A preclinical assessment to repurpose drugs to target type 1 diabetes associated type B Coxsackieviruses.

Running title: Antivirals targeting type 1 diabetes associated type B Coxsackieviruses

Amir-Babak Sioofy-Khojine1*, Anni Honkimaa1, Heikki Hyöty1,2

1Department of Virology, Faculty of Medicine and Health Technology, Tampere University, Arvo Ylpön katu 34, FI-33520, Tampere, Finland
2Fimlab Laboratories, Pirkanmaa Hospital District, Tampere, Finland.

*Corresponding author: Amir-Babak Sioofy-Khojine
Phone: 00358(0)503186295
E-mail: Amirbabak.SioofyKhojine@tuni.fi

https://orcid.org/0000-0001-5538-5153

Word count (abstract): 267 words
Word count (main text): 1548 words
Number of tables: 1
Number of figures: 1
Number of supplementary tables: 2

Conflicts of interest
Heikki Hyöty is a minor (<5%) shareholder and the chairman of the board of Vactech Ltd., which develops vaccines against picornaviruses. No other potential conflicts of interest relevant to this article are reported.

What's new?
• Type B coxsackieviruses are associated with type 1 diabetes.
• Although many drugs have shown anti-enterovirus properties, no antiviral drug has currently been licensed specifically for the treatment of enterovirus infections.
• Repurposing antiviral drugs could be an attractive opportunity in type 1 diabetes prevention trials.
• Dose and spectrum tests against type B Coxsackieviruses revealed Hizentra, Enviroxime, Ribavirin, Pleconaril, and Favipiravir would be the best candidates for this strategy.
• Ribavirin and Itraconazole were less effective but were able to impair virus replication.
• Our results can be used to design clinical trials aimed at eradication of persistent infection from the pancreas and preventing/treating type 1 diabetes.
• Using antiviral drugs to treat children with type 1 diabetes will help to elucidate the involvement of enteroviruses, including coxsackieviruses, over the course of the condition.

Acknowledgements
The authors would like to acknowledge Anne Karjalainen, Mervi Kekäläinen, Tanja Kuusela, Maria Ovaskainen, and Eveliina Paloniemi, Tampere University, for their technical assistance. This work was funded by Reino Lahtikari foundation, Sigrid Juselius foundation, The Academy of Finland, and the European Commission (Persistent Virus Infection in Diabetes Network [PEVNET] Frame Program 7, Contract No.
The funding agencies did not design, research, or analyse data and did not contribute to the development process of the manuscript nor the decision to submit it for publication.

Conflicts of interest
Heikki Hyöty is a minor (<5%) shareholder and chairman of the board of Vactech Ltd., which develops vaccines against picornaviruses. No other potential conflicts of interest relevant to this article are reported.

Abstract

Aims
Type 1 diabetes has been linked to enterovirus infections, specifically type B Coxsackieviruses; possibly through a persistent infection in beta cells. To test this hypothesis, antiviral drug treatment is currently being evaluated in a clinical trial, in children with newly diagnosed type 1 diabetes. No antiviral drug has been licensed specifically for the treatment of enterovirus infections. Therefore, repurposing licensed drugs offers an attractive option for facilitating further clinical trials. We systematically screened several antiviral drugs for their efficacy against type B Coxsackieviruses.

Methods
10 drugs with different antiviral mechanisms were analysed for their efficacy against prototype strains of type B Coxsackieviruses in A549 cells. Cell viability was quantified in fixed cells using a colorimetric assay. Median effective dose was interpolated from the triplicated experiments and the dose response curves were generated for each drug-virus combination. Drug cytotoxicity was similarly quantified and selectivity indices calculated.

Results
Hizentra, Pleconaril, Fluoxetine, Norfluoxetine, Ribavirin, Favipiravir, and Guanidine-Hydrochloride were able to abrogate infection by all tested viruses, with the exception of complete inefficacy of Pleconaril against Coxsackievirus B3 and Favipiravir against Coxsackievirus B2. The effective dose for Hizentra, Enviroxime, Ribavirin and Pleconaril were clearly below their therapeutic serum concentrations, while the effective concentration of Fluoxetine, Norfluoxetine and Itraconazole exceeded their therapeutic serum concentrations. Lovastatin and Azithromycin did not efficiently block type B Coxsackieviruses.

