Non-nucleoside Inhibitors of the Measles Virus RNA-Dependent RNA Polymerase: Synthesis, Structure−Activity Relationships, and Pharmacokinetics

J. Maina Ndungu,[†] Stefanie A. Krumm,[‡] Dan Yan,[‡] Richard F. Arrendale,[†] G. Prabhakar Reddy,[†] Taylor Evers,[†] Randy Howard,[†] Michael G. Natchus,[†] Manohar T. Saindane,[†] Dennis C. Liotta,[†,§] Richard K. Plemper,[‡,∥] James P. Snyder,[†,§] and Aiming Sun*,[†]
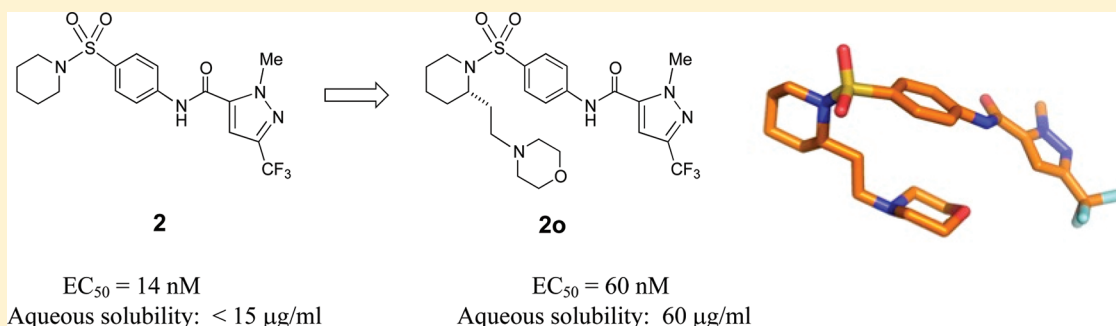
[†]Emory Institute for Drug Discovery, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322, United States
[‡]Department of Pediatrics, Emory University School of Medicine, 2015 Uppergate Drive, Atlanta, Georgia 30322, United States
[§]Department of Chemistry, Emory University, 1515 Dickey Drive, Atlanta, Georgia 30322, United States
[∥]Children's Healthcare of Atlanta, 2015 Uppergate Drive, Atlanta, Georgia 30322, United States

S *Supporting Information*

2
EC_{50} = 14 nM
Aqueous solubility: < 15 µg/ml

2o
EC_{50} = 60 nM
Aqueous solubility: 60 µg/ml

ABSTRACT: The measles virus (MeV), a member of the paramyxovirus family, is an important cause of pediatric morbidity and mortality worldwide. In an effort to provide therapeutic treatments for improved measles management, we previously identified a small, non-nucleoside organic inhibitor of the viral RNA-dependent RNA polymerase by means of high-throughput screening. Subsequent structure−activity relationship (SAR) studies around the corresponding pyrazole carboxamide scaffold led to the discovery of **2** (AS-136a), a first generation lead with low nanomolar potency against life MeV and attractive physical properties suitable for development. However, its poor water solubility and low oral bioavailability (F) in rat suggested that the lead could benefit from further SAR studies to improve the biophysical characteristics of the compound. Optimization of in vitro potency and aqueous solubility led to the discovery of **2o** (ERDRP-00519), a potent inhibitor of MeV (EC_{50} = 60 nM) with an aqueous solubility of approximately 60 µg/mL. The agent shows a 10-fold exposure (AUC/C_{max}) increase in the rat model relative to **2**, displays near dose proportionality in the range of 10−50 mg/kg, and exhibits good oral bioavailability (F = 39%). The significant solubility increase appears linked to the improved oral bioavailability.

■ INTRODUCTION

The paramyxoviruses family is comprised of nonsegmented, negative strand ribonucleic acid (RNA) viruses that are primarily responsible for acute respiratory diseases. The family includes major human and animal pathogens such as measles virus (MeV), human parainfluenza virus (HPIV), mumps virus, respiratory syncytial virus (RSV), and the Newcastle disease virus. Despite the existence of an effective vaccine protecting against MeV infection, we have witnessed in the recent past an increasing number of cases particularly in the developed world.[1,2] For example, in the United States from January 1 through May 21 of 2011, 118 cases were reported across 23 states according to the CDC. Recently, in Ashland, Oregon, 25−30% of children entering kindergarten were unvaccinated.[3] This has been attributed to elected exemption from vaccination on the basis of philosophical or religious beliefs. Vaccination rates in Europe in recent years have never fully recovered from a discredited 1998 British study linking the vaccine for measles, mumps, and rubella to autism. At that time, parents, particularly in the United Kingdom, abandoned the vaccine followed by precipitous drop in vaccination rates. For 2011, the World Health Organization reported 4937 cases of measles between January and March in France alone, as compared with 5090 cases during all of 2010. The World Health Organization reports that as of October, there have been 26000 measles cases and nine deaths in Europe since the start of 2011, rendering it the worst year for MeV activity in the Western World since 1996.[4]

1 (16677)   **2** (AS-136a)   **2o** (ERDRP-00519)
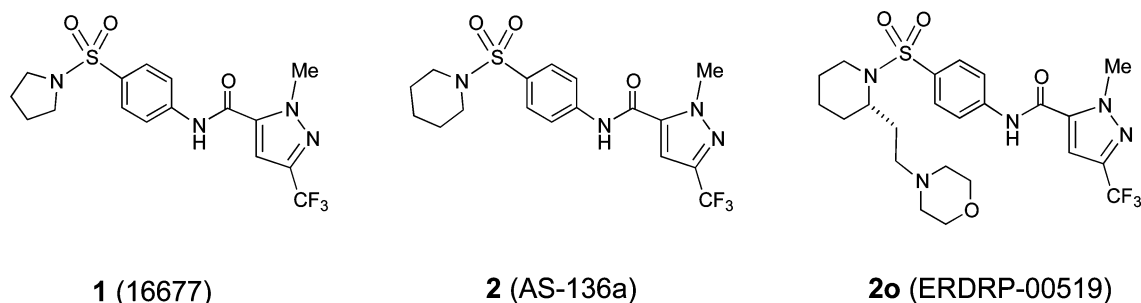
Figure 1. Structures of hit and lead compounds.

Measles is not currently treatable by drug therapy. Ribavirin, a nucleoside-based antiviral agent, is the only small molecule drug approved for paramyxoviruses (RSV) therapy.[5,6] However, efficacy is limited. To improve case management of severe measles and achieve rapid control of outbreaks through postexposure prophylaxis, the development of an effective antimeasles drug is highly desirable.[7] We previously reported the discovery of an MeV inhibitor targeting the viral RNA-dependent RNA polymerase (RdRp) complex by means of cell-based high-throughput screening (HTS).[8,9] Iterative optimization of a corresponding series of pyrazole carboxamides, exemplified by hit **1** (16677), led to the first-generation lead molecule **2** (AS-136a) (Figure 1).[10,11] The latter piperidine derivative exhibits superior in vitro cellular potency against MeV with nanomolar 50% effective concentrations (EC_{50}). The compound was also subjected to a number of in vitro toxicity and metabolism assays. There, the agent was found to be nonmutagenic in a non-GLP in vitro bacterial reverse mutation (Ames) assay, and it did not block hERG channels at a concentration of 10 μM or below. Compound **2** shows moderate metabolic stability in mouse and human S9 fractions after 1 h of incubation with 79 and 69% parent remaining, respectively. However, poor solubility and low rat plasma concentrations of **2** might hamper its in vivo efficacy. In an effort to improve pharmacological properties of **2**, in particular water solubility, we initiated a structure–activity relationship (SAR) study to identify a suitable solubilizing group. Earlier efforts had shown that the piperidine ring is amenable to chemical manipulation without adversely affecting activity. However, any changes to the central ring or the pyrazole group of **2** are detrimental to potency.[11] Consequently, the present study focuses on appending a solubilizing group to the piperidine ring or replacing it with either a substituted phenyl or an alicyclic group. This led to the identification of compound **2o** (ERDRP-00519, Figure 1), which has significantly improved water solubility, while retaining high antiviral potency. The agent shows a 10-fold exposure (AUC/C_{max}) increase in rat relative to **2** and displays near dose proportionality in the range of 10–50 mg/kg. The significant solubility increase appears to contribute to the improvement in oral bioavailability. We describe herein the synthesis and a SAR strategy that led to the discovery of **2o** as well as the pharmacokinetic comparison of first- and second-generation lead candidates.

