Identification of ezetimibe and pranlukast as pharmacological chaperones for treatment of the rare disease Mucopolysaccharidosis type IVA

Carlos J. Alméciga-Diaz[1,*], Oscar A. Hidalgo[1], Sergio Olarte-Avellaneda[1,2], Alexander Rodríguez-López[1,3], Esteban Guzman[1], Rafael Garzón[1], Luisa Natalia Pimentel-Vera[1], María Alejandra Puentes-Tellez[1], Andrés Felipe Rojas-Rodriguez[4], Kirill Gorshkov[5], Rong Li[5], Wei Zheng[5]

[1] Institute for the Study of Inborn Errors of Metabolism, Faculty of Science, Pontificia Universidad Javeriana, Bogotá D.C., 110231, Colombia

[2] Pharmacy Department, Faculty of Science, Universidad Nacional de Colombia, Bogotá D.C., 111321, Colombia

[3] Chemistry Department, Faculty of Science, Pontificia Universidad Javeriana, Bogotá D.C., 110231, Colombia

[4] Computational and Structural Biochemistry, Departamento de Nutrición y Bioquímica, Faculty of Science, Pontificia Universidad Javeriana, Bogotá D.C., 110231, Colombia

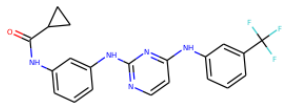
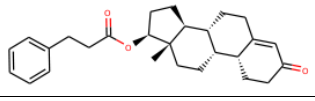
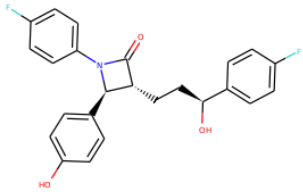
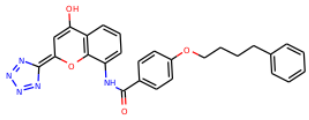
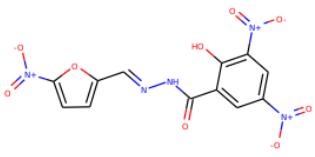
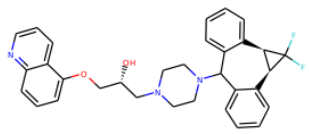
[5] National Center for Advancing Translational Sciences, National Institutes of Health, Bethesda, MD, 20892, USA

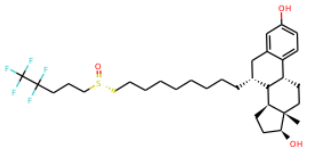
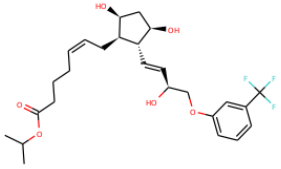
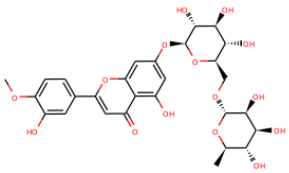
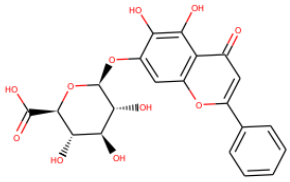
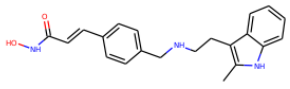
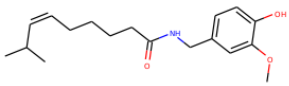
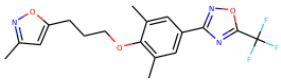
* Corresponding author:

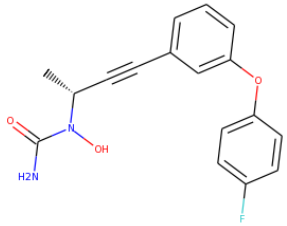
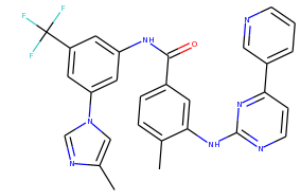
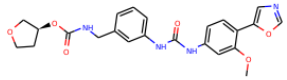
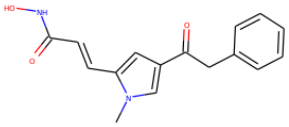
Carlos J. Alméciga-Díaz, Institute for the Study of Inborn Errors of Metabolism, Pontificia Universidad Javeriana, Cra. 7 No. 43-82 Building 54, Room 305A. Bogotá D.C., 110231, Colombia. Tel: +57-1 3208320 Ext 4140; Fax: +57-1 3208320 Ext 4099; E-mail: cjalmeciga@javeriana.edu.co.

Wei Zheng, Ph.D. National Center for Advancing Translational Sciences, National Institutes of Health, 9800 Medical Center Drive, Bethesda, MD, 20892. Tel.: 1-301-827-5722, Email: wzheng@mail.nih.gov

Table S1. Top 20 hits of the compounds interacting with GALNS after virtual screening against the ZINC In Man subset from ZINC.

