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The use of oxadiazole and triazole substituted naphthyridines as HIV-1 integrase inhibitors. Part 1: Establishing the pharmacophore

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ABSTRACT

A series of HIV-1 integrase inhibitors containing a novel metal binding motif consisting of the 8-hydroxy-1,6-naphthyridine core and either an oxadiazole or triazole has been identified. The design of the key structural components was based on a two-metal coordination pharmacophore. This report presents initial structure–activity data that shows the new chelation architecture delivers potent inhibition in both enzymatic and antiviral assays.

The advent of HAART therapy for the treatment of HIV infection over a decade ago has transformed the lives of scores of patients during that period.[1] This treatment was based on typically a triple combination of antiviral drugs resulting in numerous options for the patient. However, with all the success of HAART it needs to be stressed that the majority of treatment options have relied on two target enzymes, namely reverse transcriptase and protease. The development of fusion and entry inhibitors more recently have also had an impact but their role is yet to be completely appreciated by patients as a result of dosing regimen and tropism concerns, respectively, along with their relatively recent introduction.[2] The third and only remaining viral enzyme, integrase, has been slower to succumb to drug discovery efforts but after nearly 20 years of study the first antiviral agent utilizing integrase inhibition as its mechanism of action (raltegravir) was approved in late 2007.[3,4] It seems clear that access by patients to drugs with novel mechanisms of inhibiting the virus are going to again shift the paradigm of treatment options for HIV infected individuals.[5] While the clinical data and market excitement for raltegravir is very encouraging, it would be naïve to think that one agent in this class will suffice to meet patient medical needs in the long term. Therefore new agents within this class are needed and the search for potent and orally bioavailable inhibitors of HIV-1 integrase is currently one of the most active areas of antiviral research.

HIV integrase is a 32 kDa, 288 amino acid protein that is believed to act in a multimeric state presumably as a tetramer to catalyze a phosphodiester cleavage/formation sequence to incorporate viral double-stranded DNA into host chromatin. This enzymatic process is dependent on an active site containing dual Mg^{2+} metal ions held in place with a highly conserved triad of carboxylate amino acid residues (asp64/asp116/glu152) commonly referred to as a DD(35)E triad.[6] The integration process consists of several steps but the two viral enzyme catalyzed bond breaking and forming events consisting of 3′ processing of the respective viral LTR ends in the cytoplasm and following nuclear entry strand transfer whereby the recessed 3′ hydroxyl groups of the viral DNA ends nick host DNA resulting in a damaged DNA sequence that is repaired by host cell mechanisms providing a permanently lodged proviral DNA sequence.

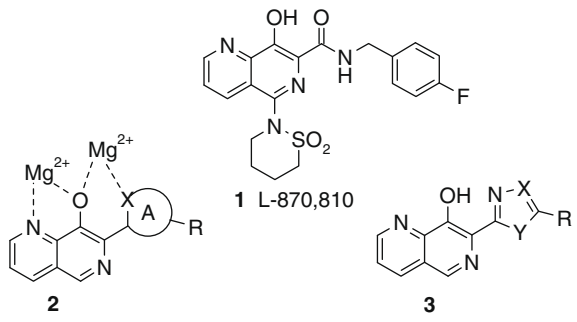

Figure 1.

