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Letters

An Orally Bioavailable Oxime Ether Capsid Binder with Potent Activity against Human Rhinovirus

Keith G. Watson,*,† Renee N. Brown,†
Rachel Cameron,‡ David K. Chalmers,†
Stephanie Hamilton,‡ Betty Jin,† Guy Y. Krippner,†
Angela Luttick,‡ Darryl B. McConnell,†
Phillip A. Reece,§ Jane Ryan,§
Pauline C. Stanislawski,† Simon P. Tucker,§
Wen-Yang Wu,† Dale L. Barnard,|| and
Robert W. Sidwell||

Biota Chemistry Laboratory, School of Chemistry, Monash University, PO Box 23 Victoria, Australia 3800; Biota Virology Laboratory, Microbiology Department, Monash University, Clayton Victoria, 3800; Biota Holdings, Level 4, 616 St Kilda Road, Melbourne, Victoria, Australia 3004; and Institute for Antiviral Research, Utah State University, Logan, Utah 84322-5600

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Abstract: A series of capsid-binding compounds was screened against human rhinovirus (HRV) using a CPE based assay. The ethyl oxime ether **14** was found to have outstanding anti-HRV activity (median IC_{50} 4.75 ng/mL), and unlike the equivalent ethyl ester compound **3** (Pirodavir), it has good oral bioavailability, making it a promising development candidate. Compound **14** illustrates that an oxime ether group can act as a metabolically stable bioisostere for an ester functionality.

Picornaviruses, particularly human rhinoviruses (HRV), cause approximately one-half of all cases of respiratory tract infection (colds)[1] and are responsible for over 25 million physician visits each year in the United States alone.[2] Although HRV infections are generally self-limiting, they are also associated with several serious upper and lower respiratory tract complications such as otitis media, chronic bronchitis, and asthma.[3] No effective antirhinoviral agent is currently available for the control of HRV, although during the past decade three classes of active compounds have been reported including HRV capsid-binding compounds,[4] RNA synthesis inhibitors of the Enviroxime type,[5] and HRV 3C protease inhibitors.[6] The most advanced compound is the capsid binder Pleconaril (**1**) (Figure 1) which has been shown to shorten the duration of upper respiratory illness in a large Phase III clinical study in adults.[7] However, it was recently announced that the development of Pleconaril for the treatment of HRV has ceased.[7b] We report here the discovery of an orally available HRV capsid binder which is significantly more active than Pleconaril (**1**).

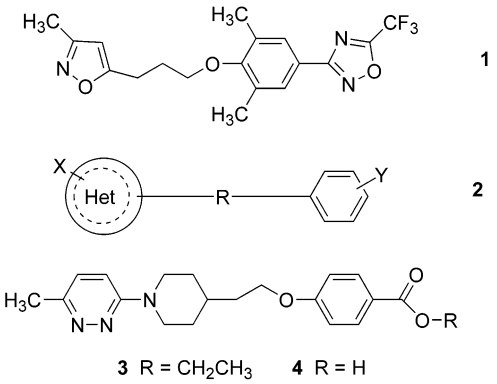

Figure 1. Structures of known HRV capsid binders.

X-ray crystallography has been used to determine the capsid protein structure for several HRV types, and the binding site has been determined for various capsid binders,[8] but the structural information has proved to be of limited use in the design of new inhibitors.[9] The published information about the structure/activity relationships of HRV capsid binders indicates[4,10] that the most active compounds have the general formula **2** wherein the group designated as Het can be a wide

* To whom correspondence should be addressed. New address: Structural Biology Division, Walter & Eliza Hall Institute of Medical Research, 1G Royal Parade, Parkville, Victoria 3050, Australia. Phone: (613) 9345 2113. Fax: (613) 9345 2211. E-mail: kwatson@wehi.edu.au.
† School of Chemistry, Monash University.
‡ Microbiology Department, Monash University.
§ Biota Holdings.
|| Utah State University.