■ CHEMISTRY

Synthesis of Substituted Piperidine Analogues. Our previous work showed that introduction of a piperidine moiety resulted in compounds that were about 10 times more active than the corresponding pyrrolidine analogues.[10] Accordingly, linkers were installed at the 2-, 3-, and 4-positions of the piperidine ring to explore which position could best accommodate

hydrophilic substituents while maintaining potency. Reaction of different amino alcohols (**4a−c**) with 4-nitrobenzene sulfonyl chloride (**5**) followed by formation of methoxymethyl (MOM) ethers and reduction of the nitro group afforded anilines **7a−c**. Coupling of acid chloride **8**, derived from 3-trifluoromethyl pyrazole using the method of Lahm,[12] with anilines **7a−c** provided analogues **1a−c** (Scheme 1). With preliminary data showing the 2-position of the piperidine to yield more active compounds as compared to the 3- or 4-position (Table 1), additional analogues of the previously reported 2-piperidinemethanol compound **2a**[13] were prepared by a sequence similar to that depicted in Scheme 1.

Further analogues were prepared by PCC oxidation of **6a** to obtain aldehyde **14**, which was subjected to reductive amination with morpholine followed by the procedures illustrated in Schemes 2 to ultimately give analogue **2b**. Tosylation of **6a**, reduction of the nitro group, coupling with acid chloride **8**, and displacement of the tosylate with an azide furnished **2c**. Reduction of the azide, dimethylation of the resultant amine, or acylation resulted in compounds **2d−f**. Further extension of the side chain including both saturated and unsaturated derivatives could be achieved from aldehyde **14**. Horner–Wadsworth–Emmons olefination of **14** gave **12**. Union of **12** with acid chloride **8** afforded analogue **2g**, which was then reduced with DIBAL-H to obtain analogue **2h**. Hydrogenation of **2g** delivered the saturated analogue **2i**, which was converted to **2j** by treatment with DIBAL-H (Scheme 2).

Preparation of two-carbon side chain analogues was accomplished by utilizing 2-(2-piperidinyl) ethanol **9**. Direct coupling of the latter with *p*-nitro-benzenesulfonyl chloride **5** gave low yields of the desired product due to further coupling of the product with the sulfonyl chloride. To circumvent this shortcoming, the NH and OH groups of **9** were protected using benzyl chloroformate[14] and *t*-butyldimethylsilyl chloride (TBSCl), respectively. Deprotection of the amine, coupling with **5**, and reduction of the nitro group afforded aniline **11**. Coupling of **11** with acid chloride **8** followed by cleavage of the silyl group furnished alcohol **2k**, which, when subjected to Swern oxidation and reductive amination with morpholine, gave **2n** (Scheme 3). Pure enantiomer **2o** was then prepared similar to **2n** starting from (*S*)-2-piperidine ethanol.

We hypothesized that attaching an ethylene glycol moiety would give compounds with better aqueous solubility. Because of the instability of **6a** under basic conditions, the synthesis of **2p** was initiated by addition of a rhodium carbenoid across the hydroxylic O−H bond[15,16] to form an ether bond. Thus, decomposition of ethyl diazoacetate in the presence of Rh_2OAc_4 generated a carbenoid that inserted into the OH bond to give **13**. Reduction of the nitro group of **13** followed by coupling with **8** afforded analogue **2p**, which on hydrolysis of the ester

Scheme 1. Exploring the Optimal Substitution Position on the Piperidine Ring[a]

4a: position=2
4b: position=3
4c: position=4

6a-c

7a-c

2a

1a: position=2
1b: position=3
1c: position=4
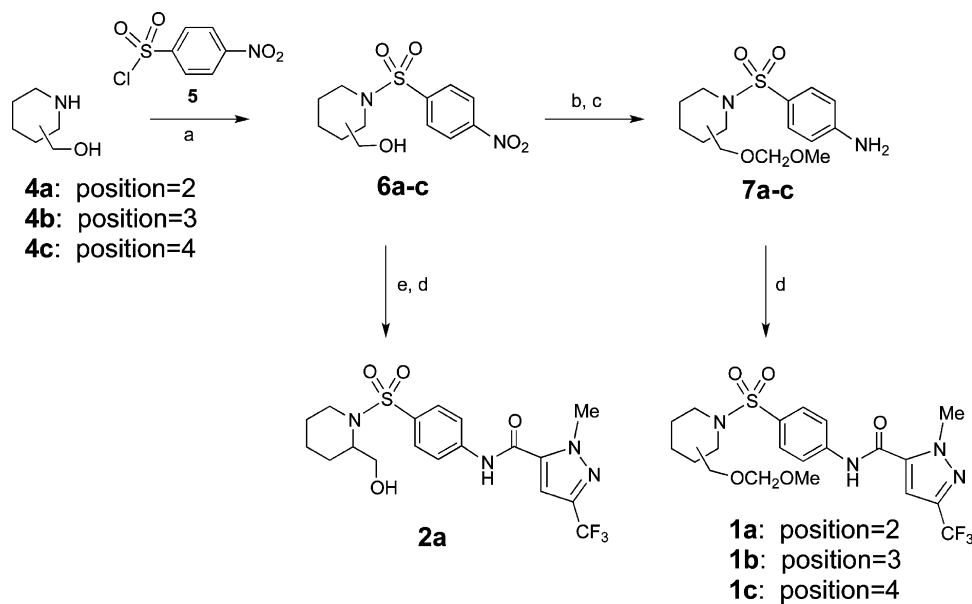
[a]Reagents and conditions: (a) Na$_2$CO$_3$, acetone. (b) MOMCl, *i*-Pr$_2$NEt, CH$_2$Cl$_2$. (c) SnCl$_2$. 2H$_2$O, EtOAc. (d) [structure] (**8**), pyridine, CH$_2$Cl$_2$. (e) H$_2$ (50 psi), Pd−C, MeOH.

and BOP/NaBH$_4$[17] mediated reduction of the resultant carboxylic acid, provided **2q** (Scheme 4).

Synthesis of the Phenyl Series. Replacement of the piperidine ring with phenyl or substituted phenyl via the general route shown in Scheme 5 was also explored. Unsubstituted phenyl analogue **3a** was found to be as active as lead compound **2**, triggering an SAR study of the series (Table 2). Coupling of 2-methoxylthiophenol **16a** with 1-fluoro-4-nitrobenzene[18] followed by oxidation of sulfur using *meta*-chloroperoxybenzoic acid (mCPBA) gave the corresponding sulfone. The nitro group was reduced followed by coupling with acid chloride **8** to furnish analogue **3b**. Demethylation of **3b** with BBr$_3$ afforded phenol analogue **3c**, which upon acylation gave analogue **3d**. Similarly, coupling of 2-bromothiophenol **16b** with 1-fluoro-4-nitrobenzene afforded **17**. To make additional analogues of the phenyl series, we envisioned utilizing bromide **17** to append substituents. However, attempts to lithiate bromide **17** using *n*-BuLi or *t*-BuLi were unfruitful, resulting in decomposition of the bromide. Stille coupling offered an alternative. When **17** was treated with tributyl(vinyl)tin in the presence of Pd(PPh$_3$)$_4$, the desired coupling product **18** was obtained in 80% yield. Reduction of the nitro group followed by coupling with acid chloride **8** afforded analogue **3e** (Scheme 5 and Table 2). Subjecting olefin **18** to osmium tetroxide-mediated oxidative cleavage of the double bond gave aldehyde **19**, a compound utilized in the synthesis of additional analogues. Reduction of the aldehyde, SnCl$_2$ reduction of the nitro group, and protection of the alcohol as a silyl ether gave aniline **20**. Coupling of **20** with acid chloride **8** followed by cleavage of the silyl group furnished analogue **3f**. Aldehyde **19** was also used for the synthesis of morpholine **3g** by means of reductive amination, followed by reduction of the nitro group and coupling with acid chloride **8** (Scheme 5).

Single Dose Antiviral Activity of Analogues of 2. To better understand the potency profile of compound **2**

analogues, the most active analogues were subjected to a MeV yield assay at a single concentration of 1.0 μM to generate data points for comparison with **2** (Figure 2).

■ RESULTS AND DISCUSSION

The SAR data are summarized in Tables 1 and 2 for the piperidine and phenyl series, respectively. From previous experience, we have learned the necessity of preserving the structure of the phenyl, amide, and fluorinated pyrazole units of the molecule to maintain antiviral potency. Modification of either the 3-trifluoromethyl-pyrazole or the central phenyl ring in most cases leads to significant loss of activity.[10,11] All analogues listed in Tables 1 and 2 incorporate only variations on the left side of lead molecule **2**. The MOM ether analogues (**1a−c**) demonstrate a trend whereby substitution at C-2 of piperidine is favored. The 2-piperidine **1a** is 2-fold more potent than the corresponding 3-piperidine, while the 4-substituted derivatives reduce activity by almost 10-fold (**1a**, **1b**, and **1c**, Table 1). Piperidines bearing a hydroxyl group, elongation of the pendant chain from one carbon to two does not adversely affect potency as exemplified by compounds **2a** and **2k**.

