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# Discovery of Imidazopyridine Derivatives as Highly Potent Respiratory Syncytial Virus Fusion Inhibitors

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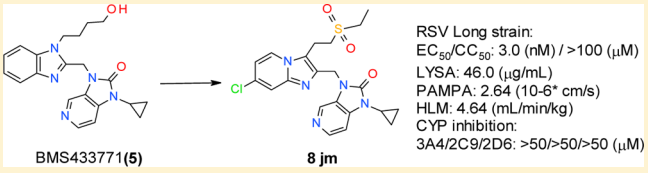
Supporting Information

**ABSTRACT:** A series of imidazolepyridine derivatives were designed and synthesized according to the established docking studies. The imidazopyridine derivatives were found to have good potency and physical-chemical properties. Several highly potent compounds such as **8ji**, **8jl**, and **8jm** were identified with single nanomolar activities. The most potent compound **8jm** showed an $IC_{50}$ of 3 nM, lower microsome clearance and no CYP inhibition. The profile of **8jm** appeared to be superior to BMS433771, and supported further optimization.




**KEYWORDS:** *Respiratory syncytial virus (RSV), virus, antiviral, fusion inhibitors, imidazopyridine, heterocycle*

Human respiratory syncytial virus (RSV) is one of the most important respiratory pathogens that cause lower respiratory tract infections such as bronchiolitis and pneumonia in infants and young children, resulting in up to 125,000 hospitalizations annually in the United States.[1] The mortality rate among children admitted to hospital is approximately 3% for those with heart and lung problems and up to 1% for those without these risk factors.[2,3] In adults and the elderly, RSV pneumonia is increasingly recognized as a significant cause of morbidity and mortality, being associated with more than 17,000 deaths annually between 1991 and 1998.[4−6]

Although the research into the prevention and treatment of RSV infection has been ongoing for almost 40 years, vaccine development is difficult,[7,8] and to date, there is no clinically approved vaccine. Passive immunization with the monoclonal antibody Palivizumab (Synagiss) has provided about 50% protection to high-risk children.[9] Ribavirin, the only approved small molecule for treatment of RSV, has to be given by a prolonged aerosol, and there are certain doubts as to its safety versus efficacy in treatment of RSV infection. As such, the unmet medical need for additional effective and safe treatments for RSV is paramount.

Fusion of the viral envelope or infected cell membranes with uninfected cell membranes is an essential step in the virus life cycle. The disruption of viral attachment and entry to cells is a common strategy in the design of antiviral therapies, as evidenced by successful approaches to influenza and HIV inhibition.[10] In the case of the Pneumovirinae subfamily, which includes RSV, a distinctive feature is the absence of hemagglutinin/neuraminidase fusion proteins and the dependence on the F protein alone for virus binding and cell entry.[11] The associated G glycoprotein appears to facilitate viral attachment. This pivotal role for the fusion protein has inspired a number of approaches over the years and led to compounds suitable for clinical evaluation.[12]

Several chemical series have been reported as RSV fusion inhibitors and two apparently progressed into early clinical development. One leading series is a class of benzimidazole pyridines.[13−16] The lead JNJ-2408068 (**1**) demonstrated nanomolar potency in RSV *in vitro* assays. TMC-353121 (**2**) was reported to access an additional binding pocket in the binding space[13−16] and displayed subnanomolar RSV *in vitro* activity with an unusual lung tissue residence half-life of 25 h. Another example of tricyclic imidazolines **3** was reported to inhibit RSV in cell culture at 100−250 ng/mL.[15,16] Recently, GS-5806 (**4**) was described as a novel RSV fusion inhibitor achieved proof-of-concept in human RSV challenge studies.[17] In addition, VP-14637 (**6**) was in Phase I trials prior to a decision not to develop it further, in part due to development costs.[18] RFI-641(**7**) was in Phase II clinical trials in 2000−2001 for the secondary prevention and therapeutic treatment of RSV infections in adults demonstrating both large therapeutic window *in vitro* and safety *in vivo*. Nevertheless, no further development information has been reported recently.[19,20]

BMS-433771 (**5**) is an orally bioavailable and modestly potent RSV inhibitor showing an $EC_{50}$ of 24 nM over a range of both laboratory and clinically relevant RSV strains.[21] BMS-433771 was progressed into preclinical evaluation.[22] Although the above advantages endorsed BMS-433771 for preclinical development, some potential concerns caught our attention according to our internal assessment, including modest activity, high *in vivo* clearance, short $T_{1/2}$ duration time (36 min), etc.

