Supplementary Information

'Suggestions for second-pass anti-COVID-19 drugs based on the Artificial Intelligence measures of molecular similarity, shape and pharmacophore distribution.'

Martyna Moskal¹⁺, Wiktor Beker¹⁺, Rafał Roszak¹, Ewa P. Gajewska², Agnieszka Wołos¹, Karol Molga¹, Sara Szymkuć¹, & Bartosz A. Grzybowski^{1,2,3,4}*

¹ Allchemy, Inc., 2145 45th Street, Highland, IN 46322, USA

² Institute of Organic Chemistry, Polish Academy of Sciences, ul. Kasprzaka 44/52, Warsaw 02-224, Poland

³ IBS Center for Soft and Living Matter and

⁴ Department of Chemistry, UNIST, 50, UNIST-gil, Eonyang-eup, Ulju-gun, Ulsan, 689-798, South Korea

⁺Authors contributed equally

*Correspondence to: <u>nanogrzybowski@gmail.com</u>



Figure S1. Full "heatmap" quantifying similarity, *s*_{*ij*}, **between drugs already tested against COVID-19** *in vitro* **and 110 unique, most-similar progenies found by the ESR method.** Each row corresponds to one parent drug annotated with its common name. Progenies are denoted along the horizontal axis by numbers corresponding to those in **Table S2**, which also provides names and primary therapeutic

indications of these progenies. Because of limited space, the matrix is divided into two parts shown one above the other.



Figure S2. Full "heatmap" quantifying similarity, s_{ij} , between drugs already being tested against COVID-19 in clinical trials and 110 unique, most-similar progenies found by the Mol2Vec method. Each row corresponds to one parent drug annotated with its common name. Progenies are denoted along the horizontal axis by numbers corresponding to those in Table S2, which also provides names and

primary therapeutic indications of these progenies. Because of limited space, the matrix is divided into two parts shown one above the other.



Figure S3. Full "heatmap" quantifying similarity, *sij*, between drugs already tested against COVID-19 *in vitro* and 110 unique, most-similar progenies found by the Mol2Vec method. Each row corresponds to one parent drug annotated with its common name. Progenies are denoted along the horizontal axis by numbers corresponding to those in **Table S2**, which also provides names and primary therapeutic indications of these progenies. Because of limited space, the matrix is divided into two parts shown one above the other.



Figure S4. Best alignments of Thalidomide-Felbamate pair with ShaEP. Parent is shown on the left as a licorice model, progeny is drawn as a ball-and-stick model on the right, and the middle portion overlays the two structures. Number quantify alignment score (including both shape and electrostatic factors).

Table S1. Parent drugs considered in various studies against COVID-19. Literature references in the "Ref." column provide relevant literature sources (cf. Supplementary References). "Drug class" specifies primary clinical indication assigned, whenever possible, after DrugBank. In some cases, additional references justifying reported class are provided in the "Additional ref." column.

Lp	Name	Ref.	Verification method	Drug class	Additional ref.
1	Emtricitabine	1	Clinical trials	Antiviral	14
2	Lopinavir	1	Clinical trials	Antiviral	14, 15, 16
3	Ritonavir	1	Clinical trials	Antiviral	14, 15, 16
4	Tenofovir	1	Clinical trials	Antiviral	14
5	Cobicistat	2	Clinical trials	Antiviral	17
6	Darunavir	2	Clinical trials	Antiviral	17
7	Baloxavir	3	Clinical trials	Antiviral	14, 16
8	Favipiravir	3	Clinical trials	Antiviral	12, 16

