

# molecular informatics

Supporting Information

## **An Integrative *in silico* Drug Repurposing Approach for Identification of Potential Inhibitors of SARS-CoV-2 Main Protease**

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# Supporting Information

## An integrative *in silico* drug repurposing approach for identification of potential inhibitors of SARS-CoV-2 main protease

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**Figure S1.** Heatmap of the final results

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**List of smiles for identified compounds**

	Structure-based molecular modeling	QSPR-PBPK modeling				Network-based drug gene-disease associations
Drug	ChemPLP score	AUC <sub>024 h</sub> ratio plasma/lungs	AUC <sub>024 h</sub> ratio plasma/brain	AUC <sub>024 h</sub> ratio plasma/heart	AUC <sub>024 h</sub> ratio plasma/kidneys	Detected association yes(1)/no(0)
<b>Salvianolic acid B</b>	121.036	4.46	16.45	5.83	7.05	1
Pralmorelin	109.378	0.19	1.34	0.32	0.15	0
Venetoclax	105.241	1.08	0.09	0.21	0.24	0
<b>Thymopentin</b>	104.279	0.91	0.83	0.95	1.05	no data
Ombitasvir	103.241	1.06	0.09	0.21	0.24	0
<b>Atorvastatin</b>	98.9959	4.23	5.09	4.39	5.17	1
<b>Naringin</b>	98.6831	3.2	5.83	3.74	4.35	1
Astilbin	97.3607	3.43	2.24	2.83	3.25	0
<b>Montelukast</b>	96.6682	1.13	0.1	0.23	0.26	1
<b>Dipyridamole</b>	95.8533	1.84	0.24	0.53	0.59	1
<b>Lopinavir</b>	95.676	1.63	0.17	0.39	0.44	1
Fulvestrant	95.3008	1.05	0.09	0.21	0.24	1
Revefenacin	95.111	0.35	0.24	0.32	0.22	0
Carfilzomib	93.5538	1.71	0.19	0.43	0.49	0
Elbasvir	93.3952	1.05	0.09	0.21	0.24	0
<b>Ritonavir</b>	92.3031	1.26	0.12	0.27	0.3	1
Dabigatran	91.9956	1.06	0.09	0.22	0.24	0
Bimatoprost	89.745	2.47	0.35	0.75	0.85	0
Sulfapyrazone	89.5815	4.25	6.42	4.72	5.56	0
Ticagrelor	89.405	1.65	0.18	0.4	0.45	0
Mitoxantrone	89.1365	0.1	0.54	0.16	0.08	0
Cilnidipine	89	1.06	0.09	0.22	0.24	0
Vilanterol	88	0.36	0.43	0.42	0.25	0
Selexipag	87.6772	3.21	0.74	1.42	1.62	0
Azilsartan	87.4639	3.66	1.28	2.15	2.46	0
<b>Telmisartan</b>	87.0781	2.65	0.42	0.89	1	1
Lifitegrast	86.0911	4.44	15.36	5.81	6.94	0
Lomitapide	85.5827	1.09	0.09	0.21	0.24	0
Neohesperidin	85.2324	2.52	3.52	2.79	3.19	0
Velpatasvir	85.0291	1.06	0.09	0.22	0.24	0
Daclatasvir	84.717	1.26	0.12	0.27	0.3	0
Lapatinib	83.8854	1.1	0.1	0.22	0.25	0
Bazedoxifene	83.5454	0.84	0.09	0.21	0.22	1
Telaprevir	81.9339	2.41	0.42	0.88	1	0
Penfluridol	81.868	0.9	0.09	0.21	0.23	0
Bortezomib	81.4749	3.72	7.22	4.39	5.16	1
Repaglinid	81.3973	2.38	0.36	0.77	0.85	0
Atazanavir	79.4297	1.58	0.17	0.38	0.43	1
Nintedanib	78.5359	0.44	0.21	0.33	0.25	0
Pimozide	77.3251	1	0.09	0.22	0.24	0
Darunavir	76.7142	3.31	1.57	2.32	2.66	0
Eltrombopag	75.0368	4.39	8.62	5.19	6.17	0
Ramipril	72.0389	3.38	10.22	4.46	4.25	1

**Figure S1.** Heatmap of the final results. Red color corresponds to unfavorable value of calculated parameters, while blue color corresponds to favorable value of calculated parameters. The most promising ligands are marked in red letters.

