Supporting Information

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α-Glucosidase Inhibitors from *Polyscias serrata* Roots in a Parallel Study of Network Pharmacology

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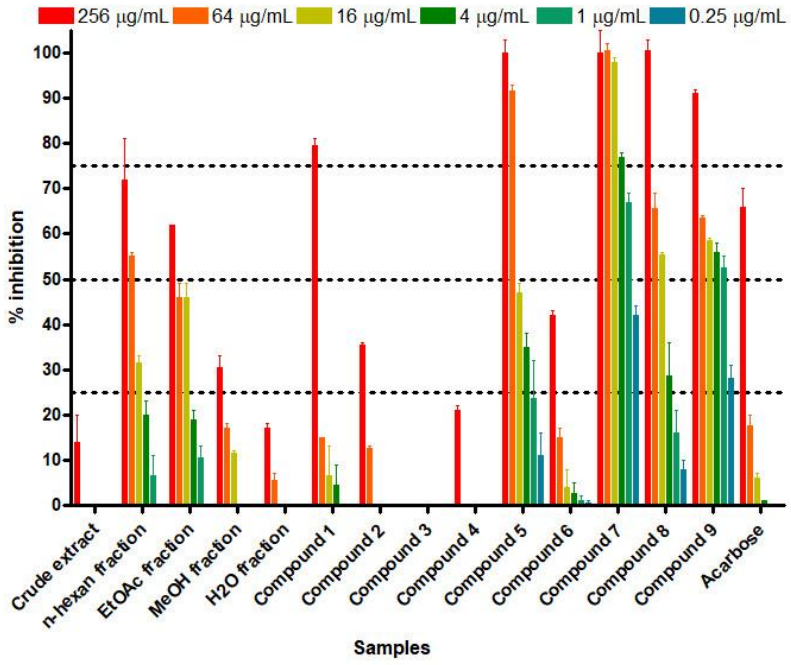


Figure S2: α-Glucosidase inhibitory activity of the extracts and isolated compounds (1-9) from *P. serrata* roots

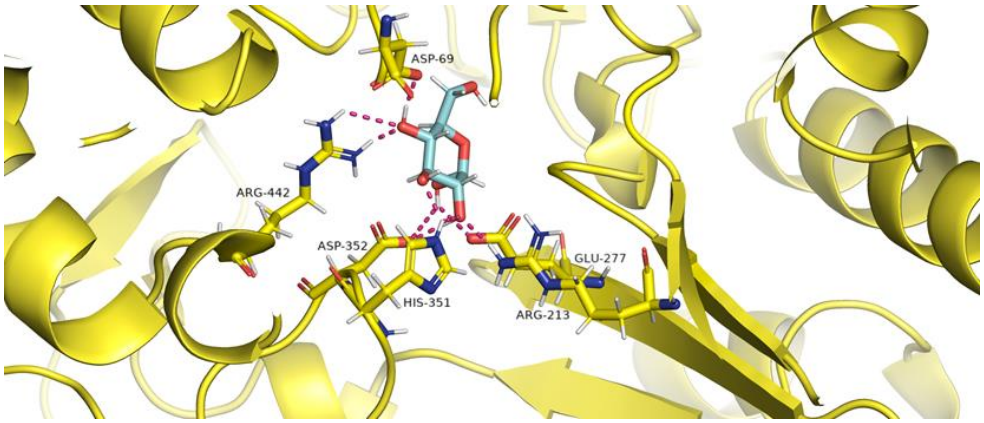


Figure S3: Interaction between α-glucose and target protein

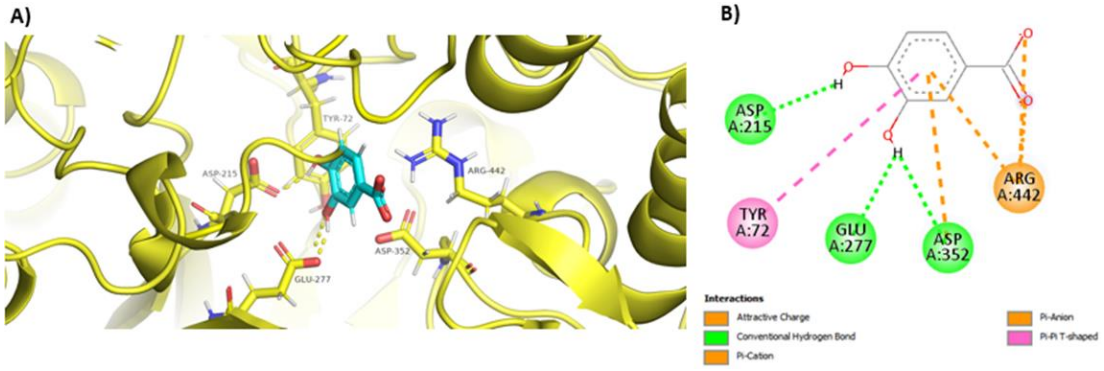


Figure S4: A) 3D binding interaction with compound **9 B**) 2D binding interaction with compound **9**

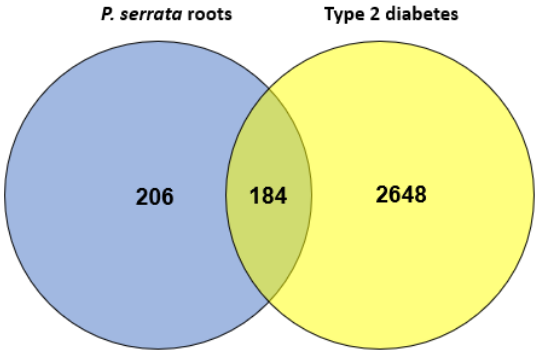


Figure S5: Overlap of targets of *P. serrata* roots' constituents and type-2-diabetes-related targets

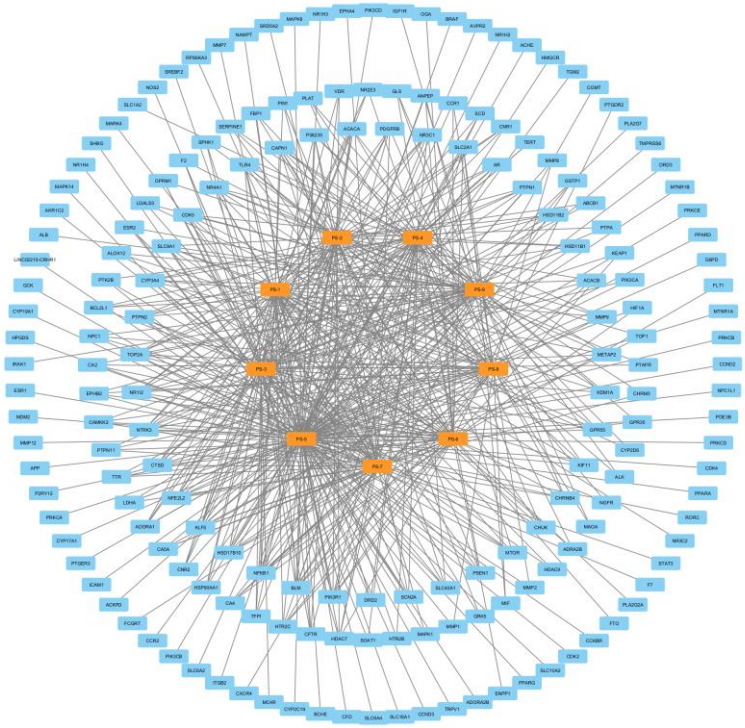


Figure S6: The compounds-targets network of *P. serrata* roots in the treatment of type 2 diabetes

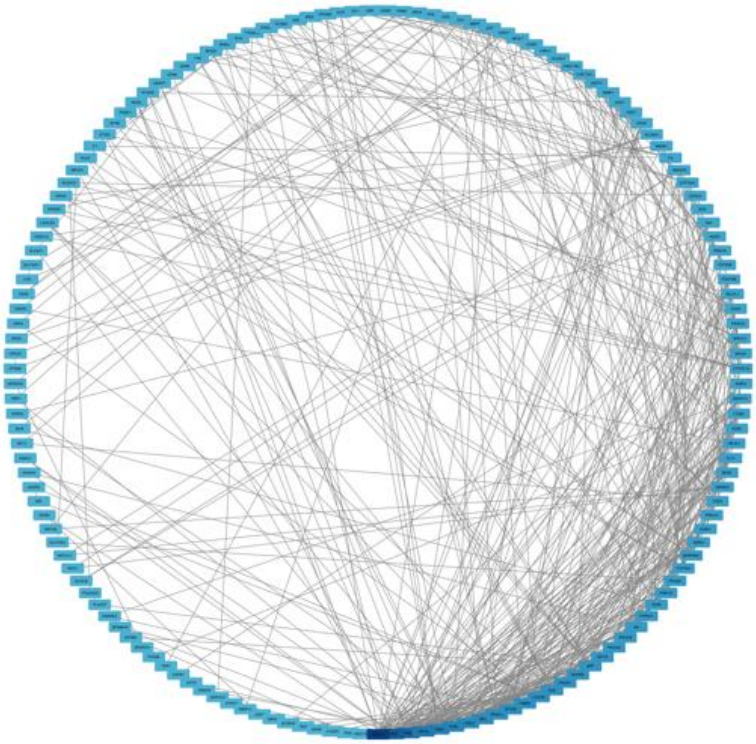


Figure S7: The protein-protein interaction (PPI) network

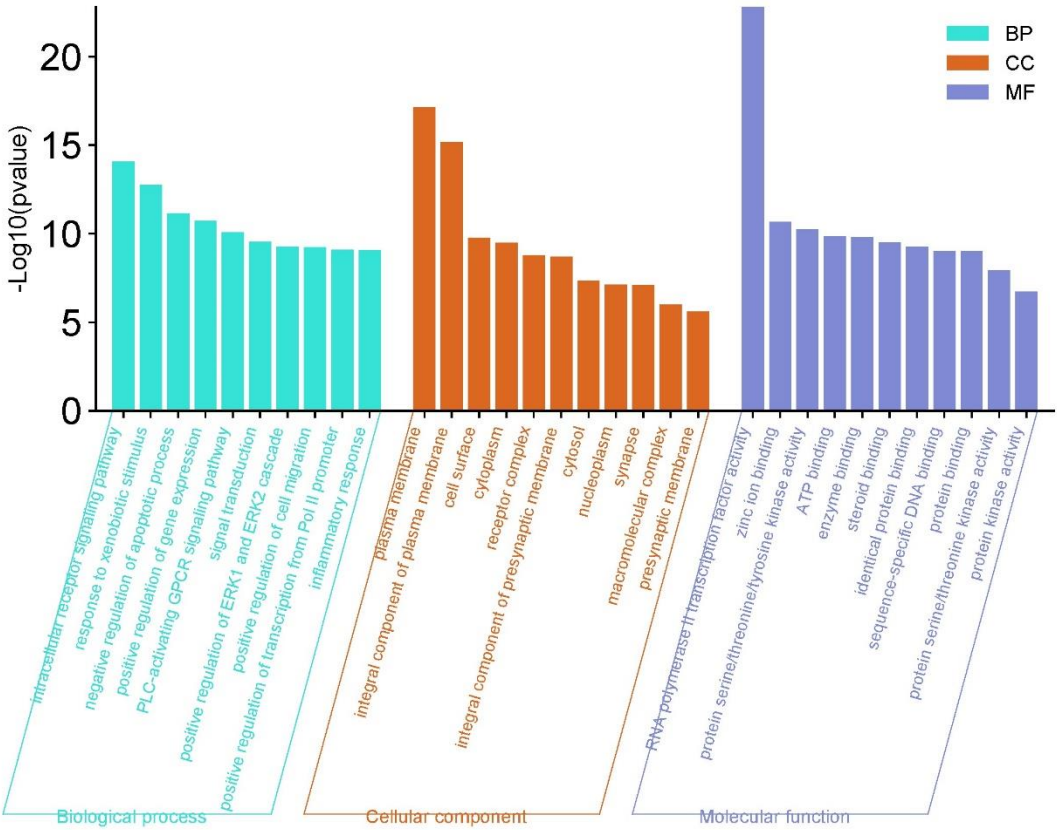


Figure S8: GO analysis of *P. serrata* roots in the treatment of type 2 diabetes through biological process (BP), cellular components (CC) and molecular functions (MF)

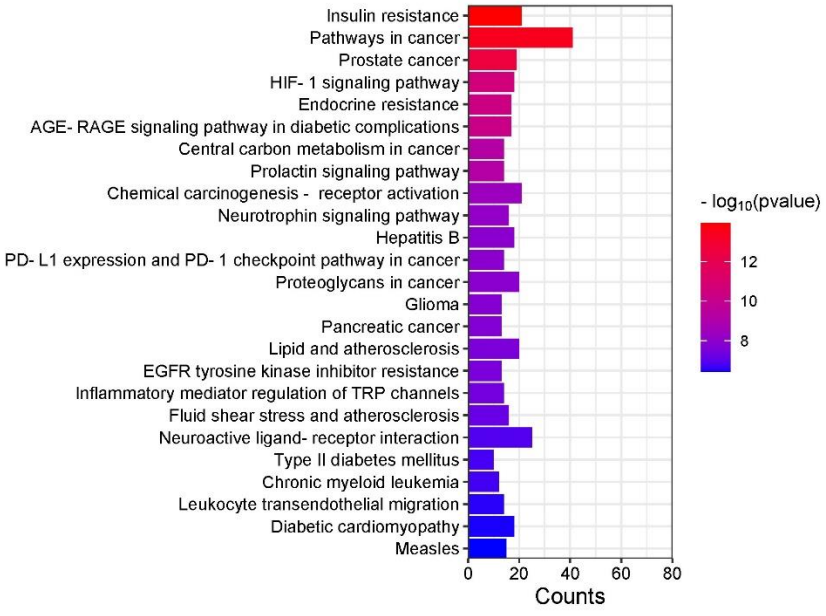


Figure S9: KEGG pathway enrichment analysis

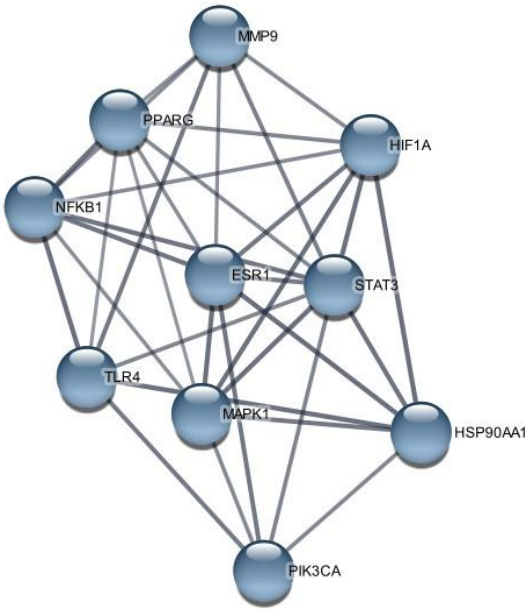


Figure S10: Subnetwork of the PPI network of 10 hub targets

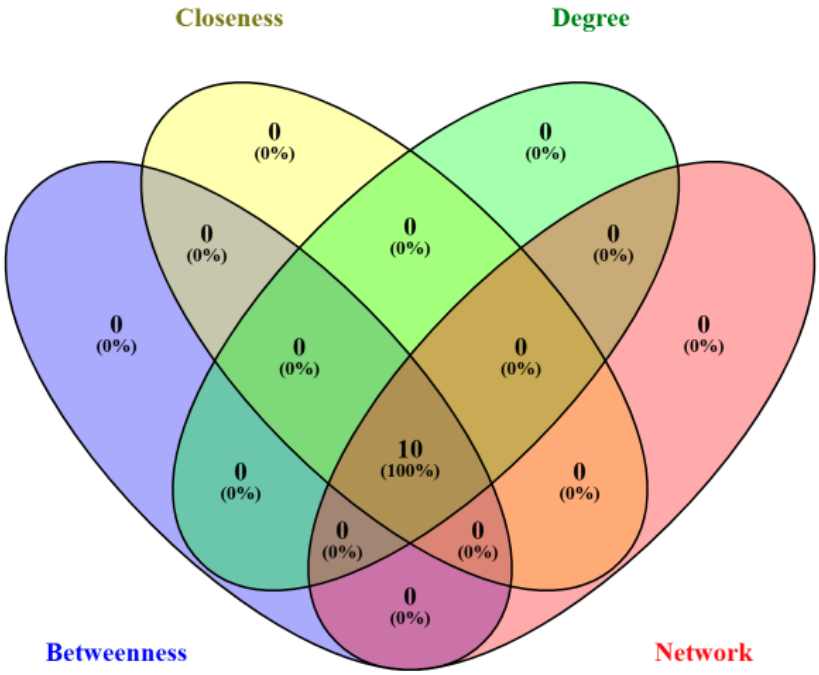


Figure S11:Venn diagram for determination of core targets

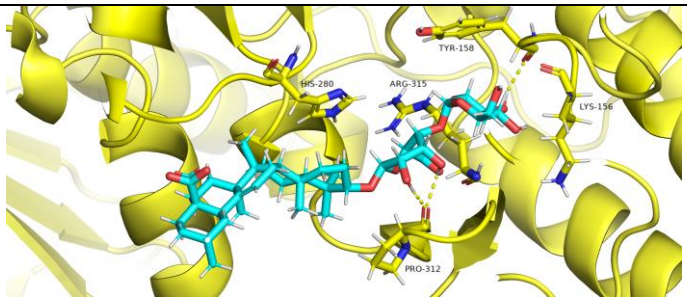
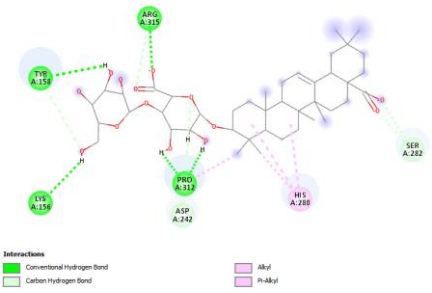
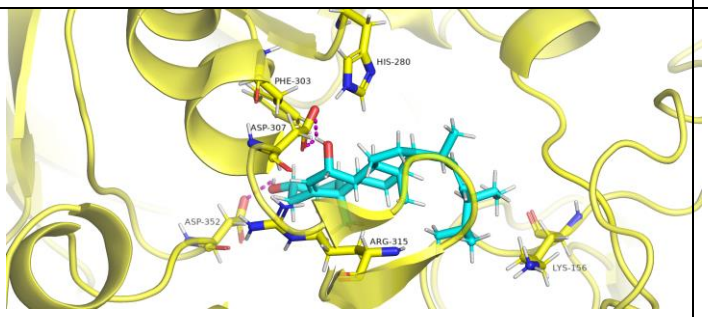
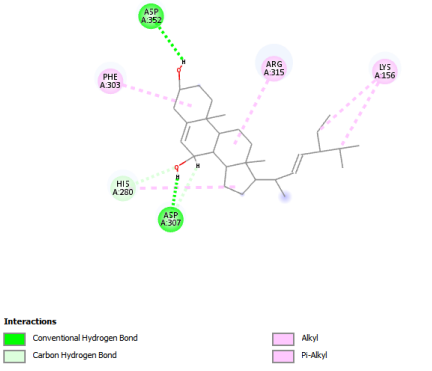
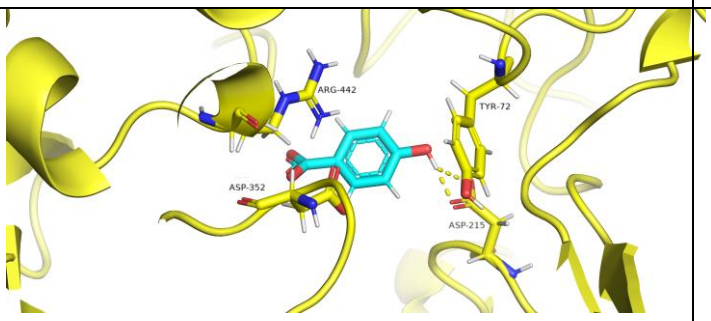
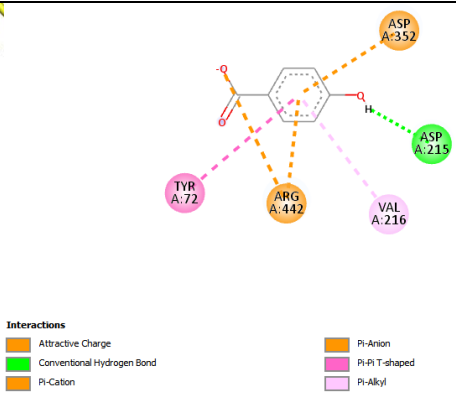
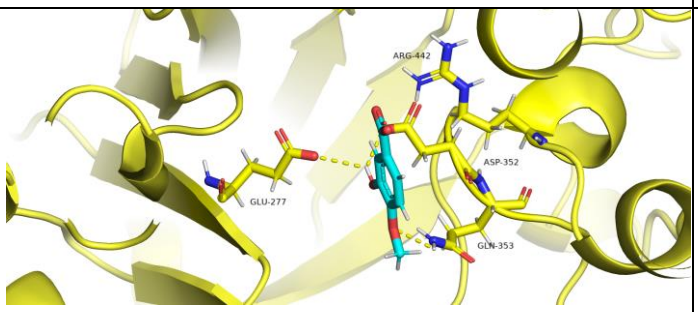
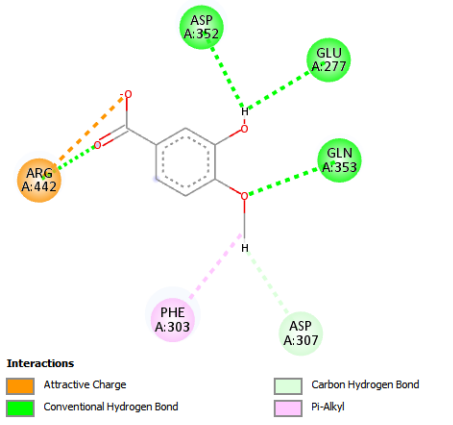
Table S1: Rank of the value of degree (k) among all chemical constituents

Chemical constituents	Degree (k)
1	52
2	50
3	56
4	49
5	112
6	46
7	45
8	46
9	47

Table S2: Core targets of *P. serrata* roots against type 2 diabetes

Gene Symbol	Uniprot ID	Description	Degree	Betweenness	Closeness	Network
STAT3	P40763	Signal transducer and activator of transcription 3	38.0	3808.6436	0.4758	24.3030
ESR1	P03372	Estrogen receptor	31.0	3352.3477	0.4673	16.7631
HSP90AA1	P07900	Heat shock protein HSP 90-alpha	29.0	1957.6998	0.4478	14.6751
HIF1A	Q16665	Hypoxia-inducible factor 1-alpha	24.0	2821.004	0.4438	11.1996
NFKB1	P19838	Nuclear factor NF-kappa-B p105 subunit	22.0	1162.8604	0.4360	10.1687
TLR4	Q5VZI9	Toll-like receptor 4	21.0	792.5919	0.4021	11.1065
MAPK1	P28482	Mitogen-activated protein kinase 1	20.0	1414.365	0.4178	10.0684
PIK3CA	P42336	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform	20.0	662.7659	0.3916	12.7180
MMP9	P14780	Matrix metalloproteinase-9	18.0	1141.2972	0.4144	10.1651
PPARG	Q15180	Peroxisome proliferator-activated receptor gamma	18.0	2080.3315	0.4202	6.8190

Table S3 : Molecular docking study

Compound	3D interaction	2D interaction
1		
5		
7		
8		

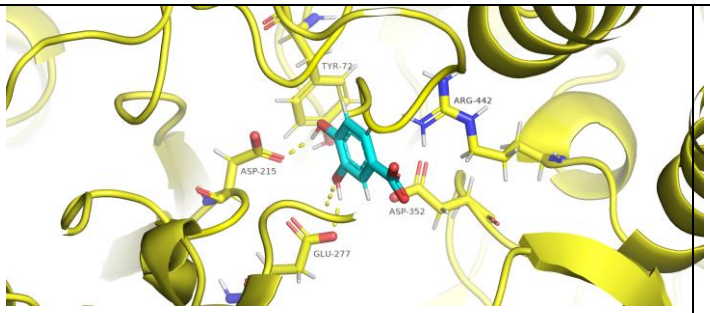
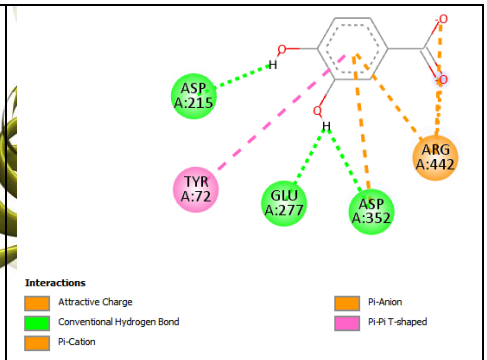
9		

