

**Supplementary Table S1:** Active compounds and corresponding target

Drug	Compound	Target
BS	Borneol, Isoborneol	TRPV3, OPRK1, TRPM8, TRPA1, KCNK4, ESRRG, COX6C, COX5B, COX7C, MT-CO1, AKR1C2, COX5A, MT-CO3, AR, COX7A1, FECH, COX4I1, PLA2G1B, COX6A2, ADH1C, COX6B1, FABP6, CES1, COX7B, MT-CO2, COX8A, NR1H4, CACNA1C, CACNA1D, CACNA1F, CACNA1S, CACNB1, CACNB2, CACNB3, CACNB4, GABRA1, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ, VDR, AKR1D1, ESR1, ESR2, HSD17B1, HSD17B11, IGHG2, NR3C2, SULT2A1, NR1I3, LSS, SLC6A2, PTGS2, PTGS1, NCOA2, MAOB, IGHG1, CHRM2, PGR, CHRM3, CHRM1, ADRA1D
BV	Bufotenidine, Bufotenine, Bufothionine, Cinobufagin, Dehydrobufotenine, Gamabufotalin, Telocinobufagin	CALR, NQO2, MTNR1A, HTR1B, ESR1, MTNR1B, ASMT, MPO, HTR1D, HTR1F, CALM2, CALM3, CALM1, EPX, SCNN1A, KCNJ8, ADRA1A, SCN1A, SCNN1G, HTR2A, ADRB2, ACACB, MTAP, ADRA2A, TLR8, ADRB1, APRT, ADRA1D, PECR, HRH1, PRKAA1, HTR7, HRH2, ADRA1B, SCNN1D, ADRA2C, AOC3, P4HA1, SRPK2, TLR7, KCNJ1, AGTR1, ADRB3, ACP1, SCNN1B, CYP2B6, ADRA2B, SLC6A2, SAXO1, SCT, UGCG, PHKG2, APLP1, ADK, ACACA, CHRNA7, PNP, ARRB2, RAB7A, PRKAA2, HTR2C, HSP90AB1, ALDH3A2, INS, CALCOCO2, SLC22A1, AOC2, ARRDC3, CALCA, HPRT1, ACTN2, NR3C1, PDE7B, PDE5A, PDE9A, PDE4A, RYR1, CYP17A1, PDE3A, ADORA2A, ITPR1, PDE6A, PRKDC, PIK3CD, PDE3B, PGD, PIK3CA, ADORA2B, PDE1A, PDE4D, PGR, PIK3CB, ITPR2, PDE1B, OPRK1, PDE7A, ITPR3, POLA2, PDE4C, PDE10A, PDE1C, ATM, PDE6B, PDE4B, PDE2A, ADORA1, CYP19A1, PDE8B, NT5E, HDAC2, PDE6C, PDE11A, PDE8A, NR3C2, RINT1, RIPK1, PIK3R1, WNT4, TACR2, AMPD3, CX3CR1, ADA, HAP1, IDNK
BCA	(8S,9S,10R,13S,14R,17S)-17-(2-	RXRA, PGR, NR3C2, NCOA2, NCOA1, PPARG, PTGS1, PTGS2, ALOX5, APOA2, SERPINE1,

Hydroxyacetyl)-  
10,13-dimethyl-  
1,2,6,7,8,9,11,12,14  
,15,16,17-  
dodecahydrocyclop  
enta[a]phenanthren-  
3-one, Biliverdin,  
Chenodeoxycholic  
acid, Cholalic Acid,  
Cholesterol, Cholic  
acid, Deoxycholic  
acid,  
Deoxycorticosteron  
e, Hyodeoxycholic  
acid, Methyl  
desoxycholate, Tyr-  
Gly,  
Ursodeoxycholic  
acid

IL1B, IL13, LDLR, NR1H4, MT-CO2, FABP6,  
FECH, COX6A2, ESRRG, ADH1C, MT-CO1,  
COX8A, COX5B, COX6B1, CES1, PLA2G1B,  
COX6C, COX5A, MT-CO3, AKR1C2, COX7B,  
COX7C, COX7A1, COX4I1, ADH1A, AKR1C1,  
ABCB4, ATCAY, AKR1C3, AKR1C4, ADH1B,  
AKR1D1, AR, SRD5A2, TYR, ADH7, ALAD,  
EIF2AK1, PLAT, GRIN2A, SCN10A, SCN1B,  
ADORA1, CACNA1A, SCN7A, SCN11A,  
ACADSB, ABAT, GRIN2C, TOP1, OGDH,  
HDAC9, CACNA2D1, SCN8A, SCN5A,  
ALDH5A1, GRIN2D, PLG, CACNA1B, SCN2B,  
GRIN3B, SCN1A, GRIN2B, SCN4B, SCN3A,  
GRIN3A, SCN9A, CACNA2D2, SCN3B, SCN4A,  
SCN2A, HDAC2, GRIN1, SLCO1B3, SLC2A4,  
SLC10A2, PPARA, NR0B2, MTPP, JUN, ICAM1,  
HNF4A, HMGCR, CYP7A1, ABCB11, ACOT8,  
ADCYAP1, ADCYAP1R1, ADM, ADM2,  
ADORA2A, ADORA2B, ADRB1, ADRB2,  
ADRB3, ALB, AVP, AVPR2, CALCA, CALCB,  
CASP3, CASP9, CEL, CETP, CRH, CRHR1,  
CRHR2, CYP3A4, DRD5, FSHR, GCG, GCGR,  
GHRH, GHRHR, GIP, GIPR, GLP1R, GLP2R,  
GNAS, GNG2, GPBAR1, HRH2, HSD11B1,  
HTR4, HTR6, HTR7, IAPP, IL2, LHCGR, MC1R,  
MC2R, MC3R, MC4R, MC5R, NPS, NPSR1,  
POMC, PRKCA, PTGDR, PTGER2, PTGER4,  
PTGIR, PTH, PTH1R, PTH2, PTH2R, PTHLH,  
RXFP1, RXFP2, SCT, SCTR, SLC27A5,  
SLCO1A2, TAAR1, TSHR, VIP, VIPR1, VIPR2,  
FABP1, RBP2, SLCO1B1, VDR, CYP27B1, GC,  
SNW1, ESR1, TRPV3, OPRK1, TRPM8, TRPA1,  
SRD5A1, CYP17A1, NR3C1, ANXA1, SLC8A1,  
F12, PRLR, TRPV1, FADS2, FADS1, ELOVL4,  
OPRD1, OPRM1, CASP8, GABRA1, GABRA2,  
GABRA4, GABRA5, GABRA6, GABRE,  
GABRG1, GABRG2, GABRG3, MTRR, NOS1,  
NOS2, NOS3, POR, PRKCB

GRE 20-  
Glucosylginsenosid  
e Rf, Ginsenoside  
F1, Ginsenoside F4,  
Ginsenoside I,  
Ginsenoside Ia,  
SLCO1B3, ATP1A1, ATP1A2, ATP1A3, VDR,  
PPP1CC, GABRB3, GLRA3, IL1B, IL6, NFKB1,  
NFKB2, TNF, YWHAE, NR3C1, CASP3,  
HSD11B1, LPL, ANXA1, HSD11B2, HSD3B1,  
AKT1, ATF1, CREB1, MAPK1, MAPK14,  
MAPK3, NOS3, BDNF, CHRFA7A, CHRNA2,

Ginsenoside	Ib,	CHRNA3, CHRNA4, CHRNA6, CHRNA7,
Ginsenoside	Ic,	CHRN2, CHRN4, FOS, SLC2A4, PTGS2,
Ginsenoside	Ii,	NFKBIA, ADCYAP1
Ginsenoside	Iii,	
Ginsenoside	La,	
Ginsenoside	R0,	
Ginsenoside	Ra0,	
Ginsenoside	Ra1,	
Ginsenoside	Ra2,	
Ginsenoside	Ra3,	
Ginsenoside	Rb1,	
Ginsenoside	Rb2,	
Ginsenoside	Rb3,	
Ginsenoside	Rc,	
Ginsenoside	Rd,	
Ginsenoside	Re,	
Ginsenoside	Rf,	
Ginsenoside	Rg1,	
Ginsenoside	Rg2,	
Ginsenoside	Rg3,	
Ginsenoside	Rh1,	
Ginsenoside	Rh2,	
Ginsenoside	Rh3,	
Ginsenoside	Rh4,	
Ginsenoside	Rs1,	
Ginsenoside	Rs2,	
Malonylginsenosid		
e	Rb2,	
Pseudoginsenoside		
F11,		
Quinquenoside	R1	
CC (-)-alpha-cedrene,		RXRA, PTGS2, NCOA2, GABRA2, GABRA1,
(-)-Aromadendrene,		CHRM3, CHRM1, LYZ, CHRM2, SOAT1, MTTP,
(-)-Epicatechin-3-		SOAT2, GABRA3, CHRNA7, CHRNA2,
O-Gallate,	(-)-	ADRA1B, FSHR, PGD, AHR, DHFRL1, DNMT1,
Sativene,	(+)-	ACTB, ATP5A1, ATP5B, ATP5C1, CBR1,
epicatechin-3-o-		CEBPB, CSNK2A1, CSNK2B, CYP1B1, EIF3F,
gallate,		ESR1, ESR2, HCK, HIBCH, HSP90AA1, HSPA2,
[Epicatechin-		JAK1, NQO2, NR1I2, PIK3CG, PIM1, RUVBL2,
(4beta->8)]5-		SF3B3, SHBG, STK17B, UBA1, UGT3A1, CDK6,
epicatechin,	6-	AR, AKR1C3, BCHE, SCN10A, ACHE, COLQ,
Glucopyranosylpro		SLC6A4, SLC6A3, PKIA, ADRB2, ADRB1,
cyandin	B1,	SLC6A2, GABRA6, F2, TRPV3, OPRK1, TRPM8,
Benzyl benzoate,		TRPA1, CASP3, CASP8, MAPK1, MAPK14,

