

Supplementary Material

Deciphering the interactions of SARS-CoV-2 proteins with human ion channels using machine learning-based method

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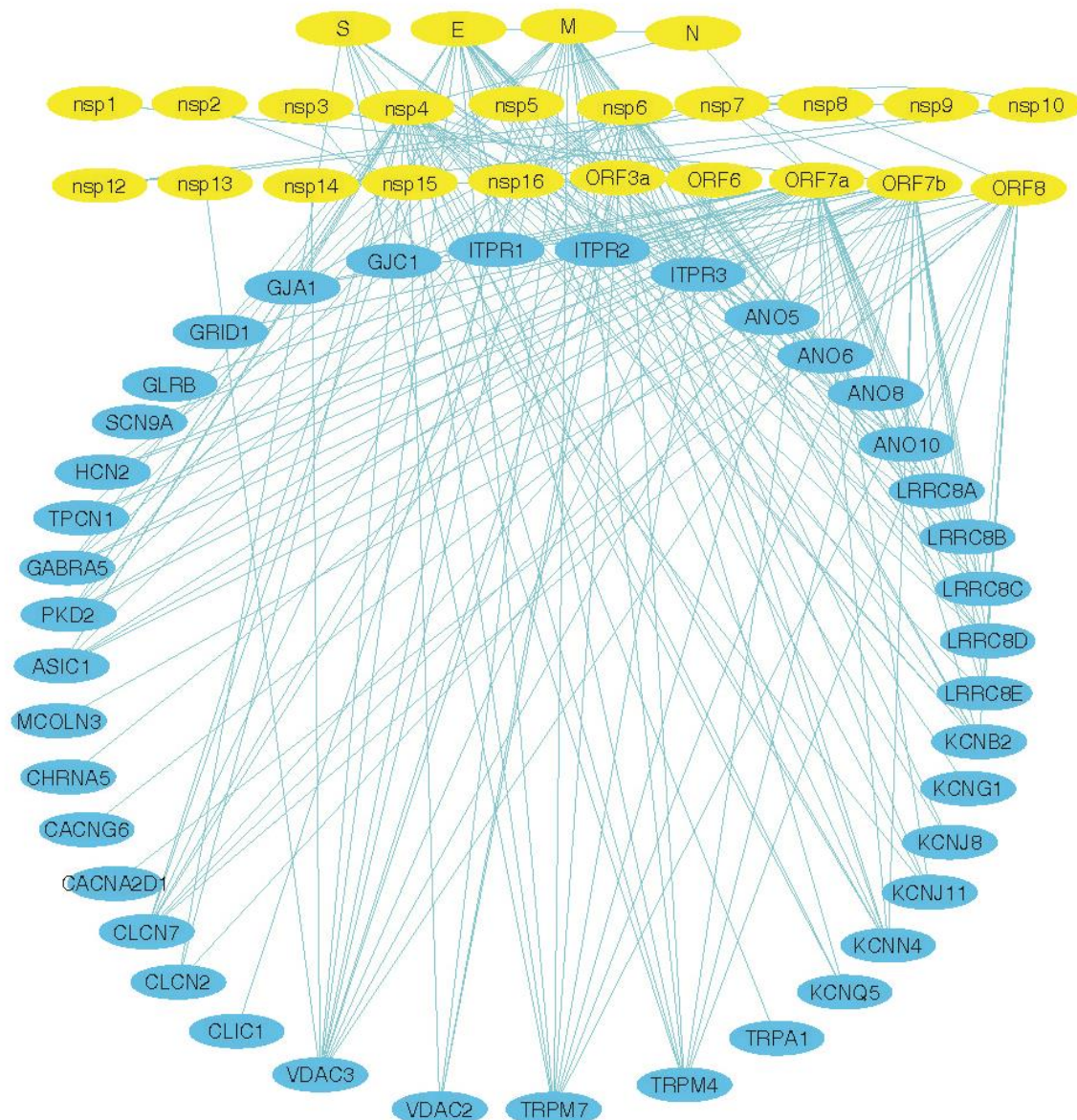
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Dataset for the prediction of PPIs using PPI MetaGO

193 PPIs of SARS-CoV-2 proteins with HICs were parsed from BioGRID database (release 4.92.192) The interactions of ORF14 and ORF3b with HICs were removed from the input. The dataset included 202 interactions; 181 from SARS-CoV-2 - HICs interactions (Supplementary Table 1). and 21 from SARS-CoV-2 – SARS-CoV-2 interactions (Supplementary Table 2).

