Electronic Supplementary Material (ESI) for Analytical Methods.
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Supplemental Materials

Table S1. Clinical and biochemical data of urine in different groups

PRM	DM(n=53)	DN(n=53)	HC(n=53)	P1[d]	P2[e]
C-PR (ng/ml)[a]	1.74(1.1)[c]	1.74(0.6)	NA	NA	0.988
AGE	62.59(7.1)	63.78(5.5)	61.19(13.3)	0.323	0.344
BMI	24.57(2.8)	25.16(3.2)	NA	NA	0.320
SP	77.10(10.1)	81.18(7.7)	NA	NA	0.024
DP	133.33(14.6)	142.22(15.6)	NA	NA	0.003
CHOL (mmol/L)[a]	5.14(1.0)	5.16(1.2)	4.42(0.4)	<0.001	0.924
LDL-C (mmol/L)[a]	2.96(0.8)	2.86(0.9)	1.34(0.2)	<0.001	0.035
HDL-C(mmol/L)[a]	1.27(0.3)	1.14(0.3)	2.86(0.4)	<0.001	0.035
TG (mmol/L)[a]	1.57(1.0)	2.27(2.1)	1.07(0.4)	<0.001	0.034
GLU (mmol/L)[a]	9.23(2.9)	10.75(3.8)	5.17(0.4)	<0.001	0.026
HbA1c (%)[a]	8.47(1.4)	9.15(1.7)	NA	NA	0.027
Crea (μmol/L)[a]	77.96(15.8)	77.41(16.5)	63.61(14.4)	<0.001	0.863
UA(μmol/L)[b]	316.02(92.4)	340.51(111.7)	297.55(70.9)	0.069	0.230
BUN(mmol/L)[b]	4.93(1.0)	5.69(1.5)	4.51(0.8)	<0.001	0.003
MALB(mg/L)[b]	15.90(27.8)	81.06(61.0)	NA	NA	<0.001
Ucrea(mg/dL)[b]	124.74(63.2)	104.18(48.6)	NA	NA	0.068
ACR(mg/g)[b]	13.25(23.0)	95.44(92.7)	NA	NA	0.001
AST(U/L)[a]	22.57(13.2)	24.43(12.2)	15.25(7.0)	<0.001	0.461
ALT(U/L)[a]	20.63(11.9)	21.82(11.4)	18.19(4.5)	0.159	0.605

[a] The urinary clinical biochemical index. [b] The blood clinical biochemical index. C-PR: C-Peptide; AGE: Average age; BMI: Body mass index; SP: systolic pressure; DP: diastolic pressure; CHOL: total cholesterol; LDL-C: Low density lipoprotein-cholesterol; HDL-C: High density lipoprotein-cholesterol; TG: triglyceride; GLU: Fasting plasma glucose; HbA1c: glycosylated hemoglobin; Crea: Serum creatinine; UA: uric acid; BUN: Urea nitrogen; MALB: Urinary microalbumin; Ucrea: Urinary creatinine; ACR: Urinary albumin creatinine; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase.

[c] The value was expressed as mean (standard deviation).

[d] The statistical significance by analysis of variance (ANOVA) and Kruskal Wallis test among multiple groups in HC, DM, and DN groups.

[e] The statistical significance by T-test and Kruskal Wallis test between groups DM and DN.

Table S2. Urinary metabolites identified from the ^{1}H-NMR spectra of the patients and healthy participants

Abbreviation	Metabolites	ppm (multiplicity)
1-MH	1-Methylhistidine	7.03(s[a]), 7.70(s)[b]
MN	1-Methylnicotinamid	4.49(s)
HIB	2-Hydroxyisobutyrate	1.36(s)
OIV	2-Oxoisovalerate	1.11(d)
HMM	3-Hydroxy-4-methoxymandelate	6.99(d)
3-HB	3-Hydroxybutyrate	1.20(d), 2.28(dd), 2.40(dd), 4.16(m)
3-MH	3-Methylhistidine	8.05(d)
AD	Acetamide	1.99(s)
Ace	Acetate	1.93(s)
AA	Acetoacetate	2.28(s)
Act	Acetone	2.24(s)
Ach	Acetylcholine	3.23(s)
Ads	Adenosine	8.34(s)
Ala	Alanine	1.49(d)
AH	Aminohippurate	6.91(d)
Asc	Ascorbate	4.03(m), 4.53(d)
Asn	Asparagine	2.84(d), 2.91(m)
Ben	Benzoate	7.48(t)
Cho	Choline	3.20(s)
Cit	Citrate	2.54(d), 2.68(d)
Cr	Creatine	3.04(s), 3.94(s)
Cn	Creatinine	3.05(s), 4.06(s)
DMA	Dimethylamine	2.72(s)

Eth	Ethanol	1.24(t), 3.65(q)
For	Formate	8.47(s)
Fum	Fumarate	6.53(s)
Glu	Glutamate	2.10(m), 2.35(m), 3.78(m)
Gln	Glutamine	2.45(m), 3.78(m)
Gly	Glycine	3.57(s)
GA	Guanidoacetate	3.80(s)
Hip	Hippurate	3.97(d), 7.56(t), 7.64(t), 7.84(d)
His	Histidine	7.15(s), 8.00(s)
HG	Homogentisate	6.67(d), 6.71(d), 6.78(d)
IL	Indole-3-lactate	7.20(d), 7.76(d)
Ino	Inosine	4.39(dd), 8.34(s)
IB	Isobutyrate	1.07(d)
Ile	Isoleucine	0.94(t), 1.01(d)
Lac	Lactate	1.34(d), 4.13(q)
Leu	leucine	0.97(t)
Lys	lysine	1.74(m), 1.93(m), 3.02(t)
MTT	Maltotriose	4.70(d)
MG	Methylguanidine	2.81(s)
MM	Methylmalonate	1.25(d)
DMG	N,N-Dimethylglycine	2.93(s)
NAA	N-Acetylaspartate	2.03(s)
NAG	N-Acetylglycoprotein	2.05(s)
NMN	N-Methylnicotinamide	8.92(d), 8.98(d), 9.30(s)
NA	Nicotinamide	8.73(d)
OAG	O-Acetylglycoprotein	2.07(s)
OA	Oxaloacetate	2.35(s)
p-HPA	para-Hydroxyphenylacetate	6.88(d), 7.17(d)
PAG	Phenylacetylglycine	3.68(s), 3.73(d), 7.30(m), 7.36(m), 7.43(m)

Phe	Phenylalanine	3.97(t)
PA	Picolinate	7.89(d), 8.55(m)
Sar	Sarcosine	2.76(s), 3.63(s)
Suc	Succinate	2.41(s)
Sum	Succinimide	2.79(s)
Tau	Taurine	3.27(t), 3.43(t)
Thr	Threonine	4.26(m)
Tri	Trigonelline	4.44(s), 8.01(m), 8.85(t), 9.13(s)
TMAO	Trimethylamine N-oxide	3.28(s)
Trp	Tryptophan	7.33(s), 7.52(d), 7.73(d)
Uc	Urocanate	6.37(d)
Val	Valine	0.99(d), 1.04(d)
α-Glc	α-Glucose	3.44(t), 3.55(dd), 3.72(t), 3.84(m), 5.26(d)
KIV	α-Ketoisovalerate	1.14(d)
β-Glc	β-Glucose	3.48(ddd), 3.51(t), 3.88(dd), 4.66(d)

[a] Multiplicity: s: singlet, d: doublet, t: triplet, q: quadruplet, m: multiplet, dd: double-doublet, ddd: double-double-doublet

[b] Underlined peaks indicate the characteristic signals of each metabolite for the quantitative analysis.

