

Supporting Information

Novel mono-lipidated dimeric glucagon-like peptide-1 receptor agonist
with improved long-acting and hypoglycemic activities

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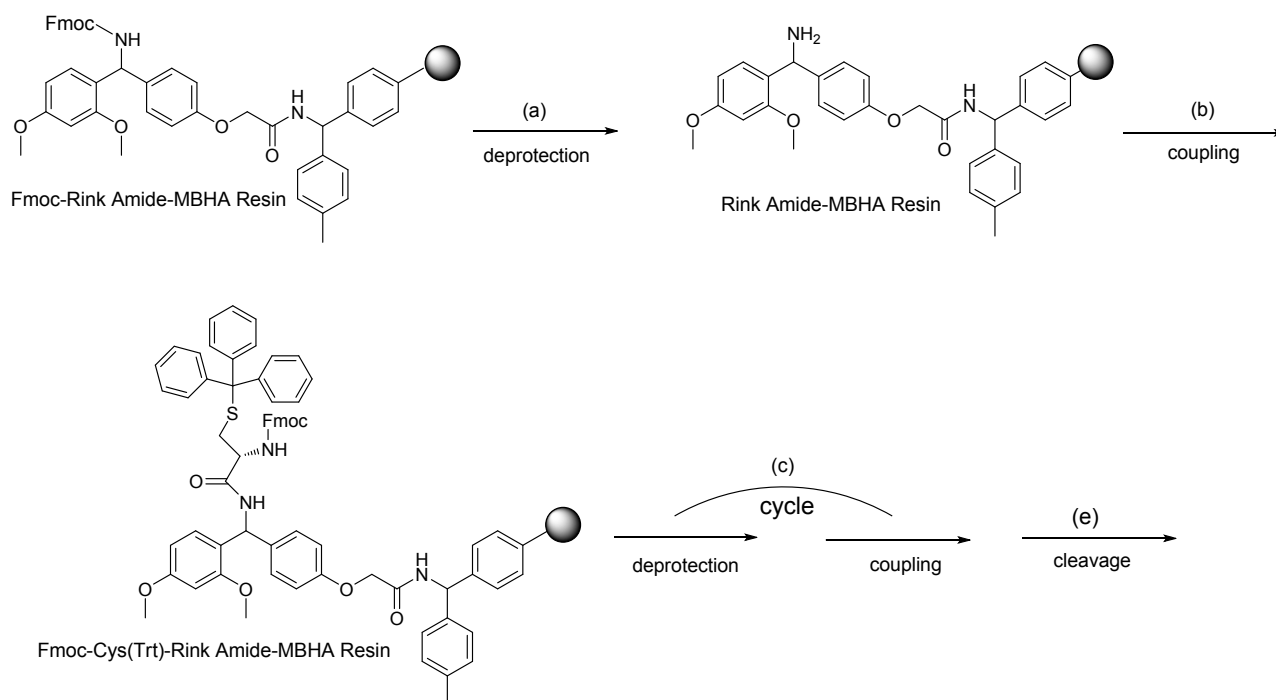


Figure S1. Synthesis route of Gly₈-Cys₃₁-GLP-1. (a) 20% Piperidine/DMF(V/V); (b) Fmoc-Cys(Trt)-OH, DIC/HOBT; (c) repeated the cycles with related protected amino acids; (d) Reagent K (EDT/phenol/water/thioanisole/TFA, 2.5:5:5:5:82.5).