Supplementary Figure 1: A schematic depiction of interactions of total SARS-CoV-2 proteins with human ion channels



Supplementary Table 1: List of interactors of SARS-CoV-2 proteins with human ion channels

	SARS-CoV-2 Protein	SARS-CoV-2 Protein name	HICs
1	M	Membrane Protein	ANO6,CLCN7,GABRA5,GJA1,ITPR3,KCNN4,PKD2,TPCN1,TRPM4,TRPM7,ANO10,LRRC8D,VDAC2,VDAC3,GRID1,ITPR1,KCNQ5,LRRC8A,ITPR2,KCNB2,KCNJ11,KCNJ8,LRRC8C
2	E	Envelope Protein	ITPR2,ITPR3,KCNN4,PKD2,TRPM4,TRPM7,ANO10,LRRC8D,VDAC3,ITPR1,KCNJ11,KCNJ8,LRRC8B,ASIC1,CLCN7,GJC1,KCNB2,KCNG1,LRRC8A,LRRC8C,ANO6
3	S	Spike Protein	ANO6,KCNN4,TRPM4,TRPM7,CLCN2,KCNQ5,ANO10,ITPR3,KCNB2
4	ORF3a	ORF3a	ANO6,LRRC8D,CLCN7,LRRC8A,VDAC2,VDAC3
5	ORF6	ORF6	ANO6,ITPR3,VDAC3,TRPM7
6	ORF7a	ORF7a	CLCN7,ANO6,GABRA5,GJA1,ITPR1,ITPR2,ITPR3,KCNN4,ASIC1,PKD2,TPCN1,TRPM4,TRPM7,ANO10,LRRC8D,LRRC8A,HCN2,SCN9A,VDAC3,GLRB,KCNJ11,LRRC8B,LRRC8E,LRRC8C,KCNB2,GJC1,CHRNA5
7	ORF7b	ORF7b	ANO6,CACNG6,TRPM4,LRRC8A,GJA1,CLCN7,GABRA5,ITPR1,ITPR2,ITPR3,KCNN4,PKD2,TPCN1,TRPM7,ANO10,LRRC8D,ANO8,HCN2,VDAC3,CLCN2,GRID1,LRRC8B,ASIC1,LRRC8C,LRRC8E
8	ORF8	ORF8	MCOLN3,TRPM7,LRRC8D,LRRC8C,LRRC8A,KCNB2,ITPR2,ITPR3,CLCN7,ASIC1,ANO6,ANO10,TRPM4,CACNA2D1,LRRC8E
9	nsp3	Nonstructural protein 3	KCNJ11
10	nsp4	Nonstructural protein 4	PKD2,TRPM7,LRRC8D,LRRC8E,LRRC8C,LRRC8B,LRRC8A,KCNB2,ITPR3,ITPR1,ITPR2,GRID1,CLCN7,ASIC1,ANO6,ANO10,ANO5,CLCN2,KCNQ5,TRPM4,GABRA5,GJA1,KCNN4,VDAC2,VDAC3,TRPA1
11	nsp5	Nonstructural protein 5	VDAC3
12	nsp6	Nonstructural protein 6	GJC1,CLCN7,ANO6,GABRA5,GJA1,ITPR2,ITPR3,KCNN4,PKD2,TRPM4,TRPM7,ANO10,LRRC8D,HCN2,VDAC2,VDAC3,LRRC8A,ASIC1,LRRC8C,KCNB2

13	nsp13	Nonstructural protein 13	VDAC3
14	nsp14	Nonstructural protein 14	VDAC3
15	nsp16	Nonstructural protein 16	CLIC1