Table S3. The potential urinary biomarkers of diabetes mellitus

Metabolites	Abbreviation	|r|[a]	FC[b]	p[c]	VIP[d]
3-Hydroxy-4-methoxymandelate	HMM	0.599	1.47	5.00E-03	1.600
Aminohippurate	AH	0.509	1.19	2.60E-02	1.570
Citrate	Cit	0.705	1.54	2.26E-06	1.883
Fumarate	Fum	0.683	8.65	1.86E-14	1.798
Glutamate	Glu	0.710	8.18E-01	1.50E-06	1.897
Glutamine	Gln	0.707	7.63E-01	2.54E-13	1.871
Homogentisate	HG	0.651	1.63	6.19E-07	1.716
Isoleucine	Ile	0.513	8.99E-01	5.76E-04	1.466
N-Acetylaspartate	NAA	0.677	7.66E-01	5.48E-13	1.855
N-Acetylglycoprotein	NAG	0.680	8.76E-01	3.31E-04	1.894
N-Methylnicotinamide	NMN	0.664	2.96	9.02E-09	1.758
Phenylacetylglycine	PAG	0.577	1.36	5.00 E-03	1.664
Taurine	Tau	0.440	5.42	2.00 E-03	1.470
Threonine	Thr	0.601	7.96E-01	2.10E-06	1.637
Urocanate	Uc	0.590	6.07	6.23E-09	1.643
α-Glucose	α-Glc	0.374	55.7	5.99E-04	1.430
β-Glucose	β-Glc	0.341	21.5	9.06E-04	1.433

[a] the absolute value of correlation coefficient [b] fold change; [c] the p value from Student's t-test; [d] Variable importance of the projection. Screening criteria for differential metabolites: VIP greater than 10% of all values, $|r| > 0.400$, $FC < 0.9$ or $FC > 1.1$ and $p < 0.05$.

Table S4. The potential urinary biomarkers of diabetic nephropathy

Metabolites	abbreviation	|r|[a]	FC[b]	p[c]	VIP[d]
1-Methylhistidine	1-MH	0.815	0.825	9.67E-05	2.093
3-Hydroxy-4-methoxymandelate	HMM	0.654	1.36	1.30E-02	1.612
Alanine	Ala	0.635	0.802	6.28E-05	1.632
Asparagine	Asn	0.718	0.891	3.00E-03	1.823
Creatinine	Cn	0.539	0.892	3.90E-02	1.979
Fumarate	Fum	0.696	8.32	3.67E-15	1.735
Glutamate	Glu	0.772	0.798	1.23E-07	1.935
Glutamine	Gln	0.788	0.695	1.02E-17	1.961
Histidine	His	0.546	0.511	5.13E-08	1.440
Homogentisate	HG	0.642	1.32	1.00E-03	1.603
Lysine	Lys	0.675	0.734	1.18E-08	1.709
Methylmalonate	MM	0.562	0.729	3.42E-10	1.414
N-Acetylaspartate	NAA	0.675	0.722	7.10E-15	1.764
N-Acetylglycoprotein	NAG	0.695	0.814	2.30E-07	1.814
N-Methylnicotinamide	NMN	0.656	2.39	9.89E-07	1.672
O-Acetylglycoprotein	OAG	0.545	0.870	9.91E-05	1.493
Phenylacetylglycine	PAG	0.588	1.32	9.00E-03	1.503
Phenylalanine	Phe	0.713	0.899	4.60E-02	1.812
Sarcosine	Sar	0.567	0.899	1.60E-02	1.552
Taurine	Tau	0.496	4.51	3.00E-03	1.454
Threonine	Thr	0.605	7.95E-01	6.72E-07	1.553
α-Glucose	α-Glc	0.432	54.9	2.98E-04	1.446

[a] the absolute value of correlation coefficient; [b] fold change; [c] the p value from Student's t-test; [d] Variable importance of the projection. Screening criteria for differential metabolites: VIP greater than 10% of all values, $|r| > 0.400$, $FC < 0.9$ or $FC > 1.1$ and $p < 0.05$.

Table S5. The classification of the medications for diabetes mellitus and diabetic nephropathy

ID	medication name	Disease	Variety	Function
D1	Saxagliptin	T2DM，DN	DPP-4I	hypoglycemic
D2	Linagliptin	T2DM	DPP-4I	hypoglycemic
D3	Sitagliptin	T2DM	DPP-4I	hypoglycemic
D4	Vildagliptin	T2DM	DPP-4I	hypoglycemic
D5	Alogliptin	T2DM	DPP-4I	hypoglycemic
D6	Metformin	T2DM，DN	Biguanides	hypoglycemic
D7	Canagliflozin	T2DM，DN	SGLT2I	hypoglycemic
D8	Dapagliflozin	T2DM，DN	SGLT2I	hypoglycemic
D9	Empagliflozin	T2DM	SGLT2I	hypoglycemic
D10	Ertugliflozin	T2DM	SGLT2I	hypoglycemic
D11	Albiglutide	T2DM	GLP-1RA	hypoglycemic
D12	Dulaglutide	T2DM	GLP-1RA	hypoglycemic
D13	Exenatide	T2DM	GLP-1RA	hypoglycemic
D14	Liraglutide	T2DM	GLP-1RA	hypoglycemic
D15	Lixisenatide	T2DM，DN	GLP-1RA	hypoglycemic
D16	Semaglutide	T2DM	GLP-1RA	hypoglycemic

D17	Glucagon	T2DM，DN	Glucagon	hypoglycemic
D18	Insulin degludec	T2DM	Insulin	hypoglycemic
D19	Insulin detemir	T2DM	Insulin	hypoglycemic
D20	Insulin glargine	T2DM，DN	Insulin	hypoglycemic
D21	Insulin glulisine	T2DM，DN	Insulin	hypoglycemic
D22	Insulin lispro	T2DM	Insulin	hypoglycemic
D23	Chlorpropamide	T2DM	Sulfonylureas	hypoglycemic
D24	Gliclazide	T2DM	Sulfonylureas	hypoglycemic
D25	Glimepiride	T2DM	Sulfonylureas	hypoglycemic
D26	Glipizide	T2DM	Sulfonylureas	hypoglycemic
D27	Gliquidone	T2DM	Sulfonylureas	hypoglycemic
D28	Glyburide	T2DM	Sulfonylureas	hypoglycemic
D29	Tolazamide	T2DM	Sulfonylureas	hypoglycemic
D30	Tolbutamide	T2DM	Sulfonylureas	hypoglycemic
D31	Glisoxepide	T2DM	Sulfonylureas	hypoglycemic
D32	Mitiglinide	T2DM	Glinides	hypoglycemic
D32	Nateglinide	T2DM	Glinides	hypoglycemic
D34	Repaglinide	T2DM	Glinides	hypoglycemic