Further extension to three carbons leads to a decrease in activity by 3-fold (**2j**, Table 1). Introduction of basic amines led to significant reduction or complete loss of activity (**2d** and **2f**, EC$_{50}$ = 55.0 and >150 μM, respectively). Replacement of the amino groups with a less basic morpholine (**2b** and **2n**) restored good potency. Esters **2g** and **2i** were found to be 2-fold less active by comparison with the corresponding alcohols (**2h** and **2j**, Table 1). There is a clear superiority of *S*-chirality over *R*- as demonstrated by the 3-fold loss of activity for **2l** compared to **2m**. For the phenyl series, analogue **3a** is as active as the lead compound in reducing virus-induced cytopathicity, and its activity is comparable to that of methoxy **3b** and alcohol **3f** (Table 3). However, the morpholine analogue **3g** loses activity completely, which stands in significant contrast to

Table 1. MeV Antiviral Action (CPE) of the Piperidine Series of Analogues (EC$_{50}$)

Comp.	R	EC$_{50}$ (μM)^a (MV-Alaska) (CPE inhib.)	Comp.	R	EC$_{50}$ (μM)^a (MV-Alaska) (CPE inhib.)
2	-H	2.0	**2h**		3.7
1a		1.5	**2i**		6.7
1b		3.8	**2j**		2.7
1c		16.0	**2k**		2.7
2a		2.8	**2l**		8.3
2b		9.3	**2m**		3.1
2c		1.5	**2n**		4.6
2d		55.0	**2o**		2.5
2e		14.0	**2p**		25.0
2f		>150.0	**2q**		8.3
2g		6.8			

^{a}Values represent averages of four experiments; the highest concentration assessed is 150 μM.

alterations in the piperidine series (**2b** and **2n**). The previous SAR and that derived from the current three series of MeV-RdRp inhibitors suggests a highly hydrophobic environment on the target protein housing the left part of the molecules, strongly disfavoring hydrogen bonding. To explore whether poor aqueous solubility contributes to the low oral bioavailability that was observed with the existing lead **2**, we measured the aqueous solubility for some of the more potent derivatives via nephelometry (buffer, pH = 7.4, Table 3). Compound **2** and phenyl analogue **3a** show equally poor solubility with values at 15 and 22 μg/mL, respectively. The alcohol analogues **2a** and **2k** both deliver improved solubility as expected with measured values at 61 and 62 μg/mL, respectively. Importantly, the morpholine analogue **2n** also furnishes similar solubility as compared with the corresponding free alcohol derivative **2k**. Compounds with moderate solubility (~60 μg/mL) and good potency (<3.0 μM) in the CPE assay were advanced to assessment of virus yield reduction. The primary alcohol derivative **2k** (EC$_{50}$ = 2.7 μM, CPE assay; solubility 62 μg/mL) delivers an

EC$_{50}$ of 100 nM in this assay (**2k**; Table 3). Optically pure analogues of compound **2k**, **2l**, and **2m** both delivered slightly decreased potency (EC$_{50}$ = 8.3 and 3.1 μM, respectively, CPE assay). Replacement of the hydroxyl group with morpholine led to racemate **2n** with an EC$_{50}$ of 4.6 μM, while the corresponding optically pure analogue **2o** provided an EC$_{50}$ of 2.5 μM in the CPE assay, 60 nM in the virus yield reduction assay, and solubility around 60 μg/mL (**2o**; Table 3).

Considering the significant potencies of **2k** and **2o** in the virus yield reduction assay (EC$_{50}$ = 100 and 60 nM, respectively), we selected these two compounds for comparison with **2** in a pharmacokinetic (PK) study in Sprague−Dawley rats.

■ PK PROFILES

Figure 3 shows oral PK parameters of compounds **2k** and **2o** in comparison with the first generation lead **2**; a summary of the numerical PK analysis is provided in Table 4. Compound **2o** shows a 10-fold exposure (with respect to both AUC and C$_{max}$) increase in the rat model relative to **2** and displays good dose

Scheme 2. Synthesis of Three-Carbon Substituents at the Piperidine C-2 Position[a]
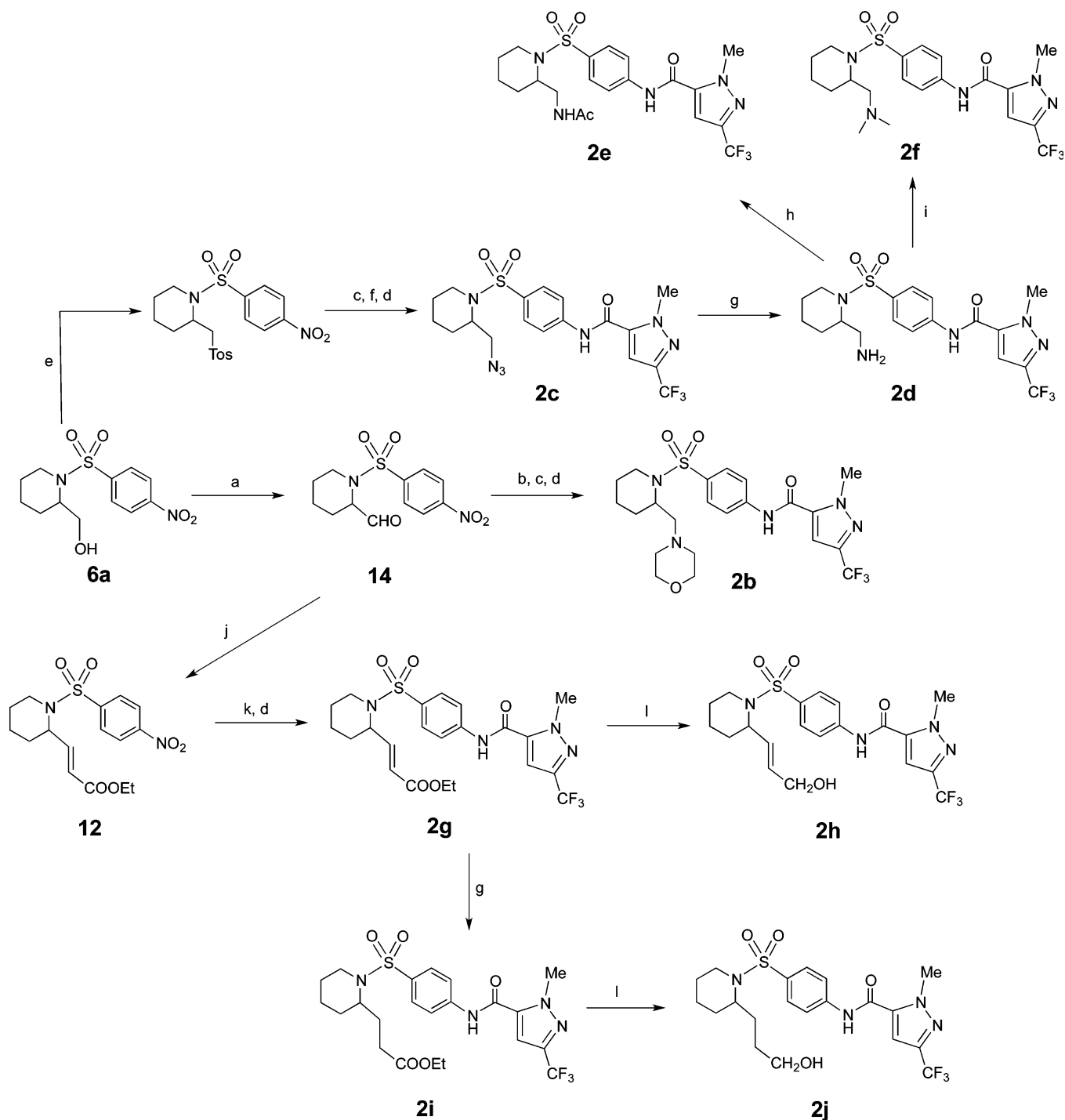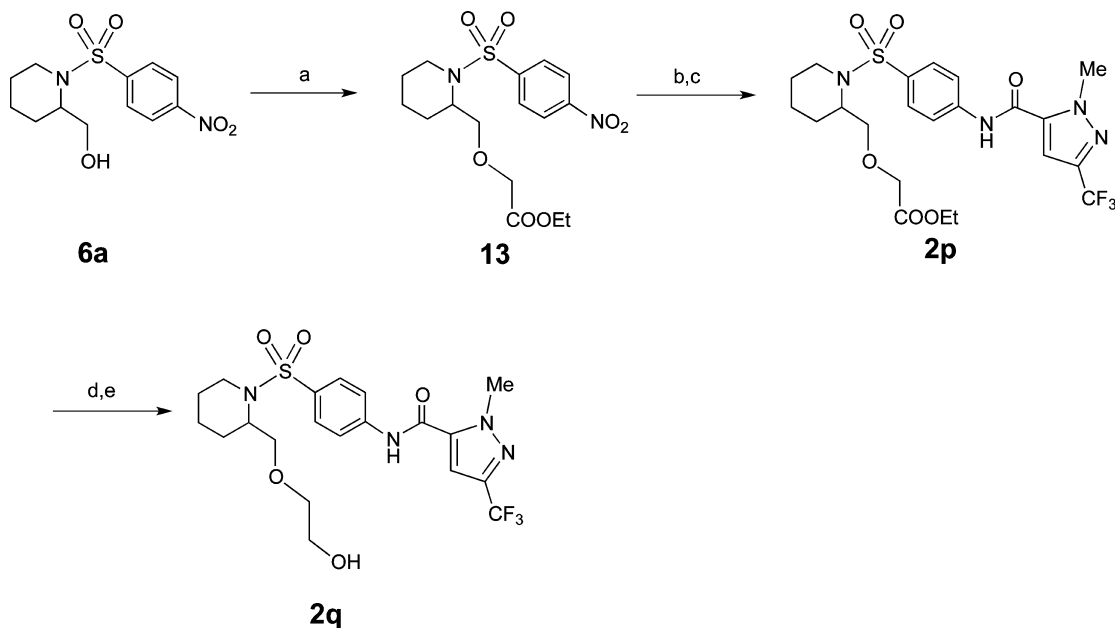

