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Azaindole *N*-methyl hydroxamic acids as HIV-1 integrase inhibitors-II. The impact of physicochemical properties on ADME and PK

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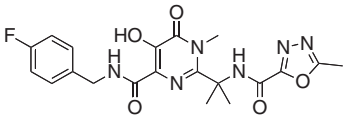
ABSTRACT

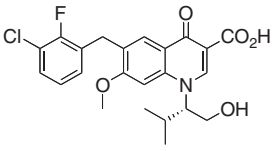
HIV-1 integrase is one of three enzymes encoded by the HIV genome and is essential for viral replication, and HIV-1 IN inhibitors have emerged as a new promising class of therapeutics. Recently, we reported the discovery of azaindole hydroxamic acids that were potent inhibitors of the HIV-1 IN enzyme. *N*-Methyl hydroxamic acids were stable against oxidative metabolism, however were cleared rapidly through phase 2 glucuronidation pathways. We were able to introduce polar groups at the β-position of the azaindole core thereby altering physical properties by lowering calculated log *D* values (*c* Log *D*) which resulted in attenuated clearance rates in human hepatocytes. Pharmacokinetic data in dog for representative compounds demonstrated moderate oral bioavailability and reasonable half-lives. These ends were accomplished without a large negative impact on enzymatic and antiviral activity, thus suggesting opportunities to alter clearance parameters in future series.

Human immunodeficiency virus type 1 (HIV-1), the causative pathogen of AIDS, replicates utilizing three essential enzymes encoded in the HIV pol gen: reverse transcriptase (RT), protease (PR), and integrase (IN). Many anti-HIV agents target either RT[1] or PR.[2] Recently, inhibitors of IN have emerged as a new promising class of therapeutics for the treatment of AIDS[3,4] highlighted by the recent approval of raltegravir (**1**),[5,6] and encouraging phase II clinical trial results with elvitegravir (**2**)[7,8] and S/GSK1349572 (**3**).[9,10] Several drivers remain, however, to discover new chemical classes with complimentary or improved properties regarding resistance,[11] dosing, and tolerability.

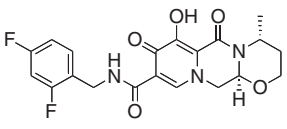
We recently disclosed the discovery of azaindole *N*-methyl hydroxamic acids **4** and **5** (Table 1) as potent HIV-1 IN inhibitors.[12] Compounds **4** and **5** were stable against oxidative metabolism in human liver microsomes but were rapidly cleared by phase 2 metabolism via glucuronidation, a well established pathway for hydroxamic acids.[13,14] Here we wish to report our efforts in attenuating glucuronidation rates and improving the metabolic stability



1 raltegravir



2 elvitegravir



3 S/GSK1349572

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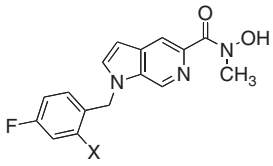
Table 1
Enzymatic and antiviral activity, metabolic stability of β-unsubstituted *n*-methyl hydroxamic acids



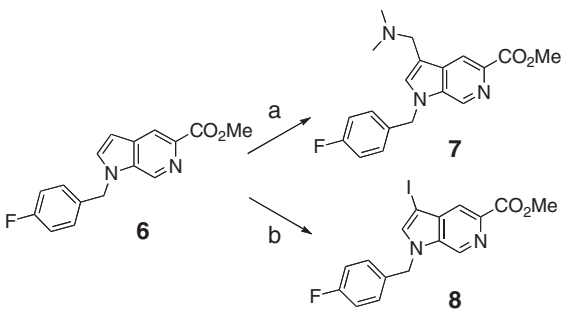
Compd	*c* Log *D*[a] (Log *D*)	IC_{50}[b] (nM)	EC_{50}[c] (nM)	CC_{50}[c] (μM)	ER[d] hHEP	LipE[e]
4 (X = H)	3.06	250	32	135	1.0	4.4
5 (X = F)	3.17 (2.40)	250	39	200	1.0	4.2

