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Respiratory syncytial virus inhibitors. Part 2: Benzimidazol-2-one derivatives☆

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Abstract—Structure–activity relationships for a series of benzimidazol-2-one-based inhibitors of respiratory syncytial virus are described. These studies focused on structural variation of the benzimidazol-2-one substituent, a vector inaccessible in a series of benzotriazole derivatives on which **2** is based, and revealed a broad tolerance for substituent size and functionality.
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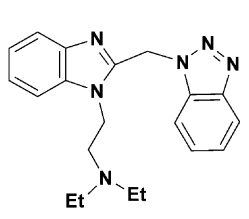
Respiratory syncytial virus (RSV) infections are common annual occurrences in the United States that are largely associated with the winter season, although the virus can also be detected during the summer months.[2–6] Children are generally exposed to RSV initially before the age of 2 years and co-infection with other respiratory pathogens can lead to exacerbated symptoms.[7,8] Infants with underlying cardiopulmonary problems are particularly susceptible to complications from RSV infection, which is the most common viral cause of death in children under 5 years of age.[6] Moreover, reinfection with RSV is common in both children and adults, a consequence of incomplete immunity of limited durability, whilst the morbidity and mortality associated with RSV infections of the elderly may be significantly underestimated since it is frequently misdiagnosed as influenza.[6,9] The humanized monoclonal antibody palavizumab (Synagis®), delivered by a series of injections, is licensed for the prevention of RSV infections,[10] whilst ribavirin, frequently administered by aerosolization, is the only approved therapeutic agent.[11] However, ribavirin is a non-selective antiviral agent and teratogenic,[12] prompting a search for more potent and selective inhibitors of RSV.[2,13] The majority of screening campaigns have relied upon a virus replication assay designed to identify leads without bias for a specific mechanistic intervention. Interestingly, many of the selective RSV inhibitors that have recently emerged have been characterized as interfering with the fusion of virus and host cell membranes.[14–20]



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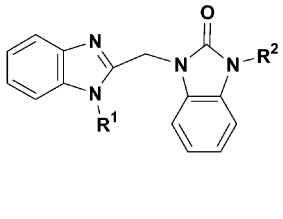

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We have recently profiled the fundamental structure–activity relationships associated with a new class of RSV fusion inhibitor, a series of benzotriazole derivatives of which **1** is representative.[1] The diethylaminoethyl side chain of **1** was found to be quite tolerant towards

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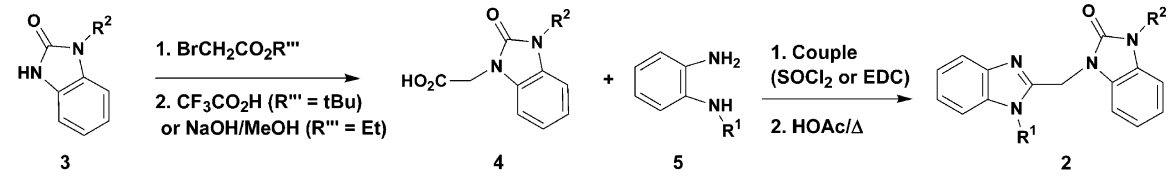
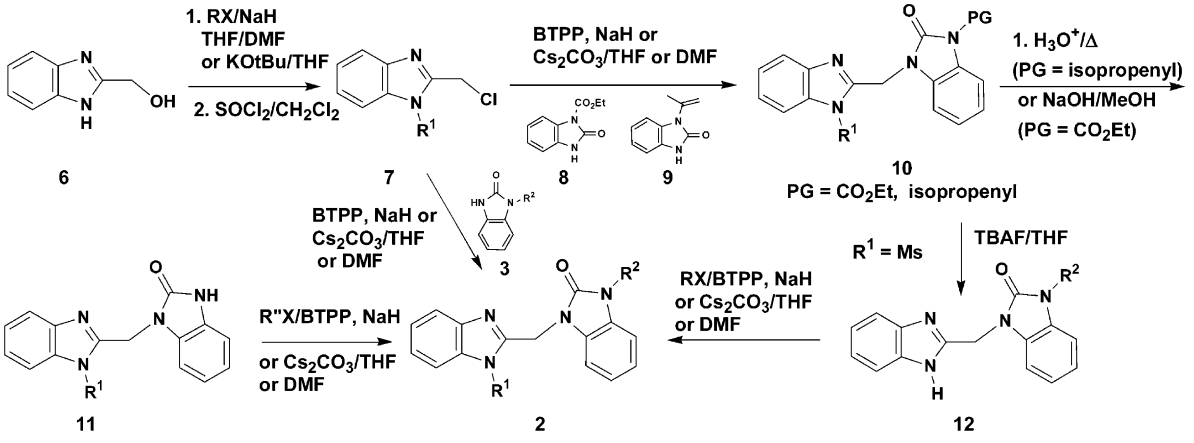
structural variation, with a broad range of polar and non-polar functionality compatible with RSV inhibition. The principal requirement related to a minimum 2 atom separation between the terminal functionality and the benzimidazole heterocycle. As part of a broad survey designed to delineate the pharmacophore associated with **1**, replacement of the benzotriazole element with a benzimidazol-2-one was examined as a means of probing a substituent vector not available to **1**.[21–24] In this communication, we demonstrate that simple derivatives of **2** are potent inhibitors of RSV in vitro and establish a correspondence with **1**.