Lp	Name	Ref.	Verification method	Drug class	Additional ref.
9	Azvudine	4	Clinical trials	Antiviral	16, 18
10	Leflunomide	5	Clinical trials	Immunosuppressant	
11	Suramin	6	Clinical trials	Antiparasitic	
12	Pirfenidone	7	Clinical trials	Antifibrotic agent	
13	Acetylcysteine	8	Clinical trials	Mucolytic agent	
14	Bromhexine	8	Clinical trials	Mucolytic agent	
15	Carriomycin	8	Clinical trials	Antibiotic	19
16	Chloroquine	8	Clinical trials	Antimalarial	12, 14
17	Danoprevir	8	Clinical trials	Antiviral	
18	Dihydroartemisinin	8	Clinical trials	Antimalarial	
19	Dipyridamole	8	Clinical trials	Circulatory system agent	
20	Ebastine	8	Clinical trials	Antihistamine	
21	Fingolimod	8	Clinical trials	Immunosuppressant	
22	Remdesivir	8	Clinical trials	Antiviral	12, 14, 16
23	Thalidomide	8	Clinical trials	Immunosuppressant	
24	Tranilast	8	Clinical trials	Antiasthmatic	
25	Triazavirin	8	Clinical trials	Antiviral	
26	Umifenovir	8	Clinical trials	Antiviral	14, 16
27	Ifenprodil	9	Clinical trials	Central nervous system agent	20
28	Hydroxychloroquine	10	Clinical trials	Antimalarial	
29	Ruxolitinib	11	Clinical trials	Anti-cancer drug	14
30	Nafamostat	12	In vitro	Serine protease inhibitor	
31	Nitazoxanide	12	In vitro	Anti-infective	
32	Ribavirin	12	In vitro	Antiviral	
33	Abemaciclib	13	In vitro	Anti-cancer drug	
34	Amodiaquine Hydrochloride	13	In vitro	Antimalarial	
35	Anidulafungin	13	In vitro	Antifungal	
36	Bazedoxifene	13	In vitro	Selective Estrogen Receptor Modulator	
37	Camostat	13	In vitro	Serine protease inhibitor	21

Lp	Name	Ref.	Verification method	Drug class	Additional ref.
38	Cepharanthine	13	In vitro	Anti-inflammatory	19
39	Ceritinib	13	In vitro	Anti-cancer drug	
40	Ciclesonide	13	In vitro	Glucocorticoid	
41	Clomiphene Citrate	13	In vitro	Selective Estrogen Receptor Modulator	
42	Cyclosporine	13	In vitro	Immunosuppressant	
43	Dihydrogambogic Acid	13	In vitro	Gap Junctional Intercellular Communication inhibitor	22
44	Droloxifene	13	In vitro	Selective Estrogen Receptor	
45	Dronedarone	13	In vitro	Circulatory system agent	
46	Eltrombopag	13	In vitro	Circulatory system agent	
47	Gilteritinib	13	In vitro	Anti-cancer drug	
48	Hexachlorophene	13	In vitro	Anti-infective	
49	Hydroxyprogesterone Caproate	13	In vitro	Hormonal	
50	Ivacaftor	13	In vitro	For cystic fibrosis	
51	Loperamide	13	In vitro	Gastrointestinal agent	
52	Lusutrombopag	13	In vitro	Circulatory system agent	
53	Mefloquine	13	In vitro	Antimalarial	
54	Mequitazine	13	In vitro	Antihistamine	
55	Niclosamide	13	In vitro	Antiparasitic	
56	Osajin	13	In vitro	Circulatory system agent	23
57	Osimertinid Mesylate	13	In vitro	Anti-cancer drug	
58	Ouabain	13	In vitro	Circulatory system agent	
59	Oxyclozanide	13	In vitro	Antiparasitic	24
60	Penfluridol	13	In vitro	Central nervous system agent	
61	Perhexiline Maleate	13	In vitro	Circulatory system agent	
62	Phenazopiridine	13	In vitro	Urological agent	