D35	Lobeglitazone	T2DM	TZD	hypoglycemic
D36	Pioglitazone	T2DM	TZD	hypoglycemic
D37	Rosiglitazone	T2DM	TZD	hypoglycemic
D38	Acarbose	T2DM	α-Glycosidase inhibitor	hypoglycemic
D39	Miglitol	T2DM	α-Glycosidase inhibitor	hypoglycemic
D40	Voglibose	T2DM	α-Glycosidase inhibitor	hypoglycemic
D41	Bromocriptine	T2DM	Dopamine receptor agonist	hypoglycemic
D41	Glisoxepide	T2DM	Sulfonylurea	hypoglycemic
D42	Pramlintide	T2DM	Amylin analogue	hypoglycemic
D43	Eplerenone	T2DM	DIU	antihypertensive
D44	Spironolactone	T2DM，DN	DIU	antihypertensive
D45	Bumetanide	T2DM	DIU	antihypertensive
D46	Chlorthalidone	T2DM	DIU	antihypertensive
D47	Indapamide	T2DM，DN	DIU	antihypertensive
D48	Captopril	T2DM，DN	ACEI	antihypertensive
D49	Cilazapril	T2DM	ACEI	antihypertensive
D50	Perindopril	T2DM，DN	ACEI	antihypertensive
D51	Spirapril	T2DM	ACEI	antihypertensive

D52	Trandolapril	T2DM，DN	ACEI	antihypertensive
D53	Enalaprilat	T2DM，DN	ACEI	antihypertensive
D54	Zofenopril	T2DM	ACEI	antihypertensive
D55	Benazepril	DN	ACEI	antihypertensive
D56	Enalapril	DN	ACEI	antihypertensive
D57	Lisinopril	DN	ACEI	antihypertensive
D58	Quinapril	DN	ACEI	antihypertensive
D59	Ramipril	DN	ACEI	antihypertensive
D60	Losartan	T2DM，DN	ARB	antihypertensive
D61	Valsartan	T2DM，DN	ARB	antihypertensive
D62	Candesartan cilexetil	DN	ARB	antihypertensive
D63	Irbesartan	DN	ARB	antihypertensive
D64	Olmesartan	DN	ARB	antihypertensive
D65	Eprosartan	T2DM，DN	ARB	antihypertensive
D66	Telmisartan	DN	ARB	antihypertensive
D67	Amlodipine	DN	CCB	antihypertensive
D68	Nisoldipine	DN	CCB	antihypertensive
D69	Verapamil	DN	CCB	antihypertensive

D70	Atenolol	T2DM，DN	BBs	antihypertensive
D71	Bisoprolol	T2DM	BBs	antihypertensive
D72	Clonidine	T2DM，DN	α2 adrenergic receptor agonist	antihypertensive
D73	Doxazosin	T2DM，DN	α1 Adrenergic receptor blockers	antihypertensive
D74	Terazosin	T2DM	α1 Adrenergic receptor blockers	antihypertensive
D75	Diazoxide	T2DM	Benzothiazines	antihypertensive
D76	Hydralazine	T2DM	Nicotinic acid derivatives	antihypertensive
D77	Evolocumab	T2DM	PCSK9IA inhibitor antibody	lipid-lowering
D78	Colesevelam	T2DM	Bile acid sequestrant	lipid-lowering
D79	Atorvastatin	T2DM，DN	HMG-CoA reductase inhibitor	lipid-lowering
D80	Pitavastatin	T2DM	HMG-CoA reductase inhibitor	lipid-lowering
D81	Pravastatin	T2DM	HMG-CoA reductase inhibitor	lipid-lowering
D82	Simvastatin	T2DM，DN	HMG-CoA reductase inhibitor	lipid-lowering
D83	Ezetimibe	T2DM	Cholesterol absorption inhibitor	lipid-lowering
D84	Lipoic acid	T2DM	Vitamin-like	Antioxidant
D85	Finerenone	T2DM	MRA	Improving glomerular filtration rate
D86	Allopurinol	T2DM，DN	XOI	Hypouricemic
D87	Febuxostat	T2DM	XOI	Hypouricemic

D88	Clopidogrel	T2DM，DN	ADP-RA	Antiplatelet
D89	Epoprostenol	T2DM	Prostacyclins	Antiplatelet
D90	Abciximab	T2DM	mAb	Prevention of diabetes peripheral neuropathy
D91	Vorapaxar	T2DM	Platelet aggregation inhibitor	Prevention of diabetes peripheral neuropathy
E1	Cetirizine	Others	Selective Histamine-1 antagonist	Antiallergic
E2	Ranibizumab	Others	Recombinant humanized monoclonal antibody and VEGF-A	Treatment of retinal vein occlusion
E3	Clozapine	Others	NMDA-RA	Atypical antipsychotics
E4	Dextromethorphan	Others	NMDA-RA	Control dry cough
E5	Topiramate	Others	Potassium channel blockers	Anticonvulsant
E6	Ziprasidone	Others	5HT2A receptor antagonist	Atypical antipsychotic
E7	Caffeine	Others	Methylxanthines	Diuresis
E8	Piperacillin	Others	Penicillin	Antibiotic
E9	Sulbactam	Others	β- lactamase inhibitor	Antibiotic
E10	Cefotaxime	Others	Third generation cephalosporins	Antibiotic
E11	Ceftriaxone	Others	Broad spectrum cephalosporins	Antibiotic
E12	Chromium	Others	Vitamin	Mineral supplement

E13	Ethinyl Estradiol	Others	Estradiol	Contraceptive
E14	Iron	Others	Essential element	Treatment of iron deficiency anemia
E15	Ledipasvir	Others	Hepatitis C virus non structural protein 5A inhibitor	Treatment of chronic hepatitis C virus
E16	Zidovudine	Others	NRTI	Antiviral
E17	Loperamide	Others	μ- Opioid receptor agonist	Long acting antidiarrheal
E18	Ofloxacin	Others	Fluoroquinolones	Anti bacterial infection
E19	Testosterone enanthate	Others	Testosterone enanthate	treat low or absent testosterone
E20	Methyltestosterone	Others	Anabolic steroids	Testosterone deficiency, anti-tumor
E21	Corticotropin	Others	Polypeptide hormone	Screening for adrenocortical insufficiency
E22	Citalopram	Others	Selective serotonin reuptake inhibitors	Antidepressant
E23	Sertraline	Others	Selective serotonin reuptake inhibitor	Antidepressant
E24	Ropivacaine	Others	Amides	Anaesthesia
E25	parecoxib	Others	Selective COX-2 inhibitor and NSAID	Short term acute analgesia
E26	Nevirapine	Others	Non nucleoside reverse transcriptase inhibitors	Anti infection treatment
E27	Methylprednisolone hemisuccinate	Others	Water-soluble corticosteroid	Not been fully annotated
E28	Lactulose	Others	Disaccharide derivative of lactose	Improve constipation
E29	Linaclotide	Others	Guanylate cyclase - C agonist	Improve constipation
E30	Dimenhydrinate	Others	Antihistamine H1 receptor	Prevention and treatment of nausea

E31	Drospirenone	Others	Progesterone	Prevent pregnancy and other diseases
E32	Chlorzoxazone	Others	Central muscle relaxant	Short term acute analgesia
E33	Pseudoephedrine	Others	α and β adrenergic agonist	Relieve cold nose discomfort
E34	Ephedrine	Others	α and β adrenergic agonist	hypotension under anesthesia
E35	Phenylephrine	Others	α1 adrenergic agonist	Treatment of hypotension
E36	Tazobactam	Others	β lactamase inhibitor	Auxiliary anti infection treatment
E37	Bupropion	Others	Noradrenaline	Anti depression and weight loss
E38	Anagliptin	Others	Not been fully annotated	Not been fully annotated