[a] Calculated log *D* at pH 7.4 using ACD/Physicochem Suite, Version 12 (ACD labs, Toronto, Canada).
[b] Strand transfer scintillation proximity assay (see Supplementary data).
[c] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration (see Supplementary data), CC_{50}, 50% cytotoxic concentration (see Supplementary data).
[d] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CLint)/(Q + (fu × CLint)).[15]
[e] LipE = $-$Log EC_{50} $-$ *c* Log *D*.[22]

of substituted variants of the monofluoro azaindole hydroxamate **4**. Our focus will be on altering physicochemical parameters (Log *P*, Log *D*, TPSA) through substitution at a more or less potency neutral locus with the hope of translating this information to future, more potent, scaffolds.

Studies of glucuronidation rates with catechols in rat liver concluded that rates are highest for hydrophobic catechols with a pK_a between 8 and 9.[16,17] Since the N–OH function (typical pK_a between 8 and 9)[18] was critical for activity[9] we explored if metabolic rates could be altered by modifying physical properties, for example basicity/acidity/lipophilicity as expressed in a calculated log *D* value (*c* Log *D*). Fortuitously, the β-position (3-position) in the azaindole ring was readily accessible for introduction of a variety of functional groups covering a range of polarities without substantial loss in antiviral activity. We explored a variety of different substituents in the β-position and herein we report the impact of these efforts on potencies and metabolic stabilities (determined in human hepatocytes) of representative examples.

The β-position of the pyrrolyl ring of the azaindole nucleus is ideally suited to the facile substitution processes we were seeking and simple electrophilic substitutions at that position should be readily achieved. The possibility of ready conversion of the initially introduced function to a variety of polar substituents made this a very attractive option to investigate. Scheme 1 illustrates our initial pyrrolyl β-functionalization chemistry. Azaindole **6**[12] was treated with *N,N*-dimethyl(methylene) ammonium chloride (MeCN)[19] to provide dimethylaminomethyl-**7**, while the exposure of **6** to NIS (DMF, 97%) afforded β-iodo-azaindole **8** (85%). With **7** and **8** in hand we were well positioned for the preparation of a variety of analogs via conversion of **7** to the related benzylic chloride[20] or carboxylic acid,[21] while iodide **8** would allow routine palladium chemistry to be performed.



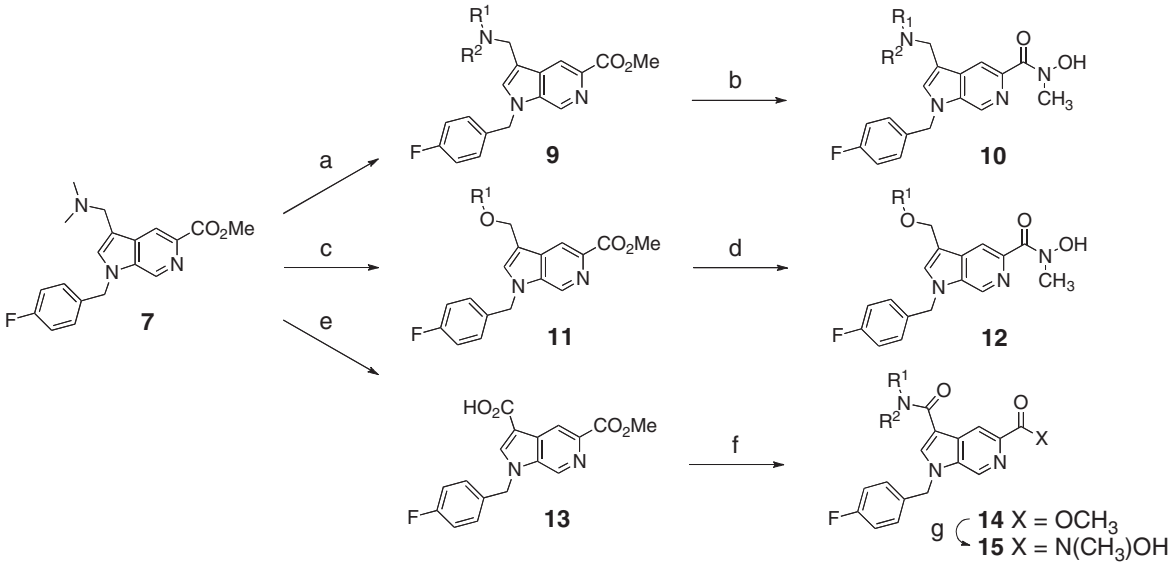
Scheme 1. Pyrrolyl β-functionalization. Reagents and conditions: (a) dimethyl(methylene) ammonium chloride, DMF, 80 °C, 97%; (b) NIS, DMF, 85%.