Access to benzimidazol-2-one derivatives **2** was accomplished by several complementary pathways, summarized in Schemes 1 and 2. The process selected for individual targets was dictated by functional group compatibility or convenience. Alkylation of a mono-protected benzimidazol-2-one derivative **3** with an ester of bromoacetic acid was followed by liberation of the acid moiety (NaOH/MeOH for the Me ester, CF_3CO_2H for the *t*-butyl ester) to afford **4**. Activation of the carboxylate of **4** using $SOCl_2$ or *N*-(3-dimethylaminopropyl)-*N*′-ethylcarbodiimide (EDC) was followed by the addition of a monosubstituted phenylene diamine derivative **5**. Dehydration of the intermediate amide was induced by heating in AcOH at reflux to provide target benzimidazoles **2** (Scheme 1). Alternatively, as depicted in Scheme 2, alkylation of 2-hydroxymethylbenzimidazole (**6**), using NaH in a mixture of DMF and THF, was followed by $SOCl_2$-mediated chlorination to afford **7**. The chloride **7** was used as an electrophile for a mono-protected benzimidazol-2-one derivative, either the carboethoxy derivative **8**[25] or the *iso*-propenyl-substituted compound **9**,[26] to provide the protected precursor **10**. For **10** in which PG = *iso*-propenyl, hydrolysis under acidic conditions removed this protecting group[26] whilst for **10** with PG = CO_2Et, mild basic hydrolysis accomplished the conversion to **11**.[25] The *iso*-propenyl moiety of **9** or **10** was hydrogenated to afford the corresponding isopropyl-substituted compounds. Alkylation of the benzimidazolone nitrogen of **11** was readily accomplished under the influence of NaH, Cs_2CO_3 or the phosphazene base *t*-butylimino-tri(pyrrolidino)phosphorane (BTPP) in the presence of an electrophilic halide or mesylate, to afford target compounds **2**. In some cases, the mono-alkyated benzimidazol-2-one **3** was preformed using literature procedures[25,26] and coupled with **7** to afford **2** in a more direct fashion. One final avenue exploited the mesyl moiety as a protecting group for the benzimidazole nitrogen atom in **7**, a moiety readily removed from **10** using TBAF in THF to give **12**. Alkylation of **12** using the same bases utilized to derivatize **11** provided target compounds **2**. The ketone moieties of **2r**, **s** and **v** were reduced with $NaBH_4$ whilst acetates **2x** and **y** were hydrolyzed to the corresponding alcohols using K_2CO_3 in methanol.

The diazirene element incorporated into **2k** and **m** was examined as a potential photolabelling moiety and was synthesized using 3,3-azo-l-(methanesulfonyloxy)-butane[27] as the electrophile to alkylate **6**, a reaction mediated by KO*t*Bu in THF.[28] Reaction of **8** with 4-(chloromethyl)phenyl acetate mediated by BTPP in the presence of $(n\text{Bu})_4\text{NBr}$ followed by saponification provided the corresponding phenol, which was protected as its TBDMS ether and coupled with the diazirene-containing chloride **7** using BTPP as the base. The TBDMS moiety was removed using TBAF in THF to provide phenol **2k**, which was doubly iodinated using NaI and

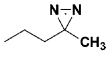
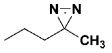


Scheme 1.



Scheme 2.

