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The discovery of 1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones as a new class of respiratory syncytial virus (RSV) fusion inhibitors. Part 1

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This paper is dedicated to our wonderful colleague and friend Roland Nearn (1940–2013)

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ABSTRACT

Respiratory syncytial virus (RSV) is a major cause of respiratory tract infections in infants, young children and adults. Compound **1a** (9*b*-(4-chlorophenyl)-1-(4-fluorobenzoyl)-1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one) was identified as an inhibitor of A and B strains of RSV targeting the fusion glycoprotein. SAR was developed by systematic exploration of the phenyl ($\mathbf{R^1}$) and benzoyl ($\mathbf{R^2}$) groups. Furthermore, introduction of a nitrogen at the 8-position of the tricyclic core resulted in active analogues with improved properties (aqueous solubility, protein binding and log*D*) and excellent rat pharmacokinetics (e.g., rat oral bioavailability of 89% for compound **17**).

Respiratory syncytial virus (RSV) is the predominant cause of acute lower respiratory tract infection in young children and results in substantive numbers of hospital admissions. Global mortality rates in children under five years of age have been estimated at 200,000 annually.[1] RSV is known primarily as a pediatric pathogen; however it can infect individuals of all ages, particularly those with underlying disease. Symptoms range from severe pneumonia and bronchiolitis to much milder symptoms similar to the common cold.[2] *Palivizumab*, a humanized monoclonal antibody targeting the fusion glycoprotein of RSV, is registered for the prevention of serious lower respiratory tract disease caused by RSV in high-risk infants less than two years old.[3] The limited prophylactic use of *palivizumab* due to its high cost supports the need for alternative cost-effective therapies to treat RSV disease. The only agent approved for the treatment of RSV infection is ribavirin but it is rarely used as it is considered to provide marginal benefit and is potentially toxic.[4] Several potent small molecule fusion inhibitors have been progressed to the preclinical stage including BMS-433771[5] and TMC353121,[6] both of which have since been discontinued (Fig. 1). Two compounds are currently in Phase 2 studies namely MDT-637 (formerly VP-14637)[7] and GS-5806.[8] RSV604, a benzodiazepine which targets the viral N-protein,[9] and the siRNA ALNRSV01[10] were advanced into clinical trials but it appears that development of these drugs has been halted.

A diverse library of compounds (assembled in-house at Biota) was screened for activity against RSV using a cytopathic effect (CPE) assay in Hep2 cells.[11] From this screening campaign, 9*b*-(4-chlorophenyl)-1-(4-fluorobenzoyl)-1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one, **1a** (Fig. 2) was identified as an RSV inhibitor, displaying very promising activity against both A and B strains. However, **1a** had relatively high lipophilicity and low aqueous solubility (see Table 1). In addition, the activity displayed by the compound shifted significantly when tested in the CPE assay in the presence of alpha-1-acid glycoprotein (AAG), indicating that compound **1a** was significantly bound to this human serum protein (no activity shift was observed in the presence of human serum albumin).[12] The antiviral activity of compound **1a** was susceptible to the known mutation D489Y in the F protein of the RSV-A Long strain (>76 fold activity shift).[5,13] In vitro resistance selection studies were attempted with compound **1a** but the maximum compound concentration

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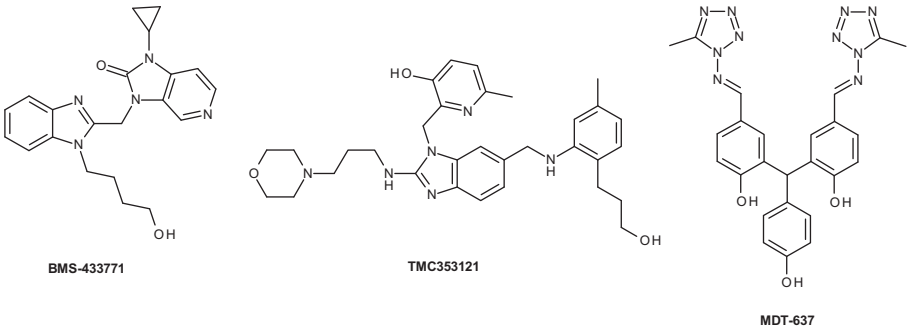


Figure 1. Selected RSV fusion inhibitors.