Lp	Name	Ref.	Verification method	Drug class	Additional ref.
63	Proscillaridin	13	In vitro	Circulatory system agent	
64	Pyronaridine	13	In vitro	Antimalarial	
65	Quinacrine	13	In vitro	Antimalarial	
66	Salinomycin	13	In vitro	Antibacterial	
67	Tetrandine	13	In vitro	Immunosuppressant	
68	Thioridazine	13	In vitro	Central nervous system agent	
69	Tilorone	13	In vitro	Antiviral	
70	Toremifene Citrate	13	In vitro	Selective Estrogen Receptor Modulator	
71	Triparanol	13	In vitro	Anti-cholesterol	25

Table S2. 110 Progeny drugs predicted by either Mol2Ven or ESR methods for the parent drugs indicated in the leftmost column. "Progeny #" corresponds to the number on the horizontal axes of heatmaps in Figures 3, S1, S2, S3. "Progeny class" specifies primary clinical indication assigned, whenever possible, after DrugBank [26]. In some cases, additional references justifying reported class are provided in the "Additional ref." column. "Mol2Vec score" and "ESR score" columns quantify the normalized distances, $100*d/d_{max}$ between a given parent and progeny drugs as calculated by these two methods. "x" means that a particular parent-progeny pair was not among the top-scoring suggestions of a given method. Note that some pairs were suggested by both methods.

Parent drug name	Parent drug verification method	Progeny name	Progeny #	Progeny class	Mol2Vec score	ESR score	Additional ref.
Acetylcysteine	Clinical trials	Acamprosate	1	Central nervous system agent	Х	0.59	
Acetylcysteine	Clinical trials	Acetylleucine	2	Anti-inflammatory	0.91	х	27
Acetylcysteine	Clinical trials	Bucillamine	3	Antirheumatic	0.95	0.62	
Acetylcysteine	Clinical trials	Carbocysteine	4	Mucolytic agent	0.91	х	
Acetylcysteine	Clinical trials	Clodronic Acid	5	Bone resorption inhibitor	Х	0.70	
Acetylcysteine	Clinical trials	Etidronic Acid	6	Bone resorption inhibitor	Х	0.61	
Acetylcysteine	Clinical trials	Fosmidomycin	7	Antibiotic	х	0.67	
Acetylcysteine	Clinical trials	Gamma-amino-beta- hydroxybutyric Acid (GABOB)	8	Central nervous system agent	х	0.40	28
Acetylcysteine	Clinical trials	Mecysteine	9	Mucolytic agent	0.87	х	29
Acetylcysteine	Clinical trials	Mesna	10	Mucolytic agent	х	0.68	
Acetylcysteine	Clinical trials	Penicillamine	11	Immunosuppressant	Х	0.53	
Acetylcysteine	Clinical trials	Timonacic	12	Antiviral	Х	0.61	
Acetylcysteine	Clinical trials	Tiopronin	13	For cystinuria	0.58	0.64	
Acetylcysteine	Clinical trials	Tromethamine	14	Anti-asthmatic	х	0.59	30, 31
Azvudine	Clinical trials	Acadesine	15	Circulatory system agent	Х	0.61	

