Elucidation on the Physicochemical Properties of Potential and Clinically Approved Antiviral Drugs: A Search for Effective Therapies against SARS-CoV-2 Infection

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Abstract

COVID-19 has been confirmed in millions of individuals worldwide, rendering it a global medical emergency. In the absence of vaccines and the unavailability of effective drugs for the SARS-CoV-2 infection, vaccine development is being continuously explored and several antiviral compounds and immunotherapies are currently being investigated. Given the high similarity in genetic identity between SARS-CoV and SARS-CoV-2, the present investigation identified the interaction between the physicochemical properties and the antiviral activity of different potential and clinically approved antiviral drugs against SARS-CoV using hierarchically weighted principal component analysis. Representative drugs from the classes of neuraminidase inhibitors, reverse transcriptase inhibitors, protease inhibitors, nucleoside analogues, and other compounds with potential antiviral activity were examined. The pharmacologic classification and the biological activity of the different antiviral drugs were described using indices, namely, rotatable bond count, molecular weight, heavy atom count, and molecular complexity (92.32% contribution rate). The physicochemical properties and inhibitory action against SARS-CoV-2 of lopinavir, chloroquine, ivermectin, and ciclesonide validated the adequacy of the current computational approach. The findings of the present study provide additional information, although further investigation is warranted to identify potential targets and establish exact mechanisms, in the emergent search and design of antiviral drug candidates and their subsequent synthesis as effective therapies for COVID-19.

Keywords: COVID-19, neuraminidase inhibitors, nucleoside analogues, principal component analysis, protease inhibitors, reverse transcriptase inhibitors

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INTRODUCTION

SARS-CoV-2, a novel severe acute respiratory syndrome coronavirus 2, has been identified to cause coronavirus disease 2019 (COVID-19)\(^1\). COVID-19 is a recent medical emergency worldwide with more than 3.5 million confirmed cases and more than a quarter of a million deaths as of May 4, 2020\(^2\). Among infected patients, supportive care to help alleviate the symptoms has been recommended\(^3\). At present, neither effective drugs exist nor vaccines are available for COVID-19; however, vaccines are being developed and several antiviral agents, chemotherapeutics, and immunotherapies are being investigated as pharmacologic interventions.

Despite the very complex process, the search for effective therapies for COVID-19 continues. As SARS-CoV and SARS-CoV-2 have high similarity in genetic identity\(^4,5\), drugs with inhibitory action against SARS-CoV would exhibit similar degrees of inhibition against SARS-CoV-2. In the present investigation, representative drugs from the classes of neuraminidase inhibitors (NAIs), reverse transcriptase inhibitors (RTIs), protease inhibitors, nucleoside analogues, and other compounds with potential antiviral activity were examined. The chemical and physical properties of drugs such as hydrogen bond donor and acceptor counts, topological polar surface area, heavy atom and rotatable bond counts, complexity, and molecular weight were identified to influence their biological activities\(^6,7\). Hence, the present study identified the relationship between the physicochemical properties and the antiviral activity against SARS-CoV of the available potential and clinically approved antiviral drugs using hierarchically weighted principal component analysis. Identifying the relationship between the properties of a compound and its biological activity has always been considered important in drug design\(^8\). The generated relationship will identify significant chemical and physical properties of these antiviral drugs explaining inhibition variations against SARS-CoV-2. The findings of the present investigation offer additional insights relevant to the search for potential antiviral drug candidates and their subsequent synthesis as effective therapies for COVID-19.

MATERIALS AND METHODS

Chemical and physical properties of drugs with antiviral activity

Information on the potential and clinically approved antiviral drugs against SARS-CoV was retrieved from the literature. These are representative drugs from the classes of NAIs, RTIs, protease inhibitors, nucleoside analogues, and compounds with potential antiviral activity. In the class of nucleoside analogues, representative drugs such as acyclovir, foscavir, and ganciclovir were identified. Another major antiviral pharmacologic class examined was the human immunodeficiency virus (HIV) antiretroviral drugs, including indinavir, nelfinavir, and saquinavir as protease inhibitors. For the HIV antiretroviral drugs classified as RTIs, selected HIV nucleoside RTIs included in this study were lamivudine and zidovudine. The fourth pharmacologic class of the antivirals examined was the NAIs with oseltamivir and zanamivir as representative drugs. In addition to these clinically approved antiviral drugs, 10 other commercially available drugs with potential antiviral activity were also included. The drugs which exhibited in vitro antiviral activity against SARS-CoV were amantadine\(^9\), calpain inhibitor III\(^10\), calpain inhibitor VI\(^11\), chloroquine\(^12\), cinanserin\(^13\), glycyrrhizin\(^14\), mizoribine\(^15\), niclosamide\(^16\), ribavirin\(^9,10,15\), and valinomycin\(^17\). The chemical and physical properties of these compounds, namely topological polar surface area, heavy atom count, hydrogen bond acceptor count, hydrogen bond donor count, complexity, rotatable bond count, and molecular weight were retrieved from online databases\(^18-37\) (Table 1).

