

Respiratory syncytial virus fusion inhibitors. Part 4: Optimization for oral bioavailability[☆]

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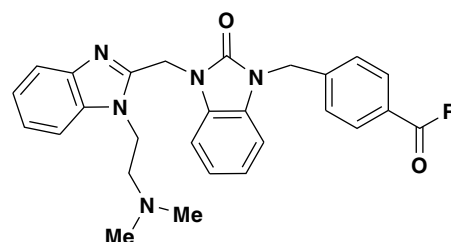
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Abstract—A series of benzimidazole-based inhibitors of respiratory syncytial virus (RSV) fusion were optimized for antiviral potency, membrane permeability and metabolic stability in human liver microsomes. 1-Cyclopropyl-1,3-dihydro-3-[[1-(4-hydroxybutyl)-1H-benzimidazol-2-yl]methyl]-2H-imidazo[4,5-c]pyridin-2-one (**6m**, BMS-433771) was identified as a potent RSV inhibitor demonstrating good bioavailability in the mouse, rat, dog and cynomolgus monkey that demonstrated antiviral activity in the BALB/c and cotton rat models of infection following oral administration.
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We have recently described the discovery of a class of benzimidazole-based inhibitors of respiratory syncytial virus (RSV) fusion and their evolution into compounds with antiviral activity in animal models of infection.^{1–3} RSV inhibitory effects in vivo were established initially in the cotton rat model using small particle aerosol delivery of compounds specifically designed to combine potent antiviral activity in vitro with the high aqueous solubility required for this method of topical administration.³ Insights from these studies led to the subsequent identification of benzoate ester **1** as a molecule demonstrating reproducible antiviral activity in the BALB/c mouse model of RSV infection following oral adminis-

tration.³ However, ester **1** is rapidly converted to acid **2** in vivo, prompting the synthesis and evaluation of the amide **3**, a compound that also demonstrated antiviral activity after oral dosing to RSV-infected mice.³ Whilst the amide moiety of **3** proved to be more robust



1: R = OMe
2: R = OH
3: R = N(Me)₂

Keywords: Respiratory syncytial virus; Respiratory syncytial virus fusion inhibitor; Antiviral agent.

[☆] See Refs. 1–3.

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towards hydrolytic cleavage than the ester **2**, overall metabolic stability in liver microsomal preparations was only marginally improved, with enzymatic modification redirected towards other pathways. The most prominent metabolites arose from demethylation of the amine and amide moieties and hydroxylation of the heterocyclic rings.³ In this article, we summarize studies directed towards further structural optimization that resulted in the discovery of BMS-433771, a potent inhibitor of RSV in vitro that is orally bioavailable in 4 species and demonstrates antiviral activity in both the BALB/c mouse and cotton rat models of RSV infection following oral administration.^{4–8}

In order to address the metabolic lability associated with the dimethylaminoethyl side chain of **3**, the 3-cyanopropyl moiety that conferred potent RSV inhibitory activity in the parent series was selected for initial studies that were focused on the optimization of the benzimidazol-2-one heterocycle and its N-substituent.² Since the structure–activity relationships established earlier indicated that potent antiviral activity can readily be obtained with small alkyl substituents attached to the benzimidazol-2-one N atom, this structural theme was also adopted.² With these structural elements determined, the introduction of nitrogen heteroatoms into the benzene element of the benzimidazol-2-one heterocycle became the immediate objective, with a view to reducing electron density and increasing both the local and overall polarity of the molecules as a means of reducing the rate of metabolism.⁹ Consequently, representative examples of the 4 possible topological isomers based on two imidazopyridin-2-one heterocycles were prepared and evaluated for their antiviral activity in vitro, data that are summarized in Table 1.

The antiviral activity of these compounds was determined as the reduction of the cytopathic effect induced by the Long (A) strain of virus replicating in HEP-2 human lung epithelial carcinoma cells.⁴ The EC₅₀ data reported are the concentration of test compound that protects 50% of infected cells, whilst the CC₅₀ is the concentration of drug that manifests cytotoxicity towards 50% of uninfected HEP-2 cells in the absence of virus, an experiment performed as a control for each assay. Test compounds were typically evaluated in two consecutive experiments with additional experiments conducted in the absence of reasonable concordance. Where the data reported is the average of 2 experiments, the individual results are provided as a measure of assay variability.

