



An *In-silico* Study Showing Potentials of Selected Anthocyanin Derivatives against Uropathogenic *E. coli* Adhesin Protein

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Authors' contributions

This work was carried out in collaboration among all authors. All the authors contributed equally to the hypothesis preparation and design of the experiments. Authors AC and MAL did all the experiments and compilation of data. Author MDC did final checking and overall proof checking before it was submitted for publication. All authors read and approved the final manuscript.

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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 anthocyanins in 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 fimH inhibitors derived from the selected plant's phytochemicals, and is significant owing to their therapeutic implication as a non-antibiotic mediated therapy for UTI.

Keywords: *Urinary tract infections; Escherichia coli; fimH; computer aided drug design.*

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1. 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] (Fig. 1). 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].

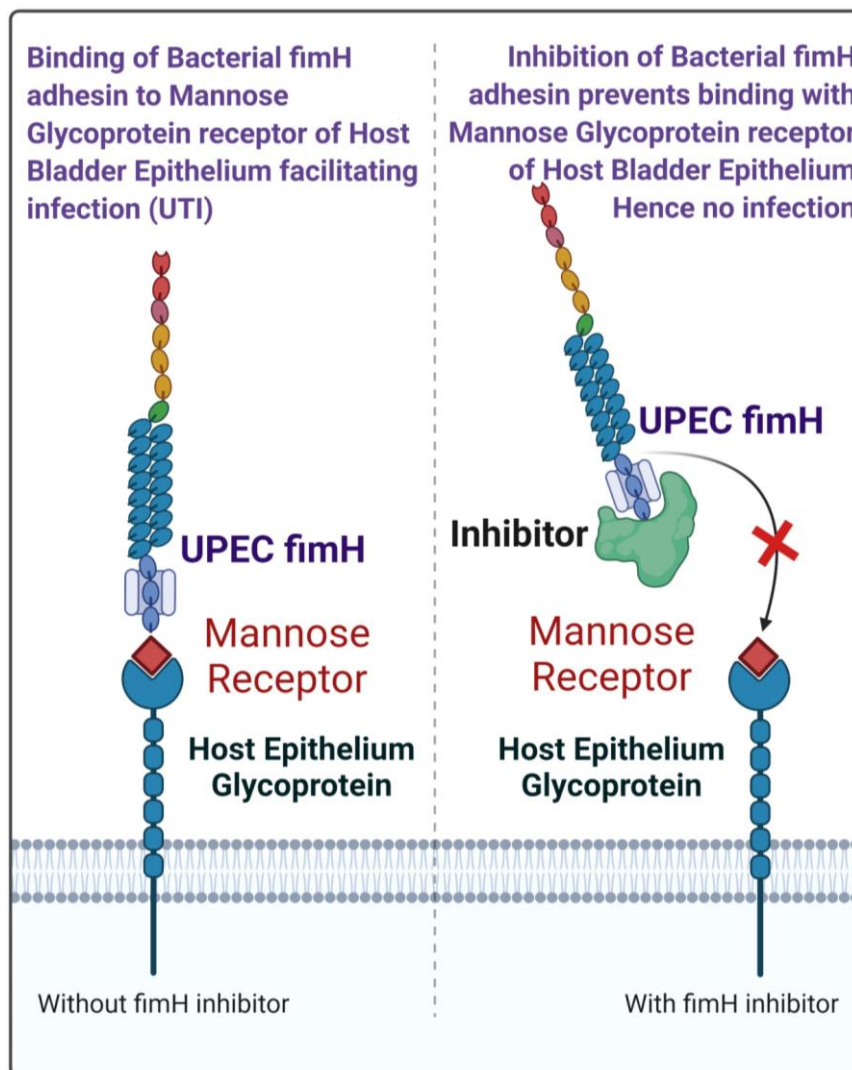


Fig. 1. fimH blocking mechanism in presence of inhibitors

This suggests that FimH can 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.

1.1 The Null Hypothesis

Compounds with better affinity towards fimH lectin domain can result in competitive binding of analogues over host cell mannose receptor. This prevents the attachment of bacterium with the host cell and thereby will be flushed from the body along with urine flow. This can help in non-antibiotic mediated therapy.

1.2 Need for New Drugs

Increase in the drug resistance in case of chronic and recurrent urinary tract infections create 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.

1.3 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, we examined novel mannoside derived drug leads for increased oral bioavailability and demonstrated their rapid-acting efficacy in the treatment of persistent urinary tract infections.