Rank	ZINC ID	Name / Structure	Molecular Weight (g/mol)	Affinity energy (kcal/mol)	Target	Indication
1	ZINC13831338	Anilinopyrimidine 1 	413.4	-9.9	• Tyrosine-protein kinase JAK1 • Mitogen-activated protein kinase 10 • Mitogen-activated protein kinase 8 Tyrosine-protein kinase ABL1 • Glycogen synthase kinase-3 beta	Fungicide
2	ZINC04026871	13-methyl-3-oxo-2,6,7,8,9,10,11,12,14,15,16,17-dodecahydro-1H-cyclopenta[a]phenanthren-17-yl 	406.5	-9.8	• Sex hormone-binding globulin • 3-oxo-5-alpha-steroid 4-dehydrogenase 1 • 3 beta-hydroxysteroid dehydrogenase/ • 3-oxo-5-alpha-steroid 4-dehydrogenase 2	None
3	ZINC3810860	Ezetimibe 	409.4	-9.7	• Niemann-Pick C1-like protein 1 • Cannabinoid receptor 1	Intestinal and biliary cholesterol absorption inhibition
4	ZINC22001688	Pranlukast 	481.5	-9.7	• Cysteinyl Leukotriene Receptor 1 • Cysteinyl Leukotriene Receptor 2 • 3-oxoacyl-[acyl-carrier-protein] synthase 3	Antiallergic Anti-asthmatic
5	ZINC38140834|	Nifursol 	365.2	-9.6	• Cytochrome P450 2C9 • Cytochrome P450 2C19	Antibiotic Antiprotozoal
6-8	ZINC22449528	Zosuquidar 	527.6	-9.5	• Beta-2 adrenergic receptor • Peroxisomal acyl-coenzyme A oxidase 1	Antineoplastic

Rank	ZINC ID	Name / Structure	Molecular Weight (g/mol)	Affinity energy (kcal/mol)	Target	Indication
9-10	ZINC29213660	Fulvestrant 	606.7	-9.5	• Androgen receptor • Estrogen receptor beta • Aldehyde oxidase • Steroid hormone receptor ERR1 • Sex hormone-binding globulin	Treatment of estrogen receptor+ or hormone-receptor positive advanced breast cancer in postmenopausal women
11	ZINC27641810	Travaprost 	500.5	-8.9	• Prostaglandin E2 receptor EP1 subtype • 15-cis-phytoene desaturase	antiglaucoma, PG-FP agonist
12	ZINC03977803	Diosmin 	608.5	-8.9	• Cytochrome P450 1A2 • Tumor necrosis factor • Ribosomal protein S6 kinase alpha-3 • Interleukin-2 • Cytochrome P450 1A1	None
13	ZINC03943903	Baicalin 	445.3	-8.8	• Prolyl endopeptidase inhibitor	Affects the GABA receptors, diuretic
14	ZINC22010649	Panobinostat 	349.4	-8.8	• Histone Deacetylases	Epigenetic regulator, refractory multiple myeloma,
15	ZINC04468952	Zucapsaicin 	305.4	-8.8	• Modulator of transient receptor potential cation channel subfamily V member 1	Topical analgesic used to treat osteoarthritis
16	ZINC01537619	Preconaril 	381.3	-8.8	• Major capsid protein • Prevents uncoating of the viral RNA genome.	Antiviral, picornaviridae infections, enteroviral sepsis syndrome

Rank	ZINC ID	Name / Structure	Molecular Weight (g/mol)	Affinity energy (kcal/mol)	Target	Indication
17	ZINC05298979	Fenleuton 	314.3	-8.8	• Arachidonate 5-lipoxygenase • Inhibits leukotriene (LTB4, LTC4, LTD4, and LTE4) formation	Chronic obstructive pulmonary disease
18	ZINC06716957	Nilotinib 	529.5	-8.8	• Tyrosine-protein kinase	Chronic myeloid leukemia
19	ZINC03975663	Merimepodib 	452.4	-8.7	• Inosine-5'-monophosphate dehydrogenase 1	Anticancer, immunosuppressive and antiviral therapy
20	ZINC13493184	(2E)-N-hydroxy-3-[1-methyl-4-(phenylacetyl)-1H-pyrrol-2-yl]prop-2-enamide 	284.3		• Histone deacetylases	Epigenetic regulator

