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1,3,4-Oxadiazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 2: SAR of the C5 position

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ABSTRACT

The use of a 1,3,4-oxadiazole in combination with an 8-hydroxy-1,6-naphthyridine ring system has been shown to deliver potent enzyme and antiviral activity through inhibition of viral DNA integration. This report presents a detailed structure–activity investigation of the C5 position resulting in low nM potency for several analogs with an excellent therapeutic index.

According to UNAIDS estimates for 2007 over 33 million people globally were living with the virus that causes AIDS. These estimates include 2.5 million individuals that became newly infected with HIV and tragically 2.1 million have perished during 2007 alone.[1] In the preceding paper,[2] the design of a novel 2-metal binding naphthyridine series was presented where oxadiazole and triazole heterocyclic groups were part of the metal chelation motif. That work not only showed the heterocycles to be a viable chelating isostere for the amido group, but also showed a series of C5-sultam containing compounds (e.g. **2**) having potency approaching that of the validated clinical candidate L-870,810 (**3**). In this paper we expand the effects of 5-substitution on the biological activity of the 1,3,4-oxadiazole series **1** (Fig. 1).

We decided that the encouraging potency of the 5-sultam containing analog **2** justified a broader set of nitrogen containing analogs. Beginning with 5-bromo naphthyridine derivative **5**,[3] hydrolysis and coupling of the bromo containing core to 4-fluorophenylmethyl hydrazide and subsequent ring condensation provided the versatile late stage intermediate **6**. The amide coupling protocol of Buchwald[4] was employed with various amido, urea, carbamate, sulfonyl urea and sulfonamide coupling partners to smoothly provide 5-N containing analogs **7–20** (Table 1). During these coupling investigations, we also found that subjecting **6** to these conditions ($Pd_2(dba)_3$) in the presence of the corresponding sultam or sulfonamides coupled smoothly to provide sulfonamides such as **2** upon deprotection of the methyl ether[5] (Table 2). This was a marked advance over the Cu_2O conditions previously described to make **2** primarily due to avoidance of copper complexed intermediates (Scheme 1).

Bromo intermediate **6** was also useful in amine couplings either employing contemporary Pd(0) catalyzed methods or by simple thermal displacement of the bromide with a 2° amine to provide **27** (Scheme 2). Interestingly, this was not able to be accomplished with 1° amines as it resulted in displacement of the methoxy group rather than the halide. However, masking a 1° amine with a removable group (*p*-methoxybenzyl) facilitated the desired selectivity to give **28** which could be converted to the 5-mono substituted amino intermediate en route to analogs such as amide **11** and amine **29** (Table 3).

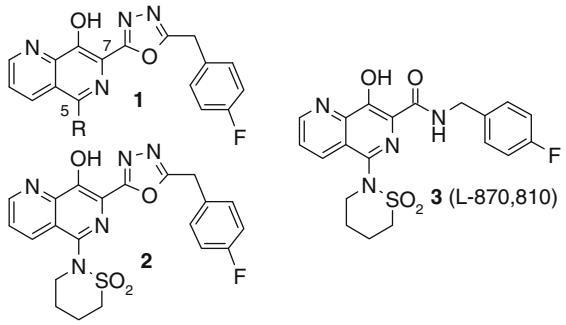

Figure 1.

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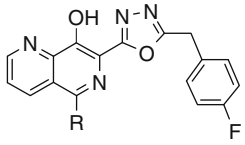
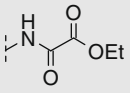
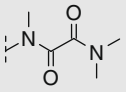
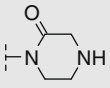
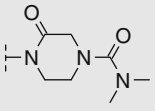
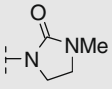
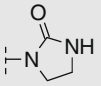
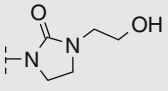
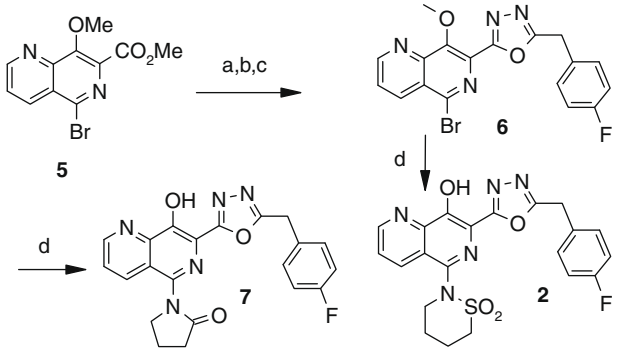
Table 1
Amide, urea and carbamate substituents