2. METHODOLOGY

2.1 Toxicity and Druglikeness Prediction

To pass druglikeness 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 Mobylye@RPBS (<https://mobylye.rpbs.univ-parisdiderot.fr/>) portal.

2.2 Receptor Quality Checking

X-ray diffraction (1.30Å) 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 checked by generating Ramachandran plot at PDBSum 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.

2.3 Molecular Docking Analysis

Molecular docking analysis was done to predict the binding pattern and binding energy of the novel compounds against fimH [22] using 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/>) and included in the docking analysis as positive control. The best docking pose for each compound were used for identification of docking pattern.

2.4 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 physicochemical properties of any compound through multiple regression analysis. ChemsKetch, a freeware was used to generate the physicochemical parameters of the selected known fimH inhibitors. Multiple linear regression analysis was performed using another freeware EasyQSAR. The QSAR equation was generated and 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.

2.5 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 performed followed by energy profile, density analysis and pressure profile analysis after a 10-ns run in the simple point charge (SPC) water model based simulation.

3. RESULTS AND DISCUSSION

1000 anthocyanin 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 Table 1.

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

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. Table 2 shows the docking score of the selected ligands.

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 -2.6×10^8 KJ/mol. On the other hand, the protein-ligand complex became stable at 2587 steps to -7.56×10^6 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 ($\text{Log}(\text{IC}_{50})^{-1}$) 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:

$$Ac = -12.289 + 1.45 \times 10^{-1} * ST$$

Ac: $1/\log(\text{IC}_{50})$, ST: Surface Tension

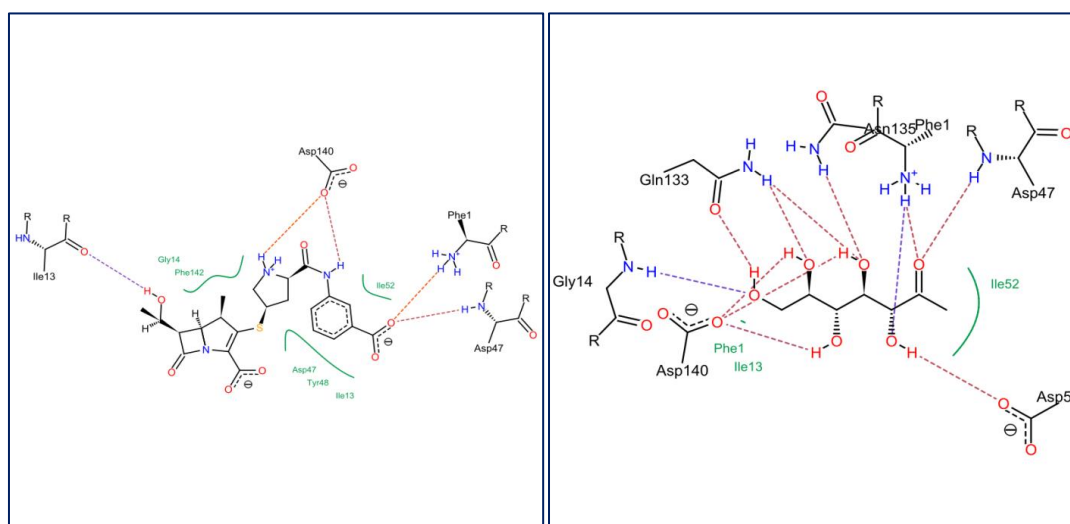


Fig. 2. Inhibitor C25 known antibiotic Ertapenem

Table 1. ADMET Properties of selected anthocyanin derivatives showing high oral bioavailability

ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C2	<chem>OC1OC(COC2CCC3C(CCC4C5CCCC5CCC34)C2)C(O)C(O)C1O</chem>	410.54	2.96	99.38	3	26	4	6	7137.12	Good
C3	<chem>OC1OC(COC2CCC3C2CCC2C3CCc3ccccc23)C(O)C(O)C1O</chem>	404.50	1.72	99.38	3	26	4	6	14825.93	Good
C4	<chem>OCc1ccccc1OCC1OC(O)C(O)C(O)C1O</chem>	286.28	-1.22	119.61	4	12	5	7	142280.17	Good
C26	<chem>OC1OC(CONc2nc3[nH]cnc3c(=O)[nH]2)C(O)C(O)C1O</chem>	329.27	-3.31	185.84	4	17	7	12	441180.13	Good
C6	<chem>CCC(O)CCOCC1OC(O)C(O)C(O)C1O</chem>	266.29	-1.97	119.61	6	6	5	7	308182.58	Good
C7	<chem>CC(=O)CC(=O)COCC1OC(O)C(O)C(O)C1O</chem>	278.26	-3.00	133.52	6	8	4	8	572123.47	Good
C8	<chem>CC(=O)C(=O)COCC1OC(O)C(O)C(O)C1O</chem>	264.23	-3.21	133.52	5	8	4	8	633269.3	Good
C9	<chem>Nc1ncnc2n(OCC3OC(O)C(O)C(O)C3O)cnc12</chem>	313.27	-2.57	169.00	3	16	6	11	270941.08	Good
C10	<chem>CC(C)COCC1OC(O)C(O)C(O)C1O</chem>	236.26	-1.92	99.38	4	6	4	6	279699.71	Good
C11	<chem>OC1OC(CON2CCC(=O)NC2=O)C(O)C(O)C1O</chem>	292.24	-3.59	148.79	3	14	5	10	655488.03	Good
C12	<chem>OC1OC(COc2cc3ccccc3oc2=O)C(O)C(O)C1O</chem>	324.28	-0.59	129.59	3	18	4	8	74516.4	Good
C13	<chem>OC1OC(CON2CNc3ccccc3S2(=O)=O)C(O)C(O)C1O</chem>	362.36	-1.71	157.17	3	19	5	10	144836.71	Good
C14	<chem>OCC1OC(O)C(O)C(O)C1O</chem>	196.16	-3.74	119.61	2	6	5	7	821345.5	Good
C15	<chem>OC1OC(COc2ccc3OCc4ccccc4Cc3c2)C(O)C(O)C1O</chem>	374.38	0.68	108.61	3	23	4	7	28573.37	Good
C17	<chem>OC1OC(CONc2ncnc3[nH]cnc23)C(O)C(O)C1O</chem>	313.27	-2.21	165.87	4	16	6	11	230696.12	Good
C19	<chem>OC1OC(CON2C3CCCC3NC2=O)C(O)C(O)C1O</chem>	318.32	-1.97	131.72	3	17	5	9	218888.85	Good
C20	<chem>OC1OC(COc2ccc3oc(=O)ccc3c2)C(O)C(O)C1O</chem>	324.28	-0.80	129.59	3	18	4	8	85056.8	Good
C21	<chem>OC1OC(COC2=CC(=O)C=CC2=O)C(O)C(O)C1O</chem>	286.23	-2.47	133.52	3	14	4	8	329065.49	Good
C22	<chem>OC1OC(CON2c3ccccc3CCc3ccccc23)C(O)C(O)C1O</chem>	373.40	1.26	102.62	3	23	4	7	19968.8	Good
C23	<chem>OC1OC(COC2SC3CC(=O)N3C=C2)C(O)C(O)C1O</chem>	319.33	-2.45	144.99	3	16	4	8	295265.91	Good
C27	<chem>OC1OC(COC2Oc3ccccc3Cc3ccccc23)C(O)C(O)C1O</chem>	374.38	0.69	108.61	3	23	4	7	28393.92	Good
C28	<chem>C\C=C\COCC1OC(O)C(O)C(O)C1O</chem>	234.25	-2.38	99.38	4	7	4	6	375195.05	Good
C29	<chem>OC1OC(CONc2ccnc(=O)[nH]2)C(O)C(O)C1O</chem>	289.24	-3.15	157.16	4	13	6	10	471352.47	Good
C30	<chem>CC(C)(C)COCC1OC(O)C(O)C(O)C1O</chem>	250.29	-1.53	99.38	4	6	4	6	212453.88	Good
C32	<chem>OC1OC(CON2c3ccccc3Sc3ccccc23)C(O)C(O)C1O</chem>	377.41	1.11	127.92	3	22	4	7	21215.91	Good
C33	<chem>OC1OC(CON2CCC34CCCC3C2Cc2ccccc42)C(O)C(O)C1O</chem>	405.48	0.83	102.62	3	26	4	7	25846.58	Good
C34	<chem>OC1OC(CON2c3ccccc3C=Cc3ccccc23)C(O)C(O)C1O</chem>	371.38	1.46	102.62	3	23	4	7	17599.25	Good
C35	<chem>OC1OC(CON2c3ccccc3Sc3ccccc23)C(O)C(O)C1O</chem>	378.40	0.38	140.81	3	22	4	8	33336.57	Good
C36	<chem>OC1OC(CON2CCN=Cc3ccccc23)C(O)C(O)C1O</chem>	324.33	-1.44	114.98	3	18	4	8	138776.19	Good
C39	<chem>CC1CN(OCC2OC(O)C(O)C(O)C2O)C(=O)NC1=O</chem>	306.27	-3.02	148.79	3	14	5	10	439745.15	Good
C40	<chem>Cn1c2ccccc2n(OCC2OC(O)C(O)C(O)C2O)c(=O)c2ccccc12</chem>	402.40	0.06	126.31	3	24	4	9	36786.37	Good
C251	<chem>OC1OC(COC23CCCC2C2CCc4ccccc4C2CC3)C(O)C(O)C1O</chem>	404.50	1.45	99.38	3	26	4	6	17575	Good
C252	<chem>CC(C)OCC1OC(O)C(O)C(O)C1O</chem>	222.24	-2.46	99.38	3	6	4	6	377540.3	Good

ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C253	<chem>CC(=O)OCC1OC(O)C(O)C(O)C1O</chem>	222.19	-3.22	116.45	3	7	4	7	609446.11	Good
C254	<chem>OCCCCOCC1OC(O)C(O)C(O)C1O</chem>	266.29	-2.87	119.61	7	6	5	7	580385.41	Good
C255	<chem>OC1OC(CON2c3ccccc3C=NCC2=O)C(O)C(O)C1O</chem>	338.31	-2.01	132.05	3	19	4	9	189619.2	Good
C257	<chem>CCOCC1OC(O)C(O)C(O)C1O</chem>	208.21	-2.89	99.38	3	6	4	6	505903.8	Good
C258	<chem>NOCC1OC(O)C(O)C(O)C1O</chem>	195.17	-4.00	125.40	2	6	6	7	968565.79	Good
C260	<chem>OC1OC(COCC(=O)C=C)C(O)C(O)C1O</chem>	248.23	-2.26	116.45	5	8	4	7	361091.03	Good
C52	<chem>OC1OC(COC=C2c3ccccc3CCc3ccccc23)C(O)C(O)C1O</chem>	384.42	1.18	99.38	3	24	4	6	20331.15	Good
C53	<chem>CC(=O)C(OCC1OC(O)C(O)C(O)C1O)C(C)=O</chem>	278.26	-2.90	133.52	5	8	4	8	502881.63	Good
C54	<chem>OCCCCOCC1OC(O)C(O)C(O)C1O</chem>	252.26	-3.22	119.61	6	6	5	7	699975.07	Good
C58	<chem>COCC1OC(O)C(O)C(O)C1O</chem>	194.18	-3.25	99.38	2	6	4	6	604479.03	Good
C59	<chem>CCCOCC1OC(O)C(O)C(O)C1O</chem>	222.24	-2.36	99.38	4	6	4	6	378674.62	Good
C60	<chem>OC1OC(COC2CCCC3CCC4C5CCCC5CCC4C23)C(O)C(O)C1O</chem>	410.54	3.15	99.38	3	26	4	6	6331.96	Good
C62	<chem>OC1OC(COc2ccc3ccc(=O)oc3c2)C(O)C(O)C1O</chem>	324.28	-0.72	129.59	3	18	4	8	80876.17	Good
C63	<chem>OC1OC(COC2Sc3ccccc3Cc3ccccc23)C(O)C(O)C1O</chem>	390.45	1.23	124.68	3	23	4	6	19075.13	Good
C65	<chem>OC1OC(COC2CCC3CCC4C5CCCC5CCC4C3C2)C(O)C(O)C1O</chem>	410.54	2.96	99.38	3	26	4	6	7137.12	Good
C68	<chem>CCCCCOCC1OC(O)C(O)C(O)C1O</chem>	264.32	-0.92	99.38	7	6	4	6	170713.67	Good
C71	<chem>CCC(CCO)OCC1OC(O)C(O)C(O)C1O</chem>	266.29	-1.97	119.61	6	6	5	7	308182.58	Good