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Recognizing the areas for improvement, our efforts were focused on the optimization of potency and PK properties.

BMS-433771 was speculated to bind in the hydrophobic pocket created by the trimerization of the N-terminal heptad repeats of the RSV F1 protein.[23,24] According to the reported binding mode and the internal docking results (Figure 1), there

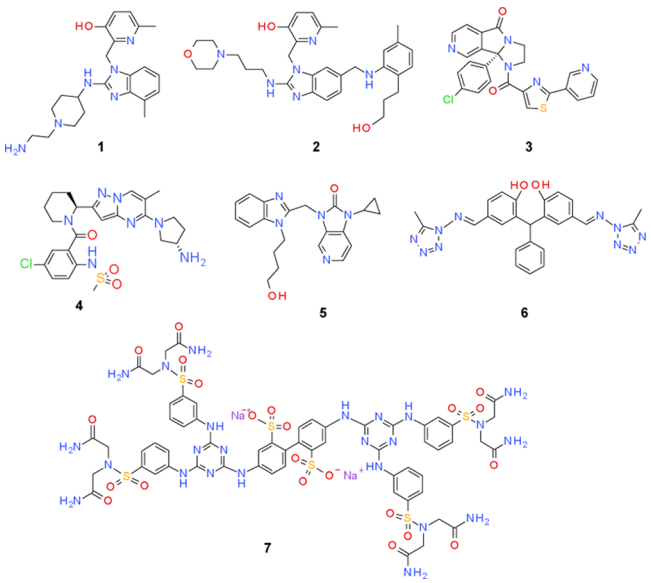


**Figure 1.** RSV fusion inhibitors under development.

remains some space around the BMS-433771 benzimidazole portion in the hydrophobic pocket close to LYS191 and Val192, as well as the side chain part, which is exposed to the surface of the pocket around Asp194 and Leu195. This observation prompted us to explore both benzimidazole region and side chain in order to improve potency and physicochemical properties.

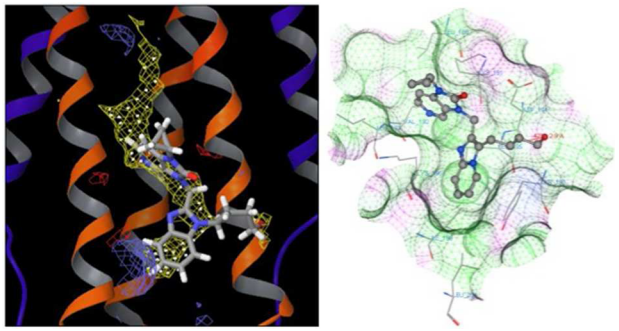
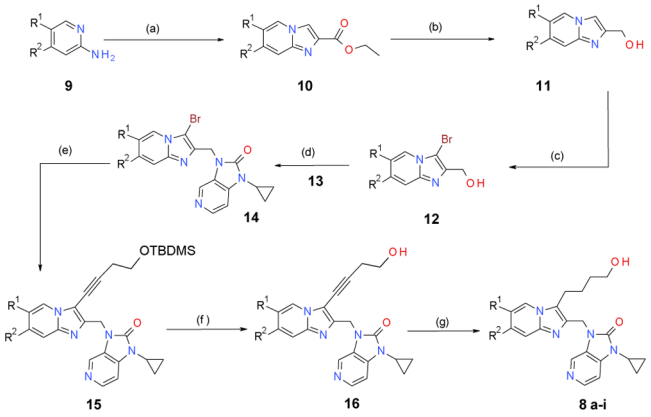


**Figure 2.** Docking model of RSV fusion inhibition with BMS-433771 (right)[16] and **8h** (left).

Several bioisosteres of the benzimidazole were examined to identify the optimal replacement (such as pyrazole, indazole, or isoxazole). Only imidazolepyridine analogue **8a** exhibited good potency presumably due to its nice fitting the binding pocket. Inspired by the promising results, some hydrophobic substitutions including methyl, fluoro, trifluor, etc., were introduced to the R1 and R2 positions of imidazole[1,2-*a*]pyridine core. The general synthesis of these derivatives **8a–i** is summarized in Scheme 1.

