

Supplementary Table S1: Homologous Models with percentage identity.

Homologous Model	% Identity
5CE1-A	43
3W94-A	42.80
5TJX-A	42.56
2ANY-A	42.50
5F8T-A	42.50
2ANW-A	42.50
5GVT-A	42.26
6A8O-A	42.26

Supplementary Table S2: The structure files and Pharmacological relevance of the Marketed drugs studied.

S.no.	Marketed Drugs	Canonical Smiles	Pharmacological Relevance (inhibition of)
1.	Camostat	<chem>CN(C)C(=O)COC(=O)CC1=CC=C(C=C1)OC(=O)C2=CC=C(C=C2)N=C(N)N.CS(=O)(=O)O</chem>	Lysine analogue - Serine Protease
2.	3-TAPAP	<chem>CC1=CC=C(C=C1)S(=O)(=O)NC(CC2=CC(=CC=C2)C(=N)N)C(=O)N3CCCCC3</chem>	Serine Protease
3.	DIF (Di-	<chem>CC(C)OP(=O)(OC(C)C)F</chem>	Broad spectrum Serine Protease Inhibitor

	isopropyl fluoro phosphate)		
4.	Meloxicam,	<chem>C1=CC(=C(C(=C1)O)O)C(=O)NCC2=CC(=CC(=C2)CNC(=O)C3=C(C(=CC=C3)O)O)CNC(=O)C4=C(C(=CC=C4)O)O</chem>	NSAID Repurposed as Lysine analogue Serine Protease
5.	AEBSF (4-(2- Aminoethyl) benzenesulfonyl fluoride)	<chem>C1=CC(=CC=C1CCN)S(=O)(=O)F</chem>	Lysine analogue - Serine Protease
6.	P-Amino benzamidine	<chem>C1=CC(=CC=C1C(=[NH2+])N)N</chem>	Lysine analogue - Serine Protease
7.	Nafamostat	<chem>C1=CC(=CC=C1C(=O)OC2=CC3=C(C=C2)C=C(C=C3)C(=N)N)N=C(N)N</chem>	Lysine analogue - Serine Protease
8.	Ulinastatin	<chem>C1CC2(CC=C1)COC(OC2)C3=CC=CO3</chem>	Anticoagulant, repurposed as Trypsin Protease inhibitor.

Supplementary Table S3: The structure files, Sources and Antiviral relevance of the natural compounds studied.

S.no.	Compound Name	Canonical SMILES	Source	Antiviral Relevance against. (1)
1.	Tetratriacontane	CCCCCCCCCCCCCCCCCCCCCCCC CCCCCCCCCCCC	Neem, <i>Plectranthus amboinicus</i> Leaves, (2) Calligonum polygonoides, <i>Crateva Adansonii</i> . (3)	Influenzavirus- NS1 Protein
2.	Baicalein	C1=CC=C(C=C1)C2=CC(=O)C3=C(O2)C=C(C(=C3O)O)O	Isoflavanoid, <i>Scutellaria baicalensis</i>	DENV E Protein (4)
3.	Hesperetin	COC1=C(C=C(C=C1)C2CC(=O)C3=C(C=C(C=C3O2)O)O)O	Isoflavanoid, citrus fruit juice	DENV E Protein, RNA Virus.
4.	Fisetin	C1=CC(=C(C=C1)C2=C(C(=O)C3=C(O2)C=C(C=C3)O)O)O	Flavanones, trawberry, apple, persimmon, grape, onion, and cucumber.(5)	DENV E Protein. (6)
5.	Naringenin	C1[C@H](OC2=CC(=CC(=C2C1=O)O)O)C3=CC=C(C=C3)O	Flavanones, citrus fruit juice	DENV E Protein,
6.	Myricetin	C1=C(C=C(C(=C1O)O)O)C2=C(C(=O)C3=C(C=C(C=C3O2)O)O)O	<i>Isatis indigotica</i> and <i>Torreya nucifera</i>	nsP13 helicase and 3CL protease of SARS-CoV, Reverse transcriptase, Protease.
7.	3,4-	C1=CC=C2C(=C1)C(=C(OC2=O)Cl)	Cinnamon	Protease.