Table S4: List of 184 potential targets

Target	Name	Annotation
P28845	HSD11B1	Corticosteroid 11-beta-dehydrogenase isozyme 1; Catalyzes reversibly the conversion of cortisol to the inactive metabolite cortisone. Catalyzes reversibly the conversion of 7-ketocholesterol to 7-beta-hydroxycholesterol. In intact cells, the reaction runs only in one direction, from 7-ketocholesterol to 7-beta- hydroxycholesterol (By similarity).
P80365	HSD11B2	Corticosteroid 11-beta-dehydrogenase isozyme 2; Catalyzes the conversion of cortisol to the inactive metabolite cortisone. Modulates intracellular glucocorticoid levels, thus protecting the nonselective mineralocorticoid receptor from occupation by glucocorticoids.
P10275	AR	Androgen receptor; Steroid hormone receptors are ligand-activated transcription factors that regulate eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Transcription factor activity is modulated by bound coactivator and corepressor proteins like ZBTB7A that recruits NCOR1 and NCOR2 to the androgen response elements/ARE on target genes, negatively regulating androgen receptor signaling and androgen-induced cell proliferation. Transcription activation is also down-regulated by NR0B2. Activated, but not phosphorylated, by HIPK3 and ZIPK/DA.
P04150	NR3C1	Glucocorticoid receptor; Receptor for glucocorticoids (GC). Has a dual mode of action: as a transcription factor that binds to glucocorticoid response elements (GRE), both for nuclear and mitochondrial DNA, and as a modulator of other transcription factors. Affects inflammatory responses, cellular proliferation and differentiation in target tissues. Involved in chromatin remodeling. Plays a role in rapid mRNA degradation by binding to the 5' UTR of target mRNAs and interacting with PNRC2 in a ligand- dependent manner which recruits the RNA helicase UPF1 and the mRNA-decapping enzyme D.
Q07817	BCL2L1	Bcl-2-like protein 1; Potent inhibitor of cell death. Inhibits activation of caspases. Appears to regulate cell death by blocking the voltage-dependent anion channel (VDAC) by binding to it and preventing the

		release of the caspase activator, CYC1, from the mitochondrial membrane. Also acts as a regulator of G2 checkpoint and progression to cytokinesis during mitosis. Isoform Bcl-X(S) promotes apoptosis.
P41595	HTR2B	5-hydroxytryptamine receptor 2B; G-protein coupled receptor for 5-hydroxytryptamine (serotonin). Also functions as a receptor for various ergot alkaloid derivatives and psychoactive substances. Ligand binding causes a conformation change that triggers signaling via guanine nucleotide-binding proteins (G proteins) and modulates the activity of down-stream effectors. Beta-arrestin family members inhibit signaling via G proteins and mediate activation of alternative signaling pathways.
P18089	ADRA2B	Alpha-2B adrenergic receptor; Alpha-2 adrenergic receptors mediate the catecholamine- induced inhibition of adenylate cyclase through the action of G proteins. The rank order of potency for agonists of this receptor is clonidine > norepinephrine > epinephrine = oxymetazoline > dopamine > p-tyramine = phenylephrine > serotonin > p-synephrine / p-octopamine. For antagonists, the rank order is yohimbine > chlorpromazine > phentolamine > mianserine > spiperone > prazosin > alprenolol > propanolol > pindolol; Belongs to the G-protein coupled receptor 1 family. Adrenergic receptor subfamily.
P14416	DRD2	D(2) dopamine receptor; Dopamine receptor whose activity is mediated by G proteins which inhibit adenylyl cyclase; Belongs to the G-protein coupled receptor 1 family.
P28335	HTR2C	5-hydroxytryptamine receptor 2C; G-protein coupled receptor for 5-hydroxytryptamine (serotonin). Also functions as a receptor for various drugs and psychoactive substances, including ergot alkaloid derivatives, 1-2,5,- dimethoxy-4-iodophenyl-2-aminopropane (DOI) and lysergic acid diethylamide (LSD). Ligand binding causes a conformation change that triggers signaling via guanine nucleotide-binding proteins (G proteins) and modulates the activity of down-stream effectors. Beta-arrestin family members inhibit signaling via G proteins and mediate activation of alternative signaling pathway.
P10635	CYP2D6	Cytochrome P450 2D6; A cytochrome P450 monooxygenase involved in the metabolism of fatty acids, steroids and retinoids. Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (NADPH--hemoprotein reductase). Catalyzes the epoxidation of double bonds of polyunsaturated fatty acids (PUFA). Metabolizes endocannabinoid arachidonoylethanolamide (anandamide) to 20-hydroxyeicosatetraenoic acid ethanolamide (20-HETE-EA) and 8,9-, 11,12-, and 14,15-epoxyei.
P14780	MMP9	67 kDa matrix metalloproteinase-9; May play an essential role in local proteolysis of the extracellular matrix and in leukocyte migration. Could play a role in bone osteoclastic resorption. Cleaves KiSS1 at a Gly-|-Leu bond. Cleaves type IV and type V collagen into

		large C-terminal three quarter fragments and shorter N-terminal one quarter fragments. Degrades fibronectin but not laminin or Pz-peptide. Belongs to the peptidase M10A family.
P18031	PTPN1	Tyrosine-protein phosphatase non-receptor type 1; Tyrosine-protein phosphatase which acts as a regulator of endoplasmic reticulum unfolded protein response. Mediates dephosphorylation of EIF2AK3/PERK; inactivating the protein kinase activity of EIF2AK3/PERK. May play an important role in CKII- and p60c-src-induced signal transduction cascades. May regulate the EFNA5-EPHA3 signaling pathway which modulates cell reorganization and cell-cell repulsion. May also regulate the hepatocyte growth factor receptor signaling pathway through dephosphorylation of MET.
P49768	PSEN1	Presenilin-1 CTF subunit; Catalytic subunit of the gamma-secretase complex, an endoprotease complex that catalyzes the intramembrane cleavage of integral membrane proteins such as Notch receptors and APP (amyloid- beta precursor protein). Requires the presence of the other members of the gamma-secretase complex for protease activity. Plays a role in Notch and Wnt signaling cascades and regulation of downstream processes via its role in processing key regulatory proteins, and by regulating cytosolic CTNNB1 levels. Stimulates cell-cell adhesion via its interaction with CDH1;
P25105	PTAFR	Platelet-activating factor receptor; Receptor for platelet activating factor, a chemotactic phospholipid mediator that possesses potent inflammatory, smooth-muscle contractile and hypotensive activity. Seems to mediate its action via a G protein that activates a phosphatidylinositol-calcium second messenger system. Belongs to the G-protein coupled receptor 1 family.
P00734	F2	Activation peptide fragment 1; Thrombin, which cleaves bonds after Arg and Lys, converts fibrinogen to fibrin and activates factors V, VII, VIII, XIII, and, in complex with thrombomodulin, protein C. Functions in blood homeostasis, inflammation and wound healing; Belongs to the peptidase S1 family.
Q15257	PTPA	Serine/threonine-protein phosphatase 2A activator; PPIases accelerate the folding of proteins. It catalyzes the cis-trans isomerization of proline imidic peptide bonds in oligopeptides. Acts as a regulatory subunit for serine/threonine- protein phosphatase 2A (PP2A) modulating its activity or substrate specificity, probably by inducing a conformational change in the catalytic subunit, a proposed direct target of the PPIase. Can reactivate inactive phosphatase PP2A-phosphatase methylesterase complexes (PP2A(i)) in presence of ATP and Mg(2+) (By similarity).
P51449	RORC	Nuclear receptor ROR-gamma; Nuclear receptor that binds DNA as a monomer to ROR response elements (RORE) containing a single core motif half-site 5'-AGGTCA-3' preceded by a short A-T-rich sequence. Key regulator of cellular differentiation, immunity, peripheral circadian rhythm as well as lipid, steroid, xenobiotics and glucose metabolism. Considered to have intrinsic transcriptional activity, have some natural ligands like oxysterols that act as

		agonists (25- hydroxycholesterol) or inverse agonists (7-oxygenated sterols), enhancing or repressing the transcriptional activity, respectively.
Q9UHC9	NPC1L1	NPC1-like intracellular cholesterol transporter 1; Plays a major role in cholesterol homeostasis. Is critical for the uptake of cholesterol across the plasma membrane of the intestinal enterocyte. Is the direct molecular target of ezetimibe, a drug that inhibits cholesterol absorption. Lack of activity leads to multiple lipid transport defects. The protein may have a function in the transport of multiple lipids and their homeostasis, and may play a critical role in regulating lipid metabolism. Acts as a negative regulator of NPC2 and down-regulates its expression and secretion by inhibit.
P04035	HMGCR	3-hydroxy-3-methylglutaryl-coenzyme A reductase; Transmembrane glycoprotein that is the rate-limiting enzyme in cholesterol biosynthesis as well as in the biosynthesis of nonsterol isoprenoids that are essential for normal cell function including ubiquinone and geranylgeranyl proteins.
Q13133	NR1H3	Oxysterols receptor LXR-alpha; Nuclear receptor that exhibits a ligand-dependent transcriptional activation activity. Interaction with retinoic acid receptor (RXR) shifts RXR from its role as a silent DNA-binding partner to an active ligand-binding subunit in mediating retinoid responses through target genes defined by LXRES (By similarity). LXRES are DR4-type response elements characterized by direct repeats of two similar hexanuclotide half-sites spaced by four nucleotides (By similarity). Plays an important role in the regulation of cholesterol homeostasis, regulating cholesterol up.
Q12772	SREBF2	Processed sterol regulatory element-binding protein 2; Transcriptional activator required for lipid homeostasis. Regulates transcription of the LDL receptor gene as well as the cholesterol and to a lesser degree the fatty acid synthesis pathway (By similarity). Binds the sterol regulatory element 1 (SRE-1) (5'- ATCACCCCAC-3') found in the flanking region of the LDRL and HMG-CoA synthase genes.
P04278	SHBG	Sex hormone-binding globulin; Functions as an androgen transport protein, but may also be involved in receptor mediated processes. Each dimer binds one molecule of steroid. Specific for 5-alpha-dihydrotestosterone, testosterone, and 17-beta-estradiol. Regulates the plasma metabolic clearance rate of steroid hormones by controlling their plasma concentration.
P11511	CYP19A1	Aromatase; A cytochrome P450 monooxygenase that catalyzes the conversion of C19 androgens, androst-4-ene-3,17-dione (androstenedione) and testosterone to the C18 estrogens, estrone and estradiol, respectively. Catalyzes three successive oxidations of C19 androgens: two conventional oxidations at C19 yielding 19-hydroxy and 19-oxo/19-aldehyde derivatives, followed by a third oxidative aromatization step that involves C1-beta hydrogen abstraction combined with cleavage of the C10-C19 bond to yield a phenolic A

		ring and formic acid.
P03372	ESR1	Estrogen receptor; Nuclear hormone receptor. The steroid hormones and their receptors are involved in the regulation of eukaryotic gene expression and affect cellular proliferation and differentiation in target tissues. Ligand-dependent nuclear transactivation involves either direct homodimer binding to a palindromic estrogen response element (ERE) sequence or association with other DNA-binding transcription factors, such as AP-1/c-Jun, c-Fos, ATF-2, Sp1 and Sp3, to mediate ERE- independent signaling.
Q92731	ESR2	Estrogen receptor beta; Nuclear hormone receptor. Binds estrogens with an affinity similar to that of ESR1, and activates expression of reporter genes containing estrogen response elements (ERE) in an estrogen-dependent manner. Isoform beta-cx lacks ligand binding ability and has no or only very low ere binding activity resulting in the loss of ligand-dependent transactivation ability. DNA-binding by ESR1 and ESR2 is rapidly lost at 37 degrees Celsius in the absence of ligand while in the presence of 17 beta-estradiol and 4-hydroxy-tamoxifen loss in DNA-binding at elevated temperature.
P05093	CYP17A1	Steroid 17-alpha-hydroxylase/17,20 lyase; A cytochrome P450 monooxygenase involved in corticoid and androgen biosynthesis. Catalyzes 17-alpha hydroxylation of C21 steroids, which is common for both pathways. A second oxidative step, required only for androgen synthesis, involves an acyl-carbon cleavage. The 17-alpha hydroxy intermediates, as part of adrenal glucocorticoids biosynthesis pathway, are precursors of cortisol (Probable). Hydroxylates steroid hormones, pregnenolone and progesterone to form 17-alpha hydroxy metabolites, followed by the cleavage of the C17-C20 bond to form C1.
P23975	SLC6A2	Sodium-dependent noradrenaline transporter; Amine transporter. Terminates the action of noradrenaline by its high affinity sodium-dependent reuptake into presynaptic terminals. Belongs to the sodium:neurotransmitter symporter (SNF) (TC 2.A.22) family. SLC6A2 subfamily.
P33261	CYP2C19	Cytochrome P450 2C19; A cytochrome P450 monooxygenase involved in the metabolism of polyunsaturated fatty acids (PUFA). Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (NADPH--hemoprotein reductase). Catalyzes the hydroxylation of carbon-hydrogen bonds. Hydroxylates PUFA specifically at the omega-1 position. Catalyzes the epoxidation of double bonds of PUFA. Also metabolizes plant monoterpenes such as limonene.
P31645	SLC6A4	Sodium-dependent serotonin transporter; Serotonin transporter whose primary function in the central nervous system involves the regulation of serotonergic signaling via transport of serotonin molecules from the synaptic cleft back into the pre-synaptic terminal for re-utilization. Plays a key role in mediating regulation of the availability of serotonin to other receptors of serotonergic systems.

		Terminates the action of serotonin and recycles it in a sodium-dependent manner.
P37231	PPARG	Peroxisome proliferator-activated receptor gamma; Nuclear receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids. Once activated by a ligand, the nuclear receptor binds to DNA specific PPAR response elements (PPRE) and modulates the transcription of its target genes, such as acyl-CoA oxidase. It therefore controls the peroxisomal beta-oxidation pathway of fatty acids. Key regulator of adipocyte differentiation and glucose homeostasis. ARF6 acts as a key regulator of the tissue-specific adipocyte P2 (aP2) enhancer.
Q07869	PPARA	Peroxisome proliferator-activated receptor alpha; Ligand-activated transcription factor. Key regulator of lipid metabolism. Activated by the endogenous ligand 1-palmitoyl-2-oleoyl-sn- glycerol-3-phosphocholine (16:0/18:1-GPC). Activated by oleylethanolamide, a naturally occurring lipid that regulates satiety. Receptor for peroxisome proliferators such as hypolipidemic drugs and fatty acids. Regulates the peroxisomal beta-oxidation pathway of fatty acids. Functions as transcription activator for the ACOX1 and P450 genes.
P11413	G6PD	Glucose-6-phosphate 1-dehydrogenase; Cytosolic glucose-6-phosphate dehydrogenase that catalyzes the first and rate-limiting step of the oxidative branch within the pentose phosphate pathway/shunt, an alternative route to glycolysis for the dissimilation of carbohydrates and a major source of reducing power and metabolic intermediates for fatty acid and nucleic acid biosynthetic processes.
P22303	ACHE	Acetylcholinesterase; Terminates signal transduction at the neuromuscular junction by rapid hydrolysis of the acetylcholine released into the synaptic cleft. Role in neuronal apoptosis. Belongs to the type-B carboxylesterase/lipase family.
P35228	NOS2	Nitric oxide synthase, inducible; Produces nitric oxide (NO) which is a messenger molecule with diverse functions throughout the body. In macrophages, NO mediates tumoricidal and bactericidal actions. Also has nitrosylase activity and mediates cysteine S-nitrosylation of cytoplasmic target proteins such PTGS2/COX2 (By similarity). As component of the iNOS-S100A8/9 transnitrosylase complex involved in the selective inflammatory stimulus-dependent S-nitrosylation of GAPDH on 'Cys-247' implicated in regulation of the GAIT complex activity and probably multiple targets including ANXA5, EZR.
Q96RI1	NR1H4	Bile acid receptor; Ligand-activated transcription factor. Receptor for bile acids (BAs) such as chenodeoxycholic acid (CDCA), lithocholic acid, deoxycholic acid (DCA) and allocholic acid (ACA). Plays a essential role in BA homeostasis through the regulation of genes involved in BA synthesis, conjugation and enterohepatic circulation. Also regulates lipid and glucose homeostasis and is involved innate immune response. The FXR-RXR heterodimer binds

		predominantly to farnesoid X receptor response elements (FXREs) containing two inverted repeats of the consensus sequence 5'-AGGTCA-3'.
Q00987	MDM2	E3 ubiquitin-protein ligase Mdm2; E3 ubiquitin-protein ligase that mediates ubiquitination of p53/TP53, leading to its degradation by the proteasome. Inhibits p53/TP53- and p73/TP73-mediated cell cycle arrest and apoptosis by binding its transcriptional activation domain. Also acts as a ubiquitin ligase E3 toward itself and ARRB1. Permits the nuclear export of p53/TP53. Promotes proteasome-dependent ubiquitin-independent degradation of retinoblastoma RB1 protein. Inhibits DAXX-mediated apoptosis by inducing its ubiquitination and degradation. Component of the TRIM28/KAP1-MDM2-p53/TP53.
P43115	PTGER3	Prostaglandin E2 receptor EP3 subtype; Receptor for prostaglandin E2 (PGE2). The activity of this receptor can couple to both the inhibition of adenylate cyclase mediated by G(i) proteins, and to an elevation of intracellular calcium. Required for normal development of fever in response to pyrinogens, including IL1B, prostaglandin E2 and bacterial lipopolysaccharide (LPS). Required for normal potentiation of platelet aggregation by prostaglandin E2, and thus plays a role in the regulation of blood coagulation.
P53985	SLC16A1	Monocarboxylate transporter 1; Proton-coupled monocarboxylate transporter. Catalyzes the rapid transport across the plasma membrane of many monocarboxylates such as lactate, pyruvate, branched-chain oxo acids derived from leucine, valine and isoleucine, and the ketone bodies acetoacetate, beta-hydroxybutyrate and acetate. Depending on the tissue and on cicumstances, mediates the import or export of lactic acid and ketone bodies. Required for normal nutrient assimilation, increase of white adipose tissue and body weight gain when on a high-fat diet.
Q12908	SLC10A2	Ileal sodium/bile acid cotransporter; Plays a critical role in the sodium-dependent reabsorption of bile acids from the lumen of the small intestine. Plays a key role in cholesterol metabolism; Belongs to the bile acid:sodium symporter (BASS) (TC 2.A.28) family.
P55055	NR1H2	Oxysterols receptor LXR-beta; Nuclear receptor that exhibits a ligand-dependent transcriptional activation activity. Binds preferentially to double-stranded oligonucleotide direct repeats having the consensus half-site sequence 5'-AGGTCA-3' and 4-nt spacing (DR-4). Regulates cholesterol uptake through MYLIP-dependent ubiquitination of LDLR, VLDLR and LRP8; DLDLR and LRP8. Interplays functionally with RORA for the regulation of genes involved in liver metabolism (By similarity). Plays an anti-inflammatory role during the hepatic acute phase response by acting as a corepressor.
P18507	GABRG2	Gamma-aminobutyric acid receptor subunit gamma-2; Ligand-gated chloride channel which is a component of the heteropentameric receptor for GABA, the major inhibitory neurotransmitter in the brain. Plays an important role in the formation of functional

		inhibitory GABAergic synapses in addition to mediating synaptic inhibition as a GABA-gated ion channel. The gamma2 subunit is necessary but not sufficient for a rapid formation of active synaptic contacts and the synaptogenic effect of this subunit is influenced by the type of alpha and beta subunits present in the receptor pentamer.
P05067	APP	Gamma-secretase C-terminal fragment 50; Functions as a cell surface receptor and performs physiological functions on the surface of neurons relevant to neurite growth, neuronal adhesion and axonogenesis. Interaction between APP molecules on neighboring cells promotes synaptogenesis. Involved in cell mobility and transcription regulation through protein-protein interactions. Can promote transcription activation through binding to APBB1-KAT5 and inhibits Notch signaling through interaction with Numb. Couples to apoptosis- inducing pathways such as those mediated by G(O) and JIP.
P30542	ADORA1	Adenosine receptor A1; Receptor for adenosine. The activity of this receptor is mediated by G proteins which inhibit adenylyl cyclase; Belongs to the G-protein coupled receptor 1 family.
P30281	CCND3	G1/S-specific cyclin-D3; Regulatory component of the cyclin D3-CDK4 (DC) complex that phosphorylates and inhibits members of the retinoblastoma (RB) protein family including RB1 and regulates the cell-cycle during G(1)/S transition. Phosphorylation of RB1 allows dissociation of the transcription factor E2F from the RB/E2F complex and the subsequent transcription of E2F target genes which are responsible for the progression through the G(1) phase. Hypophosphorylates RB1 in early G(1) phase. Cyclin D-CDK4 complexes are major integrators of various mitogenenic and antimitogenic signals.
P11802	CDK4	Cyclin-dependent kinase 4; Ser/Thr-kinase component of cyclin D-CDK4 (DC) complexes that phosphorylate and inhibit members of the retinoblastoma (RB) protein family including RB1 and regulate the cell-cycle during G(1)/S transition. Phosphorylation of RB1 allows dissociation of the transcription factor E2F from the RB/E2F complexes and the subsequent transcription of E2F target genes which are responsible for the progression through the G(1) phase. Hypophosphorylates RB1 in early G(1) phase. Cyclin D-CDK4 complexes are major integrators of various mitogenenic and antimitogenic signals.
P30279	CCND2	G1/S-specific cyclin-D2; Regulatory component of the cyclin D2-CDK4 (DC) complex that phosphorylates and inhibits members of the retinoblastoma (RB) protein family including RB1 and regulates the cell-cycle during G(1)/S transition. Phosphorylation of RB1 allows dissociation of the transcription factor E2F from the RB/E2F complex and the subsequent transcription of E2F target genes which are responsible for the progression through the G(1) phase. Hypophosphorylates RB1 in early G(1) phase. Cyclin D-CDK4 complexes are major integrators of various mitogenenic and antimitogenic signals.

