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3-PYRIDINES AS REPLACEMENTS FOR AN ISOXAZOLE RING: THE ANTIRHINOVIRAL ACTIVITY OF PYRIDINE ANALOGUES RELATED TO DISOXARIL

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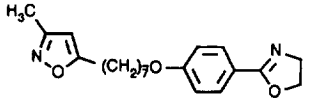
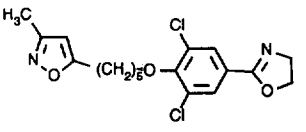
Abstract: In a series of rhinovirus inhibitors related to Disoxaril, replacement of 3-methylisoxazole with all 3 isomers of pyridine showed the 3-pyridyl isomer most similar to 3-methylisoxazole in spectrum of activity over 15 human rhinovirus serotypes.

The broad spectrum antiviral activity of Disoxaril[1] and WIN 54954[2] has firmly established this class of uncoating/adsorption inhibitors as potential chemotherapeutic agents for the treatment of picornaviral infections. Extensive structure activity relationships have been repeated for this series of compounds.[3] Very little was known about the effects of replacement of the isoxazole moiety on antiviral activity until recently when 2-acetylfurans were reported as bioisosteres for the 3-methylisoxazoles.[4] From this work, it was discovered that the *syn* 2-acetylfuran had very similar physical properties to 3-methylisoxazole as well as the ability to hydrogen bond within the drug binding site on the viral capsid protein. An unsatisfactory pharmacokinetic profile for the 2-acetylfuran series prompted a quest for additional replacements for the isoxazole ring. In this paper, we will describe antiviral results on the pyridine replacement of 3-methylisoxazole. A series of isomeric and substituted pyridines has been prepared and evaluated for inhibitory activity against 15 rhinoviral serotypes.



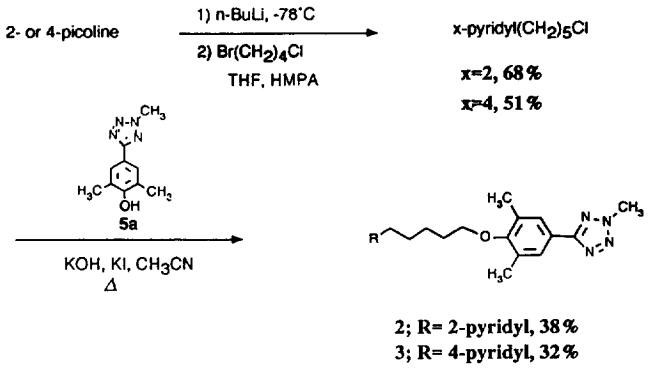
Disoxaril



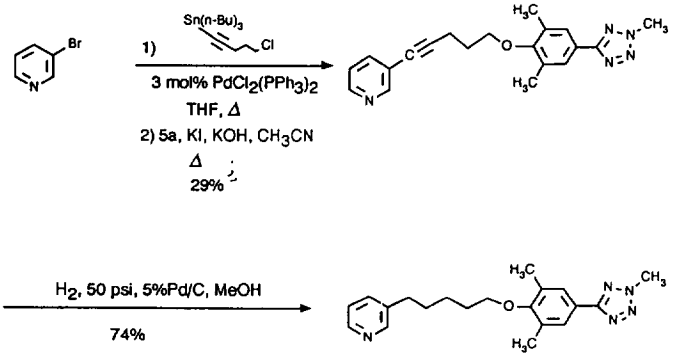
Win 54954

The pyridines were initially chosen as isoxazole replacements for their complimentary physical properties. Both pyridine and 3-methylisoxazole have similar ClogP's (0.66 vs. 0.73 respectively),[5] and each has the potential to participate as a hydrogen bond acceptor. Our previous work describing 2-acetylfurans as bioisosteres for 3-methylisoxazoles had demonstrated the importance of hydrogen bonding capabilities in that region of the inhibitor.[4] The 2- and 4-pyridyl isomers were prepared from their respective picolines in modest yields as described in Scheme 1. The 3-pyridyl example, **3**, was synthesized in 3 steps from 3-bromopyridine via a palladium catalyzed alkynyl cross-coupling as shown in Scheme 2. All three isomers were then screened against 15 human rhinovirus serotypes in a tissue culture inhibitory dose assay (TCID).[6] Comparison of individual serotype data for isoxazole **1** and pyridines **2**, **3**, and **4** against 15 human rhinoviruses revealed a trend in activity

Scheme 1



Scheme 2



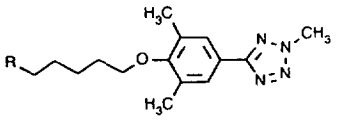
4

such that 3-methylisoxazole ≅ 3-pyridyl>>4-pyridyl≅2-pyridyl (Table 1). With both 4- and particularly the 2-pyridyl 2, the decrease in spectrum of activity was reflected by the number of serotypes insensitive to drug at the maximum testable limit (MTL). In spite of the identical physical characteristics of each isomer, the 3-substituted pyridine 3 demonstrated potency and spectrum of activity most similar to the isoxazole 1.

