Supplementary Information

Phytochemical Profiling of *Euphorbia tirucalli* Linn. Latex and Evaluation of its *In Vitro* Antibacterial Activity against Resistant *Klebsiella pneumoniae*: An Integrative Network Pharmacology and Molecular Dynamics Simulation Study

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Abstract

A phytochemical investigation of *Euphorbia tirucalli* Linn. (F. Euphorbiaceae) latex resulted in the isolation of five known compounds, namely euphol (1), euph-8-enol (2), gallic acid (3), methyl gallate (4), and rutin (5). The chemical structures of the isolated compounds were unambiguously established by extensive nuclear magnetic resonance (NMR) spectroscopic analysis. The antimicrobial activities of these compounds were evaluated against *Klebsiella pneumoniae* (ATCC 13883), extended-spectrum *β*-lactamase (ESBL)–producing *K. pneumoniae*, and carbapenem-resistant *K. pneumoniae* using the microbroth dilution method. Among the tested compounds, methyl gallate (4) exhibited the strongest activity against *K. pneumoniae* (ATCC 13883) with a minimum inhibitory concentration (MIC) of 0.01 mM, while euphol (1) showed the highest activity against ESBL *K. pneumoniae* (MIC = 13.12 mM). Notably, euph-8-enol (2) demonstrated the most potent inhibitory effect against carbapenem-resistant *K. pneumoniae,* with an MIC of 0.69 mM. Network analysis identified 33 host-response targets relevant to *Klebsiella* infection, enriched in pattern-recognition receptor signaling and inflammatory defense programs, particularly the Toll-like receptor and NOD-like pathways, alongside cytokine/chemokine-mediated recruitment and inflammasome-associated signaling. Molecular docking against *Klebsiella pneumoniae* LpxH (PDB: 8QK2) showed the strongest predicted affinity for euphol (1) (–8.13 kcal/mol). MD simulation of the euphol (1)–LpxH complex over 100 ns supported overall system stability, evidenced by a stable protein backbone RMSD, maintained compactness (Rg), equilibrated potential energy, and intermittent hydrogen bonding consistent with predominantly hydrophobic binding. Collectively, these findings suggested that *E. tirucalli*, with euphol as the top-ranked binder, could provide promising lead scaffolds for anti-*Klebsiella* development, warranting further *in vitro* validation of LpxH inhibition and antibacterial efficacy against resistant *Klebsiella* strains.

Keywords: *Euphorbia tirucalli*; Euphol; *Klebsiella pneumoniae*; LpxH; Network pharmacology; Molecular dynamics simulation.