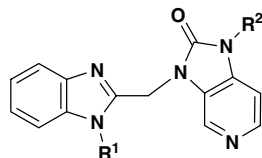
The data reported in Table 1 reveal that the *N*-isopropenyl derivatives of the 6- and 7-aza benzimidazol-2-ones, **6b** and **7b**, respectively, are equivalent in potency to the parent benzimidazol-2-one **8b** and over 30-fold more potent than the 4-aza analogue **4b**.³ Compounds **6b** and **7b** offer the additional benefit of being significantly less cytotoxic than **8b**. Since the 5-aza series (**5**) was accessed via the *N*-Boc derivative¹⁰ rather than *N*-isopropenyl protecting group chemistry,^{11,12} several alternative substituents, obtained by alkylation of **5a**, were assessed in order to determine their potency relative to representative analogues. The 4-methylsulfonylbenzyl derivative **5c** is over 30-fold weaker than the identically substituted 6-aza analogue **6c**, while the *N*-4-cyanobenzyl and *N*-SO₂-*i*-Pr derivatives **5d** and **5e**, respectively, are markedly less potent than similarly, although not identically, substituted compounds in the parent benzimidazol-2-one series.² As a consequence, the 6- and 7-aza heterocyclic templates were selected as vehicles on which to focus further study, with some bias towards the 6-aza chemotype based on the greater

Table 1. Structure, RSV inhibitory activity and cytotoxicity associated with a family of azabenzimidazol-2-one derivatives

R ²	4 W = N X, Y, Z = CH	5 X = N W, Y, Z = CH	6 Y = N W, X, Z = CH	7 Z = N W, X, Y = CH	8 W, X, Y, Z = CH
a H	Not made	EC ₅₀ = 5.71 μM; CC ₅₀ = 263.9 μM	Not made	Not made	Not made
b	EC ₅₀ = 0.202 μM; CC ₅₀ = 149.8 μM	Not made	EC ₅₀ = 0.006 μM (0.004, 0.008); CC ₅₀ = 236.6 μM (267.1, 206.1)	EC ₅₀ = 0.003 μM; CC ₅₀ > 216 μM	EC ₅₀ = 0.005 μM; CC ₅₀ = 13.1 μM
c CH ₂ -4-C ₆ H ₄ SO ₂ CH ₃	Not made	EC ₅₀ = 0.075 μM; CC ₅₀ = 40.9 μM	EC ₅₀ < 0.0023 μM; CC ₅₀ = 1.98 μM	Not made	Not made
d CH ₂ -4-C ₆ H ₄ CN	Not made	EC ₅₀ = 0.622 μM; CC ₅₀ = 36.8 μM	Not made	Not made	Not made
e SO ₂ - <i>i</i> -Pr	Not made	EC ₅₀ = 0.237 μM; CC ₅₀ > 228 μM	Not made	Not made	EC ₅₀ = 0.065 μM; CC ₅₀ > 16.9 μM

Data are means of two or more experiments performed on consecutive weeks.