Table 1. Structure, RSV inhibitory activity and cytotoxicity associated with a series of substituted benzimidazol-2-one derivatives **2**

Compd	R^1	R^2	Antiviral activity EC_{50} (μM)[a]	Cytoxicity CC_{50} (μM)[b]	Therapeutic index
2a	H	*iso*-Propenyl	0.75 (1.165/0.326)	28.4 (30.1/26.6)	38
2b	$CH_2CH_2CH(CH_3)_2$	*iso*-Propenyl	0.004 (0.005/0.003)	24.7 (11.7/37.6)	6175
2c	$CH_2CH_2CH(CH_3)_2$	H	0.057 (0.084/0.030)	61.1 (64.5/57.8)	1071
2d	$CH_2CH_2CH(CH_3)_2$	CH_2CH_3	0.011 (0.018/0.005)	18.6 (28.0/9.3)	1690
2e	$CH_2CH_2CH(CH_3)_2$	allyl	0.016 (0.010/0.021)	12.8 (14.8/10.8)	800
2f	$CH_2CH_2CH(CH_3)_2$	CH_2CN	0.028 (0.020/0.018/0.044)	46.8 (18.1/119.1/3.17)	1671
2g	$CH_2CH_2CH(CH_3)_2$	$CH_2CH_2CH_2CN$	0.040 (0.031/0.049)	59.6 (39.3/80.0)	1490
2h	$CH_2CH_2CH(CH_3)_2$	$CH_2CH_2CH_2CH_2CN$	0.035 (0.045/0.025)	15.0 (24.1/5.9)	428
2i	$CH_2CH_2CH(CH_3)_2$	$CH_2CH_2CH_2CH_2CH_2CN$	0.025 (0.018/0.031)	13.4 (10.3/16.4)	536
2j	$CH_2CH_2CH(CH_3)_2$	CH_2-4-C_6H_4-OH	0.018 (0.015/0.021/0.017)	59.9 (49.9/108.5/21.3)	3327
2k		CH_2-4-C_6H_4-OH	0.004 (0.003/0.005/0.003)	(>220/135.1/112.4)	>28,000
2l	$CH_2CH_2CH(CH_3)_2$	CH_2-3,5-di-I-4-C_6H_2-OH	0.686 (0.461/1.378/0.219)	>144.44 ($n=3$)	>209
2m		CH_2-3,5-di-I-4-C_6H_2-OH	0.038 (0.026/0.088/0.002)	27.13 (27.5/30.0/23.9)	713
2n	$CH_2CH_2CH(CH_3)_2$	CH_2-4-C_6H_4-CN	0.012 (0.014/0.010)	5.59 (5.7/5.4)	465
2o	$CH_2CH_2CH(CH_3)_2$	CH_2-4-C_6H_4-$CON(CH_3)_2$	0.021 (0.013/0.028)	26.6 (21.6/31.6)	1266
2p	$CH_2CH_2CH(CH_3)_2$	CH_2-4-C_6H_4-SO_2CH_3	0.009 (0.013/0.004)	7.5 (6.7/8.4)	833
2q	$CH_2CH_2CH(CH_3)_2$	CH_2-4-C_6H_4-$SO_2N(CH_3)_2$	0.004 (0.002/0.006)	>152.7	>38,175
2r	$CH_2CH_2CO{\cdot}CH_3$	*iso*-Propenyl	0.005 (0.005/0.004)	244.7	48,940
2s	$CH_2CH_2CO{\cdot}CH_3$	H	0.191 (0.184/0.198)	299.1	1565
2t	$CH_2CH_2CHOH{\cdot}CH_3$	*iso*-Propenyl	0.028 (0.046/0.01)	171.6 (211.2/131.9)	6128
2u	$CH_2CH_2CHOH{\cdot}CH_3$	H	0.416 (0.366/0.466)	>261.9 ($n=2$)	>629
2v	$CH_2CO{\cdot}Ph$	Et	0.112 (0.062/0.024/0.25)	27.1 (59.9/11.1/10.4)	241
2w	$CH_2CH(OH){\cdot}Ph$	Et	0.037 (0.041/0.033)	>240.7 ($n=2$)	>6505
2x	$(CH_2)_3CHOCO{\cdot}CH_3$	Et	0.018 (0.007/0.029)	246.7 (243.2/250.2)	13,705
2y	$(CH_2)_4CHOCO{\cdot}CH_3$	Et	0.021 (0.013/0.017/0.035)	160.7 (228.8/228.8/24.5)	7652