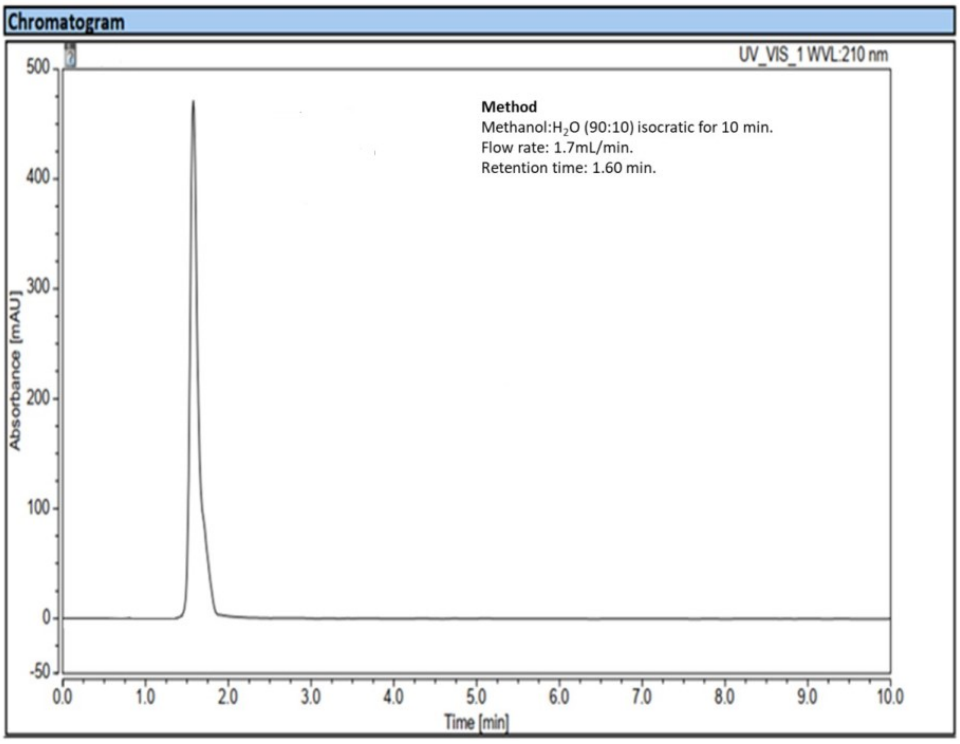

Figure S1. Impurity chart for compound 1

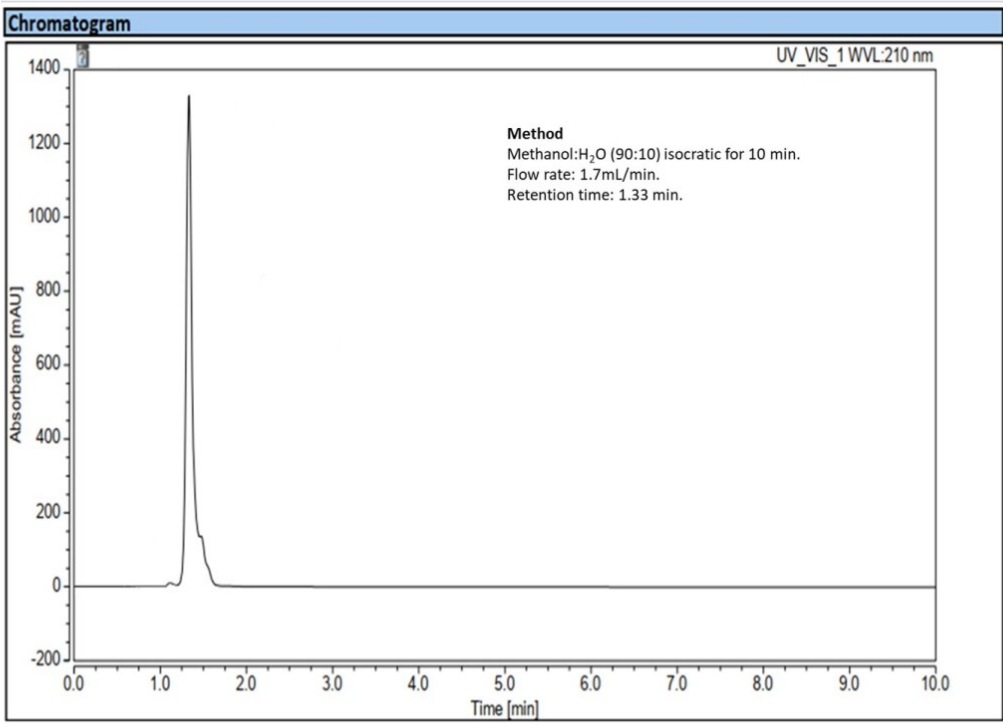

Figure S2. Impurity chart for compound 2

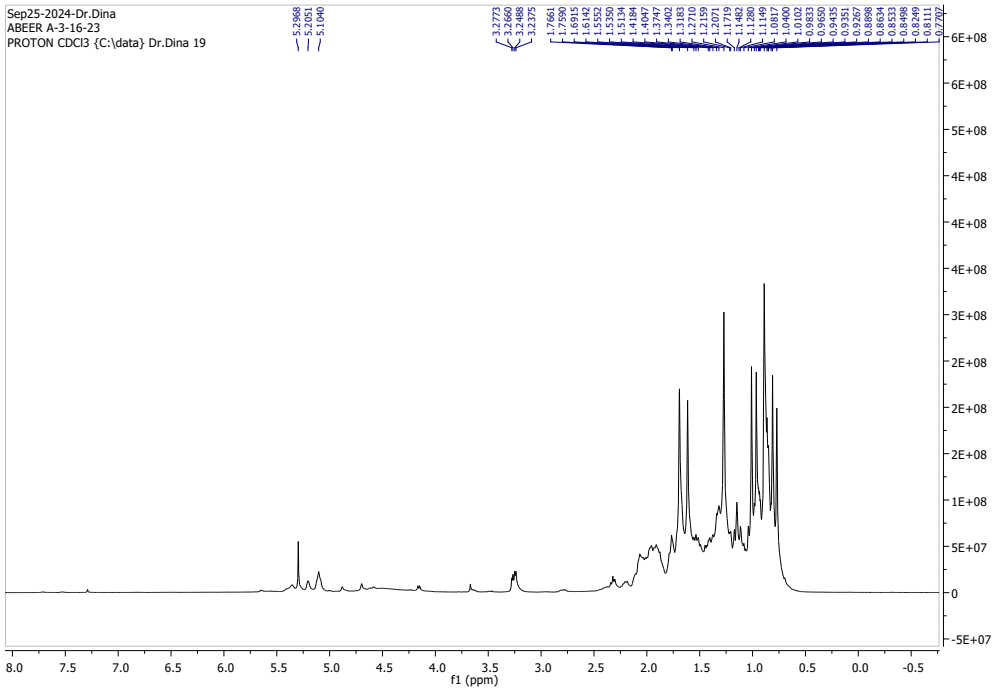

Figure S3. 1H NMR spectrum of compound **1** measured in $CDCl_3$ at 400 MHz.

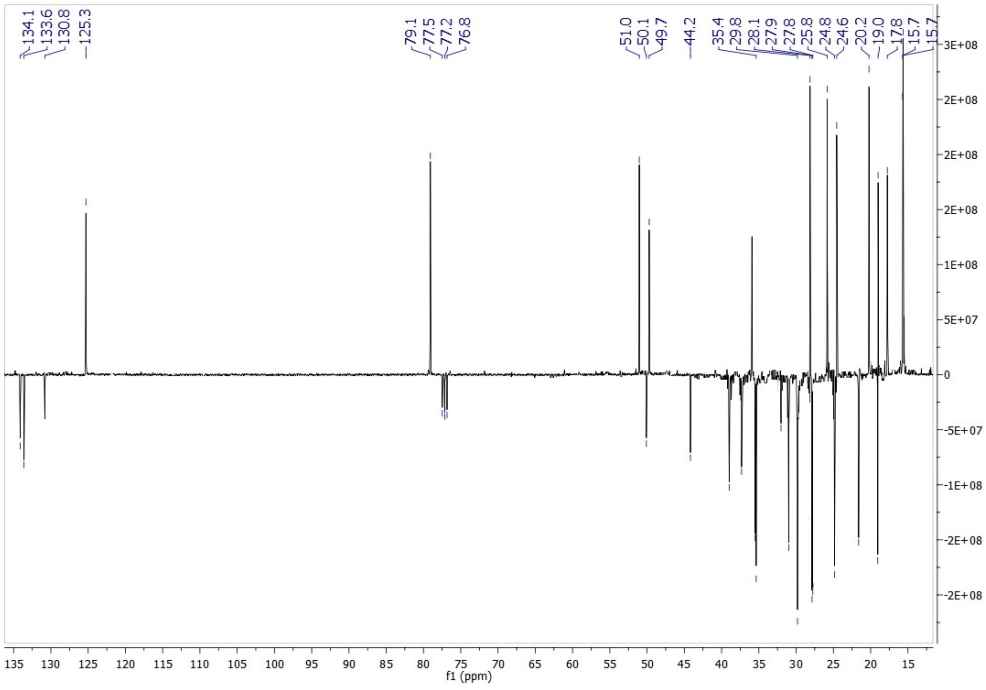

Figure S4. DEPT-Q NMR spectrum of compound **1** measured in $CDCl_3$ at 400 MHz.

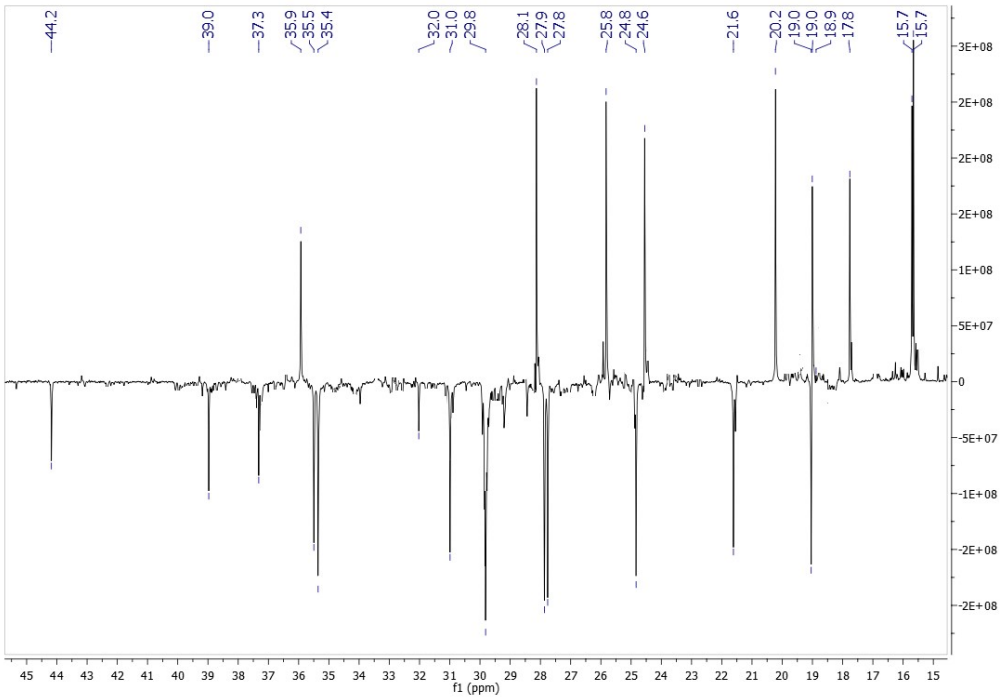

Figure S4 Cont. DEPT-Q NMR spectrum of compound **1** measured in $CDCl_3$ at 400 MHz.

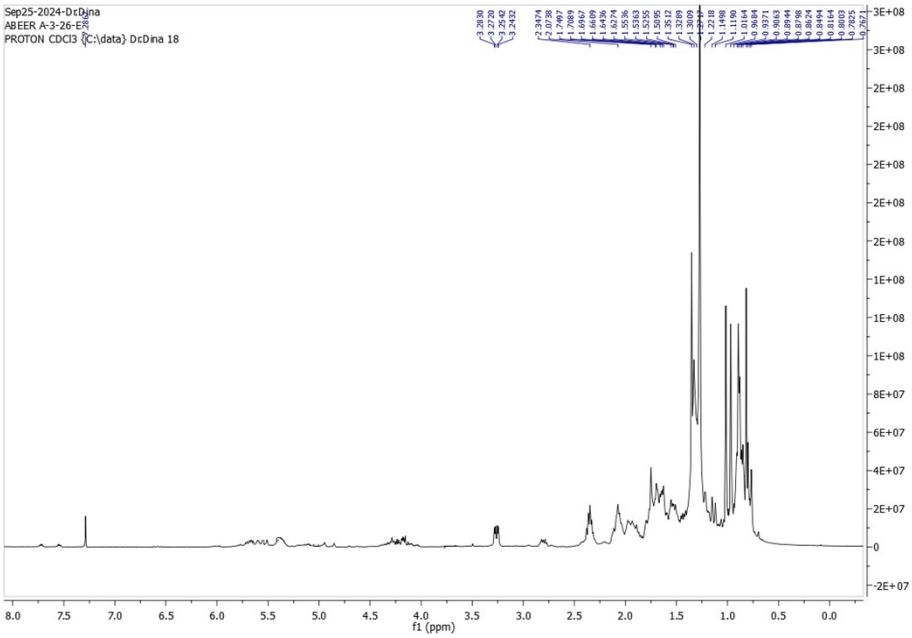

Figure S5. 1H NMR spectrum of compound **2** measured in $CDCl_3$ at 400 MHz.