Table 2. Structure of 6-aza benzimidazol-2-one derivatives



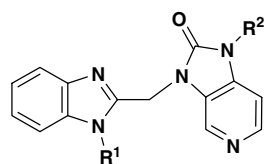
Compound	R ¹	R ²	EC ₅₀ ^a (μM)	CC ₅₀ (μM)	Therapeutic index ^b	HLM <i>t</i> _{1/2} (min)	Caco-2 Perm (nm/s)	clog <i>P</i>
6f	(CH ₂) ₃ CN	<i>i</i> -Pr	0.004 (0.003, 0.007, 0.003)	>55.6 (86.7, 55.6, >269.1)	13,900	7.4	169	2.21
6g	(CH ₂) ₃ CN	<i>t</i> -Bu	0.003 (0.003, 0.003)	>86.8 (>257.4, 86.8)	>28,933	4.0	214	2.61
6h	(CH ₂) ₃ CN	<i>c</i> -Pr	0.010 ± 0.004 (<i>n</i> = 3)	109	10,900	39	181	1.72 ^c
6i	(CH ₂) ₃ CN	<i>c</i> -Bu	0.016 (0.008, 0.024)	>258.8	>16,175	4.6	168	2.28
6j	(CH ₂) ₃ CN	CH ₂ - <i>c</i> -Pr	0.003 (0.002, 0.004)	96.5 (88.7, 104.2)	32,166	3.5		2.34
6k	(CH ₂) ₃ CN	CH ₂ CF ₃	0.015 (0.014, 0.016)	>195	>13,000	12.3	197	1.66
6l	(CH ₂) ₃ OH	<i>c</i> -Pr	0.043 (0.018, 0.068)	245.0 (271.6, 218.4)	5698	18	115	1.41
6m	(CH ₂) ₄ OH	<i>c</i> -Pr	0.021 ± 0.004 (<i>n</i> = 3)	>218	>10,380	34	122	1.53 ^d
6n	(CH ₂) ₅ OH	<i>c</i> -Pr	0.013 (0.019, 0.006)	>229.5 (>233.7, 229.5)	>17,654	18	96	2.06
6o	(CH ₂) ₄ OH	<i>c</i> -Bu	0.007 (0.005, 0.009)	>255.4	>36,343	5.6	161	2.09
6p	(CH ₂) ₄ OH	<i>c</i> -C ₅ H ₉	0.008 (0.005, 0.011)	>246.6	30,825	2.9	160	2.65
6q	(CH ₂) ₄ OH	CH ₂ CF ₃	0.037 (0.055, 0.018)	115.6 (63.3, 167.8)	3,124	13		1.47
6r	(CH ₂) ₂ C(Me) ₂ OH	<i>c</i> -Pr	0.119 (0.173, 0.065)	149.0 (50.7, 247.2)	1252	26	182	2.12
6s	(CH ₂) ₃ C(Me) ₂ OH	<i>c</i> -Pr	0.0135 (0.014, 0.013)	178.7 (241.5, 115.9)	13,237	13	145	2.24
6t	(CH ₂) ₂ C(<i>c</i> -Pr)OH	<i>c</i> -Pr	0.306 (0.260, 0.351)	56.1 (46.0, 66.2)	183	3.5	137	1.75
6u	(CH ₂) ₃ C(<i>c</i> -Pr)OH	<i>c</i> -Pr	0.008 (0.003, 0.013)	130.7 (218.8, 42.5)	16,337	4.5	233	1.87
6v	(CH ₂) ₃ SO ₂ CH ₃	<i>c</i> -Pr	0.005 (0.003, 0.006)	>227 (>235.0, 227.0)	45,400	77	27	0.90
6w	(CH ₂) ₃ SO ₂ CH ₃	<i>c</i> -Bu	0.021 (0.023, 0.018)	>227	>10,810	5.3		1.46
6x	(CH ₂) ₃ SO ₂ CH ₃	CH ₂ CF ₃	0.015 ± 0.008 (<i>n</i> = 4)	>94.6 (206.93, >185, 94.6, >185)	6307	87	36 (33, 39)	0.84
6y	(CH ₂) ₃ SO ₂ C ₂ H ₅	<i>c</i> -Pr	0.006 (0.005, 0.007)	>227	>37,833	37	34	1.43
6z	(CH ₂) ₃ SO ₂ C ₂ H ₅	CH ₂ CF ₃	0.011 (0.014, 0.008, 0.010)	>173.1 (>173.1, >207, >207)	>15,736	36	92	1.37
6aa	(CH ₂) ₃ SO ₂ - <i>i</i> -Pr	<i>c</i> -Pr	0.206 (0.342, 0.070)	49.2 (46.8, 51.5)	239	14	63	1.74
6ab	(CH ₂) ₃ SO ₂ - <i>c</i> -Pr	<i>c</i> -Pr	0.017 (0.026, 0.007)	>55.9 (>221.5, 55.9)	3,288		21 (21, 21)	1.19
6ac	(CH ₂) ₃ CF ₃	<i>c</i> -Pr	0.006 (0.003, 0.008)	55.7 (71.8, 39.6)	9,283	9.3	239	3.30
6ad	(CH ₂) ₃ CF ₃	CH ₂ CF ₃	0.051 (0.069, 0.032)	>48.3 (>188.6, 48.3)	947			2.97
6ae	(CH ₂) ₄ F	<i>c</i> -Pr	0.010 (0.014, 0.007)	158.4 (111.9, 204.9)	15,840	11	247	2.79
6af	(CH ₂) ₄ F	CH ₂ CF ₃	0.015 (0.026, 0.005)	189.9 (202.0, 167.8)	12,660	17	245	2.73