Conclusion
Hizentra, Enviroxime, Pleconaril, Ribavirin, and Favipiravir are effective against type B Coxsackieviruses, in vitro in their therapeutic serum concentrations. These antiviral drugs are therefore attractive candidates for type 1 diabetes prevention/treatment trials. They can also be used in other clinical conditions caused by type B Coxsackieviruses.

Keywords
Antiviral drug, Azithromycin, type B Coxsackievirus, Enviroxime, Favipiravir, Fluoxetine, Itraconazole, Immunoglobulin, Lovastatin, Pleconaril, Ribavirin, Repurposing drugs, Type 1 diabetes
Introduction

Type B Coxsackieviruses (CVB) belong to the species Enterovirus-B within the family Picornaviridae, icosahedral non-enveloped RNA viruses with mRNA polarity. CVB include six members (1-6) causing e.g. common-cold, aseptic meningitis, herpangina, myocarditis, pericarditis, and multi-organ life-threatening infections in young infants. They constitute about 24% of all reported enteroviruses (EV) by the National Enterovirus Surveillance System (NESS) 1970-2018 [1]. They have also been linked to chronic dilated cardiomyopathy and chronic fatigue syndrome [2-4].

Type 1 diabetes has also been linked to CVB [5-7]. It has been suggested that a persistent infection in insulin-producing pancreatic beta cells could contribute to the development of type 1 diabetes [8, 9]. Therefore, those antiviral drugs that are effective against CVB could offer an option to prevent/treat type 1 diabetes by eradicating such infections. In fact, to assess this opportunity, newly-diagnosed type 1 diabetes patients are currently being recruited into the DiViDIntervention trial in Norway (EudraCT No. 2015 003350-1), a randomized controlled trial using antiviral drugs [10].

Currently, no antiviral drug has been licensed for the treatment of EV infections, as Pleconaril did not get the approval for treatment of the common cold. Nevertheless, Pleconaril does reduce the mortality in severe EV infections in young infants [11]. In addition, certain drugs that are prescribed for other indications have shown anti-EV activity in vitro, but the effect of these compounds against different members of CVB has not been systematically studied. Therefore, we set out to evaluate the possibility of repurposing clinically used drugs, which have shown activity against at least one EV strain in vitro, to block the infection of all prototype strains of CVB in cell culture. The aim was to identify drugs with broad anti-CVB activity, to facilitate their possible use in the treatment of severe and/or persistent CVB infections and in clinical trials evaluating the possible role of CVB in type 1 diabetes.

We selected drugs targeting different steps in the viral replication cycle, including Pleconaril (a pocket factor replacer and uncoating blocker of EV), Enviroxime (EV 3A blocker), Ribavirin (a nucleoside analogue), Hizentra (an immunoglobulin that contains neutralizing CVB antibodies), Favipiravir (an inhibitor of RNA-dependent RNA polymerases of RNA viruses), Fluoxetine (commercially known as Prozac) and its active metabolite Norfluoxetine (both potential EV 2C blockers), Itraconazole (EV 3A blocker through targeting cellular oxysterol-binding protein), Azithromycin (interferon and interferon-stimulated gene up-regulator), and Lovastatin (possible viral receptor down-regulator or disruptor of the membranes of viral replication organelles). Guanidine Hydrochloride (an EV 2C ligand) was used as a positive control.

Methods

Antiviral activity assay

Mycoplasma-free A549 (human lung carcinoma epithelial, ATCC) cells were used. Cells were maintained in Ham’s F12 media (Sigma-Aldrich) with 10% Fetal Calf Serum (Gibco) and Penicillin-Streptomycin (Gibco) in a humidified chamber with 5% CO₂ at 37°C. Cell monolayers were infected in 96 well plates (Nunc) with 95% confluency in the absence of antibiotics with individual CVB (ATCC prototype strains, Wesel, Germany; supplementary Table 1) with different concentrations of drugs and 10,000 tissue culture infectivity dose 50% of each virus (quantified by Reed and Munch method). Viable plastic-bound cells were fixed-stained at 48 hours post infection using formaldehyde (0.5%)-crystal violate (0.05%) (Electron Microscopy Sciences, Oy FF-Chemicals Ab, Finland) for 20 minutes at room temperature. The intensity of the colour was identified by solubilizing the stained cells using 1% Sodium Dodecyl Sulphate in Phosphate Buffered Saline, for 10 minutes at room temperature and measuring the absorbance of each well at 595nm using an ELISA plate reader (Perkin Elmer Victor2V Multilabel Counter 1420-040). The cell viability (%) was calculated comparing the absorbance values of the test wells to those of mock-infected wells representing 100% cell viability.
Since Hizentra (human immunoglobulin) and Pleconaril interact directly with the virus to block the infectivity, they were incubated with the virus at 37°C for one hour prior to the infection and throughout the post infection period. As recommended (see supplementary Table 2), Azithromycin and Lovastatin were added to the cells 24 hours prior to infection and the other drugs were added on the cells one hour before virus infection (see supplementary Table 1). Control wells included no drug or virus. Drug cytotoxicity was also monitored by analysing cells exposed to the drug without any virus for 48 hours.