C72	<chem>CCCCOCC1OC(O)C(O)C(O)C1O</chem>	236.26	-2.00	99.38	5	6	4	6	314227.29	Good
C74	<chem>OC1OC(CON2C(=O)CC(=O)NC2=O)C(O)C(O)C1O</chem>	306.23	-3.62	165.86	3	15	5	11	641828.88	Good
C76	<chem>OC1OC(CON2CNS(=O)(=O)c3ccccc23)C(O)C(O)C1O</chem>	362.36	-1.75	157.17	3	19	5	10	148532.97	Good
C77	<chem>OC1OC(COC#N)C(O)C(O)C1O</chem>	205.17	-2.95	123.17	2	7	4	7	493879.26	Good
C78	<chem>OC1OC(COC(=O)c2ccccc2)C(O)C(O)C1O</chem>	284.26	-0.91	116.45	4	13	4	7	116914.02	Good
C81	<chem>CC(O)CCOCC1OC(O)C(O)C(O)C1O</chem>	252.26	-3.15	119.61	5	6	5	7	626998.86	Good
C84	<chem>OC1OC(CON2C3NCNC3C(=O)NC2=O)C(O)C(O)C1O</chem>	334.28	-4.29	172.85	3	18	7	12	897968.11	Good
C90	<chem>OC1OC(COCC=C)C(O)C(O)C1O</chem>	220.22	-2.61	99.38	4	7	4	6	444772.75	Good
C92	<chem>CCC(C)CCOCC1OC(O)C(O)C(O)C1O</chem>	278.34	-0.02	99.38	7	6	4	6	93478.39	Good
C97	<chem>OC1OC(COC2C3SCCN3C2=O)C(O)C(O)C1O</chem>	307.32	-2.68	144.99	3	15	4	8	353861.3	Good
C99	<chem>CC(O)COCC1OC(O)C(O)C(O)C1O</chem>	238.24	-3.51	119.61	4	6	5	7	758619.66	Good
C100	<chem>CCC(C)OCC1OC(O)C(O)C(O)C1O</chem>	236.26	-1.93	99.38	4	6	4	6	281467.38	Good
C102	<chem>OC1OC(COC2=CN3C(CC3=O)C2)C(O)C(O)C1O</chem>	287.27	-3.03	119.69	3	15	4	8	466967.54	Good
C103	<chem>CCCC(C)COCC1OC(O)C(O)C(O)C1O</chem>	278.34	-0.02	99.38	7	6	4	6	93478.39	Good
C104	<chem>NC1NC2NCNC2C(=O)N1OCC1OC(O)C(O)C(O)C1O</chem>	335.31	-5.01	181.80	3	17	9	12	1408698.41	Good
C105	<chem>OC1OC(COC2C=CN3C2CC3=O)C(O)C(O)C1O</chem>	287.27	-3.30	119.69	3	15	4	8	553554.24	Good
C109	<chem>Cn1c2ncn(OCC3OC(O)C(O)C(O)C3O)c2c(=O)n(C)c1=O</chem>	358.30	-2.35	161.20	3	18	4	12	209246.55	Good
C110	<chem>CC(CCCO)OCC1OC(O)C(O)C(O)C1O</chem>	266.29	-2.14	119.61	6	6	5	7	343021.25	Good

ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C112	<chem>CC(=O)CCOCC1OC(O)C(O)C(O)C1O</chem>	250.25	-3.60	116.45	5	7	4	7	836243.51	Good
C114	<chem>OC1OC(COCC(=O)Cc2ccccc2)C(O)C(O)C1O</chem>	312.32	-1.26	116.45	6	13	4	7	156294.92	Good
C121	<chem>OC1OC(COc2ccc3CCc4ccccc4C(=C)c3c2)C(O)C(O)C1O</chem>	384.42	1.53	99.38	3	24	4	6	16307.97	Good
C132	<chem>CC1CNC(=O)N(OCC2OC(O)C(O)C(O)C2O)C1=O</chem>	306.27	-3.02	152.36	3	14	5	10	439745.15	Good
C134	<chem>CCCC(C)OCC1OC(O)C(O)C(O)C1O</chem>	250.29	-1.57	99.38	5	6	4	6	232740.69	Good
C146	<chem>C\C=C(/C)OCC1OC(O)C(O)C(O)C1O</chem>	234.25	-1.90	99.38	3	7	4	6	259575.09	Good
C147	<chem>CCC(OCC1OC(O)C(O)C(O)C1O)C(C)=O</chem>	264.27	-1.92	116.45	5	7	4	7	280926.13	Good
C150	<chem>CC(CC(C)=O)OCC1OC(O)C(O)C(O)C1O</chem>	264.27	-2.52	116.45	5	7	4	7	409973.18	Good
C153	<chem>CC(O)CCCOCC1OC(O)C(O)C(O)C1O</chem>	266.29	-2.79	119.61	6	6	5	7	516612.14	Good
C155	<chem>OC1OC(COC2C3SCC=CN3C2=O)C(O)C(O)C1O</chem>	319.33	-2.45	144.99	3	16	4	8	295265.91	Good
C156	<chem>C\C=C\C(OCC1OC(O)C(O)C(O)C1O)=C/C</chem>	260.28	-0.61	99.38	4	8	4	6	116316.33	Good
C159	<chem>CC(CO)OCC1OC(O)C(O)C(O)C1O</chem>	238.24	-3.51	119.61	4	6	5	7	758619.66	Good
C161	<chem>OC1OC(COc2ccc(cc2)C(=O)c2ccccc2)C(O)C(O)C1O</chem>	360.36	1.01	116.45	5	19	4	7	27482.11	Good
C165	<chem>OCCOCC1OC(O)C(O)C(O)C1O</chem>	224.21	-3.94	119.61	4	6	5	7	1021149.09	Good
C180	<chem>NC1NC2C(NCN2OCC2OC(O)C(O)C(O)C2O)C(=O)N1</chem>	335.31	-4.72	181.80	3	17	9	12	1173471.16	Good
C204	<chem>Nc1ccn(OCC2OC(O)C(O)C(O)C2O)c(=O)n1</chem>	289.24	-3.75	160.29	3	13	6	10	643940.39	Good
C216	<chem>CCCC(CC)OCC1OC(O)C(O)C(O)C1O</chem>	264.32	-0.39	99.38	6	6	4	6	114444.24	Good
C234	<chem>CCCC(CO)OCC1OC(O)C(O)C(O)C1O</chem>	266.29	-1.97	119.61	6	6	5	7	308182.58	Good
C243	<chem>CCC(C)CCOCC1OC(O)C(O)C(O)C1O</chem>	264.32	-0.37	99.38	6	6	4	6	113011.29	Good
C248	<chem>CC(=O)COCC1OC(O)C(O)C(O)C1O</chem>	236.22	-3.50	116.45	4	7	4	7	756877.39	Good
C263	<chem>CCCCC(C)COCC1OC(O)C(O)C(O)C1O</chem>	278.34	0.17	99.38	7	6	4	6	82932.77	Good
C264	<chem>C\C=C\C=C\C(OCC1OC(O)C(O)C(O)C1O)</chem>	260.28	-1.74	99.38	5	8	4	6	253208.56	Good
C285	<chem>CCCCCOCC1OC(O)C(O)C(O)C1O</chem>	250.29	-1.46	99.38	6	6	4	6	231973.92	Good
C292	<chem>N\C=N\OCC1OC(O)C(O)C(O)C1O</chem>	222.20	-3.60	137.76	3	7	6	8	774288.79	Good
C315	<chem>OC1OC(COC2CC3CCC4C(CCc5ccccc45)C3C2)C(O)C(O)C1O</chem>	404.50	1.90	99.38	3	26	4	6	13236.49	Good
C316	<chem>CCC(CO)OCC1OC(O)C(O)C(O)C1O</chem>	252.26	-2.33	119.61	5	6	5	7	374033.26	Good
C320	<chem>CC(C)CC(C)COCC1OC(O)C(O)C(O)C1O</chem>	278.34	-0.77	99.38	6	6	4	6	140362.78	Good
C333	<chem>CC(C)CCCOCC1OC(O)C(O)C(O)C1O</chem>	264.32	-1.21	99.38	6	6	4	6	191844.99	Good
C334	<chem>CC(C)CCCCOCC1OC(O)C(O)C(O)C1O</chem>	278.34	-0.67	99.38	7	6	4	6	140784.5	Good
C337	<chem>CC(=O)CCCOCC1OC(O)C(O)C(O)C1O</chem>	264.27	-3.24	116.45	6	7	4	7	689310.45	Good
C338	<chem>OC1OC(COC2C3CC=CN3C2=O)C(O)C(O)C1O</chem>	287.27	-2.74	119.69	3	15	4	8	388992.38	Good
C339	<chem>CO\N=C\OCC1OC(O)C(O)C(O)C1O</chem>	237.21	-2.62	120.97	4	7	4	8	433915.31	Good
C346	<chem>CC(CCO)OCC1OC(O)C(O)C(O)C1O</chem>	252.26	-2.50	119.61	5	6	5	7	416316.06	Good
C365	<chem>OC1OC(COC=C)C(O)C(O)C1O</chem>	206.19	-2.51	99.38	3	7	4	6	399301.12	Good
C370	<chem>CC(C)CCOCC1OC(O)C(O)C(O)C1O</chem>	250.29	-1.57	99.38	5	6	4	6	232740.69	Good

