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Letter

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Discovery of MK-8718, an HIV Protease Inhibitor Containing a Novel Morpholine Aspartate Binding Group

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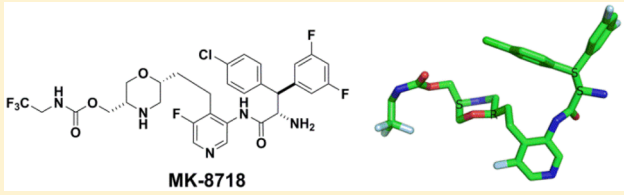
Supporting Information

ABSTRACT: A novel HIV protease inhibitor was designed using a morpholine core as the aspartate binding group. Analysis of the crystal structure of the initial lead bound to HIV protease enabled optimization of enzyme potency and antiviral activity. This afforded a series of potent orally bioavailable inhibitors of which MK-8718 was identified as a compound with a favorable overall profile.



KEYWORDS: *MK-8718, HIV, protease, inhibitor*

HIV protease is an aspartyl protease that catalyzes the proteolytic cleavage of polypeptide precursors into mature enzymes and structural proteins that are essential components of HIV.[1] Inhibition of HIV protease prevents conversion of HIV particles into their mature infectious form and is an important approach for therapeutic intervention in HIV infection.[2] HIV protease inhibitors (PIs) have played a crucial role as a therapy for the treatment of HIV.[3,4] However, challenges still remain for these molecules in the form of strict dosing regimens, high pill burden, significant side effects, and the occurrence of resistant strains.[5] In addition, HIV PIs have traditionally suffered from poor pharmacokinetic properties, including poor oral absorption and low metabolic stability.[6,7]

The first crystal structures of inhibitors bound to HIV protease were reported 25 years ago.[8,9] Since then, structure based design has played a key role in the development of new inhibitors.[10] A crucial structural feature of the majority of HIV PIs is the presence of a hydroxyl group that forms a hydrogen bond with the carboxylic acid functionalities of the catalytic Asp-25 and Asp-25′ residues in the enzyme active site.[11] We were interested in pursuing analogues of inhibitors where an amine, instead of a hydroxyl group, forms the key interaction with the Asp-25 and Asp-25′ acidic residues of the enzyme.[12] This type of inhibitor was attractive to us due to the potential improvement in physical properties offered by the polar amine functionality.

The starting point for the design of our compounds were the pyrrolidine-type inhibitors such as **1** (Figure 1) reported by

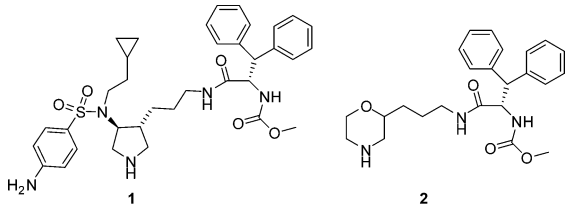


Figure 1. Pyrrolidine based inhibitor **1** and proposed morpholine based inhibitor **2**.

Coburn et al.[13] Although these molecules offered improved solubility over their hydroxyl counterparts, the pyrrolidine functionality introduced a number of undesirable off target activities, which may be attributed to the presence of a basic pyrrolidine nitrogen.[14] This prompted us to consider designing a new core that would maintain the solubility enhancing amine functionality, while reducing the basicity of the nitrogen, with the

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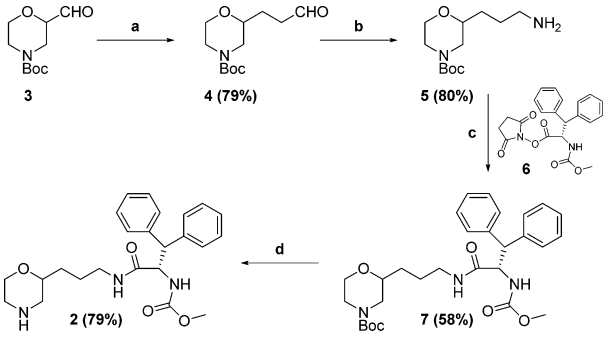
goal of reducing off target activity. To this end, we felt a morpholine core offered a number of attractive properties. First, the inductively electron withdrawing effect of the oxygen lowers the pK_a of the nitrogen; second the core provides access to a number of vectors, which could be used to append substituents to fill the remaining pockets of HIV protease.[15] Our initial design was the truncated analogue **2** shown in Figure 1. It was envisioned that **2** would have sufficient affinity for the enzyme to enable a crystal structure of the inhibitor bound to the enzyme to be solved. This in turn could be used to design in the remaining functionality required to produce a potent inhibitor.