Principal component analysis and computational validation

Similarity in the biological activity and pharmacologic classification of the different potential and clinically approved antiviral drugs were determined, and the presence of correlations among the various chemical and physical properties of these antiviral drugs was identified using principal component analysis. A principal component contains uncorrelated linear combinations of the drug indices with maximum variance, which suggests that a linear transformation must be performed among
correlated variables, and the linearly transformed variables are subsequently arranged in order of decreasing variances. A principal component is considered for inclusion when it has a loading eigenvalue of at least 1.0. For the retention of the drug property within a principal component, a minimum of 0.30 in absolute value is required as the correlation coefficient between the variable and its principal component. Sampling adequacy was assessed using Kaiser–Meyer–Olkin measure. Numerical calculations and data analysis were performed using STATA® V12.0 software. After obtaining the principal components and identifying the significant indices within the components, additional clinically approved antiviral drugs including abacavir, darunavir, didanosine, galidesivir, stavudine, and zalcitabine for pharmacologic classification and some drugs that inhibited SARS-CoV-2 such as chloroquine, lopinavir, ivermectin, and ciclesonide were utilized to validate the results of the multivariate computational approach.

### RESULTS

Twenty different compounds with potential and clinically approved antiviral activity against SARS-CoV were classified using principal component analysis. Two principal components were obtained with eigenvalues 5.41 and 1.05. Within a component, the loading values of each drug index were computed (Table 2). The important indices included in the first principal component were complexity ($r = 0.4202$), heavy atom count ($r = 0.4123$), and molecular weight ($r = 0.4118$) with a 77.35% contribution rate. The rotatable bond count, complexity, heavy atom count, and molecular weight indices primarily defined the pharmacologic classification of the compounds with potential and clinically approved antiviral activity (92.32% total contribution rate, 0.7620 Kaiser–Meyer–Olkin sampling adequacy). The main indices in the first principal component, namely complexity, heavy atom count, and molecular weight, contributed significantly to the classification of antiviral compounds.

### Table 1. Chemical and physical properties of potential and clinically approved antiviral drugs

| Drug            | HBDC | HBAC | COMPLEX | HEAVY | ROTA | TOPO | MW      |
|-----------------|------|------|---------|-------|------|------|--------|
| Acyclovir       | 3    | 5    | 308     | 16    | 4    | 115  | 225.20 |
| Amantadine      | 2    | 1    | 144     | 12    | 0    | 26.0 | 187.71 |
| Calpain Inhibitor III | 2 | 4    | 497     | 28    | 10   | 84.5 | 382.50 |
| Calpain Inhibitor VI  | 2 | 6    | 537     | 25    | 9    | 101.0| 372.50 |
| Chloroquine     | 1    | 3    | 309     | 22    | 8    | 28.2 | 319.90 |
| Cinanserin      | 1    | 3    | 391     | 24    | 8    | 57.6 | 340.50 |
| Foscavir        | 0    | 5    | 103     | 10    | 0    | 103.0| 191.95 |
| Ganciclovir     | 4    | 6    | 346     | 18    | 5    | 135.0| 255.23 |
| Glycyrrhizin    | 8    | 16   | 1730    | 58    | 7    | 267.0| 822.90 |
| Indinavir       | 4    | 7    | 952     | 45    | 12   | 118.0| 613.80 |
| Lamivudine      | 2    | 4    | 331     | 15    | 2    | 113.0| 229.26 |
| Mizoribine      | 5    | 7    | 329     | 18    | 3    | 151.0| 259.22 |
| Nelfinavir      | 4    | 6    | 830     | 40    | 10   | 127.0| 567.80 |
| Niclosamide     | 2    | 4    | 404     | 21    | 2    | 95.2 | 327.12 |
| Oseltamivir     | 4    | 4    | 318     | 22    | 8    | 90.6 | 312.40 |
| Ribavirin       | 4    | 7    | 304     | 17    | 3    | 144.0| 244.20 |
| Saquinavir      | 5    | 7    | 1140    | 49    | 13   | 167.0| 670.80 |
| Valinomycin     | 6    | 18   | 1910    | 78    | 9    | 332.0| 1111.30|
| Zanamivir       | 7    | 8    | 518     | 23    | 6    | 201.0| 332.31 |
| Zidovudine      | 2    | 6    | 484     | 19    | 3    | 93.2 | 267.24 |