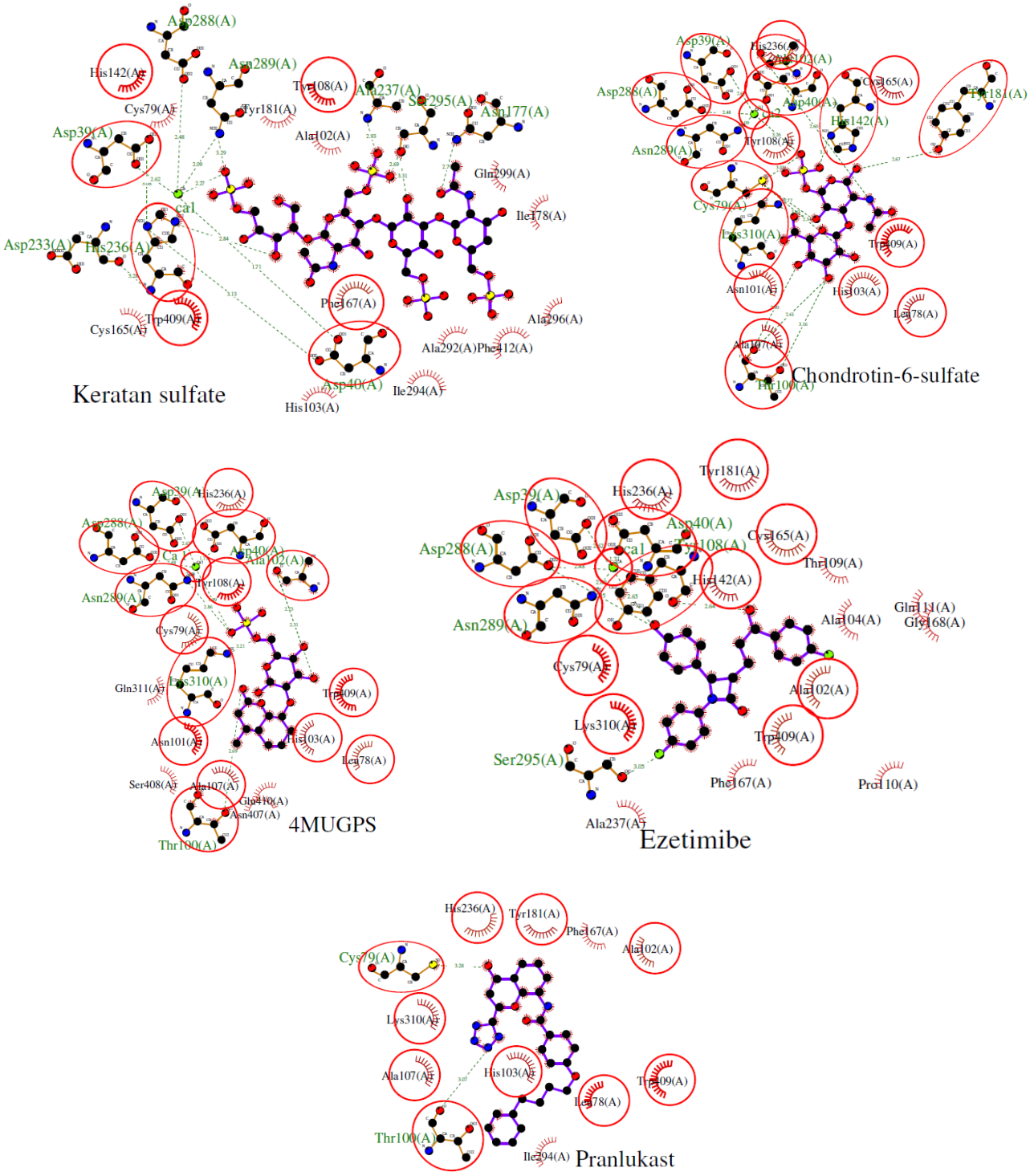


Figure S1. Protein-ligand interactions between human GALNS, keratan sulfate, chondroitin-6-sulfate, 4-methylumbelliferyl-β-d-galactopyranoside-6-sulfate (4MUGPS), ezetimibe, and pranlukast. Circle residues correspond to conserved interactions among all the ligands. Green and black residues are residues interacting through hydrogen bond and hydrophobic interactions, respectively.

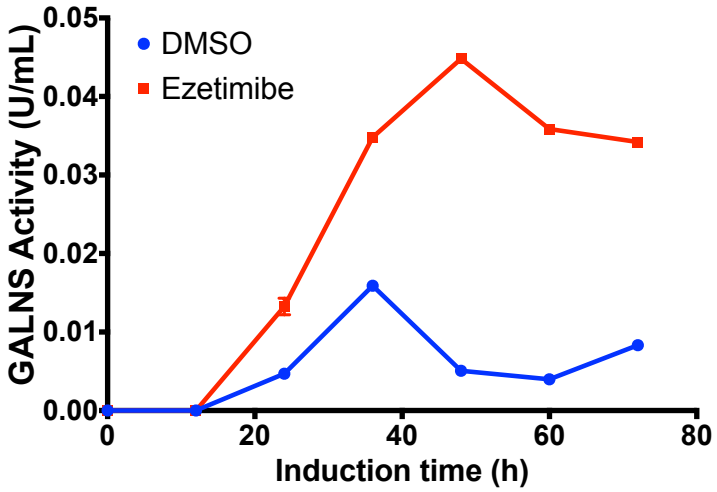


Figure S2. Production of recombinant GALNS in *P. pastoris* at bioreactor scale (1.7 L). Human recombinant GALNS was produced with or without supplementation with ezetimibe 0.001 µM. GALNS activity was measured in the extracellular fraction.