<p>beta-Cubebene, Caryophyllene oxide, Cinnamaldehyde, Cinnamic Acid, Cinnamyl Benzoate, copaene, Diisobutyl phthalate, junipene, Ledene, Linoleic acid, Melilotocarpan A, Oleic Acid, Procyanidin B1, Procyanidin B5, Procyanidin B7, zoomaric acid</p>	<p>MAPK3, MAPK8, MTRR, NOS1, NOS2, NOS3, POR, SLC2A4, TXNRD1, TRPV4, TRPV1, TLR4, RELA, NFKBIA, NFE2L2, IRF3, C5AR1, PPARG, AGTR1, APOA2, IL1B, TNF, IL13, ACTN2, DAO, HRSP12, PRDX5, RAB9A, SLC15A1, CTSB, ADIPOQ, FURIN, HAL, KDM1A, MBTPS1, PCSK1, PCSK2, PCSK4, PCSK5, PCSK7, PCSK9, RSPO1, RSPO3, RSPO4, TPP2, PTGS1, MGAM, MAOB, MAOA, F3, GABRD, GABRB1, GABRG3, GABRE, GABRG1, GABRP, GABRA4, GABRB2, GABRQ, GABRB3, GABRA5, GABRG2, ADRA2B, PGR, NR3C2, NR3C1, HTR2A, IGHG1, PRKCA, ALOX5, PRKCB, SERPINE1, RBP2, PPARA, PLG, MPO, LPL, INS, HMGCR, GCG, FABP1, CETP, BDNF</p>
<p>MA 5alpha-androstan- 3,17-dione, Cholesterol, Cyclotetradecan-1- One, Muscol, Muscone, Muscopyridine, Normuscone, 5beta-androstan- 3,17-dione, 3alpha,17beta- Dihydroxy-5alpha- androstan-3,17- Hydroxy-5alpha- Androstan-17-One, 3alpha-hydroxy- 5beta-androstan-17- one, 3beta- Hydroxy-5alpha- Androstan-17-One, 3beta-hydroxy- androst-5-ene-17- one, 5beta- androstan- 3alpha,17beta-diol, 5-Cis- Cyclotetradecen-1-</p>	<p>SHBG, AKR1C1, AKR1C3, AKR1C4, AR, HSD17B1, SRD5A1, VDR, CYP27B1, GC, SNW1, ESR1, PGR, SCN11A, SCN2B, ABAT, SCN1A, SCN3B, SCN3A, SCN7A, SCN5A, SCN10A, AKR1D1, ALDH5A1, SCN2A, HDAC9, TYR, SCN9A, SCN4A, SCN4B, SRD5A2, ACADSB, SCN8A, SCN1B, OGDH, HDAC2, TRPV3, OPRK1, TRPM8, TRPA1, KCNK4, GABRB2, GABRB3, F2, GPR27, RDH16, ESRRG, COX6C, COX5B, COX7C, MT-CO1, AKR1C2, COX5A, MT-CO3, COX7A1, FECH, COX4I1, PLA2G1B, COX6A2, ADH1C, COX6B1, FABP6, CES1, COX7B, MT-CO2, COX8A, NR1H4, CACNA2D1, PLAT, CACNA1A, GRIN3B, CACNA2D2, GRIN2A, PLG, CACNA1B, GRIN2C, GRIN2B, GRIN3A, GRIN2D, ADORA1, GRIN1, HSD17B11, SULT2A1, NQO1, PDE7B, PDE5A, PDE9A, PDE4A, RYR1, CYP17A1, PDE3A, ADORA2A, ITPR1, PDE6A, PRKDC, PIK3CD, PDE3B, PGD, PIK3CA, ADORA2B, PDE1A, PDE4D, PIK3CB, ITPR2, PDE1B, PDE7A, ITPR3, POLA2, PDE4C, PDE10A, PDE1C, ATM, PDE6B, PDE4B, PDE2A, CYP19A1, PDE8B, NT5E, PDE6C, PDE11A, PDE8A, NR3C2, RINT1, RIPK1, PIK3R1, WNT4, TACR2, AMPD3, CX3CR1, ADA, HAP1, IDNK, SLC8A1, F12, TRPV1, FADS2, FADS1, PTGS1, PTGS2, ELOVL4, PRLR,</p>

	One, Androst-4- Ene-3,17-Dione, Androsterone	NR3C1, ANXA1
SX	(1Ar,4R,7R,7bS)- 1,1,4,7- Tetramethyl- 1a,2,3,4,5,6,7,7b- octahydro-1H- cyclopropa[e]azule ne, (3R,3aR,6R,7S,8aS )-3,6,8,8- tetramethylhexahyd ro-1H-3a,7- methanoazulen- 5(4H)-one, 1,3- diinethylbenzene, 3-Epioleanolic Acid, alpha-pinene, Androstane, Benzyl benzoate, Cinnamaldehyde, Cinnamein, Cinnamic Acid, copaene, Isolapachol, Isopimaric acid, Linoleic acid, musk ambrette, Oleanolic Acid, Oleanonic Acid, Styracin	CHRM3, CHRM2, GABRA1, ACHE, HSD11B1, AR, NPPB, ESR1, HSD11B2, NFKB1, NFKB2, NR3C1, AKR1C1, AKR1C2, NCOA2, NR1I2, NR3C2, PGR, SULT2B1, PRLR, VDR, LSS, ESR2, GABRA2, GABRA3, GABRA4, GABRA5, GABRA6, GABRB1, GABRB2, GABRB3, GABRD, GABRE, GABRG1, GABRG2, GABRG3, GABRP, GABRQ, GRIN1, GRIN2A, GRIN2B, GRIN2C, GRIN2D, GRIN3A, GRIN3B, HSD17B1, NR1I3, PPARA, SULT2A1, IGHG2, ADH1C, CES1, COX4I1, COX5A, COX5B, COX6A2, COX6B1, COX6C, COX7A1, COX7B, COX7C, COX8A, ESRRG, FABP6, FECH, GPBAR1, MT- CO1, MT-CO2, MT-CO3, NR1H4, PLA2G1B, SHBG, CYP2B6, CHRM1, BCHE, SCN10A, COLQ, SLC6A4, SLC6A3, PKIA, ADRB2, ADRB1, CASP3, CASP8, MAPK1, MAPK14, MAPK3, MAPK8, MTRR, NOS1, NOS2, NOS3, POR, PTGS2, SLC2A4, TXNRD1, TRPV4, TRPV1, TLR4, RELA, NFKBIA, NFE2L2, IRF3, C5AR1, MAOB, LTA4H, DAO, HRSP12, PRDX5, RAB9A, SLC15A1, CTSB, ADIPOQ, FURIN, HAL, KDM1A, MBTPS1, PCSK1, PCSK2, PCSK4, PCSK5, PCSK7, PCSK9, RSPO1, RSPO3, RSPO4, TPP2, PTGS1, MGAM, MAOA, LYZ, F3, RXRA, ADRA1B, PIM1, PDE3A, HSP90AA1, NCOA1, SLC6A2, IGHG1, NQO1, ICAM1, CASP9, SRD5A1, CYP17A1, SLC8A1, F12, PTGER1, PTGER4, OPRK1, FADS2, FADS1, PTGER2, PTGER3, ELOVL4, ANXA1, ALOX5, ADRA2B

**Supplementary Table S2: Targets prediction of SBP on AS**

Drug	Target
SBP	MT-CO1, COX5A, AR, PLA2G1B, ADH1C, CES1, MT-CO2, COX8A, NR1H4, CACNA1C, VDR, ESR1, ESR2, NR3C2, SULT2A1, NR1I3, PTGS2, PTGS1, NCOA2, MAOB, CHRM3, CALR, MTNR1B, MPO, CALM2, CALM3, CALM1, SCNN1A, ADRA1A, SCNN1G, HTR2A, ADRB2, ADRB1, APRT, HRH1, PRKAA1, AOC3, TLR7, AGTR1, ADRB3, SCNN1B, CYP2B6, ADRA2B, ADK, ACACA, PRKAA2, HSP90AB1, INS, AOC2, CALCA, ACTN2, NR3C1, PDE5A,