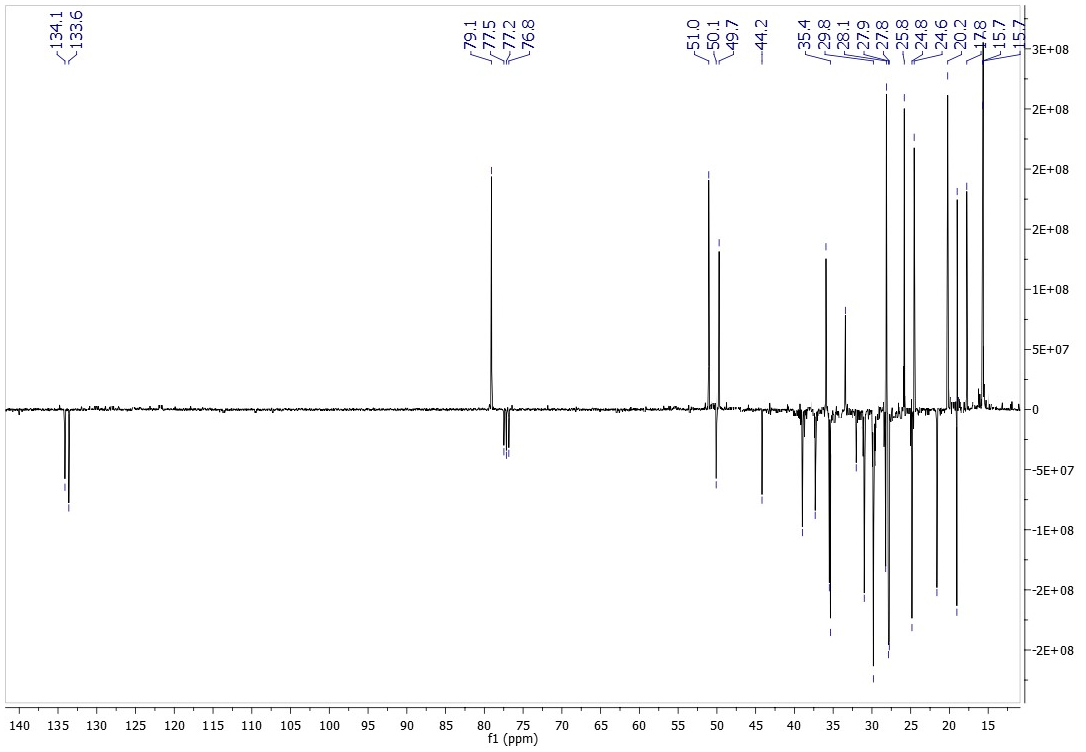

Figure S6. DEPT-Q NMR spectrum of compound **2** measured in $CDCl_3$ at 400 MHz.

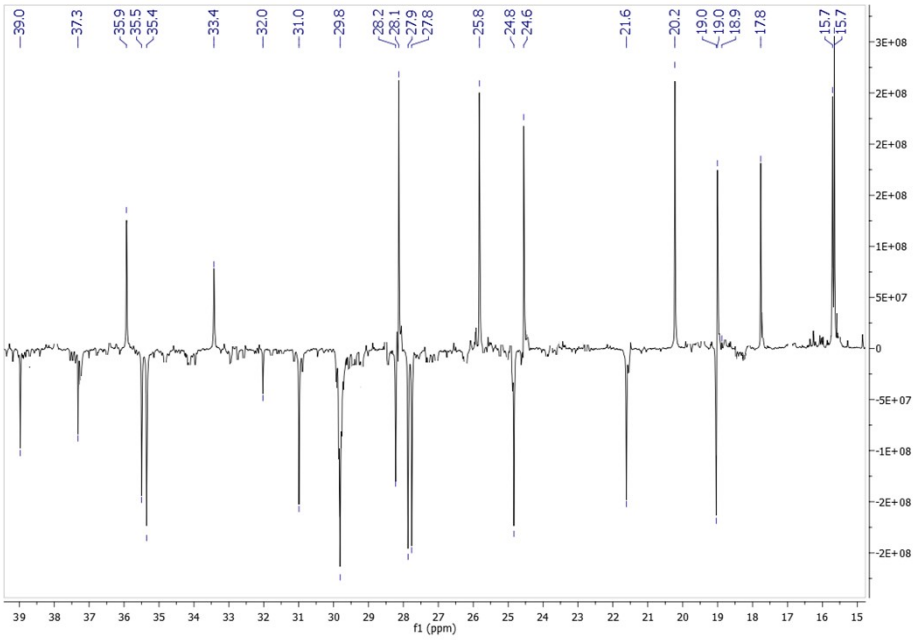

Figure S6 Cont. DEPT-Q NMR spectrum of compound **2** measured in $CDCl_3$ at 400 MHz.