[a]Reagents and conditions: (a) PCC, CH$_2$Cl$_2$. (b) Morpholine, NaBH(OAc)$_3$, CH$_2$Cl$_2$. (c) SnCl$_2$·2H$_2$O, CH$_2$Cl$_2$/MeOH. (d) Compound **8**, *i*-Pr$_2$NEt, CH$_2$Cl$_2$. (e) 4-Toluenesulfonyl chloride, CH$_2$Cl$_2$. (f) NaN$_3$, DMF, 120 °C. (g) H$_2$, Pd/C, MeOH. (h) AcCl, *i*-Pr$_2$NEt, CH$_2$Cl$_2$. (i) CH$_3$I, K$_2$CO$_3$, DMF. (j) *t*-BuOK, Et$_2$P(O)CH$_2$COOEt, THF/CH$_2$Cl$_2$. (k) SnCl$_2$·2H$_2$O, EtOAc. (l) DIBAL-H, THF.

proportionality in the range of 10−50 mg/kg. In contrast, the primary alcohol analogue **2k** reveals a good C_{max} and AUC at 50 mg/kg dosing, but it generates poor plasma concentrations in rat and nonproportionality possibly due to high first-pass metabolism of the primary alcohol. On the basis of its high in vitro potency, good solubility, and PK profile, the oral bioavailability of compound **2o** was assessed. The compound was dosed at 2 mg/kg iv and 10 mg/kg po in rat and exhibits good oral bioavailability

($F = 39\%$) (Figure S1 and Table S1 in the Supporting Information). In the Caco-2 bidirectional permeability assay, both **2** and **2o** showed high permeability with an efflux ratio of 1.1 and 2.6, respectively, which indicates that they are probably not a substrate for p-glycoprotein in humans (Figure S2 in the Supporting Information).[19,20] However, compound **2o** proved to be less stable in human liver S9 fractions after 1 h of incubation. Only 24% of the parent remains as compared with 69% for compound **2**.

Scheme 3. Introduction of a Two-Carbon Tether at the Piperidine C-2 Position[a]
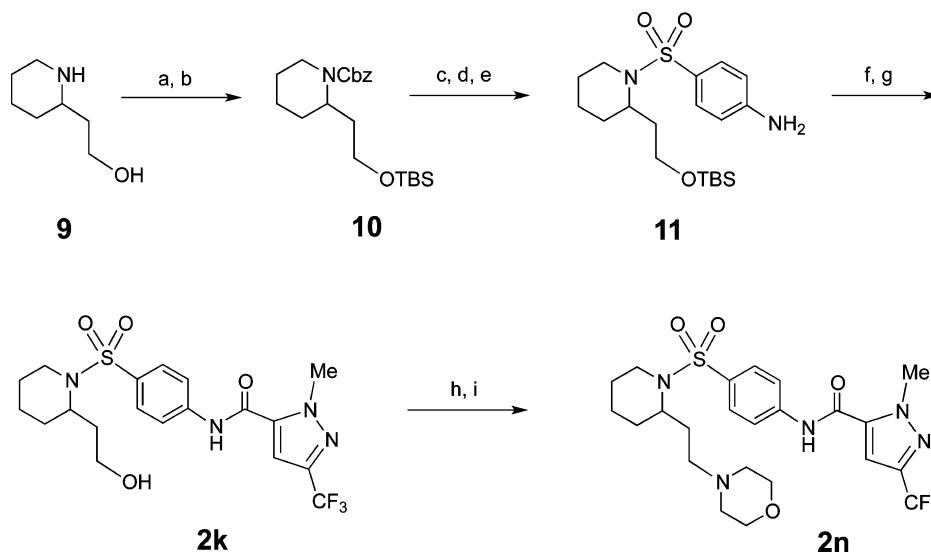
[a]Reagents and conditions: (a) Na$_2$CO$_3$, BzOCOCl, H$_2$O/acetone. (b) TBSCl, imidazole, DMF. (c) H$_2$, Pd/C, ethanol. (d) Compound **5**, i-Pr$_2$NEt, CH$_2$Cl$_2$. (e) H$_2$ (40 psi), Pd/C, ethanol. (f) Compound **8**, i-Pr$_2$NEt, CH$_2$Cl$_2$. (g) TBAF, THF. (h) (COCl)$_2$, DMSO, CH$_2$Cl$_2$. (i) Morpholine, NaBH(OAc)$_3$, CH$_2$Cl$_2$.

**Scheme 4. Synthesis of O-Alkylated Analogues**[a]

[a]Reagents and conditions: (a) Ethyl diazoacetate, Rh$_2$OAc$_4$, CH$_2$Cl$_2$. (b) H$_2$, Pd/C, MeOH. (c) Compound **8**, i-Pr$_2$NEt, CH$_2$Cl$_2$. (d) NaOH, THF/H$_2$O. (e) BOP, i-Pr$_2$NEt, THF, NaBH$_4$.

Mechanism of Action of 2o. We previously demonstrated that compound **2** blocks MeV RdRp activity by targeting the viral polymerase (L) protein.[11] To test whether this mechanism of activity likewise extends to lead molecule **2o**, a plasmid-based mini-replicon assay[21] was employed to assess RdRp activity in the presence of **2o** and **2**, respectively. BSR-T7/5 cells were transfected with plasmid DNA encoding MeV-L, N, P, and the firefly luciferse mini-genome reporter construct, and the cells were incubated in the presence of different inhibitor concentrations or vehicle for control. Relative luciferase activities in cell lysates were assessed 36 h post-transfection, and dose–response inhibition curves were generated. For both compounds,

we observed a dose-dependent inhibition of viral RdRp activity with virtually identical potency (Figure 4), supporting a comparable mechanism of antiviral activity.

■ **SUMMARY**

Modification and replacement of the piperidine moiety in the first-generation lead **2**, derived from our MeV-RdRp inhibitor program, has been investigated. An SAR study revealed that hydrophilicity in this molecular sector strongly influences antiviral activity. We identified compounds incorporating hydroxyl (**2k**) and morpholinyl (**2o**) moieties that furnish potencies within a 10-fold range of **2** but with much improved aqueous

