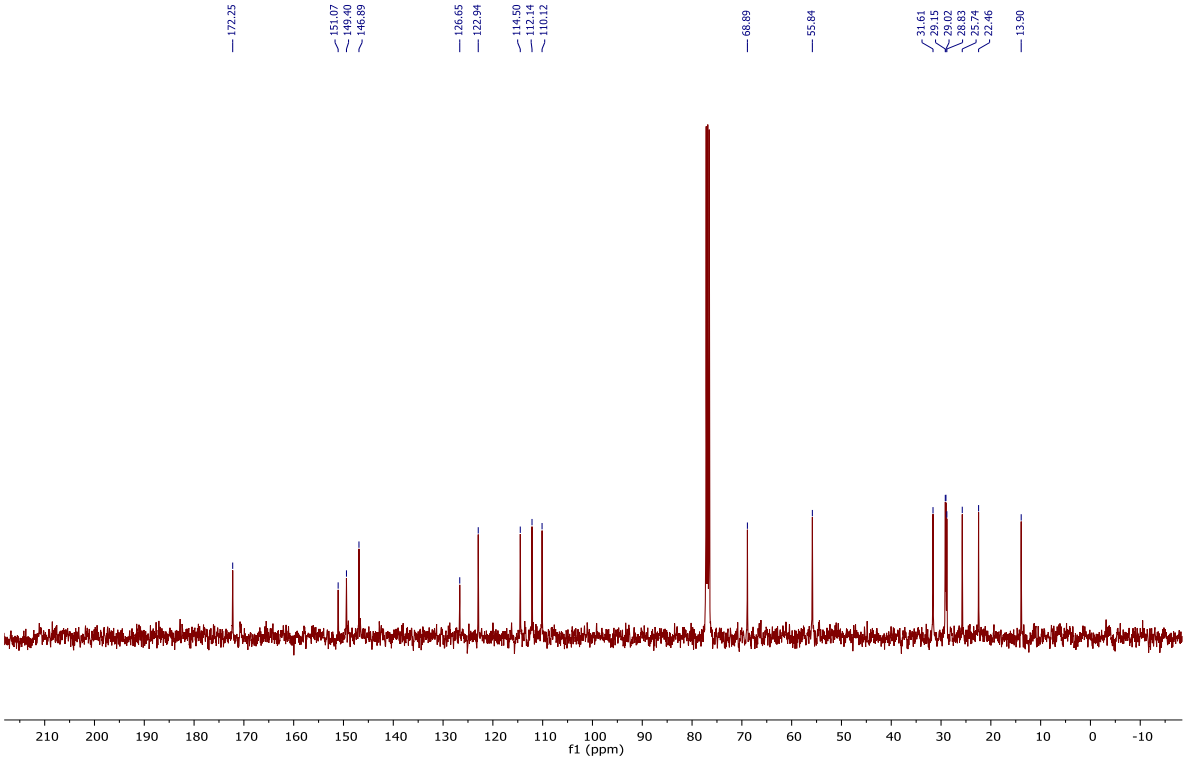

Figure S8. ^{13}C-NMR spectrum of ferulic acid 4-octyl ether (**3e**).

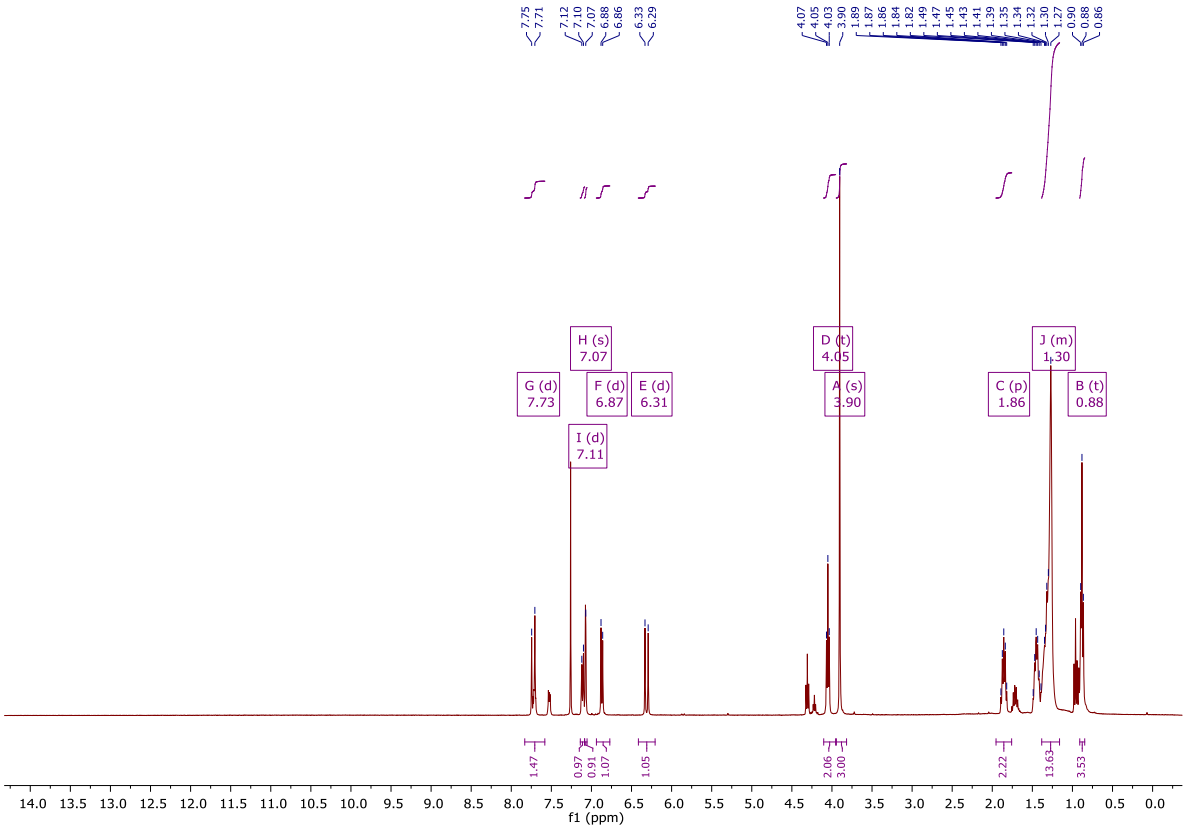

Figure S9. ^{1}H-NMR spectrum of ferulic acid 4-decyl ether (**3f**).