Q03181	PPARD	Peroxisome proliferator-activated receptor delta; Ligand-activated transcription factor. Receptor that binds peroxisome proliferators such as hypolipidemic drugs and fatty acids. Has a preference for poly-unsaturated fatty acids, such as gamma- linoleic acid and eicosapentanoic acid. Once activated by a ligand, the receptor binds to promoter elements of target genes. Regulates the peroxisomal beta-oxidation pathway of fatty acids. Functions as transcription activator for the acyl-CoA oxidase gene. Decreases expression of NPC1L1 once activated by a ligand.
P52732	KIF11	Kinesin-like protein KIF11; Motor protein required for establishing a bipolar spindle during mitosis. Required in non-mitotic cells for transport of secretory proteins from the Golgi complex to the cell surface; Belongs to the TRAFAC class myosin-kinesin ATPase superfamily. Kinesin family. BimC subfamily.
O60760	HPGDS	Hematopoietic prostaglandin D synthase; Bifunctional enzyme which catalyzes both the conversion of PGH2 to PGD2, a prostaglandin involved in smooth muscle contraction/relaxation and a potent inhibitor of platelet aggregation, and the conjugation of glutathione with a wide range of aryl halides and organic isothiocyanates. Also exhibits low glutathione-peroxidase activity towards cumene hydroperoxide. Belongs to the GST superfamily. Sigma family.
P34998	CRHR1	Corticotropin-releasing factor receptor 1; G-protein coupled receptor for CRH (corticotropin-releasing factor) and UCN (urocortin). Has high affinity for CRH and UCN. Ligand binding causes a conformation change that triggers signaling via guanine nucleotide-binding proteins (G proteins) and down-stream effectors, such as adenylate cyclase. Promotes the activation of adenylate cyclase, leading to increased intracellular cAMP levels. Inhibits the activity of the calcium channel CACNA1H. Required for normal embryonic development of the adrenal gland and for normal hormonal responses to something.
P05362	ICAM1	Intercellular adhesion molecule 1; ICAM proteins are ligands for the leukocyte adhesion protein LFA-1 (integrin alpha-L/beta-2). During leukocyte trans-endothelial migration, ICAM1 engagement promotes the assembly of endothelial apical cups through ARHGEF26/SGEF and RHOG activation. (Microbial infection) Acts as a receptor for Coxsackievirus A21 capsid proteins.
P05107	ITGB2	Integrin beta-2; Integrin ITGAL/ITGB2 is a receptor for ICAM1, ICAM2, ICAM3 and ICAM4. Integrin ITGAL/ITGB2 is also a receptor for the secreted form of ubiquitin-like protein ISG15; the interaction is mediated by ITGAL. Integrins ITGAM/ITGB2 and ITGAX/ITGB2 are receptors for the iC3b fragment of the third complement component and for fibrinogen. Integrin ITGAX/ITGB2 recognizes the sequence G-P-R in fibrinogen alpha-chain. Integrin ITGAM/ITGB2 recognizes P1 and P2 peptides of fibrinogen gamma chain. Integrin ITGAM/ITGB2 is also a receptor for factor X.
Q8NER1	TRPV1	Transient receptor potential cation channel subfamily V member 1;

		Ligand-activated non-selective calcium permeant cation channel involved in detection of noxious chemical and thermal stimuli. Seems to mediate proton influx and may be involved in intracellular acidosis in nociceptive neurons. Involved in mediation of inflammatory pain and hyperalgesia. Sensitized by a phosphatidylinositol second messenger system activated by receptor tyrosine kinases, which involves PKC isozymes and PCL. Activation by vanilloids, like capsaicin, and temperatures higher than 42 degrees Celsius.
Q05655	PRKCD	Protein kinase C delta type regulatory subunit; Calcium-independent, phospholipid- and diacylglycerol (DAG)- dependent serine/threonine-protein kinase that plays contrasting roles in cell death and cell survival by functioning as a pro-apoptotic protein during DNA damage-induced apoptosis, but acting as an anti-apoptotic protein during cytokine receptor-initiated cell death, is involved in tumor suppression as well as survival of several cancers, is required for oxygen radical production by NADPH oxidase and acts as positive or negative regulator in platelet functional responses.
P05771	PRKCB	Protein kinase C beta type; Calcium-activated, phospholipid- and diacylglycerol (DAG)- dependent serine/threonine-protein kinase involved in various cellular processes such as regulation of the B-cell receptor (BCR) signalosome, oxidative stress-induced apoptosis, androgen receptor-dependent transcription regulation, insulin signaling and endothelial cells proliferation. Plays a key role in B-cell activation by regulating BCR- induced NF-kappa-B activation. Mediates the activation of the canonical NF-kappa-B pathway (NFKB1) by direct phosphorylation of CARD11/CARMA1 at 'Ser-559'.
Q02156	PRKCE	Protein kinase C epsilon type; Calcium-independent, phospholipid- and diacylglycerol (DAG)- dependent serine/threonine-protein kinase that plays essential roles in the regulation of multiple cellular processes linked to cytoskeletal proteins, such as cell adhesion, motility, migration and cell cycle, functions in neuron growth and ion channel regulation, and is involved in immune response, cancer cell invasion and regulation of apoptosis.
P30518	AVPR2	Vasopressin V2 receptor; Receptor for arginine vasopressin. The activity of this receptor is mediated by G proteins which activate adenylate cyclase. Involved in renal water reabsorption; Belongs to the G-protein coupled receptor 1 family. Vasopressin/oxytocin receptor subfamily.
Q16539	MAPK14	Mitogen-activated protein kinase 14; Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK14 is one of the four p38 MAPKs which play an important role in the cascades of cellular responses evoked by extracellular stimuli such as proinflammatory cytokines or physical stress leading to direct activation of transcription factors. Accordingly, p38 MAPKs phosphorylate a broad range of proteins and it has been estimated that they may have approximately 200 to

		300 substrates each.
P25106	ACKR3	Atypical chemokine receptor 3; Atypical chemokine receptor that controls chemokine levels and localization via high-affinity chemokine binding that is uncoupled from classic ligand-driven signal transduction cascades, resulting instead in chemokine sequestration, degradation, or transcytosis. Also known as interceptor (internalizing receptor) or chemokine-scavenging receptor or chemokine decoy receptor. Acts as a receptor for chemokines CXCL11 and CXCL12/SDF1. Chemokine binding does not activate G-protein- mediated signal transduction.
P06276	BCHE	Cholinesterase; Esterase with broad substrate specificity. Contributes to the inactivation of the neurotransmitter acetylcholine. Can degrade neurotoxic organophosphate esters; Belongs to the type-B carboxylesterase/lipase family.
P29275	ADORA2B	Adenosine receptor A2b; Receptor for adenosine. The activity of this receptor is mediated by G proteins which activate adenylyl cyclase.
P24941	CDK2	Cyclin-dependent kinase 2; Serine/threonine-protein kinase involved in the control of the cell cycle; essential for meiosis, but dispensable for mitosis. Phosphorylates CTNNB1, USP37, p53/TP53, NPM1, CDK7, RB1, BRCA2, MYC, NPAT, EZH2. Triggers duplication of centrosomes and DNA. Acts at the G1-S transition to promote the E2F transcriptional program and the initiation of DNA synthesis, and modulates G2 progression; controls the timing of entry into mitosis/meiosis by controlling the subsequent activation of cyclin B/CDK1 by phosphorylation, and coordinates the activation of cyclin B/CDK.
P28482	MAPK1	Mitogen-activated protein kinase 1; Serine/threonine kinase which acts as an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. They participate also in a signaling cascade initiated by activated KIT and KITLG/SCF. Depending on the cellular context, the MAPK/ERK cascade mediates diverse biological functions such as cell growth, adhesion, survival and differentiation through the regulation of transcription, translation, cytoskeletal rearrangements.
P32246	CCR1	C-C chemokine receptor type 1; Receptor for a C-C type chemokine. Binds to MIP-1-alpha, MIP- 1-delta, RANTES, and MCP-3 and, less efficiently, to MIP-1-beta or MCP- 1 and subsequently transduces a signal by increasing the intracellular calcium ions level. Responsible for affecting stem cell proliferation.
O75469	NR1I2	Nuclear receptor subfamily 1 group I member 2; Nuclear receptor that binds and is activated by variety of endogenous and xenobiotic compounds. Transcription factor that activates the transcription of multiple genes involved in the metabolism and secretion of potentially harmful xenobiotics, drugs and endogenous compounds. Activated by the antibiotic rifampicin and various plant metabolites, such as hyperforin, guggulipid, colupulone, and isoflavones. Response to specific ligands is species-specific. Activated by

		naturally occurring steroids, such as pregnenolone and progesterone.
Q13093	PLA2G7	Platelet-activating factor acetylhydrolase; Modulates the action of platelet-activating factor (PAF) by hydrolyzing the sn-2 ester bond to yield the biologically inactive lyso-PAF. Has a specificity for substrates with a short residue at the sn-2 position. It is inactive against long-chain phospholipids.
P15056	BRAF	Serine/threonine-protein kinase B-raf; Protein kinase involved in the transduction of mitogenic signals from the cell membrane to the nucleus (Probable). Phosphorylates MAP2K1, and thereby activates the MAP kinase signal transduction pathway. May play a role in the postsynaptic responses of hippocampal neurons ; Belongs to the protein kinase superfamily. TKL Ser/Thr protein kinase family. RAF subfamily.
P45983	MAPK8	Mitogen-activated protein kinase 8; Serine/threonine-protein kinase involved in various processes such as cell proliferation, differentiation, migration, transformation and programmed cell death. Extracellular stimuli such as proinflammatory cytokines or physical stress stimulate the stress- activated protein kinase/c-Jun N-terminal kinase (SAP/JNK) signaling pathway. In this cascade, two dual specificity kinases MAP2K4/MKK4 and MAP2K7/MKK7 phosphorylate and activate MAPK8/JNK1. In turn, MAPK8/JNK1 phosphorylates a number of transcription factors, primarily components of AP-1 such as J.
P00746	CFD	Complement factor D; Factor D cleaves factor B when the latter is complexed with factor C3b, activating the C3bbb complex, which then becomes the C3 convertase of the alternate pathway. Its function is homologous to that of C1s in the classical pathway; Belongs to the peptidase S1 family.
P32239	CCKBR	Gastrin/cholecystokinin type B receptor; Receptor for gastrin and cholecystokinin. The CCK-B receptors occur throughout the central nervous system where they modulate anxiety, analgesia, arousal, and neuroleptic activity. This receptor mediates its action by association with G proteins that activate a phosphatidylinositol-calcium second messenger system; Belongs to the G-protein coupled receptor 1 family.
P48039	MTNR1A	Melatonin receptor type 1A; High affinity receptor for melatonin. Likely to mediate the reproductive and circadian actions of melatonin. The activity of this receptor is mediated by pertussis toxin sensitive G proteins that inhibit adenylate cyclase activity; Belongs to the G-protein coupled receptor 1 family.
P49286	MTNR1B	Melatonin receptor type 1B; High affinity receptor for melatonin. Likely to mediate the reproductive and circadian actions of melatonin. The activity of this receptor is mediated by pertussis toxin sensitive G proteins that inhibit adenylate cyclase activity.
P00918	CA2	Carbonic anhydrase 2; Essential for bone resorption and osteoclast differentiation (By similarity). Reversible hydration of carbon dioxide. Can hydrate cyanamide to urea. Involved in the regulation of fluid secretion into the anterior chamber of the eye. Contributes to

		intracellular pH regulation in the duodenal upper villous epithelium during proton- coupled peptide absorption. Stimulates the chloride-bicarbonate exchange activity of SLC26A6.
P35218	CA5A	Carbonic anhydrase 5A, mitochondrial; Reversible hydration of carbon dioxide. Low activity.
P22748	CA4	Carbonic anhydrase 4; Reversible hydration of carbon dioxide. May stimulate the sodium/bicarbonate transporter activity of SLC4A4 that acts in pH homeostasis. It is essential for acid overload removal from the retina and retina epithelium, and acid release in the choriocapillaris in the choroid; Belongs to the alpha-carbonic anhydrase family.
O60502	OGA	Protein O-GlcNAcase; [Isoform 1]: Cleaves GlcNAc but not GalNAc from O- glycosylated proteins. Can use p-nitrophenyl-beta-GlcNAc and 4- methylumbelliferone-GlcNAc as substrates but not p-nitrophenyl-beta- GalNAc or p-nitrophenyl-alpha-GlcNAc (in vitro). Does not bind acetyl-CoA and does not have histone acetyltransferase activity.
P09467	FBP1	Fructose-1,6-bisphosphatase 1; Catalyzes the hydrolysis of fructose 1,6-bisphosphate to fructose 6-phosphate in the presence of divalent cations, acting as a rate-limiting enzyme in gluconeogenesis. Plays a role in regulating glucose sensing and insulin secretion of pancreatic beta-cells. Appears to modulate glycerol gluconeogenesis in liver. Important regulator of appetite and adiposity; increased expression of the protein in liver after nutrient excess increases circulating satiety hormones and reduces appetite-stimulating neuropeptides and thus seems to provide a feedback mechanism.
P05121	SERPINE1	Plasminogen activator inhibitor 1; Serine protease inhibitor. Inhibits TMPRSS7. Is a primary inhibitor of tissue-type plasminogen activator (PLAT) and urokinase-type plasminogen activator (PLAU). As PLAT inhibitor, it is required for fibrinolysis down-regulation and is responsible for the controlled degradation of blood clots. As PLAU inhibitor, it is involved in the regulation of cell adhesion and spreading. Acts as a regulator of cell migration, independently of its role as protease inhibitor. It is required for stimulation of keratinocyte migration during cutaneous injury repair.
P02766	TTR	Transthyretin; Thyroid hormone-binding protein. Probably transports thyroxine from the bloodstream to the brain.
Q9C0B1	FTO	Alpha-ketoglutarate-dependent dioxygenase FTO; RNA demethylase that mediates oxidative demethylation of different RNA species, such as mRNAs, tRNAs and snRNAs, and acts as a regulator of fat mass, adipogenesis and energy homeostasis. Specifically demethylates N(6)- methyladenosine (m6A) RNA, the most prevalent internal modification of messenger RNA (mRNA) in higher eukaryotes. M6A demethylation by FTO affects mRNA expression and stability. Also able to demethylate m6A in U6 small nuclear RNA (snRNA). Mediates demethylation of N(6),2'-O-dimethyladenosine cap (m6A(m)), by demethylating.
P08138	NGFR	Tumor necrosis factor receptor superfamily member 16; Low affinity

		receptor which can bind to NGF, BDNF, NTF3, and NTF4. Forms a heterodimeric receptor with SORCS2 that binds the precursor forms of NGF, BDNF and NTF3 with high affinity, and has much lower affinity for mature NGF and BDNF. Plays an important role in differentiation and survival of specific neuronal populations during development (By similarity). Can mediate cell survival as well as cell death of neural cells. Plays a role in the inactivation of RHOA. Plays a role in the regulation of the translocation of GLUT4.
Q9Y5Y4	PTGDR2	Prostaglandin D2 receptor 2; Receptor for prostaglandin D2 (PGD2). Coupled to the G(i)- protein. Receptor activation may result in pertussis toxin-sensitive decreases in cAMP levels and Ca(2+) mobilization. PI3K signaling is also implicated in mediating PTGDR2 effects. PGD2 induced receptor internalization. CRTH2 internalization can be regulated by diverse kinases such as, PKC, PKA, GRK2, GPRK5/GRK5 and GRK6. Receptor activation is responsible, at least in part, in immune regulation and allergic/inflammation responses.
P31213	SRD5A2	3-oxo-5-alpha-steroid 4-dehydrogenase 2; Converts testosterone (T) into 5-alpha-dihydrotestosterone (DHT) and progesterone or corticosterone into their corresponding 5- alpha-3-oxosteroids. It plays a central role in sexual differentiation and androgen physiology.
P52895	AKR1C2	Aldo-keto reductase family 1 member C2; Works in concert with the 5-alpha/5-beta-steroid reductases to convert steroid hormones into the 3-alpha/5-alpha and 3-alpha/5- beta-tetrahydrosteroids. Catalyzes the inactivation of the most potent androgen 5-alpha-dihydrotestosterone (5-alpha-DHT) to 5-alpha- androstane-3-alpha,17-beta-diol (3-alpha-diol). Has a high bile-binding ability.
P00338	LDHA	Lactate dehydrogenase A; Belongs to the LDH/MDH superfamily. LDH family.
P03956	MMP1	22 kDa interstitial collagenase; Cleaves collagens of types I, II, and III at one site in the helical domain. Also cleaves collagens of types VII and X. In case of HIV infection, interacts and cleaves the secreted viral Tat protein, leading to a decrease in neuronal Tat's mediated neurotoxicity.
P08253	MMP2	72 kDa type IV collagenase; Ubiquitinous metalloproteinase that is involved in diverse functions such as remodeling of the vasculature, angiogenesis, tissue repair, tumor invasion, inflammation, and atherosclerotic plaque rupture. As well as degrading extracellular matrix proteins, can also act on several nonmatrix proteins such as big endothelial 1 and beta- type CGRP promoting vasoconstriction. Also cleaves KISS at a Gly-|-Leu bond. Appears to have a role in myocardial cell death pathways. Contributes to myocardial oxidative stress by regulating the activity of GSK3beta.
P22894	MMP8	Neutrophil collagenase; Can degrade fibrillar type I, II, and III collagens; Belongs to the peptidase M10A family.
P21964	COMT	Catechol O-methyltransferase; Catalyzes the O-methylation, and thereby the inactivation, of catecholamine neurotransmitters and

		catechol hormones. Also shortens the biological half-lives of certain neuroactive drugs, like L-DOPA, alpha-methyl DOPA and isoproterenol; Belongs to the class I-like SAM-binding methyltransferase superfamily. Cation-dependent O-methyltransferase family.
P08069	IGF1R	Insulin-like growth factor 1 receptor alpha chain; Receptor tyrosine kinase which mediates actions of insulin- like growth factor 1 (IGF1). Binds IGF1 with high affinity and IGF2 and insulin (INS) with a lower affinity. The activated IGF1R is involved in cell growth and survival control. IGF1R is crucial for tumor transformation and survival of malignant cell. Ligand binding activates the receptor kinase, leading to receptor autophosphorylation, and tyrosines phosphorylation of multiple substrates, that function as signaling adapter proteins including, the insulin-receptor substrates.
Q9UM73	ALK	ALK tyrosine kinase receptor; Neuronal receptor tyrosine kinase that is essentially and transiently expressed in specific regions of the central and peripheral nervous systems and plays an important role in the genesis and differentiation of the nervous system. Transduces signals from ligands at the cell surface, through specific activation of the mitogen- activated protein kinase (MAPK) pathway. Phosphorylates almost exclusively at the first tyrosine of the Y-x-x-x-Y-Y motif. Following activation by ligand, ALK induces tyrosine phosphorylation of CBL, FRS2, IRS1 and SHC1.
Q9HC97	GPR35	G-protein coupled receptor 35; Acts as a receptor for kynurenic acid, an intermediate in the tryptophan metabolic pathway. The activity of this receptor is mediated by G-proteins that elicit calcium mobilization and inositol phosphate production through G(qi/o) proteins.
P02768	ALB	Serum albumin; Serum albumin, the main protein of plasma, has a good binding capacity for water, Ca(2+), Na(+), K(+), fatty acids, hormones, bilirubin and drugs (Probable). Its main function is the regulation of the colloidal osmotic pressure of blood (Probable). Major zinc transporter in plasma, typically binds about 80% of all plasma zinc. Major calcium and magnesium transporter in plasma, binds approximately 45% of circulating calcium and magnesium in plasma (By similarity). Potentially has more than two calcium-binding sites and might additionally bind calcium in a non-specific man.
P54132	BLM	Bloom syndrome protein; ATP-dependent DNA helicase that unwinds single- and double- stranded DNA in a 3'-5' direction. Participates in DNA replication and repair. Involved in 5'-end resection of DNA during double-strand break (DSB) repair: unwinds DNA and recruits DNA2 which mediates the cleavage of 5'-ssDNA. Negatively regulates sister chromatid exchange (SCE). Stimulates DNA 4-way junction branch migration and DNA Holliday junction dissolution. Binds single- stranded DNA (ssDNA), forked duplex DNA and DNA Holliday junction.
P19838	NFKB1	Nuclear factor NF-kappa-B p105 subunit; NF-kappa-B is a

		pleiotropic transcription factor present in almost all cell types and is the endpoint of a series of signal transduction events that are initiated by a vast array of stimuli related to many biological processes such as inflammation, immunity, differentiation, cell growth, tumorigenesis and apoptosis. NF-kappa-B is a homo- or heterodimeric complex formed by the Rel-like domain- containing proteins RELA/p65, RELB, NFKB1/p105, NFKB1/p50, REL and NFKB2/p52 and the heterodimeric p65-p50 complex appears to be most abundant one.
O60341	KDM1A	Lysine-specific histone demethylase 1A; Histone demethylase that can demethylate both 'Lys-4' (H3K4me) and 'Lys-9' (H3K9me) of histone H3, thereby acting as a coactivator or a corepressor, depending on the context. Acts by oxidizing the substrate by FAD to generate the corresponding imine that is subsequently hydrolyzed. Acts as a corepressor by mediating demethylation of H3K4me, a specific tag for epigenetic transcriptional activation. Demethylates both mono- (H3K4me1) and di-methylated (H3K4me2) H3K4me. May play a role in the repression of neuronal genes.
Q9Y2T6	GPR55	G-protein coupled receptor 55; May be involved in hyperalgesia associated with inflammatory and neuropathic pain (By similarity). Receptor for L-alpha- lysophosphatidylinositol (LPI). LPI induces Ca(2+) release from intracellular stores via the heterotrimeric G protein GNA13 and RHOA. Putative cannabinoid receptor. May play a role in bone physiology by regulating osteoclast number and function.
Q13887	KLF5	Krueppel-like factor 5; Transcription factor that binds to GC box promoter elements. Activates the transcription of these genes; Belongs to the krueppel C2H2-type zinc-finger protein family.
P07339	CTSD	Cathepsin D heavy chain; Acid protease active in intracellular protein breakdown. Plays a role in APP processing following cleavage and activation by ADAM30 which leads to APP degradation. Involved in the pathogenesis of several diseases such as breast cancer and possibly Alzheimer disease.
Q16288	NTRK3	NT-3 growth factor receptor; Receptor tyrosine kinase involved in nervous system and probably heart development. Upon binding of its ligand NTF3/neurotrophin-3, NTRK3 autophosphorylates and activates different signaling pathways, including the phosphatidylinositol 3-kinase/AKT and the MAPK pathways, that control cell survival and differentiation.
O00206	TLR4	Toll-like receptor 4; Cooperates with LY96 and CD14 to mediate the innate immune response to bacterial lipopolysaccharide (LPS). Acts via MYD88, TIRAP and TRAF6, leading to NF-kappa-B activation, cytokine secretion and the inflammatory response. Also involved in LPS-independent inflammatory responses triggered by free fatty acids, such as palmitate, and Ni(2+). Responses triggered by Ni(2+) require non- conserved histidines and are, therefore, species-specific. Both M.tuberculosis HSP70 (dnaK) and HSP65 (groEL-2) act via this protein to stimulate NF-kappa-B expression.

P11388	TOP2A	DNA topoisomerase 2-alpha; Control of topological states of DNA by transient breakage and subsequent rejoining of DNA strands. Topoisomerase II makes double- strand breaks. Essential during mitosis and meiosis for proper segregation of daughter chromosomes. May play a role in regulating the period length of ARNTL/BMAL1 transcriptional oscillation (By similarity).
P08235	NR3C2	Mineralocorticoid receptor; Receptor for both mineralocorticoids (MC) such as aldosterone and glucocorticoids (GC) such as corticosterone or cortisol. Binds to mineralocorticoid response elements (MRE) and transactivates target genes. The effect of MC is to increase ion and water transport and thus raise extracellular fluid volume and blood pressure and lower potassium levels; Belongs to the nuclear hormone receptor family. NR3 subfamily.
Q99250	SCN2A	Sodium channel protein type 2 subunit alpha; Mediates the voltage-dependent sodium ion permeability of excitable membranes. Assuming opened or closed conformations in response to the voltage difference across the membrane, the protein forms a sodium-selective channel through which Na(+) ions may pass in accordance with their electrochemical gradient. Implicated in the regulation of hippocampal replay occurring within sharp wave ripples (SPW-R) important for memory (By similarity). Belongs to the sodium channel (TC 1.A.1.10) family. Nav1.2/SCN2A subfamily.
P10646	TFPI	Tissue factor pathway inhibitor; Inhibits factor X (X(a)) directly and, in a Xa-dependent way, inhibits VIIa/tissue factor activity, presumably by forming a quaternary Xa/LACI/VIIa/TF complex. It possesses an antithrombotic action and also the ability to associate with lipoproteins in plasma.
P07900	HSP90AA1	Heat shock protein HSP 90-alpha; Molecular chaperone that promotes the maturation, structural maintenance and proper regulation of specific target proteins involved for instance in cell cycle control and signal transduction. Undergoes a functional cycle that is linked to its ATPase activity which is essential for its chaperone activity. This cycle probably induces conformational changes in the client proteins, thereby causing their activation. Interacts dynamically with various co-chaperones that modulate its substrate recognition, ATPase cycle and chaperone function.
P27986	PIK3R1	Phosphatidylinositol 3-kinase regulatory subunit alpha; Binds to activated (phosphorylated) protein-Tyr kinases, through its SH2 domain, and acts as an adapter, mediating the association of the p110 catalytic unit to the plasma membrane. Necessary for the insulin-stimulated increase in glucose uptake and glycogen synthesis in insulin-sensitive tissues. Plays an important role in signaling in response to FGFR1, FGFR2, FGFR3, FGFR4, KITLG/SCF, KIT, PDGFRA and PDGFRB. Likewise, plays a role in ITGB2 signaling. Modulates the cellular response to ER stress by promoting nuclear translocation.
P17706	PTPN2	Tyrosine-protein phosphatase non-receptor type 2; Non-receptor type tyrosine-specific phosphatase that dephosphorylates receptor protein

		tyrosine kinases including INSR, EGFR, CSF1R, PDGFR. Also dephosphorylates non-receptor protein tyrosine kinases like JAK1, JAK2, JAK3, Src family kinases, STAT1, STAT3 and STAT6 either in the nucleus or the cytoplasm. Negatively regulates numerous signaling pathways and biological processes like hematopoiesis, inflammatory response, cell proliferation and differentiation, and glucose homeostasis.
Q8WUI4	HDAC7	Histone deacetylase 7; Responsible for the deacetylation of lysine residues on the N-terminal part of the core histones (H2A, H2B, H3 and H4). Histone deacetylation gives a tag for epigenetic repression and plays an important role in transcriptional regulation, cell cycle progression and developmental events. Histone deacetylases act via the formation of large multiprotein complexes. Involved in muscle maturation by repressing transcription of myocyte enhancer factors such as MEF2A, MEF2B and MEF2C.
Q99714	HSD17B10	3-hydroxyacyl-CoA dehydrogenase type-2; Mitochondrial dehydrogenase that catalyzes the beta-oxidation at position 17 of androgens and estrogens and has 3-alpha- hydroxysteroid dehydrogenase activity with androsterone. Catalyzes the third step in the beta-oxidation of fatty acids. Carries out oxidative conversions of 7-alpha-OH and 7-beta-OH bile acids. Also exhibits 20-beta-OH and 21-OH dehydrogenase activities with C21 steroids. By interacting with intracellular amyloid-beta, it may contribute to the neuronal dysfunction associated with Alzheimer disease (AD).
P08684	CYP3A4	Cytochrome P450 3A4; A cytochrome P450 monooxygenase involved in the metabolism of sterols, steroid hormones, retinoids and fatty acids. Mechanistically, uses molecular oxygen inserting one oxygen atom into a substrate, and reducing the second into a water molecule, with two electrons provided by NADPH via cytochrome P450 reductase (NADPH--hemoprotein reductase). Catalyzes the hydroxylation of carbon-hydrogen bonds. Exhibits high catalytic activity for the formation of hydroxyestrogens from estrone (E1) and 17beta- estradiol (E2), namely 2-hydroxy E1 and E2, as well as D-ring hydroxyla.
P22736	NR4A1	Nuclear receptor subfamily 4 group A member 1; Orphan nuclear receptor. May act concomitantly with NURR1 in regulating the expression of delayed-early genes during liver regeneration. Binds the NGFI-B response element (NBRE) 5'-AAAAGGTCA-3' (By similarity). May inhibit NF-kappa-B transactivation of IL2. Participates in energy homeostasis by sequestrating the kinase STK11 in the nucleus, thereby attenuating cytoplasmic AMPK activation. Plays a role in the vascular response to injury (By similarity). ECO:0000250|UniProtKB:P12813.
O15111	CHUK	Inhibitor of nuclear factor kappa-B kinase subunit alpha; Serine kinase that plays an essential role in the NF-kappa-B signaling pathway which is activated by multiple stimuli such as inflammatory cytokines, bacterial or viral products, DNA damages or other cellular stresses. Acts as part of the canonical IKK complex in the