3-Dimethylaminomethyl azaindole ester **7** was smoothly converted to the related benzylic chloride upon treatment with either ethyl- or phenyl chloroformate in DCM.[19] The benzylic chloride was coupled with a selection of amines to afford the aminomethyl azaindoles **9** which were directly converted to the related *N*-methyl hydroxamates **10** when reacted with *N*-methyl hydroxylamine and sodium methoxide in methanol. In a similar fashion, dimethylaminomethyl **7** was converted to 3-R^1O-methyl substituted azaindoles **11** (via benzylic chloride and coupling), and these entities were easily hydrolyzed (aq LiOH) and coupled with *N*-methyl hydroxylamine (2-chloro-4,6-dimethoxy-1,3,5-triazine [CDMT], *N*-methyl morpholine) to furnish the target 3-CH_2OR^1-azaindole hydroxamates **12**. Dimethylaminomethyl azaindole ester **7** was also easily oxidized to the corresponding carboxylic acid **13** with $KMnO_4$.[20] The acid was then coupled with amines (CDMT) to give amides **14**. In turn amides **14** were transformed into amido-hydroxamates **15** with Na-*t*-pentoxide and *N*-methylhydroxyl amine in NMP.

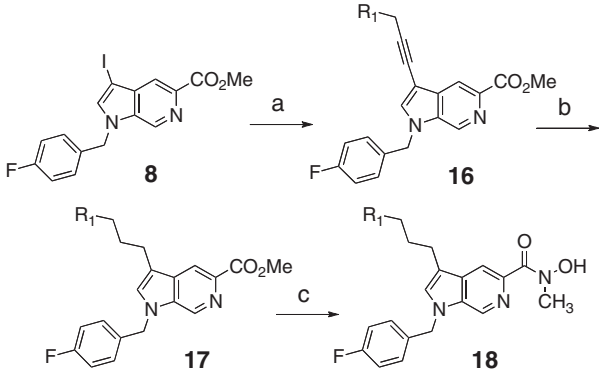
3-Iodo-azaindole ester **8** was readily coupled with alkynes in a Sonogashira reaction ($PdCl_2(PPh_3)_2$, CuI–SMe_2, Et_3N, DMF) to give alkynes (Scheme 3) **16** in good (72–98%) yield. Reduction ($Pd(OH)_2$, H_2-40 psi) led to the saturated 3-C extended azaindole esters **17** which were converted to target azaindole hydroxamates **18** when reacted with *N*-methyl hydroxylamine in the presence of Na-*t*-pentoxide (NMP, 0 °C).

The starting 3-H azaindole hydroxamates **4** and **5** (Table 1) exhibited reasonable antiviral activity (**4** EC_{50} = 32 nM; **5** EC_{50} = 39 nM) with poor metabolic stability (ER = 1.0)[15] with clearance by phase 2 metabolism via glucuronidation. The clearance mechanism is expected of hydroxamates and given the relatively high *c* Log *D* values for **4** and **5**, 3.06 and 3.17, respectively, rapid disappearance is not surprising. The combination of reasonable potency and higher than desired *c* Log *D* contributes to lipophilic ligand efficiency (LipE)[22] values of 4.4 and 4.2 for **4** and **5**, respectively. The analogs suggested in Schemes 2 and 3 were designed to alter the physicochemical attributes of the final molecules (*c* Log *D*) with an eye toward altering glucuronidation with a minimal impact upon antiviral activity (EC_{50}). Table 2 presents the data accumulated for the 3-aminomethyl substituted azaindole hydroxamates **10a–e**.