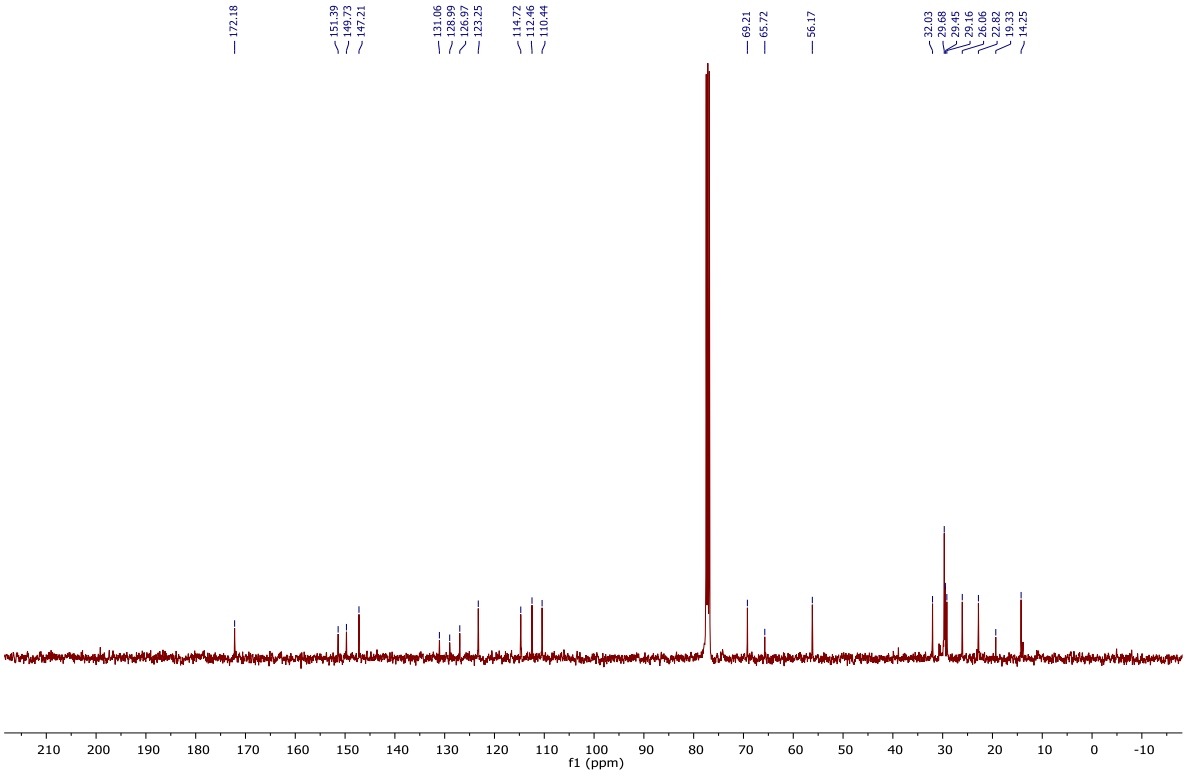

Figure S10. ^{13}C-NMR spectrum of ferulic acid 4-decyl ether (**3f**).