Parent drug name	Parent drug verification method	Progeny name	Progeny #	Progeny class	Mol2Vec score	ESR score	Additional ref.
Azvudine	Clinical trials	Apricitabine	16	Antiviral	Х	0.68	
Azvudine	Clinical trials	Azacitidine	17	Anti-cancer drug	х	0.44	
Azvudine	Clinical trials	Clevudine	18	Antiviral	Х	0.63	
Azvudine	Clinical trials	Cytarabine	19	Anti-cancer drug	х	0.28	
Azvudine	Clinical trials	Decitabine	20	Anti-cancer drug	Х	0.66	
Azvudine	Clinical trials	Floxuridine	21	Anti-cancer drug	Х	0.69	
Azvudine	Clinical trials	Gemcitabine	22	Anti-cancer drug	Х	0.52	
Azvudine	Clinical trials	Idoxuridine	23	Antiviral	Х	0.69	
Azvudine	Clinical trials	Lamivudine	24	Antiviral	Х	0.68	
Azvudine	Clinical trials	Mizoribine	25	Immunosuppressant	Х	0.52	
Azvudine	Clinical trials	Netivudine	26	Antiviral	Х	0.68	
Azvudine	Clinical trials	Pidotimod	27	Immudomodulator	Х	0.65	
Azvudine	Clinical trials	Sorivudine	28	Antiviral	Х	0.60	
Azvudine	Clinical trials	Telbivudine	29	Antiviral	Х	0.66	
Azvudine	Clinical trials	Tiazofurin	30	Anti-cancer drug	Х	0.55	
Azvudine	Clinical trials	Uridine	31	Central nervous system agent	Х	0.41	32
Bromhexine	Clinical trials	Ambroxol	32	Mucolytic agent	0.83	х	
Darunavir	Clinical trials	Amprenavir	33	Antiviral	0.89	х	
Dihydroartemisinin	Clinical trials	Artemether	34	Antimalarial	0.53	х	
Dihydroartemisinin	Clinical trials	Artemisinin	35	Antimalarial	0.73	х	
Dihydroartemisinin	Clinical trials	Artemotil	36	Antimalarial	0.68	х	

Parent drug name	Parent drug verification method	Progeny name	Progeny #	Progeny class	Mol2Vec score	ESR score	Additional ref.
Emtricitabine	Clinical trials	Apricitabine	16	Antiviral	0.70	0.29	
Emtricitabine	Clinical trials	Clevudine	18	Antiviral	Х	0.47	
Emtricitabine	Clinical trials	Cytarabine	19	Anti-cancer drug	Х	0.64	
Emtricitabine	Clinical trials	Dacarbazine	37	Anti-cancer drug	Х	0.71	
Emtricitabine	Clinical trials	Decitabine	20	Anti-cancer drug	0.91	0.58	
Emtricitabine	Clinical trials	Doxifluridine	38	Anti-cancer drug	Х	0.52	
Emtricitabine	Clinical trials	Floxuridine	21	Anti-cancer drug	Х	0.31	
Emtricitabine	Clinical trials	Gemcitabine	22	Anti-cancer drug	Х	0.46	
Emtricitabine	Clinical trials	Idoxuridine	23	Antiviral	Х	0.31	
Emtricitabine	Clinical trials	Lamivudine	24	Antiviral	0.45	0.29	
Emtricitabine	Clinical trials	Levodopa	39	Anti-neurodegenerative	Х	0.69	
Emtricitabine	Clinical trials	Stavudine	40	Antiviral	Х	0.69	
Emtricitabine	Clinical trials	Telbivudine	29	Antiviral	Х	0.50	
Emtricitabine	Clinical trials	Tiazofurin	30	Anti-cancer drug	Х	0.60	
Emtricitabine	Clinical trials	Trifluridine	41	Antiviral	Х	0.45	
Emtricitabine	Clinical trials	Uridine	31	Central nervous system agent	х	0.59	
Emtricitabine	Clinical trials	Zalcitabine	42	Antiviral	0.82	0.53	
Favipiravir	Clinical trials	Aminobenzoic Acid	43	Agent against Peyronie's disease	0.92	х	33
Favipiravir	Clinical trials	Cresotamide	44	Anti-inflammatory	0.84	х	34
Favipiravir	Clinical trials	Deferiprone	45	Iron chelator	Х	0.66	
Favipiravir	Clinical trials	Ethionamide	46	Antitubercular	0.93	х	

