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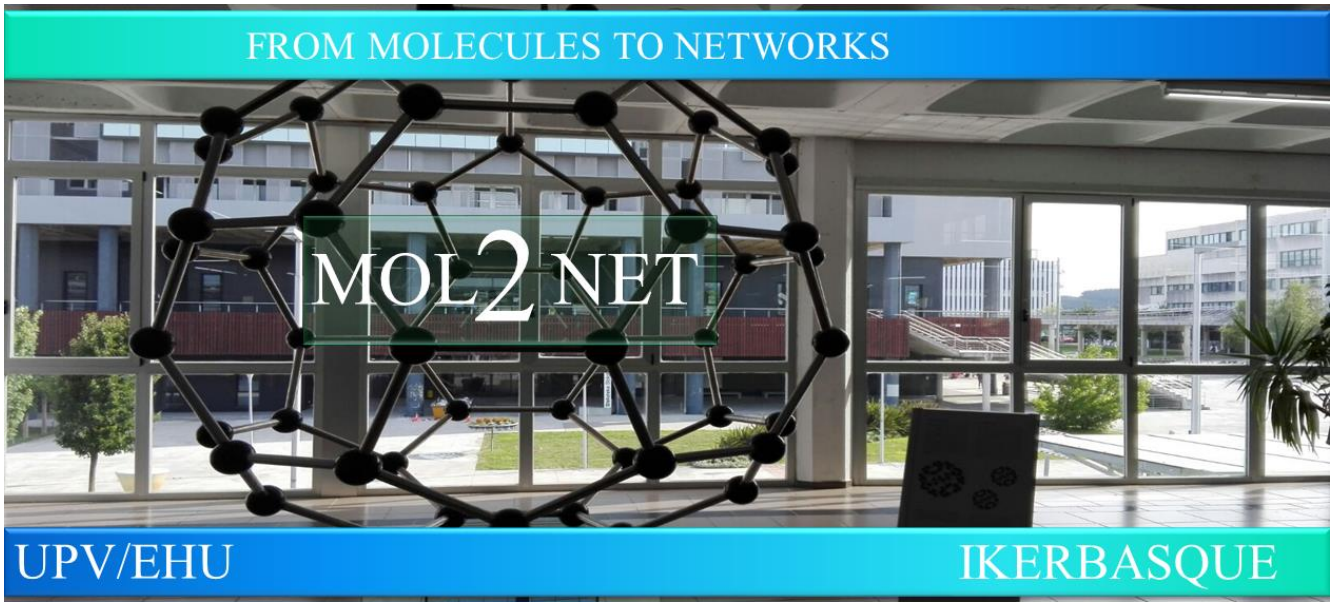

Potential Treatments for COVID-19. Recap of a Computational Repurposing Study Based on Molecular Topology

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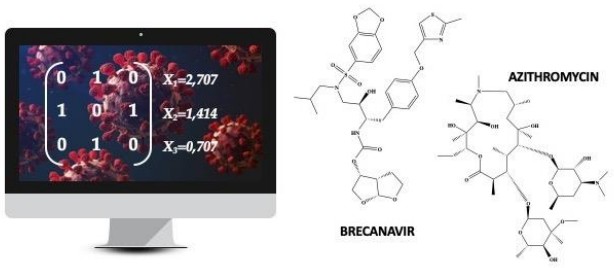
Graphical Abstract	**Abstract.**
	At the beginning of the pandemic, present communication reports the results of a computational study based on molecular topology, focused on the repositioning of drugs to treat the SARS-CoV-2 virus, better known as Coronavirus, responsible for the COVID-19

	disease. Using lopinavir, a well-known viral protease inhibitor as the reference drug, a mathematical pattern is found allowing the screening of on the market drugs, searching for potential candidates to inhibit said enzyme. This way new possible therapeutic alternatives against SARS-CoV-2 are found. Results suggest that antivirals such as brecanavir, as well as various groups of drugs, among which stand antibiotics of the macrolide family (azithromycin, clarithromycin and erythromycin among others) could be useful in treating COVID-19 infection.