		conventional pathway of NF-kappa-B activation and phosphorylates inhibitors of NF-kappa-B on serine residues. These modifications allow polyubiquitination of the inhibitors and subsequent degradation by the proteasome.
Q92753	RORB	Nuclear receptor ROR-beta; Nuclear receptor that binds DNA as a monomer to ROR response elements (RORE) containing a single core motif half-site 5'-AGGTCA-3' preceded by a short A-T-rich sequence. Considered to have intrinsic transcriptional activity, have some natural ligands such as all-trans retinoic acid (ATRA) and other retinoids which act as inverse agonists repressing the transcriptional activity. Required for normal postnatal development of rod and cone photoreceptor cells.
Q9NP59	SLC40A1	Solute carrier family 40 member 1; May be involved in iron export from duodenal epithelial cell and also in transfer of iron between maternal and fetal circulation. Mediates iron efflux in the presence of a ferroxidase (hephaestin and/or ceruloplasmin); Belongs to the ferroportin (FP) (TC 2.A.100) family. SLC40A subfamily.
P07384	CAPN1	Calpain-1 catalytic subunit; Calcium-regulated non-lysosomal thiol-protease which catalyzes limited proteolysis of substrates involved in cytoskeletal remodeling and signal transduction; Belongs to the peptidase C2 family.
P34972	CNR2	Cannabinoid receptor 2; Heterotrimeric G protein-coupled receptor for endocannabinoid 2-arachidonoylglycerol mediating inhibition of adenylate cyclase. May function in inflammatory response, nociceptive transmission and bone homeostasis.
P19634	SLC9A1	Sodium/hydrogen exchanger 1; Involved in pH regulation to eliminate acids generated by active metabolism or to counter adverse environmental conditions. Major proton extruding system driven by the inward sodium ion chemical gradient. Plays an important role in signal transduction.
Q13085	ACACA	Acetyl-CoA carboxylase 1; Cytosolic enzyme that catalyzes the carboxylation of acetyl- CoA to malonyl-CoA, the first and rate-limiting step of de novo fatty acid biosynthesis. This is a 2 steps reaction starting with the ATP-dependent carboxylation of the biotin carried by the biotin carboxyl carrier (BCC) domain followed by the transfer of the carboxyl group from carboxylated biotin to acetyl-CoA.
O00763	ACACB	Acetyl-CoA carboxylase 2; Mitochondrial enzyme that catalyzes the carboxylation of acetyl-CoA to malonyl-CoA and plays a central role in fatty acid metabolism. Catalyzes a 2 steps reaction starting with the ATP-dependent carboxylation of the biotin carried by the biotin carboxyl carrier (BCC) domain followed by the transfer of the carboxyl group from carboxylated biotin to acetyl-CoA. Through the production of malonyl-CoA that allosterically inhibits carnitine palmitoyltransferase 1 at the mitochondria, negatively regulates fatty acid oxidation (By similarity).
P50579	METAP2	Methionine aminopeptidase 2; Cotranslationally removes the N-terminal methionine from nascent proteins. The N-terminal

		methionine is often cleaved when the second residue in the primary sequence is small and uncharged (Met- Ala-, Cys, Gly, Pro, Ser, Thr, or Val). The catalytic activity of human METAP2 toward Met-Val peptides is consistently two orders of magnitude higher than that of METAP1, suggesting that it is responsible for processing proteins containing N-terminal Met-Val and Met-Thr sequences in vivo; Belongs to the peptidase M24A family.
P13569	CFTR	Cystic fibrosis transmembrane conductance regulator; Epithelial ion channel that plays an important role in the regulation of epithelial ion and water transport and fluid homeostasis. Mediates the transport of chloride ions across the cell membrane. Channel activity is coupled to ATP hydrolysis. The ion channel is also permeable to HCO(3-); selectivity depends on the extracellular chloride concentration. Exerts its function also by modulating the activity of other ion channels and transporters. Plays an important role in airway fluid homeostasis.
Q13526	PIN1	Peptidyl-prolyl cis-trans isomerase NIMA-interacting 1; Peptidyl-prolyl cis/trans isomerase (PPIase) that binds to and isomerizes specific phosphorylated Ser/Thr-Pro (pSer/Thr-Pro) motifs. By inducing conformational changes in a subset of phosphorylated proteins, acts as a molecular switch in multiple cellular processes. Displays a preference for acidic residues located N-terminally to the proline bond to be isomerized. Regulates mitosis presumably by interacting with NIMA and attenuating its mitosis-promoting activity. Down-regulates kinase activity of BTK.
Q16236	NFE2L2	Nuclear factor erythroid 2-related factor 2; Transcription factor that plays a key role in the response to oxidative stress: binds to antioxidant response (ARE) elements present in the promoter region of many cytoprotective genes, such as phase 2 detoxifying enzymes, and promotes their expression, thereby neutralizing reactive electrophiles. In normal conditions, ubiquitinated and degraded in the cytoplasm by the BCR(KEAP1) complex. In response to oxidative stress, electrophile metabolites inhibit activity of the BCR(KEAP1) complex, promoting nuclear accumulation of NFE2L2/NRF2.
Q9Y5X4	NR2E3	Photoreceptor-specific nuclear receptor; Orphan nuclear receptor of retinal photoreceptor cells. Transcriptional factor that is an activator of rod development and repressor of cone development. Binds the promoter region of a number of rod- and cone-specific genes, including rhodopsin, M- and S-opsin and rod-specific phosphodiesterase beta subunit. Enhances rhodopsin expression. Represses M- and S-cone opsin expression. Belongs to the nuclear hormone receptor family. NR2 subfamily.
P42345	MTOR	Serine/threonine-protein kinase mTOR; Serine/threonine protein kinase which is a central regulator of cellular metabolism, growth and survival in response to hormones, growth factors, nutrients, energy and stress signals. MTOR directly or indirectly regulates the phosphorylation of at least 800 proteins. Functions as part of 2

		structurally and functionally distinct signaling complexes mTORC1 and mTORC2 (mTOR complex 1 and 2). Activated mTORC1 up-regulates protein synthesis by phosphorylating key regulators of mRNA translation and ribosome synthesis.
Q9UKV0	HDAC9	Histone deacetylase 9; Responsible for the deacetylation of lysine residues on the N-terminal part of the core histones (H2A, H2B, H3 and H4). Histone deacetylation gives a tag for epigenetic repression and plays an important role in transcriptional regulation, cell cycle progression and developmental events. Represses MEF2-dependent transcription; Belongs to the histone deacetylase family. HD type 2 subfamily.
P34947	GRK5	G protein-coupled receptor kinase 5; Serine/threonine kinase that phosphorylates preferentially the activated forms of a variety of G-protein-coupled receptors (GPCRs). Such receptor phosphorylation initiates beta-arrestin-mediated receptor desensitization, internalization, and signaling events leading to their down-regulation. Phosphorylates a variety of GPCRs, including adrenergic receptors, muscarinic acetylcholine receptors (more specifically Gi-coupled M2/M4 subtypes), dopamine receptors and opioid receptors.
P21554	CNR1	Cannabinoid receptor 1; G-protein coupled receptor for endogenous cannabinoids (eCBs), including N-arachidonoylethanolamide (also called anandamide or AEA) and 2-arachidonoylglycerol (2-AG), as well as phytocannabinoids, such as delta(9)-tetrahydrocannabinol (THC). Mediates many cannabinoid-induced effects, acting, among others, on food intake, memory loss, gastrointestinal motility, catalepsy, ambulatory activity, anxiety, chronic pain. Signaling typically involves reduction in cyclic AMP.
P09619	PDGFRB	Platelet-derived growth factor receptor beta; Tyrosine-protein kinase that acts as cell-surface receptor for homodimeric PDGFB and PDGFD and for heterodimers formed by PDGFA and PDGFB, and plays an essential role in the regulation of embryonic development, cell proliferation, survival, differentiation, chemotaxis and migration. Plays an essential role in blood vessel development by promoting proliferation, migration and recruitment of pericytes and smooth muscle cells to endothelial cells. Plays a role in the migration of vascular smooth muscle cells and the formation of neointima.
P08183	ABCB1	ATP-dependent translocase ABCB1; Translocates drugs and phospholipids across the membrane. Catalyzes the flop of phospholipids from the cytoplasmic to the exoplasmic leaflet of the apical membrane. Participates mainly to the flop of phosphatidylcholine, phosphatidylethanolamine, beta-D-glucosylceramides and sphingomyelins. Energy-dependent efflux pump responsible for decreased drug accumulation in multidrug-resistant cells.
P35372	OPRM1	Mu-type opioid receptor; Receptor for endogenous opioids such as beta-endorphin and endomorphin. Receptor for natural and synthetic opioids including morphine, heroin, DAMGO, fentanyl, etorphine, buprenorphin and methadone. Agonist binding to the receptor

		induces coupling to an inactive GDP-bound heterotrimeric G-protein complex and subsequent exchange of GDP for GTP in the G-protein alpha subunit leading to dissociation of the G-protein complex with the free GTP-bound G-protein alpha and the G-protein beta-gamma dimer activating downstream cellular effectors.
Q9NYA1	SPHK1	Sphingosine kinase 1; Catalyzes the phosphorylation of sphingosine to form sphingosine 1-phosphate (SPP), a lipid mediator with both intra- and extracellular functions. Also acts on D-erythro-sphingosine and to a lesser extent sphinganine, but not other lipids, such as D,L-threo- dihydrosphingosine, N,N-dimethylsphingosine, diacylglycerol, ceramide, or phosphatidylinositol. In contrast to proapoptotic SPHK2, has a negative effect on intracellular ceramide levels, enhances cell growth and inhibits apoptosis. Involved in the regulation of inflammatory response and neuroinflammation.
O00767	SCD	Acyl-CoA desaturase; Stearyl-CoA desaturase that utilizes O(2) and electrons from reduced cytochrome b5 to introduce the first double bond into saturated fatty acyl-CoA substrates. Catalyzes the insertion of a cis double bond at the delta-9 position into fatty acyl-CoA substrates including palmitoyl-CoA and stearoyl-CoA. Gives rise to a mixture of 16:1 and 18:1 unsaturated fatty acids. Plays an important role in lipid biosynthesis. Plays an important role in regulating the expression of genes that are involved in lipogenesis and in regulating mitochondrial fatty acid oxidation.
P35610	SOAT1	Sterol O-acyltransferase 1; Catalyzes the formation of fatty acid-cholesterol esters, which are less soluble in membranes than cholesterol. Plays a role in lipoprotein assembly and dietary cholesterol absorption. In addition to its acyltransferase activity, it may act as a ligase.
O14746	TERT	Telomerase reverse transcriptase; Telomerase is a ribonucleoprotein enzyme essential for the replication of chromosome termini in most eukaryotes. Active in progenitor and cancer cells. Inactive, or very low activity, in normal somatic cells. Catalytic component of the teleromerase holoenzyme complex whose main activity is the elongation of telomeres by acting as a reverse transcriptase that adds simple sequence repeats to chromosome ends by copying a template sequence within the RNA component of the enzyme.
P32245	MC4R	Melanocortin receptor 4; Receptor specific to the heptapeptide core common to adrenocorticotropic hormone and alpha-, beta-, and gamma-MSH. Plays a central role in energy homeostasis and somatic growth. This receptor is mediated by G proteins that stimulate adenylate cyclase (cAMP).
Q14289	PTK2B	Protein-tyrosine kinase 2-beta; Non-receptor protein-tyrosine kinase that regulates reorganization of the actin cytoskeleton, cell polarization, cell migration, adhesion, spreading and bone remodeling. Plays a role in the regulation of the humoral immune response, and is required for normal levels of marginal B-cells in the spleen and normal migration of splenic B-cells. Required for normal macrophage polarization and migration towards sites of

		inflammation. Regulates cytoskeleton rearrangement and cell spreading in T-cells, and contributes to the regulation of T-cell responses.
Q00535	CDK5	Cyclin-dependent-like kinase 5; Proline-directed serine/threonine-protein kinase essential for neuronal cell cycle arrest and differentiation and may be involved in apoptotic cell death in neuronal diseases by triggering abortive cell cycle re-entry. Interacts with D1 and D3-type G1 cyclins. Phosphorylates SRC, NOS3, VIM/vimentin, p35/CDK5R1, MEF2A, SIPA1L1, SH3GLB1, PXN, PAK1, MCAM/MUC18, SEPT5, SYN1, DNM1, AMPH, SYNJ1, CDK16, RAC1, RHOA, CDC42, TONEBP/NFAT5, MAPT/TAU, MAP1B, histone H1, p53/TP53, HDAC1, APEX1, PTK2/FAK1, huntingtin/HTT, ATM, MAP2, NEFH and NEFM.
Q14145	KEAP1	Kelch-like ECH-associated protein 1; Substrate-specific adapter of a BCR (BTB-CUL3-RBX1) E3 ubiquitin ligase complex that regulates the response to oxidative stress by targeting NFE2L2/NRF2 for ubiquitination. KEAP1 acts as a key sensor of oxidative and electrophilic stress: in normal conditions, the BCR(KEAP1) complex mediates ubiquitination and degradation of NFE2L2/NRF2, a transcription factor regulating expression of many cytoprotective genes.
P42336	PIK3CA	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology.
P43004	SLC1A2	Excitatory amino acid transporter 2; Sodium-dependent, high-affinity amino acid transporter that mediates the uptake of L-glutamate and also L-aspartate and D-aspartate. Functions as a symporter that transports one amino acid molecule together with two or three Na(+) ions and one proton, in parallel with the counter-transport of one K(+) ion. Mediates Cl(-) flux that is not coupled to amino acid transport; this avoids the accumulation of negative charges due to aspartate and Na(+) symport. Essential for the rapid removal of released glutamate from the synaptic cleft, and for terminatin.
Q8IU80	TMPRSS6	Transmembrane protease serine 6; Serine protease which hydrolyzes a range of proteins including type I collagen, fibronectin and fibrinogen. Can also activate urokinase-type plasminogen activator with low efficiency. May play a specialized role in matrix remodeling processes in liver. Through the cleavage of HJV, a regulator of the expression of the iron absorption-regulating hormone hepicidin/HAMP, plays a role in iron homeostasis.
P40763	STAT3	Signal transducer and activator of transcription 3; Signal transducer

		and transcription activator that mediates cellular responses to interleukins, KITLG/SCF, LEP and other growth factors. Once activated, recruits coactivators, such as NCOA1 or MED1, to the promoter region of the target gene. May mediate cellular responses to activated FGFR1, FGFR2, FGFR3 and FGFR4. Binds to the interleukin-6 (IL-6)-responsive elements identified in the promoters of various acute-phase protein genes. Activated by IL31 through IL31RA.
P42338	PIK3CB	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit beta isoform; Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns (Phosphatidylinositol), PtdIns4P (Phosphatidylinositol 4-phosphate) and PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology.
P17252	PRKCA	Protein kinase C alpha type; Calcium-activated, phospholipid- and diacylglycerol (DAG)- dependent serine/threonine-protein kinase that is involved in positive and negative regulation of cell proliferation, apoptosis, differentiation, migration and adhesion, tumorigenesis, cardiac hypertrophy, angiogenesis, platelet function and inflammation, by directly phosphorylating targets such as RAF1, BCL2, CSPG4, TNNT2/CTNT, or activating signaling cascade involving MAPK1/3 (ERK1/2) and RAP1GAP. Involved in cell proliferation and cell growth arrest by positive and negative regulation of the cell.
P09237	MMP7	Matrilysin; Degrades casein, gelatins of types I, III, IV, and V, and fibronectin. Activates procollagenase.
O00329	PIK3CD	Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit delta isoform; Phosphoinositide-3-kinase (PI3K) that phosphorylates PtdIns(4,5)P2 (Phosphatidylinositol 4,5-bisphosphate) to generate phosphatidylinositol 3,4,5-trisphosphate (PIP3). PIP3 plays a key role by recruiting PH domain-containing proteins to the membrane, including AKT1 and PDPK1, activating signaling cascades involved in cell growth, survival, proliferation, motility and morphology. Mediates immune responses. Plays a role in B-cell development, proliferation, migration, and function.
Q13370	PDE3B	cGMP-inhibited 3',5'-cyclic phosphodiesterase B; Cyclic nucleotide phosphodiesterase with a dual-specificity for the second messengers cAMP and cGMP, which are key regulators of many important physiological processes. May play a role in fat metabolism. Regulates cAMP binding of RAPGEF3. Through simultaneous binding to RAPGEF3 and PIK3R6 assembles a signaling complex in which the PI3K gamma complex is activated by RAPGEF3 and which is involved in angiogenesis.
P08709	F7	Coagulation factor VII; Initiates the extrinsic pathway of blood coagulation. Serine protease that circulates in the blood in a

		zymogen form. Factor VII is converted to factor VIIa by factor Xa, factor XIIa, factor IXa, or thrombin by minor proteolysis. In the presence of tissue factor and calcium ions, factor VIIa then converts factor X to factor Xa by limited proteolysis. Factor VIIa will also convert factor IX to factor IXa in the presence of tissue factor and calcium.
P11166	SLC2A1	Solute carrier family 2, facilitated glucose transporter member 1; Facilitative glucose transporter, which is responsible for constitutive or basal glucose uptake. Has a very broad substrate specificity; can transport a wide range of aldoses including both pentoses and hexoses. Most important energy carrier of the brain: present at the blood-brain barrier and assures the energy-independent, facilitative transport of glucose into the brain.
P41597	CCR2	C-C chemokine receptor type 2; Key functional receptor for CCL2 but can also bind CCL7 and CCL12. Its binding with CCL2 on monocytes and macrophages mediates chemotaxis and migration induction through the activation of the PI3K cascade, the small G protein Rac and lamellipodium protrusion (Probable). Also acts as a receptor for the beta-defensin DEFB106A/DEFB106B. Regulates the expression of T-cell inflammatory cytokines and T-cell differentiation, promoting the differentiation of T-cells into T-helper 17 cells (Th17) during inflammation (By similarity).
Q9H244	P2RY12	P2Y purinoceptor 12; Receptor for ADP and ATP coupled to G-proteins that inhibit the adenylyl cyclase second messenger system. Not activated by UDP and UTP. Required for normal platelet aggregation and blood coagulation.
P39900	MMP12	Macrophage metalloelastase; May be involved in tissue injury and remodeling. Has significant elastolytic activity. Can accept large and small amino acids at the P1' site, but has a preference for leucine. Aromatic or hydrophobic residues are preferred at the P1 site, with small hydrophobic residues (preferably alanine) occupying P3; Belongs to the peptidase M10A family.
Q16665	HIF1A	Hypoxia-inducible factor 1-alpha; Functions as a master transcriptional regulator of the adaptive response to hypoxia. Under hypoxic conditions, activates the transcription of over 40 genes, including erythropoietin, glucose transporters, glycolytic enzymes, vascular endothelial growth factor, HILPDA, and other genes whose protein products increase oxygen delivery or facilitate metabolic adaptation to hypoxia. Plays an essential role in embryonic vascularization, tumor angiogenesis and pathophysiology of ischemic disease.
P35557	GCK	Hexokinase-4; Catalyzes the phosphorylation of hexose, such as D-glucose, D-fructose and D-mannose, to hexose 6-phosphate (D-glucose 6-phosphate, D-fructose 6-phosphate and D-mannose 6-phosphate, respectively). Compared to other hexokinases, has a weak affinity for D-glucose, and is effective only when glucose is abundant (By similarity). Mainly expressed in pancreatic beta cells and the liver and constitutes a rate-limiting step in glucose

		metabolism in these tissues.
P43490	NAMPT	Nicotinamide phosphoribosyltransferase; Catalyzes the condensation of nicotinamide with 5- phosphoribosyl-1-pyrophosphate to yield nicotinamide mononucleotide, an intermediate in the biosynthesis of NAD. It is the rate limiting component in the mammalian NAD biosynthesis pathway. The secreted form behaves both as a cytokine with immunomodulating properties and an adipokine with anti-diabetic properties, it has no enzymatic activity, partly because of lack of activation by ATP, which has a low level in extracellular space and plasma.
P30926	CHRNB4	Neuronal acetylcholine receptor subunit beta-4; After binding acetylcholine, the AChR responds by an extensive change in conformation that affects all subunits and leads to opening of an ion-conducting channel across the plasma membrane; Belongs to the ligand-gated ion channel (TC 1.A.9) family. Acetylcholine receptor (TC 1.A.9.1) subfamily. Beta-4/CHRNB4 sub- subfamily.
P21980	TGM2	Protein-glutamine gamma-glutamyltransferase 2; Catalyzes the cross-linking of proteins, such as WDR54, and the conjugation of polyamines to proteins.
P35462	DRD3	D(3) dopamine receptor; Dopamine receptor whose activity is mediated by G proteins which inhibit adenylyl cyclase. Promotes cell proliferation.
P15144	ANPEP	Aminopeptidase N; Broad specificity aminopeptidase which plays a role in the final digestion of peptides generated from hydrolysis of proteins by gastric and pancreatic proteases. Also involved in the processing of various peptides including peptide hormones, such as angiotensin III and IV, neuropeptides, and chemokines. May also be involved the cleavage of peptides bound to major histocompatibility complex class II molecules of antigen presenting cells. May have a role in angiogenesis and promote cholesterol crystallization.
P18054	ALOX12	Arachidonate 12-lipoxygenase, 12S-type; Catalyzes the regio and stereo-specific incorporation of a single molecule of dioxygen into free and esterified polyunsaturated fatty acids generating lipid hydroperoxides that can be further reduced to the corresponding hydroxy species. Mainly converts arachidonic acid to (12S)-hydroperoxyeicosatetraenoic acid/(12S)-HPETE but can also metabolize linoleic acid. In contrast does not react towards methyl esters of linoleic and arachidonic acids (By similarity).
Q06124	PTPN11	Tyrosine-protein phosphatase non-receptor type 11; Acts downstream of various receptor and cytoplasmic protein tyrosine kinases to participate in the signal transduction from the cell surface to the nucleus. Positively regulates MAPK signal transduction pathway. Dephosphorylates GAB1, ARHGAP35 and EGFR. Dephosphorylates ROCK2 at 'Tyr-722' resulting in stimulatation of its RhoA binding activity. Dephosphorylates CDC73.
P00750	PLAT	Tissue-type plasminogen activator chain A; Converts the abundant, but inactive, zymogen plasminogen to plasmin by hydrolyzing a single Arg-Val bond in plasminogen. By controlling plasmin-