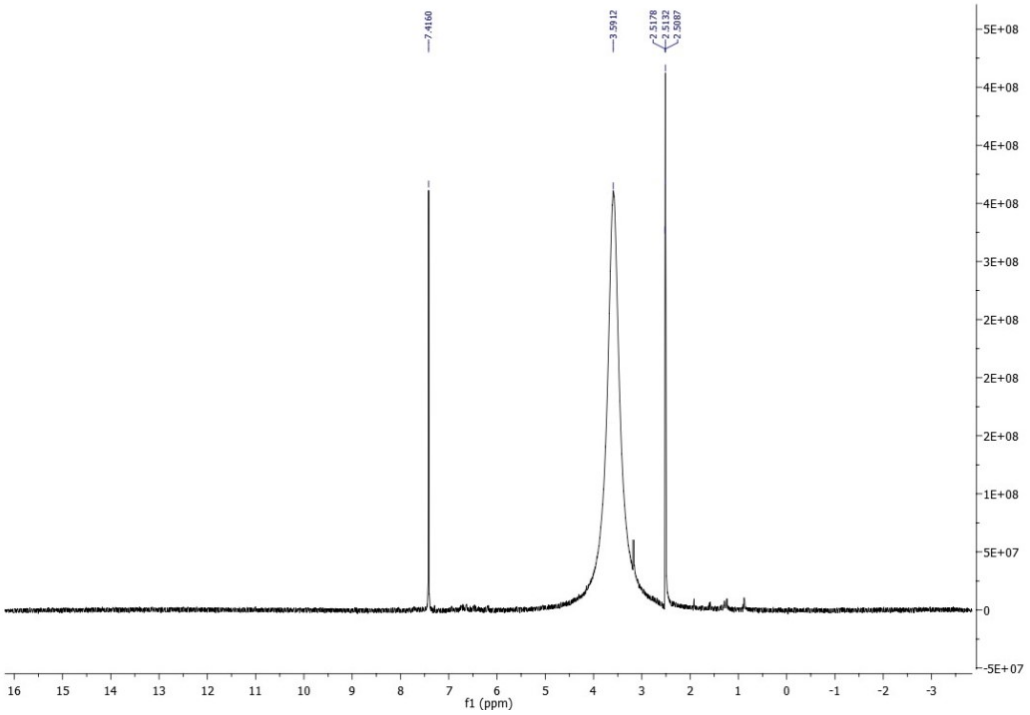

Figure S7. 1H NMR spectrum of compound 3 measured in DMSO at 400 MHz

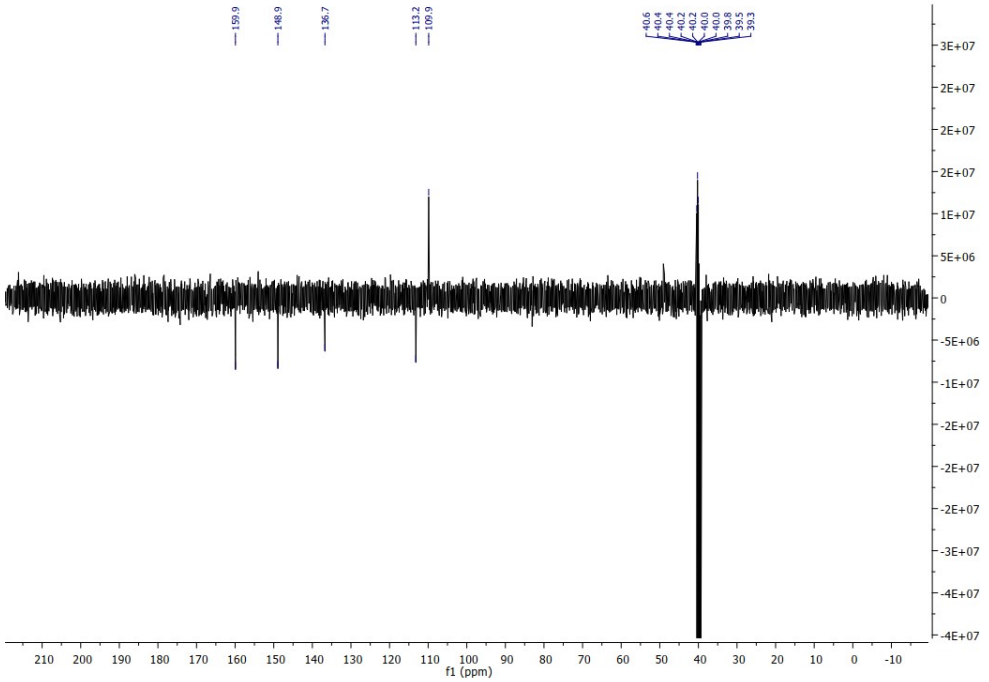

Figure S8. DEPT-Q NMR spectrum of compound 3 measured in DMSO at 100 MHz

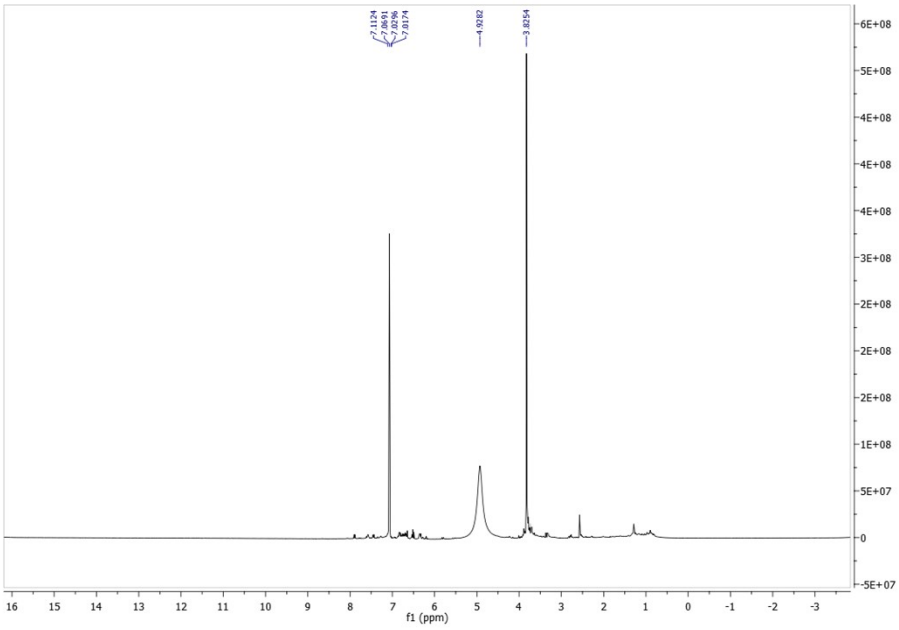

Figure S9. ^{1}H NMR spectrum of compound **4** measured in CD_3OD at 400 MHz.

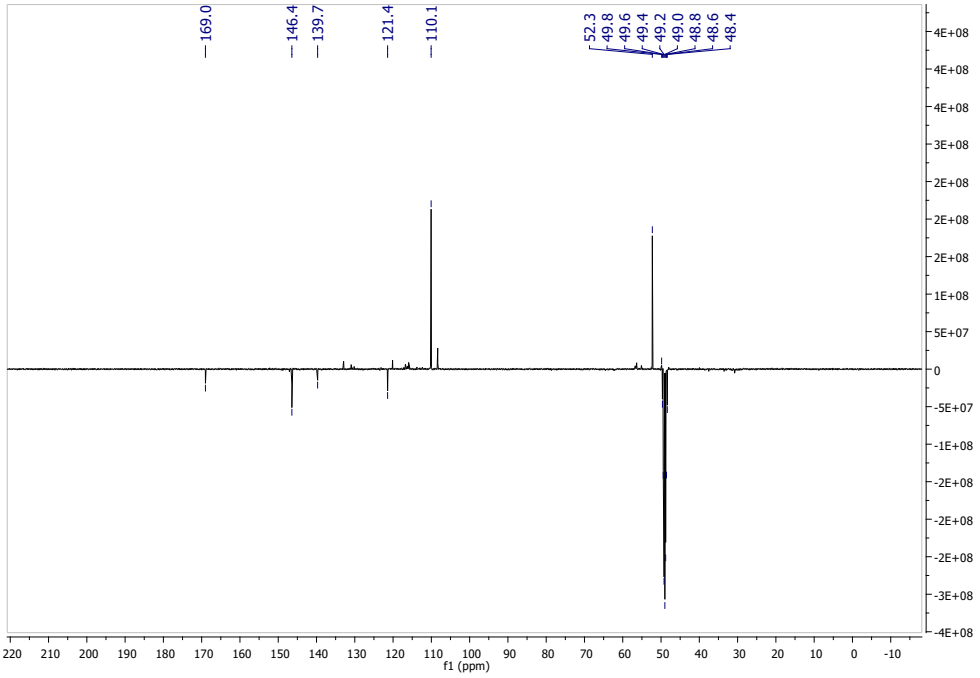

Figure S10. DEPT-Q NMR spectrum of compound **4** measured in CD_3OD at 100 MHz.

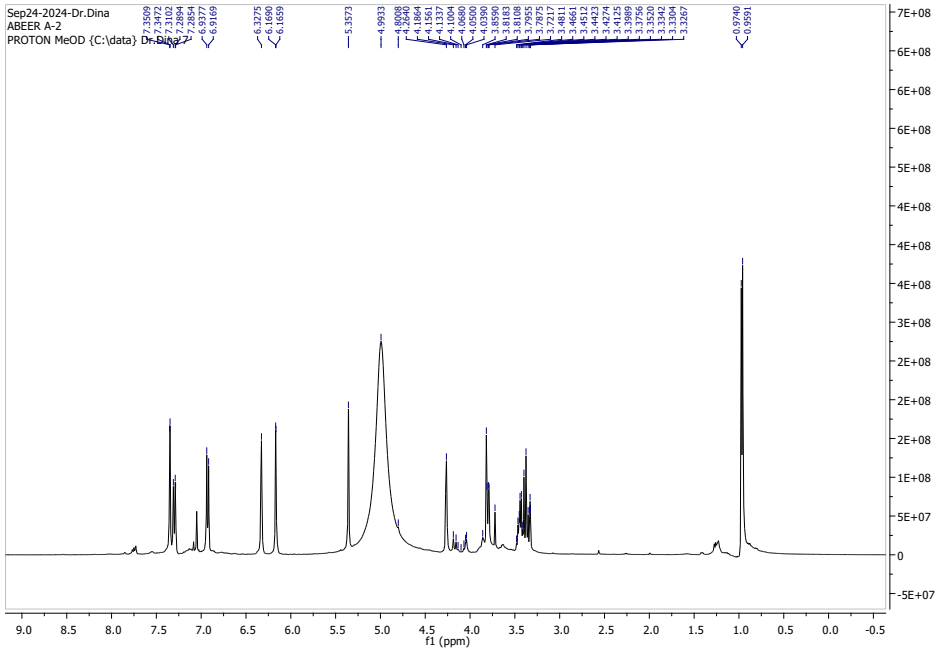

Figure S11. ^{1}H NMR spectrum of compound **5** measured in CD_3OD at 400 MHz.