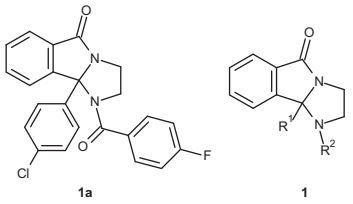


Figure 2. Structure of compound **1a** and general structure of 1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones (**1**).

was limited by poor solubility. We were successful in raising T335I as a single F protein substitution against compound **1f** in RSV Long. Compound **1a** was cross-resistant to the T335I mutation (>76 fold activity shift compared to the wild type Long virus in a CPE assay) as were the other published RSV fusion inhibitors MDT-637 (VP-14637, >1400 fold activity shift) and BMS-433771 (380 fold activity shift). Cross-resistance is a common feature for this class of fusion inhibitors which appear to have a similar mechanism of action.[5–7] In addition, a time of addition experiment demonstrated that compound **1a** acts early in the virus replication cycle providing additional support that it functions as a fusion inhibitor. A program to investigate the SAR and improve the drug-like properties of compound **1a** was undertaken, focussing initially on variation at R^1, R^2 and the fused aromatic ring (Fig. 2).

Investigations initially centred on exploring the SAR at the R^1 position. Racemic compounds were synthesised using the three step procedure outlined in Scheme 1.[16]

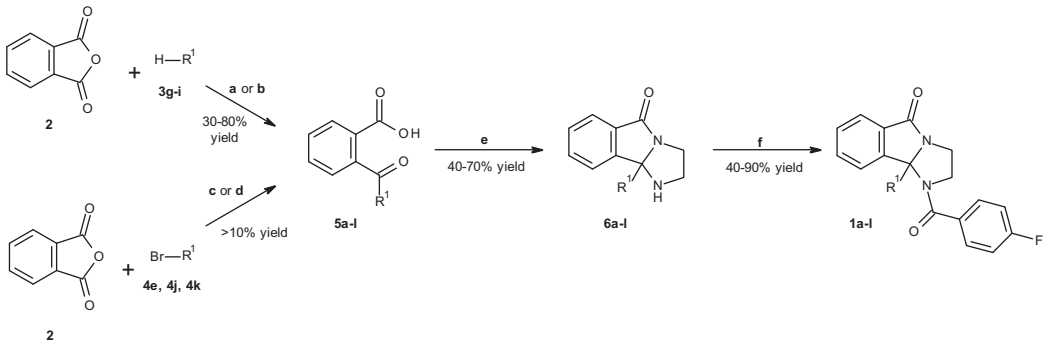
Keto acid compounds **5a–l** were either purchased or synthesised from phthalic anhydride using Friedel–Crafts acylation or organometallic chemistry.[17] They were then condensed with excess ethylenediamine in refluxing toluene or xylenes to give cores **6a–l**.[18] A number of conditions were investigated for the acylation of cores **6a–l** to give target compounds **1a–l**; the use of 2–5 equiv of acid chloride in pyridine was found to be most effective.

Compounds containing ether-substituted phenyl R^1 groups were synthesised according to Scheme 2. Demethylation of keto acid **5l** followed by condensation with ethylenediamine gave the phenol substituted core **6m**. Diacylation and hydrolysis of the resulting phenolic ester yielded target **1m**. Functionalisation of