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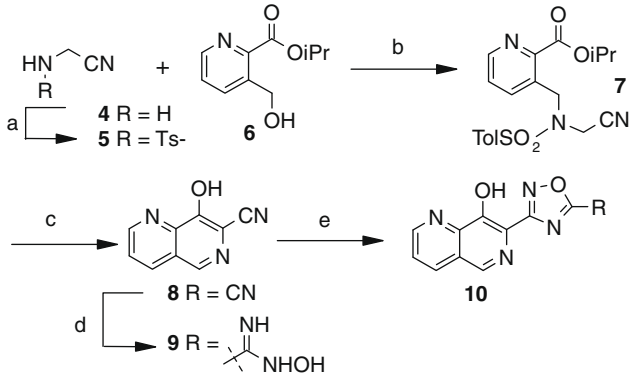
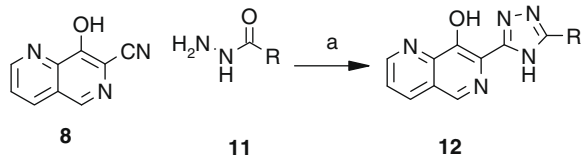
The seminal contributions from the laboratories of Merck and Shionogi resulting in the discovery of diketo-acid inhibitors and their isosteric counterparts such as S-1360 served to establish a unique pharmacophore consisting of a two-metal chelation motif and a hydrophobic aromatic appendage requiring a fairly specific spacing and orientation.[7,8] The establishment of this specific pharmacophore by the first generation of integrase inhibitors was key to aiding in the design of more drug-like scaffolds. In particular the early second generation work which evolved around the naphthyridine carboxamide scaffold represented by L-870,810 (**1**) and related analogs gave us impetus to study this heterocyclic core in an attempt to further understand the tolerance to alternative chemical functionality.[9] Our goal in this study was to investigate whether a heterocyclic amide isostere as shown in **2** would achieve the perceived co-planarity required for metal chelation and if so would that arrangement have the appropriate coordinating ability to bind the requisite magnesium ions (Fig. 1). Finally, would the pendant non-metal binding substitution achieve the correct spatial arrangement to provide potent enzymatic and antiviral activity? It was rationalized that in order to achieve the necessary co-planarity that the 5-membered ring heterocyclic amide isosteres represented by the oxazole, isoxazole, oxadiazole and triazole moieties would be less sterically encumbered than their 6-membered ring counterparts (e.g. pyridine or pyrimidine). The concerns with the larger ring sizes are a propensity for the rings to adopt an orthogonal orientation thus prohibiting the system from achieving the co-planar arrangement that was desired. We therefore set out to explore a series of 5-membered ring heterocycles to determine whether they would be viable amide isosteres at the 7-position of the 8-hydroxy-1,6-naphthyridine scaffold.

We chose the 1,2,4-oxadiazole amide isostere due to synthetic ease as our first target. To that end, the versatile intermediate 7-cyano-8-hydroxy naphthyridine (**8**) was constructed from the alcohol **6**[10] via a Mitsunobu coupling of tosylamide **5** followed by a Dieckmann-type cylization and elimination of toluenesulfinic acid served to provide nitrile **8** (Scheme 1). Nitrile **8** was subsequently treated with hydroxylamine to form the corresponding oxime amine **9**. Heating **9** with benzoyl chloride in pyridine led to acylation and dehydration to provide the desired unsymmetrical oxadiazole **10a** along with its 8-*O*-benzoyl ester which was cleaved upon treatment with basic methanol. The homologated benzyl analog was in turn made by treatment of the oxime amine **9** in dioxane with phenylacetyl chloride and subjecting the mixture to heating in a microwave to provide oxadiazole **10b**.

During the next iteration it was desired to make a series of oxadiazole analogs. It was initially expected that subjecting nitrile **8** to reaction conditions involving heating with a hydrazide such as **11** would result in the 1,3,4-oxadiazole ring system. Somewhat to our surprise, heating this mixture in a microwave in the presence of acetic acid resulted cleanly in conversion to the 1,2,4-triazole ring system (Scheme 2). While yields were modest under these conditions, the reaction appeared to be robustly providing only the triazole ring system.



Scheme 1. Reagents and conditions: (a) TsCl, pyr, 0 °C, 30 min (94%); (b) DIAD, PPh_3, THF 0 °C to rt (71%); (c) NaOMe, MeOH, 0 °C to rt (89%); (d) hydroxylamine HCl, K_2CO_3, EtOH, reflux (82%); (e) for **10a** (R = Ph), BzCl, pyr, rt to 60 °C, then K_2CO_3, MeOH (37%); for **10b** (R = $PhCH_2$–), $PhCH_2C(O)Cl$, dioxane, μw, 190 °C (6%); for **10c** (R = 4-F-$C_6H_4CH_2$–), 4-F-$C_6H_4CH_2C(O)Cl$, dioxane, μw, 160 °C (17%).