	Dichloroisocoumarin	Cl		
8.	APMSF (4-Amidinophenylmethanesulfonyl fluoride hydrochloride)	<chem>C1=CC(=CC=C1CS(=O)(=O)F)C(=N)N.Cl</chem>	Lychee seeds	Protease
9.	Aesculitannin B	<chem>C1C(C(OC2=C1C(=CC(=C2C3C(C(OC4=C3C(=CC5=C4C6C(C(O5)(OC7=CC(=CC(=C67)O)O)C8=CC(=C(C=C8)O)O)O)C9=CC(=C(C=C9)O)O)O)O)O)C1=CC(=C(C=C1)O)O)O</chem>	Lychee seeds	HSV-1
10.	Proanthocyanidine A2	<chem>C1C(C(OC2=C1C(=CC3=C2C4C(C(O3)(OC5=CC(=CC(=C45)O)O)C6=CC(=C(C=C6)O)O)O)O)C7=CC(=C(C=C7)O)O)O</chem>	Lychee seeds	HSV-1
11.	Ganoderiol D	<chem>CC(CCC(C(C)(CO)O)O)C1CCC2(C1(CCC3=C2C(=O)CC4C3(CCC(=O)C4(C)C)C)C)C</chem>	<i>Ganoderma lucidum</i>	HIV Protease
12.	Ganodermanontriol	<chem>CC(CCC(C(C)(CO)O)O)C1CCC2(C1(CC=C3C2=CCC4C3(CCC(=O)C4(C)C)C)C)C</chem>	<i>Ganoderma lucidum</i>	HIV Protease, Plasmepsin-1, Telomerase inhibitors

13.	Columbin	<chem>CC12CCC3C(=O)OC(CC3(C1C4C=CC2(C(=O)O4)O)C)C5=COC=C5</chem>	<i>Tenospora cardifolia</i>	HIV Protease,
14.	Ecdysterone	<chem>CC12CCC3C(=CC(=O)C4C3(CC(C(C4)O)O)C)C1(CCC2C(C)(C(CCC(C)C)O)O)O</chem>	<i>Tenospora cardifolia</i>	HIV Protease,
15.	Magnoflorine	<chem>C[N+](CCC2=CC(=C(C3=C2C1C4=C3C(=C(C=C4)OC)O)O)OC)C</chem>	<i>Tenospora cardifolia</i>	HIV Protease,
16.	Jatrorrhizine	<chem>COC1=C(C2=C[N+](3=C(C=C2C=C1)C4=CC(=C(C=C4CC3)O)OC)OC</chem>	<i>Tenospora cardifolia</i>	HIV Protease,
17.	Cis capsaicin	<chem>CC(C)C=CCCCC(=O)NCC1=CC(=C(C=C1)O)OC</chem>	<i>Capsicum baccatum</i>	HSV virus in guinea pigs, blocks viral replication cycle.
18.	Dihydrocapsaicin	<chem>CC(C)CCCCCCC(=O)NCC1=CC(=C(C=C1)O)OC</chem>	<i>Capsicum baccatum</i>	Trypsin Protease

Supplementary Table S4: Amino acid sequence of TMPRSS2 protein

Seq no.	Amino acid Sequence
1-70	MALNSGSPAIGPYYENHGYQPENPYPAQPTVVPTVYEVHPAQYYPSPVPQYAPRVLTQASNPVVCTQPK
70-140	SPSGTVCTSKTKKALCITLTLGTFLVGAALAAGLLWKFMSGKCSNSGIECDSSGTCINPSNWCDGVSHCP

140-210	GGEDENRCVRLYGPNFILQVYSSQRKSWHPVCQDDWNENYGRAACRDMGYKNNFYSSQGIVDDSGSTSM
210-280	KLNTSAGNVDIYKKLYHSDACSSKAVVSLRCIACGVNLNSSRQSRIVGGESALPGAWPWQVSLHVQNVHV
280-350	CGGSIITPEWIVTAAHCVEKPLNNPWHWTAFAGILRQSFMYGAGYQVEKVISHPNYDSKTKNNDIALMK
350-420	LQKPLTFNDLVKPVCLPNPGMMLQPEQLCWISGWGATEEKGKTSEVLNAAKVLLIETQRCNSRYVYDNLI
420-490	TPAMICAGFLQGNVDSCQGDSGGPLVTSKNNIWWLIGDTSWGSACAAYRPGVYGNVMVFTDWIYRQMRA
490-492	DG

Supplementary Table S5: Summary of quality check and validation scores of TMPRSS2 homology model