Supplementary Table 2: List of interactors of SARS-CoV-2 proteins

	SARS-CoV-2 Protein	SARS-CoV-2 Protein name	SARS-CoV-2 Protein	SARS-CoV-2 Protein name
1	nsp12	Nonstructural protein 12	nsp7	Nonstructural protein 7
2	nsp12	Nonstructural protein 12	nsp8	Nonstructural protein 8
3	nsp7	Nonstructural protein 7	nsp8	Nonstructural protein 8
4	nsp10	Nonstructural protein 10	nsp16	Nonstructural protein 16
5	nsp16	Nonstructural protein 16	nsp10	Nonstructural protein 10
6	nsp15	Nonstructural protein 15	nsp2	Nonstructural protein 2
7	N	Nucleocapsid protein	nsp4	Nonstructural protein 4
8	ORF7b	ORF7b	nsp7	Nonstructural protein 7
9	ORF7b	ORF7b	nsp1	Nonstructural protein 1
10	ORF7b	ORF7b	nsp7	Nonstructural protein 7
11	nsp7	Nonstructural protein 7	nsp9	Nonstructural protein 9
12	nsp14	Nonstructural protein 14	nsp10	Nonstructural protein 10
13	ORF6	ORF6	nsp14	Nonstructural protein 14
14	N	Nucleocapsid protein	E	Envelope protein
15	ORF3a	ORF3a	E	Envelope protein

16	nsp7	Nonstructural protein 14	ORF7a	ORF7a
17	nsp8	Nonstructural protein 14	ORF8	ORF8
18	ORF6	ORF6	nsp3	Nonstructural protein 14
19	ORF7a	ORF7a	N	Nucleocapsid protein
20	nsp14	Nonstructural protein 14	nsp10	Nonstructural protein 10
21	nsp10	Nonstructural protein 10	nsp16	Nonstructural protein 16

Supplementary Table 3: Function of human ion channels interacting with SARS-CoV-2 proteins

	Protein	Protein name	Function	References
1	ITPR1	inositol 1,4,5-trisphosphate receptor type 1	Calcium transportation from endoplasmic reticulum	(1)
2	ITPR2	inositol 1,4,5-trisphosphate receptor type 2	Calcium transportation from endoplasmic reticulum	(2, 3)
3	ITPR3	inositol 1,4,5-trisphosphate receptor type 3	Calcium transportation from endoplasmic reticulum	(4)
4	ANO5	anoctamin 5	Transmembrane protein, it's a calcium activated chloride channel	(5)
5	ANO6	anoctamin 6	Essential component for the calcium-dependent exposure of phosphatidylserine on the cell surface	(6-8)
6	ANO8	anoctamin 8	Membrane contact sites formation in	(9)

			the ER/PM junctions	
7	ANO10	anoctamin 10	Transmembrane protein, it's a calcium activated chloride channel	(10, 11)
8	LRRC8A	leucine rich repeat containing 8 VRAC subunit A	Four-pass transmembrane protein that plays a role in B cell development	(12, 13)
9	LRRC8B	leucine rich repeat containing 8 VRAC subunit B	Anion channel required to maintain a constant cell volume in response to extracellular or intracellular osmotic changes	(14-16)
10	LRRC8C	leucine rich repeat containing 8 VRAC subunit C	Plays a redundant role in the efflux of amino acids, such as aspartate and glutamate, in response to osmotic stress. Channel activity requires LRRC8A plus at least one other family member (LRRC8B, LRRC8C, LRRC8D or LRRC8E)	(14-16)
11	LRRC8D	leucine rich repeat containing 8 VRAC subunit D	Mediates the import of the antibiotic blasticidin-S into the cell	(17)
12	LRRC8E	leucine rich repeat containing 8 VRAC subunit E	Anion channel required to maintain a constant cell volume in	(18)

			response to extracellular or intracellular osmotic changes	
13	KCNB2	potassium voltage-gated channel subfamily B member 2	Delayed rectifier potassium channel; functions include regulating neurotransmitter release, heart rate, insulin secretion, epithelial electrolyte transport, and cell volume.	(19, 20)
14	KCNG1	potassium voltage-gated channel modifier subfamily G member 1	Form functional heterotetrameric channels with KCNB1; modulates the delayed rectifier voltage-gated potassium channel activation and deactivation rates of KCNB1	(21)
15	KCNJ8	potassium voltage-gated channel subfamily J member 8	Protein has a greater tendency to allow potassium to flow into a cell rather than out of a cell	(22, 23)
16	KCNJ11	potassium voltage-gated channel subfamily J member 11	Subunit of ATP-sensitive potassium channels; form cardiac and smooth muscle-type KATP channels with ABCC9. KCNJ11 forms the channel pore while ABCC9 is required for activation and regulation	(24-26)