Synthesis of **2** began with commercially available aldehyde **3** as outlined in Scheme 1. Homologation and subsequent olefin

Scheme 1[a]



[a]Reagents and conditions: (a) (i) $Ph_3P{=}CHCHO$, THF, 50 °C; (ii) Pd/C, 30 psi H_2, EtOAc, RT; (b) $BnNH_2$, $NaBH_4$, THF/MeOH, RT; (ii) Pd/C, 50 psi H_2, MeOH, RT; (c) $NaHCO_3$, THF/H_2O, 0 °C; (d) TFA, Et_3SiH, CH_2Cl_2, RT.

reduction afforded aldehyde **4**. Reductive amination followed by debenzylation afforded primary amine **5**. Coupling of succinate ester **6**[16] with amine **5** afforded amide **7**, which was deprotected to yield desired product **2** as a mixture of diastereoisomers.

Although morpholine **2** was shown to be a modest inhibitor of HIV protease (11% inhibition at 1 μM), we decided to pursue a crystal structure of **2** bound to the enzyme. Pleasingly, a crystal structure was solved as depicted in Figure 2. It can be seen from this structure that the morpholine nitrogen of **2** indeed forms the desired key interactions with the Asp-25 and Asp-25′ acidic residues of the enzyme. In addition, the (*R*)-stereochemistry at the 2-position of the morpholine appeared to be preferred, and it could be seen that the two aryl groups occupy the S1 and S3 regions of the enzyme. With this valuable information in hand, we sought to improve the binding affinity by adding appropriate substituents to occupy additional key pockets of the enzyme.

The design of our next generation inhibitor was inspired by overlaying the enzyme bound conformation of our initial morpholine based inhibitor **2** with that of inhibitor **8**, containing a P2 aryl substituent[17] as shown in Figure 2. This analysis suggested that incorporation of an aryl P2 substituent into our morpholine based inhibitors could be beneficial for enzyme affinity. In addition, it was evident that a substituent at the 5-position of the morpholine could be used to reach out and occupy the S1′ pocket of the enzyme. This led us to pursue compound **9a.**

Synthesis of **9a** is depicted in Scheme 2 and began by reaction of amino alcohol[18] **10** with (*R*)-epichlorohydrin, using reaction conditions reported for the enantiomer,[19] to give morpholine **11**. Swern oxidation of **11** afforded aldehyde **12**. A subsequent Wittig reaction, followed by reduction, afforded aniline **13**. Coupling of

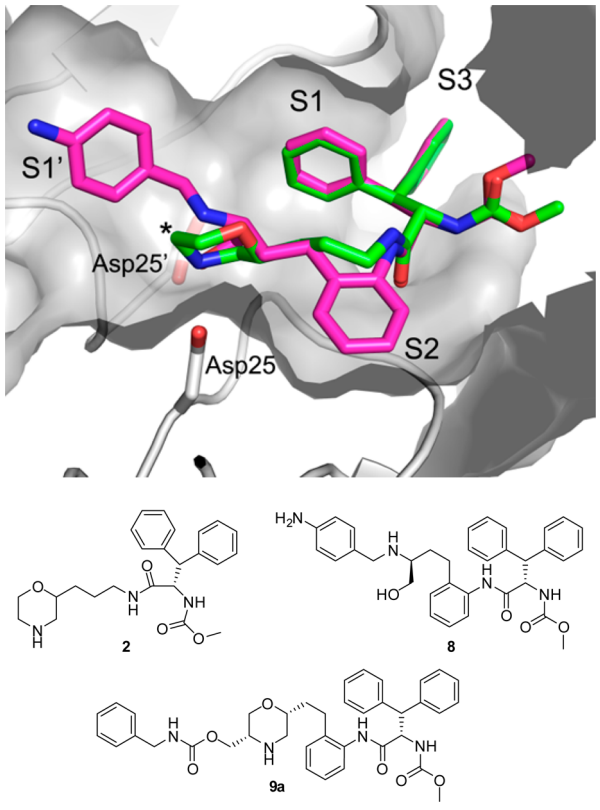


Figure 2. Overlay of the enzyme bound conformations of **2** (green) and **8** (magenta). The flaps have been cut away for optimum viewing. The 5-position is marked with an *.