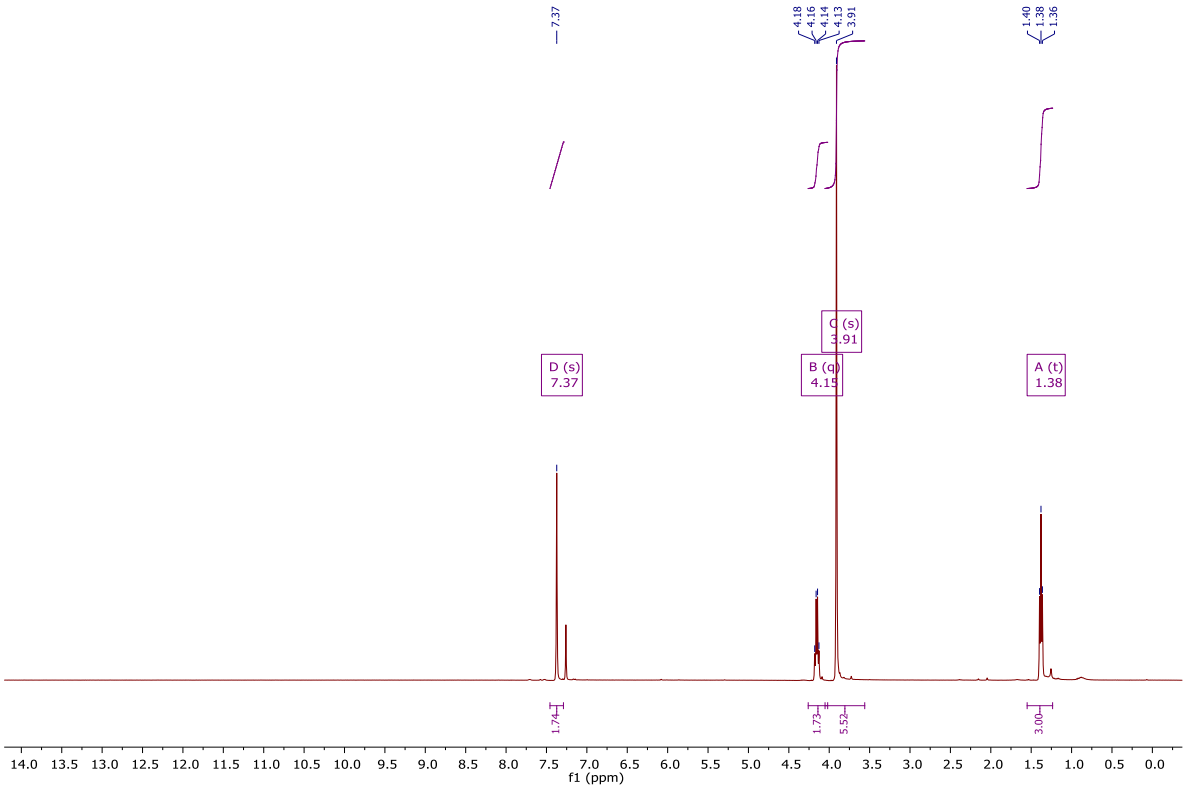

Figure S11. ^{1}H-NMR spectrum of syringic acid 4-ethyl ether (**5a**).

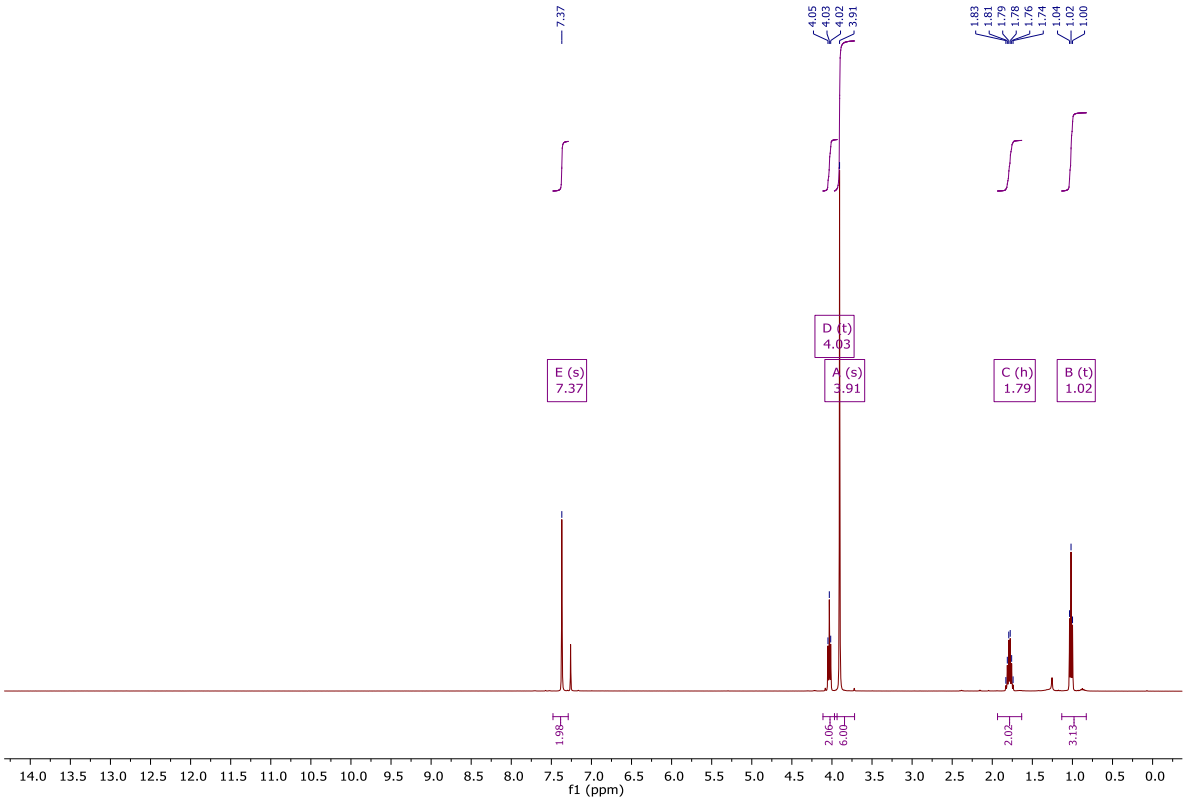

Figure S12. ^{1}H-NMR spectrum of syringic acid 4-propyl ether (**5b**).