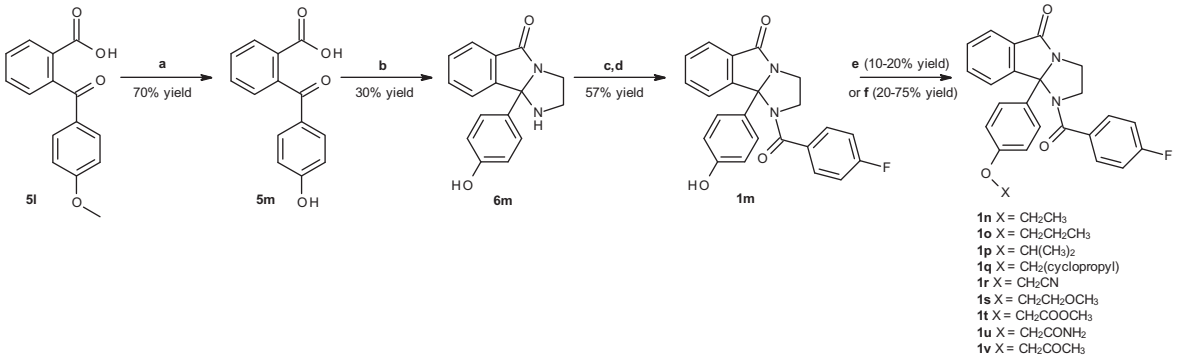
Table 1
Antiviral activity and physicochemical properties of compound **1a**

Compd	EC_{50} (μM) CPE Assay[a]			CC_{50} (μM)	log*D*[b]	EC_{50} fold shift RSV A2 + AAG[c]	Solubility (μg/mL)[d]	
	RSV A2	RSV Long	RSV B1				pH 2	pH 6.5
1a	0.28 ± 0.08 (*n* = 40)	0.26 ± 0.07 (*n* = 12)	0.75 ± 0.27 (*n* = 12)	>18	4.0	46	6.3–12.5	6.3–12.5

[a] Standard deviations are quoted where $n > 2$.
[b] Effective log*D* values were measured using a chromatographic method employing a SUPELCOSIL LC-ABZ column using an octanol saturated mobile phase at pH 7.4.[14]
[c] Alpha-1-acid glycoprotein present at a concentration of 1.5 mg/mL.
[d] Kinetic solubility measured by nephelometry.[15]



Scheme 1. Reagents and conditions: (a) $AlCl_3$, 90–110 °C, 3 to 5 h; (b) $AlCl_3$, 0 °C to rt, 16 h; (c) **4e**, Mg, cat. I_2, 40 °C then rt, 1 h followed by **2**, −60 °C, 1.5 h then rt, 1.5 h; (d) **4j** or **4k**, *n*-BuLi, Et_2O, −78 °C, 30 min followed by **2**, THF, −78 °C, 1 h then rt; (e) ethylenediamine, toluene or xylenes, Dean–Stark, reflux, 2–5 h; (f) 4-fluorobenzoyl chloride, pyridine, 0 °C to rt.



Scheme 2. Reagents and conditions: (a) pyridine hydrochloride, 195 °C, 5 h; (b) ethylenediamine, xylenes, Dean–Stark, reflux, 7 h; (c) 4-fluorobenzoyl chloride, pyridine, 0 °C to rt; (d) 1 M NaOH (aq.), MeOH, rt, 30 min; (e) XOH, PS-PPh_3, DEAD, THF, 0 °C to rt; (f) XBr or XCl, K_2CO_3, acetone, reflux.

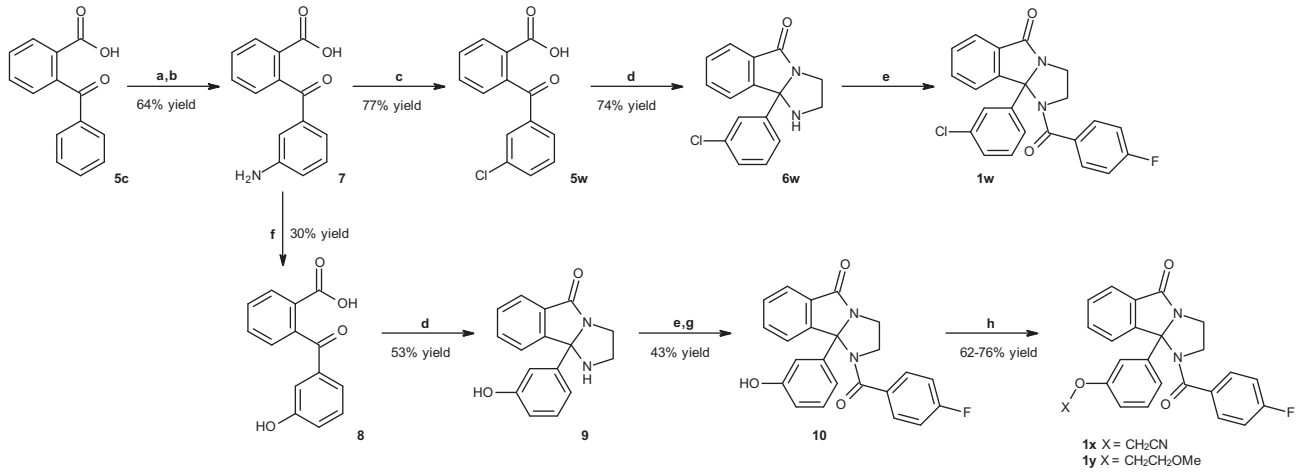
the phenol was then carried out using Mitsunobu or alkylation chemistry.