17	KCNN4	potassium calcium-activated channel subfamily N member 4	Required for maximal calcium influx and proliferation during the reactivation of naive T-cells. Plays a role in the late stages of EGF-induced macropinocytosis	(27-29)
18	KCNQ5	potassium voltage-gated channel subfamily Q member 5	Protein yields currents that activate slowly with depolarization and can form heteromeric channels with the protein encoded by the KCNQ3 gene	(30)
19	TRPA1	transient receptor potential cation channel subfamily A member 1	May involve a role in signal transduction and growth control	(31)
20	TRPM4	transient receptor potential cation channel subfamily M member 4	Calcium-activated nonselective ion channel that mediates transport of monovalent cations across membranes, thereby depolarizing the membrane	(32, 33)
21	TRPM7	transient receptor potential cation channel subfamily M member 7	Protein is both, an ion channel and a serine/threonine protein kinase. The kinase activity is essential for the ion channel function, which serves to increase intracellular calcium levels and	(34)

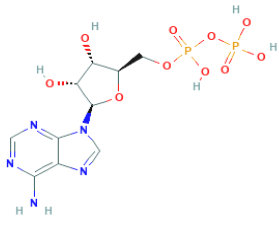
			to help regulate magnesium ion homeostasis.	
22	VDAC2	voltage dependent anion channel 2	Involvement of Ca ⁺² in viral entry	(35, 36)
23	VDAC3	voltage dependent anion channel 3	Involvement of Ca ⁺² in viral entry	(37)
24	CLIC1	chloride voltage-gated channel 1	Protein localizes principally to the cell nucleus and exhibits both nuclear and plasma membrane chloride ion channel activity	(38)
25	CLCN2	chloride voltage-gated channel 2	Transmembrane protein that maintains chloride ion homeostasis in various cells	(39)
26	CLCN7	chloride voltage-gated channel 7	Functions as antiporter and contributes to the acidification of the lysosome lumen and may be involved in maintaining lysosomal pH	(40)
27	CACNA2D1	calcium voltage-gated channel auxiliary subunit alpha2delta 1	Calcium channels mediate the influx of calcium ions into the cell upon membrane polarization	(41)
28	CACNG6	calcium voltage-gated channel auxiliary subunit gamma 6	Regulates the activity of L-type calcium channels that contain CACNA1C as pore-forming subunit	(42)

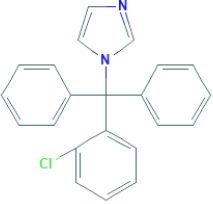
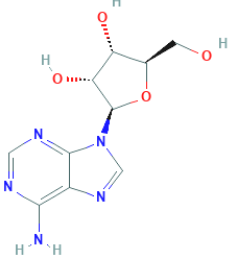
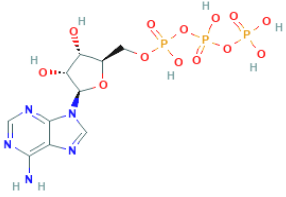
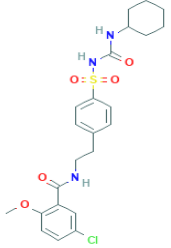
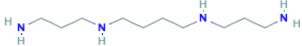
29	GJA1	gap junction protein alpha 1	Protein is a component of gap junctions, composed of arrays of intercellular channels that provide a route for the diffusion of low molecular weight materials from cell to cell. Major protein of gap junctions in the heart that have crucial role in the synchronized contraction of the heart	(43, 44)
30	GJC1	gap junction protein gamma 1	Protein is a component of gap junctions, composed of arrays of intercellular channels that provide a route for the diffusion of low molecular weight materials from cell to cell. Major protein of gap junctions in the heart that have crucial role in the synchronized contraction of the heart	(45)
31	ASIC1	acid sensing ion channel subunit 1	Part of the degenerin/epithelial sodium channel (DEG/ENaC) superfamily. Proteins function in learning, pain transduction, touch sensation, and	(46)