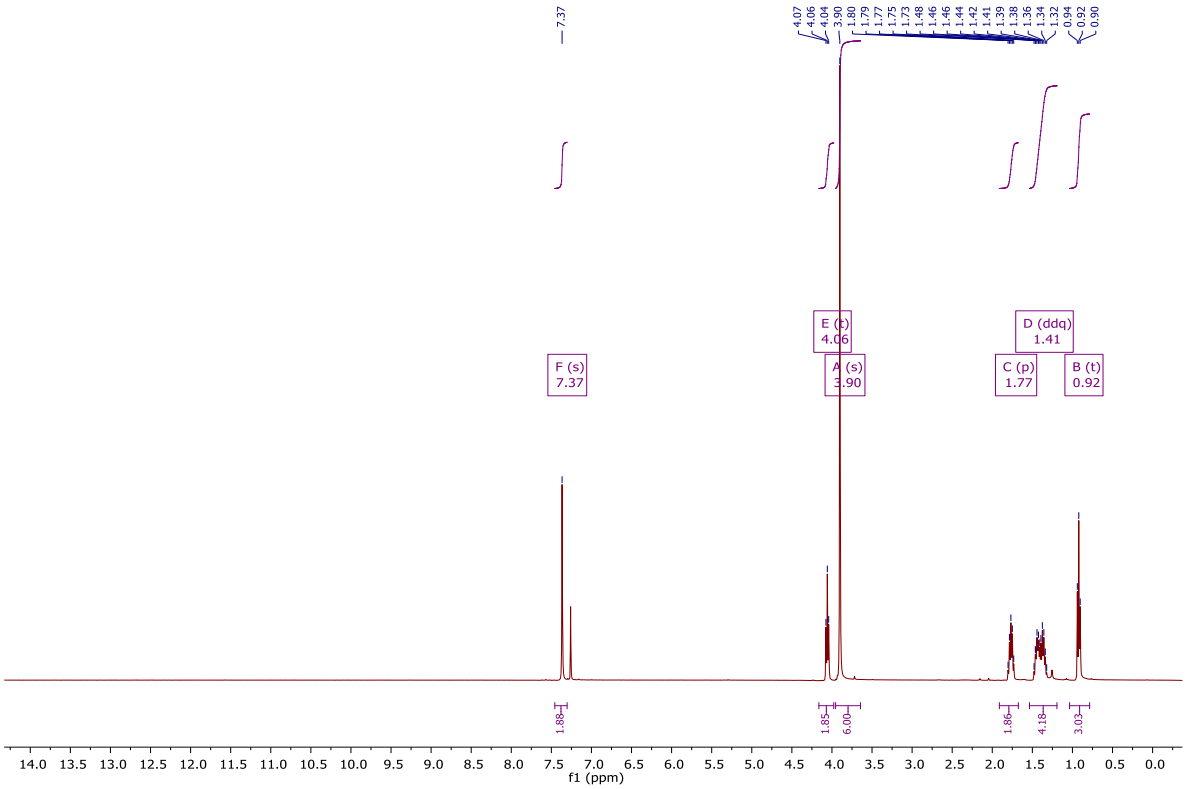

Figure S13. [1]H-NMR spectrum of syringic acid 4-pentyl ether (**5c**).

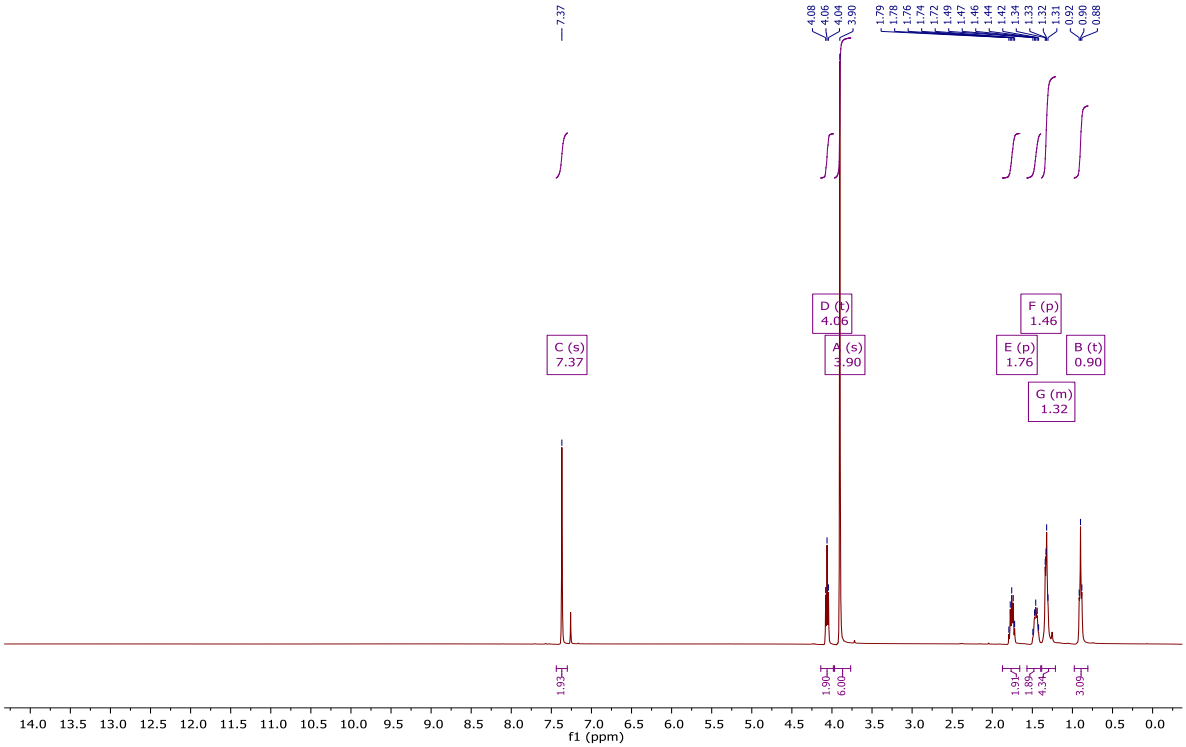

Figure S14. [1]H-NMR spectrum of syringic acid 4-hexyl ether (**5d**).

