Supplementary data: Table S1. Ligand information

No	Ligand	PubChem CID	Canonical SMILES	Relevance (Inhibition of)
1	**Camostat mesylate (Camostat)** [4-[2-[2-(dimethylamino)-2-oxoethoxy]-2-oxoethyl]phenyl] 4-(diaminomethylideneamino) benzoate;methanesulfonic acid	5284360	N(C)(C)C(=O)COC(=O)CC1C=CC(OC(=O)C2C=CC(NC(=N)N)=CC=2)=CC=1	Clinically proven protease inhibitor for trypsin-like serine proteases
3	**GBA** 4-guanidinobenzoic acid	159772	C1=CC(=CC=C1C(=O)O)N=C(N)N	Inactive metabolite of Camostat Co-crystallized with TMPRSS2, PDB ID, 7MEQ
4	**Cathepsin G Inhibitor I (CatGinh)** [2-[3-[(1-benzoylpiperidin-4-yl)-methylcarbamoyl]naphthalen-2-yl]-1-naphthalen-1-yl-2-oxoethyl]phosphonic acid	9830518	C1C=CC(C(=O)N2CCC(N(C)C(=O)C3C=C4C=CC=CC4=CC=3C(=O)C(P(O)(O)=O)C3C4C=CC=CC=4C=CC=3)CC2)=CC=1	Reversible inhibitor of CatG
5	**Suc-Val-Pro-Phe^{P}-(OPh)$_2$ (SucVPF or 1ZG)**	https://www.brenda-enzymes.org/ligand.php?brenda_ligand_id=18430	C(CCC(O)=O)(=O)N[C@@H](C(C)C)C(N1[C@H](C(=O)NC(CC2C=CC=CC=2)P(OC2C=CC=CC=2)(=O)OC2C=CC=CC=2)CCC1)=O	Irreversible inhibitor of CatG; Co-crystallized with CatG, PDB ID, 1CGH
6	**Sivelestat** 2-[[2-[[4-(2,2-dimethylpropanoyloxy)phenyl]sulfonylamino]benzoyl]amino]acetic acid	107706	CC(C)(C)C(=O)OC1=CC=C(C=C1)S(=O)(=O)NC2=CC=CC=C2C(=O)NCC(=O)O	Reversible inhibitor of neutrophil elastase, also inhibits PR3

Table S2: Amino acids involved in protein-ligand interactions for docking TMPRSS2 and CatG.

AutoDock Tools	**Redocked GBA-TMPRSS2 (7MEQ) RMSD: 0.64 A**		**Camostat-TMPRSS2**		**Redocked SucVPF-CatG (1CGH) RMSD 1.25 A**		**Camostat-CatG**		**GBA-CatG**		**CatG inhibitor-CatG**	
	H-bonds: 9 Hydrophobic: - Salt bridges: 1		H-bonds: 7 Hydrophobic: 5 Salt bridges: 1		H-bonds: 10 Hydrophobic: 5 Salt bridges: -		H-bonds: 5 Hydrophobic: 5 Salt bridges: 2 Pi-stackings: 1		H-bonds: 8 Hydrophobic: 1 Salt bridges: 3		H-bonds: 6 Hydrophobic: 5 Pi-stackings: 1	
Predicted free binding energy	-7.31 kcal/mol		-8.69 kcal/mol		-8.75 kcal/mol		-6.52 kcal/mol		-4.90kcal/mol		-9.65 kcal/mol	
Ki [Temperature = 298.15 K]	4.41 μM		424.27 nM		385.31 nM		16.67 μM		254.38 μM		83.88 nM	
	Residues	**Distance (Å)**	**Residues**	**Distance (Å)**	**Residues**	**Distance (Å)**	**Residues**	**Distance (Å)**	**Residues**	**Distance (Å)**	**Residues**	**Distance (Å)**
Hydrogen bonds	S436 G439 D440 S441 G462 R470	2.08/3.25 2.44 2.90 1.94/2.63/2.42 2.69 3.10	S436 G439 D440 S441 G462 R470	2.16/3.47 2.12 3.06 2.34 2.73 3.48	H57 F191 G193 D194 S195 G216 S218	2.88 2.29 1.90 3.24 **2.94/3.10** 2.71/2.08/2.04 3.30	Q96 A190 S195 K217	1.70 2.10/1.83 2.01 2.14	G193 D194 S195 Y215 K217	3.17 3.00 2.96/2.29/1.87 3.09 2.00/3.15	H57 K192 G193 S195 S218	2.11 2.68 3.28 **2.20/2.32** 1.73
Salt bridges	D435	3.48	D435	3.78	-	-	H57 E226	4.16 4.29	H57 E226	5.49 4.30	-	-
Hydrophobic interactions	-	-	Q438 V280	3.92 3.62	I99 F172 F191 K192 Y215	3.59 3.94 3.44 3.13 3.63	H57 I99 K192 Y215	3.05 3.09/3.66 3.76 3.44	V213	3.66	I99 F172 V213 Y215 K217	3.47 3.53 3.05 3.31 3.75
Pi-stacking	-	-	-	-			H57	3.60	-	-	H57	5.19/3.94

