Original Article

An *insilico* study of selected mannose derivatives against Uropathogenic*Escherichia coli*targeting fimH adhesin protein

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Abstract

Urinary tract infections (UTI) caused primarily by uropathogenic Escherichia coli (UPEC) are indeed an extremely contagious disease that affects people all over the world. FimH is a major virulence component in UTI pathogenesis, and inhibiting FimH function can be an efficient means to disarm UPEC bacteria, as well as a crucial target in the development of non-antibiotic mediated UTI treatment options. The goal of this study was to identify phytochemicals in Cranberry and Bearberry plant parts and assess their pharmacological characteristics. A computational methodology was used to predict the pharmacological characteristics of such substances. Compounds with pharmacophores comparable to those of known fimH inhibitors were chosen. Following that, additional research was carried out to assess their drug similarity, inhibitory potential, and IC50 values.Thus, the present study reports few novel fimHinhibitors derived from the selected plant'sphytochemicals, and is significant owing to their therapeutic ication as a non-antibiotic mediated therapy for UTI.

Keywords: Urinary tract infection,Escherichia coli,fimH,Computer aided drug design

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Introduction

Urinary tract infections (UTI) caused primarily by uropathogenic Escherichia coli (UPEC) are dangerous infectious disease that affects people all over the world.[1] UTI affects over half of all females at some point during their lives.[2-4]Although medicines are successful against sensitive UPEC strains, recurring infections provide a challenge to the treatment plan.[5-9] The latency in the creation of new antibiotics, on the other hand, necessitates the development of novel treatment techniques to combat infection.[10-11]

Targeting the virulence factors involved in UPEC attachment to the host urothelial surface[12-14]without killing the bacteria with antibiotics could be an effective therapeutic approach. This non-antibiotic mediated approach may help to prevent infection as this will prevent bacterial attachment to host cell and its viability within the host.[11,15]

FimH lectin binds to the mannosylated glycoproteins found in the bladder epithelial covering, which aids adhesion of the bacterium[16-18](as shown in Fig. 1& 2). The mostly expressed fimH lectin cap is found at the external end of type 1 pili followed by lengthy repeating FimA based pilus rods, a FimF, FimG containing fibrillum. FimH adhesin is composed of a C-terminal pilin domain that binds with the FimA pilus rod and an N-terminal lectin domain with the mannose-binding pocket that is responsible for attachment with highly mannosylated uroplakin Ia (UPIa) glycoprotein on the human urinary tract's epithelial umbrella cells.[19]

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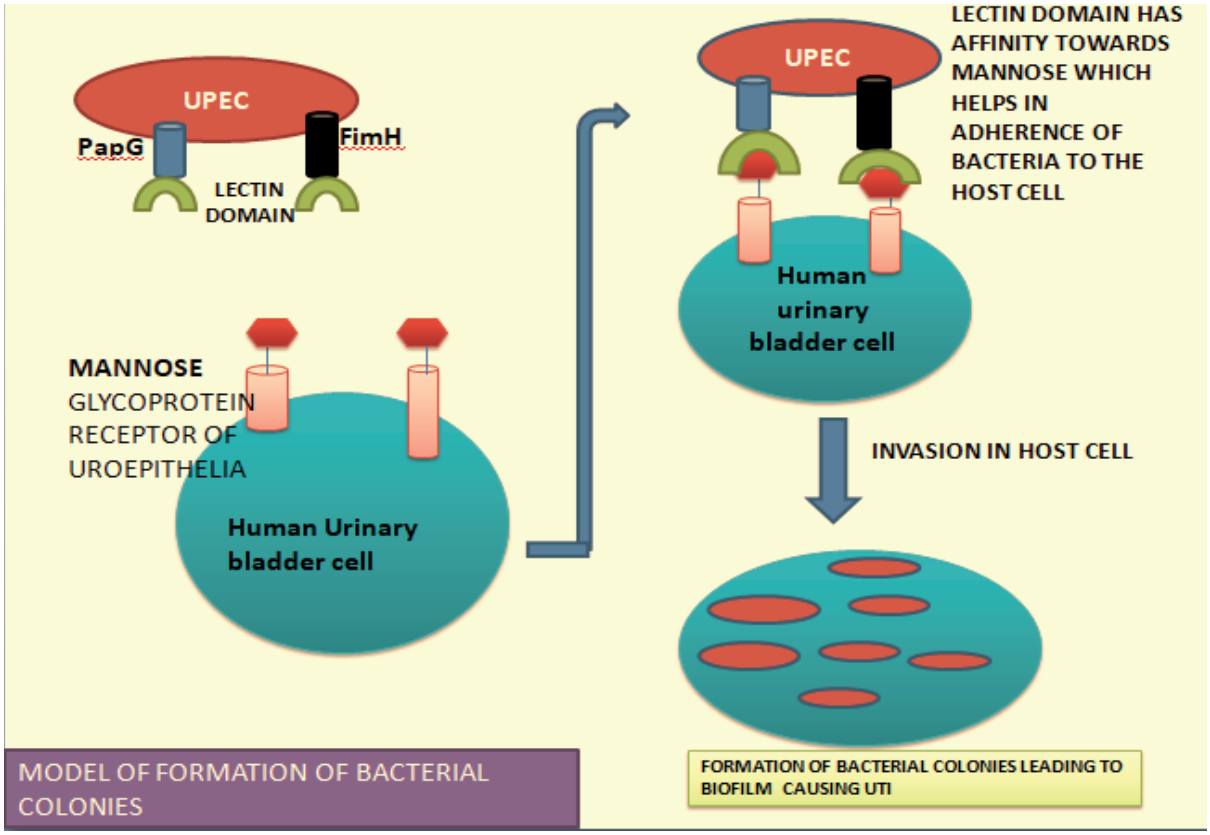


Fig. 1: Bacterial colony formation and uropathogenesis of *Escherichia coli*.