Scheme 5. Synthesis of the Phenyl Series[a]
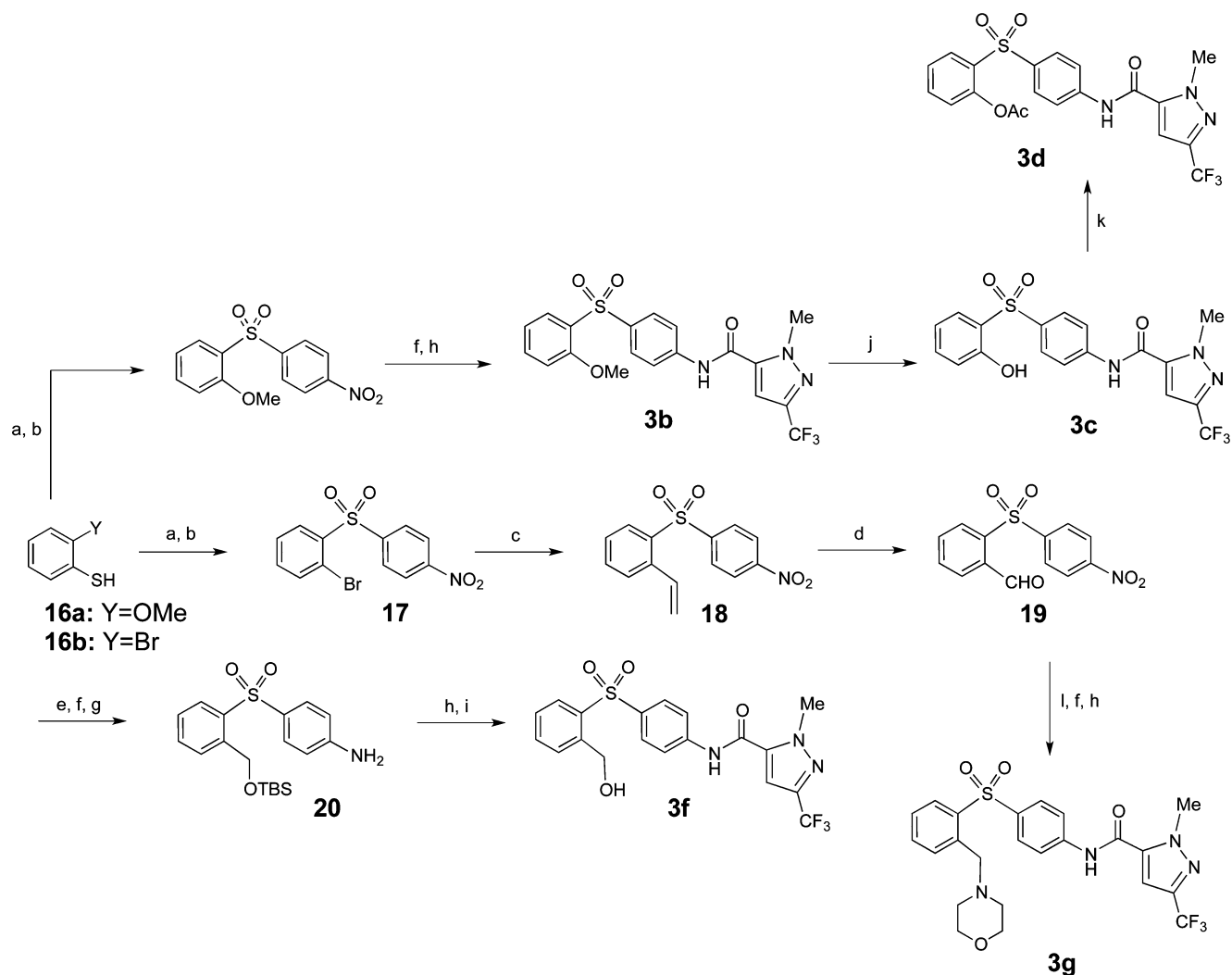
[a]Reagents and conditions: (a) 1-Fluoro-4-nitrobenzene, Na₂CO₃, EtOH, 80 °C. (b) *m*-CPBA, CH₂Cl₂. (c) Tributyl(vinyl)tin, Pd(PPh₃)₄, THF, 80 °C. (d) OsO₄, NaIO₄, THF/H₂O. (e) DIBAL-H, THF. (f) SnCl₂·2H₂O, CH₂Cl₂/MeOH. (g) TBSCl, imidazole, DMF. (h) Compound **8**, *i*-Pr₂NEt, CH₂Cl₂. (i) TBAF, THF. (j) BBr₃, CH₂Cl₂. (k) CH₃COCl, THF. (l) Morpholine, NaBH(OAc)₃, CH₂Cl₂.

solubility and oral bioavailability. In the series that replaces piperidine with the phenyl group, the most promising compound was found to be **3a** with antiviral activity around 90 nM in a virus yield reduction assay. Unfortunately, the solubility rates of **3a** and **2** are equally low, which stands in strong contrast to analogues **2k** and **2o**. Accordingly, the latter were advanced to PK studies in the Sprague−Dawley rat model. Analogue **2o** displays a 10-fold exposure (AUC/C_{max}) increase in this model relative to **2** and displays near dose propor-tionality in the range of 10−50 mg/kg. The Caco-2 per-meability assessment demonstrated high permeability for this class of molecule. This significant solubility increase might be a major determinant for the overall improvement in oral bioavailability. Compound **2o** was therefore identified as a second-generation lead for further development toward a novel measles therapeutic.

■ EXPERIMENTAL SECTION

General. Unless otherwise noted, all materials were obtained from commercial suppliers and used without purification. Dry organic solvents (DriSolv) were purchased from EMD Chemicals and packaged under nitrogen in Sure Seal bottles. Reactions were monitored using thin-layer chromatography on 250 μm plates or using Agilent 1100 series LC/MS with UV detection at 254 nm and low resonance electrospray mode (ESI). Elemental analysis was done by Atlantic Microlab. Purification of title compounds was accomplished by liquid chromatography on a Biotage SP4 purification system with normal phase silica gel. ¹H NMR spectra were recorded on a Varian spectrometer (400 MHz) at ambient temperature. Chemical shifts are reported in ppm relative to CDCl₃ or CD₃OD, and coupling constants (J) are reported in Hertz (Hz). Solvents for NMR were deuterio-chloroform (CDCl₃) (residual shifts: δ 7.26 for ¹H and δ 77.7 for ¹³C) and deuteriomethanol (CD₃OD) (residual shift: δ 3.31 for ¹H). The residual shifts were taken as internal references and reported in parts per million (ppm). Purities of all compounds were ≥95% determined by high-performance liquid chromatography (HPLC) with UV detection at two wavelengths of 220 and 254 nM. Purities of key compounds were also confirmed by elemental analysis.

Typical Procedures for the Synthesis of 1-Methyl-N-(4-(piperidin-1-ylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxa-mides (1a−c). 4-Amino-sulfonamide **7a−c** (1.0 mmol) in dichloro-methane (5 mL) and pyridine (0.1 mL) was treated with 1-methyl-3-trifluoromethyl-5-pyrazolecarbonyl chloride (**8**) at rt. The reaction was monitored by LC/MS until no more starting material was seen, and then, the mixture was poured into saturated aqueous NaHCO₃

Table 2. MeV Antiviral Action (CPE) of the Phenyl and Acyclic Series of Analogues (EC$_{50}$)

3a-g

Comp.	R$_2$	EC$_{50}$ (μM)[a] (MV-Alaska) (CPE inhib.)	Comp.	R$_2$	EC$_{50}$ (μM)[a] (MV-Alaska) (CPE inhib.)
3a	-H	2.8	**3e**	(allyl)	> 50.0
3b	-OMe	3.1	**3f**	(CH$_2$CH$_2$OH)	3.5
3c	-OH	4.5	**3g**	(CH$_2$CH$_2$-morpholine)	>75.0
3d	-OAc	4.5			

[a]Values represent averages of four experiments; the highest concentration assessed is 75 μM.
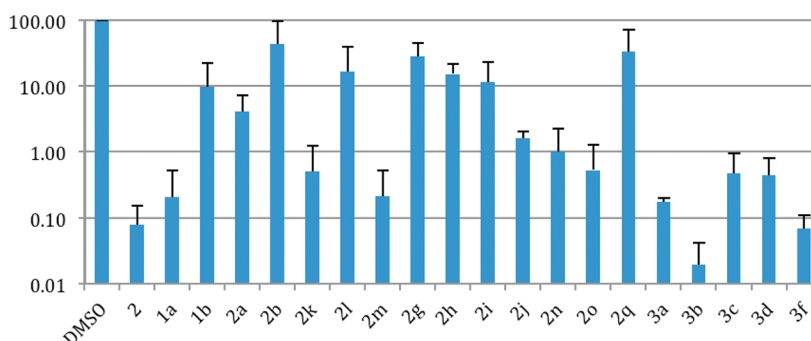

Figure 2. Evaluation of compounds **2** and analogues against MV-Alaska. All compounds were tested at 1.0 μM. Compounds comparable in activity to **2** were further examined at a range of concentrations to generate dose−response curves.

(10 mL) and extracted with CH$_2$Cl$_2$ (3 × 10 mL). The CH$_2$Cl$_2$ extracts were collected and dried over anhydrous Na$_2$SO$_4$. Products were purified by chromatography.

N-(4-((2-((Methoxymethoxy)methyl)piperidin-1-yl)sulfonyl)-phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (1a). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.17 (s, 1H), 7.74−7.79 (m, 2H), 7.64−7.69 (m, 2H), 7.06 (s, 1H), 4.51 (s, 2H), 4.19−4.28 (m, 4H), 3.76−3.68 (m, 1H), 3.54−3.65 (m, 2H), 3.27 (s, 3H), 3.03−2.94 (m, 1H), 1.76−1.70 (m, 1H), 1.42−1.60 (m, 4H), 1.20−1.37 (m, 1H). Anal. calcd for C$_{21}$H$_{29}$F$_3$N$_4$O$_5$S: C, 49.79; H, 5.77; N, 11.06. Found: C, 49.07; H, 5.06; N, 11.31.

N-(4-((3-((Methoxymethoxy)methyl)piperidin-1-yl)sulfonyl)-phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (1b). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 8.09 (s, 1H), 7.69−7.78 (m, 4H), 7.03 (s, 1H), 4.56 (s, 2H), 4.25 (s, 3H), 3.78 (d, J = 11.7 Hz, 2H), 3.30−3.38 (m, 5H), 2.27 (td, J = 2.3, 11.9 Hz, 2H), 1.72−1.83 (m, 2H), 1.50 (m, 1H), 1.29−1.42 (m, 2H). LC-MS (ESI) (LCT, 3 min) R_t 1.58 min; >95% purity at λ 254 and 210 nm. MS: m/z 491.5 [M + 1].