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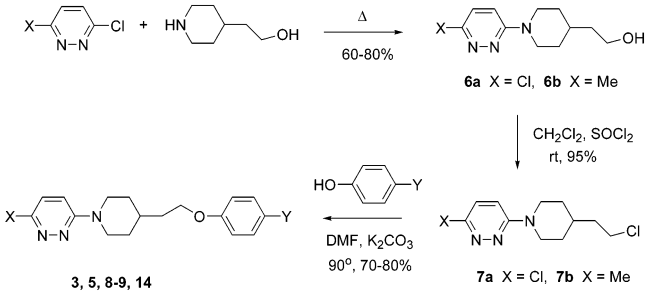
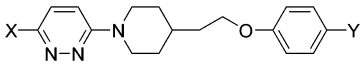
Scheme 1. Synthesis of Pirodavir (**3**) and Related Compounds



range of heterocycles, and the central flexible group R and the phenyl ring substituents can also vary quite widely. On the basis of reported in vitro assay results on a large set of HRV strains, the most active of the known capsid binders is the pyridazine derivative Pirodavir (**3**), which at a concentration of 0.064 μg/mL inhibits 80% of 100 HRV strains.[11] Pirodavir (**3**) undergoes facile hydrolysis of the ester functionality to the inactive acid derivative **4** in vivo[12] and therefore is not suitable for oral use. When used intranasally six times daily against experimental HRV, Pirodavir (**3**) was found to give protection, provided administration was commenced prior to viral exposure.[13] However, intranasal Pirodavir gave no statistically significant benefits in the treatment of naturally occurring HRV colds.[14] It was concluded that the lack of a clinical effect was the result of the poor pharmacokinetic properties of Pirodavir.[15] In 1998 we commenced a medicinal chemistry program to seek new types of capsid binder with high potency and suitable pharmacokinetic properties. We believed from the outset that for widespread acceptance and ease of use, but also to achieve and maintain effective levels of antiviral agent in the tissues of the nasal cavity, it would be vital to develop a compound which can be used orally. We disclose here a new family of compounds which are highly active against a wide range of rhinovirus serotypes in cell-based in vitro assays and we highlight a representative compound which shows good oral bioavailability in animal experiments.[16]

Taking advantage of the published structure/activity data for HRV capsid binders,[4,10,12] we made a variety of novel compounds of general formula **2** and tested them initially on 2 HRV strains using cell culture cytophathic effect (CPE) based assays.[17] Given the high anti-HRV potency but metabolic instability of Pirodavir (**3**), we considered that a particularly important area for exploration was the preparation of analogues of Pirodavir with stable bioisosteres of the ethyl ester group. It has been reported,[18] and our own CPE assays have confirmed, that the chloropyridazine analogue **5** of Pirodavir (**3**) has essentially equivalent anti-HRV activity, and therefore for ease of synthesis we used the chloropyridazine intermediates **6a** or **7a** (Scheme 1) and reacted these with a variety of phenols. We found for example that the aldehyde **8**, ketone **9**, and hydrazide **10** analogues of ester **5** were all much less active (Table 1). Aldehyde **8** was condensed with ethoxyamine to give oxime ether **11** (Scheme 2) which showed remarkably high activity on both test strains HRV-1A and HRV-2. Subsequently, various related aldehyde derivatives were made including the methylhydrazone **12** and propylimine **13**, but all such imine analogues of **11** showed only weak activity.

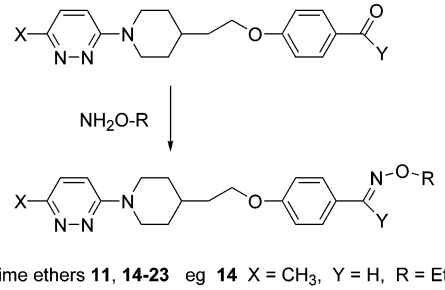
Table 1. Anti-HRV Activity of 4-Substituted Phenoxy Pyridazinamines