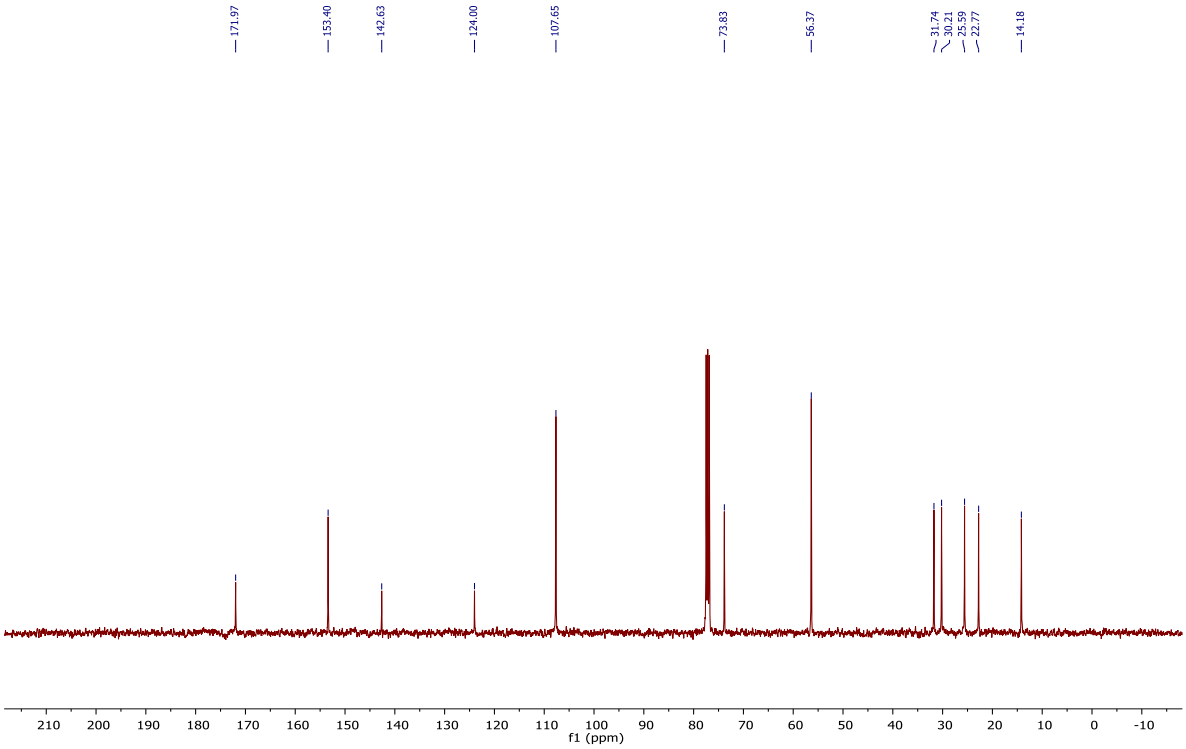

Figure S15. ^{13}C-NMR spectrum of syringic acid 4-hexyl ether (**5d**).

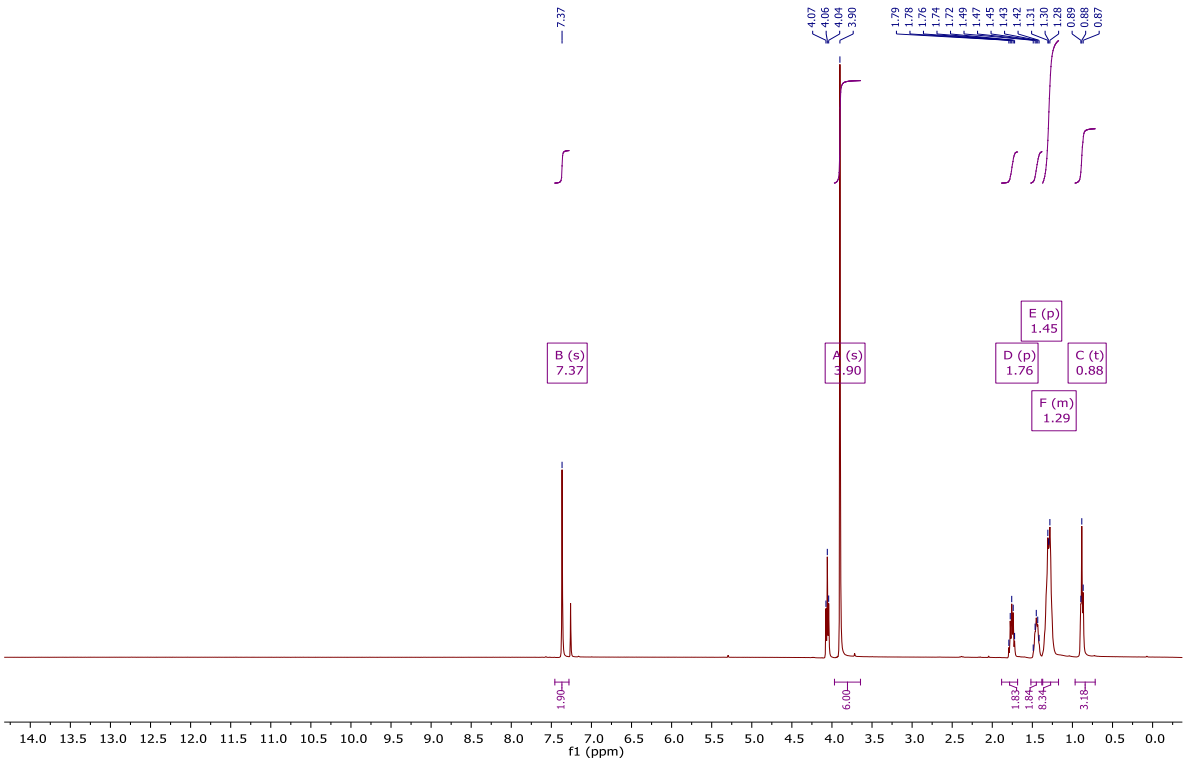

Figure S16. ^{1}H-NMR spectrum of syringic acid 4-octyl ether (**5e**).