2z	$(CH_2)_2OH$	Et	0.229 (0.285/0.173)	64.1 (98.4/29.7)	279
2aa	$(CH_2)_3OH$	Et	0.01 (0.009/0.01)	179.4 (274.1/84.7)	17,940
2ab	$(CH_2)_4OH$	*iso*-Propenyl	0.004 (0.005/0.004)	170.9 (268.0/73.8)	42,725
2ac	$(CH_2)_4OH$	H	0.173 (0.172/0.045/0.303)	>168.0	>971
2ad	$(CH_2)_4OH$	iPr	0.011 (0.013/0.010)	68.3 (56.4/80.2)	6209
2ae	$(CH_2)_4OH$	Et	0.014 (0.004/0.020/0.019)	154.0 (226.4/217/4/18.3)	11,000
2af	$(CH_2)_4OH$	CH_2-4-C_6H_4-CN	0.053 (0.093/0.012)	39.2 (43.5/35.0)	739
2ag	$(CH_2)_6OH$	*iso*-Propenyl	0.114 (0.117/0.111)	>247.2	>2166
2ah	$(CH_2)_2CN$	*iso*-Propenyl	0.015 (0.021/0.009)	79.6 (87.0/72.2)	5306
2ai	$(CH_2)_2CN$	H	0.099 (0.096/0.103)	>310.2	3133
2aj	$(CH_2)_2CN$	iPr	0.008 (0.006/0.010)	73.5 (38.2/108.8)	9187
2ak	$(CH_2)_2CN$	Ph	0.005 (0.005/0.005)	87.0 (10.5/163.4)	17,400
2al	$(CH_2)_3CN$	*iso*-Propenyl	0.005 ($n=1$)	13.1 ($n=1$)	2620
2am	$(CH_2)_4CN$	*iso*-Propenyl	0.027 (0.039/0.015)	192.8 (205.3/180.3)	7140
2an	$(CH_2)_5CN$	*iso*-Propenyl	0.013 (0.016/0.009)	12.3 (12.2/12.3)	946
2ao	$(CH_2)_6CN$	*iso*-Propenyl	0.006 (0.006/0.007)	36.0/>241.8	>6000
2ap	$(CH_2)_6CN$	iPr	0.005 (0.004/0.007)	>188.8	>37,760
2aq	$(CH_2)_3CN$	$(CH_2)_4CN$	0.025 (0.022/0.028)	>242.42	>9696
2ar	$CH_2CH_2CH_2SO_2CH_3$	*iso*-Propenyl	0.03 (0.042/0.017)	123.3 (197.2/49.4)	4110
2as	$CH_2CH_2CH_2SO_2CH_3$	H	1.489 (1.917/1.060)	215.5 (206.5/224.5)	144
2at	$CH_2CH_2CH_2SO_2CH_3$	$(CH_2)_4CN$	0.071 (0.088/0.054)	>214.29	>3018
2au	$CH_2CH_2CH_2SO_2CH_3$	$(CH_2)_4OH$	0.092 (0.071/0.028/0.179)	>229.02	>2489
2av	$CH_2CH_2CH(CH_3)_2$	CO_2Et	0.298 (0.448/0.148)	57.7 (79.5/35.9)	193
2aw	$CH_2CH_2CH(CH_3)_2$	$CO{\cdot}NH_2$	0.050 ($n=1$)	133.7 ($n=1$)	2674
2ax	$CH_2CH_2CH(CH_3)_2$	CO·NHEt	0.052 (0.093/0.011)	18.7 (31.4/6.0)	359
2ay	$CH_2CH_2CH(CH_3)_2$	CO·NHPh	0.041 (0.038/0.044)	21.6 (32.9/10.3)	526
2az	$CH_2CH_2CH(CH_3)_2$	$CO{\cdot}NHCH_2Ph$	0.086 (0.034/0.137)	6.44 (4.4/8.5)	74
2ba	$CH_2CH_2CH(CH_3)_2$	$CO{\cdot}CH_3$	0.710 (1.050/0.370)	115.6 (131.4/100.0)	162
2bb	$CH_2CH_2CH(CH_3)_2$	SO_2CH_3	0.007 (0.005/0.01)	16.3 (20.6/12.0)	2328
2bc	$CH_2CH_2CH(CH_3)_2$	$SO_2CH(CH_3)_2$	0.065 (0.059/0.080/0.055)	16.9 (29.5/29.5/22.4)	260
2bd	$CH_2CH_2CH(CH_3)_2$	$SO_2N(CH_3)_2$	0.062 (0.039/0.085)	27.1 (18.9/37.0)	437