Server/tool	Parameter	Score
SWISS-MODEL	Q Mean	-1.43
ProSA-web	Z-Score	-8.67
PROCHECK (Ramachandran plot)	Most favored regions	92.2%
	Additional allowed regions	7.5%
	Disallowed regions	0.3%
ERRAT plot	Overall quality factor	91.67%
verify 3D	Averaged 3D-1D>0.2	95.38% (Pass)
SOSUI	Signal peptide	0
	Protein type	Soluble
	Expression	Extracellular

Supplementary Table S6: Physicochemical characterization of TMPRSS2

Physico chemical property	Value
Number of amino acids	347
Molecular weight	38610.95
Theoretical pI	8.58
Ext. coefficient	94725
estimated half-life	1.4 hours
Aliphatic index	76.11
Grand average of hydropathicity (GRAVY)	-0.260
instability index (II)	35.11 (This classifies the protein as stable)

Supplementary Table S7: Active site (or) pockets in the 3D structured model of TMPRSS2

Name	Volume Å ³	Surface Å ²	Drug Score	Simple Score	Amino acid Residues
P_0 Pocket 0	1233.73	1900.73	0.81	0.65	ARG_147_A; CYS_148_A; VAL_149_A; ARG_150_A; LEU_151_A; TYR_152_A; GLY_153_A; PHE_156_A; ILE_157_A; GLN_159_A; TRP_168_A; ARG_182_A; ALA_183_A; ARG_186_A; ASP_187_A; MET_188_A; GLY_189_A; TYR_190_A; LYS_191_A; ASN_192_A; PHE_194_A; ASP_220_A; ILE_221_A; TYR_222_A; LYS_223_A; ARG_240_A; CYS_241_A; ILE_242_A; ALA_243_A; CYS_244_A; GLY_245_A; VAL_246_A; ASN_247_A; VAL_271_A; ILE_285_A; ILE_286_A; THR_287_A; PRO_288_A; GLU_289_A; TRP_290_A; ILE_291_A; LEU_351_A; LEU_355_A; THR_356_A; PHE_357_A; VAL_361_A; LYS_362_A; PRO_363_A; VAL_364_A; CYS_365_A; LEU_366_A; PRO_367_A; ASN_368_A; PRO_369_A; GLY_370_A; ILE_452_A; TRP_454_A; MET_478_A; THR_481_A; ASP_482_A; ILE_484_A; TYR_485_A; MET_488_A.

P_1	416.13	670.82	0.82	0.16	ARG_147_A; CYS_148_A; VAL_149_A; ARG_150_A; LEU_151_A; TYR_152_A; GLY_153_A; PHE_156_A; ILE_157_A; GLN_159_A; TRP_168_A; ARG_182_A; ALA_183_A; ARG_186_A; ASP_187_A; MET_188_A; GLY_189_A; TYR_190_A; LYS_191_A; ASN_192_A; PHE_194_A; ASP_220_A; ILE_221_A; TYR_222_A; LYS_223_A; ARG_240_A; CYS_241_A; ILE_242_A; ALA_243_A; CYS_244_A; GLY_245_A; VAL_246_A; ASN_247_A; VAL_271_A; ILE_285_A; ILE_286_A; THR_287_A; PRO_288_A; GLU_289_A; TRP_290_A; ILE_291_A; LEU_351_A; LEU_355_A; THR_356_A; PHE_357_A; VAL_361_A; LYS_362_A; PRO_363_A; VAL_364_A; CYS_365_A; LEU_366_A; PRO_367_A; ASN_368_A; PRO_369_A; GLY_370_A; ILE_452_A; TRP_454_A; MET_478_A; THR_481_A; ASP_482_A; ILE_484_A; TYR_485_A; MET_488_A.
P_2	404.99	488.54	0.7	0.16	GLY_259_A; GLN_270_A; VAL_271_A; HIS_279_A; CYS_281_A; GLY_282_A; GLY_283_A; ILE_381_A; SER_382_A; GLY_383_A; TRP_384_A; GLY_385_A; ALA_386_A; THR_387_A; GLU_388_A; SER_394_A; LEU_397_A; ASN_398_A; ALA_399_A; ALA_400_A; ASN_433_A; VAL_434_A; ASP_435_A; SER_436_A; CYS_437_A; GLY_439_A; ASP_440_A; SER_441_A ; GLY_443_A; PRO_444_A; LEU_445_A; ASP_458_A; THR_459_A; CYS_465_A; ALA_466_A; TYR_474_A.