Identification and quantification of antiviral effect

Median effective dose (ED$_{50}$), that prevents 50% of cell death due to virus infection, was calculated from the triplicated experiments for each drug and individual viruses. ED$_{50}$ directly demonstrates the efficiency of the drug against individual viruses. The graphs were generated using the viability data and concentrations of the drugs used in the study. The built-in log(agonist) vs. response statistics package, based on a nonlinear regression method in Graph Pad Prism program (version 5.02), was used to generate the graphs. In some cases, the ED$_{50}$ could not be calculated since some drugs did not reach 50% blockage of the virus infection. Cytotoxic concentration 50% (CC$_{50}$, the concentration of the drug that kills half of the cells in uninfected samples) of each drug was also calculated in the absence of the viruses using a similar approach and different concentrations of each drug. The selectivity index (SI = CC$_{50}$/ED$_{50}$), representing the safety profile of the drug related to antiviral dose, was calculated for each drug (Table 1). The program was not able to calculate CC$_{50}$ for Lovastatin. Therefore, the value of the highest Lovastatin concentration used in the assay was used in place of a CC$_{50}$ value. For all drugs a conservative “minimum SI” is presented using the highest concentration of the ED$_{50}$ against CVB. All background information and relevant references for virus strains and the drugs used in the study are reported in supplementary Table 1 and 2.

Results

Individual ED$_{50}$ values for each drug-virus combination are reported in Table 1 and the dose response curves are reported in Fig. 1. Briefly, Hizentra, Pleconaril, Fluoxetine, Norfluoxetine, and Guanidine Hydrochloride were able to abrogate infection by all tested viruses, with the known exception that Pleconaril was not able to block the ATCC strain of CVB3 (Table 1). Ribavirin blocked all viruses but with less than 100% efficacy and was more cytotoxic than any other drug. Lovastatin blocked only CVB2 with lower efficacy than other drugs. Azithromycin only blocked CVB3.

The ED$_{50}$ values (horizontal broken lines crossing the dose response curves in Fig. 1) for Hizentra, Enviroxime, Ribavirin and Pleconaril were clearly below the serum concentrations reached in clinical treatments (vertical lines in Fig. 1), suggesting that the antiviral effect could be reached by the doses recommended for their routine clinical indications. On the other hand, for Fluoxetine/Norfluoxetine and Itraconazole ED$_{50}$ values were higher than the serum concentrations reached by recommended doses (up to 4.5, and 2 times higher, respectively). Lovastatin and Azithromycin performed poorly and did not even reach ED$_{50}$ for many members of CVB. By contrast, Hizentra blocked the infection of all CVB even at low concentrations, therefore the ED$_{50}$ value was not calculated as it was far below the recommended doses used in the clinic. Since Hizentra is a pooled antiserum, its antiviral activity is reached mainly by neutralizing antibodies. Therefore, lower reactivity to CVB6 reflects a generally lower titer of neutralizing antibodies to this virus, that could be due to a low prevalence of CVB6 in human population.

Conclusion

This study characterized the anti-CVB activity of drugs that had already been reported to block some members of EV but not exclusively tested for activity against infection by all members of CVB (proposed to be associated with type 1 diabetes). Hizentra, Enviroxime, Pleconaril, Ribavirin, and in many cases Favipiravir, were highly effective against CVB in vitro at the concentrations reached in serum at their recommended therapeutic doses (identified by other studies shown in Table 1). Therefore, it is possible that these drugs could provide clinical benefits in acute or persistent CVB infections. Further studies, particularly carefully
designed clinical trials, would be needed to explore this possibility among patients with type 1 diabetes. This
has already started with the DIVIDintervention trial on patients newly diagnosed with type 1 diabetes [10].
This unique trial uses a combination of Pleconaril and Ribavirin which were both found to be effective against
CVBs in the present study.