Results and Discussion

The Molecular Topology and Drug Design Research Unit from the University of Valencia (Spain) has been working in a pioneering way since the 80s of the last century in designing and selecting new drugs based on a paradigm called Molecular Topology (MT). Some of these new drugs have been internationally patented in fields as diverse as cancer, Alzheimer's, malaria and more recently COVID-19 (1-2). In essence, the MT method is based on characterizing the molecules by a set of numbers, called topological indices, which basically depend on the structure of each molecule and thereby on its pharmacological activity. In this way, it is possible to group the molecules into sets that respond to different mathematical patterns according to their activity. For example, we can have the cancer pattern and even within it, the cancer pattern associated with a specific mechanism (for example, topoisomerase inhibitors). Once a mathematical pattern has been found, it is easy to ask the computer to search for new molecules matching the same pattern and therefore showing the same pharmacological activity, but with better pharmacodynamic, pharmacokinetic, or toxicological properties (more potency, better absorption, less toxicity, etc.). By using a mathematical pattern to characterize pharmacological activity, authors are able to identify a great structural variability within the potential active compounds (3).

Using the SARS-CoV-2 protease (4) and a pool of viral protease inhibitors with slightly effectivity described against COVID-19, authors disclosed in a previously published short communication the results of a topological screening of on the market drugs, selecting potential candidates with anti-COVID-19 activity.

The reference drug used was lopinavir, which according to various publications showed efficacy against SARS-CoV-2. After obtaining the topological-mathematical fingerprint of the molecules, and developing seven predictive equations (see for instance: Galvez *et al.*, 2021 and Zanni *et al.*, 2021) (2,5),

authors proceeded to screen two databases of pharmacological compounds: Comprehensive Medicinal Chemistry (6) and DrugBank (7), altogether some 15,000 molecules.

Table 1. Results obtained from the virtual screening of selected drugs as potential protease inhibitors and therefore useful in the treatment of COVID-19.

Drug	Family	Inhibitory capability to SARS-CoV-2 protease
Nonactine	Antibiotic	10,0
Diproleandomycin	Antibiotic	8,3
Flurithromycin	Antibiotic	7,3
Brecanavir	Antiviral	7,3
Clarithromycin	Antibiotic	7,0
Erythromycin	Antibiotic	6,9
Lexithromycin	Antibiotic	6,8
Ritonavir	Antiviral	6,8
Argadin	Others	6,4
Azithromycin	Antibiotic	6,1
Cethromycin	Antibiotic	5,7
Oxidized Glutathione	Antineoplastic	5,6
Fomidacillin	Antibiotic	5,4
Neutramycin	Antibiotic	5,1
Murabutide	Immunostimulant	5,0
Mirosamicin	Antibiotic	4,8
Cronidipine	Calcium channels' blocker	4,5
Cefclidin	Antibiotic	4,1
Temurtide	Antiviral	4,0
Cefuroxime	Antibiotic	3,9
Pentigetide	Antialergic	3,9
Cistinexine	Expectorant and Mucolytic	3,6
Cefbuperazone	Antibiotic	3,2
Lopinavir	**Antiviral**	**2,9**

The right column reflects through an index (in arbitrary units) the range of inhibitory potency against protease of the different drugs. The reference drug lopinavir, appears in bold at the bottom and showed a value of 2.9 on this scale. As it can be seen, there is a surprisingly high number of drugs that show a theoretical activity against the virus protease, including known antivirals, antibiotics of different types and other groups of drugs (antineoplastic, antiallergic, etc.). Among the most active are brecanavir (potency index 7.3) and a ionophore antibiotic, nonactin (index 10, the maximum). It is also noteworthy the presence of some antibiotics from the macrolide family, such as clarithromycin and erythromycin. Another potentially very interesting drug is murabutide, since it is a known immunostimulant, which could promote a synergy.

Obviously, only experimental confirmation of the activity *in vitro* and *in vivo* of these compounds against the virus, will demonstrate their real efficacy. However, the repositioning of drugs can shorten significantly the time in providing therapeutic alternatives to face the current public health crisis. In this sense, authors believe that the drugs reported in Table 1 could represent an important contribution, whose fast achievement is another proof of MT's power as a tool for the search of new drugs.

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