Table S6. The common targets of diabetes mellitus and the corresponding drugs

Number	Gene Symbol	Number	Gene Symbol	Number	Gene Symbol
1	ABCA1	71	CYP2B6	141	P4HA1
2	ABCB1	72	CYP2C18	142	PCSK9
3	ABCB11	73	CYP2C19	143	PGR
4	ABCC1	74	CYP2C8	144	POR
5	ABCC2	75	CYP2C9	145	PPARA
6	ABCC3	76	CYP2D6	146	PPARD
7	ABCC4	77	CYP2E1	147	PPARG
8	ABCC5	78	CYP2J2	148	PRKAB1
9	ABCC8	79	CYP3A4	149	PTGIR
10	ABCC9	80	CYP3A5	150	PTGIS
11	ABCG2	81	CYP3A7	151	PTGS1
12	ACE	82	DPP4	152	PTGS2
13	ACSL4	83	DRD1	153	RAMP1
14	ADRA1A	84	DRD2	154	RAMP2
15	ADRA1B	85	DRD3	155	RAMP3
16	ADRA1D	86	DRD4	156	RXRA
17	ADRA2A	87	DRD5	157	RXRB
18	ADRA2B	88	EPHX1	158	RXRG
19	ADRA2C	89	ETFDH	159	SFRP4
20	ADRB1	90	F2R	160	SHBG
21	ADRB2	91	FCGR2A	161	SI
22	AGTR1	92	FCGR2B	162	SLC10A1
23	AHR	93	GAA	163	SLC12A1
24	ALB	94	GANAB	164	SLC12A2
25	AMY1A	95	GANC	165	SLC12A3
26	AMY2A	96	GCGR	166	SLC12A4
27	ANPEP	97	GLP1R	167	SLC12A5

28	AOC3	98	GLP2R	168	SLC15A1
29	AOX1	99	GLUL	169	SLC15A2
30	AR	100	GPD1	170	SLC16A1
31	ATP1A1	101	HDAC2	171	SLC22A1
32	BCHE	102	HIF1A	172	SLC22A11
33	BDKRB1	103	HMGCR	173	SLC22A12
34	CA1	104	HTR1A	174	SLC22A2
35	CA2	105	HTR1B	175	SLC22A3
36	CACNA1A	106	HTR1D	176	SLC22A4
37	CACNA1C	107	HTR2A	177	SLC22A5
38	CACNA1D	108	HTR2B	178	SLC22A6
39	CACNA1E	109	HTR2C	179	SLC22A7
40	CACNA1F	110	HTR7	180	SLC22A8
41	CACNA1G	111	IDE	181	SLC29A4
42	CACNA1H	112	IGF1R	182	SLC2A9
43	CACNA1I	113	INSR	183	SLC47A1
44	CACNA1S	114	ITGA2B	184	SLC47A2
45	CACNA2D1	115	ITGAL	185	SLC5A2
46	CACNA2D2	116	ITGB3	186	SLC5A6
47	CACNA2D3	117	KCNH2	187	SLCO1A2
48	CACNA2D4	118	KCNH6	188	SLCO1B1
49	CACNB1	119	KCNH7	189	SLCO1B3
50	CACNB2	120	KCNJ1	190	SLCO2B1
51	CACNB3	121	KCNJ11	191	SLCO3A1
52	CACNB4	122	KCNJ8	192	SLCO4C1
53	CACNG1	123	KCNMA1	193	SOAT1
54	CACNG2	124	LIAS	194	SRD5A1
55	CACNG3	125	LIPT1	195	SRD5A2
56	CACNG4	126	LPL	196	SRD5A3

57	CACNG5	127	LTA4H	197	TGFB1
58	CACNG6	128	MAOB	198	TRPM4
59	CACNG7	129	MGAM	199	UGT1A1
60	CACNG8	130	MME	200	UGT1A10
61	CALCR	131	MMP2	201	UGT1A3
62	CES1	132	MMP9	202	UGT1A4
63	CFTR	133	NPC1L1	203	UGT1A8
64	CPT1A	134	NR1I2	204	UGT1A9
65	CYP11B1	135	NR1I3	205	UGT2B15
66	CYP11B2	136	NR3C1	206	UGT2B17
67	CYP17A1	137	NR3C2	207	UGT2B4
68	CYP1A1	138	ORM1	208	UGT2B7
69	CYP1A2	139	ORM2	209	VEGFA
70	CYP2A6	140	P2RY12	210	VTN
				211	XDH

Table S7. The common targets of diabetic nephropathy and the corresponding drugs

Number	Gene Symbol	Number	Gene Symbol	Number	Gene Symbol
1	ABCB1	47	CACNG3	93	NR3C1
2	ABCB11	48	CACNG4	94	NR3C2
3	ABCC1	49	CACNG5	95	ORM1
4	ABCC10	50	CACNG6	96	ORM2
5	ABCC2	51	CACNG7	97	P2RY12
6	ABCC3	52	CACNG8	98	PGR
7	ABCC4	53	CES1	99	PPARG
8	ABCC5	54	CYP11B1	100	PRKAB1
9	ABCG2	55	CYP11B2	101	PTGS1
10	ACE	56	CYP17A1	102	REN
11	ADRA1A	57	CYP1A1	103	SFRP4
12	ADRA1B	58	CYP1A2	104	SHBG
13	ADRA1D	59	CYP2A6	105	SLC12A3
14	ADRA2A	60	CYP2B6	106	SLC15A1
15	ADRA2B	61	CYP2C18	107	SLC15A2
16	ADRA2C	62	CYP2C19	108	SLC22A1
17	ADRB1	63	CYP2C8	109	SLC22A12
18	ADRB2	64	CYP2C9	110	SLC22A2
19	AGTR1	65	CYP2D6	111	SLC22A3
20	AHR	66	CYP2E1	112	SLC22A4
21	ALB	67	CYP3A4	113	SLC22A5
22	AOX1	68	CYP3A5	114	SLC22A6
23	AR	69	CYP3A7	115	SLC22A7
24	BCHE	70	DPP4	116	SLC22A8
25	BDKRB1	71	EPHX1	117	SLC29A4
26	CA1	72	ETFDH	118	SLC2A9
27	CACNA1A	73	GCGR	119	SLC47A1

28	CACNA1B	74	GLP1R	120	SLC47A2
29	CACNA1C	75	GLP2R	121	SLC5A2
30	CACNA1D	76	GPD1	122	SLC6A4
31	CACNA1E	77	HDAC2	123	SLCO1A2
32	CACNA1F	78	HMGCR	124	SLCO1B1
33	CACNA1G	79	IGF1R	125	SLCO1B3
34	CACNA1H	80	INSR	126	SLCO2B1
35	CACNA1I	81	ITGAL	127	SLCO4C1
36	CACNA1S	82	JUN	128	SMPD1
37	CACNA2D1	83	KCNH2	129	SRD5A1
38	CACNA2D2	84	KCNH6	130	SRD5A2
39	CACNA2D3	85	KCNH7	131	SRD5A3
40	CACNA2D4	86	KCNJ11	132	UGT1A1
41	CACNB1	87	LTA4H	133	UGT1A10
42	CACNB2	88	MMP2	134	UGT1A3
43	CACNB3	89	MMP9	135	UGT1A9
44	CACNB4	90	MTHFR	136	UGT2B17
45	CACNG1	91	NR1I2	137	UGT2B4
46	CACNG2	92	NR1I3	138	UGT2B7
				139	XDH