ID	SMILES	MW	logP	tPSA	RB	FB	HBD	HBA	SOL (mg/l)	Oral Bio-availability
C386	<chem>OC1OC(COc2cccc(c2)C(=O)c2cccc2)C(O)C(O)C1O</chem>	360.36	0.55	116.45	5	19	4	7	36720.5	Good
C2504	<chem>OCCCOCC1OC(O)C(O)C(O)C1O</chem>	238.24	-3.58	119.61	5	6	5	7	846915.17	Good
C2509	<chem>OC1OC(COc2cccc3oc(=O)ccc23)C(O)C(O)C1O</chem>	324.28	-0.80	129.59	3	18	4	8	85056.8	Good
C2520	<chem>CCC(C)(C)OCC1OC(O)C(O)C(O)C1O</chem>	250.29	-1.74	99.38	4	6	4	6	242505.63	Good
C2524	<chem>OCc1cccc(OCC2OC(O)C(O)C(O)C2O)c1</chem>	286.28	-1.22	119.61	4	12	5	7	142280.17	Good
C2525	<chem>OC1OC(COc2ccc3CCc4cccc4Cc3c2)C(O)C(O)C1O</chem>	372.41	1.43	99.38	3	23	4	6	18065.97	Good
C2528	<chem>CC(=O)C(OCC1OC(O)C(O)C(O)C1O)c1cccc1</chem>	312.32	-1.16	116.45	5	13	4	7	137379.16	Good
C2529	<chem>CCC(C)COCC1OC(O)C(O)C(O)C1O</chem>	250.29	-1.57	99.38	5	6	4	6	232740.69	Good
C2532	<chem>CC(C)CCC(C)OCC1OC(O)C(O)C(O)C1O</chem>	278.34	-0.13	99.38	6	6	4	6	93787.38	Good
C2533	<chem>OC1OC(COc2cccc3COc4cccc4Cc23)C(O)C(O)C1O</chem>	374.38	0.68	108.61	3	23	4	7	28573.37	Good
C2538	<chem>OC1OC(COC2CN3C(CC3=O)S2)C(O)C(O)C1O</chem>	307.32	-2.65	144.99	3	15	4	8	347236.12	Good
C2540	<chem>CCC(OCC1OC(O)C(O)C(O)C1O)C(C)O</chem>	266.29	-1.89	119.61	5	6	5	7	274319.2	Good
C2549	<chem>OC1OC(COc2cc(=O)oc3cccc23)C(O)C(O)C1O</chem>	324.28	-1.08	129.59	3	18	4	8	101465.54	Good
C2554	<chem>OC1OC(COc2ccc3Cc4cccc4CCc3c2)C(O)C(O)C1O</chem>	372.41	1.43	99.38	3	23	4	6	18065.97	Good
C2563	<chem>CC(C)C(OCC1OC(O)C(O)C(O)C1O)C(C)C</chem>	278.34	-0.53	99.38	5	6	4	6	112959.61	Good
C2565	<chem>OC1OC(COC2Cc3cccc3Cc3cccc23)C(O)C(O)C1O</chem>	372.41	0.88	99.38	3	23	4	6	25547.26	Good
C2588	<chem>C\C=C\OCC1OC(O)C(O)C(O)C1O</chem>	220.22	-2.28	99.38	3	7	4	6	338208.81	Good
C3585	<chem>OC1OC(CON2C(=O)CCNC2=O)C(O)C(O)C1O</chem>	292.24	-3.59	152.36	3	14	5	10	655488.03	Good
C3758	<chem>OCc1ccc(OCC2OC(O)C(O)C(O)C2O)cc1</chem>	286.28	-1.22	119.61	4	12	5	7	142280.17	Good
C4305	<chem>OC1OC(COc2cccc3Cc4cccc4COc23)C(O)C(O)C1O</chem>	374.38	0.68	108.61	3	23	4	7	28573.37	Good