The compounds of Table 2, **10a–e**, are arranged in order of increasing *c* Log *D* (**10a** *c* Log *D* = 0.93 to **10e** *c* Log *D* = 2.17). While aminomethyl compounds **10a**, **10b**, and **10c** exhibited disappointing antiviral activity (EC_{50}'s 150–747 nM) it is of note that the polarity in the pyrrolyl β-position with the accompanying alteration of *c* Log *D* did have the desired impact on the rate of glucuronidation as measured by the ER in human hepatocytes. Of



Scheme 2. The conversion of 3-dimethylaminomethyl azaindole ester **7** to 1-carbon-side chain extended azaindole hydroxamates **10**, **12**, and **15**. Reagents and conditions: (a) (i) EtOCOCl or PhOCOCl, CH_2Cl_2, (ii) R^1R^2NH, *i*-Pr_2NEt, 84–95%; (b) MeNHOH–HCl, NaOMe, MeOH, 29–41%; (c) (i) Ac_2O, NaOAc (for R^1O = AcO precursor to R^1O = HO; or (i) EtOCOCl or PhOCOCl, CH_2Cl_2, (ii) R^1OH, *i*-Pr_2NEt, 89–97%; (d) (i) aq LiOH, THF, 40 °C, (ii) chloro-dimethoxytriazine, *N*-methylmorpholine, MeNHOH–HCl, Et_3N, DMF, 40–70%; (e) $KMnO_4$, acetone, H_2O, 3 h, 86%; (f) 2-chloro-4,6-dimethoxy-1,3,5-triazine, *N*-methylmorpholine, R^1R^2NH, *i*-Pr_2NEt, DMF, 22–97%; (g) CH_3NOH–HCl, Na-*t*-pentoxide, NMP, 0 °C, 20–40%.



Scheme 3. The conversion of 3-iodo-azaindole ester **7** to 3-carbon-side chain extended azaindole hydroxamates **18**. Reagents and conditions: (a) $PdCl_2(PPh_3)_2$, CuI–SMe_2, Et_3N, alkyne, DMF, 72–98%; (b) H_2 (40 psi), $Pd(OH)_2$, MeOH, 58–95%; (c) (i) aq LiOH, THF, 40 °C, (ii) 2-chloro-4,6-dimethoxy-1,3,5-triazine, *N*-methylmorpholine, MeNHOH–HCl, Et_3N, DMF, 45–80%.

greater interest is the concatenation of antiviral activity, similar to the benchmark compounds **4** and **5**, in the proline amide enantiomeric aminomethyl azaindole hydroxamates **10d** (EC_{50} = 80 nM) and **10e** (EC_{50} = 94 nM) with stability. In these compounds we have combined reasonable antiviral activity, a lowering of the *c* Log *D* (by ca. 1 unit), good metabolic stability (ER ⩽ 0.55), and good LipE values (4.9).

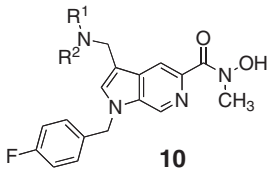
Table 3 presents our attempts to alter the characteristics in this series by introducing ethereal linkages in the form of 3-R^1OCH_2-substituted azaindole hydroxamates **12a**–**e**. With calculated Log *D* values ranging from 1.76 (**12a**) to 2.70 (**12e**), all the members of this series have lower *c* Log *D* values than the 3H-compounds **4** and **5**. Compounds of this series exhibit antiviral activity (29–57 nM) in the same range as **4** and **5**, however diethers **12b** (ER = 0.51) and **12e** (ER = 0.57) are much more metabolically stable than **4** and **5** (ER = 1.0). The unusual pattern with respect to secondary metabolic clearance shown by this series suggests a possible role for polarity in the pyrrolyl-β-position over and above the impact of *c* Log *D*. More drastic alterations to the 3-position were offered by the amides **15a**–**c**.