Table S8. The composition, classification and function of the combined drugs for diabetes mellitus

ID	Composition of combined drug	Classification	Function
CM1	Glyburide+Insulin	Sulfonylureas+ Insulin	hypoglycemic
CM2	Glyburide+Semaglutide	Sulfonylureas+ GLP-1RA	hypoglycemic
CM3	Glyburide+Rosiglitazone	Sulfonylureas+ TZD	hypoglycemic
CM4	Glyburide+Miglitol	Sulfonylureas+α- Glycosidase inhibitor	hypoglycemic
CM5	Glyburide+Metformin	Sulfonylureas+ Biguanides	hypoglycemic
CM6	Insulin+Metformin	Insulin +Biguanides	hypoglycemic
CM7	Metformin+Rosiglitazone	Biguanides +TZD	hypoglycemic
CM8	Miglitol+Semaglutide	α- Glycosidase inhibitor+ GLP-1RA	hypoglycemic
CM9	Rosiglitazone+Semaglutide	TZD +GLP-1RA	hypoglycemic
CM10	Glyburide+Rosiglitazone+Semaglutide	Sulfonylureas+ TZD+ GLP-1RA	hypoglycemic
CM11	Glyburide+Metformin+Rosiglitazone	Sulfonylureas+ Biguanides + TZD	hypoglycemic
CM12	Glyburide+Miglitol+Semaglutide	Sulfonylureas+α- Glycosidase inhibitor+ GLP-1RA	hypoglycemic
CM13	Glyburide+Miglitol+Rosiglitazone	Sulfonylureas+α- Glycosidase inhibitor + TZD	hypoglycemic
CM14	Glyburide+Metformin+Miglitol	Sulfonylureas+ Biguanides+α- Glycosidase inhibitor	hypoglycemic
CM15	Glyburide+Insulin+Metformin	Sulfonylureas+ Insulin+ Biguanides	hypoglycemic
CM16	Glyburide+Insulin+Rosiglitazone	Sulfonylureas+ Insulin + TZD	hypoglycemic

CM17	Glyburide+Insulin+Miglitol	Sulfonylureas+ Insulin +α- Glycosidase inhibitor	hypoglycemic
CM18	Bumetanide+Diazoxide+Semaglutide	DIU + Benzothiazines +GLP-1RA	hypoglycemic, antihypertensive
CM19	Bumetanide+Diazoxide+Miglitol	DIU + Benzothiazines+α- Glycosidase inhibitor	hypoglycemic, antihypertensive
CM20	Diazoxide+Glyburide+Semaglutide	Benzothiazines + Sulfonylureas +GLP-1RA	hypoglycemic, antihypertensive
CM21	Glyburide+Insulin+Spironolactone	Sulfonylureas+ Insulin+ DIU	hypoglycemic, antihypertensive
CM22	Glyburide+Rosiglitazone+Terazosin	Sulfonylureas+ TZD+α1 Adrenergic receptor	hypoglycemic, antihypertensive
CM23	Glyburide+Metformin+Terazosin	Sulfonylureas+ Biguanides+α1 Adrenergic receptor	hypoglycemic, antihypertensive
CM24	Glyburide+Insulin+Terazosin	Sulfonylureas+ Insulin+α1 Adrenergic receptor	hypoglycemic, antihypertensive
CM25	Glyburide+Miglitol+Terazosin	Sulfonylureas+α- Glycosidase inhibitor+α1 Adrenergic receptor	hypoglycemic, antihypertensive
CM26	Glyburide+Perindopril+Terazosin	Sulfonylureas+ ACEI+α1 Adrenergic receptor	hypoglycemic, antihypertensive
CM27	Bumetanide+Diazoxide+Glyburide	DIU+ Benzothiazines+ Sulfonylureas	hypoglycemic, antihypertensive
CM28	Glyburide+Rosiglitazone+Simvastatin	Sulfonylureas+ TZD+ HMG-CoA reductase	hypoglycemic, lipid-lowering
CM29	Glyburide+Metformin+Simvastatin	Sulfonylureas+ Biguanides+ HMG-CoA reductase	hypoglycemic, lipid-lowering
CM30	Glyburide+Insulin+Simvastatin	Sulfonylureas+ Insulin+ HMG-CoA reductase	hypoglycemic, lipid-lowering
CM31	Glyburide+Miglitol+Simvastatin	Sulfonylureas+α-Glycosidaseinhibitor+ HMG-CoA reductase	hypoglycemic, lipid-lowering
CM32	Glyburide+Perindopril+Simvastatin	Sulfonylureas+ ACEI+ HMG-CoA reductase	hypoglycemic, antihypertensive, lipid-lowering
CM33	Diazoxide+Rosiglitazone+Simvastatin	Benzothiazines+ TZD+ HMG-CoA reductase	hypoglycemic, antihypertensive, lipid-lowering
CM34	Glyburide+Terazosin+Simvastatin	Sulfonylureas+α1 Adrenergic receptor+ HMG-CoA reductase	hypoglycemic, antihypertensive, lipid-lowering

Table S9. The composition, classification and function of the combined drugs for diabetic nephropathy

ID	Composition of combined drug	Classification	Function
CN1	Metformin+Insulin	Biguanides+ Insulin	hypoglycemic
CN2	Metformin+Irbesartan+Captopril	Biguanides+ ARB+ ACEI	hypoglycemic, antihypertensive
CN3	Metformin+Irbesartan+Lisinopril	Biguanides+ ARB+ ACEI	hypoglycemic, antihypertensive
CN4	Metformin+Irbesartan+Losartan	Biguanides+ ARB+ ARB	hypoglycemic, antihypertensive
CN5	Metformin+Irbesartan+Telmisartan	Biguanides+ ARB+ ARB	hypoglycemic, antihypertensive
CN6	Metformin+Captopril+Lisinopril	Biguanides+ ACEI+ ACEI	hypoglycemic, antihypertensive
CN7	Metformin+Captopril+Losartan	Biguanides+ ACEI+ ARB	hypoglycemic, antihypertensive
CN8	Metformin+Captopril+Telmisartan	Biguanides+ ACEI+ ARB	hypoglycemic, antihypertensive
CN9	Metformin+Lisinopril+Losartan	Biguanides+ ACEI+ ARB	hypoglycemic, antihypertensive
CN10	Metformin+Lisinopril+Telmisartan	Biguanides+ ACEI+ ARB	hypoglycemic, antihypertensive
CN11	Metformin+Losartan+Telmisartan	Biguanides+ ARB+ ARB	hypoglycemic, antihypertensive
CN12	Insulin+Irbesartan+Captopril	Insulin+ ARB+ ACEI	hypoglycemic, antihypertensive
CN13	Insulin+Irbesartan+Lisinopril	Insulin+ ARB+ ACEI	hypoglycemic, antihypertensive
CN14	Insulin+Irbesartan+Losartan	Insulin+ ARB+ ARB	hypoglycemic, antihypertensive
CN15	Insulin+Irbesartan+Telmisartan	Insulin+ ARB+ ARB	hypoglycemic, antihypertensive