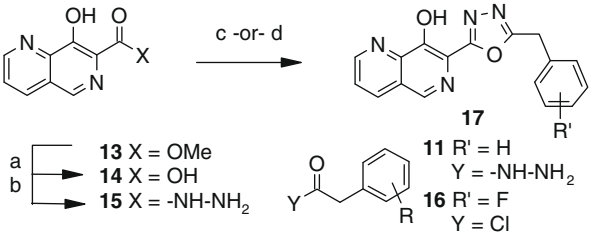


Scheme 2. Reagents and conditions: (a) Dioxane, AcOH, μw, 200 °C for **12a** (R = –CH_2Ph, 55%), **12b** (R = 4-F-$C_6H_4CH_2$–, 16%), **12c** (R = 4-Cl-$C_6H_4CH_2$–, 37%), **12d** (R = 3-Cl-$C_6H_4CH_2$–, 5%), **12e** (R = 3-OMe-$C_6H_4CH_2$–, 21%), **12f** (R = 3,4-di-OMe-$C_6H_3CH_2$–, 34%), **12g** (R = $PhCH_2CH_2$–, 50%), **12h** (R = 4-pyrCH_2, 41%), **12i** (R = 3-pyrCH_2, 38%).

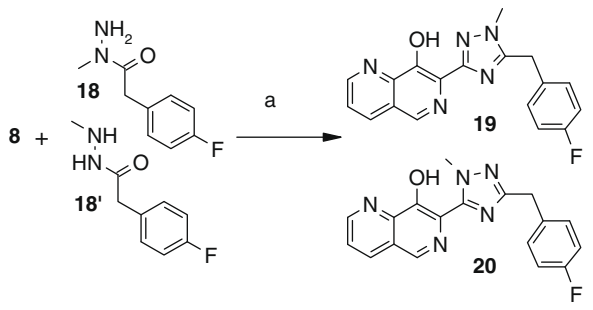
Since the above sequence was fortuitously providing the unexpected triazole series, we needed an alternative route to access the symmetrical 1,3,4-oxadiazole series. Hydrolysis of the known methyl ester **13**[11] led to acid **14** (Scheme 3). Alternatively, heating ester **13** with hydrazine in ethanol provided the hydrazide intermediate **15**. Coupling the above precursors with the appropriate arylmethyl hydrazide or phenylacetyl chloride provided a common intermediate diacyl hydrazine which could be dehydrated upon exposure to $POCl_3$. It is evident from the above sequences that we have chosen to not protect the reactive 8-hydroxyl group on the naphthyridine core. This clearly resulted in decreased chemical yield and required a final hydrolysis typically to cleave acyl and phosphorylated products present in the reaction mixture. Further optimization of the synthetic chemistry is presented in a subsequent report.[12]

As a final target to examine the pharmacophore effects of the amide mimetics, we selected a set of *N*-methyl triazoles that would help establish which heteroatom was key for metal chelation and also might suggest if ring rotomers were relevant to this same binding.

To this end, nitrile **8** was treated with an 8:1 mixture of the *N*-methyl acetylhydrazides **18** and **18′** which were prepared as an inseparable mixture from *N*-methyl hydrazide and 4-fluorophenylacetyl chloride (Scheme 4). The condensation was sluggish but



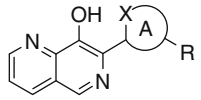
Scheme 3. Reagents and conditions: (a) **13**, LiOH, MeOH, reflux 18 h (87%); (b) **13**, NH_2NH_2, EtOH, reflux (70%); (c) for **17a** (R′ = H) **14**, **11**, EDCI, HOBt, CH_2Cl_2; $POCl_3$; MeOH, K_2CO_3 (16%); (d) for **17b** (R′ = 4-F) **15**, **16**, pyr., CH_2Cl_2; $POCl_3$; MeOH, K_2CO_3 (8%).