The advantage of the antiviral drugs we currently tested is that their safety profile is already characterized.
For example, as well as potentially causing anaemia, Ribavirin is contraindicated during pregnancy and in the
male partners of women planning pregnancy due to its teratogenic potential [12]. Fluoxetine is not licensed
in children below the age of 7 years because of a greater risk of suicide during the first few months of
treatment and it may also disturb glucose metabolism in diabetic people requiring adjustments to insulin
dosage [12]. Fluoxetine may also induce QT prolongation when used together with e.g. Azithromycin or
Itraconazole [12]. Lovastatin has been contraindicated for use with Itraconazole due to the substantial
increased risk of developing myopathy, rhabdomyolysis, and acute renal failure [12]. Immunoglobulin
(Hizentra) concentrates which have been used off-label for measles prophylaxis and for the prevention of
poliomyelitis before the polio vaccine era, is known to be associated with Thromboembolism [12].

In conclusion, the present study identified several drugs (Hizentra, Enviroxime, Pleconaril, Ribavirin, and
Favipiravir) that could be beneficial in the treatment of CVB infections and which could be useful in type 1
diabetes intervention trials.

**Funding**

This work was funded by Reino Lahtikari foundation, Sigrid Juselius foundation, The Academy of Finland, and
the European Commission (Persistent Virus Infection in Diabetes Network [PEVNET] Frame Program 7,
Contract No. 261441). The funding agencies did not design, research, or analyse data and did not contribute
to the development process of the manuscript nor the decision to submit it for publication.

**Conflicts of interest**

Heikki Hyöty is a minor (<5%) shareholder and the chairman of the board of Vactech Ltd., which develops
vaccines against picornaviruses. No other potential conflicts of interest relevant to this article are reported.

**Acknowledgements**

The authors would like to acknowledge Anne Karjalainen, Mervi Kekäläinen, Tanja Kuusela, Maria
Ovaskainen, and Eveliina Paloniemi from Tampere University, for their technical assistance.

**References**

[1] CDC-USA (May 10, 2018) The National Enterovirus Surveillance System (NESS), USA. Available from:
https://www.cdc.gov/surveillance/ness/pubs.html, accessed 06/06 2019

suggests that some cases of chronic fatigue syndrome result from a previous, inflammatory viral myopathy.

persistent heart muscle infection: quantitative analysis of virus replication, tissue damage, and inflammation.
Proc Natl Acad Sci U S A 89:314-318

chronic fatigue syndrome is associated with the abnormal production of equal amounts of positive and
negative strands of enteroviral RNA. J Gen Virol 71 ( Pt 6):1399-1402