N-(4-((4-((Methoxymethoxy)methyl)piperidin-1-yl)sulfonyl)-phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (1c). ^{1}H NMR (CDCl$_3$, 400 MHz): δ 7.97 (s, 1H), 7.71−7.77 (m, 4H), 7.01 (s, 1H), 4.56 (s, 2H), 4.26 (s, 3H), 3.79 (d, J = 11.3 Hz, 2H), 3.30−3.38 (m, 5H), 2.27 (td, J = 2.5, 11.8 Hz, 2H), 1.79 (d, J = 10.6 Hz, 2H), 1.45−1.56 (m, 1H), 1.35 (m, 2H). Anal. calcd for

Table 3. Aqueous Solubility, Virus Yields (EC$_{50}$), and Toxicity (CC$_{50}$) for Selected Compounds

		EC$_{50}$ (μM) (MV-Alaska)		
compd	solubility (μg/mL) test[a]	CPE inhibition[b]	virus titer reduction[c]	CC$_{50}$(μM) (MTT cytotoxicity)[d]
2	<15	2.0	0.014	>75
2a	61	2.8	0.85	>75
2k	62	2.7	0.1	>75
2n	55	4.6	ND	>75
2o	60	2.5	0.06	>75
3a	22	2.8	0.09	>75
3b	<15	3.1	ND	>75
3c	67	4.5	ND	75
3f	46	3.5	ND	>75

[a]Solubility data generated through nephelometer using a standard procedure. [b]Values represent averages of four experiments; the highest concentration assessed is 75 μM, and the lowest concentration assessed is 2.0 μM. [c]Determined only when CPE inhibition-based EC$_{50}$ concentration <3.0 μM. [d]Values represent averages of at least three experiments; the highest concentration assessed is 75 μM.
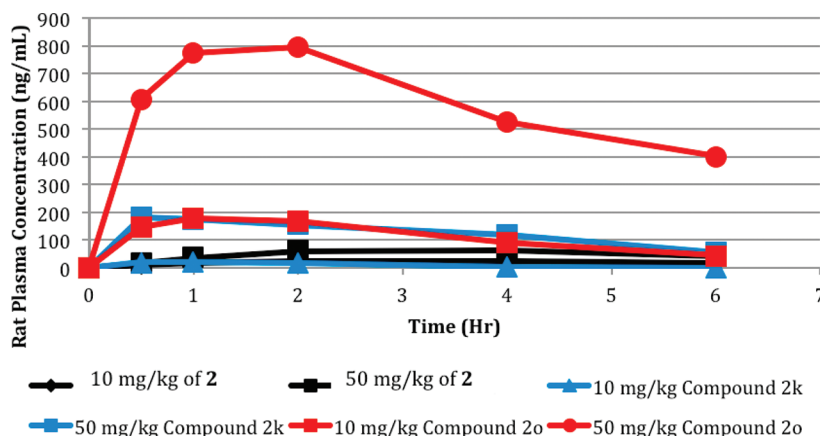
Figure 3. Time course of rat plasma concentration following po dosing by oral gavage. Preliminary PK studies in the Sprague–Dawley rat as compared to **2** with compounds **2k** and **2o** following po dosing by oral gavage at 10 and 50 mg/kg in a PEG200/0.5% methylcellulose (10/90) vehicle (*n* = 4/group).

Table 4. PK Profile for Compounds 2, 2k, and 2o

compd	oral dose (mg/kg)[a]	T_{max} (h)	C_{max} (ng/mL)[b]	T1/2 (h)[b]	AUC (0−t)	AUC (0−∞)
					h ng/mL[b]	
2	10	2.5	26.9	12.7	132	513
2	50	2.7	72.2	3.7	308	483
2k	10	1	19.8	0.8	56.3	56.8
2k	50	0.5	184	2.7	754	973
2o	10	1.1	195	2.2	683	818
2o	50	1.5	823	6.5	3521	7860

[a]Study in Sprague–Dawley rat dosed at 10 and 50 mg/kg as a suspension in PEG200/0.5% methylcellulose (10/90) formulation, respectively; *n* = 4 animals per study. [b]Estimation of PK parameters by noncompartmental analysis of these data was accomplished using standard PK software (WinNonlin 5.3, Pharsight).
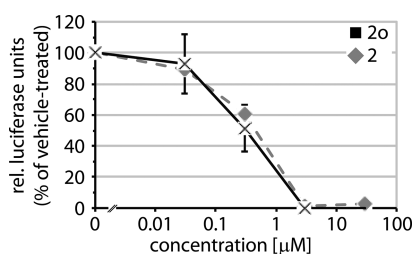

Figure 4. Compounds **2o** and **2** inhibit viral RdRp activity with equal potency. Values are expressed relative to vehicle-treated samples and represent averages of three experiments ± SDs.

$C_{21}H_{29}F_3N_4O_5S$: C, 49.79; H, 5.77; N, 11.06. Found: C, 49.17; H, 5.09; N, 11.21.

Synthesis of N-(4-((2-(hydroxymethyl)piperidin-1-yl)sulfonyl)-phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2a). A solution of (1-((4-nitrophenyl)sulfonyl)piperidin-2-yl)-methanol **6a** (90 mg, 0.3 mmol) in MeOH (10 mL) was treated with H_2 (50 Psi) for 4 h in the presence of Pd/C (32 mg, 0.03 mmol). The Pd/C residue was removed by filtration, followed by evaporation of the solvent. The crude product was purified by chromatography (hexane/EtOAc) to obtain amine product as white solid 70 mg (*Y* = 86%).

4-Amino-sulfonamide (70 mg, 0.25 mmol) in dichloromethane (5 mL) and pyridine (0.1 mL) was treated with 1-methyl-3-trifluoromethyl-5-pyrazolecarbonyl chloride (**8**) at rt. The reaction was monitored by LC-MS until no more starting material was seen, and then,

the mixture was poured into saturated aqueous $NaHCO_3$ (10 mL) and extracted with CH_2Cl_2 (3 × 10 mL). The CH_2Cl_2 extracts were collected and dried over anhydrous Na_2SO_4. Products were purified by chromatography (Hex/EtOAc) to obtain product **2a** as light yellow solid (81 mg, 73%). ^1H NMR (400 MHz, $CDCl_3$): δ 1.23−1.62 (6H, m), 2.20 (1H, m), 3.08 (1H, t, *J* = 13.2 Hz), 3.53−3.59 (1H, m), 3.77 (1H, d, *J* = 14.0 Hz), 3.84 (1H, t, *J* = 10.4 Hz), 4.00−4.06 (1H, m), 4.26 (3H, s), 7.11 (1H, s), 7.74−7.81 (4H, m), 8.48 (1H, s). Anal. calcd for $C_{18}H_{21}F_3N_4O_4S$: C, 48.43; H, 4.74; N, 12.55. Found: C, 48.33 ; H, 4.84 ; N, 12.23.

General Procedure for the Synthesis of Morpholinyl Analogue (2b, 2n, and 2o). To a solution of aldehyde (1.0 mmol) in CH_2Cl_2 (10 mL) was added morpholine (1.3 equiv, 1.3 mmol) and NaBH-$(OAc)_3$ (2.0 equiv, 2.0 mmol), and the mixture was kept stirring at room temperature for 3 h. $NaHCO_3$ (saturated aqueous) was added, and the organic layer separated and washed with brine, dried over Na_2SO_4, filtered, and concentrated. The product was purified by column to give morpholinyl analogue.

1-Methyl-N-(4-((2-(morpholinomethyl)piperidin-1-yl)sulfonyl)-phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2b). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.03 (s, 1H), 7.83−7.89 (m, 2H), 7.67−7.72 (m, 2H), 7.02 (s, 1H), 4.26 (s, 3H), 4.21 (br. s., 1H), 3.64 (m, 5H), 2.88−2.97 (m, 1H), 2.38−2.51 (m, 6H), 1.77 (m, 1H), 1.41−1.58 (m, 4H), 1.31(m, 1H). Anal. calcd for $C_{22}H_{28}F_3N_5O_4S$: C, 51.25; H, 5.47; N, 13.58. Found: C, 51.05; H, 5.45; N, 13.42.

N-(4-((2-(Azidomethyl)piperidin-1-yl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2c). ^1H NMR ($CDCl_3$, 400 MHz): δ 7.93 (s, 1H), 7.80−7.86 (m, 2H), 7.69−7.75 (m, 2H), 6.99 (s, 1H), 4.26 (s, 3H), 4.16 (m, 1H), 3.79 (d, *J* = 13.3 Hz, 1H), 3.51 (dd, *J* = 7.2, 12.3 Hz, 1H), 3.30−3.38 (m, 1H), 2.92−3.02 (m, 1H), 1.65−1.71 (m, 1H), 1.53−1.62 (m, 5H).