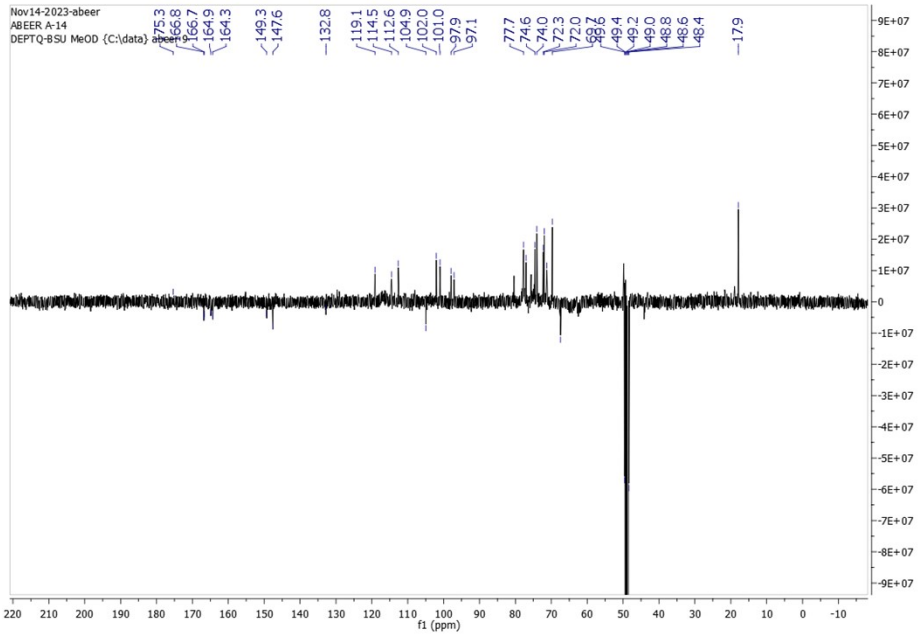

Figure S12. DEPT-Q NMR spectrum of compound **5** measured in CD_3OD at 100 MHz.

Table S1: List of proteins related to *Klebsiella*.

Protein	Online library Source
Toll Like Receptor 4	NCBI (PubMed/PMC)
CD14 Molecule	NCBI (PubMed/PMC)
Lymphocyte Antigen 96 (MD-2)	NCBI (PubMed/PMC)
Toll Like Receptor 2	NCBI (PubMed/PMC)
Nucleotide Binding Oligomerization Domain Containing 1	NCBI (PubMed/PMC)
Nucleotide Binding Oligomerization Domain Containing 2	NCBI (PubMed/PMC)
Myeloid Differentiation Primary Response 88	NCBI (PubMed/PMC)
TIR Domain Containing Adaptor Protein (TIRAP/MAL)	NCBI (PubMed/PMC)
TIR Domain Containing Adaptor Molecule 1 (TRIF)	NCBI (PubMed/PMC)
Interleukin 1 Receptor Associated Kinase 1	NCBI (PubMed/PMC)
Interleukin 1 Receptor Associated Kinase 4	NCBI (PubMed/PMC)
TNF Receptor Associated Factor 6	NCBI (PubMed/PMC)
NLR Family Pyrin Domain Containing 3	NCBI (PubMed/PMC)
PYD And CARD Domain Containing (ASC)	NCBI (PubMed/PMC)
Caspase 1	NCBI (PubMed/PMC)
Interleukin 23 Subunit Alpha	NCBI (PubMed/PMC)
Interleukin 17A	NCBI (PubMed/PMC)
Interleukin 17F	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Ligand 1	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Ligand 2	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Ligand 5	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Receptor 1	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Receptor 2	NCBI

Colony Stimulating Factor 3 (G-CSF)	NCBI (PubMed/PMC)
Complement C3	NCBI (PubMed/PMC)
Complement C5	NCBI (PubMed/PMC)
Complement C5a Receptor 1	NCBI (PubMed/PMC)
Nitric Oxide Synthase 2	NCBI (PubMed/PMC)
Cytochrome B-245 Beta Chain (NOX2/gp91phox)	NCBI (PubMed/PMC)
Myeloperoxidase	NCBI (PubMed/PMC)
Toll Like Receptor 4	NCBI (PubMed/PMC)
CD14 Molecule	NCBI (PubMed/PMC)
Lymphocyte Antigen 96 (MD-2)	NCBI (PubMed/PMC)
Toll Like Receptor 2	NCBI (PubMed/PMC)
Nucleotide Binding Oligomerization Domain Containing 1	NCBI (PubMed/PMC)
Nucleotide Binding Oligomerization Domain Containing 2	NCBI (PubMed/PMC)
Myeloid Differentiation Primary Response 88	NCBI (PubMed/PMC)
TIR Domain Containing Adaptor Protein (TIRAP/MAL)	NCBI (PubMed/PMC)
TIR Domain Containing Adaptor Molecule 1 (TRIF)	NCBI (PubMed/PMC)
Interleukin 1 Receptor Associated Kinase 1	NCBI (PubMed/PMC)
Interleukin 1 Receptor Associated Kinase 4	NCBI (PubMed/PMC)
TNF Receptor Associated Factor 6	NCBI (PubMed/PMC)
NLR Family Pyrin Domain Containing 3	NCBI (PubMed/PMC)
PYD And CARD Domain Containing (ASC)	NCBI (PubMed/PMC)
Caspase 1	NCBI (PubMed/PMC)
Interleukin 23 Subunit Alpha	NCBI (PubMed/PMC)
Interleukin 17A	NCBI

	(PubMed/PMC)
Interleukin 17F	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Ligand 1	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Ligand 2	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Ligand 5	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Receptor 1	NCBI (PubMed/PMC)
C-X-C Motif Chemokine Receptor 2	NCBI (PubMed/PMC)
Colony Stimulating Factor 3 (G-CSF)	NCBI (PubMed/PMC)

Table S2: GO enrichment entry.

category	description
GO:0009607	Negative regulation of inflammatory response
GO:0006952	Negative regulation of endothelial cell proliferation
GO:0006955	Positive regulation of protein transport
GO:0051707	Regulation of epithelial cell differentiation
GO:0002376	Regulation of cellular localization
GO:0044419	Positive regulation of cellular component biogenesis
GO:0034097	Negative regulation of interleukin-17 production
GO:0071345	Positive regulation of heterotypic cell-cell adhesion
GO:0060544	Negative regulation by host of viral transcription
GO:0001819	Positive regulation of neuron death
GO:0098542	Immunoglobulin mediated immune response
GO:0002237	Regulation of proteolysis
GO:0019221	T cell chemotaxis