Table 1: Median effective dose (EE$_{50}$) values of each drug for individual viruses. This table presents the ED$_{50}$ and cytotoxicity values showing the spectrum of antiviral activity of the drugs and their safety margin in vitro. A549 cells were used to assess the antiviral activity of prototype strains of all members of CVB. The selectivity index (SI) for each drug has been calculated using the maximum ED$_{50}$ values for CVB1-6 calculated in our study to give a conservative estimate of minimum SI values. The SI for Hizentra was not calculated as enough cytotoxicity to reach CC$_{50}$ could not be generated using this drug.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>$^1$CC$_{50}$ (µM)</th>
<th>Unit</th>
<th>CVB1</th>
<th>CVB2</th>
<th>CVB3</th>
<th>CVB4</th>
<th>CVB5</th>
<th>CVB6</th>
<th>$^3$SI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin</td>
<td>577</td>
<td>µM</td>
<td>NE</td>
<td>NE</td>
<td>32</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>18</td>
</tr>
<tr>
<td>Enviroxime</td>
<td>58</td>
<td>µM</td>
<td>0.2</td>
<td>0.2</td>
<td>0.3</td>
<td>0.1</td>
<td>0.2</td>
<td>0.1</td>
<td>193</td>
</tr>
<tr>
<td>Favipiravir</td>
<td>1069</td>
<td>µM</td>
<td>363</td>
<td>98</td>
<td>141</td>
<td>NE</td>
<td>164</td>
<td>380</td>
<td>2.8</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>60</td>
<td>µM</td>
<td>8.1</td>
<td>5.2</td>
<td>5.7</td>
<td>6.2</td>
<td>3.6</td>
<td>7.1</td>
<td>7</td>
</tr>
<tr>
<td>Guanidine Hydrochloride</td>
<td>1785</td>
<td>µM</td>
<td>4.4</td>
<td>4.2</td>
<td>4.4</td>
<td>2.9</td>
<td>2.8</td>
<td>6.0</td>
<td>297</td>
</tr>
<tr>
<td>Hizentra</td>
<td>NE</td>
<td>mg/ml</td>
<td>0.2</td>
<td>0.04</td>
<td>0.02</td>
<td>NC</td>
<td>NC</td>
<td>1.4</td>
<td>NC</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>2498</td>
<td>µM</td>
<td>5.9</td>
<td>4.0</td>
<td>2.4</td>
<td>6.9</td>
<td>7.2</td>
<td>8.0</td>
<td>312</td>
</tr>
<tr>
<td>Lovastatin</td>
<td>80</td>
<td>µM</td>
<td>NE</td>
<td>0.1</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>NE</td>
<td>800</td>
</tr>
<tr>
<td>Norfluoxetine</td>
<td>90</td>
<td>µM</td>
<td>6.7</td>
<td>4.8</td>
<td>5.5</td>
<td>4.5</td>
<td>3.3</td>
<td>6.3</td>
<td>13</td>
</tr>
<tr>
<td>Pleconaril</td>
<td>3111</td>
<td>µM</td>
<td>0.1</td>
<td>0.5</td>
<td>NE</td>
<td>0.3</td>
<td>0.04</td>
<td>0.3</td>
<td>6222</td>
</tr>
<tr>
<td>Ribavirin</td>
<td>8</td>
<td>nM</td>
<td>620</td>
<td>230</td>
<td>320</td>
<td>300</td>
<td>160</td>
<td>410</td>
<td>13</td>
</tr>
</tbody>
</table>

NE = Not effective  
NC = Not calculated  
$^1$Cytotoxic concentration 50%  
$^2$Median effective dose, values have been interpolated using Prism 5.02  
$^3$Minimum antiviral Selectivity index = CC$_{50}$/Maximum ED$_{50}$ recorded in our study

Figure 1: Dose-response curve for antiviral activity and the cytotoxicity of the tested compounds.

Drug concentrations are presented as Log(10) of either micromolar or mg/ml of the compounds indicated on the X-axis. The Y-axis represents the cell viability (%) compared to the control experiments without the virus but in the presence of the drugs. Log(agonist) vs. response statistics package, based on a nonlinear regression method in Graph Pad Prism program (version 5.02), was used to generate the graphs. The horizontal dotted lines show the ED$_{50}$ values of each drug, where 50% of the cells were kept alive because of the antiviral activity of the drugs. The vertical dotted line in each graph corresponds to the published serum concentrations of the drugs, reached by therapeutic doses of each drug, with their originally designated therapeutic use. The serum concentration for Enviroxime was not available since it was used as topical drops. Instead, the dose of Enviroxime drops has been reported here. For Guanidine Hydrochloride, the serum concentration was not reported since it is not used in humans. In other mice experiments however, the serum values for this compound have been reported. Here, Guanidine Hydrochloride served as a positive control for antiviral effect.
Figure 1: Dose-response curve for antiviral activity and the cytotoxicity of the tested compounds. Drug concentrations are presented as $\log(10)$ of either micromolar or mg/ml of the compounds in the X axis. The Y axis represents the cell viability (%) compared to the control experiments without the virus but in the presence of the drugs. Log (agonist) vs. response statistics package based on nonlinear regression method in Graph Pad Prims program (version 5.02) was used to generate the graphs. The horizontal dotted lines show the ED50 values of each drug where the 50% of the cells kept alive because of the antiviral activity of the drugs. The vertical dotted line in each graph corresponds to the published serum concentrations of the drugs reached by therapeutic doses of each drug for their originally designated use. The serum concentration for Enviroxime was not available since it was used as topical drops and the dose of the drops has been reported here. For Guanidine the serum concentration was not reported since it is not used in human, and here it served as a positive control for antiviral effect; however mice experiments reported the serum values for this compound.
Supplementary Table 1: Summary of virus strains used in the study.

All viruses were ATCC prototype strains.