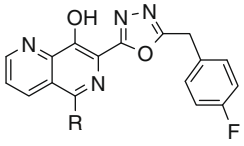


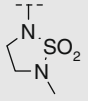
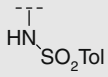
Compound	R	IC_{50}[6] (μM)	EC_{50}[7] (μM)	T.I.[8]
7		0.019	0.089	>156
8		0.088	0.087	>160
9		0.025	0.034	>411
10		0.072	0.11	127
11		0.028	0.18	428
12		0.033	1.3	10
13		0.085	0.31	>40
14		0.038	0.24	58
15		0.023	0.087	120
16		0.015	0.030	>466
17		0.012	0.045	311
18		0.013	0.094	148
19		0.013	0.021	>666
20		0.011	0.056	>250



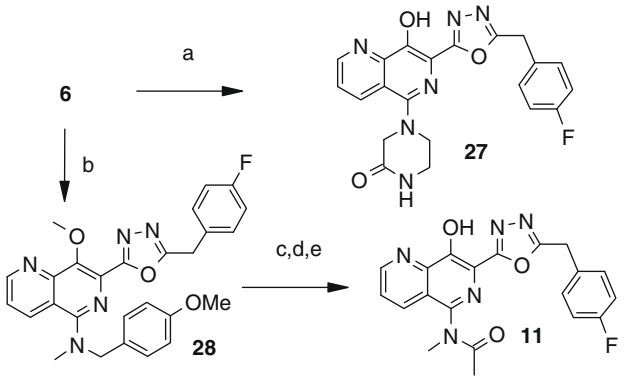
Scheme 1. Reagents and conditions: (a) LiOH (aq), THF (85%); (b) F-$C_6H_4CH_2C(O)NHNH_2$, EDCI, HOBt, CH_2Cl_2 (95%); (c) PPh_3, I_2, Et_3N, CH_2Cl_2 (87%); (d) $Pd(OAc)_2$ or $Pd_2(dba)_3$, xantphos, pyrrolidinone or sultam, Cs_2CO_3, dioxane, 65 then TMSCl, NaI, MeCN, °C (92% for **7**), (68% for **2**).

Table 2
Sulfonamide and sulfonyl urea substitutents



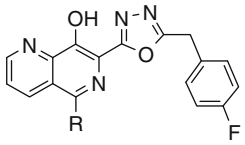
Compound	R	IC_{50}[6] (μM)	EC_{50}[7] (μM)	T.I.[8]
2		0.002	0.013	198
21		0.008	0.11	>129
22		0.019	0.11	131
23		0.015	0.084	127
24		0.006	0.031	294
25		0.004	0.063	137
26		0.042	0.19	74

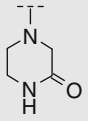
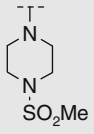
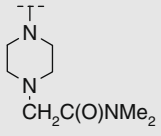
Similarly, the 5-halo intermediate **6** coupled smoothly with several aryl boronic acids to yield 5-aryl substituents using standard Suzuki conditions to provide a series of aryl derivatives (**32**–**60**) (Scheme 3 and Table 4). A related method was also effective in providing the *N*-pyrazolyl substituted analog **61**.

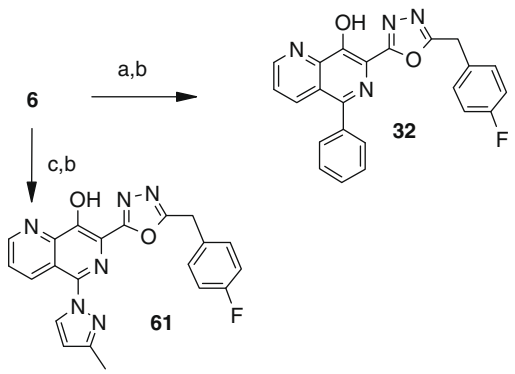


Scheme 2. Reagents and conditions: (a) piperazinone, dioxane, Δ, 2 h (53%); (b) 4-$MeOC_6H_4CH_2NHCH_3$, NMP, 70–80 °C (68%); (c) TFA (99%); (d) Ac_2O, CH_2Cl_2, 55 °C (61%); (e) TMSCl, NaI, MeCN (57%).