^a Values are means of two or more experiments performed on consecutive weeks with the data from individual experiments shown in parentheses.

^b Therapeutic index = CC₅₀/EC₅₀.

^c Measured log *P*(octanol/water) for the neutral species at pH 6.5 = 2.1.

^d Measured log *P*(octanol/water) for the neutral species at pH 6.5 = 1.9.

Table 3. Structure of 7-aza benzimidazol-2-one derivatives

Compound	R ¹	R ²	EC ₅₀ ^a (μM)	CC ₅₀ ^a (μM)	Therapeutic index ^b	HLM <i>t</i> _{1/2} (min)	Caco-2 Perm (nm/s)	clog <i>P</i>
7a	(CH ₂) ₃ CN	<i>iso</i> -propenyl	0.003 (0.003, 0.003)	>216	>72,000	11	230	2.02
7f	(CH ₂) ₃ CN	<i>c</i> -Pr	0.029 ± 0.029 (<i>n</i> = 3)	>181	6241	45	166	1.72
7g	(CH ₂) ₃ CN	CHF ₂	0.011 (0.009, 0.013)	>205	>18,636	84	188	1.67
7h	(CH ₂) ₄ OH	<i>c</i> -Pr	0.010 ± 0.006 (<i>n</i> = 9)	>211	>21,100	34	130	1.53
7i	(CH ₂) ₄ OH	CHF ₂	0.089 ± 0.042 (<i>n</i> = 3)	>186	>2090	95	197	1.47
7j	(CH ₂) ₃ SO ₂ CH ₃	<i>c</i> -Pr	0.009 (0.008, 0.010)	>230	>25,556	>100	39	0.90
7k	(CH ₂) ₃ SO ₂ C ₂ H ₅	CHF ₂	0.011 ± 0.012 (<i>n</i> = 5)	>191	>17,364	55	59	1.37

^a Values are means of two or more experiments performed on consecutive weeks with the data from individual experiments shown in parentheses.

^b Therapeutic index = CC₅₀/EC₅₀.

facility with which this series could be accessed. This is reflected in the relative scope of the two studies, compiled in **Tables 2 and 3**, where a broader range of structural themes around the N-substituent are surveyed in the 6-aza series (**Table 2**). For both chemotypes, a combination of the benzimidazole side-chain elements optimized in the earlier work^{2,3} with small, alkyl, cycloalkyl and fluoroalkyl azabenzimidazol-2-one substituents afforded potent antiviral agents, with many compounds demonstrating half-maximal inhibition at concentrations below the objective of 20 nM. These compounds also demonstrate an excellent window between antiviral activity and cytotoxicity with generally high therapeutic index ratios. Target compounds were also profiled for metabolic stability in human liver microsomes (HLM) and permeability across a confluent layer of Caco-2 cells, in vitro assays used to predict clearance and absorption across the gut wall in humans, respectively. The preferred criteria targeted were a HLM half-life (*t*_{1/2}) of >30 min, predictive of intermediate clearance in man, and Caco-2 permeability of >100 nm/s, indicative of a well-absorbed compound based on comparison with standards. From the profiling data presented in **Tables 2 and 3**, it is apparent that there is consistency across the 2 chemotypes but the trends for HLM *t*_{1/2} and Caco-2 permeability are in opposite directions, as might be anticipated. Within the butyronitrile series **6f–k**, a simple *N*-*iso*-propyl substituent combines excellent antiviral potency and Caco-2 permeability but this compound (**6f**) exhibits poor stability in HLM. The analogues **6g–k** were designed based on the precedent that these moieties have found utility in marketed drugs or demonstrated some resistance towards metabolic modification in structural contexts both similar and distinct from those at hand.^{13–16} The cyclopropyl derivative **6h** offered a unique coalescence of excellent antiviral activity, good in vitro metabolic stability and high membrane permeability. These properties appear to be attributable to a combination of the inherent electronic properties of the cyclopropyl ring coupled with a reduction in the overall lipophilicity of **6h**