<table>
<thead>
<tr>
<th>Virus type</th>
<th>Strain</th>
<th>Isolation history</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVB1</td>
<td>Conn-5</td>
<td>Stool from patient with aseptic meningitis, Connecticut, USA, 1948</td>
</tr>
<tr>
<td>CVB2</td>
<td>Ohio-1</td>
<td>Stool from patient with summer grippe, Ohio, USA, 1947</td>
</tr>
<tr>
<td>CVB3</td>
<td>Nancy</td>
<td>Stool from febrile patient with minor illness, Connecticut, USA, 1949</td>
</tr>
<tr>
<td>CVB4</td>
<td>J.V.B. (Benschoten)</td>
<td>Stool from 10-year-old child, New York, USA, 1951</td>
</tr>
<tr>
<td>CVB5</td>
<td>Faulkner</td>
<td>Child with suspected poliomyelitis, Kentucky, USA, 1952</td>
</tr>
<tr>
<td>CVB6</td>
<td>Schmitt</td>
<td>Rectal swab from 25-year-old healthy American male, Luzon, Philippine Islands, 1953</td>
</tr>
</tbody>
</table>

Supplementary Table 2: Summary of the drugs and their use in our study.

The drugs and the methods used to test their antiviral efficacy are presented here. The references cited here are the first reports of the antiviral property of the drugs and the reference for their serum concentrations when used for their clinical indications at the recommended dose. All the serum concentration values have been converted to molarity to be comparable with the reported results of the dose response curves and the ED$_{50}$ and CC$_{50}$ values.

<table>
<thead>
<tr>
<th>Drug name</th>
<th>Provider</th>
<th>Product ID</th>
<th>Concentration (µM)</th>
<th>Reported serum Concentrations</th>
<th>Pre-incubation (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Azithromycin (1)</td>
<td>Sigma</td>
<td>P20007</td>
<td>3.13-100</td>
<td>460 ng/ml (2) 0.6</td>
<td>785.02 24</td>
</tr>
<tr>
<td>Enviroxime (3)</td>
<td>ATI</td>
<td>4933161</td>
<td>0.05-1.5</td>
<td>6.8 µg/ml (4) 19</td>
<td>358.41 1</td>
</tr>
<tr>
<td>Favipiravir (5,6)</td>
<td>CT</td>
<td>C8705</td>
<td>12.5-400</td>
<td>83 µg/ml (7) 528</td>
<td>157.1 1</td>
</tr>
<tr>
<td>Fluoxetine (8)</td>
<td>Sigma</td>
<td>F132</td>
<td>1.56-50</td>
<td>620 ng/ml (9) 1.8</td>
<td>345.79 1</td>
</tr>
<tr>
<td>Guanidine HCl (10)</td>
<td>Sigma</td>
<td>G3272</td>
<td>1.04-10.4</td>
<td>-</td>
<td>95.53 0</td>
</tr>
<tr>
<td>Hizentra (11)</td>
<td>Behring Pharmacy</td>
<td>0.12-4</td>
<td>710 mg/ml (12)</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>Itraconazole (13,14)</td>
<td>Sigma</td>
<td>I6657</td>
<td>0.78-25</td>
<td>2.85 µg/ml (15) 4.0</td>
<td>705.63 1</td>
</tr>
<tr>
<td>Lovastatin (16)</td>
<td>Sigma</td>
<td>1370600</td>
<td>0.01-5</td>
<td>4 ng/ml (17) 0.01</td>
<td>404.54 24</td>
</tr>
<tr>
<td>Norfluoxetine (8)</td>
<td>Sigma</td>
<td>F133</td>
<td>1.56-50</td>
<td>496 ng/ml (9) 1.5</td>
<td>331.76 1</td>
</tr>
<tr>
<td>Pleconaril (18)</td>
<td>Sigma</td>
<td>SMD0307</td>
<td>0.05-5</td>
<td>1.27 µg/ml (19) 3.3</td>
<td>381.35 0</td>
</tr>
<tr>
<td>Ribavirin (20)</td>
<td>Sigma</td>
<td>R9644</td>
<td>80-2500</td>
<td>3.2 µg/ml (21) 10</td>
<td>244.20 1</td>
</tr>
</tbody>
</table>

aMolecular weight of the drug
bConcentration used in the form of topical droplets, not serum concentration
Hydrochloride
Sigma = Sigma-Aldrich
ATI = Advanced Technology and Industrial CO. LTD, Hong Kong
CT = Cellagen Technology, San Diego, USA
Behring = CSL Behring UK Limited
References