GO:0009617	Cellular homeostasis
GO:0071310	Negative regulation of interleukin-6 production
GO:0001817	Regulation of cellular respiration
GO:0070887	Regulation of endopeptidase activity
GO:0071219	Positive regulation of miRNA transcription
GO:0009605	Regulation of establishment of endothelial barrier
GO:0010033	Negative regulation of miRNA maturation
GO:0002682	Regulation of steroid metabolic process
GO:0032496	Regulation of T cell chemotaxis
GO:0071222	Regulation of lipid storage
GO:0006950	Positive regulation of membrane protein ectodomain proteolysis
GO:0010628	Cellular response to peptide hormone stimulus
GO:0002684	Tissue remodeling
GO:0045087	Positive regulation of cellular extravasation
GO:1901701	Positive regulation of macrophage derived foam cell differentiation
GO:0032103	Negative regulation of angiogenesis
GO:0007165	Negative regulation of myeloid cell apoptotic process
GO:0042241	Positive regulation of glial cell proliferation
GO:0032101	Regulation of lipid localization
GO:1901700	Positive regulation of immunoglobulin production
GO:0050776	Regulation of platelet activation
GO:0051240	Peptidyl-amino acid modification
GO:0048584	Regulation of tumor necrosis factor-mediated signaling pathway
GO:0033993	Positive regulation of cellular amide metabolic process

GO:0007166	Regulation of lipid biosynthetic process
GO:0071396	Negative regulation of interleukin-8 production
GO:0051716	Toll-like receptor 8 signaling pathway
GO:0031349	Toll-like receptor TLR6:TLR2 signaling pathway
GO:0002221	Detection of diacyl bacterial lipopeptide
GO:0031347	Positive regulation of type I interferon-mediated signaling pathway
GO:0051239	Positive regulation of vitamin D biosynthetic process
GO:0009615	Cellular response to exogenous dsRNA
GO:0010647	Positive regulation of cellular response to macrophage colony-stimulating factor stimulus
GO:0023056	Response to gold nanoparticle
GO:0010604	Regulation of lipid metabolic process
GO:0009967	Biological process involved in interaction with symbiont
GO:0009893	Biological process involved in symbiotic interaction
GO:1903557	Leukocyte tethering or rolling
GO:0035556	3-UTR-mediated mRNA stabilization
GO:0032760	Regulation of bicellular tight junction assembly
GO:0009966	Myeloid leukocyte mediated immunity
GO:0032677	Nitric oxide biosynthetic process
GO:0050778	Positive regulation of peptidyl-serine phosphorylation of STAT protein
GO:0048583	Positive regulation of amyloid-beta formation
GO:0002224	Negative regulation of immune response
GO:1903555	Stimulatory C-type lectin receptor signaling pathway
GO:0032755	Response to metal ion
GO:0048518	Positive regulation of steroid biosynthetic process

GO:0010646	Regulation of epithelial cell proliferation
GO:0002764	Fever generation
GO:0023051	Chronic inflammatory response to antigenic stimulus
GO:1902533	Regulation of chronic inflammatory response to antigenic stimulus
GO:0048522	Negative regulation of interleukin-18 production
GO:0032680	Cellular response to interferon-beta
GO:0051091	Fc-epsilon receptor signaling pathway
GO:0032757	Cellular response to triacyl bacterial lipopeptide
GO:0032675	Positive regulation of monocyte chemotaxis
GO:0080134	Positive regulation of matrix metallopeptidase secretion
GO:0051092	Negative regulation of primary miRNA processing
GO:0002669	Response to hypoxia
GO:0050727	Peptidyl-serine phosphorylation
GO:0043122	Positive regulation of cell killing
GO:0002697	Positive regulation of nucleocytoplasmic transport
GO:0060749	Positive regulation of miRNA-mediated gene silencing
GO:0043123	Negative regulation of immune effector process
GO:0030663	Natural killer cell activation
GO:0001775	Positive regulation of gliogenesis
GO:1902531	Myeloid dendritic cell activation
GO:0032655	Neutrophil mediated immunity
GO:0008284	Positive regulation of muscle cell apoptotic process
GO:0051090	Regulation of muscle cell apoptotic process
GO:0002700	Positive regulation of cytosolic calcium ion concentration

GO:0050867	Natural killer cell activation involved in immune response
GO:0070665	Response to muscle stretch
GO:0032722	B cell differentiation
GO:0010468	Positive regulation of reactive oxygen species metabolic process
GO:0032642	Positive regulation of apoptotic signaling pathway
GO:0002718	Sequestering of triglyceride
GO:0071347	Detection of lipopolysaccharide
GO:0002696	Granulocyte-macrophage colony-stimulating factor signaling pathway
GO:0032479	MDA-5 signaling pathway
GO:0031325	Regulation of generation of precursor metabolites and energy
GO:0042742	Regulation of steroid biosynthetic process
GO:0009891	Pyroptosis
GO:0002685	Regulation of Golgi inheritance
GO:0045321	Negative regulation of bicellular tight junction assembly
GO:0002702	Positive regulation of T-helper 17 cell lineage commitment
GO:0051173	Negative regulation of nitrogen compound metabolic process
GO:0098586	Killing of cells of another organism
GO:0042127	Neurogenesis
GO:0044093	Positive regulation of calcium ion transport
GO:0050729	Negative regulation of myoblast differentiation
GO:0031328	Response to fungus
GO:0050900	Regulation of glucose transmembrane transport
GO:0051607	Macrophage differentiation
GO:0000165	Regulation of tissue remodeling

GO:0032735	Negative regulation of intracellular signal transduction
GO:0032731	Liver regeneration
GO:0002831	Response to angiotensin
GO:0070663	Membrane to membrane docking
GO:0032481	Positive regulation of histone phosphorylation
GO:0034612	Negative regulation of myosin-light-chain-phosphatase activity
GO:0002703	Regulation of myoblast differentiation
GO:1901224	Positive regulation of complement activation
GO:0051251	Intestinal epithelial structure maintenance
GO:0071356	Caveolin-mediated endocytosis
GO:0045944	Positive regulation of macrophage proliferation
GO:0050671	Negative regulation of macrophage apoptotic process
GO:0032649	Temperature homeostasis
GO:0002274	Regulation of cyclase activity
GO:0002687	Response to sterol
GO:0051403	Positive regulation of erythrocyte differentiation
GO:0032729	Chemical homeostasis
GO:0050865	Regulation of reactive oxygen species metabolic process
GO:1901222	Gland development
GO:0002819	Response to xenobiotic stimulus
GO:0002694	Immune response-regulating cell surface receptor signaling pathway
GO:0042409	Response to toxic substance
GO:0043410	Negative regulation of osteoclast differentiation
GO:0050794	Protein modification process

GO:0032652	Positive regulation of immature T cell proliferation in thymus
GO:0002755	Positive regulation of killing of cells of another organism
GO:0002821	Cellular response to peptidoglycan
GO:0010557	Regulation of phosphatase activity
GO:0002833	Regulation of small molecule metabolic process
GO:1901698	Reproductive structure development
GO:1903037	Positive regulation of transmembrane transport
GO:0022407	Tissue homeostasis
GO:1903039	Regulation of leukocyte mediated cytotoxicity
GO:0050670	Regulation of viral genome replication
GO:2000026	Positive regulation of lipid metabolic process
GO:0002720	Positive regulation of lipid biosynthetic process
GO:0051249	Regulation of sensory perception of pain
GO:0097529	Positive regulation of vascular associated smooth muscle cell proliferation
GO:0060326	Wound healing involved in inflammatory response
GO:0002824	Positive regulation of dendritic cell antigen processing and presentation
GO:0010941	Positive regulation of humoral immune response mediated by circulating immunoglobulin
GO:0002822	Positive regulation of fever generation
GO:0030335	Negative regulation of toll-like receptor signaling pathway
GO:0032647	Negative regulation of toll-like receptor 2 signaling pathway
GO:0042325	Type III interferon signaling pathway
GO:0043408	Astrocyte cell migration
GO:0030595	Positive regulation of T-helper 2 cell differentiation
GO:0001934	Trachea formation