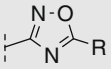
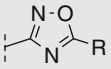
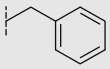
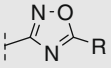
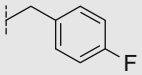
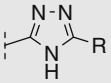
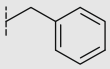
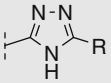
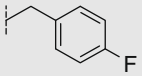
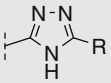
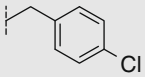
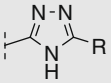
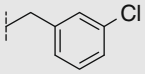
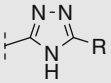
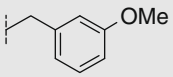
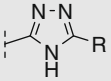
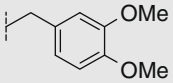
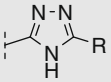
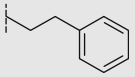
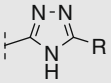
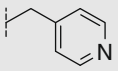
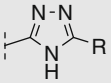
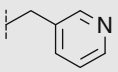
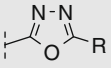
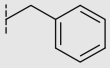
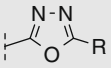
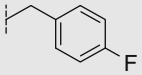
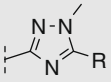
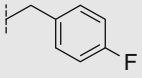
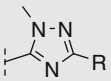
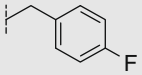
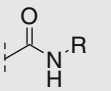
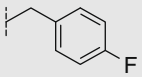


Scheme 4. Reagents and conditions: (a) AcOH, dioxane, μw, 200 °C **19** (4%), **20** (24%).

after the addition of 4 equivalents of the hydrazide mixture two products were isolated via preparative HPLC. Surprisingly, the mixture favored the expected minor triazole **20** in a 3.4–1 ratio with triazole **19** which arose from the major hydrazide **18** in the reaction mixture. Perhaps the increased nucleophilicity of the secondary terminus of **18′** reacted with nitrile **8** preferentially siphoning

Table 1



Compound	A	R	IC_{50} (μM)[a]	EC_{50} (μM)[b]	T.I.[c]
10a			>100	n.d.	n.d.
10b			0.95	1.9	55
10c			0.13	0.22	114
12a			0.36	8.7	>4[d]
12b			0.13	.32	7
12c			0.64	1.0	1
12d			1.03	1.0	2
12e			2.8	>35	n.d.
12f			6.3	>35	n.d.
12g			2.4	>20	n.d.
12h			4.6	>35	n.d.
12i			3.5	6.4	>3.6[d]
17a			0.13	0.42	111
17b			0.042	0.13	>270
19			7.9	n.d.	n.d.
20			>500	n.d.	n.d.
21			0.012	0.075	278

n.d. = not determined.

[a] Recombinant HIV-1 integrase strand transfer assay.[12]

[b] Pseudo-type HIV assay (PHIV).[13]

[c] Therapeutic index (CC_{50}/EC_{50}).

[d] Accurate determination of CC_{50} limited by solubility.

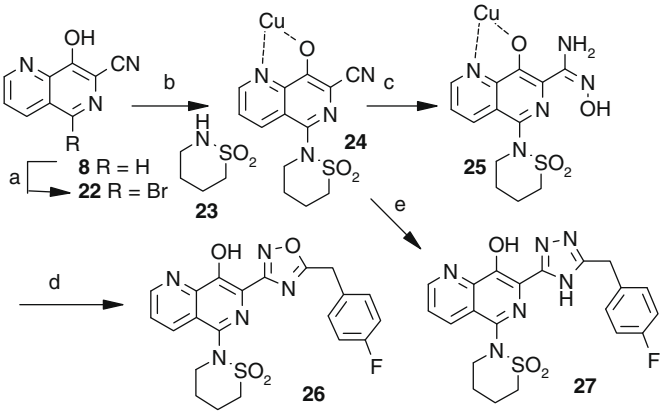
off the minor hydrazide component. One cannot rule out a mixing of the hydrazides through a diacyl hydrazine intermediate as a result of the high temperatures experienced during the condensation providing a pathway for increased amounts of **18′** and the subsequent distortion of the ratio of products. The above result, however, was useful to our needs in that it provided sufficient quantities of both isomers to examine for biological activity.