Table 3
Amine substitutents

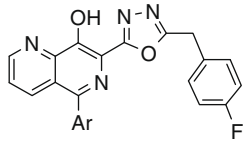


Compound	R	IC_{50}[6] (μM)	EC_{50}[7] (μM)	T.I.[8]
27		0.007	0.017	844
29		0.074	0.40	30
30		0.019	0.038	162
31		0.012	0.043	205

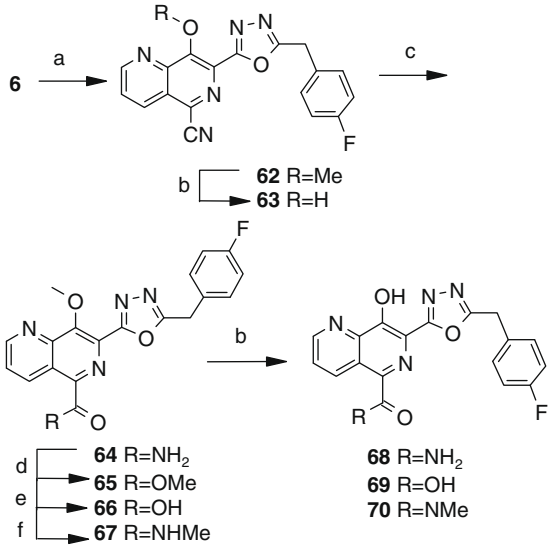


Scheme 3. Reagents and conditions: (c) $PdCl_2(PPh_3)_2$, Na_2CO_3 (aq), phenylboric acid, DMF 90 °C, (70%); (b) TMSCl, NaI, MeCN; (c) $Pd_2(dba)_3$, xantphos, 3-methylpyrazole, Cs_2CO_3, dioxane, 65 °C (89%).

Table 4
Aryl substitutents



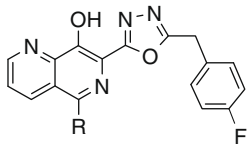
Compound	Ar	IC_{50}[6] (μM)	EC_{50}[7] (μM)	T.I.[8]
32	–Ph	0.029	0.036	49
33	–2-Pyridyl	0.030	0.056	40
34	–3-Pyridyl	0.011	0.036	194
35	–4-Pyridyl	0.008	0.035	200
36	–2-Pyrazinyl	0.020	0.17	24
37	3-C_6H_4–CO_2H	0.002	0.23	>60
38	3-C_6H_4–CONHiPr	0.010	0.028	182
39	3-C_6H_4–NH_2	0.015	0.015	546
40	3-C_6H_4–NHAc	0.080	0.010	1400
41	3-C_6H_4–$NHSO_2Me$	0.008	0.014	435
42	4-C_6H_4–CO_2H	0.002	0.058	241
43	4-C_6H_4–$CONH_2$	0.006	0.010	1220
44	4-C_6H_4–CONHMe	0.004	0.012	780
45	4-C_6H_4–$CONMe_2$	0.018	0.012	668
46	4-C_6H_4–CONHiPr	0.004	0.013	95
47	2-C_6H_4–SO_2NMe_2	0.004	0.029	67
48	4-C_6H_4–SO_2NMe_2	0.018	0.009	218
49	2-C_6H_4–SO_2NHMe	0.004	0.022	173
50	2-C_6H_4–SO_2NHiPr	0.012	0.008	295
51	4-C_6H_4–SO_2NHiPr	0.004	0.015	118
52	4-C_6H_4–NHAc	0.004	0.006	591
53	4-C_6H_4–$NHSO_2Me$	0.003	0.009	915
54	2-C_6H_4–SO_2Me	0.011	0.023	243
55	3-C_6H_4–SO_2Me	0.006	0.013	234
56	4-C_6H_4–SO_2Me	0.009	0.008	301
57	4-C_6H_4–CN	0.015	0.026	72
58	3-Furyl	0.023	0.10	116
59	2-Pyrrolyl	0.012	0.16	31
60	2-Pyrazolyl	0.004	0.016	546
61	1-(3-Methylpyrazolyl)	0.021	0.38	23

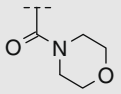
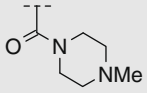
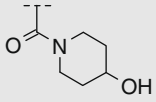
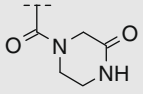


Scheme 4. Reagents and conditions: (a) $Pd(PPh_3)_4$, $Zn(CN)_2$, DMF 85 °C, (91%); (b) TMSCl, NaI, MeCN; (c) urea H_2O_2, K_2CO_3, acetone/H_2O (84%); (d) DMF–DMA, MeOH (81%); (e) LiOH, THF (89%); (f) EDCI, HOBt, $MeNH_2$, CH_2Cl_2 (63%).

