# Supplementary material

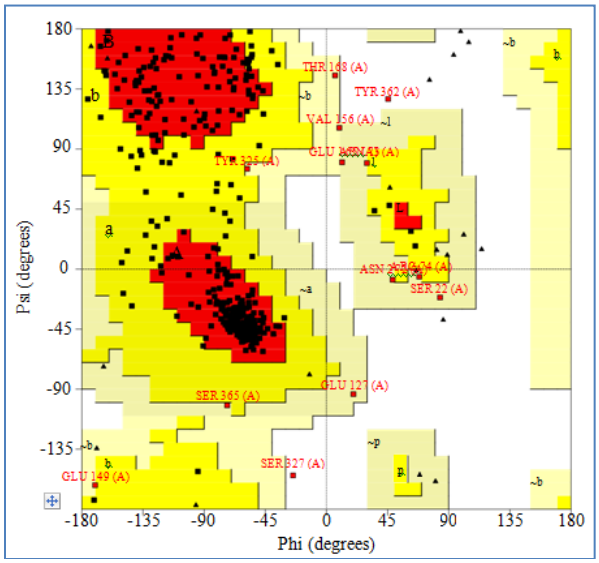



**Figure S1:** RAMPAGE plot statistics for FemB model

a) b)

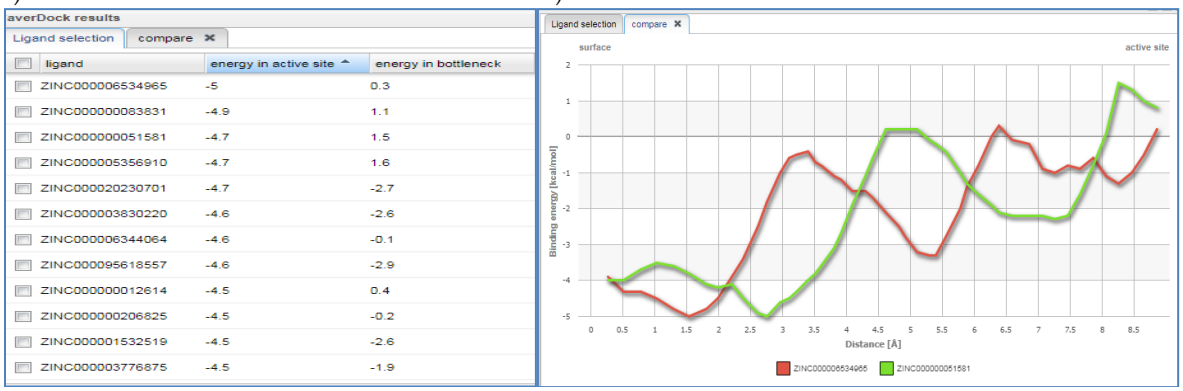



**Figure S2:** Caver web docking results. a) Caver docking results for hit binding molecules and b) Comparison between top scored ligands for active site binding, energy.

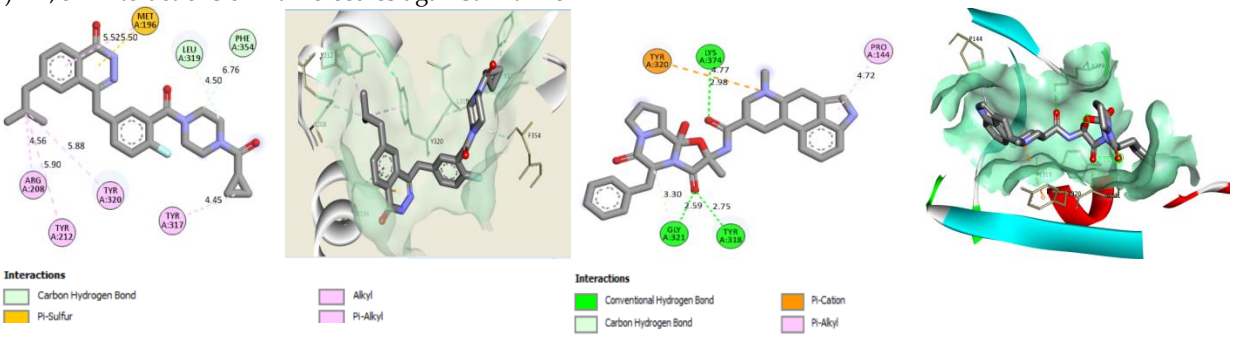
**Table S1.** DoGSite Scorer descriptors of *S. aureus* FEM X, C and B protein model binding pockets.

| Pocket No. | Volume (Å³) | Surface area (Å²) | Depth [Å] |
|---|---|---|---|
| **FemB-P1** | 658.43 | 1650.58 | 28.28 |
| **FemB-P2** | 573.95 | 1468.99 | 23.70 |
| **FemX-P1** | 669.7 | 1412.62 | 29.03 |
| **FemX-P2** | 156.67 | 614.42 | 15.37 |
| **FemC-P1** | 285.18 | 777.00 | 28.82 |
| **FemC-P2** | 263.68 | 803.72 | 22.92 |