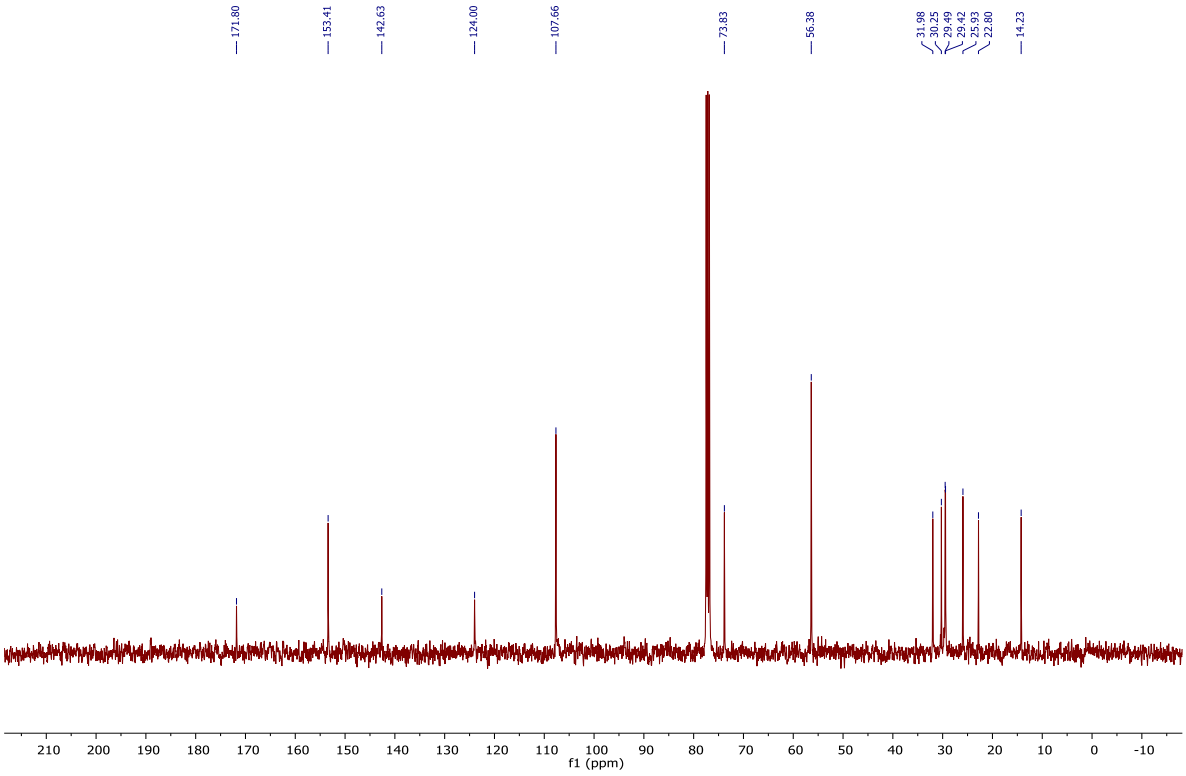

Figure S17. ^{13}C-NMR spectrum of syringic acid 4-octyl ether (**5e**).

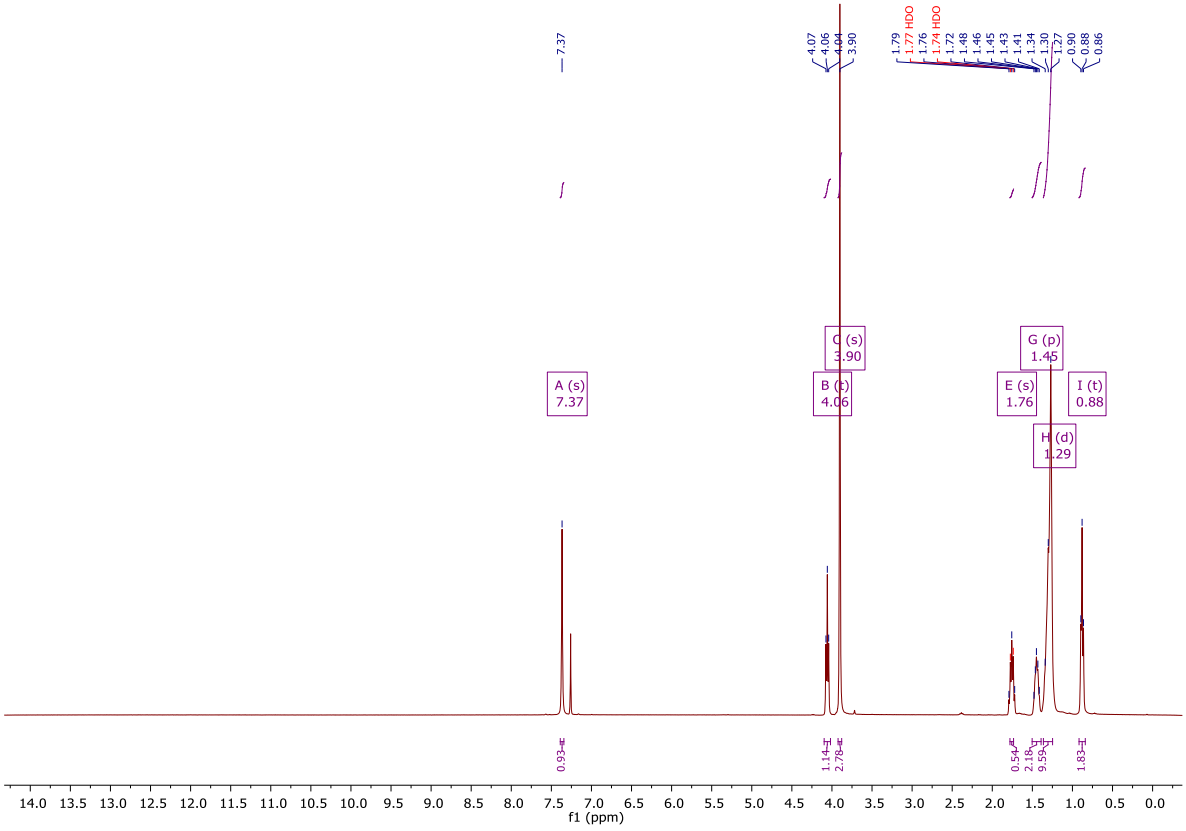

Figure S18. ^{1}H-NMR spectrum of syringic acid 4-decyl ether (**5f**).