		mediated proteolysis, it plays an important role in tissue remodeling and degradation, in cell migration and many other physiopathological events. Plays a direct role in facilitating neuronal migration; Belongs to the peptidase S1 family.
Q96RR4	CAMKK2	Calcium/calmodulin-dependent protein kinase kinase 2; Calcium/calmodulin-dependent protein kinase belonging to a proposed calcium-triggered signaling cascade involved in a number of cellular processes. Isoform 1, isoform 2 and isoform 3 phosphorylate CAMK1 and CAMK4. Isoform 3 phosphorylates CAMK1D. Isoform 4, isoform 5 and isoform 6 lacking part of the calmodulin-binding domain are inactive. Efficiently phosphorylates 5'-AMP-activated protein kinase (AMPK) trimer, including that consisting of PRKAA1, PRKAB1 and PRKAG1.
P29323	EPHB2	Ephrin type-B receptor 2; Receptor tyrosine kinase which binds promiscuously transmembrane ephrin-B family ligands residing on adjacent cells, leading to contact-dependent bidirectional signaling into neighboring cells. The signaling pathway downstream of the receptor is referred to as forward signaling while the signaling pathway downstream of the ephrin ligand is referred to as reverse signaling. Functions in axon guidance during development. Involved in the guidance of commissural axons, that form a major interhemispheric connection between the 2 temporal lobes of the cerebral corte.
O15118	NPC1	NPC intracellular cholesterol transporter 1; Intracellular cholesterol transporter which acts in concert with NPC2 and plays an important role in the egress of cholesterol from the endosomal/lysosomal compartment. Unesterified cholesterol that has been released from LDLs in the lumen of the late endosomes/lysosomes is transferred by NPC2 to the cholesterol-binding pocket in the N-terminal domain of NPC1. Cholesterol binds to NPC1 with the hydroxyl group buried in the binding pocket. Binds oxysterol with higher affinity than cholesterol.
O94925	GLS	Glutaminase kidney isoform, mitochondrial 65 kDa chain; Catalyzes the first reaction in the primary pathway for the renal catabolism of glutamine. Plays a role in maintaining acid-base homeostasis. Regulates the levels of the neurotransmitter glutamate, the main excitatory neurotransmitter in the brain ; Belongs to the glutaminase family.
P17948	FLT1	Vascular endothelial growth factor receptor 1; Tyrosine-protein kinase that acts as a cell-surface receptor for VEGFA, VEGFB and PGF, and plays an essential role in the development of embryonic vasculature, the regulation of angiogenesis, cell survival, cell migration, macrophage function, chemotaxis, and cancer cell invasion. May play an essential role as a negative regulator of embryonic angiogenesis by inhibiting excessive proliferation of endothelial cells. Can promote endothelial cell proliferation, survival and angiogenesis in adulthood.
P14555	PLA2G2A	Phospholipase A2, membrane associated; Catalyzes the calcium-

		dependent hydrolysis of the 2-acyl groups in 3-sn-phosphoglycerides. Thought to participate in the regulation of phospholipid metabolism in biomembranes including eicosanoid biosynthesis. Independent of its catalytic activity, acts as a ligand for integrins. Binds to and activates integrins ITGAV:ITGB3, ITGA4:ITGB1 and ITGA5:ITGB1. Binds to a site (site 2) which is distinct from the classical ligand-binding site (site 1) and induces integrin conformational changes and enhanced ligand binding to site 1.
P22413	ENPP1	Ectonucleotide pyrophosphatase/phosphodiesterase family member 1, secreted form; Nucleotide pyrophosphatase that generates diphosphate (PPi) and functions in bone mineralization and soft tissue calcification by regulating pyrophosphate levels (By similarity). PPi inhibits bone mineralization and soft tissue calcification by binding to nascent hydroxyapatite crystals, thereby preventing further growth of these crystals. Preferentially hydrolyzes ATP, but can also hydrolyze other nucleoside 5' triphosphates such as GTP, CTP, TTP and UTP.
P61073	CXCR4	C-X-C chemokine receptor type 4; Receptor for the C-X-C chemokine CXCL12/SDF-1 that transduces a signal by increasing intracellular calcium ion levels and enhancing MAPK1/MAPK3 activation. Involved in the AKT signaling cascade. Plays a role in regulation of cell migration, e.g. during wound healing. Acts as a receptor for extracellular ubiquitin; leading to enhanced intracellular calcium ions and reduced cellular cAMP levels. Binds bacterial lipopolysaccharide (LPS) et mediates LPS-induced inflammatory response, including TNF secretion by monocytes.
P55899	FCGRT	IgG receptor FcRn large subunit p51; Cell surface receptor that transfers passive humoral immunity from the mother to the newborn. Binds to the Fc region of monomeric immunoglobulin gamma and mediates its selective uptake from milk. IgG in the milk is bound at the apical surface of the intestinal epithelium. The resultant FcRn-IgG complexes are transcytosed across the intestinal epithelium and IgG is released from FcRn into blood or tissue fluids. Throughout life, contributes to effective humoral immunity by recycling IgG and extending its half-life in the circulation.
P09211	GSTP1	Glutathione S-transferase P; Conjugation of reduced glutathione to a wide number of exogenous and endogenous hydrophobic electrophiles. Regulates negatively CDK5 activity via p25/p35 translocation to prevent neurodegeneration.
P17931	LGALS3	Galectin-3; Galactose-specific lectin which binds IgE. May mediate with the alpha-3, beta-1 integrin the stimulation by CSPG4 of endothelial cells migration. Together with DMBT1, required for terminal differentiation of columnar epithelial cells during early embryogenesis (By similarity). In the nucleus: acts as a pre-mRNA splicing factor. Involved in acute inflammatory responses including neutrophil activation and adhesion, chemoattraction of monocytes macrophages, opsonization of apoptotic neutrophils, and activation

		of mast cells.
P11387	TOP1	DNA topoisomerase 1; Releases the supercoiling and torsional tension of DNA introduced during the DNA replication and transcription by transiently cleaving and rejoining one strand of the DNA duplex. Introduces a single-strand break via transesterification at a target site in duplex DNA. The scissile phosphodiester is attacked by the catalytic tyrosine of the enzyme, resulting in the formation of a DNA-(3'-phosphotyrosyl)- enzyme intermediate and the expulsion of a 5'-OH DNA strand.
P20309	CHRM3	Muscarinic acetylcholine receptor M3; The muscarinic acetylcholine receptor mediates various cellular responses, including inhibition of adenylate cyclase, breakdown of phosphoinositides and modulation of potassium channels through the action of G proteins. Primary transducing effect is Pi turnover.
Q96L34	MARK4	MAP/microtubule affinity-regulating kinase 4; Serine/threonine-protein kinase. Phosphorylates the microtubule-associated protein MAPT/TAU. Also phosphorylates the microtubule-associated proteins MAP2 and MAP4. Involved in regulation of the microtubule network, causing reorganization of microtubules into bundles. Required for the initiation of axoneme extension during cilium assembly. Regulates the centrosomal location of ODF2 and phosphorylates ODF2 in vitro. Plays a role in cell cycle progression, specifically in the G1/S checkpoint. Reduces neuronal cell survival. Plays a role in ene.
P51812	RPS6KA3	Ribosomal protein S6 kinase alpha-3; Serine/threonine-protein kinase that acts downstream of ERK (MAPK1/ERK2 and MAPK3/ERK1) signaling and mediates mitogenic and stress-induced activation of the transcription factors CREB1, ETV1/ER81 and NR4A1/NUR77, regulates translation through RPS6 and EIF4B phosphorylation, and mediates cellular proliferation, survival, and differentiation by modulating mTOR signaling and repressing pro-apoptotic function of BAD and DAPK1. In fibroblast, is required for EGF-stimulated phosphorylation of CREB1 and histone H3 at 'Ser-10', which results in the subseq.
P54764	EPHA4	Ephrin type-A receptor 4; Receptor tyrosine kinase which binds membrane-bound ephrin family ligands residing on adjacent cells, leading to contact-dependent bidirectional signaling into neighboring cells. The signaling pathway downstream of the receptor is referred to as forward signaling while the signaling pathway downstream of the ephrin ligand is referred to as reverse signaling. Highly promiscuous, it has the unique property among Eph receptors to bind and to be physiologically activated by both GPI- anchored ephrin-A and transmembrane ephrin-B ligands including EFNA1 and EFNB3.
P21397	MAOA	Amine oxidase [flavin-containing] A; Catalyzes the oxidative deamination of biogenic and xenobiotic amines and has important functions in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues. MAOA preferentially oxidizes biogenic amines such as 5-hydroxytryptamine

		(5-HT), norepinephrine and epinephrine.
P14174	MIF	Macrophage migration inhibitory factor; Pro-inflammatory cytokine. Involved in the innate immune response to bacterial pathogens. The expression of MIF at sites of inflammation suggests a role as mediator in regulating the function of macrophages in host defense. Counteracts the anti-inflammatory activity of glucocorticoids. Has phenylpyruvate tautomerase and dopachrome tautomerase activity (in vitro), but the physiological substrate is not known. It is not clear whether the tautomerase activity has any physiological relevance, and whether it is important for cytokine activity.
P51617	IRAK1	Interleukin-1 receptor-associated kinase 1; Serine/threonine-protein kinase that plays a critical role in initiating innate immune response against foreign pathogens. Involved in Toll-like receptor (TLR) and IL-1R signaling pathways. Is rapidly recruited by MYD88 to the receptor-signaling complex upon TLR activation. Association with MYD88 leads to IRAK1 phosphorylation by IRAK4 and subsequent autophosphorylation and kinase activation. Phosphorylates E3 ubiquitin ligases Pellino proteins (PELI1, PELI2 and PELI3) to promote pellino-mediated polyubiquitination of IRAK1.

S2. Experimental

S.2.1 Extraction and Isolation

The roots of *P. serrata* Balt (5kg) were macerated and then ultrasonicated with 10L methanol (MeOH) for three times. Evaporation of the solvent under reduced pressure gave crude extract (1,0 kg). The crude extract was suspended in H_2O and successively separated with n-hexane, EtOAc, and MeOH to yield n-hexane extract (25.4 g), EtOAc extract (70.5 g), MeOH extract (150,5g) and water layer, respectively. Ethyl acetate extract was fractionated on a silica gel column chromatography (CC) eluting with gradient solvent systems of CH_2Cl_2-MeOH (0-100% MeOH, step-wise) to obtain five fractions (E.1 through E.5). Fraction E.1 (1.21g) was isolated on silica gel CC eluting with CH_2Cl_2/MeOH (85/15, v/v) to afford eight sub-fractions (E1.1 to E1.8). Compound **7** (3 mg) and **8** (4mg) were isolated by sephadex LH-20 CC using MeOH as eluent from fraction E1.7 (250mg). Fraction E.2 (2.12g) was separated on silica gel CC with EtOAc/MeOH (9/1, v/v) as eluent to give ten sub-fractions (E.2.1 to E.2.10). Compounds **9** (3 mg) was obtained from fraction E.2.9 (370mg) by Sephadex LH-20 CC eluting with MeOH/H_2O (1/1, v/v) as eluent. Fraction E3 (3.25g) was isolated on silica gel CC eluting with EtOAc/MeOH (4/1, v/v) to given seven sub-fractions (E.3.1 to E.3.7). Compounds **5** (6 mg) and **6** (4 mg) were obtained from fraction E.3.6 (420mg) by silica gel CC eluting with CH_2Cl_2/MeOH (7/3, v/v) as eluent.

The MeOH extract (150,5g) was fractionated on a dianion HP-20 CC eluting with gradient solvent systems of MeOH/H_2O (0-100% MeOH, step-wise) to obtain four fractions (M.1 through M.4). Fraction M.4 (21g) was separated by sephadex LH-20 CC using MeOH/H_2O (3/1, v/v) as eluent to provide **2** (3 mg).

The water layer (150g) was fractionated on a dianion HP-20 CC eluting with gradient solvent systems of MeOH/H_2O (0-100% MeOH, step-wise) to obtain four fractions (W.1 through W.4). Fraction W.3 (4.2g) was separated by sephadex LH-20 CC using MeOH/H_2O (3/1, v/v) as eluent to provide twelve sub-fractions (W3.1 to W3.12). Fraction W3.9 (1.02g) was isolated by YMC-RP18 CC, eluting with solvent systems of MeOH/H_2O (1/1, v/v) to obtain compound **3** (4mg) and sub-fraction W3.9.1 (150mg), which further purified by sephadex LH-20 CC, MeOH as eluent to afforded compound **1** (3mg). Fraction W.4 (5.7g) was fractioned on sephadex LH-20 CC eluting with MeOH, and further isolated by silica gel CC using solvent system CH_2Cl_2/MeOH (4/1, v/v) to give compound **4** (4 mg).

Their structures were identified based on the direct comparison of NMR data with those reported in previous studies, including: Ladyginoside A (**1**) [1], spinasaponin A 28-O-glycoside (**2**) [2], Polyscioside J (**3**) [3] , 3-O-*β*-D–glucopyranosyl-(1→4)-*β*-D-glucuronopyranosyloleanolic acid methyl ester (**4**)[4], Stigmasta-4,22-dien-3,7-diol (**5**) [5], 4-Hydroxy-3,5-dimethoxy-benzoic acid (**6**)[6], 4-Hydroxy benzoic acid (**7**) [7].], 3-Hydroxy-4-methoxy-benzoic acid (**8**) [8], Protocatechuic acid (**9**) [9].

Ladyginoside A (1)[1]: white powder ^{1}H-NMR (600 MHz, CD_3OD) δ_H : 1.61 (m, H-1a), 1.03 (m, H-1b), 1.94 (m, H-2a), 1.73 (m, H-2b), 3.19 (m, H-3), 0.81 (br s, H-5), 1.61 (m, H-6a), 1.43 (m, H-6b), 1.51 (m, H-7a), 1.35 (m, H-7b), 1.61 (m, H-9), 1.89 (m, H-11), 5.24 (br.s, H-12), 1.86 (m, H-15a), 1.05 (m, H-15b), 1.61 (m, H-16a), 1.94 (m, H-16b), 2.91 (dd, *J* = 3.6, 15.1 Hz, H-18), 1.75 (m, H-19a), 1.11 (m, H-19b), 1.43 (m, H-21a), 1.12 (m, H-21b), 1.75 (m, H-22a), 1.55 (m, H-22b), 1.07 (s, H-23), 0.86 (s, H-24), 0.96 (s, H-25), 0.86 (s, H-26), 1.16 (s, H-27), 0.95 (s, H-29), 0.91 (s, H-30) ; 3-GlcA : 4.38 (d, *J* = 7.8 Hz, H-1'), 3.25 (m, H-2'), 3.40 (m, H-3'), 3.63 (m, H-4'), 3.51 (m, H-5') ; 3’-Glc : 4.43 (d, *J* = 7.8 Hz, H-1''), 3.25 (m, H-2''), 3.36 (m, H-3''), 3.24 (m, H-4''), 3.40 (m, H-5''), 3.68 (m, H-6''a), 3.89 (dd, *J* = 1.8, 12.0 Hz, H-6''b). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: 39.8 (C-1), 26.9 (C-2), 90.8 (C-3), 40.1 (C-4), 57.0 (C-5), 19.3 (C-6), 34.1 (C-7), 40.5 (C-8), 48.5 (C-9), 37.9 (C-10), 24.5 (C-11), 123.0 (C-12), 145.9 (C-13), 43.1 (C-14), 29. (C-15), 24.1 (C-16), 48.2 (C-17), 42.9 (C-18), 47.7 (C-19), 31.7 (C-20), 35.2 (C-21), 33.7 (C-22), 28.5 (C-23), 16.9 (C-24), 15.9 (C-25), 17.9 (C-26), 26.4 (C-27), 180.0 (C-28), 24.0 (C-29), 33.7 (C-30); 3-GlcA : 106.5 (C-1'), 75.0 (C-2'), 77.8 (C-3'), 83.3 (C-4'), 76.7 (C-5'), 176.4 (C-6'), 3'-Glc : 104.7 (C-1''), 75.2 (C-2''), 78.1 (C-3''), 71.2 (C-4''), 77.8 (C-5''), 62.4 (C-6'').

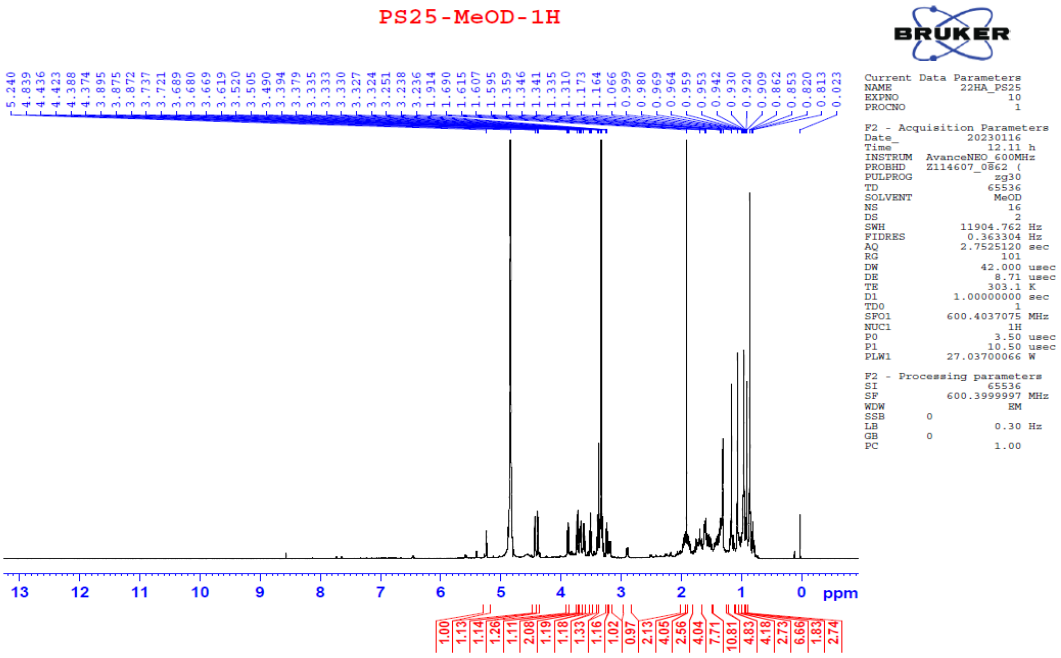


Figure S12: ^{1}H NMR spectra (600 MHz, CD_3OD) of compound **1**

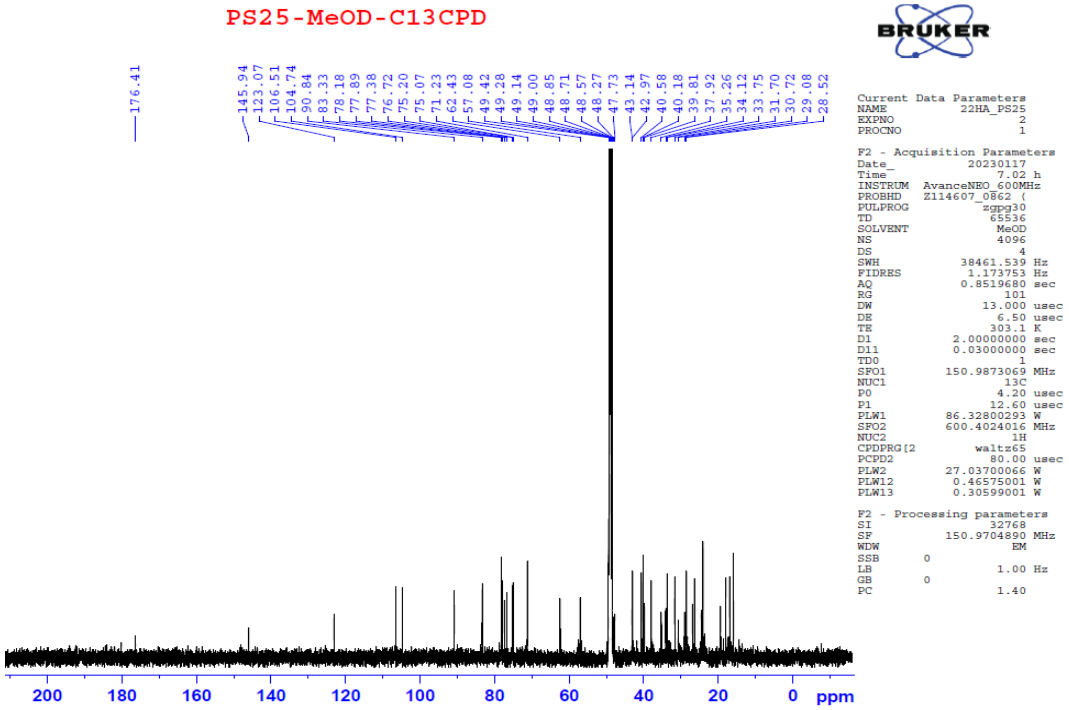


Figure S13: ^{13}C NMR spectra (150 MHz, CD_3OD) of compound **1**

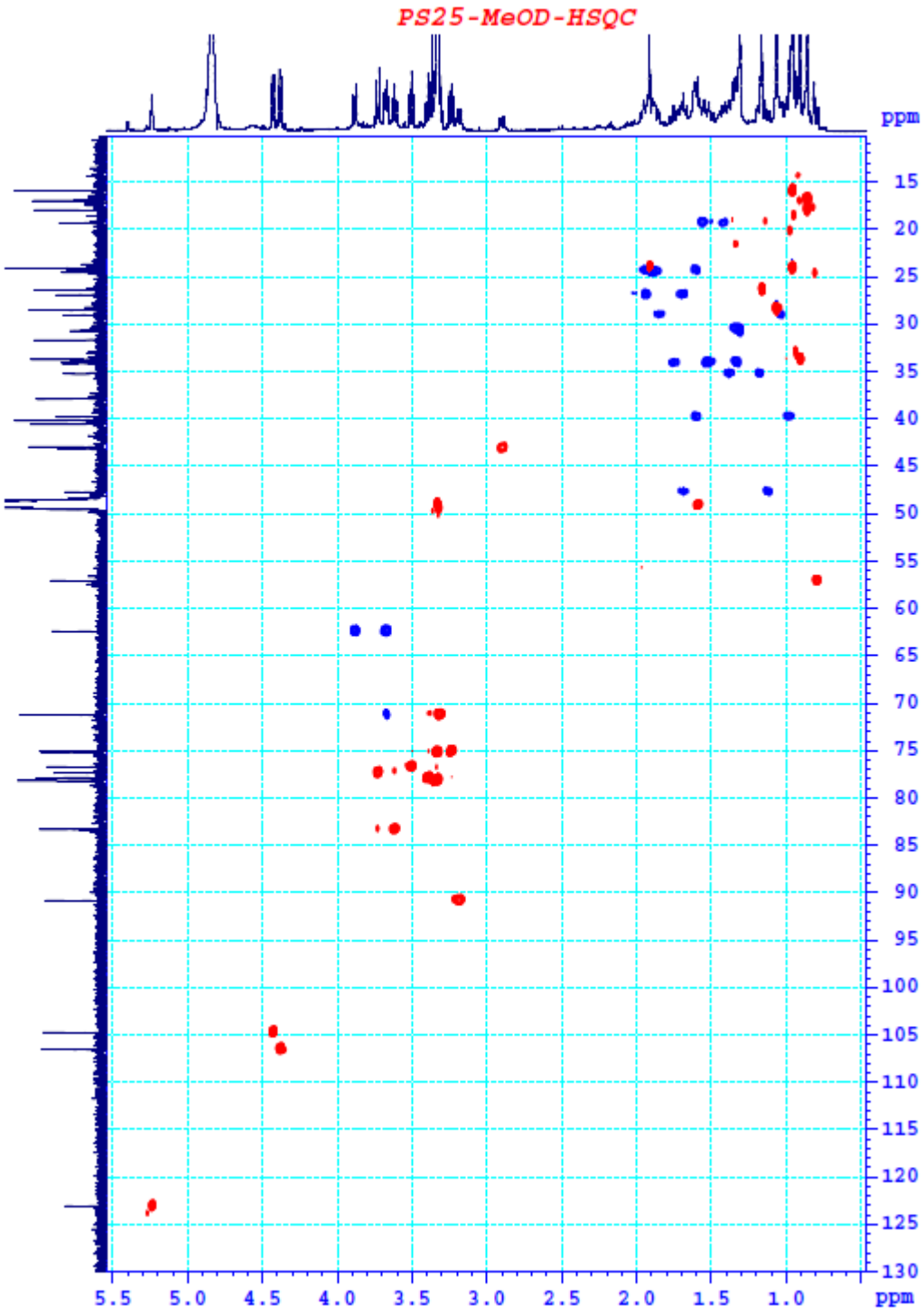


Figure S14: HSQC spectra of compound **1**

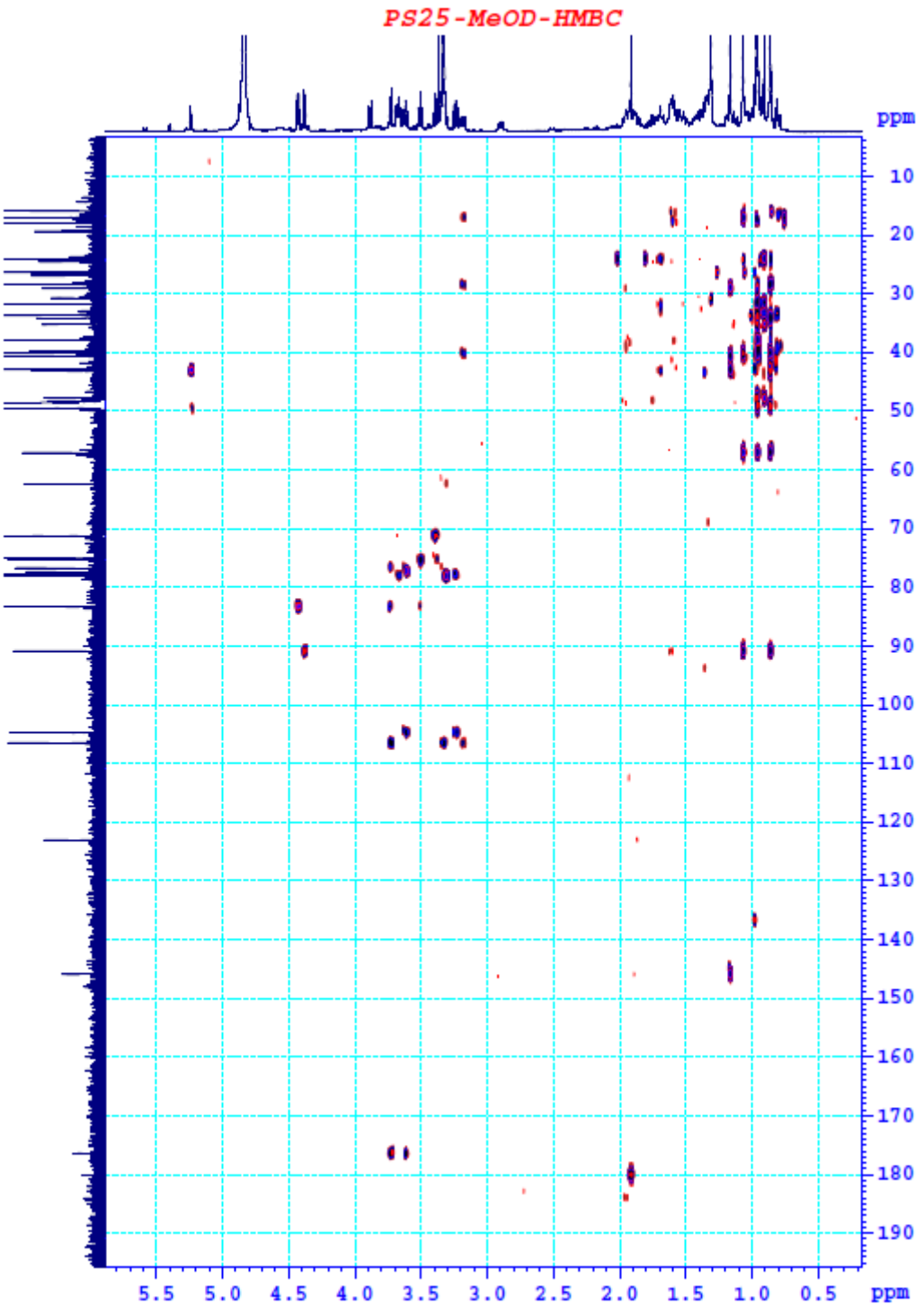


Figure S15: HMBC spectra of compound **1**

Spinasaponin A 28-O-glycoside (2)[2]: white powder; ^{1}H-NMR (600 MHz, CD_3OD) δ_H: 1.59 (m, H-1a), 1.02 (m, H-1b), 2.01 (m, H-2a), 1.63 (m, H-2b), 3.25 (m, H-3), 0.78 (br s, H-5), 1.57 (m, H-6a), 1.43 (m, H-6b), 1.50 (m, H-7a), 1.36 (m, H-7b), 1.59 (m, H-9), 1.90 (m, H-11), 5.26 (br s, 1H, H-12), 1.80 (m, H-15a), 1.08 (m, H-15b), 1.75 (m, H-16a), 2.07 (m, H-16b), 2.88 (dd, J = 3.6, 15.1 Hz, H-18), 1.75 (m, H-19a), 1.15 (m, H-19b), 1.43 (m, H-21a),