The inhibitory activity of the above heterocyclic amide replacements were initially measured using a recombinant HIV-1 integrase strand transfer assay.[12] Where possible, these results were followed up with an assessment of antiviral activity in a whole cell pseudo-type HIV assay (PHIV).[13] The 1,2,4-oxadiazole analog **10a** resulted in no measurable activity, however, when the benzylic link was put in place in compound **10b** activity in the micromolar range was observed in the enzymatic assay along with measurable antiviral effect in the PHIV assay. In comparison, the triazole containing compounds showed similar potency against the enzyme system for the benzyl and 4-fluorobenzyl substituted analogs **12a** and **12b**, however, moving beyond the small halogens in the 4-position appeared to be detrimental to both enzyme and antiviral activities (compounds **12d**–**12f**) (see Table 1). In addition basic nitrogens in the pyridylmethyl substituents (**12h** and **12i**) also decreased activity as did the chain extended phenethyl group in analog **12g**. The corresponding 1,3,4-oxadiazole analogs showed the most promising activity resulting in an improvement in both enzyme and antiviral activity when comparing the 4-fluoro derivative (**17b**) to the unsubstituted benzyl group (**17a**) consistent with the triazole SAR. In addition, convincing therapeutic windows were evident for both 1,3,4-oxadiazole analogs helping to validate a robust antiviral effect. For comparison, the naphthyridine benzyl amide **21** was examined in both assay systems and provided data 2- to 3-fold more potent than the corresponding oxadiazole **17b**.

The methyl substituted triazole analogs **19** and **20** while not extremely potent do shed some light on the metal binding motif present within these scaffolds. The lack of any measurable activity in compound **20** is consistent with the methylated nitrogen removing an obligatory chelation group from coordination of the active site magnesium. It also suggests the alternative rotomeric isomer of these systems whereby the single lone nitrogen in position 4 of the triazole in **20** would coordinate the metals is not operable. Meanwhile compound **19** while less potent than the non-methylated example **12b** does retain some activity suggesting metal coordination.

Now that we had established that the 5-membered heterocycles were viable metal chelation components in conjunction with the 8-hydroxynaphthyridine scaffold, we desired to examine further structural effects on activity levels. The C5 position appeared to be the most amenable for further functionalization and since the sultam group in L-870,810 appeared to have beneficial effects on the amide series of compounds we chose this as our first group to explore.[9] To that end, nitrile **8** was brominated followed by a copper mediated coupling of sultam **23**[11] resulting in the desired adduct **24**, however, the material was isolated as a fairly insoluble copper complex. Nonetheless this intermediate served useful as it could be taken on as the complex and treated with hydroxylamine and subsequently condensed with 4-fluorophenyacetyl chloride or condensed directly with 4-fluorophenylacetic hydrazide to provide the 1,2,4-oxadiazole **26** or 1,2,4-triazole **27**, respectively (Scheme 5).

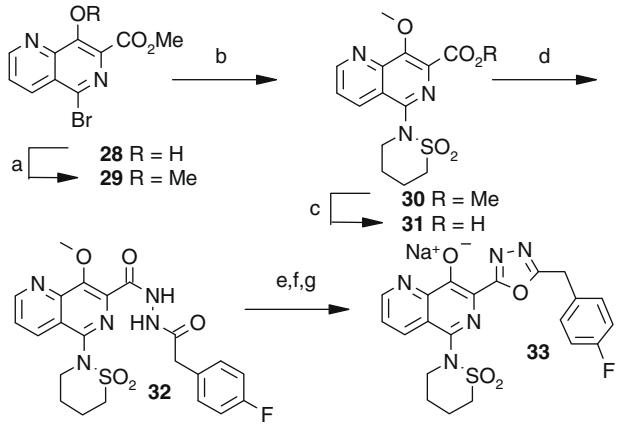
Similarly, we also wanted to look at the 1,3,4-oxadiazole isomer. This material was made starting with known 5-bromo ester **28**.[11] Since the phenol hydroxyl group has been problematic throughout several of the previous syntheses we decided to block that position as the corresponding methyl ether **29**. The protected hydroxyl group not surprisingly behaved much better in the subsequent sultam coupling to give ester **30** which was hydrolyzed and coupled to 4-fluorophenylacetic hydrazide to provide the diacyl hydrazine derivative