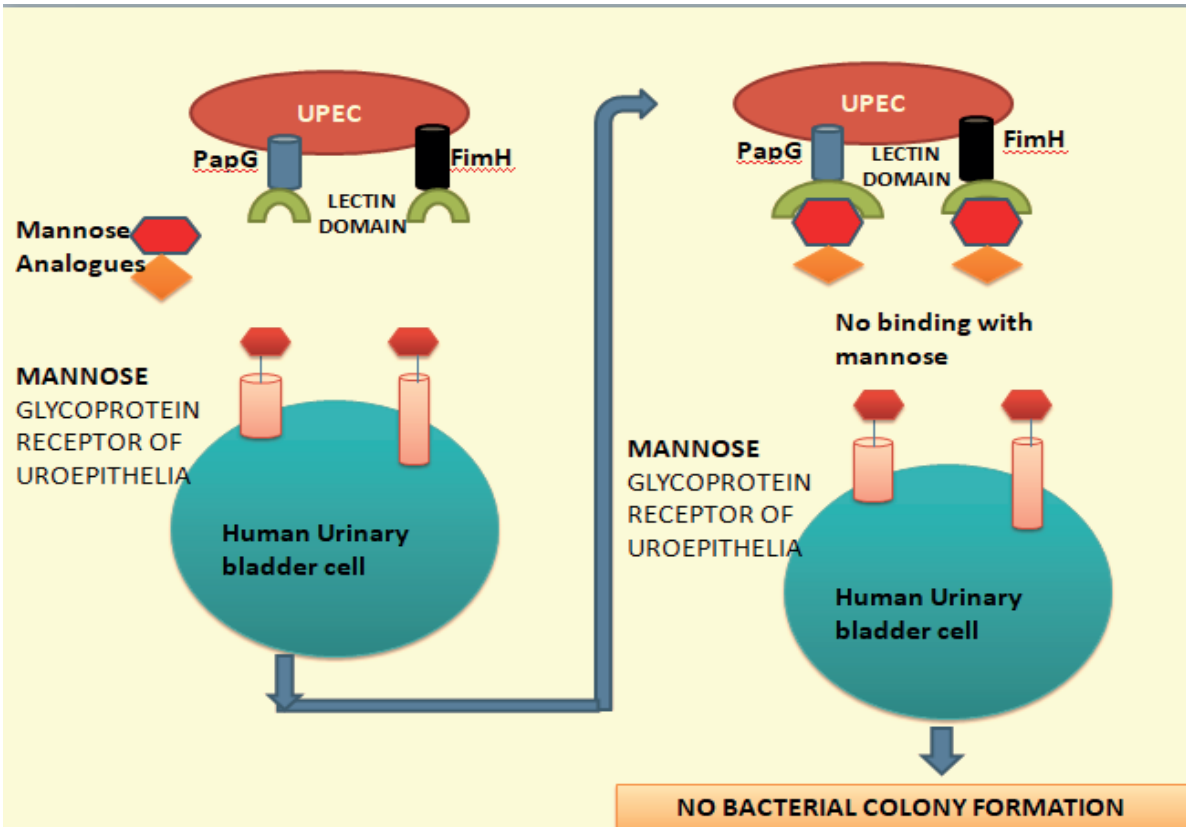


Fig. 2:fimH blocking mechanism of natural mannosides agonist

This suggests that FimHcan be a significant factor in UTI pathogenesis, and that inhibiting FimH function can be effective in preventing UPEC bacterial attachment. This may serve as the alternative to antibiotic mediated treatment that are much needed for future therapeutic usage.

The hypothesis

It was seen that the bacterial colonization takes place after the binding of fimH like adhesin to host urinary bladder epithelium containing oligo-mannose receptors. Hence, mannose analogue with better affinity towards fimH can result in competitive binding of the analogues over host cell mannose receptor. This will prevent the attachment of bacterium with the host cell and thereby will be flushed from the body along with urine flow. This will help in non-antibiotic mediated therapy.

Need fornew drugs

Because there are very few effective therapy options for chronic and recurrent urinary tract infections, these represent a serious medical problem. Antibiotic mediated treatment of persistent urinary tract infections enhances the development of antibiotic-resistant UPEC and complicates therapy.[20]UTIs in women are a common occurrence throughout their lives, especially when the infection becomes persistent, recurrent and drug resistant. Multidrug resistance always challenge drug discovery process and hence demands for newer effective alternatives in the pipeline.

Ligand selection

FimH type 1 pilus lectin of UPEC, which mediates bacterial colonisation, invasion, and development of intracellular bacterial communities (IBCs) in the bladder epithelium, is inhibited by mannosides.[20,21]Here in this work, weexaminednovelmannoside derived drug leads for increased oral bioavailability and demonstrated their rapid-acting efficacy in the treatment of persistent urinary tract infections.

Methods

Toxicity and druglikeness prediction

To pass druglikeliness criteria, each novel chemical compound must be able to pass the toxicity and bioavailability filters. MolSoft server (http://molsoft.com/mprop/) was used to determine the physicochemical parameters, including the octanol/water partition coefficient (LogP) of the ligands. Other parameters like absorption, distribution, metabolism, excretion, and toxicity (ADME/Tox)were screened using the Mobyle@RPBS (https://mobyle.rpbs.univ-parisdiderot.fr/) portal.