[a] Values are the means of two experiments performed on consecutive weeks with the data from individual experiments shown in parentheses. (NA = not active).

[b] CC_{50} refers to the concentration of drug causing a 50% reduction in cell viability in the absence of respiratory syncytial virus infection. Therapeutic Index = CC_{50}/EC_{50}.

iodogen. This chemistry was developed initially using a structurally simple and chemically inert isoamyl side chain, to afford **2l**.

The compounds that comprise this survey of benzimidazol-2-one-derived RSV inhibitors were evaluated as inhibitors of the cytopathic effect induced by the Long (A) strain of RSV in the HEp-2 human lung epithelial carcinoma cell line. The antiviral activity is reported as an EC_{50}, which represents the concentration of compound required to provide 50% protection, and is compared with the concentration of compound that causes cytotoxicity to uninfected HEp-2 cells. The results are compiled in Table 1 where the therapeutic index is calculated as the ratio of CC_{50} to EC_{50}.

The survey delineated by the examples compiled in Table 1 establishes the viability of the benzimidazol-2-one moiety as a scaffold from which potent RSV inhibitors can readily be derived. The benzimidazol-2-one moiety provides an opportunity to probe a vector unavailable to the benzotriazole ring system by modulating the N substituent. In general, when the urea nitrogen is substituted, this heterocycle provides a potency advantage that can be substantial when compared to similarly substituted benzotriazole derivatives described earlier.[1] The nature and scope of the benzimidazol-2-one N substituents examined in Table 1 were selected to provide not only insight into basic aspects of structure–activity correlates, but were also designed to incorporate structural elements and substituents capable of additional functionalization and modification. This formed the basis of a broader campaign to obtain a suitable compromise between antiviral potency and physical chemical properties that would allow evaluation in animal models of infection. The unsubstituted benzimidazole **2a** is 40-fold more potent than the analogous N-1 substituted benzotriazole,[1] providing an initial indication of the superior intrinsic potency associated with the N-substituted benzimidazolone heterocycle. Whilst **2a** demonstrates respectable inhibitory activity, it was anticipated based on the earlier studies that the introduction of an isoamyl side chain element would enhance potency. This expectation was indeed realized with **2b**, which is over 2 orders of magnitude more potent than **2a** and more than 10-fold better than the best benzotriazole derivative examined.[1] Within the context of the interrogation of isoamyl derivatives defined by **2b–j**, **2l**, **2n–q**, and **2av–bd**, it is readily apparent that the range of N substituents compatible with potent RSV inhibition is quite expansive, providing ample opportunity for structural variation and manipulation. The excellent activity intrinsic to prototype **2c** is readily improved by substitution of the benzimidazol-2-one N atom with structurally simple alkyl and alkenyl groups (**2b**, **d**, and **e**), alkyl nitriles that exhibit little dependence on chain length (**2f–i**), functionalized benzyl derivatives (**2j**, **l**, and **n–q**) and several polar, electron withdrawing substituents (**2av–bd**).

Included in this work are several new benzimidazole side chain elements (R^1) that extend and further define the silhouette associated with this class of RSV fusion inhibitor. From the homologous series of nitriles defined by **2ah** and **2al–ao**, it is evident that side chain length exerts only a limited effect on potency since the EC_{50} variation across this series is 5-fold with no clearly discernible pattern. This effect appears to be reproduced in the 2 *i*-Pr-substituted compounds **2aj** and **ap**, although this series was not examined as systematically as the *iso*-propenyl homologues. For the series of alkyl alcohol derivatives **2z–ag**, antiviral activity potency appears to be optimal with 3 and 4 CH_2 units separating the polar hydroxyl moiety from the heterocyclic nucleus. The two diazirine-derivatives **2k** and **m** provided potent antiviral agents, the result with **2m** particularly gratifying since this molecule could readily be labeled with ^{125}I to furnish a photoaffinity agent with the potential to provide more detailed insights into the mode of action of this class of RSV fusion inhibitor at a molecular level.[28–30] From the limited comparisons available, the diazirine side chain exhibits advantage over the simpler isoamyl moiety.

The safety margin for this series of RSV inhibitors, as determined by the therapeutic index, ranges from 10 for **a** to 48940 for **2r**. Three compounds, **2a**, **p**, and **az**, demonstrated measurable cytotoxicity towards the host cell line at concentrations of less than 10 μM. Nevertheless, the high intrinsic antiviral potency associated with **2n** and **p** result in a significant therapeutic index. In general, the safety margin for this series of RSV inhibitors series is acceptable with no obvious patterns based on overall lipophilicity, a documented correlate with cytotoxicity.[31]

In summary, the data presented in Table 1 establish the benzimidazol-2-one moiety as an effective structural background for the generation of potent inhibitors of RSV and both broadens and extends structure–activity relationships for this chemotype.[1] The availability of an additional structural vector unavailable to the benzotriazole prototypes has provided significant potency advantage and there is broad tolerance for functionality in this region of the pharmacophore. Structural evolution of the benzimidazol-2-one class of RSV inhibitor towards compounds that demonstrate antiviral activity in animal models of RSV infection will be described in due course.

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