Table 4 presents our attempts to impart minimal impact upon antiviral activity while altering clearance through the introduction of amide moieties to the 3-position of the azaindole-hydroxamate scaffold. This short series of 3 compounds presents a narrow 1 unit range of *c* Log *D* values (1.60–2.64), uniformly disappointing antiviral activity (EC_{50} = 110–210 nM) and uniformly excellent metabolic stability (ER ca. 0.20–0.25).

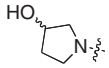
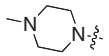
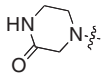
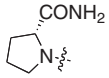
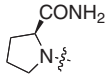
The final compounds of this study, the Sonogashira derived 3-carbon-extended **18a**–**c** are depicted in Table 5. As a result of chain length, *c* Log *D* for this short series trends toward that of **4** and **5**. With the exception of the propyl alcohol **18b** (EC_{50} = 41 nM), poorer antiviral activity was associated with this series than the 3H-compounds **4** and **5**. Unfortunately compounds **18a**–**c** also suffered rapid clearance (ER = 0.97–1.0) with the data for **18b** (ER = 1.0) in good agreement with that observed for the 1-carbon-alcohol **12a** (ER = 1.0) despite a ca. 1 unit difference in *c* Log *D*.

An examination of the data presented in Tables 2–5 presents the amides of Table 4 as curious outliers. Within this small set of compounds we did not discover a member exhibiting antiviral activity (EC_{50}) comparable to the R^1O-methyl-compounds of Table 3 (**12b** EC_{50} = 29 nM, *c* Log *D* = 2.19, TPSA = 76.8), or the 3-carbon extended compounds of Table 5 (**18b** EC_{50} = 41 nM, *c* Log *D* = 2.66, TPSA = 76.8). A comparison of the EC_{50} data as well as *c* Log *D* and TPSA values of **12b** and **18b** (vide infra) with that of amide **15c** (EC_{50} = 110 nM, *c* Log *D* = 2.64, TPSA = 87.5) suggests we consider alternatives for the drop-off in antiviral potency. The amides of Table 4 provide an electronic pertubation to the system bearing the metal binding domain and a steric pertubation in the form of branching proximal to the azaindole ring. The electronic impact is observed in the calculated pK_a for the hydroxamate in the amide series (c-pK_a ca. 7.9) versus the compounds of Table 2 (c-pK_a ca. 8.2–8.6), Table 3 (c-pK_a ca. 8.1–8.2), and Table 5 (c-pK_a ca. 8.1–8.2). A somewhat larger impact is observed when we examine the pyridine-N of the azaindole system which exhibits an altered c-pK_a for the conjugate acid in the amide compounds of Table 4 (c-pK_a ca. 4.5) compared to the compounds of Tables 2, 3, and 5 (c-pK_a ca. 5.3–5.7). We might surmise that this electronic

Table 2
Enzymatic and antiviral activity, cellular cytotoxicity, stability and lipophilic ligand efficiency (LipE) of the acyclic 3-aminomethyl-azaindole *N*-methyl hydroxamates **10**

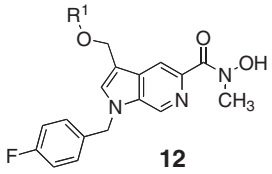


10

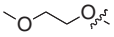
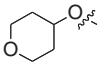
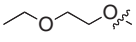
Compd	R^1R^2N	*c* Log *D*[a] (Log *D*)	TPSA	IC_{50}[b] (nM)	EC_{50}[c] (nM)	CC_{50}[c] (μM)	ER[d] (hHEP)	LipE[e]
10a		0.93	81.8	1421	747	>100	0.55	5.2
10b		1.53 (1.80)	64.8	534	220	>224	0.55	5.1
10c		1.62	90.7	388	150	>100	0.30	5.2
10d		2.17	104.7	466	80	>100	0.50	4.9
10e		2.17	104.7	558	94	216	0.36	4.9

[a] Calculated log *D* at pH 7.4 using ACD/Physicochem Suite, Version 12 (ACD labs, Toronto, Canada).
[b] Strand transfer scintillation proximity assay (see Supplementary data).
[c] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration (see Supplementary data). CC_{50}, 50% cytotoxic concentration (see Supplementary data).
[d] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CLint)/(Q + (fu × CLint)).[15]
[e] LipE = −Log EC_{50} − *c* Log *D*.[22]