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	ADORA2A, PRKDC, PIK3CD, PIK3CA, ADORA2B, PDE4D, PIK3CB, ATM, CYP19A1, NT5E, HDAC2, PIK3R1, CX3CR1, ADA, RXRA, PPARG, ALOX5, APOA2, SERPINE1, IL1B, IL13, LDLR, ADH1B, PLAT, TOP1, HDAC9, CACNA2D1, SCN5A, PLG, SLC01B3, SLC2A4, SLC10A2, PPARA, MTTP, JUN, ICAM1, HNF4A, HMGCR, CYP7A1, ABCB11, ADM, ALB, CASP3, CASP9, CEL, CETP, CYP3A4, GCG, GHRHR, GIP, GLP1R, GNAS, GPBAR1, HSD11B1, IL2, MC1R, MC4R, POMC, PRKCA, PTGIR, PTH, SLC01A2, SLC01B1, CYP27B1, GC, ANXA1, F12, TRPV1, FADS1, CASP8, MTRR, NOS1, NOS2, NOS3, PRKCB, IL6, NFKB1, NFKB2, TNF, LPL, AKT1, CREB1, MAPK1, MAPK14, MAPK3, BDNF, CHRNA4, FOS, NFKBIA, SOAT1, SOAT2, AHR, DNMT1, ACTB, HSP90AA1, JAK1, NR1I2, PIK3CG, SHBG, F2, MAPK8, TXNRD1, TRPV4, TLR4, RELA, NFE2L2, IRF3, C5AR1, PRDX5, SLC15A1, CTSB, ADIPOQ, FURIN, MBTPS1, PCSK2, PCSK5, PCSK9, MAOA, F3, NPPB, LTA4H, NQO1
BS	MT-CO1, COX5A, AR, PLA2G1B, ADH1C, CES1, MT-CO2, COX8A, NR1H4, CACNA1C, VDR, ESR1, ESR2, NR3C2, SULT2A1, NR1I3, PTGS2, PTGS1, NCOA2, MAOB, CHRM3
BV	CALR, ESR1, MTNR1B, MPO, CALM2, CALM3, CALM1, SCNN1A, ADRA1A, SCNN1G, HTR2A, ADRB2, ADRB1, APRT, HRH1, PRKAA1, AOC3, TLR7, AGTR1, ADRB3, SCNN1B, CYP2B6, ADRA2B, ADK, ACACA, PRKAA2, HSP90AB1, INS, AOC2, CALCA, ACTN2, NR3C1, PDE5A, ADORA2A, PRKDC, PIK3CD, PIK3CA, ADORA2B, PDE4D, PIK3CB, ATM, CYP19A1, NT5E, HDAC2, NR3C2, PIK3R1, CX3CR1, ADA
BCA	RXRA, NR3C2, NCOA2, PPARG, PTGS1, PTGS2, ALOX5, APOA2, SERPINE1, IL1B, IL13, LDLR, NR1H4, MT-CO2, ADH1C, MT-CO1, COX8A, CES1, PLA2G1B, COX5A, ADH1B, AR, PLAT, TOP1, HDAC9, CACNA2D1, SCN5A, PLG, HDAC2, SLC01B3, SLC2A4, SLC10A2, PPARA, MTTP, JUN, ICAM1, HNF4A, HMGCR, CYP7A1, ABCB11, ADM, ADORA2A, ADORA2B, ADRB1, ADRB2, ADRB3, ALB, CALCA, CASP3, CASP9, CEL, CETP, CYP3A4, GCG, GHRHR, GIP, GLP1R, GNAS, GPBAR1, HSD11B1, IL2, MC1R, MC4R, POMC, PRKCA, PTGIR, PTH, SLC01A2, SLC01B1, VDR, CYP27B1, GC, ESR1, NR3C1, ANXA1, F12, TRPV1, FADS1, CASP8, MTRR, NOS1, NOS2, NOS3, PRKCB
GRE	SLC01B3, VDR, IL1B, IL6, NFKB1, NFKB2, TNF, NR3C1, CASP3, HSD11B1, LPL, ANXA1, AKT1, CREB1, MAPK1, MAPK14, MAPK3, NOS3, BDNF, CHRNA4, FOS, SLC2A4, PTGS2, NFKBIA
CC	RXRA, PTGS2, NCOA2, CHRM3, SOAT1, MTTP, SOAT2, AHR, DNMT1, ACTB, ESR1, ESR2, HSP90AA1, JAK1, NR1I2, PIK3CG, SHBG, AR, ADRB2, ADRB1, F2, CASP3, CASP8, MAPK1, MAPK14, MAPK3, MAPK8, MTRR, NOS1, NOS2, NOS3, SLC2A4, TXNRD1, TRPV4, TRPV1, TLR4, RELA, NFKBIA, NFE2L2, IRF3, C5AR1,

	PPARG, AGTR1, APOA2, IL1B, TNF, IL13, ACTN2, PRDX5, SLC15A1, CTSB, ADIPOQ, FURIN, MBTPS1, PCSK2, PCSK5, PCSK9, PTGS1, MAOB, MAOA, F3, ADRA2B, NR3C2, NR3C1, HTR2A, PRKCA, ALOX5, PRKCB, SERPINE1, PPARA, PLG, MPO, LPL, INS, HMGCR, GCG, CETP, BDNF
MA	SHBG, AR, VDR, CYP27B1, GC, ESR1, SCN5A, HDAC9, HDAC2, F2, MT-CO1, COX5A, PLA2G1B, ADH1C, CES1, MT-CO2, COX8A, NR1H4, CACNA2D1, PLAT, PLG, SULT2A1, NQO1, PDE5A, ADORA2A, PRKDC, PIK3CD, PIK3CA, ADORA2B, PDE4D, PIK3CB, ATM, CYP19A1, NT5E, NR3C2, PIK3R1, CX3CR1, ADA, F12, TRPV1, FADS1, PTGS1, PTGS2, NR3C1, ANXA1
SX	CHRM3, HSD11B1, AR, NPPB, ESR1, NFKB1, NFKB2, NR3C1, NCOA2, NR1I2, NR3C2, VDR, ESR2, NR1I3, PPARA, SULT2A1, ADH1C, CES1, COX5A, COX8A, GPBAR1, MT-CO1, MT-CO2, NR1H4, PLA2G1B, SHBG, CYP2B6, ADRB2, ADRB1, CASP3, CASP8, MAPK1, MAPK14, MAPK3, MAPK8, MTRR, NOS1, NOS2, NOS3, PTGS2, SLC2A4, TXNRD1, TRPV4, TRPV1, TLR4, RELA, NFKBIA, NFE2L2, IRF3, C5AR1, MAOB, LTA4H, PRDX5, SLC15A1, CTSB, ADIPOQ, FURIN, MBTPS1, PCSK2, PCSK5, PCSK9, PTGS1, MAOA, F3, RXRA, HSP90AA1, NQO1, ICAM1, CASP9, F12, FADS1, ANXA1, ALOX5, ADRA2B

**Supplementary Table S3: Top 20 signaling pathways of each medicine in SBP**

Medicine	Pathway	P value	FDR
MA	Purine metabolism	1.37E-18	2.24E-16
	Morphine addiction	4.34E-18	3.56E-16
	Metabolic pathways	4.09E-17	2.23E-15
	Prion disease	8.57E-16	3.51E-14
	Cardiac muscle contraction	3.76E-12	1.23E-10
	Chemical carcinogenesis - reactive oxygen species	2.66E-11	7.28E-10
	Alzheimer disease	1.58E-10	3.71E-09
	Nicotine addiction	3.59E-10	7.35E-09
	cAMP signaling pathway	1.23E-09	2.24E-08
	Non-alcoholic fatty liver disease	1.97E-09	3.22E-08
	Spinocerebellar ataxia	5.22E-09	7.78E-08
	Pathways of neurodegeneration - multiple diseases	6.73E-08	9.20E-07
	Diabetic cardiomyopathy	9.51E-08	1.20E-06
	Steroid hormone biosynthesis	3.76E-07	4.41E-06
	Calcium signaling pathway	9.36E-07	1.02E-05
	Oxidative phosphorylation	1.09E-06	1.12E-05
	Huntington disease	1.16E-06	1.12E-05
	Inflammatory mediator regulation of TRP channels	2.75E-06	2.50E-05
	Amyotrophic lateral sclerosis	3.42E-06	2.95E-05