Receptor quality checking

X-ray diffraction (1.30A) three-dimensional structure of the receptor, UPEC FimH lectin domain (PDB id: 5AAP) was obtained from RCSB Protein Databank (https://www.rcsb.org/structure/5AAP). Structural quality of the receptor was checkedby generating Ramachandran plot atPDBSum server (https://www.ebi.ac.uk/thornton-srv/software/PROCHECK/). The plot revealed that only 6.8% of the amino acid residues falls under the allowed region and rest under most favourable regions. This indicates the receptor as a good quality protein to be used in molecular docking studies.

Molecular docking analysis

Molecular docking analysis was done to predict the binding pattern and binding energy of the novel compounds againstfimHusing BioSolveIT (LeadIT) FlexX 2.1.3 following standard protocol. The receptor was bound to D-mannose as reference ligand and the binding site of D-mannose was used as active site for molecular docking studies. Few known fimH inhibitors were retrieved from ChEMBL database (https://www.ebi.ac.uk/chembl/)andincluded in the docking analysis as positive control. The best docking pose for each compound were used for identification of docking pattern.

Quantitative structure activity relationship (QSAR) analysis

QSAR is an important tool to correlate the experimental efficacy (in terms of Half-maximal inhibitory concentration, IC_{50}) with the physiochemical properties of any compound through multiple regression analysis.Chemsketch, a freeware was used to generate the physiochemical parameters of the selected known fimH inhibitors. Multiple linear regression analysis was performed using another freeware EasyQSAR. The QSAR equation was generated,and also a regression plot was generated with experimental activity against the predicted activity (Fig. 3). The QSAR equation was recorded to predict the efficacy of selected ligands through their best docking scores (Fig. 4).

Molecular dynamic simulation

Molecular dynamic simulation was performed using Gromacs 5.0 to check the binding stability and final bonding status for the best docked ligands. Energy minimization was performedfollowed by energyprofile, density analysisand pressureprofile analysisafter a 10-nsrun in the simple point charge (SPC) water model based simulation.

Resultsand Discussion

1000 mannose derivatives were prepared using side-chain modification by Ilib Diverse 2.0 for the docking study. Out of these, 124 ligands successfully cleared the ADMET filter with good oral bioavailability. No ligand found with abnormal ADMET properties hence selected for further screening. The list of 124 selected ligands is given with their selected ADMET properties in Table1.

Table1. ADMET Properties of selected mannose derivatives showing high oral bioavailability

ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C2	OC1OC(COC2CCC3C (CCC4C5CCCC5CCC34)C2)C(O) C(O) C1O	410.54	2.96	99.38	3	26	4	6	7137.12	Good
C3	OC1OC(COC2CCC3 C2CCC2C3CCc3ccccc23)C(O) C(O) C1O	404.50	1.72	99.38	3	26	4	6	14825.93	Good
C4	OCc1ccccc1OCC1OC(O)C(O)C(O)C1O	286.28	-1.22	119.61	4	12	5	7	142280.17	Good
C26	OC1OC(CONc2nc3[nH]cnc3c(=O) [nH]2)C(O)C(O)C1O	329.27	-3.31	185.84	4	17	7	12	441180.13	Good
C6	CCC(O)CCOCC1OC(O)C(O)C(O)C1O	266.29	-1.97	119.61	6	6	5	7	308182.58	Good
C7	CC(=O)CC(=O)COCC1OC(O)C(O) C(O)C1O	278.26	-3.00	133.52	6	8	4	8	572123.47	Good
C8	CC(=O)C(=O)COCC1OC(O)C(O)C(O) C1O	264.23	-3.21	133.52	5	8	4	8	633269.3	Good
C9	Nc1ncnc2n(OCC3OC(O)C(O)C(O) C3O)cnc12	313.27	-2.57	169.00	3	16	6	11	270941.08	Good
C10	CC(C)COCC1OC(O)C(O)C(O)C1O	236.26	-1.92	99.38	4	6	4	6	279699.71	Good
C11	OC1OC(CON2CCC(=O)NC2=O)C(O) C(O)C1O	292.24	-3.59	148.79	3	14	5	10	655488.03	Good
C12	OC1OC(COc2cc3ccccc3oc2=O)C(O) C(O)C1O	324.28	-0.59	129.59	3	18	4	8	74516.4	Good
C13	OC1OC(CON2CNc3ccccc3S2(=O)=O) C(O)C(O)C1O	362.36	-1.71	157.17	3	19	5	10	144836.71	Good
C14	OOCC1OC(O)C(O)C(O)C1O	196.16	-3.74	119.61	2	6	5	7	821345.5	Good
C15	OC1OC (COc2ccc3O Cc4ccccc4Cc3c2) C(O) C(O)C1O	374.38	0.68	108.61	3	23	4	7	28573.37	Good
C17	OC1OC (CONc2ncnc3 [nH]cnc23) C(O) C(O)C1O	313.27	-2.21	165.87	4	16	6	11	230696.12	Good
C19	OC1OC(CON2 C3CCCCC3NC2=O) C(O)C(O)C1O	318.32	-1.97	131.72	3	17	5	9	218888.85	Good
C20	OC1OC(COc2ccc3oc(=O)ccc3c2)C(O) C(O)C1O	324.28	-0.80	129.59	3	18	4	8	85056.8	Good
C21	OC1OC(COC2=CC(=O)C=CC2=O) C(O)C(O)C1O	286.23	-2.47	133.52	3	14	4	8	329065.49	Good
C22	OC1OC(CON2c3ccccc3CCc3ccccc23) C(O)C(O)C1O	373.40	1.26	102.62	3	23	4	7	19968.8	Good