Table 3
Enzymatic and antiviral activity, cellular cytotoxicity, stability and lipophilic ligand efficiency (LipE) of the acyclic 3-R^1O-methyl-azaindole *N*-methyl hydroxamates **12**



12

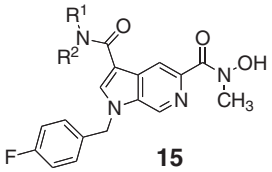
Compd	R^1O	*c* Log *D*[a] (Log *D*)	TPSA	IC_{50}[b] (nM)	EC_{50}[c] (nM)	CC_{50}[c] (μM)	ER[d] (hHEP)	LipE[e]
12a		1.76	78.6	145	54	>266	1.0	5.5
12b		2.19 (1.79)	76.8	382	29	>100	0.51	5.3
12c		2.35	76.9	313	57	>100	0.86	4.9
12d		2.52	67.6	242	41	266	1.0	4.8
12e		2.70	76.8	308	57	81	0.57	4.5

[a] Calculated log *D* at pH 7.4 using ACD/Physicochem Suite, Version 12 (ACD labs, Toronto, Canada).
[b] Strand transfer scintillation proximity assay (see Supplementary data).
[c] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration (see Supplementary data). CC_{50}, 50% cytotoxic concentration (see Supplementary data).
[d] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CLint)/(Q + (fu × CLint)).[15]
[e] LipE = −Log EC_{50} − *c* Log *D*.[22]

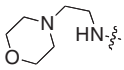
pertubation has had a negative impact on permeability (not measured) that is manifest in EC_{50} values. In addition, one cannot dismiss the impact of the amide *N*–H of **15c** on permeability as well. The aminomethyl compounds of Table 2 are a bit easier to analyze as the ablation of antiviral activity with increasing *c* Log *D* (viz. **10d** EC_{50} = 80 nM, *c* Log *D* = 2.17, TPSA = 104.7: vs **12b**/**18b**) might be attributed to the permeability impact of increasing TPSA.

After considering the data of Tables 2–5, we selected the 3-aminomethyl compounds **10c**, and **10e** as representative compounds for further evaluation in animal species for assessment of their pharmacokinetic (PK) parameters. Preliminary metabolism studies suggested that these compounds were readily hydrolyzed to their corresponding carboxylic acids in rat plasma, possibly by carboxyesterases. This was consistent with literature reports

Table 4
Enzymatic and antiviral activity, cellular cytotoxicity, stability and lipophilic ligand efficiency (LipE) of the acyclic 3-carboxamido-azaindole *N*-methyl hydroxamates **15**

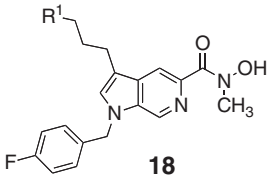


15

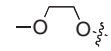
Compd	R^1, R^2	*c* Log D[a] (Log *D*)	TPSA	IC_{50}[b] (nM)	EC_{50}[c] (nM)	CC_{50}[c] (μM)	ER[d] (hHEP)	LipE[e]
15a		1.60 (1.44)	99.3	503	210	32	0.25	5.1
15b		2.21	98.9	319	170	>32	<0.20	4.5
15c		2.64 (2.36)	87.5	251	110	>100	0.25	4.3

[a] Calculated log *D* at pH 7.4 using ACD/Physicochem Suite, Version 12 (ACD labs, Toronto, Canada).
[b] Strand transfer scintillation proximity assay (see Supplementary data).
[c] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration (see Supplementary data). CC_{50}, 50% cytotoxic concentration (see Supplementary data).
[d] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CLint)/(Q + (fu × CLint)).
[e] LipE = $-$Log EC_{50} $-$ *c* Log *D*.[22]

Table 5
Enzymatic and antiviral activity, cellular cytotoxicity, stability and lipophilic ligand efficiency (LipE) of the 3-R^1-propyl-azaindole *N*-methyl hydroxamates **18**