GO:0045935	T-helper 17 cell lineage commitment
GO:0045893	Regulation of viral process
GO:0001932	Inflammatory response to antigenic stimulus
GO:0019220	Regulation of anion transport
GO:0034341	Negative regulation of viral process
GO:0051247	Response to corticosteroid
GO:0002688	Inflammatory cell apoptotic process
GO:0097530	Release of sequestered calcium ion into cytosol by sarcoplasmic reticulum
GO:0009889	Outer ear morphogenesis
GO:1900015	Regulation of cell adhesion molecule production
GO:0065009	T cell extravasation
GO:0071346	Positive regulation of apoptotic cell clearance
GO:0032727	Regulation of interleukin-1-mediated signaling pathway
GO:0032648	Organ or tissue specific immune response
GO:0045937	Superoxide metabolic process
GO:0032786	Negative regulation of RNA metabolic process
GO:0030334	Acute-phase response
GO:0051246	Response to heat
GO:0050793	Cellular response to vascular endothelial growth factor stimulus
GO:0002252	Positive regulation of protein import into nucleus
GO:0014070	Positive regulation of calcium-mediated signaling
GO:1990266	Toll-like receptor 3 signaling pathway
GO:0010243	Positive regulation of memory T cell differentiation
GO:0031389	Cellular response to muramyl dipeptide

GO:0045765	Negative regulation of amyloid-beta clearance
GO:0070498	Positive regulation of T-helper 2 cell cytokine production
GO:0043067	Regulation of calcium ion transport
GO:0043085	Peptidyl-tyrosine phosphorylation
GO:1903706	Negative regulation of interferon-gamma production
GO:0031401	Response to hydrogen peroxide
GO:0002250	T cell receptor signaling pathway
GO:0009612	Positive regulation of mitotic nuclear division
GO:0002705	Regulation of binding
GO:0002706	Leukocyte apoptotic process
GO:0030593	Positive regulation of binding
GO:0007254	Tube development
GO:1900017	Postsynapse to nucleus signaling pathway
GO:0030155	Positive regulation of glial cell migration
GO:0070098	Negative regulation of I-kappaB kinase/NF-kappaB signaling
GO:0045089	Negative regulation of leukocyte differentiation
GO:0006355	Negative regulation of lipid localization
GO:0032728	Negative regulation of epithelial cell differentiation
GO:0042981	Cellular response to heat
GO:0010556	Positive regulation of secretion by cell
GO:0060337	Regulation of ion transmembrane transport
GO:0046330	Positive regulation of dendritic cell cytokine production
GO:0050870	Bergmann glial cell differentiation
GO:0050830	Positive regulation of podosome assembly

GO:0002690	Endothelial cell apoptotic process
GO:0031323	Response to steroid hormone
GO:0045595	Positive regulation of organelle organization
GO:0051171	Positive regulation of lipid localization
GO:0050863	Positive regulation of extrinsic apoptotic signaling pathway
GO:1901652	Positive regulation of protein kinase B signaling
GO:0042102	Positive regulation of toll-like receptor 4 signaling pathway
GO:0019219	Positive regulation of smooth muscle cell apoptotic process
GO:0038061	Type 2 immune response
GO:0050790	Cardiac neural crest cell development involved in heart development
GO:0006935	Positive regulation of platelet aggregation
GO:0032872	Positive regulation of tumor necrosis factor-mediated signaling pathway
GO:0002708	Positive regulation of miRNA maturation
GO:0045088	Immune response-activating cell surface receptor signaling pathway
GO:0002709	Cellular response to metal ion
GO:0051094	Cellular cation homeostasis
GO:0007252	Cellular chemical homeostasis
GO:0042116	Regulation of metal ion transport
GO:0032660	Positive regulation of cyclase activity
GO:0033554	Negative regulation of smooth muscle cell proliferation
GO:0009719	Regulation of hormone levels
GO:0002460	Regulation of cell junction assembly
GO:0016477	Heterophilic cell-cell adhesion via plasma membrane cell adhesion molecules
GO:1902105	Osteoclast differentiation

GO:0045637	Positive regulation of inflammatory response to antigenic stimulus
GO:0009628	Tyrosine phosphorylation of STAT protein
GO:0080090	p38MAPK cascade
GO:0010942	Regulation of tau-protein kinase activity
GO:0006357	Regulation of ossification
GO:0071260	B cell activation involved in immune response
GO:0007259	Negative regulation of viral genome replication
GO:0048660	Positive regulation of epithelial cell proliferation
GO:0051770	Negative regulation of type 2 immune response
GO:0042129	Positive regulation of prostaglandin secretion
GO:0002269	Positive regulation of monocyte chemotactic protein-1 production
GO:0045860	Positive regulation of cellular respiration
GO:1901699	Positive regulation of leukocyte mediated cytotoxicity
GO:0070372	Positive regulation of DNA binding
GO:0048661	Regulation of phosphoprotein phosphatase activity
GO:0061900	Negative regulation of cellular metabolic process
GO:0002724	Positive regulation of calcium ion import
GO:0060759	Reactive oxygen species biosynthetic process
GO:0051347	Regulation of neuron apoptotic process
GO:0033273	Negative regulation of transport
GO:0045766	Regulation of myeloid leukocyte mediated immunity
GO:0070374	Negative regulation of tumor necrosis factor production
GO:0042531	Liver development
GO:0060907	Positive regulation of protein secretion

GO:0045639	Complement activation, alternative pathway
GO:0048519	Positive regulation of T cell chemotaxis
GO:0001818	Myeloid cell apoptotic process
GO:1902622	Cellular response to hepatocyte growth factor stimulus
GO:0032740	Response to radiation
GO:0002366	Response to wounding
GO:0006468	Regulation of fat cell differentiation
GO:0071622	Positive regulation of synaptic transmission
GO:0001774	Regulation of lymphocyte apoptotic process
GO:0045859	Endocytosis
GO:0051241	Response to UV-B
GO:0071407	Positive regulation of telomere capping
GO:0006915	Positive regulation of neurogenesis
GO:0071674	Cellular response to hydrogen peroxide
GO:0043068	Negative regulation of glucose transmembrane transport
GO:0002711	Ectopic germ cell programmed cell death
GO:0033209	Positive regulation of reactive oxygen species biosynthetic process
GO:0043331	Regulation of microglial cell activation
GO:0002761	Regulation of early endosome to late endosome transport
GO:0045428	Regulation of intracellular transport
GO:0006959	Negative regulation of leukocyte mediated immunity
GO:0071675	Response to activity
GO:0051338	Response to ionizing radiation
GO:0050829	Response to glucocorticoid

GO:0071417	Macrophage activation involved in immune response
GO:0045429	Positive regulation of lymphocyte apoptotic process
GO:0045670	Positive regulation of endothelial cell apoptotic process
GO:0043065	Regulation of nervous system process
GO:0060227	Receptor internalization
GO:1901653	Regulation of cold-induced thermogenesis
GO:0046427	Nervous system development
GO:0071223	Positive regulation of small molecule metabolic process
GO:0050731	Negative regulation of nervous system development
GO:0034121	Negative regulation of cellular catabolic process
GO:0016310	Negative regulation of leukocyte chemotaxis
GO:0002726	Negative regulation of nervous system process
GO:0001959	Positive regulation of sprouting angiogenesis
GO:0002756	Protein metabolic process
GO:0048534	Regulation of behavior
GO:0002753	Placenta development
GO:0031410	Cytoplasmic vesicle
GO:0031982	Vesicle
GO:0031226	Intrinsic component of plasma membrane
GO:0043235	Receptor complex
GO:0005768	Endosome
GO:0009897	External side of plasma membrane
GO:0098552	Side of membrane
GO:0098802	Plasma membrane signaling receptor complex

GO:0005576	Extracellular region
GO:0012506	Vesicle membrane
GO:0005886	Plasma membrane
GO:0005887	Integral component of plasma membrane
GO:0009986	Cell surface
GO:0005615	Extracellular space
GO:0030659	Cytoplasmic vesicle membrane
GO:0098797	Plasma membrane protein complex
GO:0010008	Endosome membrane
GO:0072536	interleukin-23 receptor complex
GO:0012505	Endomembrane system
GO:0045335	Phagocytic vesicle
GO:0035631	CD40 receptor complex
GO:0098796	Membrane protein complex
GO:0045121	Membrane raft
GO:0030139	Endocytic vesicle
GO:0036020	Endolysosome membrane
GO:0030141	Secretory granule
GO:0046696	Lipopolysaccharide receptor complex
GO:0098588	Bounding membrane of organelle
GO:0008385	IkappaB kinase complex
GO:0042022	interleukin-12 receptor complex
GO:0072559	NLRP3 inflammasome complex
GO:0005773	Vacuole