acid **6** with aniline **13** afforded amide **14**. Silyl deprotection to afford **15**, followed by carbamate formation and morpholine deprotection afforded the desired compound **9a**. Pleasingly, **9a** was shown to be a potent inhibitor of HIV protease (IC_{50} = 6 nM). In addition, the compound showed antiviral activity in a cell based assay (IC_{95} = 202 nM). This promising activity encouraged us to benchmark the pharmacokinetic profile of **9a**, shown in Table 1. The compound displayed moderate clearance in rat, coupled with a short half-life, and low bioavailability. With these results in hand and given our ability to introduce a P1′ substituent late in the synthesis, we decided to prepare analogues to explore the impact of this substituent on potency and pharmacokinetic properties. A subset of the analogues are shown in Table 1. A variety of substituents were tolerated; however, the trifluorethylcarbamate substituent present in **9i** afforded a nice balance of potency, clearance, and oral bioavailability.

Having identified an acceptable P1′ substituent, we decided to see if additional potency or pharmacokinetic improvements could be realized by optimizing the P2 substituent. A series of analogues were designed and the requisite anilines necessary for P2 SAR exploration were synthesized as shown in Scheme 3 and Scheme 4. For the fluorophenyl P2 precursor shown in Scheme 3, Wittig reaction of aldehyde **12** afforded olefin **16**. Subsequent TBS deprotection gave alcohol **17**. Carbamate formation followed by reduction (nitro and olefin) afforded aniline **18**.

For the pyridyl P2 precursors in Scheme 4, Seyferth−Gilbert homologation[21] of aldehyde **12** afforded alkyne **19**. Sonagashira coupling,[22] followed by alkyne reduction gave anilines **20** and **21**. Cbz protection followed by TBS deprotection afforded alcohols **22** and **23**. Carbamate formation followed by Cbz-deprotection gave the desired anilines **24** and **25**. As described in Scheme 7,

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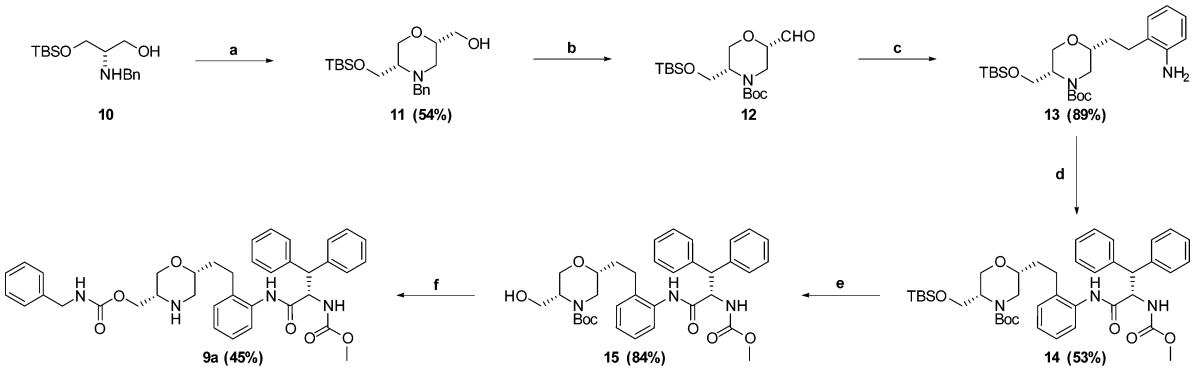
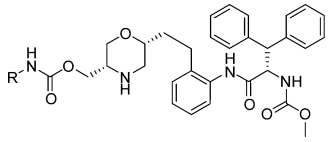
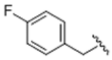
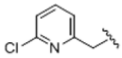
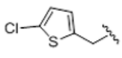
Scheme 2[a]



[a]Reagents and conditions: (a) (*R*)-epichlorohydrin, $LiClO_4$, NaOMe, toluene/MeOH, RT; (b) (i) $Pd(OH)_2$, Boc_2O, NEt_3, 45 psi H_2, RT; (ii) oxalyl chloride, NEt_3, DMSO, CH_2Cl_2, −78 °C; (c) (i) K_2CO_3, 18-crown-6, (2-nitrobenzyl)triphenylphosphonium bromide, DME, RT; (ii) Pd/C, 50 psi H_2, EtOH, RT; (d) (*S*)-2-((methoxycarbonyl)amino)-3,3-diphenylpropanoic acid, HATU, 2,6-lutidine, DMF, RT; (e) TBAF, THF, RT; (f) (i) benzylisocyanate, DCM, RT; (ii) TFA, DCM, 0 °C.