The introduction of 3-substituted phenyl R^1 groups was achieved by nitration of the commercially available keto-acid **5c** followed by reduction to give amine **7** (Scheme 3). This was used to access chloro-substituted intermediate **5w** and phenol **8** which were then carried through the remaining steps of the synthesis to give targets **1w**–**y**.

The importance of the R^1 group for activity against RSV was demonstrated when its replacement with a hydrogen (compound **1b**) resulted in an inactive compound (see Table 2). The presence of a substituent on the aromatic ring was also found to be desirable, with the phenyl analogue **1c** showing a loss of activity when compared to its 4-chlorophenyl counterpart (**1a**). Attempts to replace the chloro substituent on the phenyl ring with a small range of different functional groups (compounds **1d**–**i**) generally resulted in compounds with similar or slightly reduced potency. Replacement of the phenyl group with 2- or 3-pyridine (compounds **1j** and **1k**) gave compounds with poor or no activity. Varying substituent chain length did not have a significant impact on activity; little variation was seen among the alkyl-substituted compounds (compounds **1f**–**h**), and a less than two-fold change in potency was observed within the alkyl ether series (compounds **1l**, **1n** and **1o**). Chain branching was not well tolerated in either series (compounds **1i** and **1p**), however the introduction of a cyclopropylmethylether substituent (compound **1q**) gave a three-fold improvement in activity compared to the original hit. Further functionalisation of the ether substituent demonstrated that the introduction of a nitrile (compound **1r**) or an additional ether group (compound **1s**) was tolerated without improving activity, while the introduction of polar, electron-withdrawing groups (compounds **1t**–**v**) resulted in losses of potency. The change in aryl substitution position did not result in a significant change in potency when the chloro substituent was investigated (compare **1a** to **1w**), but caused considerable losses in activity when the substituents were ethers (compare **1r** to **1x** and **1s** to **1y**).

A preliminary investigation into the SAR around the R^2 group was also conducted. Compounds were synthesised according to the chemistry outlined in Scheme 4. Analogues lacking carbonyl functionality at R^2 were synthesised by direct condensation of keto acid **5a** with the appropriate mono-functionalised ethylenediamine.[17] The remaining compounds were synthesised from the core **6a**. A range of conditions were investigated for the formation of amides and ureas **1ac**–**1av**, and performing the reaction in pyridine was again found to be the most effective method.

The presence of the R^2 substituent was found to be critical for activity against RSV, with the core (**6a**) proving to be inactive (see Table 3). Removal of the carbonyl functionality (compounds **1aa** and **1ab**) also rendered compounds inactive, while replacing the 4-fluorobenzoyl group with its corresponding homologue (compound **1ac**) resulted in a loss of potency. Investigation of a small set of 4-substituted benzoyl analogues revealed that



Scheme 3. Reagents and conditions: (a) HNO_3, H_2SO_4, 0 °C; (b) H_2, Pd/C, EtOH, rt, 6 h; (c) H_2SO_4 (aq.), $NaNO_2$, 0 °C, 1 h, then CuCl, HCl (aq.), rt, o/n; (d) ethylenediamine, xylenes, Dean–Stark, reflux, 5 h; (e) 4-fluorobenzoyl chloride, pyridine, 0 °C to rt; (f) $NaNO_2$, H_2SO_4 (aq.), 0 °C, 1 h then rt to 50 °C, 2 h; (g) 1 M NaOH (aq.), MeOH, rt, 1 h; (h) XBr or XCl, K_2CO_3, acetone, reflux, 30 h.