HBDC: hydrogen bond donor count, HBAC: hydrogen bond acceptor count, COMPLEX: complexity, HEAVY: heavy atom count, ROTA: rotatable bond count, TOPO: topological polar surface area (Å²), MW: molecular weight (g/mol)
molecular weight were positively correlated with the rest of the chemical and physical properties of the antiviral drugs (Table 3). Rotatable bond count, the leading index in the second principal component, was positively correlated with heavy atom count, complexity, and molecular weight (Table 3).

The comprehensive scores for the different antiviral drugs were calculated using hierarchical weighted principal component analysis (range: 117.41–1087.30, Table 4). Interestingly, higher comprehensive scores (497.74–644.64) were identified among protease inhibitors (indinavir, nelfinavir, and saquinavir).

Table 3. Correlation between the physicochemical properties of the antiviral drugs

| Property | Component 1 (e: 5.4145, p: 0.7735) | Component 2 (e: 1.0479, p: 0.1497) | KMO (Overall: 0.7620) |
|----------|----------------------------------|----------------------------------|----------------------|
| MW       | 0.4118                           | 0.1920                           | 0.7286               |
| HBDC     | 0.3426                           | -0.3493                          | 0.7441               |
| HBAC     | 0.3986                           | -0.2926                          | 0.8107               |
| ROTA     | 0.2434                           | 0.7441                           | 0.6416               |
| TOPO     | 0.3852                           | -0.3843                          | 0.7583               |
| HEAVY    | 0.4123                           | 0.2180                           | 0.7183               |
| COMPLEX  | 0.4202                           | 0.0816                           | 0.8754               |

KMO: Kaiser-Meyer-Olkin measure of sampling adequacy, e: eigenvalue, p: proportion

The pharmacologic classes of clinically approved antivirals with high scores next to that of protease inhibitors were NAIs (267.02–334.50) and RTIs (214.44–273.51). Among the clinically approved antiviral drugs, the nucleoside analogues had the lowest comprehensive scores (124.11–235.21). Moreover, among the drugs with potential antiviral activity against SARS-CoV, valinomycin and glycyrrhizin had the highest comprehensive scores (1087.30 and 914.51, respectively), whereas amantadine had the lowest comprehensive score (117.41). The comprehensive scores of the calpain inhibitors III and VI (412.73 and 431.33, respectively) were close to those of the protease inhibitors. Chloroquine and ribavirin had comprehensive scores comparable to those of lamivudine. Cinanserin and mizoribine were comparable with ganciclovir, whereas niclosamide and oseltamivir had similar comprehensive scores.

In the validation of the computational approach for pharmacologic classification (Table 5), compounds such as abacavir, didanosine, galidesivir, stavudine, and zalcitabine obtained the lowest comprehensive scores (201.12–259.92). The comprehensive scores of these compounds were within the range of the comprehensive scores for nucleoside analogues and the RTIs (Table 4). Darunavir and lopinavir obtained comprehensive scores similar to those of other protease inhibitors examined in this study. The comprehensive score of ciclesonide was within the range of protease inhibitors, whereas ivermectin scored higher than any of the examined protease inhibitors but was inferior to glycyrrhizin and valinomycin. Moreover,
validation of the statistical methods for inhibitory potency (Table 5) using drugs with established inhibitory action against SARS-CoV-2, revealed the following comprehensive scores: chloroquine (218.15), lopinavir (553.40), ciclesonide (569.06), and ivermectin (891.27).