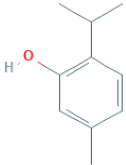
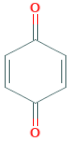
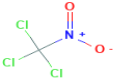
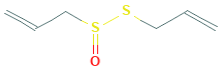
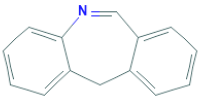
			development of memory and fear	
32	PKD2	polycystin 2, transient receptor potential cation channel	Multi-pass membrane protein that functions as a calcium permeable cation channel	(47)
33	GABRA5	gamma-aminobutyric acid type A receptor alpha5 subunit	Ligand-gated chloride channel subunit which is a component of the heteropentameric receptor for GABA; may be involved in GABA-A receptor assembly	(55)
34	TPCN1	two pore segment channel 1	Function as one of the major voltage-gated Ca ²⁺ channels (VDCC) across the lysosomal and endosomal membrane	(49)
35	HCN2	hyperpolarization activated cyclic nucleotide gated potassium and sodium channel 2	Ion channel exhibiting weak selectivity for potassium over sodium ions. Contributes to the native pacemaker currents in heart	(50)
36	SCN9A	sodium voltage-gated channel alpha subunit 9	Protein forms a sodium-selective channel through which Na ⁺ ions may pass in accordance with their electrochemical gradient	(51)

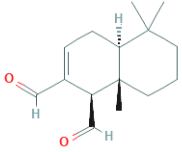

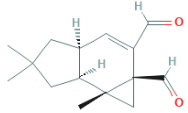

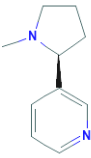
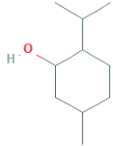
37	GLRB	glycine receptor beta	GLRB does not form ligand-gated ion channels by itself, but is part of heteromeric ligand-gated chloride channels	(52)
38	GRID1	glutamate ionotropic receptor delta type subunit 1	Subunit of glutamate receptor channels; play key roles in synaptic plasticity	(48)
39	CHRNA5	cholinergic receptor nicotinic alpha 5 subunit	Protein subunit is a member of a superfamily of ligand-gated ion channels that mediate fast signal transmission at synapses	(53)
40	MCOLN3	mucolipin 3	Acts as Ca ²⁺ -permeable cation channel with inwardly rectifying activity	(54)


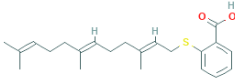
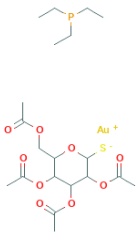
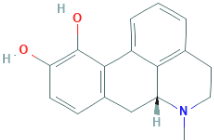
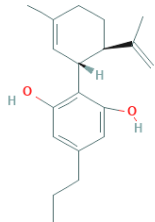
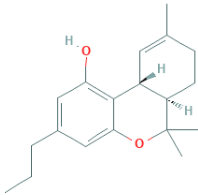
Supplementary Table 4: List of drugs interacting with HICs

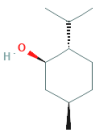
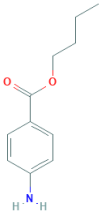

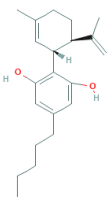
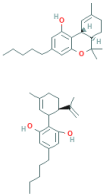
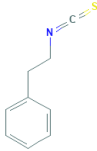
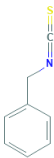
S No.	Compound Name	Compound Structure	Human Protein	Viral Protein
1	Adenosine Diphosphate		TRPM4	ORF8, ORF14, M, E, S, ORF7a, ORF7b, nsp4, nsp6,


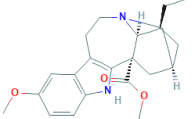

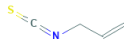
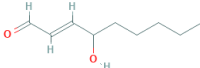
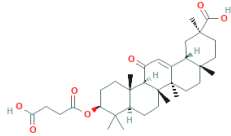
2	Clotrimazole			
3	Adenosine			
4	Adenosine Triphosphate			
5	Glyburide			
6	Spermine			