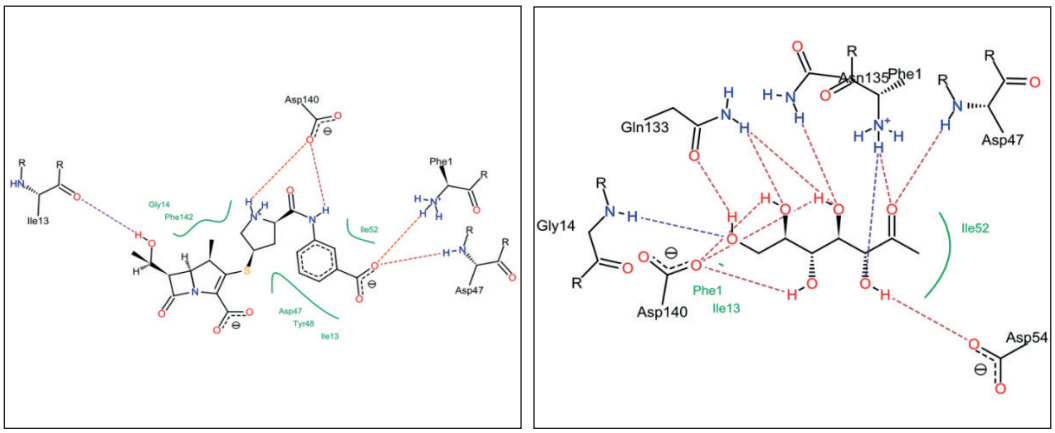
ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C23	OC1OC(COC2SC3CC(=O)N3C=C2)C(O)C(O)C1O	319.33	-2.45	144.99	3	16	4	8	295265.91	Good
C27	OC1OC(COC2Oc3ccccc3Cc3ccccc23)C(O)C(O)C1O	374.38	0.69	108.61	3	23	4	7	28393.92	Good
C28	C\C=C\COCC1OC(O)C(O)C(O)C1O	234.25	-2.38	99.38	4	7	4	6	375195.05	Good
C29	OC1OC(CONc2ccnc(=O)[nH]2)C(O)C(O)C1O	289.24	-3.15	157.16	4	13	6	10	471352.47	Good
C30	CC(C)(C)COCC1OC(O)C(O)C(O)C1O	250.29	-1.53	99.38	4	6	4	6	212453.88	Good
C32	OC1OC(CON2c3ccccc3Sc3ccccc23)C(O)C(O)C1O	377.41	1.11	127.92	3	22	4	7	21215.91	Good
C33	OC1OC(CON-2CCC34CCCCC3C2Cc2ccccc42)C(O)C(O)C1O	405.48	0.83	102.62	3	26	4	7	25846.58	Good
C34	OC1OC(CON2c3ccccc3C=Cc3ccccc23)C(O)C(O)C1O	371.38	1.46	102.62	3	23	4	7	17599.25	Good
C35	OC1OC(CON2c3ccccc3Sc3cccnc23)C(O)C(O)C1O	378.40	0.38	140.81	3	22	4	8	33336.57	Good
C36	OC1OC(CON2CCN=Cc3ccccc23)C(O)C(O)C1O	324.33	-1.44	114.98	3	18	4	8	138776.19	Good
C39	CC1CN(OCC2OC(O)C(O)C(O)C2O)C(=O)NC1=O	306.27	-3.02	148.79	3	14	5	10	439745.15	Good
C40	Cn1c2ccccc2n(OCC2OC(O)C(O)C(O)C2O)c(=O)c2ccccc12	402.40	0.06	126.31	3	24	4	9	36786.37	Good
C251	OC1OC(COC-23CCCC2C2CCc4ccccc4C2CC3)C(O)C(O)C1O	404.50	1.45	99.38	3	26	4	6	17575	Good
C252	CC(C)OCC1OC(O)C(O)C(O)C1O	222.24	-2.46	99.38	3	6	4	6	377540.3	Good
C253	CC(=O)OCC1OC(O)C(O)C(O)C1O	222.19	-3.22	116.45	3	7	4	7	609446.11	Good
C254	OCCCCCOCC1OC(O)C(O)C(O)C1O	266.29	-2.87	119.61	7	6	5	7	580385.41	Good
C255	OC1OC(CON2c3ccccc3C=NCC2=O)C(O)C(O)C1O	338.31	-2.01	132.05	3	19	4	9	189619.2	Good
C257	CCOCC1OC(O)C(O)C(O)C1O	208.21	-2.89	99.38	3	6	4	6	505903.8	Good
C258	NOCC1OC(O)C(O)C(O)C1O	195.17	-4.00	125.40	2	6	6	7	968565.79	Good
C260	OC1OC(COCC(=O)C=C)C(O)C(O)C1O	248.23	-2.26	116.45	5	8	4	7	361091.03	Good
C52	OC1OC(COC=C-2c3ccccc3CCc3ccccc23)C(O)C(O)C1O	384.42	1.18	99.38	3	24	4	6	20331.15	Good
C53	CC(=O)C(OCC1OC(O)C(O)C(O)C1O)C(C)=O	278.26	-2.90	133.52	5	8	4	8	502881.63	Good
C54	OCCCCOCC1OC(O)C(O)C(O)C1O	252.26	-3.22	119.61	6	6	5	7	699975.07	Good
C58	COCC1OC(O)C(O)C(O)C1O	194.18	-3.25	99.38	2	6	4	6	604479.03	Good
C59	CCCOCC1OC(O)C(O)C(O)C1O	222.24	-2.36	99.38	4	6	4	6	378674.62	Good
C60	OC1OC(COC-2CCCC3CCC4C5CCCC5CCC4C23)C(O)C(O)C1O	410.54	3.15	99.38	3	26	4	6	6331.96	Good
C62	OC1OC(COc2ccc3ccc(=O)oc3c2)C(O)C(O)C1O	324.28	-0.72	129.59	3	18	4	8	80876.17	Good
C63	OC1OC(COC2Sc3ccccc3Cc3ccccc23)C(O)C(O)C1O	390.45	1.23	124.68	3	23	4	6	19075.13	Good

ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C65	OC1OC(COC-2CCC3CCC4C5CCCC5CCC4C3C2)C(O)C(O)C1O	410.54	2.96	99.38	3	26	4	6	7137.12	Good
C68	CCCCCCOCC1OC(O)C(O)C(O)C1O	264.32	-0.92	99.38	7	6	4	6	170713.67	Good
C71	CCC(CCO)OCC1OC(O)C(O)C(O)C1O	266.29	-1.97	119.61	6	6	5	7	308182.58	Good
C72	CCCCOCC1OC(O)C(O)C(O)C1O	236.26	-2.00	99.38	5	6	4	6	314227.29	Good
C74	OC1OC(CON2C(=O)CC(=O)NC2=O)C(O)C(O)C1O	306.23	-3.62	165.86	3	15	5	11	641828.88	Good
C76	OC1OC(CON2CNS(=O)(=O)c3ccccc23)C(O)C(O)C1O	362.36	-1.75	157.17	3	19	5	10	148532.97	Good
C77	OC1OC(COC#N)C(O)C(O)C1O	205.17	-2.95	123.17	2	7	4	7	493879.26	Good
C78	OC1OC(COC(=O)c2ccccc2)C(O)C(O)C1O	284.26	-0.91	116.45	4	13	4	7	116914.02	Good
C81	CC(O)CCOCC1OC(O)C(O)C(O)C1O	252.26	-3.15	119.61	5	6	5	7	626998.86	Good
C84	OC1OC(CON2C3NCNC3C(=O)NC2=O)C(O)C(O)C1O	334.28	-4.29	172.85	3	18	7	12	897968.11	Good
C90	OC1OC(COCC=C)C(O)C(O)C1O	220.22	-2.61	99.38	4	7	4	6	444772.75	Good
C92	CCC(C)CCCOCC1OC(O)C(O)C(O)C1O	278.34	-0.02	99.38	7	6	4	6	93478.39	Good
C97	OC1OC(COC2C3SCCN3C2=O)C(O)C(O)C1O	307.32	-2.68	144.99	3	15	4	8	353861.3	Good
C99	CC(O)COCC1OC(O)C(O)C(O)C1O	238.24	-3.51	119.61	4	6	5	7	758619.66	Good
C100	CCC(C)OCC1OC(O)C(O)C(O)C1O	236.26	-1.93	99.38	4	6	4	6	281467.38	Good
C102	OC1OC(COC2=CN3C(CC3=O)C2)C(O)C(O)C1O	287.27	-3.03	119.69	3	15	4	8	466967.54	Good
C103	CCCC(CC)COCC1OC(O)C(O)C(O)C1O	278.34	-0.02	99.38	7	6	4	6	93478.39	Good
C104	NC1NC2NCNC2C(=O)N1OCC1OC(O)C(O)C(O)C1O	335.31	-5.01	181.80	3	17	9	12	1408698.41	Good
C105	OC1OC(COC2C=CN3C2CC3=O)C(O)C(O)C1O	287.27	-3.30	119.69	3	15	4	8	553554.24	Good
C109	Cn1c2ncn(OCC3OC(O)C(O)C(O)C3O)c2c(=O)n(C)c1=O	358.30	-2.35	161.20	3	18	4	12	209246.55	Good
C110	CC(CCCO)OCC1OC(O)C(O)C(O)C1O	266.29	-2.14	119.61	6	6	5	7	343021.25	Good
C112	CC(=O)CCOCC1OC(O)C(O)C(O)C1O	250.25	-3.60	116.45	5	7	4	7	836243.51	Good
C114	OC1OC(COCC(=O)Cc2ccccc2)C(O)C(O)C1O	312.32	-1.26	116.45	6	13	4	7	156294.92	Good
C121	OC1OC(COc2ccc3CCc4ccccc4C(=C)c3c2)C(O)C(O)C1O	384.42	1.53	99.38	3	24	4	6	16307.97	Good
C132	CC1CNC(=O)N(OCC2OC(O)C(O)C(O)C2O)C1=O	306.27	-3.02	152.36	3	14	5	10	439745.15	Good
C134	CCCC(C)OCC1OC(O)C(O)C(O)C1O	250.29	-1.57	99.38	5	6	4	6	232740.69	Good
C146	C\C=C(/C)OCC1OC(O)C(O)C(O)C1O	234.25	-1.90	99.38	3	7	4	6	259575.09	Good
C147	CCC(OCC1OC(O)C(O)C(O)C1O)C(C)=O	264.27	-1.92	116.45	5	7	4	7	280926.13	Good
C150	CC(CC(C)=O)OCC1OC(O)C(O)C(O)C1O	264.27	-2.52	116.45	5	7	4	7	409973.18	Good

ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C153	CC(O)CCCOCC1OC(O)C(O)C(O)C1O	266.29	-2.79	119.61	6	6	5	7	516612.14	Good
C155	OC1OC(COC2C3SCC=CN3C2=O)C(O)C(O)C1O	319.33	-2.45	144.99	3	16	4	8	295265.91	Good
C156	C\C=C\C(\OCC1OC(O)C(O)C(O)C1O)=C/C	260.28	-0.61	99.38	4	8	4	6	116316.33	Good
C159	CC(CO)OCC1OC(O)C(O)C(O)C1O	238.24	-3.51	119.61	4	6	5	7	758619.66	Good
C161	OC1OC(COc2ccc(cc2)C(=O)c2ccccc2)C(O)C(O)C1O	360.36	1.01	116.45	5	19	4	7	27482.11	Good
C165	OCCOCC1OC(O)C(O)C(O)C1O	224.21	-3.94	119.61	4	6	5	7	1021149.09	Good
C180	NC1NC2C(NCN2OCC2OC(O)C(O)C(O)C2O)C(=O)N1	335.31	-4.72	181.80	3	17	9	12	1173471.16	Good
C204	Nc1ccn(OCC2OC(O)C(O)C(O)C2O)c(=O)n1	289.24	-3.75	160.29	3	13	6	10	643940.39	Good
C216	CCCC(CC)OCC1OC(O)C(O)C(O)C1O	264.32	-0.39	99.38	6	6	4	6	114444.24	Good
C234	CCCC(CO)OCC1OC(O)C(O)C(O)C1O	266.29	-1.97	119.61	6	6	5	7	308182.58	Good
C243	CCC(C)CCOCC1OC(O)C(O)C(O)C1O	264.32	-0.37	99.38	6	6	4	6	113011.29	Good
C248	CC(=O)COCC1OC(O)C(O)C(O)C1O	236.22	-3.50	116.45	4	7	4	7	756877.39	Good
C263	CCCCC(C)COCC1OC(O)C(O)C(O)C1O	278.34	0.17	99.38	7	6	4	6	82932.77	Good
C264	C\C=C\C=C\COCC1OC(O)C(O)C(O)C1O	260.28	-1.74	99.38	5	8	4	6	253208.56	Good
C285	CCCCCOCC1OC(O)C(O)C(O)C1O	250.29	-1.46	99.38	6	6	4	6	231973.92	Good
C292	N\C=N\OCC1OC(O)C(O)C(O)C1O	222.20	-3.60	137.76	3	7	6	8	774288.79	Good
C315	OC1OC(COC2CC3CCC4C(C-Cc5ccccc45)C3C2)C(O)C(O)C1O	404.50	1.90	99.38	3	26	4	6	13236.49	Good
C316	CCC(CO)OCC1OC(O)C(O)C(O)C1O	252.26	-2.33	119.61	5	6	5	7	374033.26	Good
C320	CC(C)CC(C)COCC1OC(O)C(O)C(O)C1O	278.34	-0.77	99.38	6	6	4	6	140362.78	Good
C333	CC(C)CCCOCC1OC(O)C(O)C(O)C1O	264.32	-1.21	99.38	6	6	4	6	191844.99	Good
C334	CC(C)CCCCOCC1OC(O)C(O)C(O)C1O	278.34	-0.67	99.38	7	6	4	6	140784.5	Good
C337	CC(=O)CCCOCC1OC(O)C(O)C(O)C1O	264.27	-3.24	116.45	6	7	4	7	689310.45	Good
C338	OC1OC(COC2C3CC=CN3C2=O)C(O)C(O)C1O	287.27	-2.74	119.69	3	15	4	8	388992.38	Good
C339	CO\N=C\OCC1OC(O)C(O)C(O)C1O	237.21	-2.62	120.97	4	7	4	8	433915.31	Good
C346	CC(CCO)OCC1OC(O)C(O)C(O)C1O	252.26	-2.50	119.61	5	6	5	7	416316.06	Good
C365	OC1OC(COC=C)C(O)C(O)C1O	206.19	-2.51	99.38	3	7	4	6	399301.12	Good
C370	CC(C)CCOCC1OC(O)C(O)C(O)C1O	250.29	-1.57	99.38	5	6	4	6	232740.69	Good
C386	OC1OC(COc2cccc(c2)C(=O)c2ccccc2)C(O)C(O)C1O	360.36	0.55	116.45	5	19	4	7	36720.5	Good
C2504	OCCCOCC1OC(O)C(O)C(O)C1O	238.24	-3.58	119.61	5	6	5	7	846915.17	Good
C2509	OC1OC(COc2cccc3oc(=O)ccc23)C(O)C(O)C1O	324.28	-0.80	129.59	3	18	4	8	85056.8	Good
C2520	CCC(C)(C)OCC1OC(O)C(O)C(O)C1O	250.29	-1.74	99.38	4	6	4	6	242505.63	Good

ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C2524	OCc1cccc(OCC2OC(O)C(O)C(O)C2O)c1	286.28	-1.22	119.61	4	12	5	7	142280.17	Good
C2525	OC1OC(COc2ccc3CCc4ccccc4Cc3c2)C(O)C(O)C1O	372.41	1.43	99.38	3	23	4	6	18065.97	Good
C2528	CC(=O)C(OCC1OC(O)C(O)C(O)C1O)c1ccccc1	312.32	-1.16	116.45	5	13	4	7	137379.16	Good
C2529	CCC(C)COCC1OC(O)C(O)C(O)C1O	250.29	-1.57	99.38	5	6	4	6	232740.69	Good
C2532	CC(C)CCC(C)OCC1OC(O)C(O)C(O)C1O	278.34	-0.13	99.38	6	6	4	6	93787.38	Good
C2533	OC1OC(COc2cccc3COc4ccccc4Cc23)C(O)C(O)C1O	374.38	0.68	108.61	3	23	4	7	28573.37	Good
C2538	OC1OC(COC2CN3C(CC3=O)S2)C(O)C(O)C1O	307.32	-2.65	144.99	3	15	4	8	347236.12	Good
C2540	CCC(OCC1OC(O)C(O)C(O)C1O)C(C)O	266.29	-1.89	119.61	5	6	5	7	274319.2	Good
C2549	OC1OC(COc2cc(=O)oc3ccccc23)C(O)C(O)C1O	324.28	-1.08	129.59	3	18	4	8	101465.54	Good
C2554	OC1OC(COc2ccc3Cc4ccccc4CCc3c2)C(O)C(O)C1O	372.41	1.43	99.38	3	23	4	6	18065.97	Good
C2563	CC(C)C(OCC1OC(O)C(O)C(O)C1O)C(C)C	278.34	-0.53	99.38	5	6	4	6	112959.61	Good
C2565	OC1OC(COC2Cc3ccccc3Cc3ccccc23)C(O)C(O)C1O	372.41	0.88	99.38	3	23	4	6	25547.26	Good
C2588	C\C=C\OCC1OC(O)C(O)C(O)C1O	220.22	-2.28	99.38	3	7	4	6	338208.81	Good
C3585	OC1OC(CON2C(=O)CCNC2=O)C(O)C(O)C1O	292.24	-3.59	152.36	3	14	5	10	655488.03	Good
C3758	OCc1ccc(OCC2OC(O)C(O)C(O)C2O)cc1	286.28	-1.22	119.61	4	12	5	7	142280.17	Good
C4305	OC1OC(COc2cccc3Cc4ccccc4COc23)C(O)C(O)C1O	374.38	0.68	108.61	3	23	4	7	28573.37	Good

Docking with known drugs and derived mannosides had some similar amino acid residues in their bonding pattern (Fig. 3).



MannosideC25 Known antibiotic Ertapenem

Fig. 3. Chemical structure of Mannoside C25 and antibiotic Ertapenem

The docking pattern above reveals that the mannosides and known drugs share common bonding residues Gln41, Asp37, ASN23, and VAL35. The docking score of the selected mannoside is significantly higher than that of Ertapenem, known antibiotic. The number of H-bonds was also higher in the case of mannoside C25, indicating that C25 is more effective against fimH. Table2 shows the docking score of the selected ligands.

Table2. Top 10 docking score shown by the selected ligands with bonding patterns

Compounds	Total Score (Kcal/mol)	Hydrogen Bond Properties		
		Hydrogen Bonds	Bond Energy (Kcal/mol)	Bond Length (A)
C26	-29.98	OASN23A - H34	-4.3	1.97
		OLEU24A - H18	-3.9	2.08
		OVAL35A - H30	-4.7	2.04
		HASP37A - O4	-4.4	2.20
		OASP37A - H32	-4.2	1.99
		HE22GLN41A - O12	-4.6	1.88
C339	-28.89	OASN23A - H34	-4.3	1.97
		OLEU24A - H18	-3.9	2.08
		OVAL35A - H30	-4.7	2.04
		HASP37A - O4	-4.4	2.20
		OASP37A - H32	-4.2	1.99
		HE22GLN41A - O12	-4.6	1.88
C74	-27.63	OASN23A - H32	-4.7	2.08
		OVAL35A - H28	-4.7	1.81
		HASP37A - O4	-4.4	2.10
		OASP37A - H30	-4.7	2.19
		HE22GLN41A - O12	-4.7	2.18
C112	-26.70	OASN23A - H30	-3.9	2.26
		OVAL35A - H26	-4.6	1.85
		HVAL35A - O17	-4.1	1.77
		OASP37A - H28	-4.6	2.20
		HASP37A - O4	-4.4	2.12
		HE22GLN41A - O12	-4.7	2.12
C359	-25.92	OASN23A - H36	-4.7	2.09
		OVAL35A - H32	-4.7	2.08
		HASP37A - O4	-4.4	2.05
		OASP37A - H34	-4.7	2.14
		OASP37A - H38	-3.4	1.83
		HE22GLN41A - O12	-4.7	2.01
C346	-25.64	OASN23A - H35	-4.7	2.17
		OVAL35A - H31	-4.5	1.94
		HASP37A - O4	-4.4	2.16
		OASP37A - H33	-4.7	2.18
		HE22GLN41A - O12	-4.7	1.99
C315	-25.12	OASN23A - H33	-4.7	2.18
		OVAL35A - H29	-4.6	2.20
		HVAL35A - O24	-3.4	2.27
		OASP37A - H31	-4.3	2.02
		HASP37A - O4	-3.3	2.30
		HE22GLN41A - O12	-4.7	1.90

Compounds	Total Score (Kcal/mol)	Hydrogen Bond Properties		
		Hydrogen Bonds	Bond Energy (Kcal/mol)	Bond Length (A)
C310	-24.82	OASN23A - H36	-3.2	2.32
		OVAL35A - H32	-4.3	2.05
		OASP37A - H38	-4.4	1.73
		OASP37A - H34	-4.7	2.19
		HASP37A - O4	-3.9	1.97
		HE22GLN41A - O12	-4.7	1.88
C386	-24.83	OASN23A - H35	-4.7	2.07
		OVAL35A - H31	-4.4	1.92
		OASP37A - H37	-3.6	1.92
		OASP37A - H33	-4.7	2.14
		HE22GLN41A - O12	-4.7	1.99
C3758	-22. 63	OASN23A - H35	-4.7	2.07
		OVAL35A - H31	-4.4	1.92
		OASP37A - H37	-3.6	1.92
		HE22GLN41A - O12	-4.7	1.99