**Table S1.** PBPK input data based on literature information

<b>Drug</b>	<b>Dosage form</b>	<b>Dose (mg)</b>	<b>References/Notes</b>
Salvianolic acid	IV infusion	3	Only animal data are available
Pralmorelin	IV bolus	0.10	(Okano et al., 2010)
Venetoclax	IR tablet	400	(Salem et al., 2017)
Thymopentin	IV infusion	50	(Clumeck et al., 1985)
Ombitasvir	IR tablet	12.50	(Badri et al., 2017)
Ritonavir	IR tablet	600	( <i>Norvir®</i> , EMA 2005, n.d.)
Atorvastatin	IR tablet	80	(Chung et al., 2006)
Naringin	IR capsule	500	Only animal data are available
Montelukast	IR tablet	10	(Graff et al., 2003)
Astilbin	IV bolus	70	Only animal data are available
Dipiridamol	IR tablet	100	(Gregov et al., 1987)
Lopinavir	IR tablet	200	( <i>Kaletra 200 Mg/50 Mg Film-Coated Tablets - Summary of Product Characteristics (SmPC) - (Emc)</i> )
Fulvestrant	IR tablet	400	(Harrison et al., 2003)
Revefenacin	IV infusion	0.02	(Bourdet et al., 2018)
Carfilzomib	IV bolus	60	(Brown et al., 2017)
Elbasvir	IR tablet	50	(Marshall et al., 2018)
Dabigatran	IR capsule	150	(Joachim Stangier, 2008)
Bimatoprost	IV bolus	0.22	( <i>Lumigan®</i> , FDA 2006, 2020)
Sulfapyrazone	IR tablet	200	(Lecaillon et al., 1979)
Ticagrelor	IR tablet	90	(Holmberg et al., 2013)
Mitoxantrone	IV bolus	2	(Richard et al., 1992)
Cilnidipine	IR tablet	10	(Lee et al., 2014)
Selexipag	IR tablet	1.60	(Kaufmann et al., 2015)
Azilsartan	IR tablet	80	(Webb et al., 2016)
Telmisartan	IR tablet	80	(J. Stangier et al., 2000)
Ramipril	IR tablet	10	( <i>Ramipril Sandoz® Product Monograph</i> , 2018, n.d.)
Lifitegrast	IV bolus	3	Only animal data are available
Lomitapide	IR capsule	60	(Taubel et al., 2016)
Neohesperidin	IR capsule	35	(Bae et al., 2004)
Velpatasvir	IR tablet	100	(Mogalian et al., 2017)
Daclatasvir	IR tablet	60	(Bifano et al., 2013)
Lapatinib	IR tablet	250	( <i>Tyverb®</i> , EMA 2015, n.d.)
Bazedoxifene	IR tablet	20	(McKeand, 2017)
Vilanterol	IV bolus	0.055	(Allen et al., 2011)
Telaprevir	IR tablet	375	( <i>Incivo®</i> , EMA 2011, n.d.)
Penfluridol	IR tablet	60	(Migdalof et al., 1979)
Bortezomib	IV bolus	3.50	(Tan et al., 2019)
Repaglinide	IR tablet	1	(Hatorp, 2002)
Atazanavir	IR capsule	300	(Le Tiec et al., 2005)
Nintedanib	IR capsule	150	(Dallinger et al., 2016)
Pimozide	IR tablet	4	( <i>Orap® Product Information</i> , 2002, n.d.)
Darunavir	IR tablet	800	(Kakuda et al., 2014)
Eltrombopag	IR tablet	25	(Shida et al., 2011)