### Table 4. Comprehensive evaluation of the antiviral drugs based on the identified principal components

| Drug          | Component 1 | Component 2 | Comprehensive Score | Rank |
|---------------|-------------|-------------|---------------------|------|
| Amantadine    | 153.85      | -10.69      | 117.41              | 1    |
| Foscavir      | 168.12      | -39.58      | 124.11              | 2    |
| Acyclovir     | 276.07      | -42.27      | 207.22              | 3    |
| Lamivudine    | 285.49      | -42.64      | 214.44              | 4    |
| Chloroquine   | 283.05      | -5.23       | 218.15              | 5    |
| Ribavirin     | 294.94      | -54.50      | 219.98              | 6    |
| Mizoribine    | 315.08      | -57.54      | 235.10              | 7    |
| Ganciclovir   | 313.68      | -49.56      | 235.21              | 8    |
| Cinanserin    | 338.14      | -16.53      | 259.07              | 9    |
| Niclosamide   | 352.08      | -35.80      | 266.97              | 10   |
| Oseltamivir   | 350.94      | -29.56      | 267.02              | 11   |
| Zidovudine    | 360.24      | -34.28      | 273.51              | 12   |
| Calpain inhibitor III | 412.73 | -25.73 | 315.39 | 13 |
| Calpain inhibitor VI | 431.33 | -32.82 | 328.72 | 14 |
| Zanamivir     | 447.00      | -75.22      | 334.50              | 15   |
| Nelfinavir    | 651.76      | -42.76      | 497.74              | 16   |
| Indinavir     | 720.96      | -37.82      | 552.00              | 17   |
| Saquinavir    | 844.30      | -56.25      | 644.64              | 18   |
| Glycyrrhizin  | 1201.70     | -100.19     | 914.51              | 19   |
| Valinomycin   | 1429.49     | -122.99     | 1087.30             | 20   |

### Table 5. Physicochemical properties and PCA comprehensive evaluation of potential and clinically approved antiviral drugs

| Drug              | Component Scores |
|-------------------|------------------|
|                   | Component       | 1   | 2   | Overall |
| Zalcitabine       | 266.43          | -33.11 | 201.12 |
| Didanosine        | 287.36          | -33.30 | 217.29 |
| Chloroquine       | 283.05          | -5.23  | 218.15 |
| Stavudine         | 294.94          | -9.53  | 223.48 |
| Galidesivir       | 316.19          | -54.41 | 236.43 |
| Abacavir          | 343.24          | -37.27 | 259.92 |
| Darunavir         | 316.19          | -54.41 | 236.43 |
| Lopinavir         | 661.65          | -49.38 | 504.39 |
| Ciclesonide       | 722.48          | -36.35 | 553.40 |
| Ivermectin        | 1163.96         | -60.43 | 891.27 |

PCA: principal component analysis, HBDC: hydrogen bond donor count, HBAC: hydrogen bond acceptor count, COMPLEX: complexity, HEAVY: heavy atom count, ROTA: rotatable bond count, TOPO: topological polar surface area (Å²), MW: molecular weight (g/mol)

### DISCUSSION

Among the chemical and physical properties of the potential and clinically approved antiviral drugs evaluated in this study, a positive correlation was identified in all drug properties, including complexity, heavy atom count, and molecular weight. Molecular weight has been considered an important compound property in small drug discovery and is closely examined in drug optimization steps. In addition to the

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molecular weight in the first principal component, the main index complexity was positively correlated with hydrogen bond acceptor and rotatable bond counts. Molecular complexity, which includes the cardinality of rings, stereocenters, and sp<sup>2</sup>-hybridized carbons, has been related to biological activity<sup>33</sup>. A compound with at least four aromatic rings has high toxicity risks and low compound developability<sup>33</sup> which justifies the preference for moderately complex structures as lead compounds<sup>54</sup>.