CN16	Insulin+Captopril+Lisinopril	Insulin+ ACEI+ ACEI	hypoglycemic, antihypertensive
CN17	Insulin+Captopril+Losartan	Insulin+ ACEI+ ARB	hypoglycemic, antihypertensive
CN18	Insulin+Captopril+Telmisartan	Insulin+ ACEI+ ARB	hypoglycemic, antihypertensive
CN19	Insulin+Lisinopril+Losartan	Insulin+ ACEI+ ARB	hypoglycemic, antihypertensive
CN20	Insulin+Lisinopril+Telmisartan	Insulin+ ACEI+ ARB	hypoglycemic, antihypertensive
CN21	Insulin+Losartan+Telmisartan	Insulin + ARB+ ARB	hypoglycemic, antihypertensive

Table S10. The signaling pathway of diabetes mellitus screened with FDR<0.05

Pathway	HitM[a]	HitG[b]	Hits_ratio[c]	FDR[d]	Metabolites	Genes
Neuroactive ligand-receptor interaction	2	2	0.079	2.57E-11	Taurine, Glutamate	NR3C1, GLP1R, GLP2R, GCGR, CALCR, PTGIR, F2R, BDKRB1, AGTR1, HTR1A, HTR1B, HTR1D, HTR2A, HTR2B, HTR2C, HTR7, DRD1, DRD2, DRD3, DRD4, DRD5, ADRA1D, ADRA1B, ADRA1A, ADRA2A, ADRA2B, ADRA2C, ADRB1, ADRB2
ABC transporters	5	5	0.093	3.30E-7	Glutamate, Taurine, Glutamine, Isoleucine, Threonine	ABCB11, ABCG2, CFTR, ABCC4, ABCC9, ABCC8, ABCC5, ABCC3, ABCC2, ABCC1, ABCB1, ABCA1
GABAergic synapse	2	2	0.092	5.26E-14	Glutamate, Glutamine	CACNA1A, GLUL, CACNA1C, CACNA1D, CACNA1F, CACNA1S, SLC12A5
Proximal tubule bicarbonate reclamation	3	3	0.125	5.00E-03	Glutamine, Glutamate, alpha-Glucose	CA2, ATP1A1
Gap junction	1	1	0.071	1.20E-02	Glutamate	HTR2A, HTR2B, HTR2C, ADRB1, DRD2, DRD1
Protein digestion and absorption	4	4	0.056	2.30E-02	Glutamate, Isoleucine, Threonine, Glutamine	SLC15A1, ATP1A1, DPP4, MME
Taste transduction	2	2	0.060	2.60E-02	Glutamate, Citrate	CACNA1A, CACNA1C, HTR1A, HTR1B, HTR1D
Pathways in cancer	1	1	0.034	2.60E-02	Fumarate	ITGA2B, IGF1R, AR, HIF1A, TGFB1, HDAC2, PPARG, RXRA, RXRB, RXRG, PTGS2, VEGFA, MMP2, MMP9, PPARD, AGTR1, F2R, BDKRB1

Arginine biosynthesis	3	3	0.091	4.10E-02	Fumarate, Glutamine, Glutamate	GLUL
Porphyrin metabolism	2	2	0.065	1.00E-03	Glutamate, Threonine	UGT1A10, UGT1A8, UGT1A9, UGT1A4, UGT1A1, UGT1A3, UGT2B4, UGT2B7, UGT2B15, UGT2B17
Nitrogen metabolism	2	2	0.14	3.00E-03	Glutamine, Glutamate	CA1, CA2, GLUL
Alanine, aspartate and glutamate metabolism	5	5	0.094	7.00E-03	Fumarate, N-Acetylaspartate, lutamate, Glutamine, Citrate	GLUL

[a] number of the enriched metabolites; [b] number of the enriched genes; [c] the total number of the enriched genes and metabolites divided by the total number of genes and metabolites in the signaling pathway; [d] false discovery rate.

Table S11. The signaling pathway of diabetic nephropathy screened with FDR<0.05

Pathway	HitM[a]	HitG[b]	Hits_ratio[c]	FDR[d]	Metabolites	Genes
ABC transporters	8	9	0.093	1.53E-09	Lysine, Glutamate, Glutamine, Histidine, Threonine, Taurine, Alanine, Phenylalanine	ABCB11, ABCG2, ABCC10, ABCC4, ABCC5, ABCC3, ABCC2, ABCC1, ABCB1
Protein digestion and absorption	8	2	0.070	1.01E-04	Glutamate, Alanine, Phenylalanine, Threonine, Asparagine, Glutamine, Lysine, Histidine	SLC15A1, DPP4
Neuroactive ligand-receptor interaction	2	14	0.041	2.19E-04	Taurine, Glutamate	GLP1R, GLP2R, GCGR, BDKRB1, AGTR1, ADRA1D, ADRA1B, ADRA1A, ADRA2A, ADRA2B, ADRA2C, ADRB1, ADRB2, NR3C1
GABAergic synapse	2	6	0.082	2.60E-04	Glutamate, Glutamine	CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1F, CACNA1S
Aminoacyl-tRNA biosynthesis	8	0	0.068	8.94E-04	Threonine, Lysine, Alanine, Glutamate, Glutamine, Phenylalanine, Histidine, Asparagine	/[e]
Circadian entrainment	1	5	0.057	1.40E-02	Glutamate	CACNA1I, CACNA1H, CACNA1G, CACNA1C, CACNA1D
Mineral absorption	5	0	0.057	2.80E-02	Alanine, Phenylalanine, Threonine, Asparagine, Glutamine	/

Retrograde endocannabinoid signaling	1	6	0.042	2.80E-02	Glutamate	CACNA1A, CACNA1B, CACNA1C, CACNA1D, CACNA1F, CACNA1S
Taurine and hypotaurine metabolism	3	0	0.091	4.90E-02	Alanine, Taurine, Glutamate	/
Alanine, aspartate and glutamate metabolism	6	0	0.094	1.00E-03	Fumarate, Alanine, Asparagine, N-Acetylaspartate, Glutamate, Glutamine	/
Central carbon metabolism in cancer	7	0	0.066	3.00E-03	Glutamine, Glutamate, Fumarate, Phenylalanine, Histidine, Alanine, Asparagine	/
Porphyrin metabolism	2	7	0.049	3.00E-03	Glutamate, Threonine	UGT1A10, UGT1A9, UGT1A1, UGT1A3, UGT2B4, UGT2B7, UGT2B17

[a] number of the enriched metabolites; [b] number of the enriched genes; [c] the total number of enriched genes and metabolites divided by the total number of genes and metabolites in the signaling pathway; [d] false discovery rate; [e] no enrichment.