	Parkinson disease	3.62E-06	2.97E-05
GRE	TNF signaling pathway	6.99E-14	4.68E-12
	IL-17 signaling pathway	1.21E-11	4.07E-10
	C-type lectin receptor signaling pathway	3.39E-11	7.57E-10
	Cholinergic synapse	7.83E-11	1.31E-09
	cAMP signaling pathway	2.36E-10	3.04E-09
	Osteoclast differentiation	2.72E-10	3.04E-09
	AGE-RAGE signaling pathway in diabetic complications	6.74E-10	6.45E-09
	Chagas disease	8.06E-10	6.75E-09
	Toll-like receptor signaling pathway	9.60E-10	7.15E-09
	Pertussis	1.89E-09	1.27E-08
	Leishmaniasis	2.10E-09	1.28E-08
	Chemical carcinogenesis - receptor activation	2.48E-09	1.37E-08
	Hepatitis B	2.78E-09	1.37E-08
	Lipid and atherosclerosis	2.87E-09	1.37E-08
	Human cytomegalovirus infection	4.64E-09	2.07E-08
	Tuberculosis	7.73E-09	3.24E-08
	Yersinia infection	1.12E-08	4.42E-08
	Kaposi sarcoma-associated herpesvirus infection	1.59E-08	5.92E-08
	Insulin resistance	3.16E-08	1.11E-07
	Relaxin signaling pathway	1.27E-07	4.27E-07
SX	Nicotine addiction	1.59E-29	2.10E-27
	Neuroactive ligand-receptor interaction	1.30E-20	8.61E-19
	Non-alcoholic fatty liver disease	9.26E-14	4.07E-12
	Retrograde endocannabinoid signaling	3.98E-13	1.31E-11
	Alzheimer disease	9.11E-13	2.40E-11
	Morphine addiction	1.64E-12	3.60E-11
	Chemical carcinogenesis - reactive oxygen species	2.03E-12	3.82E-11
	Prion disease	2.92E-12	4.82E-11
	Pathways of neurodegeneration - multiple diseases	8.21E-12	1.20E-10
	GABAergic synapse	1.60E-11	2.12E-10
	Cocaine addiction	3.63E-10	4.36E-09
	cAMP signaling pathway	6.84E-10	7.53E-09
	Diabetic cardiomyopathy	1.08E-09	1.09E-08
	Cardiac muscle contraction	1.83E-09	1.73E-08
	Parkinson disease	9.22E-08	8.11E-07
	Lipid and atherosclerosis	1.08E-07	8.88E-07
	Amyotrophic lateral sclerosis	1.60E-07	1.24E-06
	Toxoplasmosis	3.51E-07	2.58E-06
	Amphetamine addiction	2.08E-06	1.45E-05
	Pathways in cancer	2.35E-06	1.47E-05
BCA	Neuroactive ligand-receptor interaction	1.31E-58	2.62E-56
	Nicotine addiction	7.09E-18	5.71E-16
	cAMP signaling pathway	8.52E-18	5.71E-16

	Bile secretion	2.32E-10	1.17E-08
	Morphine addiction	3.28E-10	1.32E-08
	Cardiac muscle contraction	1.60E-09	5.35E-08
	Non-alcoholic fatty liver disease	4.00E-09	1.15E-07
	Calcium signaling pathway	1.09E-08	2.75E-07
	GABAergic synapse	1.96E-08	4.37E-07
	Prion disease	1.22E-07	2.46E-06
	Amphetamine addiction	5.93E-07	1.08E-05
	Steroid hormone biosynthesis	1.50E-06	2.51E-05
	Diabetic cardiomyopathy	6.44E-06	9.96E-05
	Retrograde endocannabinoid signaling	1.09E-05	1.57E-04
	Alzheimer disease	1.35E-05	1.81E-04
	Serotonergic synapse	1.76E-05	2.01E-04
	Cocaine addiction	1.79E-05	2.01E-04
	Circadian entrainment	1.80E-05	2.01E-04
	Pathways of neurodegeneration - multiple diseases	2.20E-05	2.25E-04
	Chemical carcinogenesis - reactive oxygen species	2.23E-05	2.25E-04
CC	Nicotine addiction	2.61E-19	2.95E-17
	Neuroactive ligand-receptor interaction	6.76E-18	3.82E-16
	Retrograde endocannabinoid signaling	6.47E-16	2.44E-14
	GABAergic synapse	2.38E-14	6.72E-13
	Morphine addiction	3.51E-14	7.93E-13
	AGE-RAGE signaling pathway in diabetic complications	4.15E-10	7.81E-09
	Toxoplasmosis	1.92E-09	2.99E-08
	IL-17 signaling pathway	2.12E-09	2.99E-08
	Serotonergic synapse	2.74E-09	3.44E-08
	Lipid and atherosclerosis	6.08E-09	6.87E-08
	Leishmaniasis	2.75E-08	2.83E-07
	Influenza A	6.66E-08	6.28E-07
	Chemical carcinogenesis - receptor activation	1.94E-07	1.68E-06
	Measles	2.51E-07	2.02E-06
	Pertussis	2.70E-07	2.03E-06
	Alcoholic liver disease	3.22E-07	2.27E-06
	Chagas disease	5.26E-07	3.49E-06
	TNF signaling pathway	1.35E-06	8.50E-06
	Hepatitis B	1.47E-06	8.74E-06
	Pathways in cancer	2.30E-06	1.30E-05
BV	Purine metabolism	6.30E-25	1.03E-22
	Calcium signaling pathway	1.94E-16	1.58E-14
	cGMP-PKG signaling pathway	9.57E-16	5.20E-14
	Morphine addiction	5.72E-15	2.33E-13
	Renin secretion	2.30E-14	7.51E-13
	Neuroactive ligand-receptor interaction	7.82E-14	2.13E-12
	cAMP signaling pathway	2.68E-11	6.25E-10

	Aldosterone-regulated sodium reabsorption	1.54E-09	3.13E-08
	Inflammatory mediator regulation of TRP channels	1.11E-08	2.01E-07
	Insulin signaling pathway	5.95E-08	8.95E-07
	Salivary secretion	6.04E-08	8.95E-07
	Regulation of lipolysis in adipocytes	1.03E-07	1.39E-06
	Glucagon signaling pathway	2.91E-07	3.65E-06
	Vascular smooth muscle contraction	3.75E-07	4.09E-06
	Metabolic pathways	3.76E-07	4.09E-06
	Estrogen signaling pathway	5.17E-07	5.26E-06
	Taste transduction	3.18E-06	3.05E-05
	Phosphatidylinositol signaling system	8.67E-06	7.85E-05
	C-type lectin receptor signaling pathway	1.53E-05	1.32E-04
	Longevity regulating pathway - multiple species	2.51E-05	2.02E-04
BS	Cardiac muscle contraction	1.34E-24	1.14E-22
	GABAergic synapse	1.06E-22	4.50E-21
	Nicotine addiction	3.29E-22	9.32E-21
	Retrograde endocannabinoid signaling	1.08E-19	2.29E-18
	Morphine addiction	3.23E-16	5.49E-15
	Neuroactive ligand-receptor interaction	4.40E-12	6.24E-11
	Alzheimer disease	1.16E-10	1.41E-09
	Prion disease	3.83E-10	4.07E-09
	Oxidative phosphorylation	6.47E-10	6.11E-09
	Non-alcoholic fatty liver disease	3.49E-09	2.97E-08
	Pathways of neurodegeneration - multiple diseases	4.38E-09	3.38E-08
	Chemical carcinogenesis - reactive oxygen species	2.29E-08	1.62E-07
	Diabetic cardiomyopathy	7.29E-08	4.77E-07
	Parkinson disease	1.83E-07	1.11E-06
	Thermogenesis	3.14E-07	1.78E-06
	Serotonergic synapse	3.44E-07	1.83E-06
	Arrhythmogenic right ventricular cardiomyopathy	2.78E-06	1.39E-05
	Huntington disease	5.84E-06	2.62E-05
	Taste transduction	5.86E-06	2.62E-05
	Hypertrophic cardiomyopathy	7.95E-06	3.38E-05

**Supplementary Table S4:** Enriched pathways based on the identified differential metabolites

Group	Pathway	Rich factor	P value
model/N C	ABC transporters	0.11827957	0.000644763
	Adrenergic signaling in cardiomyocytes	0.3	0.005250671
	Alanine, aspartate and glutamate metabolism	0.142857143	0.01990678
	Alcoholism	0.4	0.000346274

	Amphetamine addiction	0.4	0.000346274
	Arginine and proline metabolism	0.102564103	0.008598214
	Arginine biosynthesis	0.217391304	0.001403045
	beta-Alanine metabolism	0.125	0.031138825
	Butanoate metabolism	0.119047619	0.019977377
	Caffeine metabolism	0.181818182	0.008470696
	cAMP signaling pathway	0.24	0.000257517
	Central carbon metabolism in cancer	0.166666667	0.00480409
	Circadian entrainment	0.222222222	0.043115854
	Citrate cycle (TCA cycle)	0.15	0.03785407
	Cocaine addiction	0.5	0.000122485
	D-Glutamine and D-glutamate metabolism	0.230769231	0.011513745
	Dopaminergic synapse	0.333333333	0.00076927
	Endocrine and other factor-regulated calcium reabsorption	0.25	0.034374409
	GABAergic synapse	0.333333333	0.003779352
	Gap junction	0.454545455	2.78068E-05
	Glucagon signaling pathway	0.16	0.013420232
	Glutamatergic synapse	0.25	0.034374409
	Glutathione metabolism	0.210526316	6.39E-05
	Linoleic acid metabolism	0.25	5.79006E-05
	Long-term depression	0.222222222	0.043115854
	Long-term potentiation	0.285714286	0.026428534
	Lysine degradation	0.14	0.00243975
	Melanogenesis	0.333333333	0.01935331
	Neuroactive ligand-receptor interaction	0.175	0.000623882
	Parkinson disease	0.2	0.005948848
	Pentose and glucuronate interconversions	0.125	0.004692637
	Phenylalanine metabolism	0.133333333	0.001659043
	Primary bile acid biosynthesis	0.106382979	0.0310226
	Prolactin signaling pathway	0.272727273	0.007021576
	Purine metabolism	0.084210526	0.0261104
	Regulation of lipolysis in adipocytes	0.214285714	0.014253945
	Retrograde endocannabinoid signaling	0.157894737	0.033068287
	Serotonergic synapse	0.176470588	0.024514707
	Spinocerebellar ataxia	0.285714286	0.026428534
	Sulfur metabolism	0.121212121	0.034425978
	Taurine and hypotaurine metabolism	0.136363636	0.048421524
	Tyrosine metabolism	0.115384615	0.002413175
	Vitamin digestion and absorption	0.135135135	0.011895312
SBP/mod el	Alanine, aspartate and glutamate metabolism	0.142857143	0.0012815