Compounds classified as NAI s, RTIs, protease inhibitors, nucleoside analogues, and some drugs with potential antiviral activity were examined. Among the nucleoside analogues, when acyclovir, foscavir, and ganciclovir were compared, there was an inverse relationship between the calculated comprehensive score and the biological activity (IC<sub>50</sub>) of the antiviral drugs. For instance, when foscavir and acyclovir were examined against herpes simplex virus, acyclovir (IC<sub>50</sub>: 0.06 μmol/mL) was more potent than foscavir (IC<sub>50</sub>: 0.44 μmol/mL)<sup>3</sup>. The comprehensive score of acyclovir and foscavir was 207.22 and 124.11, respectively. Similarly, ganciclovir (IC<sub>50</sub>: 0.014 μmol/mL) was more potent than foscavir (IC<sub>50</sub>: 0.80 μmol/mL) against cytomegalovirus<sup>9</sup>. Ganciclovir had a higher comprehensive score (235.11) than foscavir (124.11). These observations led to the examination of a possible relationship between the comprehensive score based on physicochemical properties and the potency of the nucleoside analogues against viruses. The higher the comprehensive score of the nucleoside analogue, the more potent was the antiviral drug (lower IC<sub>50</sub>). A nucleoside analogue inhibits viral polymerase and interferes with nucleic acid synthesis<sup>18,24,25</sup>. Acyclovir<sup>18</sup>, foscavir<sup>24</sup>, and ganciclovir<sup>25</sup> target DNA viruses such as varicella-zoster virus and herpes simplex virus. However, acyclovir is more potent than foscavir (Foscarnet) as the former targets herpesvirus and varicella-zoster virus polymerases<sup>18</sup>, whereas the latter selectively blocks the pyrophosphate binding site of herpes virus-specific DNA polymerases<sup>24</sup>. Among the nucleoside analogues examined in the present study, ganciclovir was the most potent (the lowest IC<sub>50</sub> and the highest comprehensive score). Ganciclovir inhibits replication of several viruses including varicella zoster virus, herpes simplex virus-1 and -2, Epstein–Barr virus, and cytomegalovirus<sup>25</sup>.

Another major antiviral pharmacologic class examined was the protease inhibitor HIV antiretroviral drugs, including indinavir, nelfinavir, and saquinavir. Among these protease inhibitors, saquinavir (Fortovase) had the highest comprehensive score (644.64) and was the most potent (IC<sub>50</sub>: 3 x 10<sup>-8</sup> μmol/mL) against HIV<sup>9</sup>. Indinavir (Crixivan) was less potent (IC<sub>50</sub>: 1 x 10<sup>-4</sup> μmol/mL) than saquinavir<sup>9</sup> and had a lower comprehensive score (552.00). Nelfinavir inhibited SARS-CoV replication in Vero cells<sup>35</sup>, whereas SARS-CoV replication in FRhK-4 cells was inhibited by lopinavir<sup>56</sup>. Moreover, lopinavir (IC<sub>50</sub>: 4 μg/mL) was more potent than ribavirin (IC<sub>50</sub>: 50 μg/mL) against SARS-CoV<sup>56</sup>. Among the HIV antiretroviral drugs classified as RTIs, those examined were lamivudine and zidovudine. Zidovudine (IC<sub>50</sub>: 4.86 x 10<sup>-5</sup> μmol/mL) was more potent than lamivudine (Epivir, IC<sub>50</sub>: 1.5 x 10<sup>-4</sup> μmol/mL)<sup>9</sup>. This finding explains why zidovudine had a higher comprehensive score than lamivudine. Zidovudine<sup>37</sup> has activity against HIV-1, whereas lamivudine<sup>38</sup> has activity against hepatitis B virus and HIV.

The fourth pharmacologic class of the antivirals examined was the NAI s. Representative drugs included were oseltamivir and zanamivir. Zanamivir had a higher comprehensive score than oseltamivir (334.50 vs. 267.02), suggesting that zanamivir is more potent than oseltamivir, and this comparison was supported by previous studies. When the two NAI s were tested against influenza virus, zanamivir (Relenza) had a lower inhibitory concentration value than oseltamivir (Tamiflu)<sup>4</sup>. In addition, zanamivir (IC<sub>50</sub>: 2.7 nM) was significantly more potent than oseltamivir (IC<sub>50</sub>: 8.5 nM) when tested against influenza B virus isolates<sup>57</sup>. In addition to the clinically approved antiviral drugs, 10 other commercially available drugs with potential antiviral activity were also examined. The drugs exhibiting <i>in vitro</i> antiviral activity against SARS-CoV were amantadine<sup>9</sup>, calpain inhibitor I<sup>10</sup>, calpain inhibitor V<sup>11</sup>, chloroquine<sup>12</sup>, cinanserin<sup>13</sup>, glycyrrhizin<sup>14</sup>, mizoribine<sup>15</sup>, niclosamide<sup>16</sup>, ribavirin<sup>9,10,15</sup>, and valinomycin<sup>17</sup>. Among these drugs, amantadine obtained the lowest comprehensive score (117.41). Amantadine (Symmetrel) exhibited antiviral activity against influenza virus (ED<sub>50</sub>: 0.1–
but did not inhibit, even at 1 mg/mL, SARS-CoV in culture. Next to amantadine, five drugs with potential antiviral activities against SARS-CoV had comprehensive scores of less than 300, and these were chloroquine, cinanserin, mizoribine, niclosamide, and ribavirin. Ribavirin inhibits both DNA and RNA viruses (ED$_{50}$: 1–100 μg/mL). At 5 mg/mL, ribavirin displayed complete inhibition of SARS-CoV in culture but cytotoxic on VeroE6 cells (0.2–1 mg/mL). Despite ribavirin and mizoribine having comparable comprehensive scores (219.98 and 235.10), neither was recommended as a single treatment agent of SARS.