1.23 (m, H-21b), 1.75 (m, H-22a), 1.63 (m, H-22b), 1.06 (s, H-23), 0.86 (s, H-24), 0.96 (s, H-25), 0.81 (s, H-26), 1.17 (s, H-27), 0.95 (s, H-29), 0.93 (s, H-30) ; 3-GlcA : 4.38 (d, *J* = 7.8 Hz, H-1'), 3.44 (m, H-2'), 3.62 (m, H-3'), 3.52 (m, H-4'), 3.36 (m, H-5') ; 3'-Glc : 4.43 (d, *J* = 7.8 Hz, H-1''), 3.25 (m, H-2''), 3.36 (m, H-3'', 4'', 5''), 3.71 (m, H-6''a), 3.89 (dd, *J* = 1.8, 12.0 Hz, H-6''b) ; 28-COO-Glc : 5.40 (d, *J* = 8.4 Hz, H-1'''), 3.36 (m, H-2''', 3''', 4''', 5'''), 3.84 (d, *J* = 11.4 Hz, H-6'''a), 3.71 (m, H-6'''b) ^{13}C-NMR (150 MHz, CD_3OD) δ_C: 39.8 (C-1), 26.9 (C-2), 90.8 (C-3), 40.1 (C-4), 57.0 (C-5), 19.3 (C-6), 33.9 (C-7), 40.7 (C-8), 48.5 (C-9), 37.8 (C-10), 24.5 (C-11), 123.8 (C-12), 144.8 (C-13), 42.6 (C-14), 28.9 (C-15), 24.1 (C-16), 48.0 (C-17), 42.9 (C-18), 47.2 9C-19), 31.5 (C-20), 34.9 (C-21), 33.1 (C-22), 28.5 (C-23), 16.9 (C-24), 16.0 (C-25), 17.7 (C-26), 26.2 (C-27), 178.1(28- COOH), 24.0 (C-29), 33.4 (C-30) ; 3-GlcA : 106.5 (C-1'), 78.6 (C-2'), 83.3 (C-3'), 76.7 (C-4'), 77.8 (C-5'), 180.2 (C-6') ; 3'-Glc : 104.7 (C-1''), 75.0 (C-2''), 77.7 (C-3''), 71.2 (C-4''), 77.8 (C-5''), 62.4 (C-6'') ; 28-COO-Glc : 95.7 (C-1'''), 73.9 (C-2'''), 78.1 (C-3'''), 71.1 (C-4'''), 78.3 (C-5'''), 62.4 (C-6''').

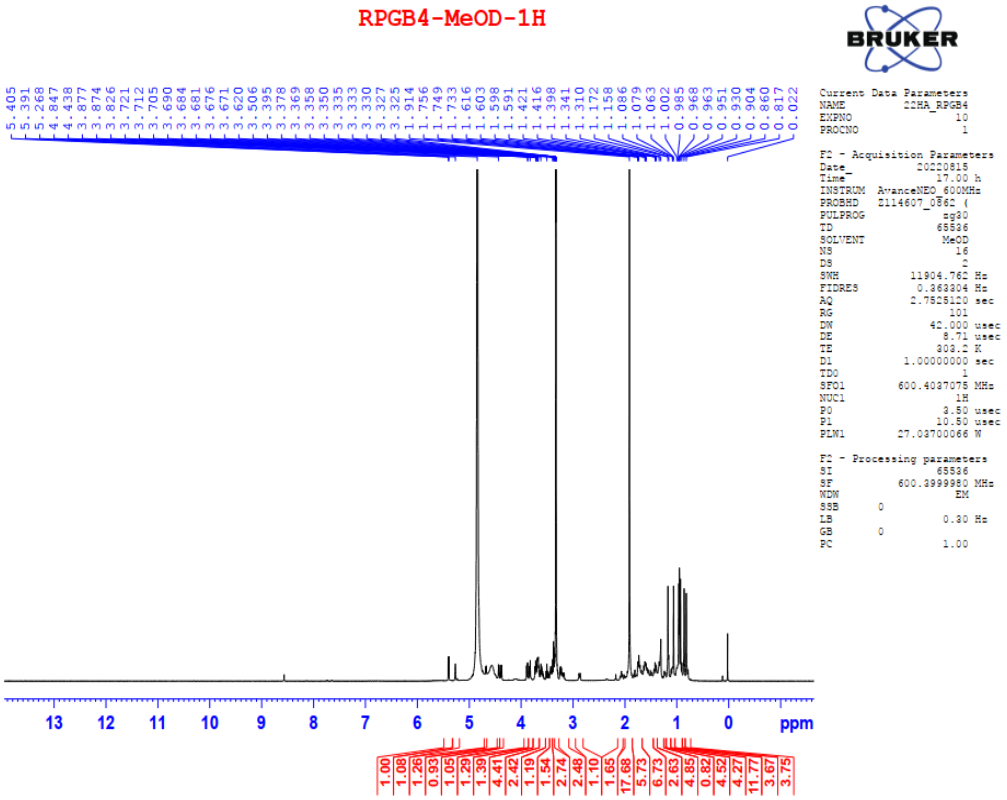


Figure S16: ^{1}H NMR spectra (600 MHz, CD_3OD) of compound **2**

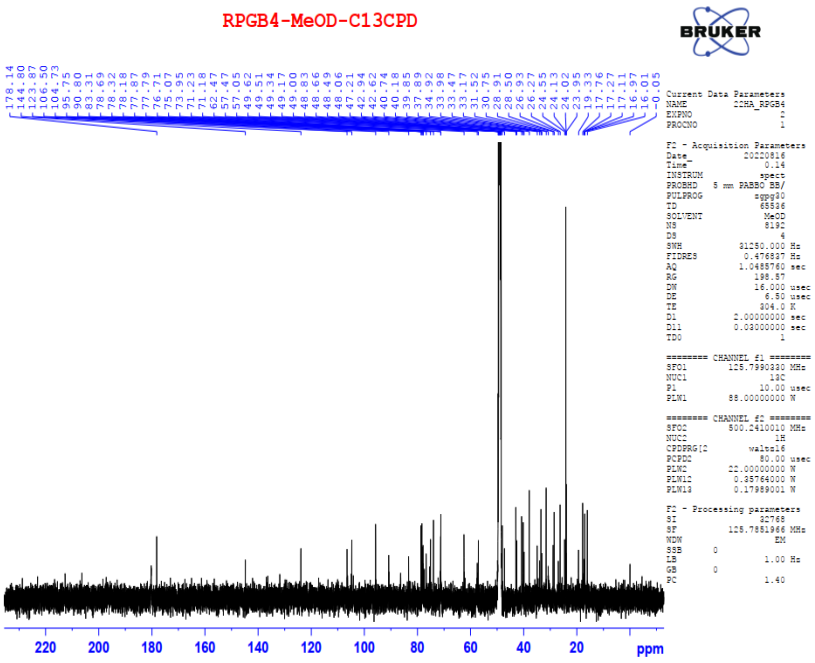


Figure S17: ^{13}C NMR spectra (150 MHz, CD_3OD) of compound **2**

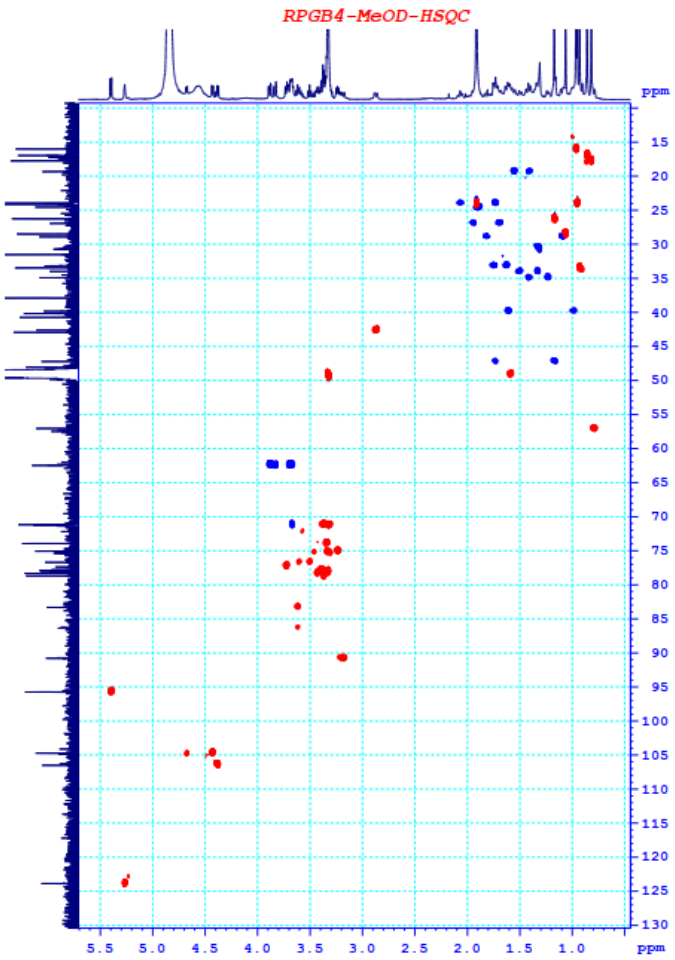


Figure 18:HSQC spectra of compound **2**

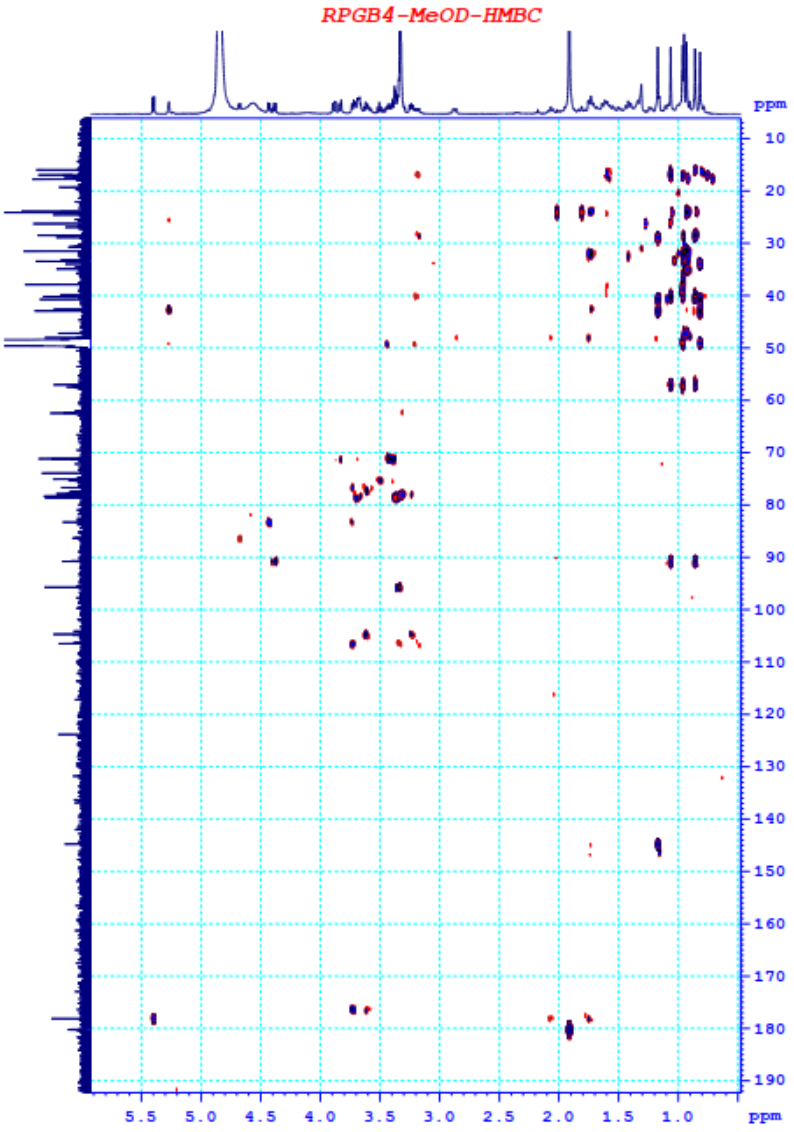


Figure 19: HMBC spectra of compound **2**

Polyscioside J (3) [3]: white powder; ^{1}H-NMR (600 MHz, CD_3OD) δ_H : 1.62 (m, H-1a), 0.98 (m, H-1b), 1.80 (m, H-2a), 1.70 (m, H-2b), 3.19 (m, H-3), 0.79 (br s, H-5), 1.57 (m, H-6a), 1.43 (m, H-6b), 1.52 (m, H-7a), 1.32 (m, H-7b), 1.59 (m, H-9), 1.93 (m, H-11), 5.27 (br.s, H-12), 1.81 (m, H-15a), 1.09 (m, H-15b), 1.77 (m, H-16a), 2.07 (m, H-16b), 2.88 (dd, *J* = 3.6, 15.1 Hz, H-18), 1.72 (m, H-19a), 1.18 (m, H-19b), 1.40 (m, H-21a), 1.25 (m, H-21b), 1.75 (m, H-22a), 1.63 (m, H-22b), 1.07 (s, H-23), 0.86 (s, H-24), 0.97 (s, H-25), 0.80 (s, H-26), 1.18 (s, H-27), 0.93 (s, H-29), 0.95 (s, H-30) ; 3-Me-GlcA : 4.46 (d, *J* = 7.8 Hz, H-1'), 3.25 (m, H-2'), 3.36 (m, H-3'), 3.62 (m, H-4'), 4.03 (d, *J* = 3.6 Hz, H-5'), 3.82 (s, H-7') ; 4'-Glc : 4.33 (d, *J* = 7.8 Hz, H-1''), 3.25 (m, H-2''), 3.36 (m, H-3'', 4'', 5''), 3.70 (m, H-6''a), 3.84 (dd, *J* = 1.8, 12.0 Hz, H-6''b); 28-COO-Glc : 5.41 (d, *J* = 8.4 Hz, H-1'''), 3.36 (m, H-2''', 3''', 4'''), 3.44 (m, H-5'''), 3.84 (d, *J* = 11.4 Hz, H-6'''a), 3.70 (m, H-6'''b). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: 40.1 (C-1), 26.9 (C-2), 91.2 (C-3), 40.1 (C-4), 57.0 (C-5), 19.3 (C-6), 33.9 (C-7), 40.7 (C-8), 48.8 (C-9), 37.8 (C-10), 24.5 (C-11), 123.8 (C-12), 144.8 (C-13), 42.6 (C-14),

28.9 (C-15), 23.9 (C-16), 48.0 (C-17), 42.9 (C-18), 47.2 (C-19), 31.5 (C-20), 34.8 (C-21), 33.1 (C-22), 28.4 (C-23), 16.9 (C-24), 15.9 (C-25), 17.7 (C-26), 26.2 (C-27), 178.0 (C-28), 33.4 (C-29), 23.9 (C-30) ; 3-Me-GlcA : 106.9 (C-1'), 75.5 (C-2'), 76.3 (C-3'), 81.9 (C-4'), 74.9 (C-5'), 170.8 (C-6'), 53.1 (C-7') ; 4'-Glc : 104.6 (C-1"), 74.6 (C-2"), 78.1 (C-3"), 71.3 (C-4"), 77.7 (C-5"), 62.4 (C-6") ; 28-COO-Glc : 95. (C-1'"), 73.9 (C-2'"), 78.1 (C-3'"), 71.1 (C-4'"), 78.6 (C-5'"), 62.4 (C-6'").