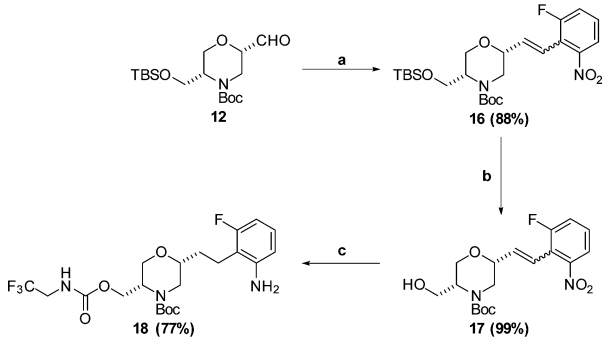
Table 1. Profiles of Compounds 9a−9j



Compound	R	Enzyme[a] IC_{50} (nM)	Antiviral[b] IC_{95} (nM)	Rat PK[c] Cl (ml/min/kg)	%F
9a		6.1	200	27	<5
9b		3.6	180	61	nd
9c		4.1	170	49	47
9d		3.4	150	45	17
9e		2.4	170	33	13
9f		9.7	370	110	<5
9g		3.5	63	87	<5
9h		37	190	60	33
9i		27	120	36	19
9j		20	120	30	16

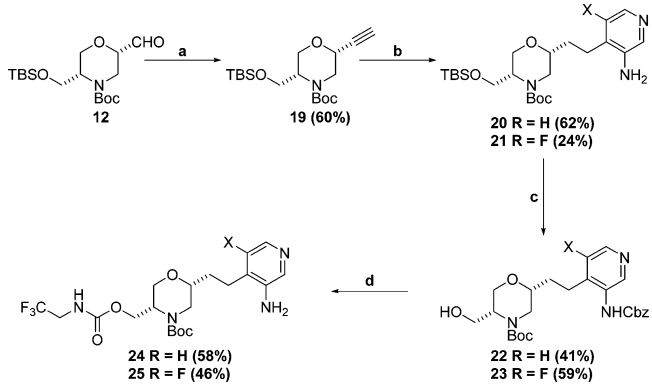
[a]Assay for inhibition HIV protease as described in the Supporting Information (n = 2). [b]Assay for inhibition of viral infection as described in the Supporting Information (n = 2). [c]1 mpk IV (60% PEG 400/water), 5 mpk PO (0.5% methylcellulose). n = 2 rats.

Scheme 3[a]



[a]Reagents and conditions: (a) K_2CO_3, 18-crown-6, (2-fluoro-6-nitrobenzyl)triphenylphosphonium bromide,[20] DME, RT; (b) HCl, MeOH, RT; (c) (i) 2,2,2-trifluoroethylamine, CDI, pyridine, RT; (ii) $Pd(OH)_2$, 50 psi H_2, CF_3CH_2OH, RT.

Scheme 4[a]



[a]Reagents and conditions: (a) dimethyl (1-diazo-2-oxopropyl)-phosphonate, K_2CO_3, MeOH, RT; (b) (i) 5-fluoro-4-iodopyridin-3-amine, 7% $(PPh_3)_2PdCl_2$, 10% CuI, Et_3N, CH_3CN, 70 °C; (ii) 50% PtO_2, 50 psi H_2, CF_3CF_2OH, RT; (c) (i) Cbz-Cl, pyridine, 0 °C; (ii) TBAF, THF, RT; (d) (i) 2,2,2-trifluoroethylamine, CDI, pyridine, 60 °C; (ii) Pd/C, 1 atm H_2, EtOH, RT.