compared to **6f**, which may increase the resistance to metabolic modification. The lipophilicity coefficient, π , for an *i*-Pr substituent is 1.53¹⁷ whilst π for *c*-Pr = 1.20,¹⁸ differences that are reflected in the calculated log *P* data determined for **6h** (1.72) and **6f** (2.21).¹⁹ The log *P* (octanol/water) measured for the neutral species of **6h** at pH = 6.5 is 2.1.

The theme of reducing overall lipophilicity was further explored by replacing the butyronitrile side-chain terminus with more polar functionality, leading to the series of alkyl alcohols **6l–u** and sulfones **6v–ab**, both of which provided an opportunity to further adjust physical properties by elaboration with proximal substituents. Several molecules in the series of alkyl alcohols **6l–u** demonstrated improved metabolic stability without substantially compromising Caco-2 permeability. For the homologous series **6l–n**, the metabolic stability of the butanol derivative **6m** is clearly superior. However, more lipophilic N-substituents or masking the polarity of the alcohol moiety, as exemplified by compounds **6o–u**, reduced metabolic stability whilst preserving excellent membrane permeability. The effect of further increasing the polarity of the side-chain terminus was probed with the collection of sulfone derivatives **6v–ab**. The *N*-cyclopropyl analogue **6v** demonstrated the anticipated metabolic stability which extended to the *N*-CH₂CF₃ analogue **6x** but not to the *N*-cyclobutyl compound **6w**. Reduced but adequate metabolic stability was retained with the ethyl sulfones **6y** and **6z**, but this was further compromised by additional homologation to the *iso*-propyl compound **6aa**. However, whilst the sulfone-containing molecules demonstrate excellent antiviral activity, membrane permeability was generally lower than preferred, particularly for the methyl derivatives **6v** and **6x**, and only marginally better for the *iso*-propyl homologue **6aa**, a consequence of the low lipophilicity associated with a sulfone moiety.¹⁷

The results for the series of 7-aza derivatives defined by **7a** and **7f–k** largely recapitulate the trends observed with

Table 4. Pharmacokinetic properties and in vivo antiviral activity associated with five inhibitors of RSV

