Table S1. Treatment conditions and residual infectivity data from combination treatment assay.

Treatment[a]	Concentration (μM)[b]		Residual Infectivity (%)[c]		
	AMA	REM	AMA	REM	Combi
1	14.5	0.3	96	94	85
2	21.7	0.5	93	92	88
3	32.5	0.8	96	83	98
4	48.8	1.1	97	70	81
5	73.2	1.7	80	60	59
6	109.7	2.5	72	30	51
7	164.6	3.8	51	10	22
8	246.9	5.7	31	3	5
9	370.4	8.6	9	0	0
10	555.6	12.9	3	1	-1
Ratio[d]	43	1			

Treatment[a]	Concentration (μM)[b]		Residual Infectivity (%)[c]		
	MEM	REM	MEM	REM	Combi
1	44.7	1.1	84	80	97
2	55.9	1.4	81	80	75
3	69.9	1.8	74	56	69
4	87.4	2.2	39	64	46
5	109.2	2.8	23	46	22
6	136.5	3.5	13	27	10
7	170.7	4.3	5	13	4
8	213.3	6.5	3	3	1
9	266.7	9.7	1	1	0
10	333.3	12.2	1	1	1
Ratio[d]	27	1			

Treatment[a]	Concentration (μM)[b]		Residual Infectivity (%)[c]		
	RIM	REM	RIM	REM	Combi
1	5.5	0.3	96	94	101
2	8.2	0.5	101	92	92
3	12.4	0.8	86	83	87
4	18.5	1.1	74	70	62
5	27.8	1.7	44	60	40
6	41.7	2.5	26	30	17
7	62.6	3.8	7	10	0
8	93.8	5.7	1	3	-1
9	140.7	8.6	1	0	-2
10	211.1	12.9	1	1	0
Ratio[d]	16	1			

[a]Treatment, number of treatment condition and the specified concentrations of inhibitors. Infected cultures were treated with inhibitors either singly or in combination in antiviral treatment assays for analysis of interactions; results of these assays are shown in Figure 2.

[b] Concentration (µM), concentrations of inhibitors, AMA, amantadine, MEM, memantine, RIM, rimantadine, REM, remdesivir.

[c] Residual infectivity (%), calculated by relating the number of infected cells in treated cultures to the mean number of infected cells in infected-nontreated control cultures. Residual infectivity is given for single treatments with the specified inhibitors and the respective combination treatments (Combi) for each treatment condition.

[d] Ratio, for all inhibitor combinations a fixed concentration ratio was applied as specified.

Table S2. Analysis of interactions of ion-channel inhibitors with remdesivir in Compusyn.

	CI[a]				DRI[b]					
	Key Fa[c]		Experimental Fa[b]		Key Fa[c]			Experimental Fa[d]		
	Key Fa	CI	Exp. Fa	CI	Key Fa	AMA DRI	REM DRI	Exp. Fa	AMA DRI	REM DRI
AMA+REM	0.25	1.8	0.02	5.1	0.25	1.7	0.9	0.02	0.5	0.3
	0.5	1.8	0.12	1.3	0.5	1.7	0.9	0.12	2.1	1.2
	0.75	1.8	0.15	0.7	0.75	1.8	0.8	0.15	4.1	2.2
	0.9	1.8	0.19	2.2	0.9	1.9	0.8	0.19	1.3	0.7
			0.41	2.1				0.41	1.4	0.7
			0.49	2.6				0.49	1.2	0.6
			0.78	2.2				0.78	1.5	0.7
			0.95	1.5				0.95	2.3	1.0
			0.99	1.0				0.99	3.6	1.3
			0.99	1.5				0.99	2.4	0.9
						MEM	REM		MEM	REM
MEM+REM	0.25	1.8	0.03	2.7	0.25	1.4	1.0	0.03	1.0	0.6
	0.5	1.7	0.25	1.6	0.5	1.4	1.0	0.25	1.5	1.1
	0.75	1.7	0.31	1.9	0.75	1.3	1.1	0.31	1.3	0.9
	0.9	1.6	0.54	1.7	0.9	1.3	1.2	0.54	1.4	1.1
			0.78	1.5				0.78	1.5	1.2
			0.9	1.4				0.9	1.6	1.4
			0.96	1.2				0.96	1.7	1.6
			0.99	1.2				0.99	1.7	1.7
			0.99	1.8				0.99	1.1	1.2
			0.99	2.2				0.99	0.9	0.9
						RIM	REM		RIM	REM
RIM+REM	0.25	1.9	0.01	2.7	0.25	1.2	1.0	0.01	0.9	0.6
	0.5	1.8	0.08	1.8	0.5	1.2	1.1	0.08	1.3	1.0
	0.75	1.7	0.13	2.3	0.75	1.2	1.2	0.13	1.0	0.8
	0.9	1.6	0.38	1.7	0.9	1.2	1.3	0.38	1.2	1.1
			0.6	1.9				0.6	1.1	1.0
			0.83	1.7				0.83	1.2	1.2
			0.99	0.8				0.99	2.4	3
			0.99	1.1				0.99	1.6	2
			0.99	1.7				0.99	1.0	1.3
			0.99	2.6				0.99	0.7	0.9

CI	
	0.1 ≤ CI < 0.3, strong synergism
	0.3 ≤ CI < 0.7, synergism
	0.7 ≤ CI < 0.85, moderate synergism
	0.9 ≤ CI < 1.1, nearly additive
	1.1 ≤ CI < 1.2, slight antagonism
	1.2 ≤ CI < 1.45, moderate antagonism
	1.45 ≤ CI < 3.3, antagonism
	3.3 ≤ CI, strong antagonism