II. Physicochemical, drug-likeness, and pharmacokinetic properties

Table S1. Physicochemical and drug-likeness properties of the compounds

	1	3a	3b	3c	3d	3e	3f	4	5a	5b	5c	5d	5e	5f
Physicochemical properties														
Molecular Weight (g/mol)	194.06	222.09	236.1	264.14	278.15	306.18	334.21	198.05	226.08	240.1	268.13	282.15	310.18	338.21
Volume	194.938	229.53	246.826	281.418	298.714	333.306	367.898	189.069	223.661	240.957	275.549	292.845	327.437	362.029
Density	0.995	0.968	0.957	0.939	0.931	0.919	0.908	1.048	1.011	0.996	0.973	0.963	0.947	0.934
nHA	4	4	4	4	4	4	4	5	5	5	5	5	5	5
nHD	2	1	1	1	1	1	1	2	1	1	1	1	1	1
nRot	3	5	6	8	9	11	13	3	5	6	8	9	11	13
nRing	1	1	1	1	1	1	1	1	1	1	1	1	1	1
MaxRing	6	6	6	6	6	6	6	6	6	6	6	6	6	6
nHet	4	4	4	4	4	4	4	5	5	5	5	5	5	5
fChar	0	0	0	0	0	0	0	0	0	0	0	0	0	0
nRig	8	8	8	8	8	8	8	7	7	7	7	7	7	7
Flexibility	0.375	0.625	0.75	1.0	1.125	1.375	1.625	0.429	0.714	0.857	1.143	1.286	1.571	1.857
StereoCenters	0	0	0	0	0	0	0	0	0	0	0	0	0	0
TPSA	66.76	55.76	55.76	55.76	55.76	55.76	55.76	75.99	64.99	64.99	64.99	64.99	64.99	64.99
logS	-1.761	-3.317	-4.003	-4.502	-4.647	-4.785	-4.86	-1.975	-2.684	-3.36	-3.917	-4.13	-4.334	-4.407
logP	1.803	2.101	2.606	3.501	3.876	4.748	5.691	1.212	2.018	2.467	3.357	3.734	4.561	5.531
logD	2.724	1.905	2.596	3.228	3.458	3.878	4.074	3.978	2.412	2.876	2.88	3.167	3.725	4.106
Medicinal Chemistry properties														
QED	0.715	0.776	0.771	0.578	0.552	0.482	0.392	0.760	0.829	0.825	0.734	0.703	0.622	0.517
SAscore	1.869	1.749	1.815	1.826	1.848	1.896	1.946	1.726	1.702	1.762	1.779	1.804	1.855	1.909
Fsp3	0.100	0.250	0.308	0.400	0.438	0.5	0.550	0.222	0.364	0.417	0.5	0.533	0.588	0.632
MCE-18	7.0	7.0	7.0	7.0	7.0	7.0	7.0	8.0	8.0	8.0	8.0	8.0	8.0	8.0
NPscore	0.926	0.056	0.113	0.249	0.29	0.264	0.242	0.544	-0.021	0.035	0.18	0.224	0.204	0.187
Lipinski Rule	A	A	A	A	A	A	A	A	A	A	A	A	A	A
Pfizer Rule	A	A	A	R	R	R	R	A	A	A	R	R	R	R
GSK Rule	A	A	A	A	A	R	R	A	A	A	A	A	R	R

Golden Triangle	R	A	A	A	A	A	A	R	A	A	A	A	A	A
PAINS	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts
ALARM NMR	2 alerts	1 alerts	1 alerts	1 alerts	1 alerts	1 alerts	1 alerts	3 alerts	2 alerts	2 alerts	2 alerts	2 alerts	2 alerts	2 alerts
BMS	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	1 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	1 alerts
Chelator Rule	1 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	1 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts	0 alerts

Abbreviation: A, Accepted; R, Rejected; PAINS, Pan-assay interference compounds, ALARM NMR, a La assay to detect reactive molecules by nuclear magnetic resonance; QED, measure of drug-likeness based on the concept of desirability; SAscore, Synthetic accessibility score, NPscore, Natural Product-likeness score; BMS, Undesirable, reactive compounds.