The final area we chose to exploit was 5-carbonyl substituted analogs including several 5-amido analogs. These were accessed through a Negishi coupling of $Zn(CN)_2$ under Pd(0) mediated conditions to provide nitrile **62** (Scheme 4). Mild hydrolysis conditions

Table 5
5-Nitrile, acid and amide substituents



Compound	R	IC_{50}[6] (μM)	EC_{50}[7] (μM)	T.I.[8]
63	–CN	0.24	>35	n.d.
68	$-CONH_2$	0.10	0.16	75
69	$-CO_2H$	0.86	4.4	>3
70	–CONHMe	0.12	0.15	43
71	–CONHiPr	0.19	0.098	22
72	$-CONH(CH_2)_2OH$	0.13	1.49	>9
73	$-CONH(CH_2)_3OH$	0.071	0.47	>30
74	$-CONH(CH_2)_2OMe$	0.19	0.072	139
75		0.13	0.097	134
76		0.044	0.097	>144
77		0.027	0.22	>65
78		0.074	>14	n.d.

were employed using urea–hydrogen peroxide to produce the corresponding 1° amide **64**. From the amide, treatment with DMF–DMA smoothly converted the material to the methyl ester **65** which was then hydrolyzed and coupled using carbodiimide conditions to provide the desired substituted amide **67**. The amide **67** and its precursors were deprotected using the standard TMSI conditions to provide the free phenols shown in Table 5.

The compounds presented in Tables 1–5 were evaluated in for strand transfer activity against the recombinant enzyme[6] and for antiviral activity in a pseudotyped HIV cell-based assay (PHIV).[7] It was clear when we started that 5-amido groups would be promising based on the initial activity of sultam derivative **2**. As can be seen from Tables 1 and 2, many of the 5-amido and sulfonamide analogs are well below 100 nM potency in the antiviral assay. There do not appear to be major trends amongst the derivatives that were made other than nearly all of the compounds showed very encouraging enzyme potency that for the most part translated very closely into antiviral activity. All of the data from the sub-100 nM compounds showed excellent separation from cytotoxicity clearly establishing the antiviral effect for these series of analogs. It also became apparent that the size of the C5 substituent was quite independent from activity. Both amides and amino groups at C5 were well tolerated and the relatively smaller derivatives such as carbamate **19** compared nearly equally to the amino analog **31** containing a somewhat extended chain on a piperazinyl ring system. This trend of tolerance of size and polarity is also evident in the 5-aryl series shown in Table 4. Little difference is noted when phenyl is replaced with the pyridyl isomers (**33**–**35**). Not surprisingly the carboxylic acid analogs **37** and **42** show a modest
fall-off between the enzyme and cellular data suggesting perhaps limited penetration due to decreased membrane permeability. Overall, the 5-aryl series showed excellent antiviral potency with several analogs in the single digit nM range very much in line with some of the more potent drug candidates from other groups.

Finally, the C5-amide series shown in Table 5 displayed slightly less potency in both the enzyme and cellular systems. It is unclear if this trend is due to an increased acidity of the phenolic group of the two-metal binding motif due to conjugation through the ring or other effects of the amido group itself but in general these analogs were around an order of magnitude less potent than some of the 5-aryl and 5-N substituted derivatives.

In summary, we have presented significant data to support the potency profile of C5 substituted 7-(1,3,4-oxadiazole)-1,6-naphthyridine integrase inhibitors. A preference for 5-amido, sulfonamido and aryl substitutions is clear from the data that was obtained. Many of these analogs have a potency profile consistent with previously reported clinical compounds that have been efficacious in human trials. The above results continue to show the oxadiazole can serve as an amide isostere for metal coordination within the integrase two-metal binding pharmacophore.

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8. Therapeutic index (CC_{50}/EC_{50}).