DRI	
	DRI ≥ 20
	10 ≤ DRI < 20
	5 ≤ DRI < 10
	3 ≤ DRI < 5
	1.5 ≤ DRI < 3
	DRI < 1.5

[a] CI, Combination index values generated by analysis in CompuSyn of data from short-term treatment assays carried out for analysis of interactions of ion-channel inhibitors amantadine (AMA), memantine (MEM), rimantadine (RIM) and remdesivir (REM) (Figure 2 and Table S1). Graphical illustrations of these results are shown in Figure S5 B and C. CI are color-coded

according to the legend below the table and reflect the mode of interaction. In the range $0.85 \leq CI < 0.9$ (slight synergism), no values were recorded.

[b] DRI, Drug reduction index values generated by CompuSyn analysis. DRI values are color-coded according to the legend below the table. Graphical illustrations of these results are shown in Figure S5 D.

[c] Key Fa, key fractional effects identical with key inhibition percentages (0.25, 0.5, 0.75 and 0.9).

[d] Experimental Fa, fractional effects identical with inhibition percentages achieved at experimental datapoints

Table S3. Next generation sequencing of SARS-CoV-2 genomes from long-term treatment experiments.

Nucleotide position[a]	Reference nucleotide[b]	Nucleotide change[c]	Frequency in non-treated day 5 (%)[d]	Frequency in Amantadine 3xEC50 day 5 (%)[e]	Frequency in Memantine 3xEC50 day 5 (%)[e]	Frequency in Rimantadine 3xEC50 day 5 (%)[e]	Frequency in Rimantadine 7xEC50 day 7 (%)[e]	Amino acid change[f]	SARS-CoV-2 protein[g]
2343	T	G	-	-	-	-	99.7	I513S	nsp2
3162	C	A	-	-	21.6	-	-	S148Y	nsp3
3482	G	A	-	-	52.0	-	-	G255R	nsp3
11522	T	G	-	-	-	98.6	-	F184V	nsp6
16534	A	G	5.5	-	-	-	-	S100G	nsp13
17368	A	G	5.2	-	-	-	-	M378V	nsp13
17964	G	T	6.3	-	-	-	-	M576I	nsp13
22487	A	G	52.6	89.8	23.1	99.5	-	K309E	S

[a]Nucleotide position relating to the SARS-CoV-2/human/Denmark/DK-AHH1/2020 genome sequence (GenBank accession number MZ049597). Coding nucleotide changes occurring in at least one of the analyzed virus populations with ≥5% prevalence are listed.

[b]Nucleotide identity in the SARS-CoV-2/human/Denmark/DK-AHH1/2020 sequence.

[c]Changed nucleotide detected in cell culture derived virus.

[d]Frequency of the indicated nucleotide change in the genomes of the viral population in the nontreated culture on day 5 post infection. -, frequency of the indicated nucleotide change was below the limit of detection.

[e]Frequency of the indicated nucleotide change in the genomes in the viral populations in cultures subjected to the specified treatments at the given timepoint post infection and treatment initiation. -, frequency of the indicated nucleotide change was below the limit of detection

[f]Amino acid change encoded by the given nucleotide change. Position numbers relate to the respective protein of SARS-CoV-2/human/Denmark/DK-AHH1/2020.

[g]SARS-CoV-2 protein, where the given amino acid change is located.

Table S4. Pharmacokinetics of adamantane derivatives

Inhibitor	Cmax (μM)[a]	Cmax/EC50[b]	Dose[c]	PPB[d]	Distribution to lungs[e]	References[f]
Amantadine	2.7	0.02/0.02/0.03	200mg single dose	67%	High	*https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/016023s041,018101s016lbl.pdf, Bleidner, W. E., Harmon, J. B., Hewes, W. E., Lynes, T. E. & Hermann, E. C. ABSORPTION, DISTRIBUTION AND EXCRETION OF AMANTADINE HYDROCHLORIDE. J. Pharmacol. Exp. Ther. 150, (1965)*
Memantine	0.1	0.001/0.001/0.001	20mg single dose	45%	High	*doi: 10.1007/s12325-019-01044-y, Kuns, B., Rosnai, A. & Varghese, D. Memantine - StatPearls - NCBI Bookshelf. Memantine (2020)*
Rimantadine	2.2	0.06/0.08/0.03	100mg/12hrs	40%	na	*https://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019649s015lbl.pdf*

[a]Cmax, maximum plasma concentrations (μM) of ion-channel inhibitors achieved in patients after administration of specified dose(s). For rimantadine Cmax values were determined at steady state after multiple dosings.

[b]Cmax/EC50, peak plasma concentration (μM) relative to the EC50 (μM) of inhibitor against SARS-CoV-2 determined in VeroE6, Huh7.5 and A549-hACE2 cells, respectively (Figure 1, Table 1).

[c]Dose, dosing scheme leading to the reported Cmax values. All doses are in accordance to recommended clinical dosings.

[d]PPB, plasma protein binding, % of compound bound to plasma proteins according to FDA reports.

[e]Distribution of inhibitor to pulmonary tissue relative to Cmax. na, data not available.

[f]References for listed Cmax values and distribution. Values were extracted from either FDA reports or if not available, values were extracted from publications on representative clinical studies