	Arginine and proline metabolism	0.051282051	0.046737042
	Biosynthesis of unsaturated fatty acids	0.057971014	0.03179253
	Butanoate metabolism	0.071428571	0.036403319
	Central carbon metabolism in cancer	0.133333333	0.001670989
	Citrate cycle (TCA cycle)	0.15	0.004743603
	Cysteine and methionine metabolism	0.063492063	0.023665189
	GABAergic synapse	0.222222222	0.010089855
	Glucagon signaling pathway	0.16	0.00082343
	Glycolysis / Gluconeogenesis	0.096774194	0.016319325
	HIF-1 signaling pathway	0.133333333	0.027509229
	Insulin resistance	0.1	0.047076369
	Insulin secretion	0.166666667	0.017883476
	Nicotinate and nicotinamide metabolism	0.072727273	0.015024581
	Pantothenate and CoA biosynthesis	0.1	0.014923291
	Pentose and glucuronate interconversions	0.089285714	0.0027031
	Phenylalanine metabolism	0.066666667	0.020137741
	Regulation of lipolysis in adipocytes	0.142857143	0.024110003
	Starch and sucrose metabolism	0.081081081	0.026198533
	Terpenoid backbone biosynthesis	0.066666667	0.04337456
	Tyrosine metabolism	0.076923077	0.002177173
	Valine, leucine and isoleucine biosynthesis	0.173913043	0.000591691
	Vascular smooth muscle contraction	0.153846154	0.020898901
SBP- BV/mode 1	ABC transporters	0.075268817	0.010132461
	Adrenergic signaling in cardiomyocytes	0.2	0.026637033
	African trypanosomiasis	0.25	0.017147121
	Alanine, aspartate and glutamate metabolism	0.142857143	0.005562369
	Alcoholism	0.2	0.026637033
	Arginine biosynthesis	0.130434783	0.021061222
	beta-Alanine metabolism	0.125	0.009022997
	Caffeine metabolism	0.136363636	0.018660755
	cAMP signaling pathway	0.2	0.000385768
	Carbohydrate digestion and absorption	0.115384615	0.029232606
	Central carbon metabolism in cancer	0.133333333	0.007154851
	Choline metabolism in cancer	0.363636364	0.000125973
	C-type lectin receptor signaling pathway	0.181818182	0.032009491
	D-Glutamine and D-glutamate metabolism	0.153846154	0.043887603
	Dopaminergic synapse	0.166666667	0.037767476
	GABAergic synapse	0.333333333	0.001301446

	Gap junction	0.272727273	0.002460972
	Glucagon signaling pathway	0.12	0.026347271
	Glutamatergic synapse	0.25	0.017147121
	Glycerophospholipid metabolism	0.096153846	0.010842355
	Insulin secretion	0.166666667	0.037767476
	Lysine degradation	0.08	0.040538974
	Morphine addiction	0.222222222	0.021674457
	Neuroactive ligand-receptor interaction	0.125	0.003508692
	Pantothenate and CoA biosynthesis	0.133333333	0.007154851
	Parkinson disease	0.15	0.014342661
	Prolactin signaling pathway	0.181818182	0.032009491
	Pyrimidine metabolism	0.076923077	0.026458839
	Regulation of lipolysis in adipocytes	0.214285714	0.005128694
	Retrograde endocannabinoid signaling	0.157894737	0.012422856
	Vascular smooth muscle contraction	0.230769231	0.004106778
Ato/mode 1	ABC transporters	0.064516129	0.009282183
	Alanine, aspartate and glutamate metabolism	0.178571429	0.000176737
	Alcoholism	0.2	0.015571983
	Aminoacyl-tRNA biosynthesis	0.096153846	0.003246337
	Arginine and proline metabolism	0.064102564	0.017816573
	Arginine biosynthesis	0.173913043	0.000920834
	beta-Alanine metabolism	0.09375	0.024176005
	Butanoate metabolism	0.071428571	0.048721485
	cAMP signaling pathway	0.12	0.012360172
	Central carbon metabolism in cancer	0.2	1.90652E-05
	Choline metabolism in cancer	0.181818182	0.0187925
	D-Glutamine and D-glutamate metabolism	0.153846154	0.025984924
	GABAergic synapse	0.333333333	0.000565421
	Gap junction	0.181818182	0.0187925
	Glucagon signaling pathway	0.12	0.012360172
	Glutathione metabolism	0.078947368	0.037835688
	Glycerophospholipid metabolism	0.076923077	0.018371866
	Histidine metabolism	0.085106383	0.013022949
	Lysine degradation	0.08	0.016092331
	Neuroactive ligand-receptor interaction	0.125	0.00098592
	Pantothenate and CoA biosynthesis	0.1	0.020347739
	Protein digestion and absorption	0.103448276	0.018569915
	Proximal tubule bicarbonate reclamation	0.117647059	0.043079732
	Regulation of lipolysis in adipocytes	0.142857143	0.029935247
	Renin secretion	0.117647059	0.043079732
	Sulfur metabolism	0.090909091	0.026226557

Taurine and hypotaurine metabolism	0.136363636	0.008630996
Valine, leucine and isoleucine biosynthesis	0.130434783	0.009787521
Valine, leucine and isoleucine degradation	0.073170732	0.045869544
Vascular smooth muscle contraction	0.153846154	0.025984924

**Supplementary Table S5:** The differential metabolites sharing the similar trends with normal group

Groups	Metabolites
SBP/model	2-hydroxy-iminostilbene, D-Urobilin, PtdIns-(1,2-dioctanoyl) (sodium salt), Nebramycin factor 5', 3,4,5-trihydroxy-6-(5-hydroxy-4-{2-hydroxy-3-[4-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl]propanoyl}-2-(3-methylbut-2-en-1-yl)phenoxy)oxane-2-carboxylic acid, D-Urobilinogen, Benfuresate, PC(16:1(9Z)/0:0)[U], 2',7-Dihydroxy-4'-methoxy-8-prenylflavan 2',7-diglucoside, 1-(2-methoxy-6Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine, Bisindolylmaleimide IV, Hydromorphone, N1-Caffeoyl-N10-feruloylspermidine, PS(O-18:0/0:0), PC(8:2(2E,4E)/8:2(2E,4E)), 1-Methyluric acid, Tenovin-6, Farnesyl Alcohol Azide, 4-hydroxybenzeneacetic acid, N1,N10-Dicoumaroylspermidine, Chenodeoxycholic acid sulfate, Piperazine citrate, Sphinganine-phosphate, Ritodrine, Dinoflagellate luciferin, N-oleoyl threonine, 1,25-Dihydroxy-20S-21-(3-hydroxy-3-methylbutyl)-23-yne-26,27-hexafluorovitamin D3, Demissine, 2-Hexenoylcholine, Mesobilirubinogen, (3Z)-Phycoerythrobilin, Oxoglutaric acid, Integerrenine, Phenmedipham, eurysterol B sulfonic acid, 5beta-Cholestane-3alpha,7alpha,12alpha,24,26,27-hexol, OKOHA-PG, Kynurenic acid, Letrozole, azaperone, 5-((8Z,11Z)-nonadeca-8,11-dien-1-yl)resorcinol, Coproporphyrin I, Prasugrel, Kudzusaponin SA4, Piplartine, Adhumulinic acid,

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Norcocaine, Erysopine, 4-Hydroxybenzyl isothiocyanate 4"-acetylramnoside, 5-aminovaleric acid, 4-hydroxycyclohexylcarboxylic acid, Acetohexamide, Morphine, 3alpha,12alpha,22-Trihydroxy-5beta-cholestan-26-oic acid, Melilotigenin, 2-O-(beta-D-galactopyranosyl-(1->6)-beta-D-galactopyranosyl) 2S-hydroxyundecanoic acid, beta-Allocortolone, 9,10,13-TriHOME, alpha-N-(3-hydroxyhexadecanoyl) L-ornithine, LysoPE(14:1(9Z)/0:0), 3,6,12-Trioxo-5β-cholelan-24-oic Acid, 1,7-Dimethyluric acid, Mukoenine A, 3,17,20-trihydroxy-pregn-5-en-11-one, 3α,7α,12α,22-Tetrahydroxy-5β-cholestan-26-oic acid, Barogenin, 3-(3-hydroxyphenyl)-2-phenyl-4-[(E)-2-phenylethenyl]-2,3-dihydro-1-benzofuran-6-ol, 1-(2-methoxy-6Z-tetradecenyl)-sn-glycero-3-phosphoserine, Euscaphic acid, C17 Sphinganine, 3beta,6alpha-dihydroxy-5alpha-cholesta-9(11),24-dien-23-one, α-hydroxy Farnesyl Phosphonic Acid, Prazerigenin A, (R)-Shinanolone, dihydroergocornine, PS(14:0/0:0), Calcipotriol, Varanic acid, Secosterol-B, 2beta,7alpha,12alpha-Trihydroxy-3-oxo-5beta-cholelan-24-oic Acid, 2β,3α,7α,12α-Tetrahydroxy-5β-cholestan-26-oic acid, PS(15:0/0:0), 3α,7α-Dihydroxy-5β-cholest-24-en-26-oic acid, Beta-hydroxymyristic acid, 3alpha,7alpha,22S-trihydroxy-5alpha-cholestan-26-oic acid, LysoPE(16:1(9Z)/0:0), (17alpha,23S)-Epoxy-28,29-dihydroxy-27-norlanost-8-ene-3,24-dione, Carbaprostacyclin-biotin, Desmethylnortriptyline, 1alpha,25-Dihydroxy-previtamin D3, LysoPE(0:0/22:4(7Z,10Z,13Z,16Z)), 3alpha,12alpha,24R-Trihydroxy-5beta-cholestan-26-oic acid, Norprotriptyline, 5-Cholestene-3beta,7alpha,12alpha,25-tetrol, Dihomohydrocholic acid, Ergoline-8-methanol, 10-methoxy-, (8b)-, Dihomo-alpha-muricholic acid, Isoleucyl-Aspartate, Denticulaflavonol, 9-oxo-24-methylene-9,11-seco-cholest-5-en-