The synthesis of imidazole[1,2-*a*]pyridine analogue **8** commenced with commercially available 2-amino-pyridine

**Scheme 1. Synthesis of 8a–i Imidazopyridine Derivatives**[a]



[a]Reagents and conditions: (a) ethyl bromopyruvate, ethanol; (b) $LiAlH_4$, THF, 0 °C; (c) (i) NBS, $CH_3CN$, reflux; (ii) $SOCl_2$, DCM; (d) 1-cyclopropyl-1,3-dihydroimidazo[4,5-*c*] pyridin-2-one(**13**), DMF, NaH; (e) 4-(TBDMSO)-butyne, CuI, $Pd(PPh_3)_2Cl_2$, $Et_3N$, $CH_3CN$, microwave, 100 °C; (f) TBAF/THF 0 °C to rt; (g) Pd/C, $H_2$, 3 h, 70–85%

(**9**), which was cyclized with ethyl bromopyruvate via heating in ethanol to generate the imidazole[1,2-*a*]pyridine-2-ethyl ester **10**, followed by reduction with LAH, bromination, chlorination, and then alkylation with the right part: 1-cyclopropyl-1,3-dihydroimidazo[4,5-*c*]pyridin-2-one(**13**)[23] to yield intermediate 3-bromo-imidazole[1,2-*a*]pyridine **14**. This intermediate was then subjected to a Sonogashira coupling with 4-(*t*-butyldimethylsiloxy) butyne under microwave conditions. After removal of TBDMS, the intermediate **16** was quickly reduced with palladium on activated carbon to afford imidazole[1,2-*a*]pyridine derivatives **8a–i** in good yield (70–80%).

The antiviral activity of these compounds was evaluated by the reduction of the cytopathic effect (CPE) induced by the long (A) strain of virus replicating in HEp-2 human lung epithelial carcinoma cells[4] (Table 1). The introduction of fluoro at 6 position of **8b** resulted in the reduction of activity about 4-fold with an $EC_{50}$ of 96 nM in comparison to BMS-433771. It was found that the substitutions at 6-position (R1) of

**Table 1. Antiviral Activity of Imidazole[1,2-*a*]pyridine Analogues 8a–j**

| compds | R1 | R2 | $EC_{50}$ ($\mu$M)[a] A strain | $CC_{50}$ ($\mu$M)[a] |
|---|---|---|---|---|
| **5** | | | 0.028 | >100 |
| **8a** | Me | H | 0.217 | >100 |
| **8b** | F | H | 0.096 | >100 |
| **8c** | Cl | H | 0.422 | >100 |
| **8d** | $CF_3$ | H | 2.89 | >100 |
| **8e** | H | Me | 0.006 | >100 |
| **8f** | H | Et | 0.007 | >100 |
| **8g** | H | F | 0.023 | >100 |
| **8h** | H | H | 0.017 | >100 |
| **8i** | H | $CF_3$ | 0.217 | >100 |
| **8j** | H | Cl | 0.007 | >100 |

[a]$EC_{50}$: the concentration of test compound that protects 50% of infected cells. $CC_{50}$: the concentration of drug that manifests cytotoxicity toward 50% of uninfected HEp-2 cells in the absence of virus. Values are means of two or more experiments performed on consecutive weeks.[25]



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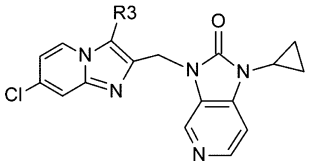
imidazolepyridine were very rigid and could not tolerate imidazolepyridine derivatives. Some of the results are presented below. The 6- methyl and chloro analogues (**8a** and **8c**) were much less potent with an $EC_{50}$ of 0.217 and 0.422 $\mu$M, respectively. Replacing the chloro with trifluoro substitution at 6-position (R1) resulted in a nearly inactive analogue **8d** with an $EC_{50}$ of 2.89 $\mu$M. Surprisingly, the substitutions at the 7-position (R2) can tolerate more broad modification and exhibited a trend toward potency improvement. Lastly, unprecedented single digital nanomolar potency was obtained when methyl (**8e**), ethyl (**8f**) or chloro (**8j**) were introduced as R2 of **8**, these compounds demonstrated 3−5 folds activity improvement in comparison to **5** with an $EC_{50}$ below 10 nM and $CC_{50}$ greater than 100 $\mu$M. The introduction of 7-substitution chloro or methyl had a significant impact on retaining potency. These promising results encouraged us to further explore the appropriate substitution pattern as shown in Table 1.