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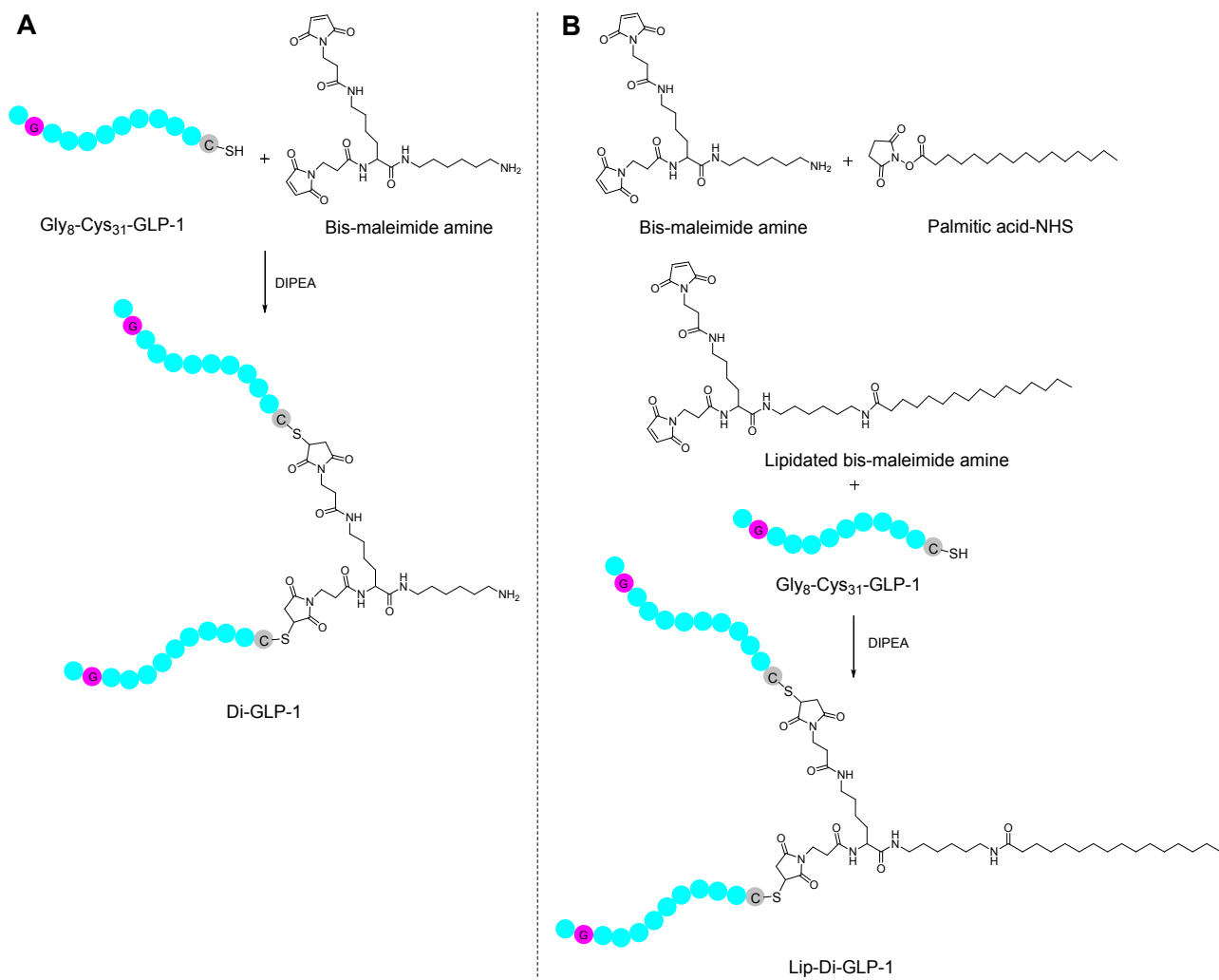


Figure S2. Synthesis route of Di-GLP-1 (A) and Lip-Di-GLP-1 (B).

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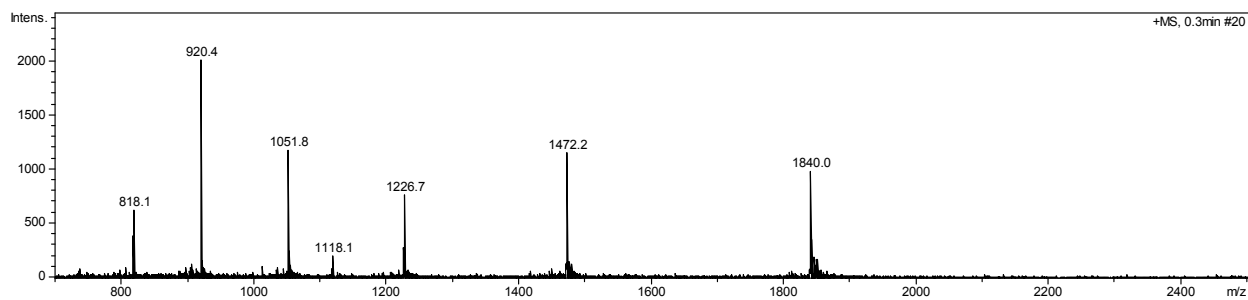


Figure S3. MS spectrum of Di-GLP-1.