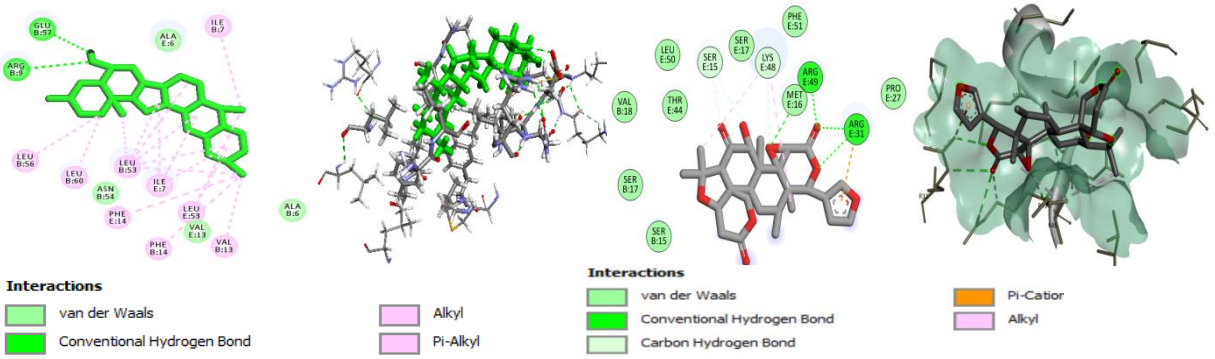
**Table S2:** Estimated bound free energies forFemB with potential hit repurposed drugs.

| FDA approved drug | Pubchem ID | MolDock Score | Rerank Score | H-Bond |
|---|---|---|---|---|
| **3-Hydroxyhippurate** | 6931069 | -137.66 | -107.41 | -5.15 |
| **Procodazole** | 65708 | -131.07 | -102.36 | -0.36 |
| **Succinanilic acid** | 7598 | -164.30 | -126.88 | -5.00 |

a) 2D, 3D interactions of hit molecules against with FemX




b) 2D, 3D interactions of hit molecules against with FemC.




c) 2D, 3D interactions of hit molecules against with FemB.

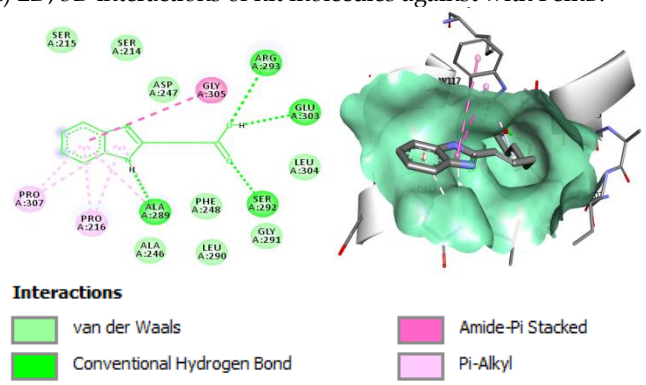



**Figure S3:** 2D, 3D dimensional interactions of FDA-hit similars against *S.aureus* Fem proteins.

**Table S3.** Details of the final identified hit compounds

| S. No. | Compound pub chem ID | Formula | SMILES |
|---|---|---|---|
| **1** | 90080139 | $C_{24}H_{18}F_2N_2O_5$ | CC1=C(N=C(C=C1)NC(=O)C2C(C2(F)F)C3=CC4=C(C=C3)OCO4)C5=CC(=CC=C5)C(=O)O |
| **2** | 155309251 | $C_{28}H_{31}FN_4O_3$ | CC(C)CC1=CC2=C(C=C1)C(=O)NN=C2CC3=CC(=C(C=C3)F)C(=O)N4CCN(CC4)C(=O)C5CC5 |
| **3** | 11870334 | $C_{33}H_{38}N_5O_5^+$ | CC1(C(=O)N2C(C(=O)N3CCCC3C2(O1)O)CC4=CC=CC=C4)NC(=O)C5CC6C(CC7=CNC8=CC=CC6=C78)[NH+](C5)C |
| **4** | 90473176 | $C_{26}H_{43}NO_6$ | CC(CCC(=O)NCC(=O)O)C1CCC2C1(C(CC3C2C(CC4C3(CCC(C4)O)C)O)O)C |
| **5** | 122173174 | $C_{27}H_{45}NO_3$ | CC1CCC2C(C3CCC4C(C3CN2C1)CC5C4CC(C6C5(CCC(C6)O)C)O)(C)O |
| **6** | 95223056 | $C_{28}H_{32}O_{10}$ | CC(=O)OC1C2C(OC3C2(COC(=O)C3)C4CCC5(C(OC(=O)C6C5(C4(C1=O)C)O6)C7=COC=C7)C)(C)C |
| **7** | 150666978 | $C_9H_8BrNO_4$ | C1=CC(=CC(=C1)O)C(=O)NC(C(=O)O)Br |
| **8** | 163586828 | $C_{10}H_9N_3O_2$ | C1=CC=C2C(=C1)NC(=N2)CC(=N)C(=O)O |