Scheme 5. Reagents and conditions: (a) NBS, $CHCl_3$(90%); (b) **23**, Cu_2O, pyr, 105 °C (73%); (c) NH_2OH HCl, K_2CO_3, EtOH reflux (65%); (d) 4-F-$C_6H_4CH_2C(O)Cl$, dioxane, μw, 160 °C, then EDTA (aq) (11%); (e) 4-F-$C_6H_4CH_2C(O)NHNH_2$, Dioxane, AcOH, μw, 200 °C (23%).

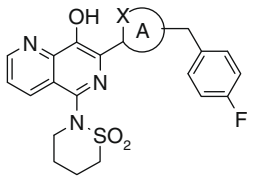
32. This material was found to undergo smooth dehydration to give the desired oxadiazole upon treatment with modified Mitsunobu conditions. Other methods including using the Burgess Reagent or $POCl_3$ also gave product but were not as preferable in our hands as the PPh_3/I_2 conditions. Finally, the 8-hydroxyl group was freed up using the in situ generated TMSI conditions of Jung to provide the 1,3,4-oxadiazole **33**.[14] (Scheme 6).

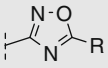
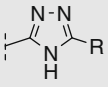
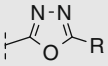
With the three sultam containing analogs in hand we were able to evaluate the effects of the 5-substition on activity versus the 5-protio analogs for each as well as again compare the triazole and oxadiazoles to one another with similar analogs (Table 2). Interestingly, the 1,2,4-oxadiazole analog **26** was completely inactive in our hands. This was surprising to us and not consistent with our expectations nor is it explained by solubility or permeability properties. A modest improvement in potency was observed for triazole **27** compared to protio derivative **12b**. However, more noteworthy is the improved therapeutic index observed in the C5-substituted analog (>104-fold for **27** vs 7-fold for **12b**). A significant improvement of antiviral potency was also observed for the 1,3,4-oxadiazole analog **33** compared to its 5-protio counterpart **17b**. This low nM potency is now approaching that of L-870,810 (**1**) which has shown clinical efficacy.



Scheme 6. Reagents and conditions: (a) MeI, Cs_2CO_3, DMF (76%); (b) **23**, Cu_2O, 2,2′-dipyridyl, DMF 125 °C, then EDTA (61%); (c) LiOH (aq), THF/MeOH (99%); (d) F-$C_6H_4CH_2C(O)NHNH_2$, EDCI, HOBt, CH_2Cl_2 (90%); (e) PPh_3, I_2, Et_3N, CH_2Cl_2 (56%); (f) TMSCl, NaI, MeCN (93%); (g) NaOH, MeOH (52%).

Table 2
Comparison of C5-sultam substituted analogs



Compound	A	IC_{50} (μM)[a]	EC_{50} (μM)[b]	T.I.[c]
26		>100	n.d.	n.d.
27		0.011	0.24	>104
33		0.002	0.013	198
1		0.013	0.002	1795

n.d. = not determined.
[a] Recombinant HIV-1 integrase strand transfer assay.[12]
[b] Pseudo-type HIV assay (PHIV).[13]
[c] Therapeutic index (CC_{50}/EC_{50}).

In summary, the work presented in this communication has served to establish the oxadiazole and triazole heterocycles as viable components of the chelation motif involved in the 8-hydroxynaphthyridine integrase scaffold. Furthermore, a preliminary examination of C5 substitution showed significant improvements in antiviral activity on par with that of the validated clinical candidate L-870,810. Further SAR optimization of these heterocycle substituted 8-hydroxy-naphthyridine integrase inhibitors is presented in due course.[15]

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