Table S1. Molecular mass data analysis of Di-GLP-1 ($M_w = 7321.9$).

(m/z)calad	(m/z)found
$[M+3H+K]^{4+}$ 1840.9	$[M+3H+K]^{4+}$ 1840.0
$[M+4H+K]^{5+}$ 1472.9	$[M+4H+K]^{5+}$ 1472.2
$[M+5H+K]^{6+}$ 1227.6	$[M+5H+K]^{6+}$ 1226.7
$[M+6H+K]^{7+}$ 1052.4	$[M+6H+K]^{7+}$ 1051.8
$[M+7H+K]^{8+}$ 920.9	$[M+7H+K]^{8+}$ 920.4
$[M+8H+K]^{9+}$ 818.7	$[M+8H+K]^{9+}$ 818.1

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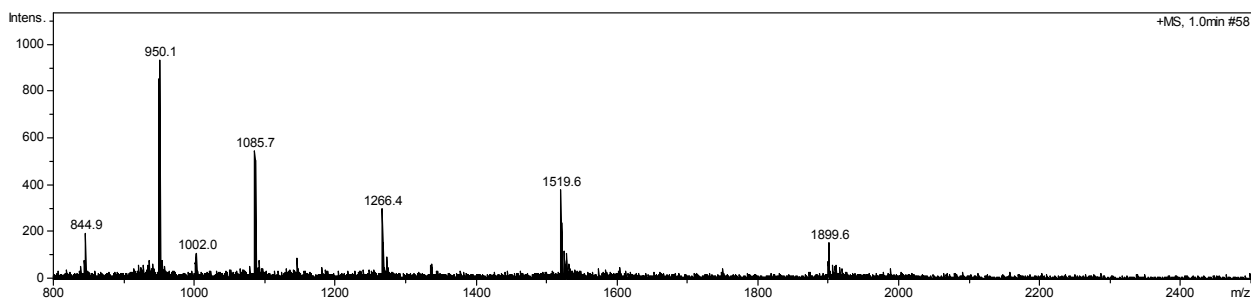


Figure S4. MS spectrum of Lip-Di-GLP-1.

Table S2. Molecular mass data analysis of Lip-Di-GLP-1 ($M_w = 7560.1$).

(m/z)calad	(m/z)found
$[M+3H+K]^{4+}$ 1900.5	$[M+3H+K]^{4+}$ 1899.6
$[M+4H+K]^{5+}$ 1520.6	$[M+4H+K]^{5+}$ 1519.6
$[M+5H+K]^{6+}$ 1267.3	$[M+5H+K]^{6+}$ 1266.4
$[M+6H+K]^{7+}$ 1086.4	$[M+6H+K]^{7+}$ 1085.7
$[M+7H+K]^{8+}$ 950.7	$[M+7H+K]^{8+}$ 950.1
$[M+8H+K]^{9+}$ 845.2	$[M+8H+K]^{9+}$ 844.9

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Table S3. Pharmacokinetic parameters of liraglutide and Lip-Di-GLP-1 in Kunming mice^a

Samples	C _{max}	T _{max} (h)	AUC _{inf} (ng·h·mL ⁻¹)	t _{1/2} (h)	MRT _{s.c.} (h)
Liraglutide	557.7 ± 21.7	2.3 ± 0.5	2693.6 ± 175.5	3.9 ± 0.3	5.4 ± 0.4
Di-GLP-1	559.2 ± 56.5	1.0 ± 0.0	1637.3 ± 39.3	1.8 ± 0.2	2.6 ± 0.2
Lip-Di-GLP-1	595.6 ± 52.8	3.3 ± 0.5	7456.6 ± 564.4	7.0 ± 0.7	11.3 ± 0.5

^aData are the means ± SD (n = 3). T_{max}, time to reach maximum plasma concentration; C_{max}, maximum plasma concentration; AUC_{inf}, area under the curve from zero to infinity; t_{1/2}, elimination half-life; MRT_{s.c.}, mean residence time by subcutaneous injection.