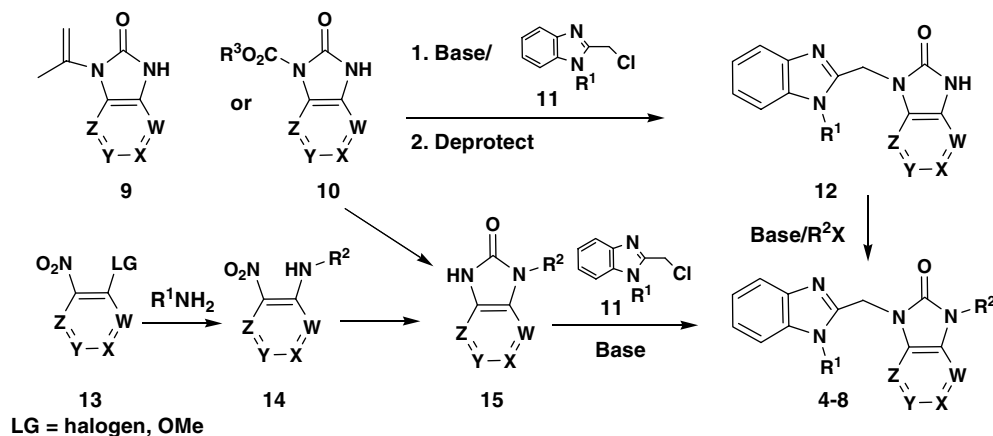
Compound	Mouse oral AUC at 10 mpk ($\mu\text{g min/mL}$) ^{a,b}	Rat oral AUC at 5 mpk ($\mu\text{g min/mL}$) ^a	Dog oral AUC at 0.5 mpk ($\mu\text{g min/mL}$) ^a	Monkey oral AUC at 0.5 mpk ($\mu\text{g min/mL}$) ^a	RSV mouse $\log_{10}$ TCID ₅₀ /g lung versus control (dose in mpk) ^c	RSV cotton rat $\log_{10}$ TCID ₅₀ /g lung versus control (dose in mpk) ^d
6h	36	58.4 $\pm$ 18.4	45.3 $\pm$ 5.0	16.2 $\pm$ 8.1	2.97 $\pm$ 0.36; 4.12 $\pm$ 0.21 (100 mpk/day)	3.83 $\pm$ 0.61; 4.58 $\pm$ 0.19 (100 mpk/day) ^c
6m	32	13.0 $\pm$ 5.3	18.0 $\pm$ 0.6	25.3 $\pm$ 15	2.49 $\pm$ 0.47; 3.63 $\pm$ 0.28 (50 mpk/day)	4.74 $\pm$ 0.23; 5.32 $\pm$ 0.06; (50 mpk/day)
6x	86	2.4 $\pm$ 1.1	18.4 $\pm$ 2.8	11.1 $\pm$ 9.7	2.77 $\pm$ 0.43; 4.05 $\pm$ 0.38 (100 mpk/day)	Not done
6z	120	8.0 $\pm$ 2.7	26.3 $\pm$ 2.5	7.1 $\pm$ 5.5	2.33 $\pm$ 0.01; 3.72 $\pm$ 0.15 (100 mpk/day)	Not done
7k	2.8	8.0 $\pm$ 2.9	166.0 $\pm$ 16.5	11.0 $\pm$ 0.91	Not done	Not done

^a $n = 3$ for all experiments. Data in dogs and monkeys were obtained from cassette dosing.^b Composite data.^c Drugs were administered in divided doses for 4 days with the first dose given 1 h prior to inoculation with RSV.^d Single dose of drug administered 1 h prior to inoculation with RSV.

the 6-aza analogues, with potent antiviral activity observed with all examples examined and the sulfone series once again associated with poorer membrane permeability properties. For both series, a reasonable correlation between Caco-2 permeability and calculated $\log P$ ($\text{clog}P$) is evident: for the 6-aza series, Caco-2 permeability = 93.9 $\text{clog}P - 38.7$, $R^2 = 0.6543$, while for the 7-aza compounds, Caco-2 permeability = 178.0 $\text{clog}P - 127.6$, $R^2 = 0.7419$. However, the negative correlation between metabolic stability and lipophilicity is less pronounced with HLM $t_{1/2} = -24.1 \text{ clog}P + 66.9$, $R^2 = 0.4374$, for the 6-aza compounds and HLM $t_{1/2} = -69.2 \text{ clog}P + 166.2$, $R^2 = 0.5175$, for the 7-aza series.

Two compounds, the nitrile **6h** and alcohol **6m**, that meet the target antiviral criterion of $\text{EC}_{50} \leq 20 \text{ nM}$ and combine Caco-2 permeability of greater than 100 nm/s with good metabolic stability, HLM $t_{1/2}$ of >30 min, were selected for a more detailed assessment of pharmacokinetic properties in vivo. In addition, the 3 sulfones **6x**, **6z** and **7k**, which are potent RSV inhibitors demonstrating excellent metabolic stability, were also selected, recognizing that they represented somewhat of a compromise with respect to Caco-2 permeability.