N-(4-((2-(Aminomethyl)piperidin-1-yl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2d). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.27 (s, 1H), 7.77−7.83 (m, 2H), 7.68−7.75 (m, 2H), 7.03 (s, 1H), 4.25 (s, 3H), 3.87−3.96 (m, 1H), 3.77 (d, *J* = 11.0 Hz, 1H), 2.92−3.06 (m, 2H), 2.64 (dd, *J* = 5.7, 13.5 Hz, 1H), 1.28−1.60 (m, 6H). LC-MS (ESI) (LCT, 3 min) R_t 0.54 min; >95% purity at λ 254 and 210 nm. MS: *m/z* 446.0 [M + 1].

N-(4-((2-(Acetamidomethyl)piperidin-1-yl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2e). ^1H NMR ($CDCl_3$, 400 MHz): δ 9.31 (s, 1H), 7.83−7.90 (m, 2H), 7.76−7.82 (m, 2H), 7.22 (s, 1H), 6.08 (t, *J* = 5.5 Hz, 1H), 4.26 (s, 3H), 4.03−4.13 (m, 1H), 3.67−3.77 (m, 1H), 3.56 (ddd, *J* = 5.3, 10.9, 14.0 Hz, 1H), 3.20−3.28 (m, 1H), 3.02−3.11 (m, 1H), 2.0 (m, 3H), 1.38−1.53 (m, 4H), 1.20−1.34 (m, 1H). Anal. calcd for $C_{20}H_{25}F_3N_4O_4S$: C, 49.28; H, 4.96; N, 14.37. Found: C, 49.02; H, 4.98; N, 14.08.

(E)-Ethyl 3-(1-((4-(1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamido)phenyl)sulfonyl)piperidin-2-yl)acrylate (2g). ^1H NMR ($CDCl_3$, 400 MHz): δ 8.19 (s, 1H), 7.69−7.78 (m, 4H),

7.03 (s, 1H), 6.75 (dd, J = 4.0, 16.0 Hz, 1H), 5.89 (dd, J = 2.0, 16.0 Hz, 1H), 4.69 (br. s., 1H), 4.25 (s, 3H), 4.15 (q, J = 7.0 Hz, 2H), 3.67 (d, J = 12.9 Hz, 1H), 2.95−3.05 (m, 1H), 1.63−1.78 (m, 2 H), 1.56 (d, J = 11.0 Hz, 7 H), 1.32−1.47 (m, 7 H), 1.25 (t, J = 8.0 Hz, 3H). Anal. calcd for $C_{22}H_{25}F_3N_4O_5S$: C, 51.36; H, 4.90; N, 10.89. Found: C, 51.36; H, 4.90; N, 10.89. Found: C, 51.42; H, 4.90; N, 10.79.

(E)-N-(4-((2-(3-Hydroxyprop-1-en-1-yl)piperidin-1-yl)sulfonyl)-phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2h). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.32 (s, 1H), 7.63−7.77 (m, 4H), 7.05−7.10 (m, 1H), 5.63−5.72 (m, 1H), 5.52−5.61 (m, 1H), 4.54 (br. s., 1H), 4.24 (s, 3H), 3.95−4.08 (m, 2H), 3.64 (d, J = 12.5 Hz, 1H), 3.47 (d, J = 5.1 Hz, 1H), 2.91−3.02 (m, 1H), 1.81 (t, J = 5.9 Hz, 1H), 1.34−1.74 (m, 6H). Anal. calcd for $C_{20}H_{23}F_3N_4O_4S$: C, 50.84; H, 4.91; N, 11.86. Found: C, 50.57; H, 4.98; N, 11.63.

Ethyl 3-(1-((4-(1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamido)phenyl)-sulfonyl)piperidin-2-yl)propanoate (2i). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.34 (s, 1H), 7.66−7.83 (m, 4H), 7.07 (s, 1H), 4.25 (s, 3H), 4.02 (s, 1H), 3.73 (d, J = 14.5 Hz, 1H), 3.63 (m, 2H), 2.93−3.05 (m, 1H), 2.16 (s, 3H), 1.59−1.81 (m, 2H), 1.28−1.59 (m, 6H). LC-MS (ESI) (LCT, 3 min) R_t 2.11 min; >95% purity at λ 254 and 210 nm. MS: m/z 517.1 [M + 1].

N-(4-((2-(3-Hydroxypropyl)piperidin-1-yl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2j). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.26 (s, 1H), 7.67−7.79 (m, 4H), 7.06 (s, 1H), 4.25 (s, 3H), 4.11 (q, J = 7.0 Hz, 2H), 3.99−4.07 (m, 1H), 3.74 (d, J = 14.5 Hz, 1H), 2.96−3.07 (m, 1H), 2.36 (t, J = 7.4 Hz, 2H), 2.00−2.13 (m, 1H), 1.60−1.72 (m, 1H), 1.30−1.55 (m, 5H), 1.24 (t, J = 7.2 Hz, 3H), 1.01−1.17 (m, 1H). Anal. calcd for $C_{20}H_{25}F_3N_4O_4S$: C, 50.62; H, 5.31; N, 11.81. Found: C, 50.35; H, 5.28; N, 11.62.

N-(4-((2-(2-Hydroxyethyl)piperidin-1-yl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2k). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.00 (s, 1H), 7.86 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H), 6.99 (s, 1H), 4.26 (s, 3H), 4.17−4.25 (m, 1H), 3.90 (d, J = 14.1 Hz, 1H), 3.74−3.83 (m, 1H), 3.67 (d, J = 5.1 Hz, 1H), 2.97−3.06 (m, 1H), 2.84 (dd, J = 4.9, 8.4 Hz, 1H), 1.93−2.02 (m, 1H), 1.40−1.54 (m, 5H), 1.32−1.40 (M, 1H). Anal. calcd for $C_{19}H_{23}F_3N_4O_4S$: C, 49.56; H, 5.03; N, 12.17. Found: C, 49.36; H, 5.08; N, 11.98.

(R)-N-(4-((2-(2-Hydroxyethyl)piperidin-1-yl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2l). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.34 (s, 1H), 7.84 (d, J = 8.4 Hz, 2H), 7.78 (d, J = 8.4 Hz, 2H), 7.07 (s, 1H), 4.27 (s, 3H), 4.22−4.19 (m, 1H), 3.91 (d, J = 14.4 Hz, 1H), 3.80 (t, J = 11.2 Hz, 1H), 3.67 (br, 1H), 3.06 − 2.04 (m, 2H), 2.03−1.95 (m, 1H), 1.57−1.41 (m, 4H), 1.28−1.21 (m, 2H). LC-MS (ESI) (LCT, 3 min) R_t 1.09 min; >95% purity at λ 254 and 210 nm. MS: m/z 461.2 [M + 1].

(S)-N-(4-((2-(2-Hydroxyethyl)piperidin-1-yl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2m). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.12 (m, 1H), 7.86 (d, J = 8.6 Hz, 2H), 7.75 (d, J = 8.6 Hz, 2H), 7.03 (s, 1H), 4.28 (s, 3H), 4.20−4.23 (m, 1H), 3.91 (d, J = 14.1 Hz, 1H), 3.81 (t, J = 11.6 Hz, 1H), 3.68 (m, 1H), 3.03 (t, J = 12.8 Hz, 1H), 2.88 (m, 1H), 2.05−1.96 (m, 1H), 1.58−1.26 (m, 5H), 1.13−1.08 (m, 1H). LC-MS (ESI) (LCT, 3 min) R_t 1.09 min; >95% purity at λ 254 and 210 nm. MS: m/z 461.2 [M + 1]. Anal. calcd for $C_{19}H_{23}F_3N_4O_4S$: C, 49.56; H, 5.03; N, 12.17. Found: C, 49.50; H, 5.05; N, 11.95.

(S)-1-Methyl-N-(4-((2-(2-morpholinoethyl)piperidin-1-yl)-sulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2o). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.18 (s, 1H), 7.74−7.80 (m, 2H), 7.65−7.72 (m, 2H), 7.05 (s, 1H), 4.25 (s, 3H), 4.04−4.11 (m, 1H), 3.76 (dd, J = 4.1, 14.3 Hz, 1H), 3.67 (t, J = 4.5 Hz, 1H), 2.97−3.08 (m, 1H), 2.23−2.45 (m, 6H), 1.78−1.90 (m, 1H), 1.55−1.66 (m, 1H), 1.30−1.53 (m, 5H). LC-MS (ESI) (LCT, 3 min) R_t 0.57 min; >95% purity at λ 254 and 210 nm. MS: m/z 530.2 [M + 1]. Anal. calcd for $C_{23}H_{30}F_3N_5O_4S \cdot H_2O$: C, 50.45; H, 5.89; N, 12.79. Found: C, 50.98; H, 5.72; N, 12.74.