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3beta,11-diol, 1beta,3alpha,7alpha,12alpha-Tetrahydroxy-5beta-cholestan-26-oic acid, Pennogenin, 6-hydroxysphingosine, 5beta-scymnol sulfate, 5-Hydroxymethyl tolterodine, alpha-Micropteroxanthin B, Isorhodeasapogenin, Hexadecyl ferulate, 2,6-octadienoylglycine, 7alpha-Hydroxy-3-oxo-4-cholestenoate, 6-Deoxodolichosterone, 2beta,3alpha,7alpha,12alpha-Tetrahydroxy-5beta-cholestan-26-oic acid, 7alpha,24-dihydroxycholest-4-en-3-one, Phytol, (5x,6x)-5,6-Epoxyergosta-7,22-dien-3-ol, (25R)-5beta-spirostan-1beta,3alpha-diol, zymosterol intermediate 1b, Gamabufogenin, 24-Hydroxyglabrolide, 7alpha,12alpha-dihydroxy-3-oxocholest-4-en-27-oic acid, 5beta-Chola-3,8(14),11-trien-24-oic Acid, Glutamylvaline, 1-(2-methoxy-13-methyl-6Z-tetradecenyl)-sn-glycero-3-phosphoethanolamine, Glycerophospho-N-Palmitoyl Ethanolamine, 20(17->12beta)-abeo-1alpha,25-dihydroxy-24-dihomo-21-norvitamin D3, 3alpha,7alpha,12alpha,24(S)-tetrahydroxy-5beta-cholestan-27-al, 3alpha,7alpha,12alpha,25-Tetrahydroxy-5beta-cholestane-24-one, Setariol, gamma-Glutamylleucine, Valyl-Glutamate, Cryptogenin, 3-Methyleneoxindole, gamma-Glutamylvaline, PE(18:1(9Z)/0:0), 7alpha,12alpha,26-Trihydroxy-5beta-cholestan-3-one, [(oxolan-2-yl)methoxy]sulfonic acid, LysoPE(18:1(9Z)/0:0), 3alpha,7alpha,12alpha,24-Tetrahydroxy-5alpha-cholestan-26-oic acid, 3-(2-hydroxyphenyl)oxirane-2-carbaldehyde, 2,4,6-Octatriyn-1-ol, (25S)-5alpha-cholestan-3beta,6alpha,8,15beta,16beta,26-hexol, 5-Aminopentanoic acid, 25-Hydroxyvitamin D3-26,23-lactol, 3a,6b,7b,12b-Tetrahydroxy-5b-cholanoic acid

SBP-BV/model 2-hydroxy-iminostilbene, D-Urobilin, PtdIns-(1,2-dioctanoyl) (sodium salt), Nebramycin factor 5', Bilirubin, INDOPROFEN, 3,4,5-trihydroxy-6-(5-hydroxy-4-{2-hydroxy-3-[4-hydroxy-3-(3-

methylbut-2-en-1-yl)phenyl]propanoyl}-2-(3-methylbut-2-en-1-yl)phenoxy)oxane-2-carboxylic acid, D-Urobilinogen, 2',7-Dihydroxy-4'-methoxy-8-prenylflavan 2',7-diglucoside, Harderoporphyrinogen, Benfuresate, PC(16:1(9Z)/0:0)[U], Americine, Hydromorphone, 1-(2-methoxy-6Z-hexadecenyl)-sn-glycero-3-phosphoethanolamine, Phenmedipham, 1-Methyluric acid, Biliverdin, W123, Leukotriene E3, Farnesyl Alcohol Azide, N1-Caffeoyl-N10-feruloylspermidine, 4-hydroxycyclohexylcarboxylic acid, PC(8:2(2E,4E)/8:2(2E,4E)), 5-((8Z,11Z)-nonadeca-8,11-dien-1-yl)resorcinol, OKOHA-PG, N1,N10-Dicoumaroylspermidine, (3Z)-Phycoerythrobilin, Ritodrine, azaperone, Integerrenine, Kynurenic acid, Oxoglutaric acid, LysoPE(0:0/20:1(11Z)), Chenodeoxycholic acid sulfate, Sphinganine-phosphate, Mesobilirubinogen, 5-NITRO-2-PHENYLPROPYLAMINO BENZOIC ACID [NPPB], N-trans-Feruloyloctopamine, N-oleoyl threonine, Dinoflagellate luciferin, 5beta-Cholestane-3alpha,7alpha,12alpha,24,26,27-hexol, 5-aminovaleric acid, eurysterol B sulfonic acid, Citpressine II, 3-epicholic acid, 2-Hexenoylcholine, 4-Hydroxybenzyl isothiocyanate 4"-acetylramnoside, Prasugrel, Acetohexamide, 3alpha,12alpha,22-Trihydroxy-5beta-cholestan-26-oic acid, Adhumulinic acid, Morphine, Letrozole, LysoPE(14:1(9Z)/0:0), Erysopine, 6β-Testosterone Enanthate, 1,7-Dimethyluric acid, 11'-Carboxy-gamma-chromanol, Coproporphyrin I, Melilotigenin, Norcocaine, beta-Allocortolone, Euscaphic acid, Piplartine, Hypercalin B, Kudzusaponin SA4, 1-(2-methoxy-6Z-tetradecenyl)-sn-glycero-3-phosphoserine, 3,6,12-Trioxo-5β-cholan-24-oic Acid, Clomipramine, Formononetin, 3α,7α,12α,22-Tetrahydroxy-5β-cholestan-26-oic acid, 3,17,20-trihydroxy-pregn-5-en-11-one,

TG(8:0/13:0/12:0), 2-monoolein, Barogenin, C17 Sphinganine, 2-O-(beta-D-galactopyranosyl-(1->6)-beta-D-galactopyranosyl) 2S-hydroxyundecanoic acid, (R)-Shinanolone, Mukoenine A, dihydroergocornine, Secosterol-B, Latanoprost (free acid), Phytol, 5-Cholestene-3beta,7alpha,12alpha,25-tetrol, PS(14:0/0:0), PS(15:0/0:0), 3alpha,7alpha-Dihydroxy-5beta-cholest-24-en-26-oic acid, alpha-N-(3-hydroxyhexadecanoyl) L-ornithine, 5b-Cholestane-3a,7a,12a,23S,25-pentol, Beta-hydroxymyristic acid, Varanic acid, Undecanoylcarnitine, 3beta,6alpha-dihydroxy-5alpha-cholesta-9(11),24-dien-23-one, (-)-8-(2-Carboxy-1-phenylethyl)-3,5,7-trihydroxyflavone delta-lactone, 2beta,3alpha,7alpha,12alpha-Tetrahydroxy-5beta-cholestan-26-oic acid, alpha-hydroxy Farnesyl Phosphonic Acid, L-Glutamine, Calcipotriol, 4,8 dimethylnonanoyl carnitine, Desmethylnortriptyline, 3alpha,12alpha,25-Trihydroxy-5beta-cholestan-7-one, 1alpha,25-Dihydroxy-previtamin D3, 3alpha,7alpha,22S-trihydroxy-5alpha-cholestan-26-oic acid, Pennogenin, (17alpha,23S)-Epoxy-28,29-dihydroxy-27-norlanost-8-ene-3,24-dione, Oxidized Oplophorus luciferin, 3alpha,12alpha,24R-Trihydroxy-5beta-cholestan-26-oic acid, Isoleucyl-Aspartate, 2beta,7alpha,12alpha-Trihydroxy-3-oxo-5beta-cholestan-24-oic Acid, Dihomo-alpha-muricholic acid, 7alpha-hydroxy-4-cholesten-3-one-d7, alpha-Microperoxanthin B, LysoPE(16:1(9Z)/0:0), 7alpha,24-dihydroxycholest-4-en-3-one, Carbaprostacyclin-biotin, Prazerigenin A, 13'-Carboxy-gammatacopherol, 6-Deoxodolichosterone, Glutamylvaline, 6-hydroxysphingosine, 1-(2-methoxy-13-methyl-6Z-tetradecenyl)-sn-glycero-3-phosphoethanolamine, 1beta,3alpha,7alpha,12alpha-Tetrahydroxy-5beta-cholestan-26-oic acid, 1-(2-methoxy-6Z-pentadecenyl)-sn-glycero-3-phosphoethanolamine,