To further examine the 3-pyridyl analogues, four examples were assembled where the tetrazole and oxadiazole rings were incorporated at the terminus of the molecule and the connecting chain shortened from 5 to 3 carbons. Since alkylation of the phenol **5a** with the alkyl chlorides gave generally lower yields, a Mitsunobu coupling strategy[7] was employed. The 3-pyridylpropanols[8] were reacted with phenols **5a** and **5b** in more respectable yields as shown in Scheme 3. Surprisingly, the simple 3-pyridyl analogues **7a** and **7b** exhibited a reduced spectrum of activity as reflected by inactivity against one or more rhinovirus serotypes (Table 2). When the connecting chain was shortened from 5-carbons to 3-carbons in the isoxazole or 2-acetylfuran series, potency has been shown to be comparable.[9] By adding a methyl group to the 6-position of the pyridine ring, analogues **8a** and **8b** demonstrated potency and spectrum most closely paralleling the activity of the 3-methylisoxazole examples **6a** and **6b**. Despite the physical similarities shared by pyridine and 3-methylisoxazole, it can be seen that addition of the methyl substituent at the 6-position of pyridine is critical for broad spectrum antirhinoviral

activity in this series. This result is also consistent with findings in the 3-carbon connected isoxazole series where elongation of the alkyl chain on the 3-position of isoxazole improved potency and spectrum of activity.[9]

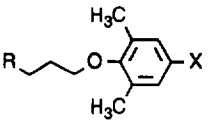
Table 1. Comparison of Antirhinoviral Activity of Isoxazole **1**, and Pyridine Isomers **2**, **3**,and **4**.



HRV Serotype	MIC (μM)			
R=				
	1	**2**	**3**	**4**
R1A	0.42	0.66	0.28	0.68
R1B	0.10	0.11	0.10	0.27
R2	0.04	0.34	0.20	0.26
R6	0.98	*NA*	0.82	*NA*
R14	0.62	3.84	1.05	*NA*
R15	0.77	1.91	1.25	2.13
R21	0.04	0.05	0.03	0.08
R22	0.08	0.21	0.17	0.20
R25	0.31	0.08	0.04	0.11
R30	0.11	0.25	0.17	0.36
R41	1.43	*NA*	2.16	*NA*
R50	0.23	0.36	2.28	0.36
R67	0.35	1.19	0.37	0.51
R86	0.84	*NA*	1.08	0.43
R89	0.04	0.06	0.03	0.07
Mean	**0.40**	*NA*	**0.67**	*NA*

NA=not active.

Table 2. Antirhinoviral Activity



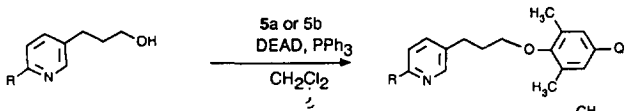
compd	R	X	mp, °C	in vitro antiviral activity, μM[a] Mean
6a[6]				0.73
7a		"	64.5-66	b
8a		"	72-74	0.54
6b				0.22
7b		"	175-177	c
8b		"	66-69	0.25

[a] Screened against 15 serotypes.

[b] Inactive against HRV-6, -14, -86.

[c] Inactive against HRV-86.

Scheme 3



7a; R=-H; Q=  ; 83%

7b; R=-H; Q=  ; 55%

8a; R=-Me; Q=  ; 61%

8b; R=-Me; Q=  ; 44%

Given the equivalence of logP for the three pyridine isomers, other factors that more strongly influence potency and spectrum of activity must be involved. The difference in inhibitory activity between the pyridine isomers infers that heteroatom position on that end of the molecule is critical to spectrum of activity as demonstrated in Table 1. Giranda et al[10] have proposed that a hydrogen bonding network between drug, structural water, and ASN 1219 in the pore of the rhinovirus pocket[11] in certain rhinovirus serotypes may contribute to the observed spectrum of activity. Geometrically, neither the 2- or 4-pyridyl isomers may be able to effectively participate in the hydrogen bonding interaction. As in the acetylfuran series, the 3-pyridines share similar physicochemical and electrostatic properties with 3-methylisoxazole. The relative logP's of isoxazole **6b** (3.2), and 3-pyridyls **7b** (3.3) and **8b** (3.8) as measured by HPLC are quite close. Recently, Garvey et al. reported 3-methylisoxazoles as bioisosteres for the unsubstituted 3-pyridine ring of nicotine.[12] Our work generally supports this bioisosteric relationship, but for our chain shortened series, the 3-(6-methyl)pyridyl analogue more closely approximates 3-methylisoxazole.

Investigation of pyridine replacements for the 3-methylisoxazole of our rhinoviral inhibitor series has identified the 3-pyridyl isomer as a potent inhibitor. Consistent with earlier findings about steric bulk contributions to activity,[13] adding an alkyl group ortho to the pyridine nitrogen improves potency. As in the 2-acetylfuran series,[4] the importance of the position of the heteroatom at the pore of the viral pocket for broad spectrum antirhinoviral activity has been confirmed. Although hydrogen bonding capabilities are only one factor in contributing to activity, it does appear that a heteroatom hydrogen bond acceptor meta to the inhibitor alkyl chain may be required for meaningful broad spectrum activity to be observed. Work on other replacements which fit this motif is in progress and will be reported shortly.

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8. The 3-(3-pyridyl)propanol is commercially available from Aldrich. The 5-methyl-3-pyridine was synthesized as follows: A suspension of 5-methyl-3-pyridinepropenoic acid ethyl ester[14] (2.2 g, 12.4 mmol) and 5% Pd/C (0.38 g) in 100 mL of EtOAc was hydrogenated at 50 psi in a Paar apparatus for 3 h. Filtration throuh celite and concentration afforded 2.0 g (91%) of the saturated ethyl ester as a yellow oil. The yellow oil was added as a solution in 4 mL THF to a suspension of LAH (0.5 g, 12.3 mmol) in 20 mL THF at 5-15° C under N_2. The grey-green slurry was allowed to warm to room temperature and quenched sequentially with H_2O (0.5 mL), 10% NaOH (0.5 mL), and H_2O (1.5 mL). The light grey suspension was filtered through celite and concentrated in vacuo providing the propanol as a yellow oil (1.7 g, 100% yield).

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