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CNS Penetration Ability: A Critical Factor for Drugs in the Treatment of SARS-CoV-2 Brain Infection

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ABSTRACT: Now, it has been evidenced that Covid19 (SARS-CoV-2) infects the brain tissues. Along with this, a challenge has been raised for research professionals to find effective drugs for its treatment since the recent spread of this virus from Wuhan, China. Targeting the treatment of brain infection, it has also been a challenge that the clinical drug should have good CNS penetration ability to cross the blood−brain barrier.

KEYWORDS: *SARS-CoV-2, COVID19, CNS infection, drug treatment, log P, CNS penetration*

Following the early evolutionary history of coronaviruses, it has been determined that the novel COVID19 coronavirus is homologous (based on genome sequence analysis) to human coronaviruses such as severe acute respiratory syndrome (SARS-CoV) and the Middle East respiratory syndrome (MERS-CoV). All coronaviruses are zoonotic pathogens possessing single-strand RNA as their genetic material. Furthermore, following their clinical symptoms of infections in the human body, it was found to be similar. The COVID19 coronavirus not only causes infection of the respiratory and gastrointestinal systems but also causes infection of brain tissues.[1] It has been reported that COVID19 uses spike (S) protein to enter into host cells through the angiotensin-converting enzyme 2 (ACE2) receptors. The ACE2 receptors are expressed and distributed well in brain cells, so they allow chances for brain infections.[2] The experiment carried out by Netland et al.[3] in transgenic mice showed that SARS coronavirus infections caused neuronal death. This experiment demonstrated that the virus enters the brain primarily through the olfactory bulb, and the infection spread rapidly to trans-neurons and then to connected areas of the brain. The extensive neuronal infection was the main cause of death. Importantly, it was also noticed that intracranial inoculation with low doses of virus resulted in a uniformly lethal disease. They found that the death of mice was due to the death of infected neurons located in cardiorespiratory centers in the medulla. Furthermore, the virus induced minimal cellular infiltration in the brain. These results revealed that SARS-CoV can potentially target neurons.[3] Recently, the neuroinvasive and neurodegeneration-like potential of COVID19 are well reported.[1,4]

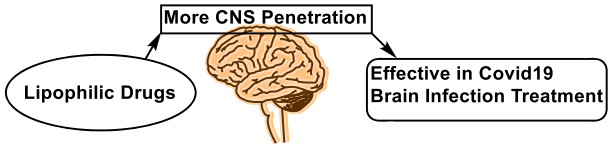

Figure 1. Lipophilic drugs can exhibit better CNS penetration ability to treat COVID19 infection.

Therefore, it has become urgent to think about the screening of potential drugs (Figure 1) for the treatment of COVID19 CNS infections.

Earlier clinical reports suggested that drugs used for the treatment of viral CNS infections showed poor CNS penetration abilities and therefore exhibited lower CSF concentrations and were unable to inhibit or stop viral RNA replication.[5] Chemical structure analysis of those drugs revealed that they possessed lower log *P* values (the critical factor for CNS penetration) and hence were unable to cross the BBB. The low log *P* value of some drugs is due to the presence of more polar atoms such as O, N, S, P, F, etc. in functional groups. A list of drugs (Table 1) that are currently under clinical trial or in the pipeline for the treatment of COVID19 infection has been summarized.[6,7]

The chemical structures were drawn and the log *P* value was calculated using an *in silico* tool. Ideally, according to Lipinski's rule of 5, a log *P* value less than 5 is useful for a pharmacologically effective drug.[7] Most probably, this information would be highly useful for the biologists in screening drugs, for physicians to select drugs for their prescriptions, and for medicinal chemists to further design potential antiviral drugs targeting the effective treatment of COVID19 CNS infection.

AUTHOR INFORMATION

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Table 1. List of Drugs Currently Undergoing Clinical Trial or in Pipelines with Their log *P* Values*