Table S12. Parameters of molecular docking of target proteins and corresponding drug molecule

Target	center_x	center_y	center_z	size_x	size_y	size_z
CFTR	26.60	47.21	98.37	120.0	112.0	112.0
ABCC8	203.9	292.5	246.1	108.0	94.00	126.0
AGTR1	-10.73	10.23	40.39	63.80	62.10	106.4

Table S13. Affinity (kcal/mol) of target proteins and corresponding drug molecule

Medication	CFTR(1XMI[a])	ABCC8(7S5V)	AGTR1(4YAY)
Glyburide	-8.5	-9.3	/[b]
Metformin	-5.5	-5.6	-4.8
Miglitol	-5.3	-5.5	/
Irbesartan	/	/	-10
Captopril	/	/	-5.3

[a] PDB ID of protein; [b] no molecular docking.

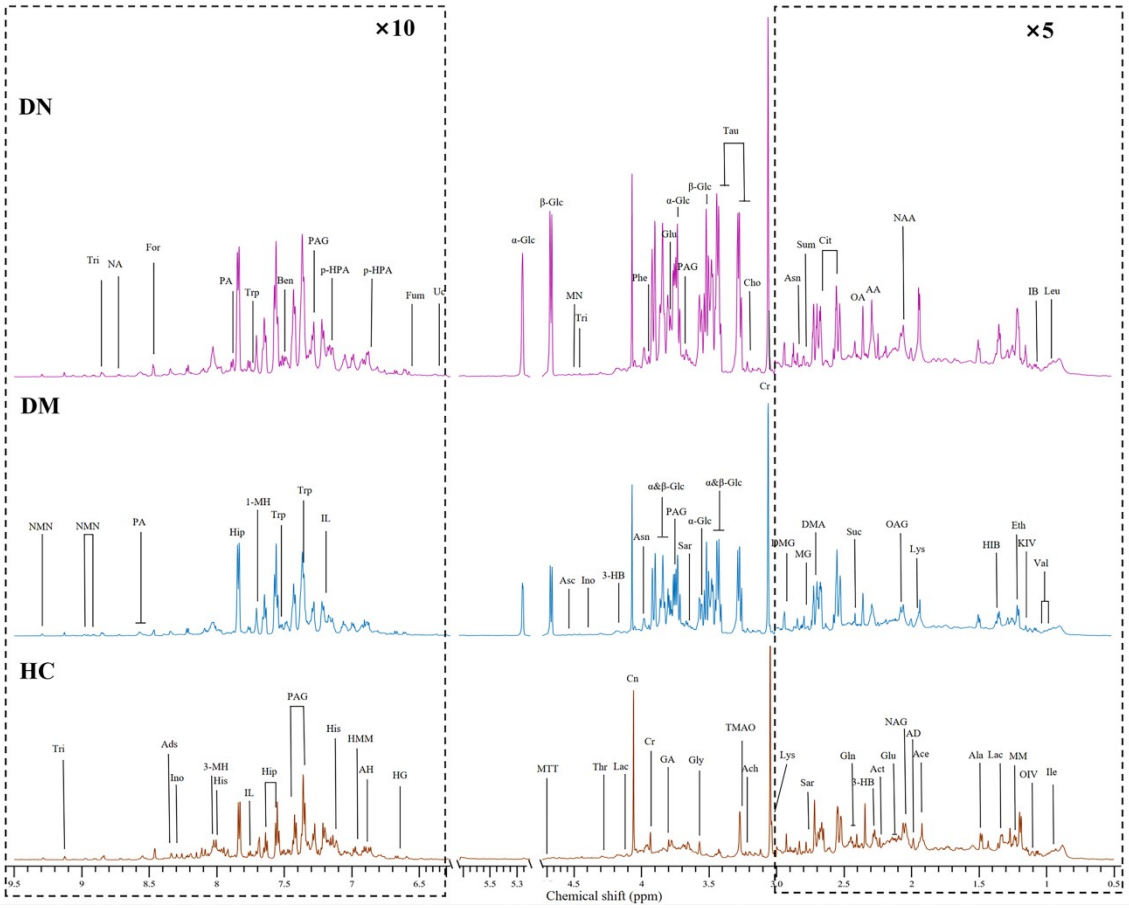

Figure S1. Mean 600 MHz ^{1}H NMR spectra of urine samples obtained from the diabetes mellitus (DM) and diabetic nephropathy (DN) patients and the healthy controls (HC). For clarity, the spectral regions of δ 0.50–3.00 and δ 6.25–9.30 were vertically magnified 5 and 10 times relative to the spectral regions of δ 3.00–6.25, respectively. The keys and the detailed spectral information of the metabolites are shown in Table S4 in the supplemental materials.

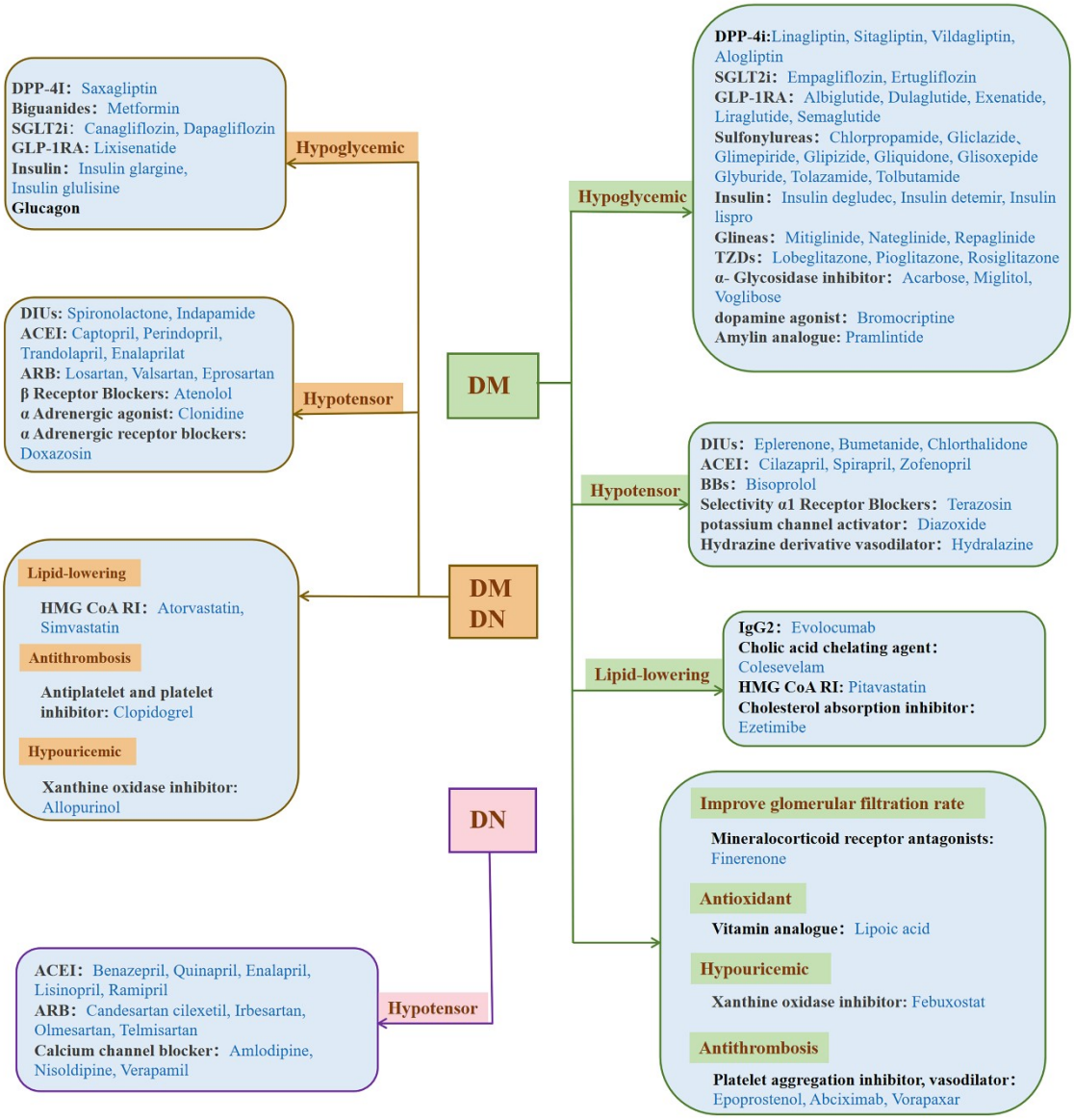

Figure S2. The classification of drugs for diabetes mellitus (DM) and diabetic nephropathy (DN).