Recently, chloroquine exhibited inhibitory action against SARS-CoV-2 (IC$_{50}$: 9.12 μM). Previous study on chloroquine (EC$_{50}$: 8.8 μM) revealed inhibition of SARS-CoV replication in Vero cells. When compared with another antiparasitic drug, niclosamide, inhibition of SARS-CoV replication in Vero cells was likewise observed (EC$_{50}$: 2 μM). These findings support niclosamide having a higher comprehensive score than chloroquine (266.97 vs. 218.15), as niclosamide was more potent than chloroquine. Moreover, drugs including calpain inhibitors III and VI, and cinanserin have been shown to inhibit SARS-CoV replication. Cinanserin inhibited replication of SARS-CoV via inhibition of the 3CL protease, whereas calpain inhibitor III, a cathepsin-L-specific inhibitor, inhibited cathepsin-L activity (IC$_{50}$: 2.5 nM). In comparison, glycyrrhizin inhibited SARS-CoV replication, but was difficult to obtain in vivo (EC$_{50}$: 300 μg/mL ~365 μM), whereas valinomycin, a peptidic insecticide K$^+$-transporter, remained as the most potent inhibitor (EC$_{50}$: 0.85 μM) of SARS-CoV replication in Vero cells, and had the highest comprehensive score among the investigated compounds.

Of the ten compounds utilized for validation, six were investigated for the pharmacologic classification and the remaining four for inhibitory potency. Validation of the computational approach for pharmacologic classification revealed low comprehensive scores among abacavir, didanosine, and stavudine are nucleoside RTIs. Abacavir has activity against HIV-1 (HIV-1IIIB EC$_{50}$: 3.7–5.8 μM and HIV-1BaL EC$_{50}$: 0.07–1.0 μM). Moreover, darunavir and lopinavir, both protease inhibitors, had comprehensive scores similar to those of other protease inhibitors (indinavir, nelfinavir, and saquinavir). Similar to darunavir, lopinavir also inhibits the activity of an enzyme critical for the HIV viral lifecycle but has a high likelihood of drug interactions.

Despite the scarcity of literature regarding compounds inhibiting SARS-CoV-2, validation of the computational methods revealed congruence between the calculated comprehensive score and the inhibitory potency against SARS-CoV-2 of the following drugs: chloroquine < lopinavir < ciclesonide < ivermectin. Recently, chloroquine (IC$_{50}$: 9.12 μM) and lopinavir (IC$_{50}$: 7.28 μM) were found to inhibit SARS-CoV-2. In comparison, ciclesonide inhibits (IC$_{50}$: 4.33 μM) and blocks (EC$_{90}$: 6.3 μM) SARS-CoV-2 replication. Lastly, ivermectin (IC$_{50}$: ~2 μM) was effective, with no toxicity observed at all tested concentrations, against SARS-CoV-2.

**CONCLUSION**

The chemical and physical properties of potential and clinically approved antiviral drugs explained their pharmacologic classification and biological activity. Hierarchically weighted principal component analysis elucidated the interaction between the physicochemical properties and SARS-CoV inhibition of these antiviral drugs. The physicochemical properties and inhibitory action against SARS-CoV-2 of lopinavir, chloroquine, ivermectin, and ciclesonide validated the adequacy of the current computational approach. The findings of the present study provide additional information, although further investigation is warranted to identify potential targets and establish exact mechanisms, in the emergent search and design of potential antiviral drug candidates and their subsequent synthesis as effective treatment against SARS-CoV-2.

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This research is registered with the Research Grants Administration Office, University of the Philippines Manila (RGAO-2020-0448) and does not contain any studies with human participants or animals performed by the author.

DATA AVAILABILITY
All data analyzed in the study are included in the manuscript and presented as tables.

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