Ethyl 2-((1-((4-(1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamido)phenyl)sulfonyl)piperidin-2-yl)methoxy)acetate (2p). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.14 (s, 1H), 7.77−7.83 (m, 2H), 7.65−7.70 (m, 2H), 7.02−7.06 (m, 1H), 4.25 (s, 3H), 4.14−4.23

(m, 3H), 3.99 (d, J = 3.1 Hz, 2H), 3.73 (d, J = 14.1 Hz, 1H), 3.60−3.67 (m, 2H), 2.96−3.06 (m, 1H), 1.77 (d, J = 12.9 Hz, 1H), 1.37−1.56 (m, 3H), 1.26 (t, J = 8.0 Hz, 3H). LC-MS (ESI) (LCT, 3 min) R_t 1.71 min; >95% purity at λ 254 and 210 nm. MS: m/z 533.2 [M + 1].

N-(4-((2-((2-Hydroxyethoxy)methyl)piperidin-1-yl)sulfonyl)-phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (2q, JMN6-093). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.73 (s, 1H), 7.70−7.83 (m, 4H), 7.11 (s, 1H), 4.30−4.39 (m, 1H), 4.25 (s, 3H), 3.72 (t, J = 9.4 Hz, 2H), 3.58−3.68 (m, 2H), 3.45−3.54 (m, 2H), 3.40 (d, J = 10.6 Hz, 1H), 3.25 (br. s., 1H), 2.98 (td, J = 2.5, 13.2 Hz, 1H), 1.63−1.74 (m, 2H), 1.35−1.63 (m, 3H). Anal. calcd for $C_{20}H_{25}F_3N_4O_5S$: C, 48.97; H, 5.14; N, 11.42. Found: C, 48.94; H, 5.08; N, 11.26.

1-Methyl-N-(4-(phenylsulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (3a). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.10 (s, 1H), 7.85−7.93 (m, 4H), 7.69−7.75 (m, 2H), 7.53−7.59 (m, 1H), 7.46−7.53 (m, 2H), 7.03 (s, 1H), 4.22 (s, 3H). Anal. calcd for $C_{18}H_{14}F_3N_3O_3S$: C, 52.81; H, 3.45; N, 10.26. Found: C, 52.31; H, 3.41; N, 9.95.

N-(4-((2-Methoxyphenyl)sulfonyl)phenyl)-1-methyl-3-(trifluoro-methyl)-1H-pyrazole-5-carboxamide (3b). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.11 (dd, J = 1.8, 8.0 Hz, 1H), 8.04 (s, 1H), 7.90−7.95 (m, 2H), 7.66−7.71 (m, 2H), 7.51−7.57 (m, 1 H), 7.07−7.13 (m, 1 H), 7.02 (s, 1 H), 6.87−6.91 (m, 1 H), 4.24 (s, 3 H), 3.76 (s, 3H). LC-MS (ESI) (LCT, 3 min) R_t 1.11 min; >95% purity at λ 254 and 210 nm. MS: m/z 440.0 [M + 1].

Synthesis of N-(4-((2-Hydroxyphenyl)sulfonyl)phenyl)-1-methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (3c). To a solution of 3b (110.0 mg, 0.250 mmol) in CH_2Cl_2 (6.0 mL) was added BBr_3 (1.0 mL, 1.0 mmol), and the mixture was stirred overnight. The reaction was cooled to 0 °C, and $NaHCO_3$ solution (3.0 mL) slowly was added. The reaction was allowed to warm to rt, and CH_2Cl_2 (9.0 mL) and MeOH (1.0 mL) were added. The organic layer was separated and washed with $NaHCO_3$ and brine, dried over Na_2SO_4, filtered, and concentrated. The product was purified by column (CH_2Cl_2/MeOH) and dried under vacuum to give 106.0 mg of a white solid in 96% yield. ^{1}H NMR (CDCl₃, 400 MHz): δ 7.86−7.92 (m, 2 H), 7.77−7.82 (m, 2 H), 7.65 (dd, J = 1.6, 8.2 Hz, 1 H), 7.37−7.43 (m, 1H), 7.11 (s, 1H), 6.90−6.96 (m, 2H), 4.20 (s, 3H). Anal. calcd for $C_{18}H_{14}F_3N_3O_4S$: C, 50.82; H, 3.32; N, 9.88. Found: C, 50.67; H, 3.29; N, 9.61.

Synthesis of 2-((4-(1-Methyl-3-(trifluoromethyl)-1H-pyrazole-5-carboxamido)phenyl)sulfonyl)phenylacetate (3d). To a solution of 3c (52.0 mg, 0.122 mmol) in dimethylformamide (1.0 mL) were added K_2CO_3 (33.8 mg, 0.244 mmol) and acetic anhydride (0.023 mL, 0.244 mmol), and the mixture was allowed to stir overnight. DMF was removed under vacuum, and the residue was purified by column (hexanes/ethylacetate) to give 43.4 mg of 3d as a white solid in 76% yield. ^{1}H NMR (CDCl₃, 400 MHz): δ 8.14 (dd, J = 1.76, 8.02 Hz, 1H), 7.87−7.93 (m, 3H), 7.70−7.76 (m, 2H), 7.58−7.63 (m, 1H), 7.41 (dt, J = 1.17, 7.83 Hz, 1H), 7.14 (dd, J = 0.98, 8.02 Hz, 1H), 6.96 (s, 1H), 4.24 (s, 3H), 2.32 (s, 3H). Anal. calcd for $C_{20}H_{16}F_3N_3O_5S$: C, 51.39; H, 3.45; N, 8.99. Found: C, 51.31; H, 3.32; N, 8.80.

1-Methyl-3-(trifluoromethyl)-N-(4-((2-vinylphenyl)sulfonyl)-phenyl)-1H-pyrazole-5-carboxamide (3e). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.12−8.17 (m, 1H), 8.08 (s, 1H), 7.76−7.83 (m, 2H), 7.65−7.71 (m, 2H), 7.51−7.59 (m, 2H), 7.41−7.50 (m, 2H), 7.02 (s, 1H), 5.52 (dd, J = 1.17, 17.22 Hz, 1H), 5.33 (dd, J = 0.78, 10.96 Hz, 1H), 4.22 (s, 3H). Anal. calcd for $C_{20}H_{16}F_3N_3O_3S$: C, 55.17; H, 3.70; N, 9.65. Found: C, 54.99; H, 3.60; N, 9.64.

N-(4-((2-(Hydroxymethyl)phenyl)sulfonyl)phenyl)-1-methyl-3-(tri-fluoromethyl)-1H-pyrazole-5-carboxamide (3f). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.10 (dd, J = 1.17, 7.83 Hz, 1H), 8.00 (s, 1H), 7.84−7.90 (m, 2H), 7.71−7.77 (m, 2H), 7.59−7.65 (m, 1H), 7.48−7.57 (m, 2H), 6.98 (s, 1H), 4.73 (d, J = 6.26 Hz, 2H), 4.23 (s, 3H). Anal. calcd for $C_{19}H_{16}F_3N_3O_4S$: C, 51.93; H, 3.67; N, 9.56. Found: C, 52.01; H, 3.53; N, 9.40.

1-Methyl-N-(4-((2-(morpholinomethyl)phenyl)sulfonyl)phenyl)-3-(trifluoromethyl)-1H-pyrazole-5-carboxamide (3g). ^{1}H NMR (CDCl₃, 400 MHz): δ 8.16 (dd, J = 1.2, 7.8 Hz, 1 H), 7.99 (s, 1H), 7.83−7.89 (m, 2H), 7.68−7.74 (m, 3H), 7.54−7.60 (m, 1H), 7.42−7.48 (m, 1H), 7.01 (s, 1H), 4.24 (s, 3H), 3.77 (s, 2H), 3.50−3.57

(m, 4H), 2.27 (m, 4H). Anal. calcd for $C_{23}H_{23}F_3N_4O_4S$: C, 54.32; H, 4.56; N, 11.02. Found: C, 54.36; H, 4.42; N, 10.85.

Biology. Antiviral assays and toxicity measurements were performed as described previously.[22]

ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details for the preparation of compounds **7a–c**, **2b–j**, **2o–q**, **3b**, **17–19**, **3f**, and **3g**; Synthetic scheme for the synthesis of morpholinyl analogue **2o**; mean plasma concentration following iv and po dosing of **2o** in Sprague–Dawley rat; and summary of **2o** PK properties. This material is available free of charge via the Internet at http://pubs.acs.org.

AUTHOR INFORMATION

Corresponding Author
*Tel: 404-712-8680. E-mail: asun2@emory.edu.

Notes
The authors declare no competing financial interest.

ABBREVIATIONS USED

MeV, measles virus; RNA, ribonucleic acid; RdRp, RNA-dependent RNA polymerase; HTS, high-throughput screening; HPIV, human parainfluenza virus; RSV, respiratory syncytial virus; EC_{50}, 50% effective concentration; CC_{50}, 50% cytotoxicity concentration; MOM, methoxymethyl; TBSCl, *t*-butyldimethylsilyl chloride; DIBALH, diisobutylaluminium hydride; MCPBA, *meta*-chloroperoxybenzoic acid; PK, pharmacokinetic

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