**Table S2.** QSPR predicted data used as inputs for PBPK modeling

Drug	MW (g/mol)	logP	pKa (s)	Intrinsic solubility (mg/ml)	Peff (cm/s)	DiffCoef (cm <sup>2</sup> /s)	RBP	fup (%)	CLint (μL/min/mg HLM protein)
Salvianolic acid	718.63	3.88	12.02, 11.53, 11.05, 9.88, 9.38, 8.92, 8.35, 3.94, 3.17 (a)	0.01	0.26	0.49	0.68	6.26	9.71
Pralmorelin	746.92	3.15	12.89 (a); 10.01, 8.02 (b)	0.85	0.13	0.43	0.70	6.07	65.99
Venetoclax	868.46	6.84	11.61, 5.53 (a); 7.09, 3.17, 2.60, 0.96 (b)	2.14 x 10 <sup>-5</sup>	0.25	0.41	0.71	2.72	213.87
Thymopentin	681.79	-4.37	4.06, 3.37 (a); 10.94, 9.66, 7.84; 4.77, 0.61 (b)	9.64	0.11	0.45	0.79	82.35	10.64
Ombitasvir	894.13	5.49	11.77, 11.28, 10.84, 10.35 (a); 4.22 (b)	5.00 x 10 <sup>-2</sup>	0.47	0.38	0.66	5.79	440.77
Ritonavir	720.96	4.2	11.83, 11.18 (a); 4.46; 2.47 (b)	0.01	0.47	0.44	0.64	3.67	1387.57
Atorvastatin	558.65	4.28	11.05, 4.71 (a);	0.15	1.73	0.51	0.67	5.04	40.11
Naringin	582.56	-0.27	10.20, 9.36, 7.13 (a)	4.91	0.11	0.54	0.69	24.29	4.06
Montelukast	586.2	7.55	4.80 (a); 4.03 (b)	2.63 x 10 <sup>-5</sup>	1.72	0.50	0.66	2.81	275.39
Astilbin	594.53	1.74	11.77, 11.23, 10.69, 10.24, 9.77, 9.30, 8.80, 8.19 (a)	0.08	0.23	0.56	0.76	10.57	18.49
Dipiridamol	504.64	3.04	5.83, 3.56, 1.83, 1.63, 1.43, 1.13, 0.71, 0.29 (b)	2.34	0.45	0.55	0.67	8.99	15.50
Lopinavir	628.82	3.53	12.31 (a)	0.01	0.71	0.46	0.64	5.24	1981.52
Fulvestrant	606.78	7.2	10.75 (a)	2.00 x 10 <sup>-2</sup>	2.39	0.49	0.67	2.81	15000.00
Revefenacin	597.76	3.89	11.00 (a); 7.90, 6.82 (b)	0.08	0.70	0.49	0.72	5.40	50.00
Carfilzomib	719.93	3.26	5.61 (b)	0.05	0.32	0.43	0.65	8.17	1249.06
Elbasvir	882.04	6.34	11.19, 10.75, 10.39, 9.94 (a); 4.54, 3.84 (b)	3.00 x 10 <sup>-2</sup>	0.59	0.40	0.69	4.03	87.32
Dabigatran	627.75	5.55	10.65 (a); 6.02, 3.82, 2.88, 2.36, -0.71 (b)	0.03	1.12	0.48	0.67	3.84	141.73
Bimatoprost	415.58	2.76	/	0.13	1.17	0.57	0.67	9.37	183.49
Sulfinpyrazone	404.49	2.21	6.69 (a)	0.30	4.07	0.64	0.69	4.91	14.17
Ticagrelor	522.58	3.52	2.82, 0.98, 0.18, -0.57, -2.53 (a)	0.77	1.25	0.58	0.70	5.15	26.16
Mitoxantrone	444.49	0.0685	6.89 (a); 9.61, 8.96, 8.30, -1.50, -2.27 (b)	0.53	0.30	0.60	1.01	40.95	15.73