18

Compd	R^1	*c* Log D[a]	TPSA	IC_{50}[b] (nM)	EC_{50}[c] (nM)	CC_{50}[c] (μM)	ER[d] (hHEP)	LipE[e]
18a		2.36	70.8	559	470	>10	0.98	4.0
18b		2.66	78.6	340	41	>10	1.0	4.7
18c		3.07	76.8	552	220	>10	0.97	3.6

[a] Calculated log *D* at pH 7.4 using ACD/Physicochem Suite, Version 12 (ACD labs, Toronto, Canada).
[b] Strand transfer scintillation proximity assay (see Supplementary data).
[c] HIV-1 cytopathic effect (CPE) inhibition assay; EC_{50}, 50% effective concentration (see Supplementary data). CC_{50}, 50% cytotoxic concentration (see Supplementary data).
[d] Extraction ratio in human hepatocytes (hHEP) after 4 h incubation; ER = (fu × CLint)/(Q + (fu × CLint)).[15]
[e] LipE = $-$Log EC_{50} $-$ *c* Log *D*.[22]

which indicated that hydroxamic acids undergo hydrolytic cleavage by carboxyesterases in rodent plasma.[23,24] Since the selected compounds were stable in human and dog plasma, further PK assessment of these compounds were conducted in the dog.

Compound **10c** had higher clearance relative to **10e** in the dog (Table 6) while the volume of distribution (V_{dss}) for these compounds was similar in the dogs and ranged from 1.8 to 2.3. The moderate to high clearance and moderate volume of distribution resulted in half-lives of 1.8 h and 6.2 h for **10c** and **10e**, respectively. Given its more lengthy half life, human PK parameters for **10e** were projected using the dog PK data and a single species scaling approach.[25] *N*-Methyl hydroxamate **10e** is projected to have low blood clearance (Cl_b = 5.5 mL/min/kg), moderate volume of distribution (V_{dss} = 2.15 L/kg), moderate bioavailability (*F* = 41%) and an estimated half-life in humans of 4.5 h.

Table 6
Pharmacokinetic profile of compounds **10c** and **10e** in dog[a]

Compd	Cl^b (mL/min/kg)	V_{dss}[c] (L/kg)	$T_{1/2}$[d] (h)	*F* (%)[e]
10c	24	1.8	1.27	20
10e	15	2.32	6.2	53

[a] Dose: iv, 1 mg/kg, citrate buffer, pH = 4; po, 5 mg/kg, 5% PEG/methylcellulose.
[b] Plasma clearance.
[c] Volume of distribution.
[d] Half-life.
[e] Oral bioavailability.

The specificity of **10e** for HIV IN was determined by testing the inhibitor against a variety of human DNA modifying and metal-dependent enzymes. Compound **10e** showed no significant

inhibition of HCV polymerases, and matrix metalloproteases (IC_{50} >50 μM) and 102 magnesium dependent protein kinases (IC_{50} >1 μM), and is not an inhibitor or a substrate of the 6 major CYP isoforms (IC_{50} >30 μM for 1A2, 2C8, 2D6, 3A4, 2C9 and 2C19). Compound **10e** modestly inhibited hERG potassium channels with an IC_{50} of 8.6 μM.

Azaindole hydroxamic acids **4** and **5** are HIV Integrase inhibitors with antiviral cell-based activities comparable to the currently marketed HIV Integrase inhibitor raltegravir **1** (EC_{50}: 10 nM).[5] They are stable against oxidative metabolism but were rapidly cleared by glucuronidation. We were able to attenuate clearance rates in human hepatocytes by introducing polarity at the pyrrolyl-β-position of the azaindole hydroxamate nucleus without a dramatic impact upon the antiviral activity of the compounds of interest (viz. **4** and **5** vs **10e** and **12b**). These observations suggest the utility of a similar paradigm (substitution to alter clearance) within a series of intrinsically greater antiviral potency. These activities will be disclosed in subsequent reports from these laboratories.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.10.022.

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