Table S3: Amino acids involved in protein-ligand interactions for docking of NE and PR3.

AutoDock Tools	**Camostat-NE**		**Sivelestat-NE**		**Camostat-PR3**		**Sivelestat-PR3**	
	H-bonds: 5 Hydrophobic: 5 Salt bridges: 2 Pi-stackings: 1		H-bonds: 6 Hydrophobic: 5 Salt bridges: 1		H-bonds: 3 Hydrophobic: 2 Salt bridges: 2		H-bonds: 4 Hydrophobic: 2 Salt bridges: 1	
Predicted free binding energy	-6.35 kcal/mol		-7.03 kcal/mol		-6.19 kcal/mol		-6.50 kcal/mol	
***K*i [Temperature = 298.15 K]**	21.97 µM		7.01 µM		29.17 µM		17.26 µM	
	Residues	**Distance (Å)**	**Residues**	**Distance (Å)**	**Residues**	**Distance (Å)**	**Residues**	**Distance (Å)**
Hydrogen bonds	R177 S214 V216	2.8 3.43 2.48	H57 G193 D194 S195 S214	2.70 1.91 3.58 2.83/1.88 1.95	H40 W141 S195	2.25 3.40 1.79	H57 S195 S214 V216	3.18 1,64 2.41 2.51
Salt bridges	R177	3.74	H57	3.93	H57 R143	5.15 5.06	K99	3.43
Hydrophobic interactions	F192 F215 216	3.08 3.21/3.22 3.86	V62 F192 V216	3.99 3.80/3.84 2.23/3.38	P151	3.28/3.44	F41 P161	3.84 3.63

Table S4: Software and online tools used.

Software (version)/ online tool	Website	Reference
AutoDock 4.2.6	http://autodock.scripps.edu/downloads/autodock-registration/autodock-4-2-download-page/	doi.org/10.1002/jcc.21334
AutoDockTools 1.5.7	http://autodock.scripps.edu/resources/adt	doi.org/10.1002/jcc.21256
Avogadro 1.2.0	http://avogadro.cc/	doi.org/10.1186/1758-2946-4-17
PyMOL 2.4.2	https://pymol.org/2/	The PyMOL Molecular Graphics System, Version 1.2r3pre, Schrödinger, LLC.
PLIP	https://plip-tool.biotec.tu-dresden.de/plip-web/plip/index	doi.org/10.1093/nar/gkab294
PDB	http://www.rcsb.org/pdb/	doi.org/10.1093/nar/28.1.235
PubChem	https://pubchem.ncbi.nlm.nih.gov/	doi.org/10.1093/nar/gkab294
OpenBabel 3.1.1	http://openbabel.org/wiki/Main_Page	doi.org/10.1186/1758-2946-3-33