Cilnidipine	492.53	5.41	11.21 (a); 1.81 (b)	$1.00 \times 10^{-2}$	1.10	0.56	0.70	4.19	45.87
Selexipag	496.63	4.05	6.06 (a); 4.41, 2.13, 0.29 (b)	0.02	0.97	0.54	0.66	4.42	25.93
Azilsartan	568.55	4.53	5.28 (a); 2.25; -3.70 (b)	$1.00 \times 10^{-2}$	2.96	0.56	0.68	4.71	10.99
Telmisartan	514.63	5.8	4.03, 3.43 (a)	0.06	1.11	0.54	0.68	3.42	27.30
Ramipril	416.52	1.43	3.45 (a); 6.05 (b)	1.26	0.51	0.60	0.70	10.13	8.75
Lifitegrast	615.49	3.76	10.49, 3.53 (a);	$3.77 \times 10^{-5}$	0.95	0.53	0.66	4.20	18.33
Lomitapide	693.74	6.87	11.24 (a); 7.52 (b)	$5.12 \times 10^{-5}$	2.05	0.47	0.67	2.45	1200.07
Neohesperidin	610.57	-0.46	9.85, 8.15 (a);	6.64	0.11	0.54	0.72	32.86	5.30
Velpatasvir	883.02	5.48	11.43, 10.96, 10.56, 10.10 (a); 4.43, 3.14 (b)	$1.00 \times 10^{-2}$	0.52	0.41	0.67	4.27	76.37
Daclatasvir	738.89	4.03	11.34, 10.96, 10.57, 10.21 (a); 4.67, 3.92 (b)	0.01	0.71	0.44	0.67	5.37	37.19
Lapatinib	581.07	5.18	6.53, 4.12, 0.60, -0.98 (b)	$2.76 \times 10^{-4}$	0.72	0.53	0.68	2.45	2638.02
Bazedoxifene	470.62	6.18	10.78, 10.00 (a); 8.16 (b)	0.07	1.33	0.56	0.75	4.72	458.07
Vilanterol	486.44	4.24	10.34 (a); 8.99 (b)	0.39	0.72	0.56	0.70	8.12	79.11
Telaprevir	679.87	2.59	11.46, 10.88 (a); 1.88, -1.92 (b)	0.45	0.70	0.45	0.67	10.74	276.02
Penfluridol	523.98	6.8	7.80 (b)	$7.29 \times 10^{-5}$	2.87	0.56	0.75	4.66	3727.52
Bortezomib	384.25	1.32	12.74, 11.20, 6.52 (a); 1.38, -2.87 (b)	6.72	0.69	0.64	0.66	15.97	25.08
Repaglinide	452.6	4.9	4.56 (a); 5.62 (b)	0.06	0.85	0.56	0.70	4.19	40.54
Atazanavir	704.87	3.36	11.51, 10.97, 10.42 (a); 4.63, 3.66 (b)	0.01	0.42	0.44	0.64	8.33	257.16
Nintedanib	539.64	3.94	11.21, 9.94 (a); 8.11, 2.55, -0.72 (b)	0.13	1.20	0.53	0.72	7.91	80.29
Pimozide	461.56	6.05	12.56 (a); 8.30 (b)	$2.00 \times 10^{-2}$	2.18	0.58	0.74	4.60	62.19
Darunavir	547.67	1.93	11.32 (a); 3.37 (b)	0.10	0.37	0.53	0.68	9.50	44.92
Eltrombopag	442.48	4.92	9.09, 3.80 (a); -1.30, -3.04, -4.07 (b)	$1.78 \times 10^{-4}$	5.20	0.61	0.68	3.93	8.91

MW - molecular weight; (a) - acidic pKa value(s); (b) - basic pKa value(s); Peff - human effective permeability; DiffCoef - diffusion coefficient; RBP - blood/plasma concentration ratio; fup - plasma fraction unbound; CLint – overall human liver microsomal intrinsic clearance

**Table S3.** Interactions (mRNA expression, protein expression, gene expression and protein secretion) between the candidate drugs and genes obtained from the CTD database (<http://ctdbase.org>)

Gene	Interaction	Atorvastatin	Naringin	Lopinavir	Fulvestrant	Telmisartan	Ramipril	Bortezomib	Atazanavir	Ritonavir	Salvianolic acid B	Dipyridamole
ACE2	mRNA expression	↑				↑↓						
	Protein expression	↑				↑↓						
AGT	mRNA expression					↓						
	Protein expression					↓	↓					
CCL2	mRNA expression	↓		↑			↓	↓				
	Protein expression					↓			↑	↑		
	Gene expression									↓		
	Protein secretion			↑						↑		
CCL3	mRNA expression							↑↓				
	Protein expression			↑				↑	↑	↑		
	Gene expression									↓		
CRP	Protein expression	↓				↓					↓	
CSF3	mRNA expression				↓							
CXCL10	Protein expression	↓										
	Gene expression									↓		
	Protein expression					↑						
IL1B	mRNA expression			↑	↑							
	Protein activity		↓									
IL2	mRNA expression											↓
	Protein expression							↓				
IL6	mRNA expression	↓			↑	↓		↑		↑		
	Protein expression	↓	↓	↑		↓		↓		↑		
	Protein secretion	↓		↑				↓		↑		
IL7	mRNA expression									↓		
	Protein expression									↓		
CXCL8	mRNA expression	↓			↑	↓		↑				
	Protein expression	↓										
	Gene expression	↓										
	Protein secretion	↓						↑				
TNF	mRNA expression	↓		↑						↑		↓
	Protein expression	↓				↓				↓		
	Protein secretion	↓								↓		











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