ters, which are predictive of moderate rather than high permeability. Exposure data for these 5 compounds following oral administration to mice, rats, dogs and monkeys are compiled in Table 4. Plasma AUCs for both **6h** and **6m** were good in all 4 species but exposure of the sulfones **6x**, **6z** and **7k** was inconsistent across the species, variability that presumably reflects their less than optimal in vitro Caco-2 permeability coefficients. The nitrile **6h** and the 2 sulfones **6x** and **6z** that are well absorbed in mice demonstrated antiviral activity in the BALB/c mouse model of RSV infection at doses of 100 mpk/day for 4 days administered on a 50 mpk BID regimen whilst the alcohol **6m** showed comparable activity at the lower dose of 50 mpk/day.⁵ The in vivo antiviral activity associated with **6h** and **6m** was confirmed in the cotton rat model of infection and further experiments demonstrated that both compounds produced dose-dependent reductions in RSV titres in the lungs in both infection models.⁵ Both nitrile **6h** and butanol **6m** were evaluated in toxicological studies with **6m**, designated as BMS-433771, ultimately selected as a development candidate based on its overall safety profile.^{4–8} BMY-433771 (**6m**) is a selective RSV inhibitor, inactive towards several related and unrelated viruses, that demonstrates no significant activity towards a



Scheme 1.

broad panel of receptors at a concentration of 10 μM .^{4–8} The compound is not mutagenic in the Ames reverse mutation assay and does not significantly inhibit the major cytochrome P450 isoforms, $\text{IC}_{50}\text{s} > 26 \mu\text{M}$, a possible source of concern for pyridine-containing compounds.^{20,21} BMY-433771 (**6m**) is readily accessible at scale²² and the dihydrochloride salt offers properties sought in a developmental candidate.²³

The compounds in Tables 1–3 were prepared by adaptation of synthetic protocols previously described.^{2,3} Mono-*N*-protected imidazopyridin-2-ones **9** and **10** were obtained using literature methods and alkylated with an *N*-substituted 2-chloromethyl benzimidazole derivative **11**.^{2,3,10–12,24} For target compounds with primary alcohol moieties in R^1 , an acetate protecting group was typically employed. Removal of the imidazopyridin-2-one protecting group produced **12**, allowing introduction of an *N*-substituent by alkylation to give target compounds **4–8**. For the cycloalkyl *N* substituents, a halogen or methoxy moiety at the 2- or 4-position of a 3-nitropyridine (**13**) was displaced in an ipso fashion by heating with a cycloalkylamine, to afford **14**. Reduction of the nitro group and ring formation to **15** were accomplished using phosgene or by heating the diamine intermediate with urea.²⁴ Subsequent alkylation of **15** with **11** provided target compounds. These strategies are summarized in Scheme 1.

Annual RSV infections produce significant morbidity and mortality in the young and elderly populations, and can be particularly problematic in those individuals with underlying cardiopulmonary insufficiency.^{25–30} The immunocompromised population is also at significant risk of complications and RSV has emerged as the leading cause of death in bone marrow transplant recipients.^{31–33} Rapid immunoassay kits are available to diagnose RSV infection, an important prelude to initiating therapy, but these are currently more effective in children who typically display higher virus titres than adults. Currently, the most effective diagnostic methodology for adults is direct immunofluorescence staining, illuminating the need for a more sensitive and rapid point-of-care diagnostic for the detection of RSV infection.³⁴ Consequently, RSV is frequently misdiagnosed as influenza and the full extent of the annual burden posed by RSV infection on the US population has begun to be appreciated only recently.^{26,30,35} This observation, coupled with the dearth of clinically effective antiviral agents for the prevention and treatment of RSV infection, has stimulated considerable interest in identifying inhibitors suitable for development.^{8,36} Several structurally distinct inhibitors of RSV–host cell fusion that function mechanistically by interfering with six helix bundle assembly in a fashion analogous to BMS-433771 (**6m**) have been described.^{8,36} However, BMS-433771 (**6m**) is the only RSV fusion inhibitor described to date that is orally bioavailable and demonstrates antiviral activity in animal models following oral administration.

References and notes

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- For Part 2 of this series, see: Yu, K.-L.; Zhang, Y.; Civiello, R. L.; Trehan, A. K.; Pearce, B. C.; Yin, Z.; Combrink, K. D.; Gulgeze, H. B.; Wang, X. A.; Kadow, K. F.; Cianci, C.; Krystal, M.; Meanwell, N. A. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 1133.
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