Table 2
RSV inhibitory activity and cytotoxicity for 1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones with variation at R1

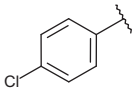
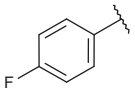
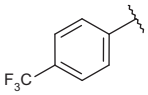
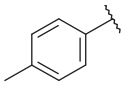
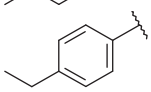
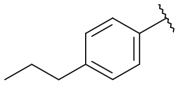
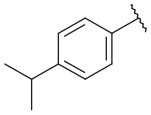
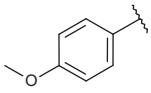
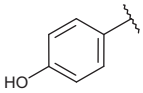
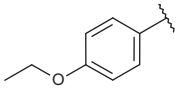
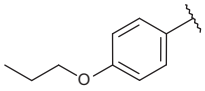
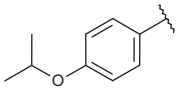
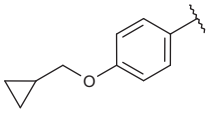
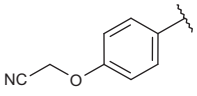
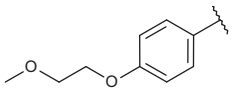
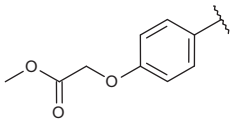
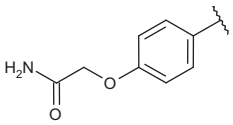
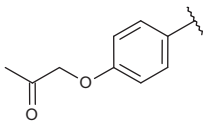
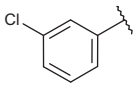
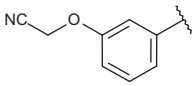
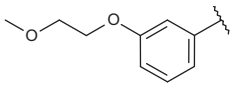
Compd	R^1	RSV A2 EC_{50} (μM) CPE assay[a]	Cytotoxicity, CC_{50} (μM)
1a		0.28 ± 0.08 (*n* = 40)	>20
1b		>20	>20
1c		1.1, 1.1	>20
1d		0.71 ± 0.29 (*n* = 3)	>20
1e		0.55, 0.51	>20
1f		0.18, 0.23	>20
1g		0.21 ± 0.07 (*n* = 3)	>18
1h		0.27 ± 0.12 (*n* = 3)	18
1i		1.2 ± 0.3 (*n* = 3)	>20
1j		>20	>20
1k		10	>20
1l		0.57, 0.53	>20
1m		11	>20
1n		0.50, 0.20	>20
1o		0.63 ± 0.27 (*n* = 3)	>20
1p		1.1, 1.8	>20
1q		0.11, 0.079	>20
1r		0.24, 0.30	>17

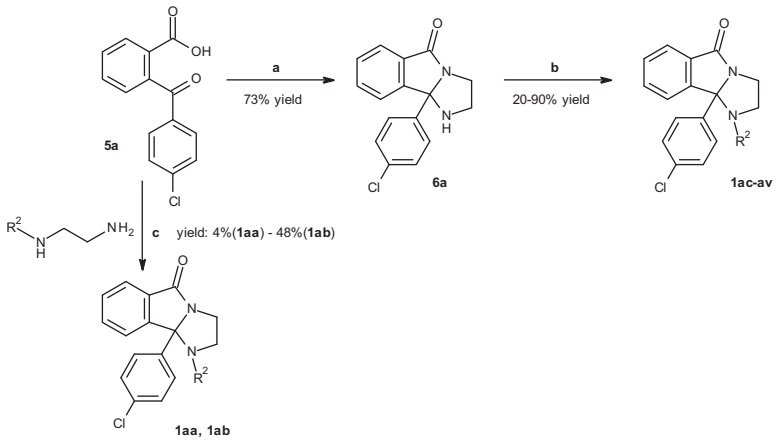
Table 2 (*continued*)