Glycerophospho-N-Palmitoyl Ethanolamine, PE(0:0/18:2(9Z,12Z)), Ecabet, 2beta,3alpha,7alpha,12alpha-Tetrahydroxy-5beta-cholestan-26-oic acid, Schleicherastatin 5, (25R)-3beta-hydroxycholest-5-en-7-one-26-oate, Ergoline-8-methanol, 10-methoxy-, (8b)-, (25R)-5beta-spirostan-1beta,3alpha-diol, 7alpha-Hydroxy-3-oxo-4-cholestenoate, Isorhodeasapogenin, PE(18:1(9Z)/0:0), LysoPE(18:2(9Z,12Z)/0:0), 7alpha,12alpha-dihydroxy-3-oxocholest-4-en-27-oic acid, 2,22-Dideoxy-3-dehydroecdysone, 5beta-Chola-3,8(14),11-trien-24-oic Acid, N-palmitoyl serine, Gamabufogenin, PE(16:0/0:0), Valyl-Glutamate, Heneicosanoic acid, LysoPE(18:1(9Z)/0:0), 3alpha,7alpha,12alpha,25-Tetrahydroxy-5beta-cholestane-24-one, Setariol, Citrulline, Glycerol-3-galactoside, gamma-Glutamylleucine, [(oxolan-2-yl)methoxy]sulfonic acid, 7alpha,12alpha,26-Trihydroxy-5beta-cholestan-3-one, gamma-Glutamylvaline, 3-Methyleneoxindole, 3alpha,12alpha-Dihydroxy-5beta-cholest-24-en-26-oic acid, 3alpha,7alpha,12alpha,24-Tetrahydroxy-5alpha-cholestan-26-oic acid, 5-Aminopentanoic acid, Glutaminyglutamic acid, 2,4,6-Octatriyn-1-ol, 3-(2-hydroxyphenyl)oxirane-2-carbaldehyde, (25S)-5alpha-cholestan-3beta,6alpha,8,15beta,16beta,26-hexol, 3a,6b,7b,12b-Tetrahydroxy-5b-cholanoic acid, Armillarin, PC(20:1(11Z)/24:1(15Z))

Ato/model

PtdIns-(1,2-dioctanoyl) (sodium salt), D-Urobilin, INDOPROFEN, Nebramycin factor 5', Spiramycin II, 3,4,5-trihydroxy-6-(5-hydroxy-4-{2-hydroxy-3-[4-hydroxy-3-(3-methylbut-2-en-1-yl)phenyl]propanoyl}-2-(3-methylbut-2-en-1-yl)phenoxy)oxane-2-carboxylic acid, 2',7-Dihydroxy-4'-methoxy-8-prenylflavan 2',7-diglucoside, D-Urobilinogen, TG(8:0/8:0/a-13:0)[rac], Benfuresate, 2-Methyl-6-phytylhydroquinone, Americine, Hydromorphone,

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(3Z)-Phycoerythrobilin, Biliverdin, Phenmedipham, 1-Methyluric acid, 6,7-Epoxy-3Z,9Z-tricosadiene, N1-Caffeoyl-N10-feruloylspermidine, Neryl propionate, PC(8:2(2E,4E)/8:2(2E,4E)), Farnesyl Alcohol Azide, 5-((8Z,11Z)-nonadeca-8,11-dien-1-yl)resorcinol, Dinoflagellate luciferin, Integerrenine, N1,N10-Dicoumaroylspermidine, LysoPE(0:0/20:1(11Z)), OKOHA-PG, Ritodrine, 1,25-Dihydroxy-20S-21-(3-hydroxy-3-methylbutyl)-23-yne-26,27-hexafluorovitamin D3, Tenovin-6, 11'-Carboxy-gamma-chromanol, Mesobilirubinogen, 4-hydroxycyclohexylcarboxylic acid, Adhumulinic acid, 5beta-Cholestane-3alpha,7alpha,12alpha,24,26,27-hexol, Euscaphic acid, Sphinganine-phosphate, N-oleoyl threonine, Kynurenic acid, azaperone, Coproporphyrin I, 3-Methyl-alpha-ionyl acetate, Letrozole, 5-NITRO-2-PHENYLPROPYLAMINO BENZOIC ACID [NPPB], Melilotigenin, Ricinoleic Acid methyl ester, 3,6,12-Trioxo-5beta-cholestan-24-oic Acid, LysoPE(14:1(9Z)/0:0), Calcitriol, Piplartine, Secosterol-B, 2-Hexenoylcholine, 5-aminovaleric acid, 6beta-Testosterone Enanthate, Citpressine II, Norcocaine, 3alpha,12alpha,22-Trihydroxy-5beta-cholestan-26-oic acid, Clomipramine, beta-Allocortolone, 1-(2-methoxy-6Z-tetradecenyl)-sn-glycero-3-phosphoserine, Prasugrel, Hypercalin B, 3-epicholic acid, Homodeoxycholic acid, Castasterone, Tokorogenin, eurysterol B sulfonic acid, 3beta-Hydroxy-5alpha,6alpha-epoxy-9-oxo-9,10-seco-5-cholest-7-en-11-al, 4-Hydroxybenzyl isothiocyanate 4"-acetylramnoside, Hippurin-1, C17 Sphinganine, Pennogenin, 3alpha,7alpha,12alpha,22-Tetrahydroxy-5beta-cholestan-26-oic acid, PS(14:0/0:0), 5-Cholestene-3beta,7alpha,12alpha,25-tetrol, Latanoprost (free acid), Barogenin, Oxoglutaric acid, Secasterone, Morphine, 25,26-dihydroxyvitamin D, 6-Deoxodolichosterone, 3alpha,7alpha-Dihydroxy-5beta-

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cholest-24-en-26-oic acid, 5b-Cholestane-3a,7a,12a,23S,25-pentol, PS(15:0/0:0), Erysopine, 3,17,20-trihydroxy-pregn-5-en-11-one, Mukoenine A, Undecanoylcarnitine, Thymidine, sn-3-O-(geranylgeranyl)glycerol 1-phosphate, Carbaprostacyclin-biotin, 1alpha,25-Dihydroxy-previtamin D3, 13'-Carboxy-gammatocopherol, 1,7-Dimethyluric acid, (R)-Shinanolone, Formononetin, 7alpha,24-dihydroxycholest-4-en-3-one, dihydroergocornine, Varanic acid, Ornithine, 4,8 dimethylnonanoyl carnitine, 3alpha,12alpha,25-Trihydroxy-5beta-cholestan-7-one, Mycalamide A, (17alpha,23S)-Epoxy-28,29-dihydroxy-27-norlanost-8-ene-3,24-dione, (5x,6x)-5,6-Epoxyergosta-7,22-dien-3-ol, Tauroursolic acid, 3beta,6alpha-dihydroxy-5alpha-cholesta-9(11),24-dien-23-one, 9-oxo-24-methylene-9,11-seco-cholest-5-en-3beta,11-diol, 2-O-(beta-D-galactopyranosyl-(1->6)-beta-D-galactopyranosyl) 2S-hydroxyundecanoic acid, 5alpha-cholestanol, 2beta,3alpha,7alpha,12alpha-Tetrahydroxy-5beta-cholestan-26-oic acid, 2beta,7alpha,12alpha-Trihydroxy-3-oxo-5beta-cholan-24-oic Acid, Beta-hydroxymyristic acid, alpha-hydroxy Farnesyl Phosphonic Acid, Isorhodeasapogenin, (25R)-3beta-hydroxycholest-5-en-7-one-26-oate, 7alpha-hydroxy-4-cholesten-3-one-d7, 5beta-scyminol sulfate, 5-Cholestene-3beta,7alpha,12alpha,24,25-pentol, Calcipotriol, 3alpha,7alpha,22S-trihydroxy-5alpha-cholestan-26-oic acid, 3alpha,7beta,12alpha-Trihydroxy-6-oxo-5alpha-cholan-24-oic Acid, 20(17->12beta)-abeo-1alpha,25-dihydroxy-24-dihomo-21-norvitamin D3, (22E)-3alpha,7alpha,12alpha-Trihydroxy-5beta-chol-22-en-24-oic Acid, PE(0:0/18:2(9Z,12Z)), 3alpha,12alpha,24R-Trihydroxy-5beta-cholestan-26-oic acid, Dihomo-alpha-muricholic acid, alpha-Microperoxanthin B, Glycerophospho-N-Palmitoyl Ethanolamine, 1-(2-methoxy-13-methyl-6Z-tetradecenyl)-sn-glycero-3-phosphoethanolamine,

