Supplementary Materials

Structure Activity Related, Mechanistic, and Modeling Studies of Gallotannins containing a Glucitol-Core and α–Glucosidase

Hang Ma,[a†] Ling Wang,[b, c†] Daniel B. Niesen,[a] Ang Cai,[a] Bongsup P. Cho,[a] Wen Tan,[c] Qiong Gu,[b] Jun Xu,[b*] and Navindra P. Seeram[a*]

[a]*Bioactive Botanical Research Laboratory, Department of Biomedical and Pharmaceutical Sciences, College of Pharmacy, University of Rhode Island, Kingston, RI 02881, USA*

[b]*Pre-Incubator for Innovative Drugs & Medicine, School of Bioscience and Bioengineering, South China University of Technology, Guangzhou 510006, China*

[c]*School of Pharmaceutical Sciences, Sun Yat-Sen University, 132 East Circle Road at University City, Guangzhou 510006, China*

[†]*Equal contribution*

*Authors to whom correspondence should be addressed;

N. P. S.: Phone/Fax: 401-874-9367/5787 Email: nseeram@mail.uri.edu

J. X.: Phone: 86-20-3994-3023 Email: xujun9@mail.sysu.edu.cn

Synthesis of tetragalloylglucitol (maplexin J)

The tetragalloylglucitol gallotannin (assigned the common name of maplexin J) was synthesized by modification of the previously published method[20] as shown in **Scheme S1**. Briefly, gallic acid (**i**, 101 mg, 0.6 mmol) was dissolved in dry *N*,*N*-dimethylformamide (DMF, 2 mL). Imidazole (513 mg, 7.5 mmol) and *tert*-butyldimethylsilyl chloride (TBDMS, 521 mg, 3.5 mmol) were added to the solution and stirred at room temperature under nitrogen for 24 hours. A white crystalline solid product was formed and precipitated out of the reaction solution. Trisilyl-protected gallic acid (**ii**) was isolated (244 mg, 82%) from the precipitant using silica gel column chromatography. Compound **ii** (187 mg, 0.4 mmol) and glucitol (**iii**, 10.4 mg, 0.06 mmol) were dissolved in dry dichloromethane (DCM, 2 mL). *N,N′*-diisopropylcarbodiimide (DIC, 61.4 mg, 0.5 mmol) was added followed by 4-dimethylaminopyridin (DMAP, 74.4 mg, 0.06 mmol). The mixture was stirred at room temperature under nitrogen for 96 hours. The crude product was purified using silica gel column chromatography to yield compound **iv**. Compound **iv** (843 mg, 64.6%) was isolated and its structure was confirmed by 2D NMR heteronuclear multiple bond correlations (HMBC) from the three sugar methines and the sugar methylene to the respective carbonyl carbons of the gallic acids. Deprotection of compound **iv** was accomplished in the presence of tetra-*n*-butylammonium fluoride (TBAF). Compound **iv** (50 mg, 0.023 mmol) was dissolved in dry tetrahydrofuran (THF, 2 mL). TBAF (61.1 mg, 0.23 mmol) was added, and the mixture was stirred at room temperature under a nitrogen atmosphere for 10 minutes. The crude product was purified using reverse-phase high-pressure liquid chromatography (HPLC) to yield the final product (10 mg, 52.3%), which was characterized as tetragalloylglucitol and assigned the common name of maplexin J (MJ) based on its nuclear magnetic resonance (NMR) spectroscopic data (**Table S1**; HMBC shown in **Figure S1**).

Scheme S1: Synthetic scheme of maplexin J.