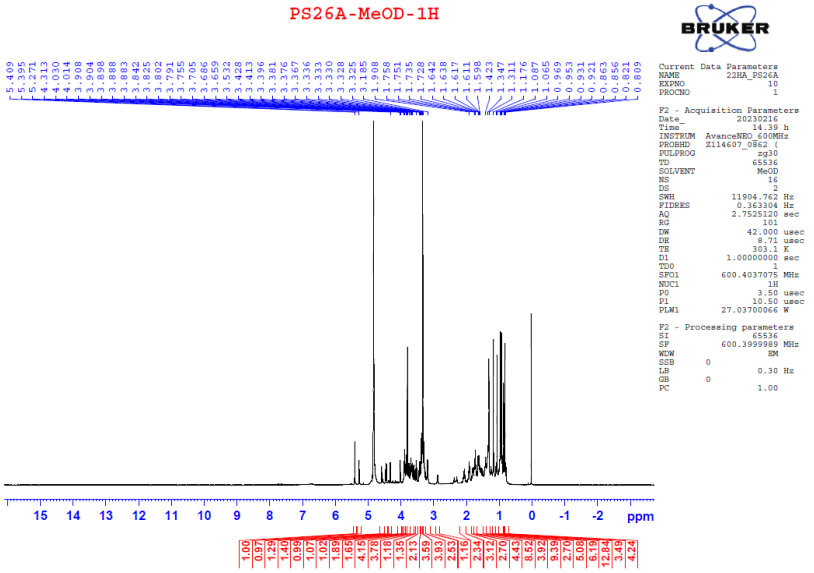


Figure 20: ^{1}H NMR spectra (600 MHz, CD_3OD) of compound **3**

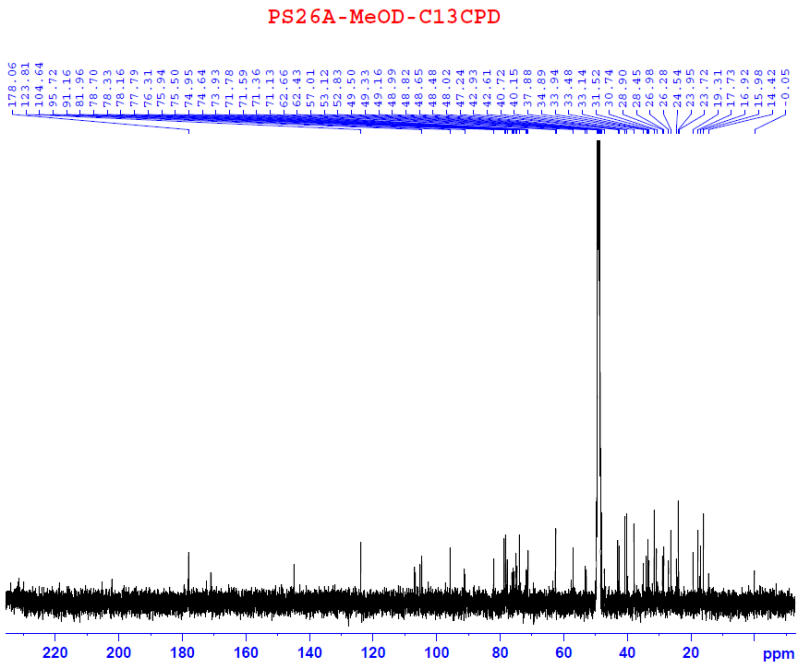


Figure 21: ^{13}C NMR spectra (150 MHz, CD_3OD) of compound **3**

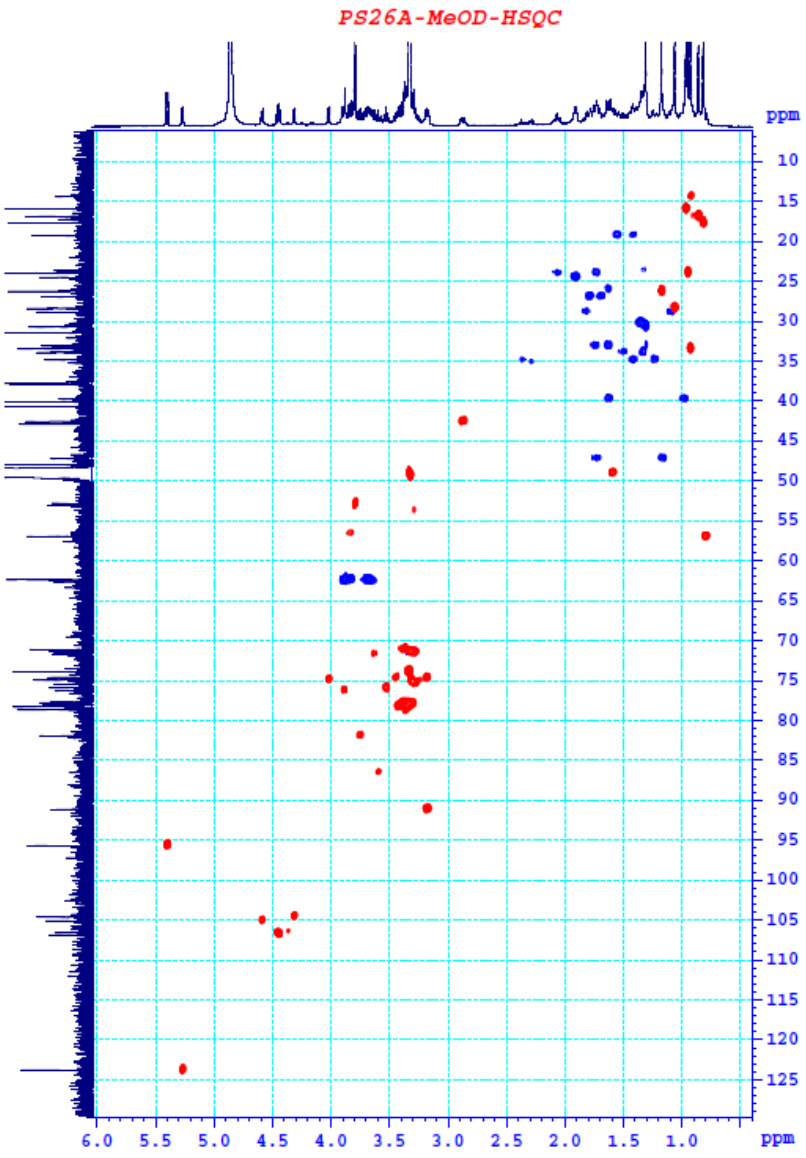


Figure 22: HSQC spectra of compound **3**

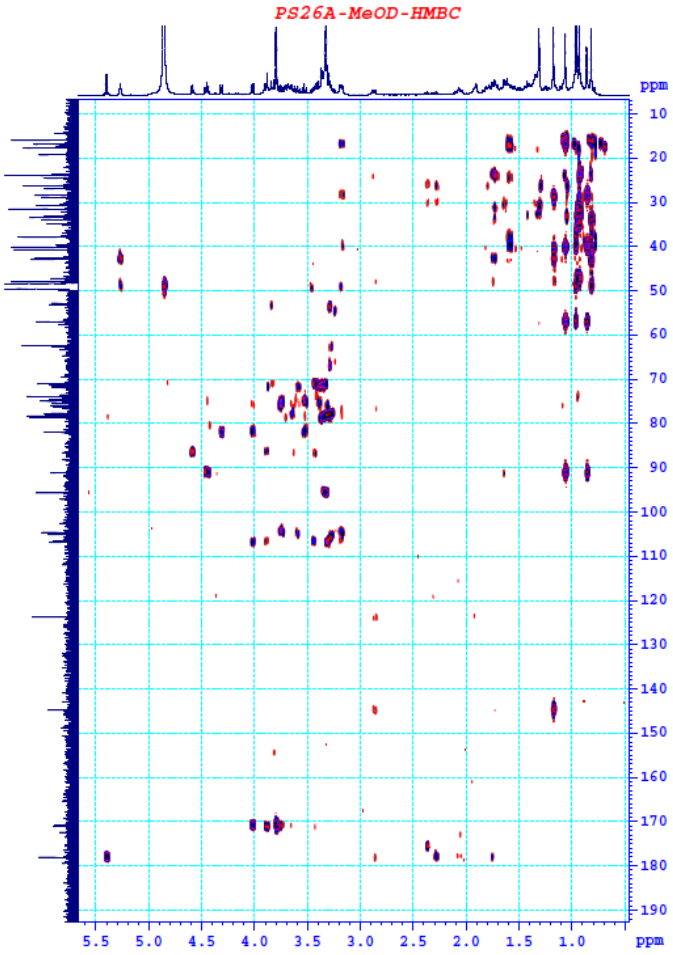


Figure 23: HMBC spectra of compound **3**

3-O-β-D–glucopyranosyl-(1→4)-β-D-glucuronopyranosyloleanolic acid methyl ester (4) [4]: white powder; ^{1}H-NMR (600 MHz, CD_3OD) δ_H : 1.61(m, H-1a), 1.03 (m, H-1b), 1.94 (m, H-2a), 1.73 (m, H-2b), 3.19 (t, *J* = 6.0 Hz, H-3), 0.81 (br s, H-5), 1.61 (m, H-6a), 1.43 (m, H-6b), 1.51 (m, H-7a), 1.35 (m, H-7b), 1.61 (m, H-9), 1.89 (m, H-11), 5.24 (br s, H-12), 1.86 (m, H-15a), 1.05 (m, H-15b), 1.61 (m, H-16a), 1.94 (m, H-16b), 2.91 (brd, *J* = 13.2 Hz, H-18), 1.75 (m, H-19a), 1.11 (m, H-19b), 1.43 (m, H-21a), 1.12 (m, H-21b), 1.75 (m, H-22a), 1.55 (m, H-22b), 1.07 (s, H-23), 0.86 (s, H-24), 0.96 (s, H-25), 0.86 (s, H-26), 1.17 (s, H-27), 0.93 (s, H-29), 0.91 (s, H-30) ; 3-Me-GlcA : 4.45 (d, *J* = 7.8 Hz, H-1'), 3.25 (m, H-2'), 3.36 (m, H-3'), 3.62 (m, H-4'), 4.03 (d, *J* = 9.6 Hz, H-5'), 3.80 (s, H-7') ; 4'-Glc : 4.33 (d, *J* = 7.8 Hz, H-1''), 3.25 (m, H-2''), 3.36 (m, H-3'', 4'', 5''), 3.75 (m, H-6''a), 3.90 (d, *J* = 10.8 Hz, H-6''b). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: 39.8 (C-1), 26.9 (C-2), 91.2 (C-3), 40.1 (C-4), 57.0 (C-5), 19.3 (C-6), 34.1 (C-7), 40.5 (C-8), 48.5 (C-9), 37.9 (C-10), 24.5 (C-11), 122.9 (C-12), 146.0 (C-13), 43.1 (C-14), 29.0 (C-15), 24.0 (C-16), 48.2 (C-17), 42.9 (C-18), 47.8 (C-19), 31.7 (C-20), 35.2 (C-21), 33.7 (C-22), 28.4 (C-23), 16.9 (C-24), 15.9 (C-25), 18.0 (C-26), 26.4 (C-27), 180.0 (C-28), 24.1 (C-29), 33.7 (C-30) ; 3-Me-GlcA : 106.8 (C-1'), 74.9 (C-2'), 75.9 (C-3'), 81.9 (C-4'), 74.9 (C-5'), 170.9 (C-6'), 53.1 (C-7') ; 4'-Glc : 104.6 (C-1''), 74.6 (C-2''), 78.1 (C-3''), 71.3 (C-4''), 77.7 (C-5''), 62.4 (C-6'').

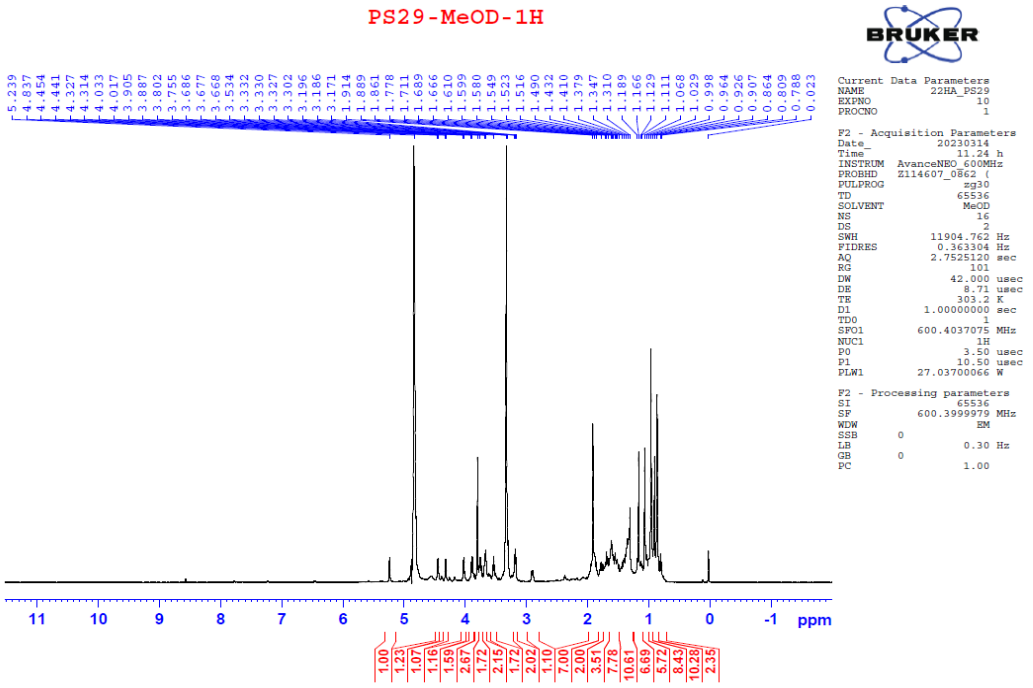


Figure 24: ^{1}H NMR spectra (600 MHz, CD_3OD) of compound **4**

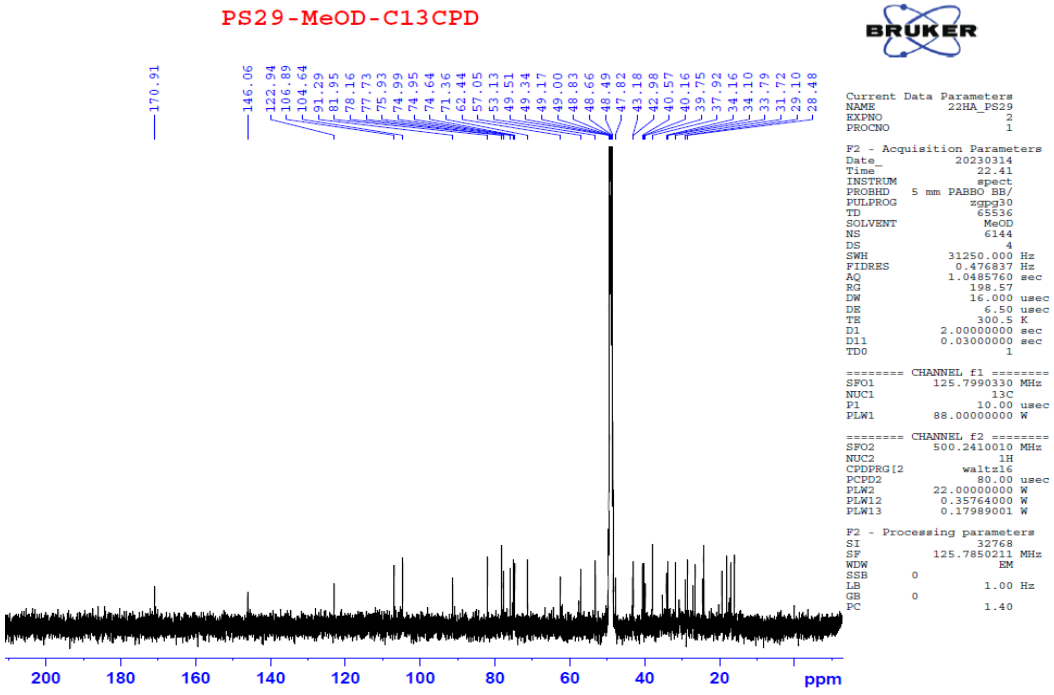


Figure 25: ^{13}C NMR spectra (125 MHz, CD_3OD) of compound **4**

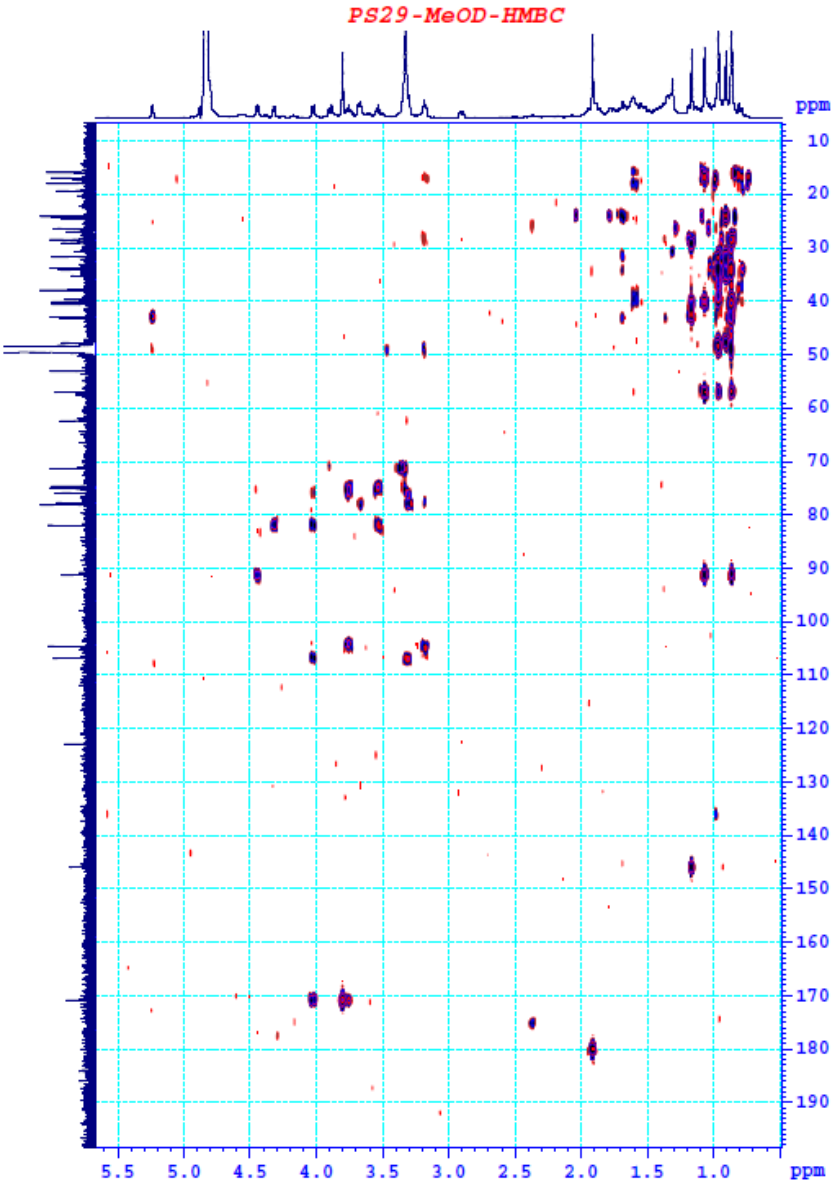


Figure 26:HMBC spectra of compound **4**

Stigmasta-4,22-dien-3,7-diol (5) [5]: white crystalline powder; ^{1}H-NMR (600 MHz, CD_3OD) δ_H: 1.88 (m, H-1a), 1.22 (m, H-1b), 1.78 (m, H-2a), 1.53 (m, H-2b), 3.50 (m, H-3), 2.29 (m, H-4), 5.56 (dd, *J* = 1.5, 4.5 Hz, H-6), 3.78 (m, H-7), 0.76 (s, H-18), 1.03 (s, H-19), 0.86 (d, *J* = 7.2 Hz, H-21), 5.08 (dd, *J* = 9.0, 15.0 Hz, H-22), 5.21 (dd, *J* = 8.4, 15.0 Hz, H-23), 1.11 (d, *J* = 6.0 Hz, H-26), 0.90 (d, *J* = 5.4 Hz, H-27), 0.85 (t, *J* = 6.0 Hz, H-29). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: 38.1 (C-1), 32.1 (C-2), 72.0 (C-3), 43.1 (C-4), 146.6 (C-5), 124.9 (C-6), 65.9 (C-7), 38.5 (C-8), 41.9 (C-9), 37.3 (C-10), 21.8 (C-11), 40.5 (C-12), 42.9 (C-13), 50.7 (C-14), 26.5 (C-15), 30.2 (C-16), 57.3 (C-17), 12.3 (C-18), 18.6 (C-19), 41.9 (C-20), 19.4 (C-21), 130.6 (C-22), 139.8 (C-23), 52.8 (C-24), 33.2 (C-25), 19.4 (C-26), 21.5 (C-27), 25.1 (C-28), 12.5 (C-29).

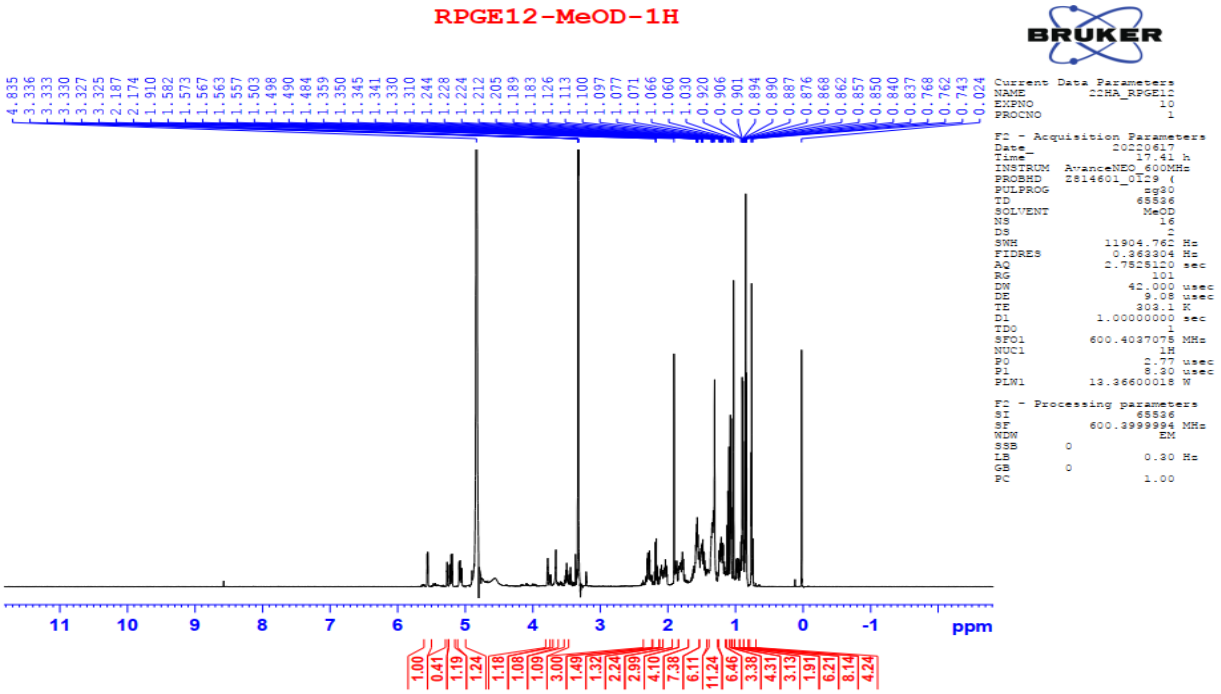


Figure 27: ^{1}H NMR spectra (600 MHz, CD_3OD) of compound **5**

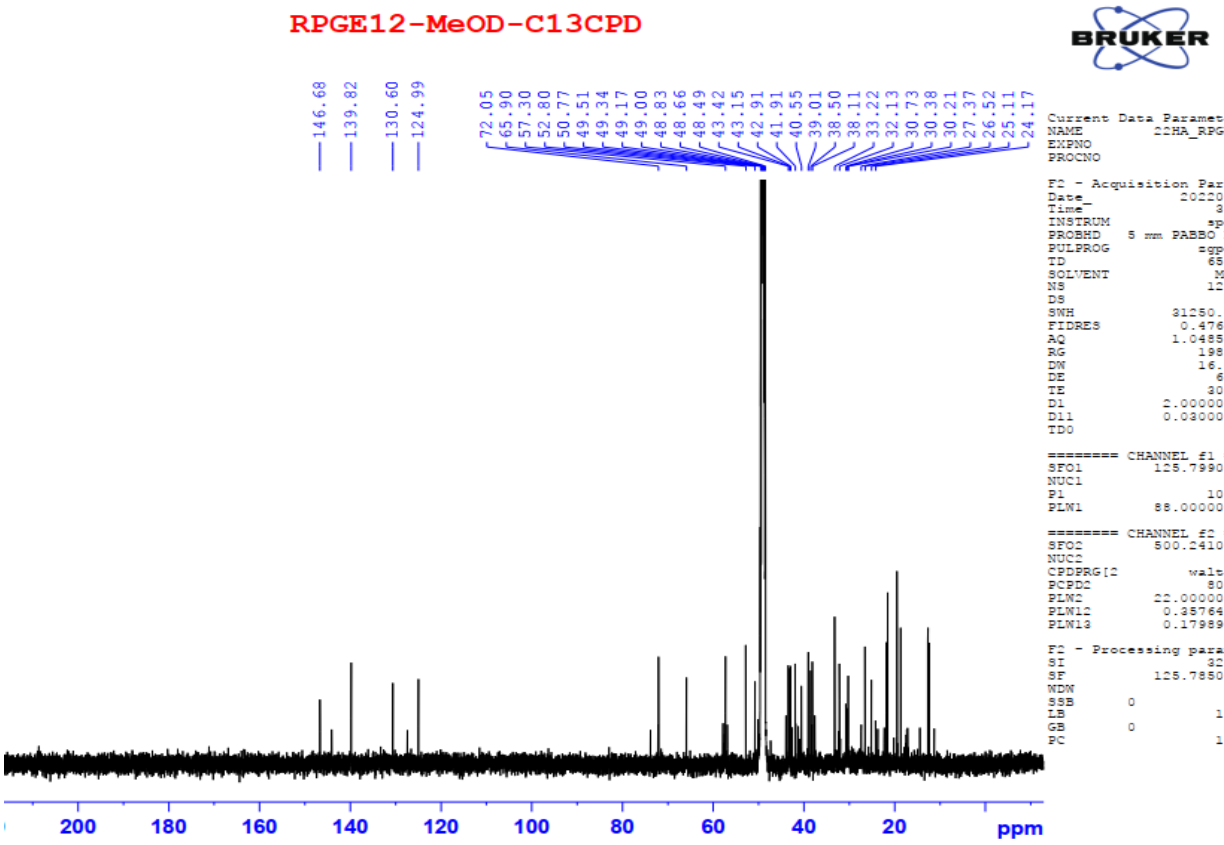


Figure 28: ^{13}C NMR spectra (150 MHz, CD_3OD) of compound **5**

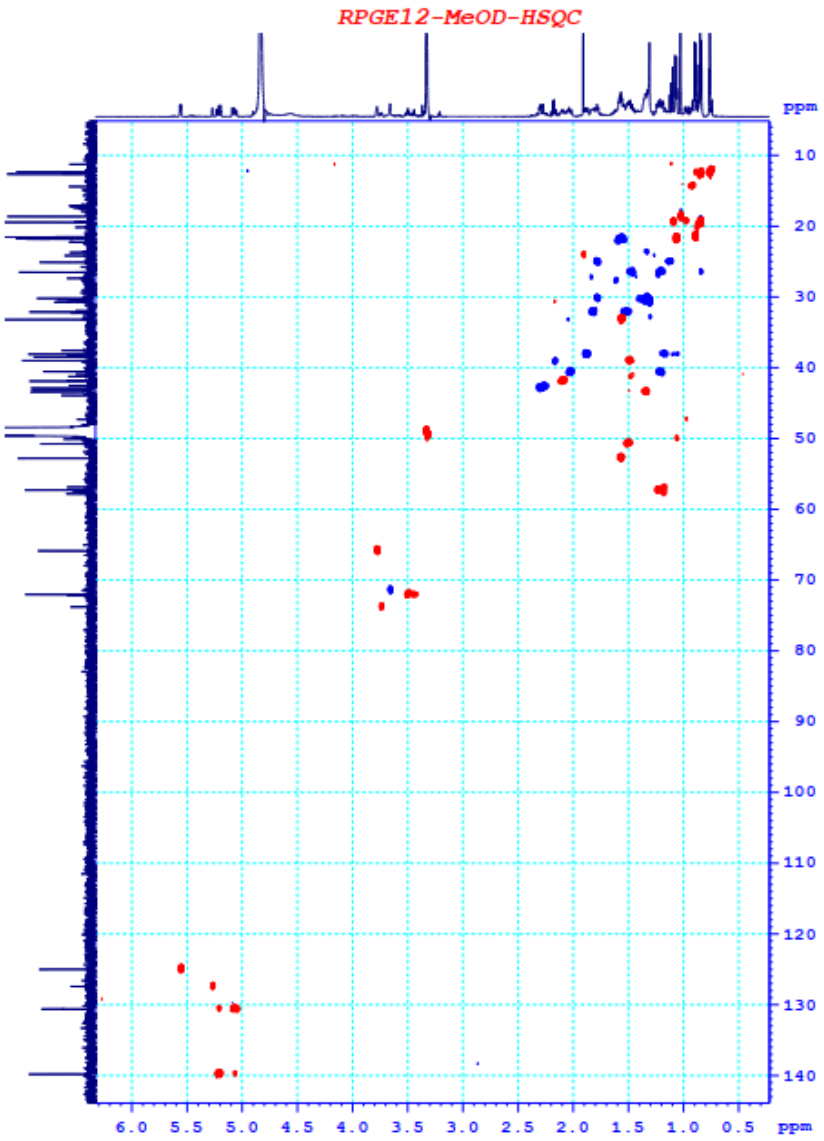


Figure 29: HSQC spectra of compound **5**

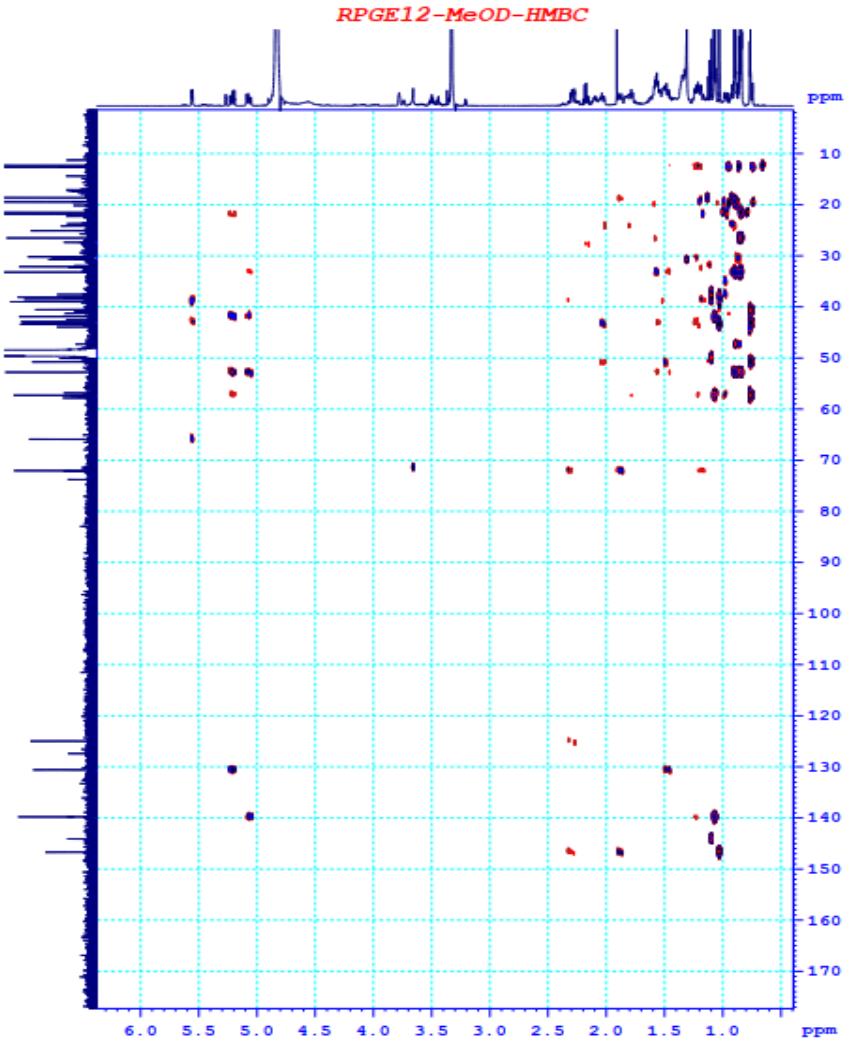


Figure 30: HMBC spectra of compound **5**

4-Hydroxy-3,5-dimethoxy-benzoic acid (6) [6]: white powder;^{1}H-NMR (600 MHz, CD_3OD) δ_H: 7.35 (br s, 2H, H-2, 6), 3.89 (br s, 6H, 3, 5- OCH_3).^{13}C-NMR (150 MHz, CD_3OD) δ_C: 127.1 (C-1), 108.1 (C-2, 6), 148.5 (C-3, 5), 139.8 (C-4), 56.7 (3,5-OCH_3), 173.5 (COOH).