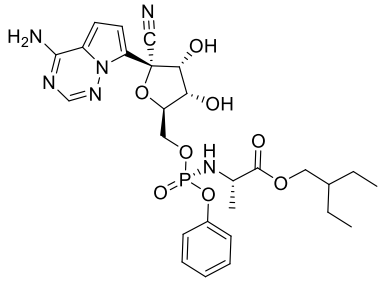
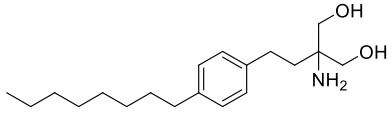
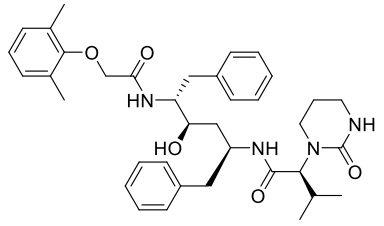
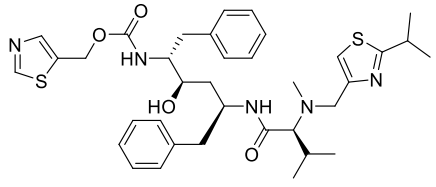
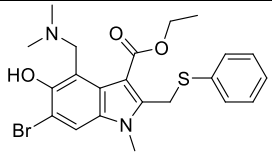
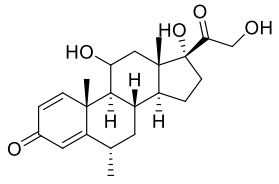
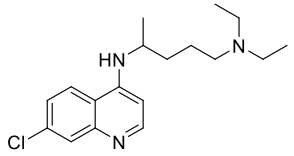
SN	Chemical Structure* (Name)	Log p*	Clinical status[6,7]
1	 (Remdesivir)	3.2	On going
2	 (Fingolimod)	4.01	On going
3	 (Lopinavir)	4.56	On going
4	 (Ritonavir)	6.8	On going
5	 (Umifenovir)	4.58	On going
6	 (Methylprednisolone)	0.81	On going
7	 (Chloroquine)	3.73	On going

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Table 1. continued

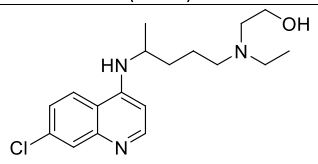
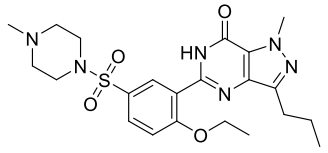
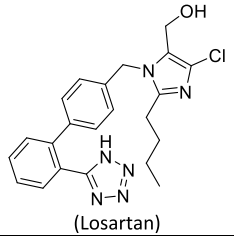
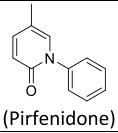
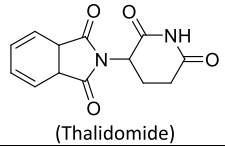
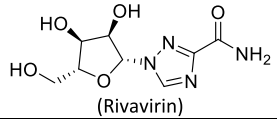
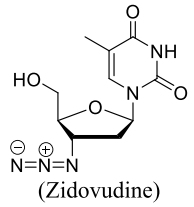
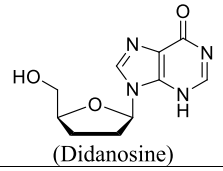
SN	Chemical Structure* (Name)	Log p*	Clinical status[6,7]
8	 (Hydroxychloroquine)	2.87	On going
9	 (Sildenafil)	2.12	On going
10	 (Losartan)	4.95	Pipeline drug
11	 (Pirfenidone)	2.02	Pipeline drug
12	 (Thalidomide)	-1.1	Pipeline drug
13	 (Rivavirin)	-1.85	Pipeline drug
14	 (Zidovudine)	...	Pipeline drug
15	 (Didanosine)	-0.8	Pipeline drug

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Table 1. continued

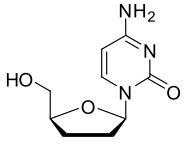
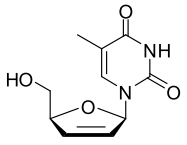
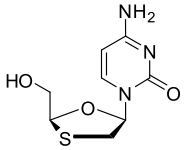
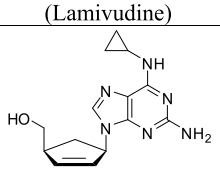
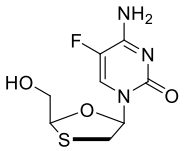
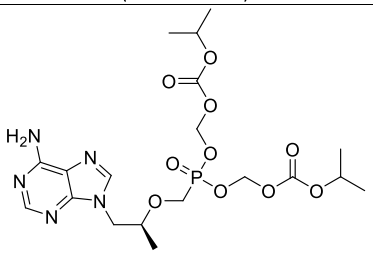
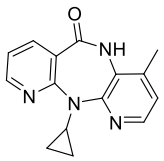
SN	Chemical Structure* (Name)	Log p*	Clinical status[6,7]
16	 (Zalcitabine)	-0.58	Pipeline drug
17	 (Stavudine)	...	Pipeline drug
18	 (Lamivudine)	0.06	Pipeline drug
19	 (Abacavir)	...	Pipeline drug
20	 (Emtricitabine)	-0.3	Pipeline drug
21	 (Tenofovir disoproxil)	3.16	Pipeline drug
22	 (Nevirapine)	2.05	Pipeline drug