P_3	381.38	815.26	0.53	0.18	GLY_245_A; VAL_246_A ; ASN_247_A; LEU_248_A; ASN_249_A; SER_250_A; ARG_252_A; GLN_253_A; SER_254_A; ARG_255_A; LEU_263_A; PRO_264_A; GLY_265_A; ALA_266_A ; ASP_359_A; LEU_360_A; LYS_362_A; SER_448_A; ASN_451_A; ILE_452_A; TRP_453_A.
P_4	336.19	488.29	0.71	0.09	HIS_296_A ; GLU_389_A; VAL_402_A; ILE_405_A; TYR_416_A; ALA_427_A; GLY_428_A; PHE_429_A; LEU_430_A; GLY_432_A; ASN_433_A; VAL_434_A; ASP_435_A; SER_436_A; CYS_437_A; GLN_438_A; ASP_440_A; SER_441_A ; THR_459_A; SER_460_A; TRP_461_A; GLY_462_A; SER_463_A; GLY_464_A; CYS_465_A; ALA_466_A; LYS_467_A; ALA_468_A; TYR_469_A; ARG_470_A; PRO_471_A; GLY_472_A; VAL_473_A; TYR_474_A.
P_5	259.26	522.54	0.47	0.17	GLU_376_A; LEU_403_A; LEU_404_A; ILE_405_A; ARG_409_A; CYS_410_A; SER_412_A; TYR_414_A; VAL_415_A; GLY_428_A; PHE_429_A; LEU_430_A; ALA_468_A; TYR_469_A; ARG_470_A; PRO_471_A.
P_6	200.32	278.85	0.47	0.01	LEU_273_A; CYS_281_A; THR_293_A; ALA_294_A; ALA_295_A; CYS_297_A; VAL_298_A; LEU_302_A; ASN_303_A; ASN_304_A; PRO_305_A; TRP_308_A; VAL_328_A; LYS_330_A; VAL_331_A; ALA_347_A; LEU_348_A; MET_349_A.

P_7	169.22	362.83	0.43	0.0	PRO_367_A; MET_371_A; MET_372_A; LEU_373_A; GLN_374_A; GLN_377_A; CYS_379_A; LEU_404_A; THR_447_A; LYS_449_A; TRP_454_A; ILE_456_A; ASN_476_A; MET_478_A.
P_8	152.06	304.69	0.31	0.0	MET_372_A; LEU_373_A; GLN_374_A; PRO_375_A; GLU_376_A; LEU_404_A; ILE_405_A; GLU_406_A; THR_407_A; ILE_425_A; CYS_426_A.
P_9	149.63	131.67	0.44	0.0	ALA_294_A; LYS_342_A; ASN_343_A; ASN_344_A; ASP_345_A ; ILE_346_A; ALA_423_A; MET_424_A; ASP_458_A; SER_460_A; TRP_461_A; VAL_473_A; TYR_474_A; GLY_475_A; ASN_476_A; VAL_477_A; PHE_480_A.
P_10	148.03	186.34	0.37	0.0	LEU_263_A; PRO_264_A; GLY_265_A; ALA_266_A; TRP_267_A; PRO_268_A; TRP_269_A; GLN_270_A; VAL_271_A; ILE_285_A; PHE_311_A; ALA_312_A; GLY_313_A; ILE_314_A; LEU_315_A; ASP_359_A; LEU_360_A; VAL_361_A; TRP_384_A; LEU_397_A.
P_11	121.54	413.02	0.14	0.0	SER_162_A; SER_163_A; GLN_164_A; ARG_165_A; HIS_169_A; MET_210_A; TYR_226_A; SER_228_A.
P_12	113.22	271.91	0.21	0.0	HIS_274_A; ASN_277_A; THR_309_A; ALA_310_A; PHE_311_A; MET_320_A; ALA_324_A; GLY_325_A.
P_13	113.09	204.89	0.21	0.0	ALA_312_A; GLY_313_A ; TYR_322_A; GLY_323_A; ALA_324_A; LEU_355_A; THR_356_A; ASN_358_A.

P_14	110.66	272.01	0.26	0.0	TYR_152_A; ILE_157_A; GLN_159_A; PRO_170_A; GLY_199_A; ILE_200_A; VAL_201_A; SER_204_A; GLY_205_A; SER_206_A; THR_207_A; VAL_236_A.
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