compd	X	Y	EC_{50} (μg/mL) HRV-1A[a]	CC_{50} (μg/mL)[b]	EC_{50} (μg/mL) HRV-2[a]	CC_{50} (μg/mL)[c]
3	CH_3	$CO_2CH_2CH_3$	<0.16	>50	<0.05	50
5	Cl	$CO_2CH_2CH_3$	<0.16	>50	<0.05	50
8	Cl	CH=O	9.72	>50	2	20
9	Cl	$C(=O)CH_2CH_3$	<0.16	>50	0.6	7
10	Cl	$CONHNH_2$	8.52	>50	4	20
11	Cl	$CH=NOCH_2CH_3$	<0.16	>50	<0.05	50
12	Cl	$CH=NNHCH_3$	1.01	>50	2	10
13	Cl	$CH=NCH_2CH_2CH_3$	4.12	>50	6	30
Enviroxime			NT	NT	0.009	2

[a] Compounds **3**, **5**, and **8**−**11** were run in a single parallel experiment against each HRV strain. [b] Cellular toxicity/MRC-5 cells. [c] Cellular toxicity/KB cells.

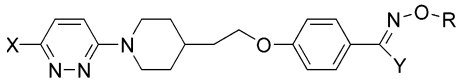
Scheme 2. Synthesis of **14** and Related Oxime Ethers



Using intermediate **6b** we next prepared the ethyl oxime ether analogue **14** of Pirodavir and confirmed that on the two test strains HRV-2 and HRV-14 the anti-rhinovirus activity of **3**, **11**, and **14** are similar (Table 2). We have assigned compounds **11** and **14** as the trans or *E* stereoisomer forms of the oxime ether, and close examination of the ^{1}H NMR spectra and also the thin layer chromatogram of the initially prepared sample of **14** showed the presence of a minor (<10%) product which we believe is the cis or *Z* stereoisomer. Recrystallization of crude **14** allowed isolation of the pure *E* isomer, the ^{1}H NMR spectrum of which confirmed the structural assignment, with the oxime ether vinylic proton being at δ 8.02 compared to δ 7.21 for the minor *Z* isomer.[19] To follow-up the discovery of the high activity of compounds **11** and **14**, we carried out a structure/activity study of the oxime ether group itself. As shown by the data in Table 2 for the oxime ethers **14**−**22**, the anti-HRV activity is very sensitive to alterations of either the acyl function Y or the oxime substituent R, and none of the analogues **15**−**22** were found to be as active as **11** and **14**.

Given the large number of HRV serotypes, it is possible that screening against just two serotypes could be very misleading, but Andries has demonstrated[20] that it is possible to use a panel of 17 representative viruses to accurately predict the median value for all 102 known HRV serotypes. To gain a better evaluation of the breadth of activity of the oxime ethers and to compare with known inhibitors, Pleconaril (**1**) and Pirodavir (**3**), we tested compound **14** against a panel of representative HRV types, including 15 from the

Table 2. Anti-HRV Activity of Compound **14** and Related Oxime Ethers



compd	X	Y	R	EC_{50} (μg/mL) HRV-2[a]	CC_{50} (μg/mL)[b]	EC_{50} (μg/mL) HRV-14[a]	CC_{50} (μg/mL)[b]
11	Cl	H	CH_2CH_3	<0.001	>1	0.002	0.8
14	CH_3	H	CH_2CH_3	0.0003	2	0.001	16
15	CH_3	CH_3	CH_2CH_3	0.01	>1	0.004	>1
16	CH_3	H	CH_3	0.15	>1	0.004	>1
17	CH_3	CH_3	CH_3	0.08	>1	0.023	>1
18	Cl	CH_2CH_3	CH_3	0.4	>1	0.2	0.6
19	Cl	H	$CH_2CH_2CH_3$	0.004	>1	0.01	0.4
20	Cl	H	$CH(CH_3)_2$	0.02	1	0.018	0.7
21	Cl	H	$CH_2CH{=}CH_2$	0.006	0.5	0.006	0.4
22	Cl	H	$CH_2C_6H_5$	0.9	0.6	0.4	0.6
23	CH_3	H	H	>0.25	>0.25	0.062	>0.25
3	CH_3	-	-	0.001	>1	0.0016	>1

[a] Compounds **3**, **11**, and **15**−**22** were run in a single parallel experiment against each HRV strain. [b] Cellular toxicity/KB cells.