**Table S4:** Pharmacokinetic properties of potent hit molecules predicted by pkCSM webserver

| S. No. | Protein target | Compound pubchem ID | Molecular Weight (Da) | Log P | Rotatable Bonds | H-bond Acceptors | H-bond Donors |
|---|---|---|---|---|---|---|---|
| **1** | FemX | 90080139 | 452.4 | 4.47 | 5 | 5 | 2 |
| **2** | | 155309251 | 490.5 | 3.54 | 6 | 4 | 1 |
| **3** | | 11870334 | 584.6 | 0.66 | 4 | 5 | 4 |
| **4** | FemC | 90473176 | 465.6 | 2.56 | 6 | 5 | 5 |
| **5** | | 122173174 | 431.6 | 3.67 | 0 | 4 | 3 |
| **6** | | 95223056 | 528.5 | 2.67 | 2 | 10 | 0 |
| **7** | FemB | 150666978 | 274.0 | 0.92 | 3 | 3 | 3 |
| **8** | | 163586828 | 203.2 | 1.20 | 3 | 3 | 3 |

**Table S5:** ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties of hit similars predicted by pkCSM webserver

| Properties (Units) | 90080139 | 155309251 | 11870334 | 90473176 | 122173174 | 95223056 | 150666978 | 163586828 |
|---|---|---|---|---|---|---|---|---|
| **Absorption** | | | | | | | | |
| **Water solubility (log mol/L)** | -3.16 | -4.30 | -2.93 | -4.03 | -3.92 | -3.99 | -2.37 | -2.86 |
| **$Caco_2$ permeability (log Papp in 10-6 cm/s)** | 0.73 | 1.00 | 0.21 | 0.45 | 0.84 | 1.09 | 0.71 | 0.63 |
| **Intestinal absorption (human) (%)** | 74.52 | 93.71 | 57.76 | 44.63 | 92.73 | 100 | 76.52 | 83.02 |
| **Skin Permeability (log Kp)** | -2.73 | -2.73 | -2.73 | -2.73 | -3.46 | -2.74 | -2.73 | -2.73 |
| **P-glycoprotein substrate** | Yes | Yes | Yes | Yes | Yes | No | No | Yes |
| **P-glycoprotein I inhibitor** | No | Yes | Yes | No | Yes | Yes | No | No |
| **P-glycoprotein II inhibitor** | No | Yes | Yes | No | No | No | No | No |
| **Distribution** | | | | | | | | |
| **VDss (human) (log L/kg)** | -1.69 | -0.30 | 1.32 | -1.08 | 0.11 | 0.22 | -0.91 | -0.39 |
| **Fraction unbound (human) (Fu)** | 0.02 | 0 | 0.30 | 0.26 | 0.32 | 0.11 | 0.64 | 0.28 |
| **Blood Brain Barrier (BBB) Permeability (Log BB)** | -0.54 | -0.79 | -0.33 | -0.81 | -0.03 | -1.25 | -0.78 | -0.89 |
| **CNS permeability (Log PS)** | -2.86 | -2.46 | -2.98 | -3.14 | -1.92 | -3.07 | -3.00 | -2.76 |
| **Metabolism** | | | | | | | | |
| **CYP2D6 substrate** | No | No | No | No | No | No | No | Yes |
| **CYP3A4 substrate** | No | Yes | Yes | Yes | Yes | Yes | No | No |
| **CYP1A2 inhibitor** | No | No | No | No | No | No | No | No |
| **CYP2C19 inhibitor** | No | Yes | No | No | No | No | No | No |
| **CYP2C9 inhibitor** | No | Yes | Yes | No | No | No | No | No |
| **CYP2D6 inhibitor** | No | No | No | No | Yes | No | No | No |
| **CYP3A4 inhibitor** | No | Yes | Yes | No | No | Yes | No | No |
| **Excretion** | | | | | | | | |
| **Total Clearance (log ml/min/kg)** | -0.079 | 0.41 | 0.95 | 0.65 | -0.08 | -0.01 | -0.007 | 0.79 |
| **Renal OCT2 substrate** | No | No | No | No | No | No | No | No |
| **Toxicity** | | | | | | | | |
| **AMES toxicity** | No | No | No | No | No | No | Yes | No |
| **Oral Rat Acute Toxicity (LD50) (mol/kg)** | 2.79 | 2.51 | 2.71 | 2.07 | 2.78 | 3.82 | 2.50 | 2.39 |
| **Oral Rat Chronic Toxicity (LOAEL) (log mg/kg_bw/day)** | 1.52 | 2.11 | 3.22 | 2.53 | 1.26 | 1.36 | 1.87 | 1.90 |
| **hERG I inhibitor** | No | No | No | No | No | No | No | No |
| **hERG II inhibitor** | No | Yes | Yes | No | Yes | No | No | No |
| **Skin Sensitisation** | No | No | No | No | No | No | No | No |
| **T.Pyriformis toxicity** | 0.28 | 0.29 | 0.28 | 0.28 | 0.30 | 0.28 | 0.28 | 0.28 |