SMILES: Simple Molecular Input Line Entry Specification; MW: Molecular weight; logP: Octanol-Water coefficient; tPSA: Polar Surface Area; RB: Rigid Bonds; FB: Flexible Bond; HBD: Hydrogen bond donor; HBA: Hydrogen bond acceptor; SOL: Solubility

Table 2. 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 (Å)
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
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

Compounds	Total Score (Kcal/mol)	Hydrogen bond properties		
		Hydrogen Bonds	Bond Energy (Kcal/mol)	Bond Length (Å)
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

O: oxygen, H/HE: Hydrogen; ASN: Asparagine; LEU: Leucine; ASP: Aspartic acid; GLN: Glutamine; VAL: Valine; A: Chain A of receptor; numbers after amino acids represents the residue number

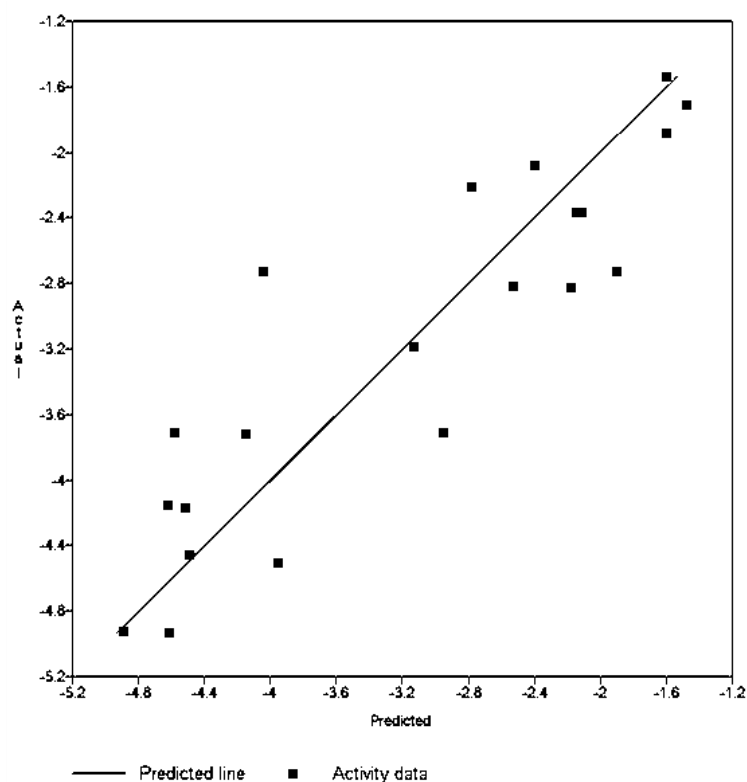


Fig. 3. QSAR multiple regression plot showing good correlation

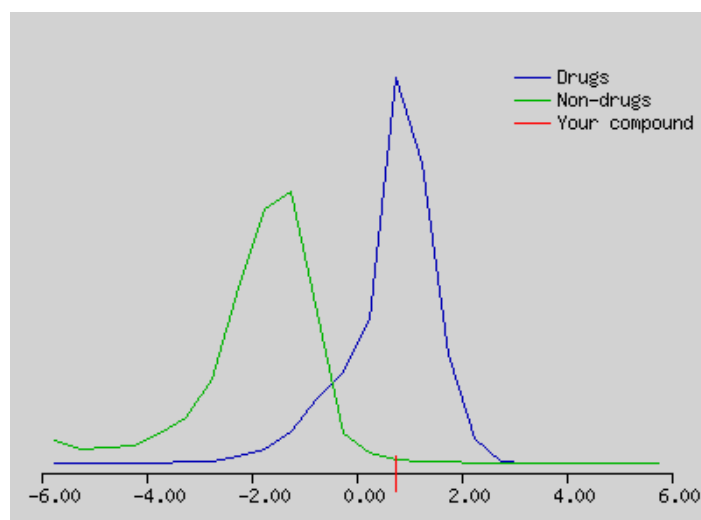


Fig. 4. High druglikeness shown by the best docked ligand C25 (Drug Score: 0.77)

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 19.23 while 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 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 [$\text{Log}(\text{IC}_{50})^{-1}$] of the selected compound C25 with Surface Tension 54.9 dyne/cm was found to be -4.50 which is equal to $\text{IC}_{50} = 32.06\mu\text{M}$.

4. CONCLUSION

The analysis suggested that the selected mannosides may attach to the receptor 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 IC_{50} of ligand C25 indicates that the use of C25 i.e. 6-((((1-phenylpropan-2-yl)amino)oxy)methyl)tetrahydro-2H-pyran-2,3,4,5-tetraol can be useful as an alternative medication to treat UTI.

AVAILABILITY OF DATA AND MATERIAL

All the data provided in the article can be reproduced as the authors used mostly the open source programs to perform the experiments.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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