Compd	R^1	RSV A2 EC_{50} (μM) CPE assay[a]	Cytotoxicity, CC_{50} (μM)
1s		0.25	>16
1t		3.3	>16
1u		1.5, 1.0	11
1v		0.86	>16
1w		0.19, 0.47	>18
1x		3.4	>17
1y		>16	>16

[a] Standard deviations are quoted where *n* > 2.

compound activity was highly sensitive to the nature of the substituent at the 4 position. Removal of the fluoro substituent (compound **1ad**) resulted in a small loss of activity, while replacing it with a chloro (compound **1ae**) or methyl (compound **1af**) group resulted in a greater than 10-fold drop in potency. Analogues containing a trifluoromethyl (**1ag**), methoxy (**1ah**) or trifluoromethoxy (**1ai**) substituent were all inactive. The synthesis of a small set of urea analogues (compounds **1aj**–**1am**) gave compounds with a range of activities against RSV. Although none were as active as the original hit, the level of activity displayed by compounds **1al** and **1am** indicated the urea series could provide a promising starting point for future optimisation efforts. Similarly, the activity displayed by compounds containing 5- and 6-membered heterocyclic amides (**1an** and **1ao**) was also encouraging. Attempts to replace the aromatic amide substituent with a range of acyclic, cyclic and functionalised alkyl groups (compounds **1ap**–**1av**) all resulted in losses in potency.

Having gained a broad indication of the SAR requirements of the R^2 substituent and identified a number of avenues for further investigation in this area, our attention turned to improving the drug-like properties of the hit series. Investigations into improving the solubility, log*D* and protein binding centred on introducing nitrogen atoms into the fused, left-hand ring (Fig. 3). Synthesis of the modified cores from the appropriate anhydrides was initially achieved using the same chemistry outlined in Scheme 1. Compounds **12** and **13** and compounds **15** and **16** were obtained as mixtures of isomers which were separated by chromatography or crystallisation during the synthesis. N-oxide **17** was synthesised from pyridine **16** according to the method of Sharpless.[19]



Scheme 4. Reagents and conditions: (a) ethylenediamine, toluene, Dean–Stark, reflux, 5 h; (b) acid chloride or isocyanate, pyridine, 0 °C to rt; (c) xylenes, Dean–Stark, reflux.

Table 3
Structure, RSV inhibitory activity and cytotoxicity for 1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones with variation at R^2

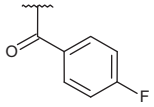
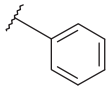
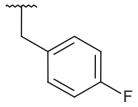
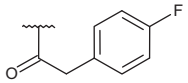
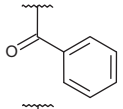
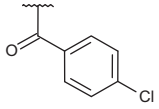
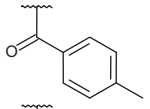
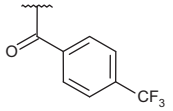
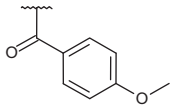
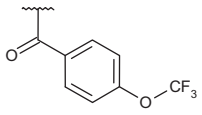
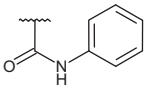
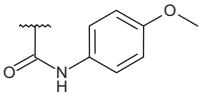
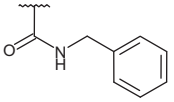
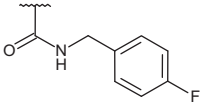
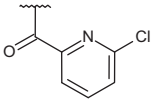
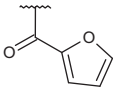
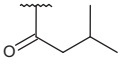
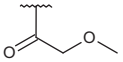
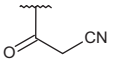
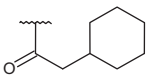
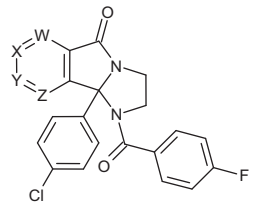
Compd	R^2	RSV A2 EC_{50} (μM) CPE assay[a]	Cytotoxicity, CC_{50} (μM)
1a		0.28 ± 0.08 (*n* = 40)	>20
6a		>20	>70
1aa		>20	>20
1ab		>20	16
1ac		0.97 ± 0.21 (*n* = 4)	>20
1ad		0.45, 0.54	>20
1ae		3.7	17
1af		5.8	17
1ag		>20	17
1ah		>20	16
1ai		>20	5.7