Table 3. Activity of Compound **14** against a Representative Panel of HRV Serotypes

HRV serotype	$EC_{50} \pm SD$ (ng/mL) for compound **14**[a]	$EC_{50} \pm SD$ (ng/mL) for Pirodavir (**3**)[a]	$EC_{50} \pm SD$ (ng/mL) for Pleconaril (**1**)[a]
2	$9.23 \pm 8.72^{(37)}$	$2.77 \pm 2.23^{(37)}$	$26.47 \pm 13.84^{(35)}$
9	$1.09 \pm 0.74^{(6)}$	$2.05 \pm 1.05^{(6)}$	$37.16 \pm 15.44^{(6)}$
14	$1.78 \pm 3.05^{(37)}$	$3.65 \pm 1.95^{(38)}$	$34.31 \pm 15.57^{(37)}$
15	$7.77 \pm 2.84^{(9)}$	$7.92 \pm 2.92^{(9)}$	$69.80 \pm 10.19^{(8)}$
16	$11.12 \pm 5.86^{(8)}$	$15.24 \pm 6.25^{(8)}$	$108.03 \pm 44.55^{(3)}$
29	$5.99 \pm 4.13^{(6)}$	$3.74 \pm 2.59^{(6)}$	$45.40 \pm 29.27^{(6)}$
39	$2.89 \pm 2.86^{(6)}$	$1.80 \pm 1.92^{(6)}$	$44.88 \pm 7.78^{(6)}$
45	$>5000^{(2)}$	$>5000^{(2)}$	$1908.35 \pm 910.19^{(4)}$
51	$2.90 \pm 2.15^{(4)}$	$5.21 \pm 4.50^{(6)}$	$30.40 \pm 16.95^{(6)}$
59	$5.08 \pm 2.93^{(6)}$	$4.37 \pm 3.17^{(6)}$	$387.33 \pm 314.13^{(6)}$
63	$2.06 \pm 2.18^{(9)}$	$0.83 \pm 0.57^{(7)}$	$62.30 \pm 13.98^{(8)}$
70	$3.13 \pm 1.61^{(10)}$	$2.14 \pm 0.71^{(10)}$	$53.87 \pm 14.16^{(8)}$
72	$21.01 \pm 8.93^{(6)}$	$34.77 \pm 6.07^{(6)}$	$468.70 \pm 299.52^{(6)}$
85	$7.90 \pm 6.94^{(6)}$	$4.72 \pm 5.59^{(6)}$	$34.00 \pm 30.56^{(6)}$
86	$4.42 \pm 2.25^{(6)}$	$9.56 \pm 6.72^{(6)}$	$70.04 \pm 17.23^{(6)}$
89	$0.83 \pm 0.71^{(6)}$	$5.70 \pm 1.90^{(6)}$	$29.33 \pm 45.99^{(6)}$
median	4.75	4.54	49.63

[a] The superscript number is the number of separate assays used to calculate the EC_{50} and standard deviation (SD).

Andries panel, and the results are shown in Table 3. The anti-HRV data for oxime ether **14** shows that the compound is very similar to the ester **3** in the level and spectrum of activity. For example, both compounds are inactive on HRV-45, only moderately active on HRV's 16 and 72, but highly active on HRV's 9, 39, and 63. Compound **14** has also been tested on a range of enterovirus types and was found to inhibit echoviruses (EC_{50} 0.2−9.0 μg/mL), polioviruses (EC_{50} 0.2−3.0 μg/mL), and coxsackie A and B viruses (EC_{50} 0.59−10.0 μg/mL). Overall the antiviral data is consistent with our assumption that compounds **3** and **14** occupy a very similar position in the HRV capsid pocket and that the oxime ether group in **14** is acting as a bioisostere for the ethyl ester moiety in **3**. Recent reviews on bioisosterism[21] describe relatively few functional group alternatives to the ester moiety and do not mention oxime ethers as potential bioisosteres for esters. To our knowledge the only previous example of oxime ether/carboxylic ester bioisosterism is in the field of muscarinic agonists.[22]