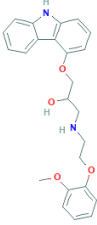
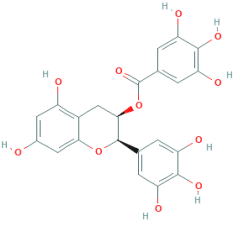
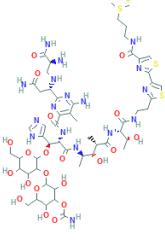
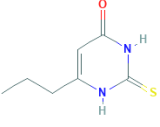
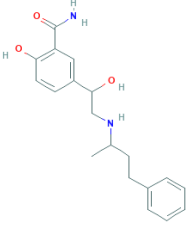
7	Thymol		TRPA1	nsp4
8	Benzoquinone			
9	Chloropicrin			
10	Allicin			
11	Morphanthridine			

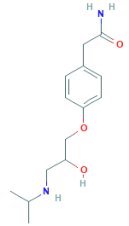
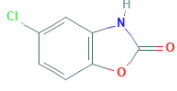
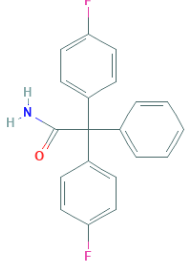
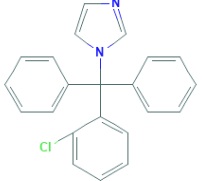
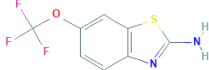
12	Polygodial			
13	Methylglyoxal			
14	Isovelleral			
15	Acrolein			
16	Nicotine			
17	Menthol			

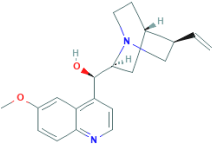

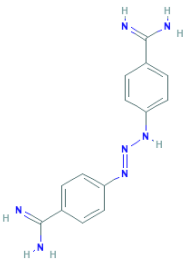
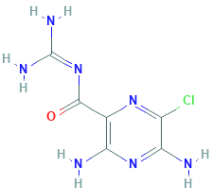
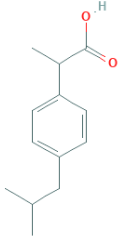
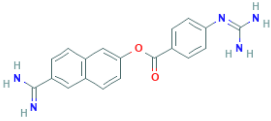
18	Acetaldehyde			
19	Salirasib			
20	Auranofin			
21	Apomorphine			
22	Cannabidivarin			
23	Tetrahydrocannabivarin			

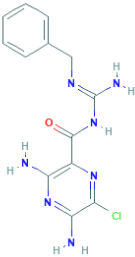
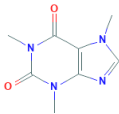
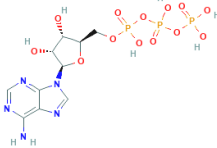
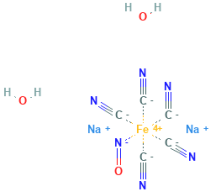
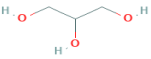
24	Levomenthol			
25	Butamben			
26	Camphor			
27	Cannabidiol			
28	Nabiximols			
29	Phenethylisothiocyanate			
30	Benzyl isothiocyanate			

31	Isopropyl isothiocyanate			
32	Voacangine			
33	Erucin			
34	Allyl isothiocyanate			
35	4-Hydroxynon-2-enal			
36	Carbenoxolone		GJA1	M, ORF7a, ORF7b, nsp4, nsp6, ORF14, ORF3b,

37	Octanol			
38	Carvedilol			
39	Epigallocatechin Gallate			
40	Bleomycin			
41	Propylthiouracil			
42	Labetalol			

43	Atenolol			
44	Chlorzoxazone		KCNN4	M, E, S, ORF7a, ORF7b, nsp4, nsp6,
45	Senicapoc			
46	Clotrimazole			
47	Nitredipine	NA		
48	Riluzole			

49	Quinine			
50	Halothane			
51	Diminazene		ASIC1	E, ORF7a, ORF7b, nsp4, nsp6, ORF8,
52	Amiloride			
53	Ibuprofen			
54	Nafamostat			

55	Benzamil			
56	Caffeine		ITPR1	M, E, ORF7a, ORF7b, nsp4,
57	Adenosine Triphosphate			
58	Nitroprusside			
59	Glycerin			

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