Table 3 (*continued*)

Compd	R^2	RSV A2 EC_{50} (μM) CPE assay[a]	Cytotoxicity, CC_{50} (μM)
1aj		7.1	>20
1ak		1.6	>20
1al		0.79, 0.73	>20
1am		0.60 ± 0.20 (*n* = 3)	12, 10
1an		0.47	>17
1ao		0.58, 0.26	12
1ap		1.3, 1.2	>20
1aq		1.0 ± 0.2 (*n* = 4)	>20
1ar		0.94, 0.74	>20
1as		4.9	>21
1at		2.7, 3.5	>21
1au		4.5	>21
1av		4.5	14

[a] Standard deviations are quoted where *n* > 2.



1a W = X = Y = Z = CH
12 W = N, X = Y = Z = CH
13 Z = N, W = X = Y = CH
14 W = Z = N, X = Y = CH
15 X = N, W = Y = Z = CH
16 Y = N, W = X = Z = CH
17 Y = N$^+$O$^-$, W = X = Z = CH

Figure 3. Structures of compounds **1a** and **12**–**17**.

While analogues **12** to **15** all demonstrated losses in activity compared to the hit compound **1a**, the introduction of a nitrogen at the 8-position (compound **16**) was well tolerated (see Table 4). The corresponding N-oxide (**17**) showed a similar level of potency. Both compounds also retained the cross-strain activity seen for compound **1a** (see Table 5). Gratifyingly, compounds **16** and **17** showed considerably improved properties when compared to the original hit, displaying reduced log*D* and increased kinetic solubility. In addition, both compounds showed a reduced shift in RSV activity when tested in the CPE assay in the presence of the purified human serum protein alpha-1-acid glycoprotein (AAG), and compound **16** displayed reduced rat plasma protein binding compared to compound **1a**.

Pyridine analogue **16** demonstrated good bioavailability in rat, but the PK profile had a very long elimination half-life (see Table 6). However, the corresponding N-oxide (**17**) had a good pharmacokinetic profile, demonstrating high exposure and bioavailability with a moderate half-life (presumably due in part to a smaller volume of distribution).

Compounds **16** and **17** were separated into their enantiomers using chiral chromatography to establish the effect of the chiral centre on biological activity. In both cases the antiviral activity appeared to reside in only one enantiomer when tested in the CPE assay against RSV A2. The enantiomers of **16** were separated with >95% enantiomeric excess (ee) and had EC_{50} values of 0.11 μM and 14 μM. For **17** one enantiomer had EC_{50} = 0.21 μM (92% ee) versus EC_{50} = 11 μM (95% ee) for the opposite enantiomer. The weak activity observed for the 'inactive enantiomer' was likely due to the presence of low levels of the active chiral species due to incomplete chromatographic separation although this was not proven.

In summary, 1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-ones have been identified as a new class of RSV inhibitors. Initial SAR investigations revealed that 4-substituted aryl groups are

Table 4
Structure, RSV inhibitory activity and cytotoxicity for 1,2,3,9*b*-tetrahydro-5*H*-imidazo[2,1-*a*]isoindol-5-one derivatives with variation at the fused aromatic ring

Compd	W	X	Y	Z	RSV A2 EC_{50} (μM) CPE assay[a]	Cytotoxicity, CC_{50} (μM)
1a	CH	CH	CH	CH	0.28 ± 0.08 (*n* = 40)	>20
12	N	CH	CH	CH	1.9, 0.88	>20
13	CH	CH	CH	N	1.2 ± 0.7 (*n* = 4)	>20
14	N	CH	CH	N	>18	>18
15	CH	N	CH	CH	2.7	>18
16	CH	CH	N	CH	0.23 ± 0.07 (*n* = 40)	>49
17	CH	CH	N^+–O^-	CH	0.25 ± 0.10 (*n* = 3)	>47

[a] Standard deviations are quoted where *n* > 2.