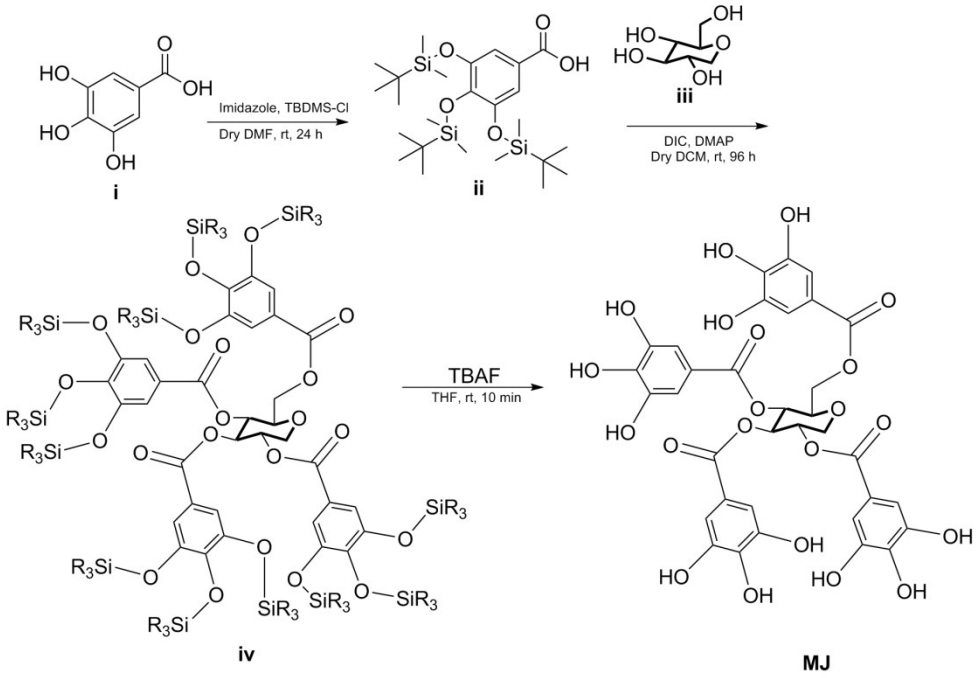
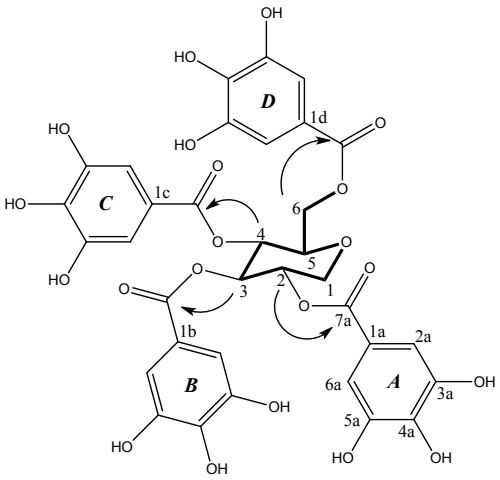


Table S1. The ^{1}H and ^{13}C NMR data of maplexin J. Data was measured in CH_3OD at 500 MHz (^{1}H) and 125 MHz (^{13}C).

No.	δC	δH (mult, J in Hz)
Glucitol Sugar Core		
1	66.62	4.20 (m)
		3.54 (t, 11.1, 12.2)
2	69.66	5.19 (ddd)
3	73.86	5.65 (t, 9.9, 11.1)
4	68.9	5.39 (t, 9.9, 10.7)
5	76.77	3.94 (m)
6	62.33	4.36 (d, 12.1)
		4.19 (m)
Galloyl A		
1a	118.98	
2a, 6a	108.92	6.88 (2H, s)
3a, 5a	145.08	
4a	138.87	
7a	165.81	
Galloyl B		
1b	119.23	
2b, 6b	108.92	6.82 (2H, s)
3b, 5b	144.87	
4b	138.64	
7b	166.25	
Galloyl C		
1c	118.91	
2c. 6c	109	6.87 (2H, s)
3c, 5c	145.01	
4c	138.82	
7c	165.63	
Galloyl D		
1d	119.73	
2d, 6d	108.85	7.00 (2H, s)
3d, 5d	145.03	
4d	138.53	
7d	166.61	

Figure S1. Key HMBC correlations of maplexin J.


OH
HO
D
1d
HO
O
HO
C
1c
O
6
O
HO
4
O
5
O
O
3
2
1
O
O
7a
1b
1a
2a
B
A
6a
3a
OH
5a
4a
HO
OH
HO
OH