The simulation result suggested that after 10ns of run the protein-ligand complex of C25-FimH became stable and there was not much fluctuation in the radius of gyration and radius of fluctuation studies. The minimization state was attained by the open protein at 145 steps to -2.6x10^{8}KJ/mol. On the other hand, the protein-ligand complex became stable at 2587 steps to -7.56x10^{6}KJ/mol. This indicates that after binding to the C25, the system remained stable indicating the stable binding of C25.

The numbers of H-bonds were found to be 2 (two) after simulation indicating that the bonds were high energy bonds which need more energy to break and hence, the bonding can be treated as strong. Binding of repressor analogues may change protein conformation leading to lowering of efficacy of the proteins and hence the host-bacteria attachment can be avoided.[23]

The descriptors molecular weight (MW), Molar Refractivity, Molar Volume, parachor, Index of Refraction, Surface Tension, Density, LogP, and Polarizability (Pol) against their bioactivities (Log(IC50)$^{-1}$) were used to generate the multiple regression model. The QSAR equation obtained from the investigation shows that the descriptor Surface Tension contributes 49.56 percent to the activity, with a descriptor-activity correlation of 0.72. The multiple regression equation was shown below:

Ac= -12.289+1.45x10^{-1}*ST, *asAc: 1/log(IC$_{50}$) ,*

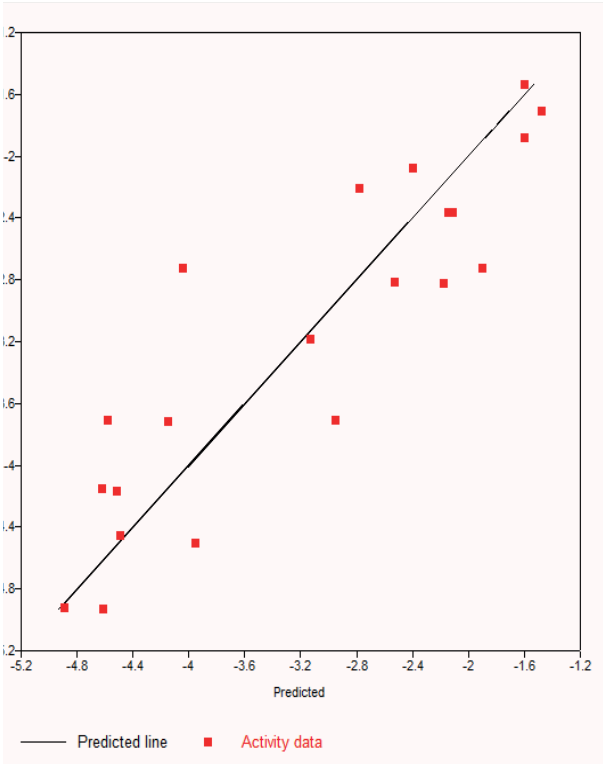


Fig 3.QSAR multiple regression plot showing good correlation

and ST: Surface Tension

The multiple regression plot analysis shows the R^2 to be 49.92% and adjusted R^2 to be 47.63%. The F Statistics was recorded as 19.23while the critical F value (5.25) was lower than that of F value, indicating significance of the QSAR model. From the above QSAR equation, bioactivities of the 21

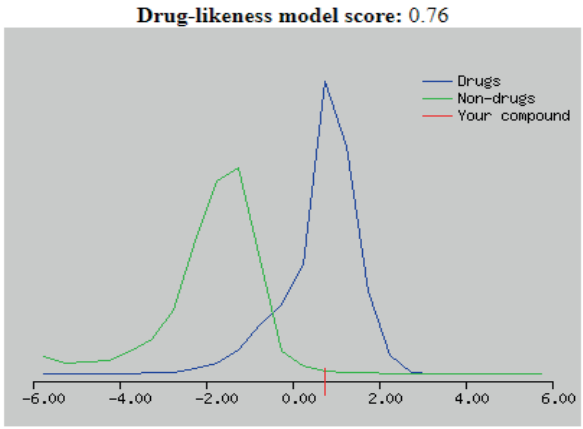


Fig. 4. High druglikeness shown by the best docked ligand C25 (Drug Score: 0.77)

known inhibitors were predicted and compared with the experimental bioactivities and plotted in a scattered plot (Fig. 3). It was clearly seen in the scattered plot that most of the points fall on or close to the trend line indicating a good QSAR equation. From the equation, the bioactivity [Log$(IC50)^{-1}$)] of the selected compound C25 with Surface Tension 54.9 dyne/cm was found to be -4.50which is equal to IC50 = 32.06µM.

Conclusion

The analysis suggested that the selected mannosides may attach to the adhesin fimH more effectively than host oligo-mannose. As a result, utilising ligands as a non-antibiotic based inhibitor in the treatment of UTIs could be tremendously advantageous. The improved binding score, good oral bioavailability, and lower IC50 of ligand C25 indicates the use of C25 i.e6-((((1-phenylpropan-2-yl)amino)oxy)methyl)tetrahydro-2H-pyran-2,3,4,5-tetraol as an alternative medication to treat UTI.

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