Table 5
Antiviral activity and physicochemical properties of compounds **1a**, **16** and **17**

Compd	EC_{50} (μM) CPE assay[a]			log*D*[b]	EC_{50} fold shift RSV A2 + AAG[c]	Protein binding % (rat plasma)	Solubility (μg/mL)[d]	
	RSV A2	RSV Long	RSV B1				pH 2	pH 6.5
1a	0.28 ± 0.08 (*n* = 40)	0.26 ± 0.07 (*n* = 12)	0.75 ± 0.27 (*n* = 12)	4.0	39	98	6.3–12.5	6.3–12.5
16	0.23 ± 0.07 (*n* = 40)	0.22 ± 0.10 (*n* = 12)	0.68 ± 0.34 (*n* = 12)	2.8	<10	73	25–50	12.5–25
17	0.25 ± 0.10 (*n* = 3)	0.35, 0.12	0.91	2.3	<10	ND	50–100	25–50

[a] Standard deviations are quoted where *n* > 2.
[b] Effective logD values were measured using a chromatographic method employing a SUPELCOSIL LC-ABZ column using an octanol saturated mobile phase at pH 7.4.[14]
[c] Alpha-1-acid glycoprotein present at a concentration of 1.5 mg/mL.
[d] Kinetic solubility measured by nephelometry.[15]

Table 6
Intravenous and oral PK properties of compounds **1a**, **16** and **17** in male Sprague Dawley rat.

Compd	Rat PK IV (*n* = 2)				Rat PK Oral (*n* = 2)			
	Dose (mg/kg)	$T_{1/2}$ (hr)	CLtotal (mL/min/kg)	V_z (L/kg)	Dose (mg/kg)	C_{max} (μM)	$T_{1/2}$ (hr)	*F* (%)
1a	1.4[a]	16	2.1	2.7	22[b]	2.0	17	15
16	2.0[a]	>24	2.7	6.0	19[b]	6.3	>24	28
17	2.0[c]	6.5	2.4	1.3	20[d]	23	5.6	89

[a] Dosed as a solution in 0.1 M Captisol and 10-12.5% DMSO.
[b] Dosed as a suspension with hydroxypropylmethylcellulose.
[c] Dosed as a solution in 5% glucose and 10% DMSO.
[d] Dosed as a suspension with carboxymethylcellulose.

preferred at R^1 and identified ureas and heterocyclic amides as promising starting points for further optimisation at R^2. The introduction of a nitrogen at the 8-position of the tricyclic core (1,2,3,9*b*-tetrahydro-5*H*-imidazo[1′,2′:1,2]pyrrolo[3,4-*c*]pyridin-5-one compounds **16** and **17**) resulted in a significant improvement in the drug-like properties of the series without compromising activity, providing encouragement for further optimisation of this class of RSV fusion inhibitors. Details of this work will be reported in a subsequent publication.

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16. *Example preparation of compound* **1h**: To **2** (2.0 g) and $AlCl_3$ (4.0 g, 2.2 equiv) was added *n*-propylbenzene (8.4 mL, 4.0 equiv) at 0 °C. The mixture was stirred at room temperature (rt) for 16 h and poured into a slurry of ice/1 M HCl. The solids were collected by filtration and recrystallised from toluene/hexane to give **5h** (1.84 g, 51%). A solution of **5h** (1.0 g) in xylene (50 mL) was treated with ethylenediamine (2.5 mL, 10 equiv) and heated to reflux for 5 hours with a Dean–Stark condenser. The solvent was evaporated and the residue purified by flash chromatography (1:1 EtOAc/hexane) to yield **6h** (750 mg, 69%). A solution of **6h** (40 mg) in pyridine (0.50 mL) was treated with 4-fluorobenzoyl chloride (3.3 equiv) at 0 °C. After stirring for 16 h at rt the mixture was diluted with CH_2Cl_2, washed with water, filtered and concentrated. The residue was purified by flash chromatography (3:17 EtOAc/hexane) to yield **1h** as a white crystalline solid (47 mg, 83%).
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