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Denticulaflavonol, 1beta,3alpha,7alpha,12alpha-Tetrahydroxy-5beta-cholestan-26-oic acid, 3alpha,7alpha,12alpha,25-Tetrahydroxy-5beta-cholestane-24-one, LysoPE(18:2(9Z,12Z)/0:0), 7alpha-Hydroxy-3-oxo-4-cholestenoate, 2beta,3alpha,7alpha,12alpha-Tetrahydroxy-5beta-cholestan-26-oic acid, dolichyl diphosphate, Ecabet, (3,4,5,6-tetrahydroxyoxan-2-yl)methyl 4-hydroxybenzoate, Ergoline-8-methanol, 10-methoxy-, (8b)-, LysoPE(16:1(9Z)/0:0), 1-(2-methoxy-6Z-pentadecenyl)-sn-glycero-3-phosphoethanolamine, 5beta-Chola-3,8(14),11-trien-24-oic Acid, 5-L-Glutamyl-L-alanine, 2-aminoheptanedioic acid, Clitidine 5'-phosphate, 2,22-Dideoxy-3-dehydroecdysone, Gamabufogenin, Setariol, PE(16:0/0:0), Danazol, 7alpha,12alpha,26-Trihydroxy-5beta-cholestan-3-one, 7alpha,12alpha-dihydroxy-3-oxocholest-4-en-27-oic acid, Asitribin, PE(18:1(9Z)/0:0), Desmethylnortriptyline, 12a-Hydroxy-3-oxocholadienic acid, 3alpha,12alpha-Dihydroxy-5beta-chol-6-en-24-oic Acid, (25R)-5beta-spirostan-1beta,3alpha-diol, LysoPE(18:1(9Z)/0:0), N-palmitoyl serine, 3alpha,12alpha-Dihydroxy-5beta-cholest-24-en-26-oic acid, Nonadecanoic acid, 3alpha,7alpha,12alpha,24(S)-tetrahydroxy-5beta-cholestan-27-al, 3alpha,7alpha,12beta-Trihydroxy-11-oxo-5beta-cholan-24-oic Acid, [(oxolan-2-yl)methoxy]sulfonic acid, 3-Methyleneoxindole, Heneicosanoic acid, 3alpha,7alpha,12alpha,24-Tetrahydroxy-5alpha-cholestan-26-oic acid, 23S,25,26-Trihydroxyvitamin D3, D-Lysine, Asperagenin, CYCLOLEUCINE, 3-(2-hydroxyphenyl)oxirane-2-carbaldehyde, 2,4,6-Octatriyn-1-ol, 2-Hydroxycinnamic acid, L-Proline, Benzofuran, L-Isoleucine, (25S)-5alpha-cholestan-3beta,6alpha,8,15beta,16beta,26-hexol, L-Alloisoleucine, 3-Methyl sulfolene, THTC, 5-Aminopentanoic acid,

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**Supplementary Table S6:** The overlapped pathways and the differential metabolites from these pathways

Group	Pathway	Metabolites
SBP/mo del	Alanine, aspartate and glutamate metabolism	Butanedioic acid, N-acetylaspartate, N-acetylaspartic acid, Oxoglutaric acid, Pyruvic acid
	Arginine and proline metabolism	5-Aminopentanoic acid, 5-amino-pentanoic acid, 5-aminovaleric acid, L-Phosphoarginine, Pyrrole-2-carboxylic acid, Pyruvic acid
	Butanoate metabolism	Butanedioic acid, Oxoglutaric acid, Pyruvic acid
	Central carbon metabolism in cancer	Butanedioic acid, Glucose 6-phosphate, Oxoglutaric acid, Pyruvic acid
	Citrate cycle (TCA cycle)	Butanedioic acid, Oxoglutaric acid, Pyruvic acid
	GABAergic synapse	Butanedioic acid, Oxoglutaric acid
	Glucagon signaling pathway	Butanedioic acid, Glucose-1-phosphate, Oxoglutaric acid, Pyruvic acid
	Pentose and glucuronate interconversions	Digalacturonic acid, Glucose-1-phosphate, Oxoglutaric acid, Pyruvic acid, Xylonic acid
	Phenylalanine metabolism	3-hydroxyphenylacetic acid, 4-hydroxybenzeneacetic acid, Butanedioic acid, Pyruvic acid
	Regulation of lipolysis in adipocytes	Arachidonic acid, Palmitoylcarnitine
SBP- BV/mod el	Tyrosine metabolism	3-hydroxyphenylacetic acid, 4-hydroxybenzeneacetic acid, Butanedioic acid, Hydroquinone, Palmitoylcarnitine, Pyruvic acid
	ABC transporters	Adenosine, Digalacturonic acid, D-ribose, L-Glutamine, L-histidine, Taurine, Trehalose
	Adrenergic signaling in cardiomyocytes	DG(16:1(9Z)/18:2(9Z,12Z)/0:0), Palmitoylcarnitine
	Alanine, aspartate and glutamate metabolism	Butanedioic acid, L-Glutamine, N-acetylaspartate, N-acetylaspartic acid, Oxoglutaric acid
	Alcoholism	Adenosine, Dopamine
	Arginine biosynthesis	Citrulline, L-Glutamine, Oxoglutaric acid
	beta-Alanine	3-ureidopropionate, L-histidine, Pantothenic

metabolism	acid, Uracil
Caffeine metabolism	1,7-Dimethyluric acid, 1-Methyluric acid, Xanthine
cAMP signaling pathway	Adenosine, Butanedioic acid, DG(16:1(9Z)/18:2(9Z,12Z)/0:0), Dopamine, Palmitoylcarnitine
Central carbon metabolism in cancer	Butanedioic acid, Glucose 6-phosphate, L-Glutamine, Oxoglutaric acid
D-Glutamine and D-glutamate metabolism	L-Glutamine, Oxoglutaric acid
Dopaminergic synapse	DG(16:1(9Z)/18:2(9Z,12Z)/0:0), Dopamine
GABAergic synapse	Butanedioic acid, L-Glutamine, Oxoglutaric acid
Gap junction	DG(16:1(9Z)/18:2(9Z,12Z)/0:0), Dopamine, Palmitoylcarnitine
Glucagon signaling pathway	Butanedioic acid, Glucose-1-phosphate, Oxoglutaric acid
Glutamatergic synapse	DG(16:1(9Z)/18:2(9Z,12Z)/0:0), L-Glutamine
Lysine degradation	5-Aminopentanoic acid, 5-amino-pentanoic acid, 5-aminovaleric acid, Butanedioic acid, L-2-hydroxyglutaric acid, Oxoglutaric acid
Neuroactive ligand-receptor interaction	Adenosine, Dopamine, Morphine, Palmitoyl Ethanolamide, Taurine
Parkinson disease	Adenosine, DG(16:1(9Z)/18:2(9Z,12Z)/0:0), Dopamine
Prolactin signaling pathway	Dopamine, Glucose 6-phosphate
Regulation of lipolysis in adipocytes	Adenosine, DG(16:1(9Z)/18:2(9Z,12Z)/0:0), Palmitoylcarnitine
Retrograde endocannabinoid signaling	DG(16:1(9Z)/18:2(9Z,12Z)/0:0), Ethanolamine, PC(20:1(11Z)/24:1(15Z))
Ato/mod el	Adenosine, Digalacturonic acid, L-Aspartic Acid, L-Glutamate, L-histidine, Taurine
ABC transporters	Butanedioic acid, L-Aspartic Acid, L-Glutamate, N-acetylaspartate, N-acetylaspartic acid, Oxoglutaric acid
Alanine, aspartate and glutamate metabolism	Adenosine, L-Glutamate
Alcoholism	5-Aminopentanoic acid, 5-amino-pentanoic acid, 5-aminovaleric acid, L-Glutamate, L-Phosphoarginine, L-Proline, Ornithine
Arginine and proline metabolism	L-Aspartic Acid, L-Glutamate, Ornithine, Oxoglutaric acid
Arginine biosynthesis	L-Aspartic Acid, L-histidine, Pantothenic acid
beta-Alanine metabolism	

Butanoate metabolism	Butanedioic acid, L-Glutamate, Oxoglutaric acid
cAMP signaling pathway	Adenosine, Butanedioic acid, Palmitoylcarnitine
Central carbon metabolism in cancer	Butanedioic acid, Glucose 6-phosphate, L-Aspartic Acid, L-Glutamate, L-Proline, Oxoglutaric acid
D-Glutamine and D-glutamate metabolism	L-Glutamate, Oxoglutaric acid
GABAergic synapse	Butanedioic acid, L-Glutamate, Oxoglutaric acid
Gap junction	L-Glutamate, Palmitoylcarnitine
Glucagon signaling pathway	Butanedioic acid, Glucose-1-phosphate, Oxoglutaric acid
Glutathione metabolism	5-L-Glutamyl-L-alanine, L-Glutamate, Ornithine
Lysine degradation	5-Aminopentanoic acid, 5-amino-pentanoic acid, 5-aminovaleric acid, Butanedioic acid, D-Lysine, Oxoglutaric acid
Neuroactive ligand-receptor interaction	Adenosine, L-Aspartic Acid, L-Glutamate, Morphine, Taurine
Regulation of lipolysis in adipocytes	Adenosine, Palmitoylcarnitine
Sulfur metabolism	Butanedioic acid, Homoserine, Taurine
Taurine and hypotaurine metabolism	L-Glutamate, Oxoglutaric acid, Taurine

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