According to the new insight of the distinct impact of 7-substitution on potency improvement, a number of 7-chloroimidazopyridine analogues **8ja−r** bearing various side chain were synthesized as shown in Table 2 to identify more

**Table 2. Antiviral Activity of Imidazole[1,2-*a*]pyridine Analogues 8j−jr**



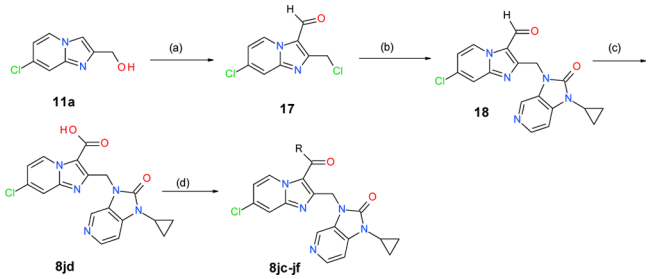

**8j-jr**

| compds | R3 | $EC_{50}$ ($\mu$M) | $CC_{50}$ ($\mu$M) |
|---|---|---|---|
| **8j** | $(CH_2)_4OH$ | 0.007 | >100 |
| **8ja** | H | 3.06 | 22.27 |
| **8jb** | CN | 0.086 | 22.49 |
| **8jc** | $CH_2OH$ | 1.93 | >100 |
| **8jd** | COOH | 25.5 | >100 |
| **8je** | $CONH(CH_2)_2OH$ | 2.23 | >100 |
| **8jf** | $CONH(CH_2)_2SO_2Me$ | 0.082 | >100 |
| **8jg** | CH=CHCOOH | 0.207 | >100 |
| **8jh** | $(CH_2)_2COOH$ | 0.053 | >100 |
| **8ji** | $(CH_2)_2CONH_2$ | 0.005 | >100 |
| **8jj** | $(CH_2)_2CONH(CH_2)_2OH$ | 0.010 | >100 |
| **8jk** | $(CH_2)_2CONHSO_2Me$ | 0.046 | >100 |
| **8jl** | $(CH_2)_2SO_2Me$ | 0.006 | >100 |
| **8jm** | $(CH_2)_2SO_2Et$ | 0.003 | >100 |
| **8jn** | NH-*n*-butyl | 0.041 | >100 |
| **8jo** | NH-cyclohexane | 0.072 | >100 |
| **8jp** | $NH(CH_2)_2$−morpholine | 0.083 | >100 |
| **8jq** | $CH_2NH(CH_2)_2OH$ | 0.683 | >100 |
| **8jr** | Ph(*p*-$SO_2Me$) | 0.089 | >100 |

potent compounds with favorite MDO properties. The synthesis of **8jc−jf** was described in Scheme 2 below, whereas the preparation of **8jg−jm** followed the coupling and reduction steps in Scheme 1 and condensation step in Scheme 2.

It was speculated from the docking results that the R3 position might be exposed to an open surface area of the pocket, which could be flexible. Various modifications in this region may be tolerable, although there is potential hydrogen bond interaction between the terminal hydroxyl with Lys191.

**Scheme 2. Synthesis of 7-Substituted Imidazopyridine Derivatives[a]**




[a]Reagents and conditions: (a) $POCl_3$, DMF, 70 °C; (b) NaH, DMF, 70 °C; (c) $NaClO_2$, *t*BuOH/THF; (d) HATU, $Et_3N$.

On the basis of this model, new analogues **8ja−r** with a variety of terminal groups at 3-position (R3) were investigated.

