Supplementary Materials

A molecular modelling approach to identify novel inhibitors of the major facilitator superfamily of efflux pump transporters

Table S1.- Topological domain of MFS transporters (NorA from *S. aureus* and EmrD from *E. coli*).

Topological domain	NorA model		EmrD (pdb ID:2gfp)*[22]	
	Stard	End	Stard	End
Helix I	5	25	9	29
Helix II	42	62	47	67
Helix III	69	89	74	94
Helix IV	99	119	96	116
Helix V	129	149	135	183
Helix VI	157	167	163	176
Helix VII	201	221	213	233
Helix VIII	239	259	243	263
Helix IX	269	289	277	297
Helix X	293	313	299	319
Helix XI	331	351	330	350
Helix XII	355	375	365	385

Figure S1.- Pairwise alignment of NorA and EmrD MFS transporter proteins (Swiss-Model, https://swissmodel.expasy.org/).

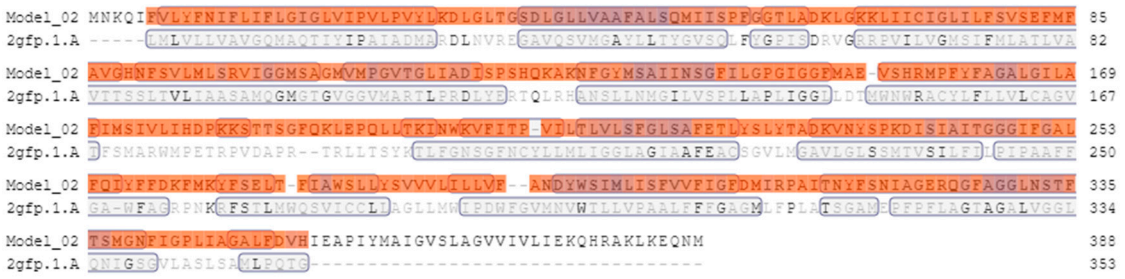
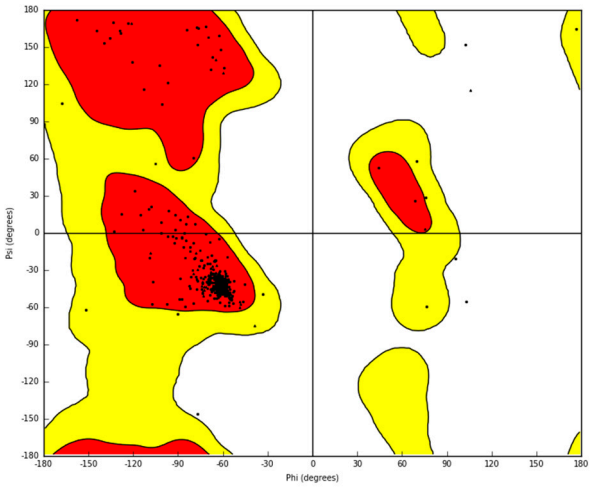


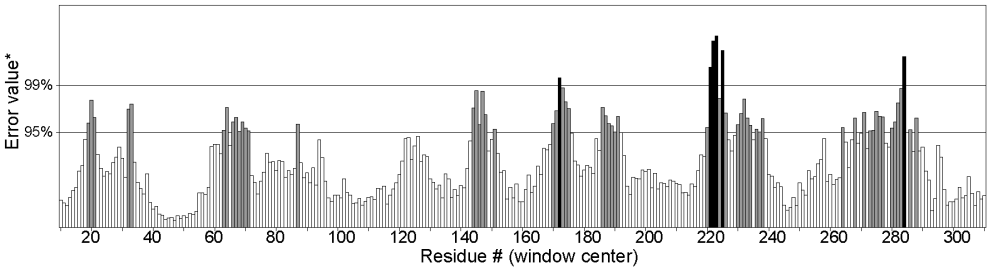
Figure S2.- Quality of the NorA model

A) Ramachandran plot: Residues in favorable regions 84%, in allowed 12,3% and in disallowed regions 0.7% (Ala[316], Leu[28] and Gly[61]). Good quality NorA model with the residues >90% in the most favored regions. (Plot done with Maestro suit). Red: Favorable, Yellow: Allowed, white: disallowed.



B) 3D profiles of NorA model: The non-bonded interactions between various types of atoms were computed with ERRAT2 program which showed an overall quality factor of **79,12.

*On the error axis, two lines are drawn to indicate the confidence with which it is possible to reject regions that exceed that error value. **Expressed as the percentage of the protein for which the calculated error value falls below the 95% rejection limit. Good high resolution structures generally produce values around 95% or higher. For lower resolutions (2.5 to 3A) the average overall quality factor is around 91%.