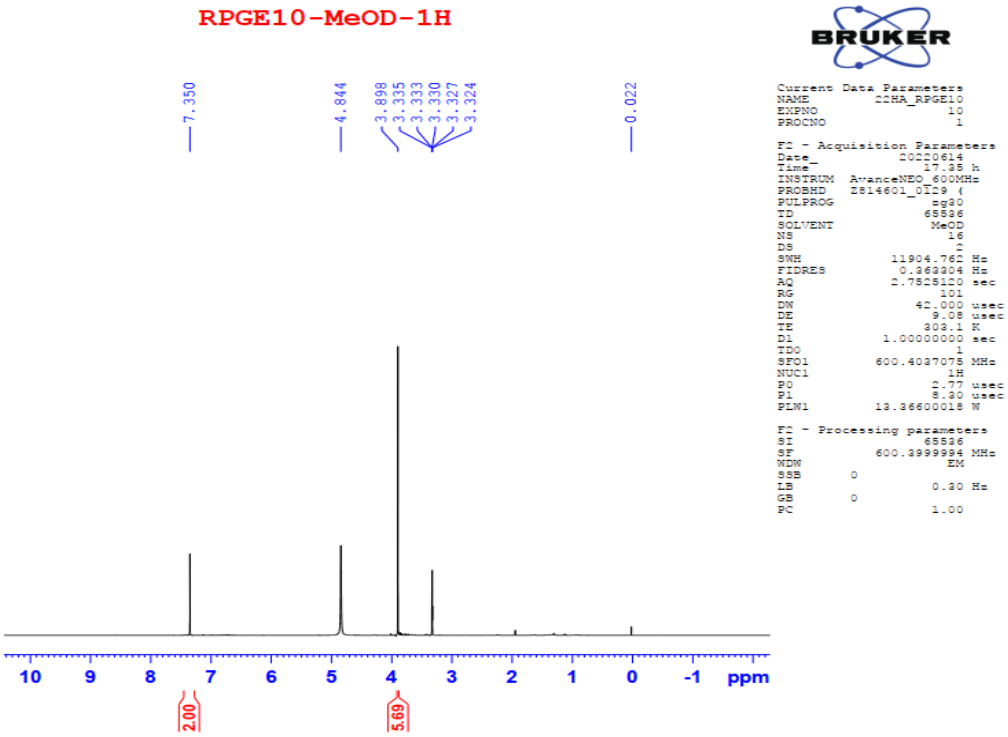


Figure 31: ^{1}H NMR spectra (600 MHz, CD_3OD) of compound **6**

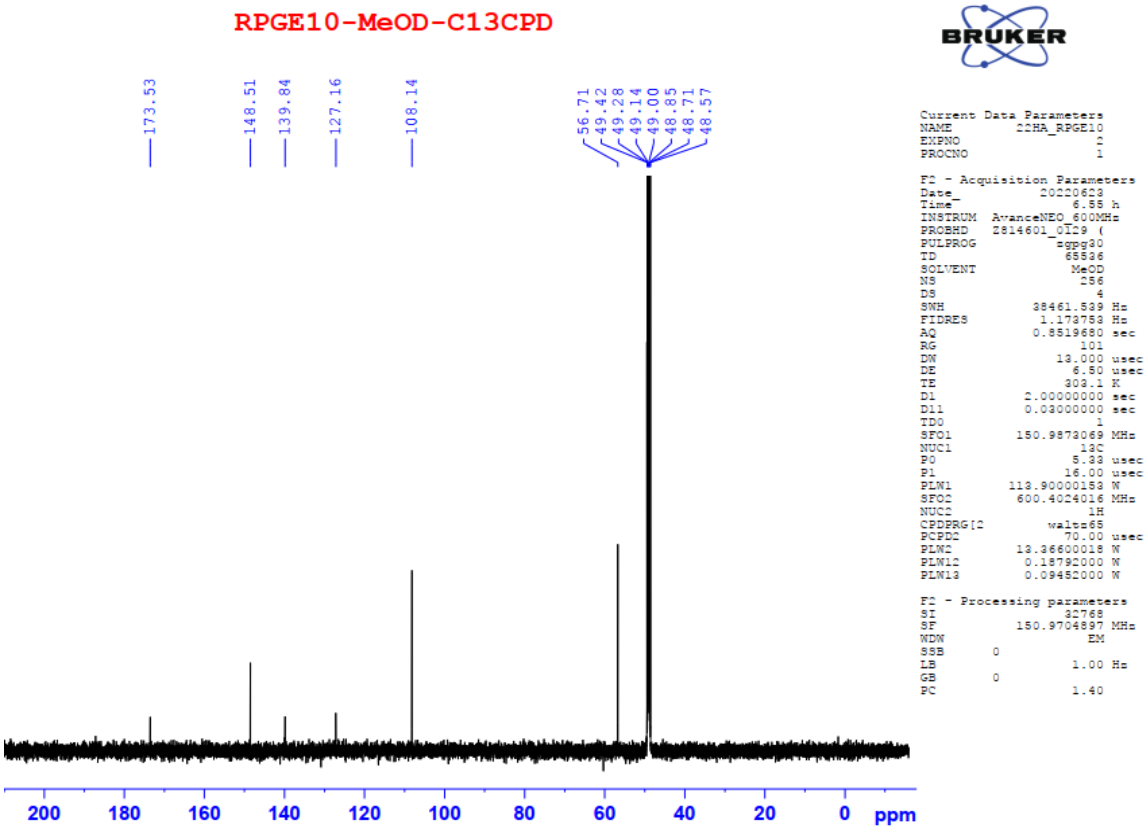


Figure 32: ^{13}C NMR spectra (150 MHz, CD_3OD) of compound **6**

4-Hydroxy benzoic acid (7) [7]: white powder;^{1}H-NMR (600 MHz, CD_3OD) δ_H:7.85 (d, J = 9.0 Hz, H-2, 6), 6.77 (d, J = 9.0 Hz, H-3, 5). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: 128.7 (C-1), 132.4 (C-2, 6), 115.3 (C-3, 5), 161.2 (C-4), 174.5 (COOH).

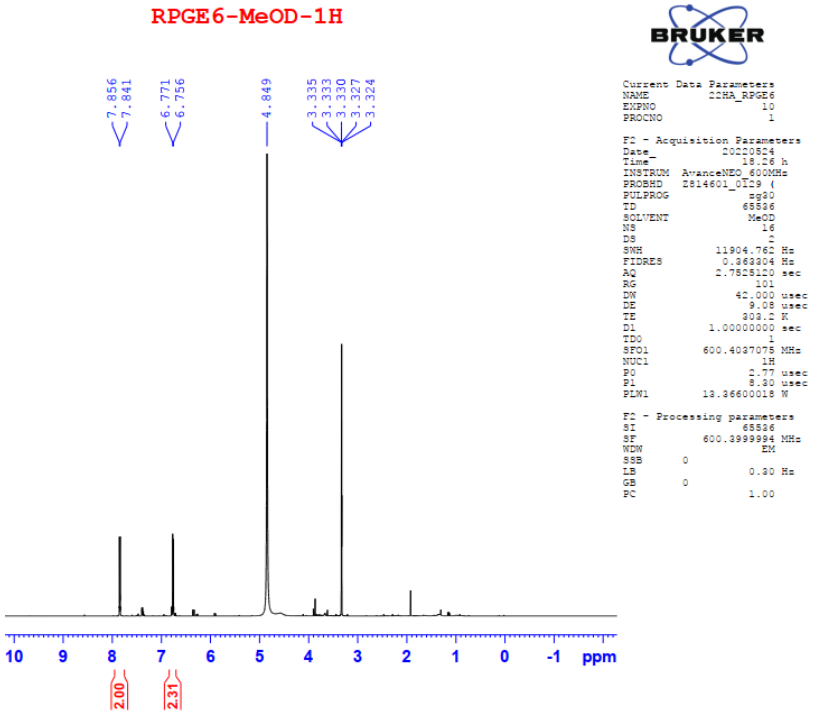


Figure 33: ^{1}H NMR spectra (600 MHz, CD_3OD) of compound **7**

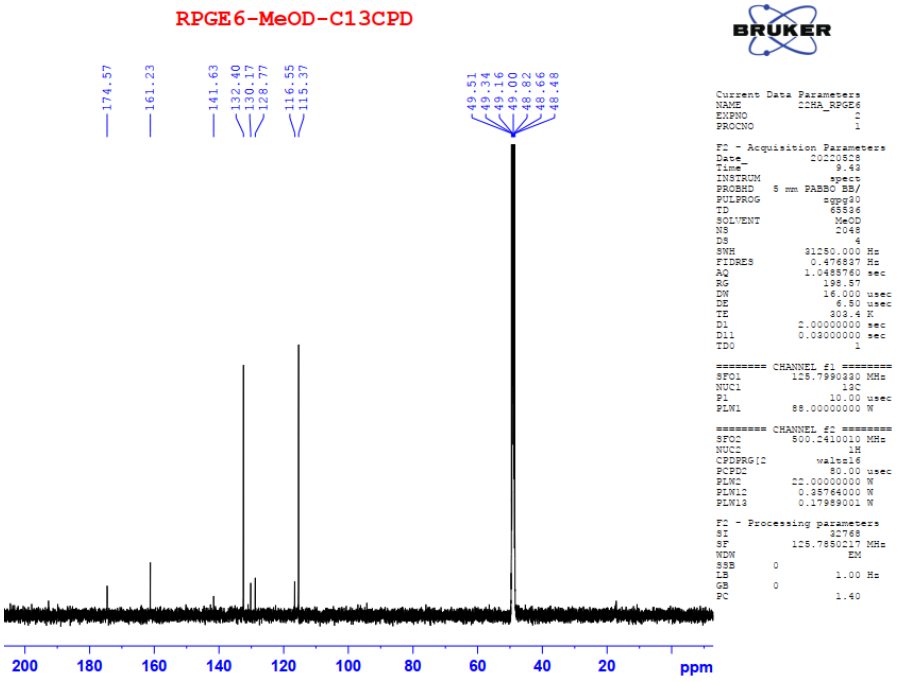


Figure 34:^{13}C NMR spectra (150 MHz, CD_3OD) of compound **7**

3-Hydroxy-4-methoxy-benzoic acid (8) [8]: white powder; ^{1}H-NMR (600 MHz, CD_3OD) δ_H : 7.57 (d, *J* = 2.4 Hz, H-2), 6.86 (d, *J* = 9.0 Hz, H-5), 7.58 (dd, *J* = 1.8, 9.0 Hz, H-6), 3.91 (s, OCH_3). ^{13}C-NMR (150 MHz, CD_3OD) δ_C: 123.1 (C-1), 115.8 (C-2), 148.6 (C-3), 152.6 (C-4), 113.8 (C-5), 125.2 (C-6), 56.4 (OCH_3), 170.0 (COOH).

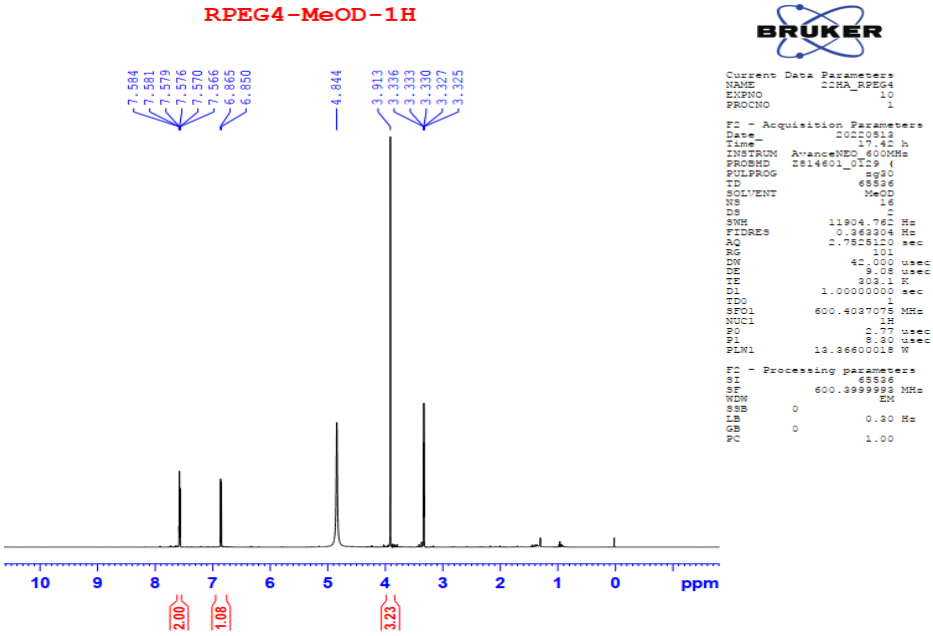


Figure 35: ^{1}H NMR spectra (600 MHz, CD_3OD) of compound **8**

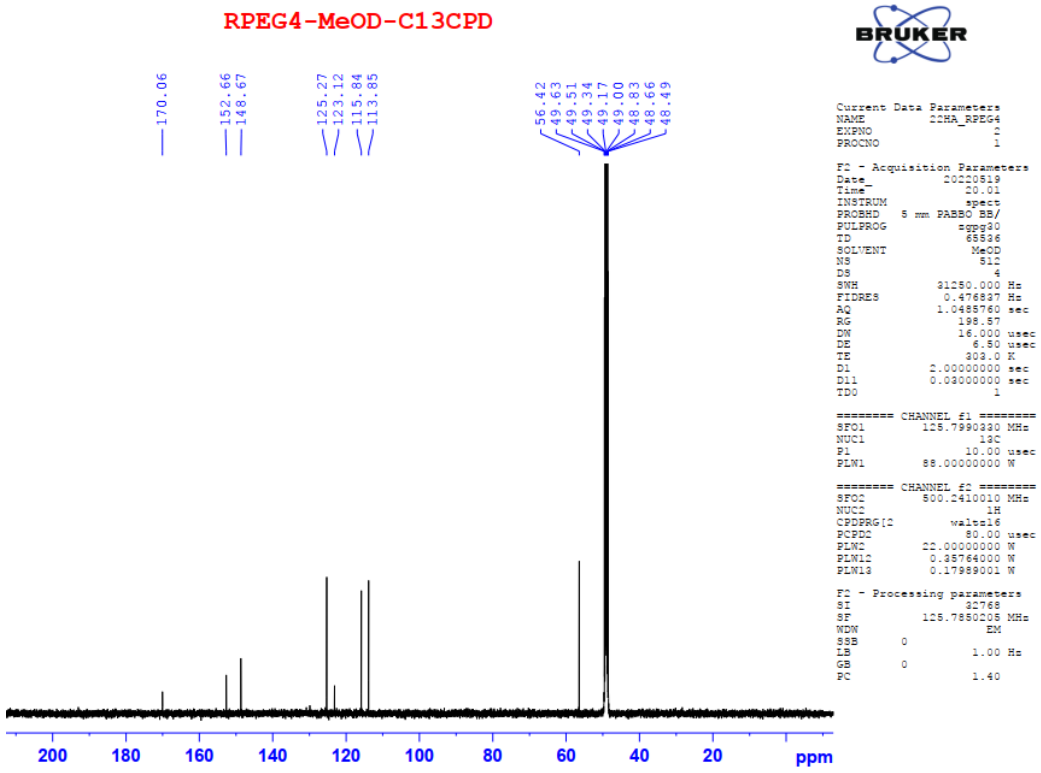


Figure 36: ^{13}C NMR spectra (125 MHz, CD_3OD) of compound **8**

Protocatechuic acid (9)[9]: white powder;[1]H-NMR (600 MHz, CD_3OD) δ_H: 7.45 (d, J = 1.8 Hz, H-2), 6.78 (d, J = 8.4 Hz, H-5), 7.41 (dd, J = 1.8, 8.4 Hz, H-6). [13]C-NMR (150 MHz, CD_3OD) δ_C: 123.3 (C-1), 117.8 (C-2), 149.9 (C-3), 144.5 (C-4), 115.4 (C-5), 127.5 (C-6), 173.4 (COOH).

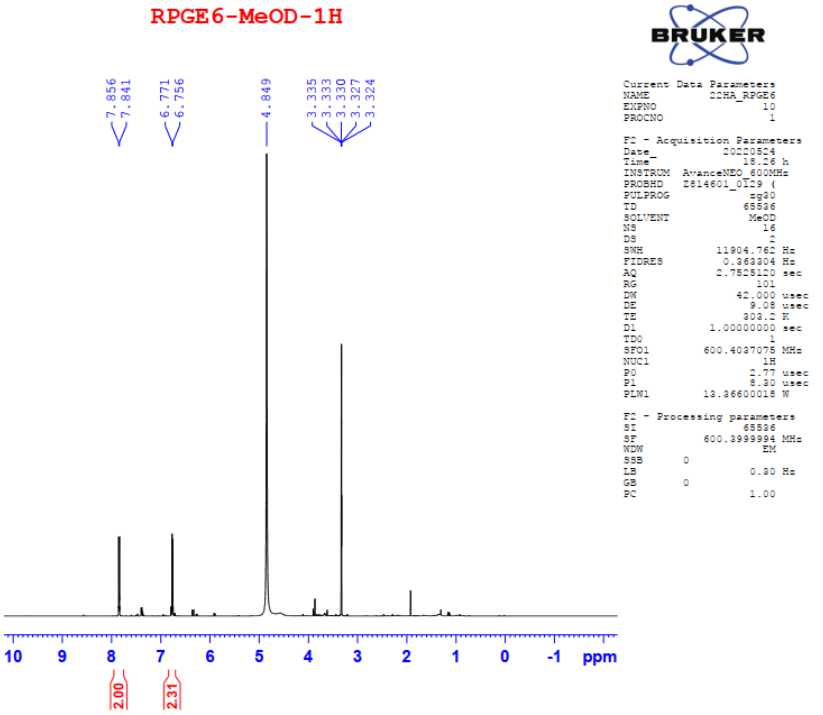


Figure 37: [1]H NMR spectra (600 MHz, CD_3OD) of compound **9**

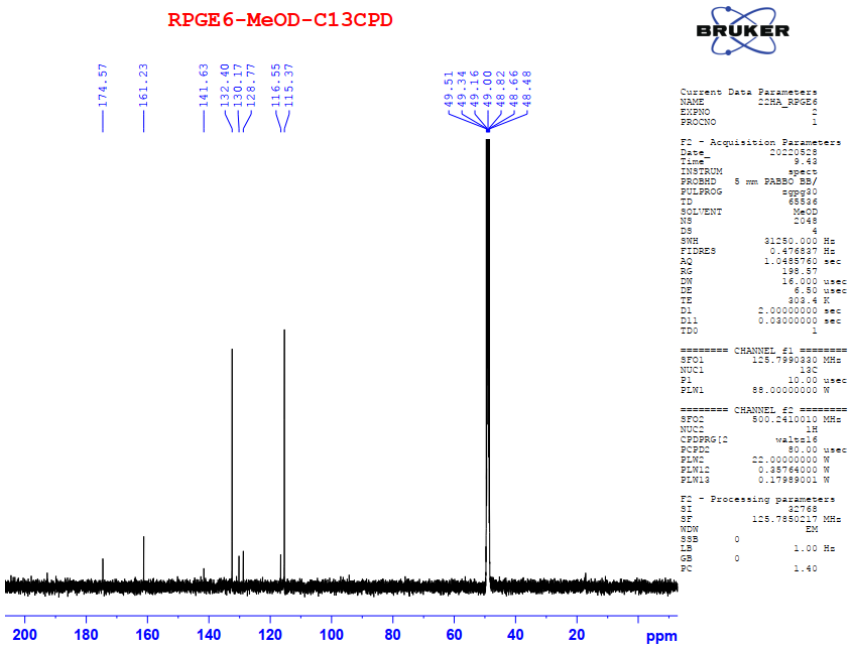


Figure 38: [13]C NMR spectra (150 MHz, CD_3OD) of compound **9**

2.2. α-Glucosidase Assay

The α-glucosidase (CAS No 9001-42-7, Sigma-Aldrich, St. Louis, MO) enzyme inhibition assay was performed according to the previously described method [10]. The sample solution (dissolved in dimethyl sulfoxide and deion water to give the concentrations ranging from 4 to 256 µg/ml) and 0.2 U/ml α-glucosidase were mixed in 100 mM phosphate buffer (pH 6.8). After 5 min pre-incubation, 2.5 mM *p*-nitrophenyl-*α*-D-glucopyranoside solution was added, and the solution was incubated at 37°C for 30 min. The reaction was stopped using sodium carbonate. The absorbance of released *p*-nitrophenol was measured at 410 nm by using a BIOTEK machine. Acarbose was used as a reference compound. α-glucosidase inhibitory activity for each sample was calculated as follows:

$$\text{Inhibitory activity (\%)} = \frac{A\,(control) - A\,(sample)}{A\,(control)} \times 100$$

2.3. Molecular Docking and Network Pharmacology

Molecular docking was performed using MOE 2015.10 to explore the bioactive compounds and enzyme. The 3D enzyme structure was retrieved from the RCSB Protein Data Bank (PDB code: 3A4A). The 3D structure of isomaltase has 85% similar and 72% identical sequencing with α-glucosidase [11]. Binding interactions between ligands and target protein were analyzed by PyMol and Discovery Studio 2021.

2.4. The target screening of P. serrata roots related to diabetes and the construction of compounds-targets network

Isolated compounds were inputted into the Swiss Target Prediction database and SuperPred (**http://prediction.charite.de/**) to obtain the potential targets. DisGeNet database was used to acquire gene symbols of type-2-diabetes-related targets. Overlapping targets were used for the construction of the compounds-targets network related to type 2 diabetes. Cytoscape 3.10.0 was used for analysis and visualization.

2.5. The Construction of PPI Network

The protein-protein interaction was constructed by STRING database and then analyzed and visualized by Cytoscape. The species was defined as “Homo sapiens” and the protein interaction relationship was determined based on high confidence (0.700). Key targets were identified by using the CytoNCA plugin with Betweenness, Closeness, Degree and Network methods.

2.6. GO and KEGG Analysis

GO-KEGG enrichment analysis was performed by using the DAVID database. The GO enrichment analysis resulted in three categories: GO biological process, GO cellular component and GO molecular function.

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