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Table 1. continued

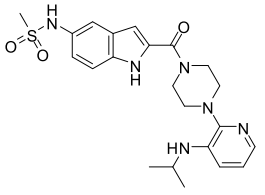
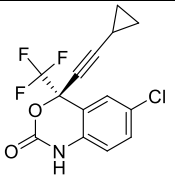
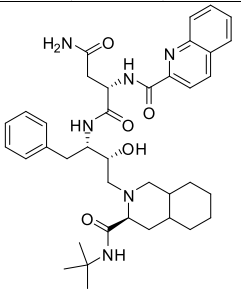
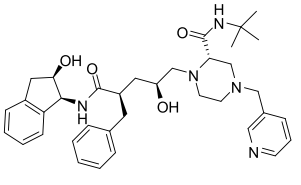
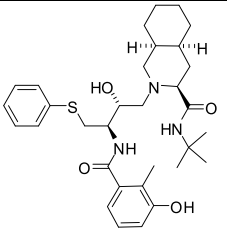
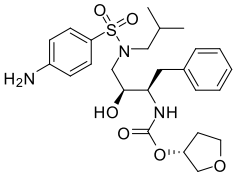
SN	Chemical Structure* (Name)	Log p*	Clinical status[6,7]
23	 (Delavirdine)	0.59	Pipeline drug
24	 (Efavirenz)	3.68	Pipeline drug
25	 (Saquinavir)	2.73	Pipeline drug
26	 (Indinavir)	2.49	Pipeline drug
27	 (Nelfinavir)	4.62	Pipeline drug
28	 (Amprenavir)	2.5	Pipeline drug

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Table 1. continued

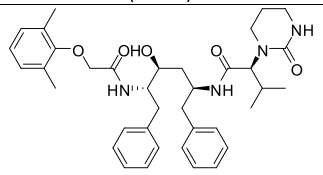
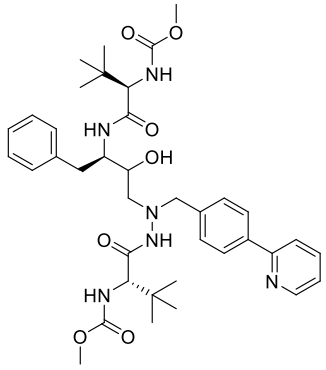
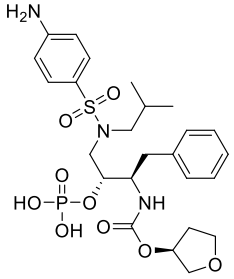
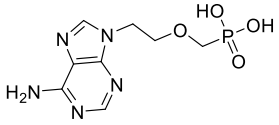
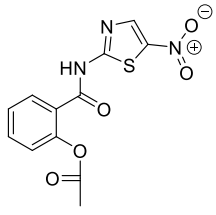
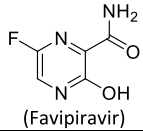
SN	Chemical Structure* (Name)	Log p*	Clinical status[6,7]
29	 (Lopinavir)	4.56	Pipeline drug
30	 (Atazanavir)	...	Pipeline drug
31	 (Fosamprenavir)	3.75	Pipeline drug
32	 (Adefovir)	-0.18	Pipeline drug
33	 (Nitazoxanide)	...	Pipeline drug
34	 (Favipiravir)	-0.36	Pipeline drug

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Table 1. continued

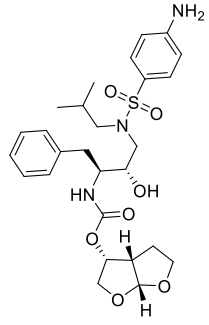
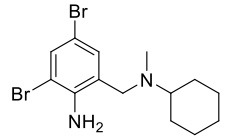
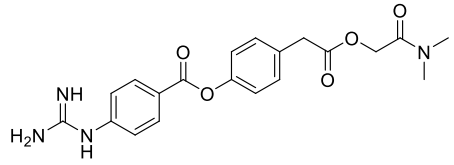
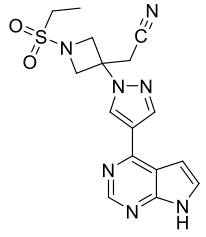
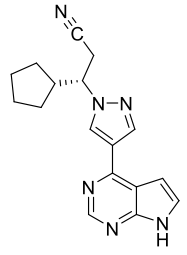
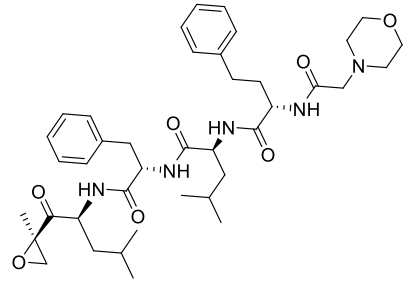
SN	Chemical Structure* (Name)	Log p*	Clinical status[6,7]
35	 (Darunavir)	2.85	Pipeline drug
36	 (Bromhexine)	4.38	On going
37	 (Camostat)	1.49	Pipeline drug
38	 (Baricitinib)	-0.13	Pipeline drug
39	 (Ruxolitinib)	2.39	Pipeline drug
40	 (Carfilzomib)	...	Pipeline drug