Table S2. Pharmacokinetics properties of the compounds

	1	3a	3b	3c	3d	3e	3f	4	5a	5b	5c	5d	5e	5f
Absorption properties														
Caco-2 Permeability (log cm/s)	-4.902	-4.604	-4.631	-4.678	-4.702	-4.736	-4.768	-5.142	-4.707	-4.660	-4.647	-4.648	-4.664	-4.678
MDCK Permeability	1.5e-05	1.2e-05	1.4e-05	2.2e-05	2.6e-05	3.1e-05	3.1e-05	1.1e-05	1.4e-05	1.2e-05	2.1e-05	2.4e-05	2.5e-05	2.5e-05
P-glycoprotein $_{\text{inhibitor}}$	0.0	0.001	0.001	0.002	0.004	0.03	0.146	0.002	0.006	0.005	0.023	0.06	0.414	0.844
P-glycoprotein $_{\text{substrate}}$	0.086	0.711	0.843	0.822	0.777	0.648	0.464	0.003	0.001	0.005	0.019	0.031	0.052	0.034
HIA	0.03	0.005	0.005	0.005	0.005	0.005	0.005	0.028	0.003	0.003	0.003	0.003	0.003	0.003
F20%	0.047	0.002	0.003	0.005	0.018	0.700	0.975	0.011	0.005	0.006	0.004	0.005	0.023	0.840
F30%	0.584	0.327	0.271	0.036	0.029	0.148	0.87	0.067	0.007	0.006	0.009	0.013	0.043	0.222
Distribution properties														
PPB (%)	89.75	87.03	90.00	94.68	96.12	97.98	98.97	50.89	50.45	60.70	87.47	93.34	96.87	97.67
VD (L/kg)	0.339	0.207	0.22	0.207	0.214	0.259	0.332	0.459	0.354	0.385	0.312	0.287	0.269	0.274
BBB	0.329	0.243	0.242	0.233	0.215	0.165	0.125	0.457	0.498	0.417	0.311	0.249	0.155	0.11
Fu (%)	6.394	5.545	4.766	2.888	2.130	1.243	0.879	38.56	30.15	26.29	11.72	6.815	3.234	2.112
Metabolism properties														
P450 CYP1A2$_{\text{inhibitor}}$	0.059	0.285	0.350	0.543	0.592	0.625	0.588	0.032	0.088	0.111	0.185	0.248	0.360	0.360
P450 CYP1A2$_{\text{substrate}}$	0.478	0.633	0.737	0.766	0.754	0.634	0.445	0.911	0.910	0.916	0.913	0.908	0.894	0.859
P450 CYP3A4$_{\text{inhibitor}}$	0.042	0.053	0.057	0.103	0.123	0.173	0.294	0.025	0.034	0.036	0.056	0.068	0.105	0.168
P450 CYP3A4$_{\text{substrate}}$	0.057	0.062	0.063	0.067	0.078	0.114	0.120	0.058	0.106	0.169	0.341	0.444	0.535	0.509
P450 CYP2C9$_{\text{inhibitor}}$	0.142	0.05	0.102	0.443	0.551	0.606	0.498	0.028	0.033	0.057	0.228	0.346	0.497	0.474
P450 CYP2C9$_{\text{substrate}}$	0.367	0.766	0.779	0.840	0.871	0.921	0.950	0.131	0.231	0.220	0.261	0.299	0.394	0.547
P450 CYP2C19$_{\text{inhibitor}}$	0.02	0.028	0.028	0.043	0.052	0.082	0.139	0.012	0.011	0.012	0.020	0.024	0.038	0.060
P450 CYP2C19$_{\text{substrate}}$	0.199	0.356	0.467	0.466	0.488	0.533	0.530	0.141	0.149	0.149	0.148	0.146	0.142	0.136
P450 CYP2D6$_{\text{inhibitor}}$	0.026	0.022	0.022	0.020	0.021	0.036	0.061	0.016	0.015	0.017	0.023	0.027	0.043	0.066
P450 CYP2D6$_{\text{substrate}}$	0.075	0.108	0.091	0.091	0.086	0.077	0.062	0.071	0.146	0.110	0.090	0.079	0.060	0.046
Excretion properties														
CL (mL/min/kg)	7.48	5.042	6.754	5.082	4.251	2.991	2.622	7.208	5.499	6.362	5.227	4.646	3.724	3.139
T $_{1/2}$ (h)	0.926	0.873	0.849	0.797	0.74	0.606	0.446	0.946	0.918	0.906	0.891	0.875	0.826	0.738
Toxicity properties														
hERG Blockers	0.023	0.018	0.024	0.040	0.050	0.075	0.127	0.034	0.072	0.092	0.113	0.125	0.168	0.227
H-HT	0.345	0.112	0.100	0.073	0.056	0.041	0.034	0.154	0.129	0.084	0.070	0.064	0.054	0.045
DILI	0.511	0.927	0.909	0.845	0.817	0.748	0.706	0.795	0.885	0.863	0.857	0.870	0.891	0.907

AMES Mutagenicity	0.114	0.018	0.010	0.007	0.006	0.006	0.005	0.009	0.008	0.005	0.003	0.003	0.003	0.002
Rat Oral Acute Toxicity	0.733	0.015	0.023	0.021	0.020	0.018	0.016	0.011	0.007	0.009	0.011	0.012	0.013	0.013
FDAMDD	0.076	0.012	0.011	0.011	0.011	0.010	0.009	0.023	0.020	0.019	0.019	0.018	0.017	0.016
Skin Sensitization	0.929	0.675	0.77	0.908	0.930	0.945	0.952	0.129	0.106	0.110	0.185	0.221	0.373	0.660
Carcinogencity	0.443	0.689	0.569	0.410	0.335	0.221	0.144	0.034	0.055	0.037	0.047	0.055	0.052	0.049
Eye Corrosion	0.515	0.055	0.097	0.125	0.129	0.137	0.145	0.292	0.025	0.017	0.021	0.021	0.021	0.023
Eye Irritation	0.979	0.941	0.915	0.910	0.91	0.905	0.899	0.977	0.923	0.824	0.809	0.804	0.793	0.785
Respiratory Toxicity	0.720	0.137	0.177	0.358	0.451	0.555	0.599	0.044	0.022	0.026	0.042	0.062	0.158	0.367

Abbreviations: HIA, Human intestinal absorption; $F_{20\%}$, Human oral bioavailability 20%; $F_{30\%}$, Human oral bioavailability 30%; PPB, Plasma protein binding; VD, Volume distribution; BBB, Blood brain barrier; Fu, Fraction unbound in plasm; CL, Clearance; $T_{1/2}$, Half-life; H-HT, Human hepatotoxicity; DILI, Drug induced liver injury; FDAMDD, FDA maximum (recommended) daily dose.