As a first experiment to test the oral availability and metabolic stability of compound **14**, single oral doses of **14** or Pirodavir (**3**) (33 mg/kg) were given to separate groups of mice ($n = 5$), sera was taken from individual animals at several time points from 0.5 to 12 h, and then the sera was assayed for anti-HRV-2 activity using a CPE inhibition assay in KB cells run in 96-well microplates.[17] The sera from animals dosed with oxime ether **14** showed strong antiviral activity in all samples up to the 6 h time point. Thus, for example, at the 1 and 6 h time points the required mean serum dilution factors to give an EC_{50} effect were 7412 (±4757) and 304 (±198), respectively. In contrast, the sera taken from animals dosed with Pirodavir (**3**) showed no anti-HRV activity at all time points when tested at the minimum 10-fold dilution. The experiment thus confirmed that compound **14** has much higher oral availability and in vivo stability than Pirodavir.

Table 4. Pharmacokinetic Parameters of **14** Following iv Administration to Rats[a]

parameter	male[b]	female[b]
$C_{(t)}$ (μg/mL)	12.1 ± 3.5	10.2 ± 1.4
AUC (μg h/mL)	16.86	20.95
$t_{1/2}$ (h)	3.09	3.76
CL (L/h/kg)	0.56	0.43
V_z (L/kg)	2.51	2.31

[a] Compound was formulated as a solution in 10% DMSO in Intralipid 20 and administered at 10 mg/kg. [b] $n = 3$.

To determine the pharmacokinetic behavior in vivo, the oxime ether **14** was administered to rats by oral gavage or intravenous injection, and blood samples were collected at intervals up to 48 h postdose. There were no deaths and no treatment-related effects on body weight or clinical observations. The plasma was analyzed by LC/MS for the concentration of **14**, and the calculated pharmacokinetic parameters are summarized in Tables 4 and 5. Compound **14** is cleared rapidly following intravenous administration and has a relatively short half-life. The apparent volume of distribution is large relative to the plasma volume of the rat, indicating extensive distribution into tissues which is consistent with the lipophilic properties of **14**. Absorption of **14** is protracted following oral administration with maximal concentrations reached at 8 and 1 h postdose for males and females, respectively. For both sexes, plasma concentrations remained close to peak levels over the period 30 min to 12 h postdose with concentration ranges of 2.4−4.5 μg/mL for males and

Table 5. Pharmacokinetic Parameters of **14** Following Oral Administration to Rats[a]

parameter	male[b]	female[b]
C_{max} (μg/mL)	4.5 ± 0.7	4.70 ± 1.6
T_{max} (h)	8.0	1.0
AUC (μg h/mL)	62.28	80.10
$t_{1/2}$ (h)	5.36	-[c]
bioavailability (%)	61.6	63.7

[a] Compound was formulated as a suspension in 1% methylcellulose and administered at 60 mg/kg. [b] $n = 3$. [c] Insufficient time points to accurately estimate $t_{1/2}$.

3.5−4.7 μg/mL for females. Bioavailability was approximately 62−63% for both males and females.

In conclusion, we have discovered a promising new type of antipicornaviral compound with outstanding potency and broad-spectrum anti-HRV activity. Using an ethyl oxime ether group to replace an ester functionality we have completely retained the antiviral activity of Pirodavir (**3**) and at the same time overcome the lack of oral availability. Thus the ethyl oxime ether acts as an excellent bioisostere for an ethyl ester group, and the good oral availability of compound **14** provides encouragement for detailed evaluation and development of an HRV inhibitor of this type.

Supporting Information Available: Experimental details including synthetic methods, physical data for new compounds, and details of the CPE assay method and pharmacokinetic evaluation. This material is available free of charge via the Internet at http://pubs.acs.org.

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