Table 2 revealed that many 7-chloro derivatives including **8jb**, **8jf**, **8jh−jp**, and **8jr** were very potent RSV inhibitors, with $EC_{50}$ of below 100 nM. Interestingly, even without a side chain, a cyano analogue **8jb** still exhibited prominent antiviral activity compared to **8ja**, although mild cytotoxicity was observed. Hydroxylmethyl, carboxylic acid, or amide replacement at R3 led to remarkable activity loss (**8jc**, **8jd**, and **8je**). The antiviral potency of methyl sulfone analogue **8jf** still remained with an $IC_{50}$ below 100 nM. For **8jf**, acid elongation derivatives **8jg** and **8jh** were not very potent. In contrast, several 7-chloro derivatives **8ji**, **8jj**, **8jl**, and **8jm** containing amide and alkyl sulfonyl as terminal groups of side chain demonstrated high antiviral acidity with single digital nanomolar $IC_{50}$s. The most potent compound **8jm** has an $IC_{50}$ of 3 nM, which is around 9-fold more potent than BMS-433771 (**5**). A few substituted amino-linked analogues like **8jn** and **8jp** exhibited some potency decline, and **8jq** had much weak activity with an $IC_{50}$ of 0.68 $\mu$M. Replacing the hydroxyl butyl with more hinderous *para*-methyl sulfonyl phenyl at R3 position resulted in more than 10-fold activity loss (0.089 $\mu$M).

The physicochemical and metabolic properties of several potent 7-chloroimidazolepyridine analogues and BMS compound **5** were profiled below (Table 3). Compound **8jh** exhibited highly enhanced solubility and metabolic stability; however, its activity and permeability were not optimal. The solubility of the amide **8ji** is slightly better than BMS compound **5**; **8jj** is more soluble with up to 3-fold LYSA increase. The PAMPA value of **8ji** is subtly increased; however,

**Table 3. Physicochemical and Metabolic Properties of Leading Compounds**

| compds | solubility LYSA[a] ($\mu$g/mL) | permeability PAMPA[a] ($10^{-6}$ cm/s) | microsome clearance human[b] /mouse[c] (mL/min/kg) | CYP inhibition 3A4/2C9/2D6 ($IC_{50}$, $\mu$M) |
|---|---|---|---|---|
| **5** | 39 | 2.2 | 16.3/82 | 27.5/>50/>50 |
| **8j** | 20 | 3.1 | 11.5/80 | NA |
| **8jh** | 541 | 0.30 | 0.0/9.1 | >50/>50/>50 |
| **8ji** | 87 | 2.5 | 13.5/59 | NA |
| **8jj** | 107 | 0.96 | 2.9/47 | NA |
| **8jl** | 59 | 3.6 | 2.5/35 | >50/>50/>50 |
| **8jm** | 46 | 2.6 | 4.6/62 | >50/>50/>50 |

[a]Values are means of two or more experiments performed on consecutive weeks. [b]Human: high (>15), medium (5−15), low (<5). [c]Mouse: high (>68), medium (23−68), low (<23).



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**8jj** has a little lower one (Table 3). Compounds **8jl** and **8jm** appear equally soluble as BMS compound **5** and much more permeable. All five compounds significantly improved microsome stabilities. These significant advantages suggested superior PK properties with higher bioavailability and lower clearance could be achieved for these several leading compounds toward further development. More DMPK and *in vivo* data will be reported in due course.

In summary, a series of imidazolepyridine derivatives were conceived and synthesized according to our docking studies. It was found 7-substitution is crucial for potency maintaining and improvement. Several highly potent compounds, **8ji**, **8jl**, and **8jm**, were identified with single digital nanomolar activities of which the most potent compound **8jm** showed an $IC_{50}$ of 3 nM with up to 9-fold activity improvement relative to **5**, low to medium microsome clearance, and no CYP inhibition. The promising profile of **8jm** supported further optimization efforts of this series, which will be reported in due course.

## ■ ASSOCIATED CONTENT

### Ⓢ Supporting Information

Biological assays, synthetic procedures, and analytical data for selected compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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### Notes

The authors declare no competing financial interest.

## ■ ABBREVIATIONS

RSV, respiratory syncytial virus; LYSA, lyophilization solubility assay; PAMPA, partial permeability assay; MDO, multiple dimensional optimization; CYP, Cytochrome P450 enzymes

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