Parent drug name	Parent drug verification method	Progeny name	Progeny #	Progeny class	Mol2Vec score	ESR score	Additional ref.
Favipiravir	Clinical trials	Flucytosine	47	Antifungal	0.96	х	
Favipiravir	Clinical trials	Fluorouracil	48	Anti-cancer drug	0.80	х	
Favipiravir	Clinical trials	Gimeracil	49	Anti-cancer drug	0.96	х	
Favipiravir	Clinical trials	Hypoxanthine	50	Anti-neurodegenerative	0.91	х	
Favipiravir	Clinical trials	Isaxonine	51	Anti-neurodegenerative	Х	0.67	35
Favipiravir	Clinical trials	Isoniazid	52	Antitubercular	0.89	х	
Favipiravir	Clinical trials	Methyl Nicotinate	53	Analgesic	0.97	х	
Favipiravir	Clinical trials	Moxonidine	54	Circulatory system agent	Х	0.68	
Favipiravir	Clinical trials	Oteracil	55	Anti-cancer drug	0.88	х	
Favipiravir	Clinical trials	Pyrazinamide	56	Antitubercular	0.78	х	
Favipiravir	Clinical trials	Salicylamide	57	Analgesic	0.86	х	
Favipiravir	Clinical trials	Uracil	58	Anti-cancer drug	0.97	х	
Favipiravir	Clinical trials	Uracil Mustard	59	Anti-cancer drug	Х	0.68	
Leflunomide	Clinical trials	Flufenamic Acid	60	Anti-inflammatory	0.87	х	
Pirfenidone	Clinical trials	Aminopyrine	61	Analgesic	х	0.57	
Pirfenidone	Clinical trials	Antipyrine	62	Analgesic	0.75	0.35	
Pirfenidone	Clinical trials	Coumarin	63	Anticoagulant	0.85	0.54	
Pirfenidone	Clinical trials	Edaravone	64	Neuroprotective	0.81	0.49	
Pirfenidone	Clinical trials	Ethotoin	65	Central nervous system agent	0.88	Х	
Pirfenidone	Clinical trials	Felbinac	66	Anti-inflammatory	0.92	Х	
Pirfenidone	Clinical trials	Inamrinone	67	Circulatory system agent	0.94	х	

Parent drug name	Parent drug verification method	Progeny name	Progeny #	Progeny class	Mol2Vec score	ESR score	Additional ref.
Pirfenidone	Clinical trials	Oxyquinoline	68	Antiseptic	0.86	0.66	
Pirfenidone	Clinical trials	Phensuximide	69	Central nervous system agent	0.83	х	
Tenofovir	Clinical trials	Adefovir	70	Antiviral	0.62	0.41	
Tenofovir	Clinical trials	Cidofovir	71	Antiviral	0.98	х	
Tenofovir	Clinical trials	Dyphylline	72	Anti-asthmatic	х	0.61	
Thalidomide	Clinical trials	Felbamate	73	Central nervous system agent	х	0.65	
Thalidomide	Clinical trials	Lenalidomide	74	Anti-cancer drug	0.62	0.71	
Thalidomide	Clinical trials	Pomalidomide	75	Anti-cancer drug	0.43	0.71	
Bazedoxifene	In vitro	Arzoxifene	76	Selective Estrogen Receptor Modulator	0.95	х	
Bazedoxifene	In vitro	Raloxifene	77	Selective Estrogen Receptor Modulator	0.83	0.46	
Ciclesonide	In vitro	Triamcinolone Hexacetonide	78	Anti-inflammatory	Х	0.69	
Clomiphene Citrate	In vitro	Afimoxifene	79	Anti-cancer drug	0.84	х	
Clomiphene Citrate	In vitro	Tamoxifen	80	Anti-cancer drug	0.74	0.71	
Cyclosporine	In vitro	Alisporivir	81	Antiviral	0.79	х	
Cyclosporine	In vitro	Valspodar	82	Anti-cancer drug	0.88	0.56	
Cyclosporine	In vitro	Voclosporin	83	Immunosuppressant	0.68	0.21	
Droloxifene	In vitro	Afimoxifene	79	Anti-cancer drug	0.10	0.32	
Droloxifene	In vitro	Lasofoxifene	84	Selective Estrogen Receptor Modulator	х	0.61	
Droloxifene	In vitro	Tamoxifen	80	Anti-cancer drug	0.42	0.70	
Hexachlorophene	In vitro	Tiratricol	85	Hormonal	х	0.61	