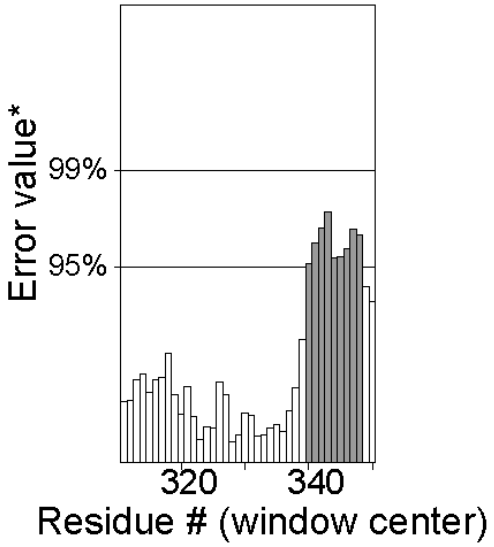


Figure S3.- Locate binding sites of NorA model.

Red: binding core (D-II), Blue: periplasmic side (D-I) and Green: Cytoplasmatic side (D-III).

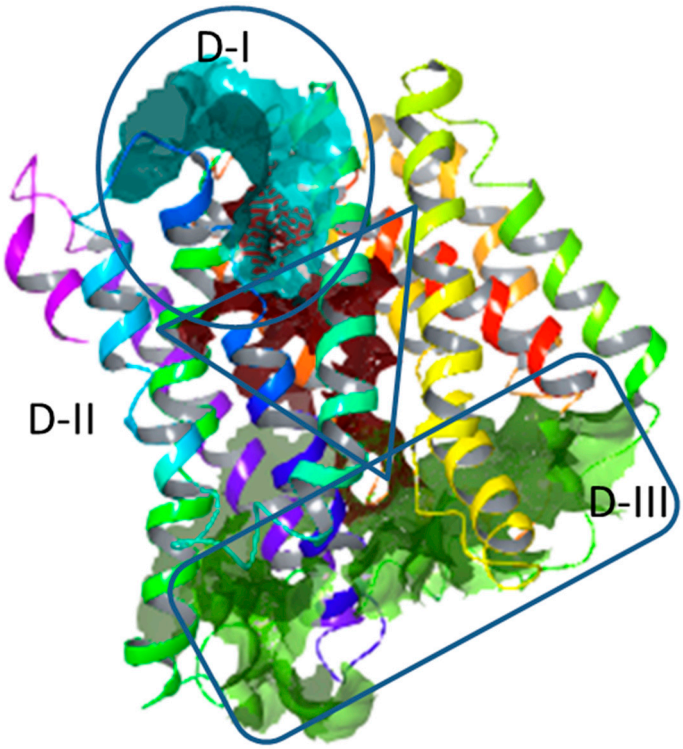


Figure S4.- Stereoimage view of the hydrophobic core of NorA (Phe^{47}, Tyr^{292}, Tyr^{131} and Trp^{293} residues)

Table 2. Conserved residues for EmrD and NorA efflux pump proteins.

Cavities	Amino Acid	EmrD efflux pump	Amino Acid	NorA efflux pump
Binding Site	Ile	28	Ile	23
	Ile	217	Ile	209
	Tyr	52	Phe	47
	Trp	300	Trp	293
	Phe	249	Ile	244
Cytoplasmic side	Arg	118	Thr	113
Periplasmic side	Thr	25	Ile	19
	Asp	33	Asp	32
	Glu	227	Glu	222

Table S3.- Computational prediction of drug likeness properties of potential new 18 lead compounds. Yellow: Compounds do not present good druglikeness.

CID PudChem	HBA	HBD	MW	QPlogS	QPlogHERG	QPPCaco	QPlogKp	QPlogKhsa	Percent Human Oral Absorption
Capsaicin	3	2	305	–4.08	–3.76	178,6	–1.90	0.14	100
Ciprofloxacin	7	2	331	–3.79	–3.43	13	–6.48	0.01	49
44330438	5	2	385	–4.55	–4.05	505	–2.05	0.08	95
2900500	3	1	327	–4.75	–4.49	3400	–0.39	0.31	100
14557750	4	3	331	–4.09	–4.12	1002	–1.31	0.11	100
2107051	5	1	347	–4.02	–3.65	2406	–0.94	0.10	100
1740989	3	1	327	–3.57	–3.56	2494	–0.58	0.20	100
822484	3	1	297	–2.98	–3.49	2666	–0.69	–0.06	100
742523	4	0	320	–1.99	–4.02	964	–3.29	–0.45	93
11516039	5	2	361	–3.48	–1.27	194	–2.27	–0.29	86
790127	4	1	285	–3.43	–4.99	3711	–1.04	–0.03	100
877843	3	1	269	–2.83	–3.86	2892	–0.71	–0.24	100
5459532	3	2	299	–3.64	–3.97	1097	–1.54	–0.06	100
1909740	3	1	313	–3.87	–3.69	3132	–0.64	0.12	100
2107051	5	1	347	–4.14	–3.18	2653	–1.04	0.18	100
754514	4	1	299	–2.34	–3.20	1725	–1.22	–0.26	100
44316847	3	2	320	–3.51	–4.01	1016	–1.41	–0.06	100
742523	4	0	320	–2.02	–4.12	835	–3.35	–0.43	92
44330438	5	2	385	–4.34	–4.33	250	–2.42	0.08	89
288409	3	1	299	–3.51	–3.61	3457	–0.57	–0.01	100