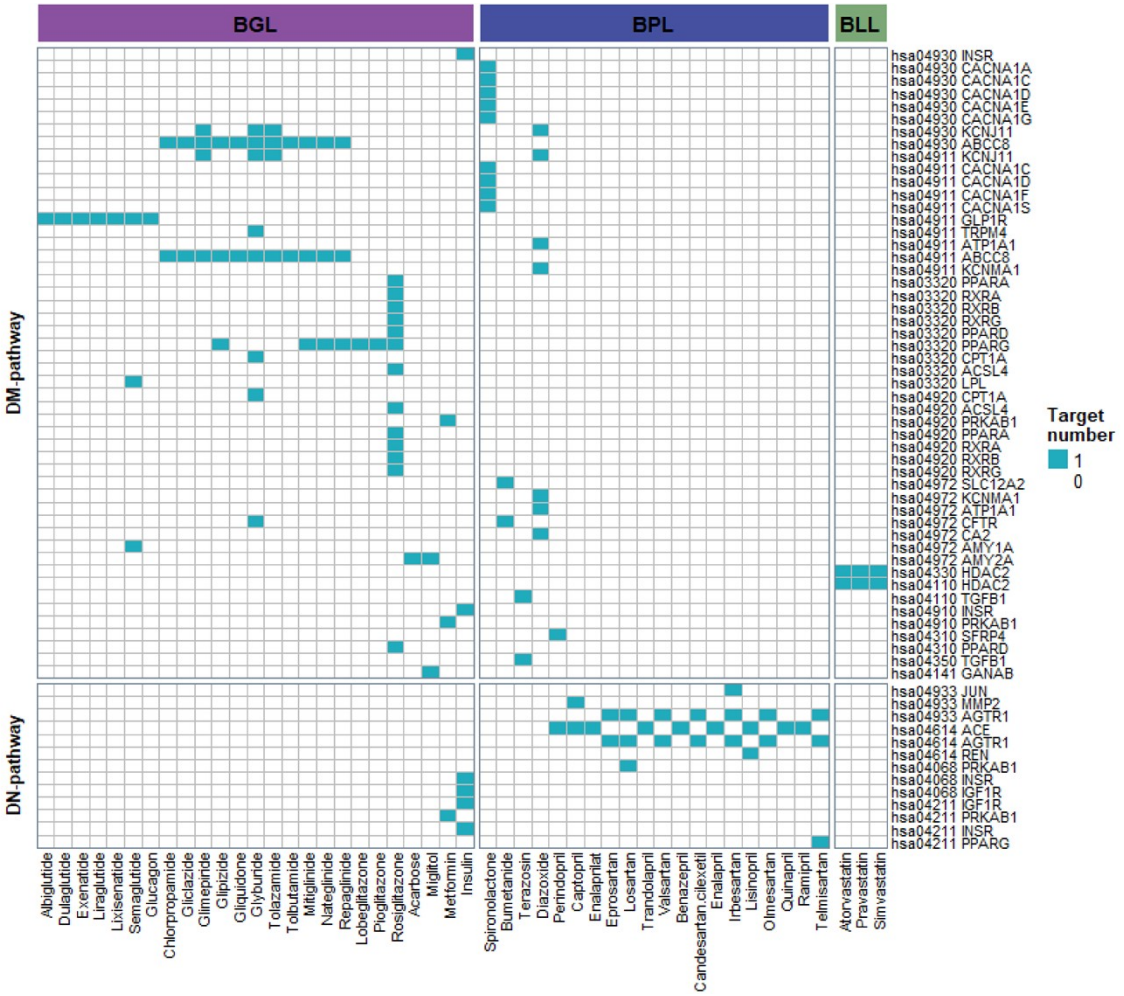

Figure S3. The detailed target matching diagram of pathways and corresponding drugs for diabetes mellitus (DM) and diabetic nephropathy (DN). BGL, blood glucose lowering; BPL, blood pressure lowering; BLL, blood lipid lowering.

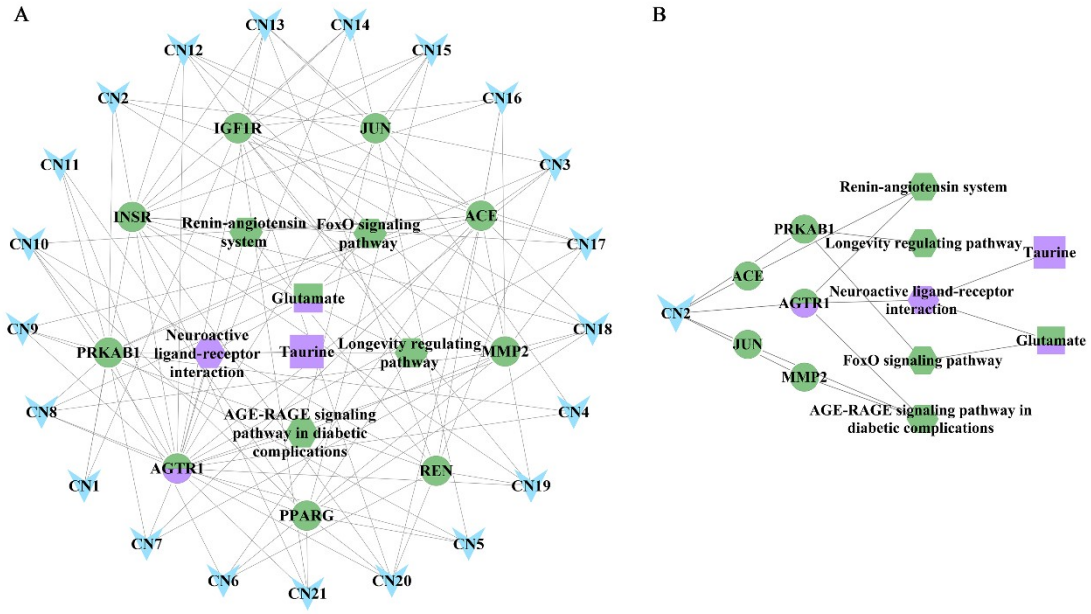

Figure S4. The drug-target-metabolite-pathway network of DN (A) and CN2 (B). Drug, pink arrow; target, circular; metabolite, square; pathway, hexagon; The purple parts were screened out with FDR < 0.05, and the green parts were derived from KEGG database records, no hub targets.