GO:0005764	Lysosome
GO:0035355	Toll-like receptor 2-Toll-like receptor 6 protein complex
GO:0035525	NF-kappaB p50/p65 complex
GO:0070743	interleukin-23 complex
GO:0005829	Cytosol
GO:0030526	Granulocyte macrophage colony-stimulating factor receptor complex
GO:0072558	NLRP1 inflammasome complex
GO:0097169	AIM2 inflammasome complex
GO:0030667	Secretory granule membrane
GO:0034774	Secretory granule lumen
GO:0016020	Membrane
GO:0097342	Ripoptosome
GO:0035578	Azurophil granule lumen
GO:0032991	Protein-containing complex
GO:0005775	Vacuolar lumen
GO:1902554	Serine/threonine protein kinase complex
GO:0005126	Cytokine receptor binding
GO:0005102	Signaling receptor binding
GO:0005125	Cytokine activity
GO:0005515	Protein binding
GO:0042802	Identical protein binding
GO:0042379	Chemokine receptor binding
GO:0070851	Growth factor receptor binding
GO:0005488	Binding

GO:0038187	Pattern recognition receptor activity
GO:0008009	Chemokine activity
GO:0001664	G protein-coupled receptor binding
GO:0098772	Molecular function regulator activity
GO:0005149	interleukin-1 receptor binding
GO:0031730	CCR5 chemokine receptor binding
GO:0048020	CCR chemokine receptor binding
GO:0004672	Protein kinase activity
GO:0038023	Signaling receptor activity
GO:0035325	Toll-like receptor binding
GO:0046983	Protein dimerization activity
GO:0045236	CXCR chemokine receptor binding
GO:0019899	Enzyme binding
GO:0019955	Cytokine binding
GO:0140375	Immune receptor activity
GO:0004896	Cytokine receptor activity
GO:0042803	Protein homodimerization activity
GO:0001530	Lipopolysaccharide binding
GO:0019900	Kinase binding
GO:0004707	MAP kinase activity
GO:0019901	Protein kinase binding
GO:0042834	Peptidoglycan binding
GO:0050135	NAD(P)+ nucleosidase activity
GO:0061809	NAD+ nucleotidase, cyclic ADP-ribose generating

GO:0004674	Protein serine/threonine kinase activity
GO:0032813	Tumor necrosis factor receptor superfamily binding
GO:0001875	Lipopolysaccharide immune receptor activity
GO:0097367	Carbohydrate derivative binding
GO:0004888	Transmembrane signaling receptor activity
GO:0016493	C-C chemokine receptor activity
GO:0019957	C-C chemokine binding
GO:0031726	CCR1 chemokine receptor binding
GO:0005539	Glycosaminoglycan binding
GO:0071723	Lipopeptide binding
GO:0019902	Phosphatase binding
GO:0106310	Protein serine kinase activity
GO:0005131	Growth hormone receptor binding
GO:0046982	Protein heterodimerization activity
GO:0001223	Transcription coactivator binding
GO:0050700	CARD domain binding
GO:0004708	MAP kinase kinase activity
GO:0008656	Cysteine-type endopeptidase activator activity involved in apoptotic process
GO:0004918	interleukin-8 receptor activity
GO:0005143	interleukin-12 receptor binding
GO:0008384	IkappaB kinase activity
GO:0019959	interleukin-8 binding
GO:0035663	Toll-like receptor 2 binding
GO:0001847	Opsonin receptor activity

GO:0035662	Toll-like receptor 4 binding
GO:0005138	interleukin-6 receptor binding
GO:0005164	Tumor necrosis factor receptor binding
GO:0005524	ATP binding
GO:0019903	Protein phosphatase binding
GO:0031702	Type 1 angiotensin receptor binding
GO:0031727	CCR2 chemokine receptor binding
GO:0048273	Mitogen-activated protein kinase p38 binding
GO:0042056	Chemoattractant activity
GO:0008083	Growth factor activity
GO:0019904	Protein domain specific binding
GO:0043168	Anion binding

Table S3: KEGG enrichment entry.

category	description
hsa05164	Influenza A
hsa05162	Measles
hsa04620	Toll-like receptor signaling pathway
hsa05160	Hepatitis C
hsa04623	Cytosolic DNA-sensing pathway
hsa05161	Hepatitis B
hsa04621	NOD-like receptor signaling pathway
hsa05168	Herpes simplex virus 1 infection
hsa04060	Cytokine-cytokine receptor interaction
hsa05169	Epstein-Barr virus infection
hsa05152	Tuberculosis
hsa04622	RIG-I-like receptor signaling pathway
hsa05142	Chagas disease
hsa05144	Malaria
hsa05321	Inflammatory bowel disease
hsa05167	Kaposi sarcoma-associated herpesvirus infection

hsa04217	Necroptosis
hsa04630	JAK-STAT signaling pathway
hsa05135	Yersinia infection
hsa05323	Rheumatoid arthritis
hsa04625	C-type lectin receptor signaling pathway
hsa05143	African trypanosomiasis
hsa05163	Human cytomegalovirus infection
hsa04380	Osteoclast differentiation
hsa05165	Human papillomavirus infection
hsa05170	Human immunodeficiency virus 1 infection
hsa04061	Viral protein interaction with cytokine and cytokine receptor
hsa04668	TNF signaling pathway
hsa04657	IL-17 signaling pathway
hsa04659	Th17 cell differentiation
hsa05146	Amoebiasis
hsa05140	Leishmaniasis
hsa04062	Chemokine signaling pathway
hsa05332	Graft-versus-host disease
hsa05132	Salmonella infection
hsa04933	AGE-RAGE signaling pathway in diabetic complications
hsa05145	Toxoplasmosis
hsa05134	Legionellosis
hsa04650	Natural killer cell mediated cytotoxicity
hsa05133	Pertussis
hsa05131	Shigellosis
hsa04940	Type I diabetes mellitus
hsa05235	PD-L1 expression and PD-1 checkpoint pathway in cancer
hsa05200	Pathways in cancer
hsa04151	PI3K-Akt signaling pathway
hsa04144	Endocytosis
hsa01523	Antifolate resistance
hsa04658	Th1 and Th2 cell differentiation
hsa04640	Hematopoietic cell lineage
hsa05330	Allograft rejection
hsa04660	T cell receptor signaling pathway
hsa05130	Pathogenic Escherichia coli infection
hsa04672	Intestinal immune network for IgA production
hsa05166	Human T-cell leukemia virus 1 infection
hsa05320	Autoimmune thyroid disease
hsa05418	Fluid shear stress and atherosclerosis
hsa04612	Antigen processing and presentation
hsa04932	Non-alcoholic fatty liver disease
hsa05410	Hypertrophic cardiomyopathy

hsa04350	TGF-beta signaling pathway
hsa05205	Proteoglycans in cancer
hsa04064	NF-kappa B signaling pathway
hsa04962	Vasopressin-regulated water reabsorption
hsa05020	Prion disease
hsa04145	Phagosome

Table S4. Binding energies (kcal/mol) and RMSD (Å) of *E. tirucalli* compounds docked into the active-site pocket of ***Klebsiella pneumoniae*** **LpxH (PDB ID: 8QK2)**.

NO	Compound	S kcal/mol	RMSD_Refine
1	Euphol	-8.13	1.02
2	Euph-8-enol	-6.16	1.61
3	Gallic acid	-6.37	1.57
4	Methyl gallate	-6.12	1.69
5	Rutin	-7.04	1.63