Parent drug name	Parent drug verification method	Progeny name	Progeny #	Progeny class	Mol2Vec score	ESR score	Additional ref.
Hydroxyprogesterone Caproate	In vitro	Clascoterone	86	Steroidal Antiandrogen	0.89	Х	
Hydroxyprogesterone Caproate	In vitro	Gestonorone Caproate	87	Hormonal	0.79	0.51	
Hydroxyprogesterone Caproate	In vitro	Testosterone Enanthate	88	Hormonal	0.94	0.64	
Mequitazine	In vitro	Mepazine	89	Central nervous system agent	0.58	0.40	36
Mequitazine	In vitro	Methdilazine	90	Antihistamine	0.71	0.46	
Mequitazine	In vitro	Methixene	91	Anti-neurodegenerative	0.79	х	
Mequitazine	In vitro	Methylpromazine	92	Antihistamine	х	0.69	
Niclosamide	In vitro	3,3',4',5- tetrachlorosalicylanilide (TCSA)	93	Calcium pump activator	0.94	0.57	37
Niclosamide	In vitro	Tolcapone	94	Anti-neurodegenerative	0.84	х	
Nitazoxanide	In vitro	Clonazepam	95	Central nervous system agent	x	0.61	
Nitazoxanide	In vitro	Icillin	96	Circulatory system agent	х	0.65	37
Nitazoxanide	In vitro	Nitrazepam	97	Central nervous system agent	х	0.68	
Nitazoxanide	In vitro	Tizoxanide	98	Antiparasitic	0.84	х	
Oxyclozanide	In vitro	3,3',4',5- tetrachlorosalicylanilide (TCSA)	93	Calcium pump activator	0.67	Х	37
Ribavirin	In vitro	Acadesine	15	Circulatory system agent	0.60	0.63	
Ribavirin	In vitro	Azacitidine	17	Anti-cancer drug	0.97	0.65	
Ribavirin	In vitro	Cladribine	99	Anti-cancer drug	Х	0.69	
Ribavirin	In vitro	Clofarabine	100	Anti-cancer drug	х	0.70	

Parent drug name	Parent drug verification method	Progeny name	Progeny #	Progeny class	Mol2Vec score	ESR score	Additional ref.
Ribavirin	In vitro	Decitabine	20	Anti-cancer drug	Х	0.66	
Ribavirin	In vitro	Dyphylline	72	Anti-asthmatic	Х	0.66	
Ribavirin	In vitro	Enoxacin	101	Antibacterial	Х	0.58	
Ribavirin	In vitro	Inosine	102	Anti-inflammatory	0.98	0.60	
Ribavirin	In vitro	Mizoribine	25	Immunosuppressant	0.57	0.63	
Ribavirin	In vitro	Pipemidic Acid	103	Antibacterial	Х	0.70	37
Ribavirin	In vitro	Taribavirin	104	Antiviral	0.56	0.55	
Ribavirin	In vitro	Thioinosine	105	Immunosuppressant	Х	0.60	37
Ribavirin	In vitro	Uridine	31	Central nervous system agent	0.96	0.68	
Thioridazine	In vitro	Levomepromazine	106	Central nervous system agent	х	0.53	
Thioridazine	In vitro	Mepazine	89	Central nervous system agent	0.90	Х	36
Thioridazine	In vitro	Metitepine	107	Central nervous system agent	0.74	Х	37
Thioridazine	In vitro	Perazine	108	Central nervous system agent	0.87	Х	
Thioridazine	In vitro	Prochlorperazine	109	Central nervous system agent	0.90	Х	
Thioridazine	In vitro	Thiethylperazine	110	Central nervous system agent	0.91	Х	
Toremifene Citrate	In vitro	Afimoxifene	79	Anti-cancer drug	0.65	х	
Toremifene Citrate	In vitro	Tamoxifen	80	Anti-cancer drug	0.55	0.16	

Supplementary References

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