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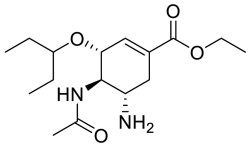
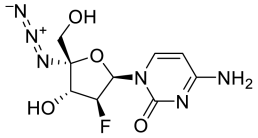
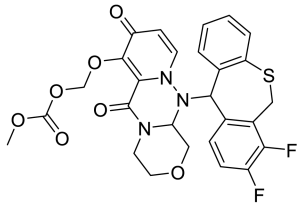
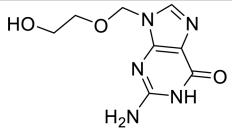
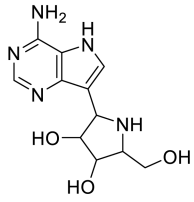
Table 1. continued

SN	Chemical Structure* (Name)	Log p*	Clinical status[6,7]
41	 (Oseltamivir)	0.19	Pipeline drug
42	 (Azvudine)	...	Pipeline drug
43	 (Baloxavir marboxil)	...	Pipeline drug
44	 (Acyclovir)	-1.59	Pipeline drug
45	 (Galidesivir)	-2.33	Pipeline drug

*Both chemical structure drawn and log *P* calculation was done using ChemDraw Professional 15.0.

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Complete contact information is available at: https://pubs.acs.org/10.1021/acschemneuro.0c00335

Notes

The author declares no competing financial interest.

REFERENCES

(1) Li, Y. C., Bai, W. Z., and Hashikawa, T. (2020) The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J. Med. Virol. 92*, 552−55.

(2) Baig, A. M., Khaleeq, A., Ali, U., and Syeda, H. (2020) Evidence of the COVID-19 virus targeting the CNS: tissue distribution, host-virus interaction, and proposed neurotropic mechanisms. *ACS Chem. Neurosci. 11*, 995−98.

(3) Netland, J., Meyerholz, D. K., Moore, S., Cassell, M., and Perlman, S. (2008) Severe acute respiratory syndrome coronavirus infection causes neuronal death in the absence of encephalitis in mice transgenic for human ACE2. *J. Virol. 82* (15), 7264−75.

(4) Ramani, A., Muller, L., Ostermann, P. N., Gabriel, E., Abida-Islam, P., Muller Schiffmann, A., Mariappan, A., Goureau, O., Gruell, H., Walker, A., Andree, M., Hauka, S., Houwaart, T., Dilthey, A., Wohlgemuth, K., Omran, H., Klein, F., Wieczorek, D., Adams, O., Timm, J., Korth, C., Schaal, H., and Gopalakrishnan, J. (2020). SARS-CoV-2 targets cortical neurons of 3D human brain organoids and shows neurodegeneration-like effects. *bioRxiv*, DOI: 10.1101/2020.05.20.106575.

(5) Nightingale, S., Winston, A., Letendre, S., Michael, B. D., McArthur, J. C., Khoo, S., and Solomon, T. (2014) Controversies in HIV-associated neurocognitive disorders. *Lancet Neurol. 13*, 1139−51.

(6) Vellingiri, B., Jayaramayya, K., Iyer, M., Narayanasamy, A., Govindasamy, V., Giridharan, B., Ganesan, S., Venugopal, A., Venkatesan, D., Ganesan, H., Rajagopalan, K., Rahman, P. K. S. M., Cho, S. G., Kumar, N. S., and Subramaniam, M. D. (2020) COVID-19: A promising cure for the global panic. *Sci. Total Environ. 725*, 138277.

(7) Liu, C., Zhou, Q., Li, Y., Garner, L. V., Watkins, S. P., Carter, L. J., Smoot, J., Gregg, A. C., Daniels, A. D., Jervey, S., and Albaiu, D. (2020) Research and development on therapeutic agents and vaccines for COVID-19 and related human coronavirus diseases. *ACS Cent. Sci. 6*, 315−31.