anilines **18**, **24**, and **25** were coupled to commercially available (*S*)-2-((methoxycarbonyl)amino)-3,3-diphenylpropa-noic acid and (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-diphenylpropanoic acid using $POCl_3$. Boc-deprotection gave final compounds **9k** to

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Table 2. Profile of Compounds 9i, 9k−9t, and Atazanavir

Compound	X	R_1	R_2	R_3	R_4	R_5	R_6	Enzyme[a] IC_{50} (nM)	Antiviral[b] IC_{95} (nM)	Rat PK[c] Cl (mL/min/kg)	Rat PK[c] %F
atazanavir								0.04	17	nd	nd
9i	C	H	H	H	H	H	Moc	27	120	36	19
9k	C	F	H	H	H	H	Moc	12	95	36	37
9l	C	F	H	H	H	H	H	3.1	230	nd	nd
9m	N	H	H	H	H	H	Moc	14	330	81	<5
9n	N	F	H	H	H	H	Moc	3.5	94	11	15
9o	N	F	H	H	H	H	H	9.9	150	13	59
9p	C	F	F	H	H	F	H	6.4	75	45	30
9q	C	F	F	F	H	F	H	8.2	61	22	14
9r	N	F	F	H	H	F	H	2.4	66	16	37
9s	N	F	F	F	H	F	H	2.4	130	nd	nd
9t (MK-8718)	N	F	Cl	F	H	F	H	0.8	49	11	25

[a]Assay for inhibition HIV protease as described in the Supporting Information (n = 2). [b]Assay for inhibition of viral infection as described in the Supporting Information (n = 2). [c]For compounds **9i−9n**: 1 mpk IV (60% PEG 400/water), 5 mpk PO (0.5% methylcellulose). n = 2 rats. For compounds **9o−9t**: 2 mpk IV (1:1 DMSO/PEG400), 10 mpk PO (10% tween 80/water). n = 2 rats.

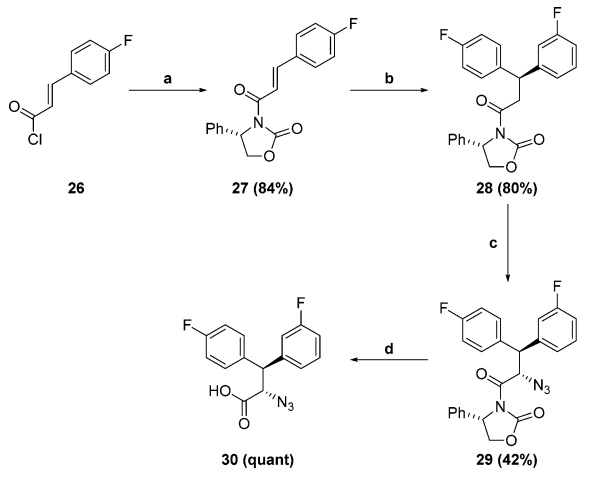
9o shown in Table 2. Key discoveries from this set of compounds were as follows.

A pyridyl P2 improved binding affinity (**9i** vs **9m**) and a fluorophenyl P2 improved binding affinity and oral bioavailability (**9i** vs **9k**). Combining these two findings afforded **9n**, which offered a favorable combination of antiviral activity (IC_{95} = 94 nM) and rat clearance. Two primary amine derivatives were also prepared and offered improvements in binding affinity (**9l** vs **9k**) and bioavailability (**9o** vs **9n**).

At this point we turned our attention to optimizing the P1 and P3 phenyl substituents. It is evident from Figure 2 that the S1 and S3 pockets of the enzyme are not equivalent, even though they are occupied by identical P1 and P3 substituents. This inspired us to examine unsymmetrical P1 and P3 groups to further improve enzyme affinity. A series of designs were modeled and prioritized for synthesis. Synthesis of the requisite acid precursors was carried out as shown in Scheme 5. *para*-Fluorophenyl substituted acryloyl chloride **26**[23] was treated with the anion of (*S*)-4-phenyloxazolidin-2-one to afford the desired acryloyloxazolidinone **27**.[24] Copper-catalyzed Grignard addition was used to introduce the desired P3 substituent in a highly stereoselective manner.[25] Subsequent electrophilic azide transfer to the chiral enolate of **28** afforded the desired α-azidocarboximide **29**. Hydrogen peroxide mediated hydrolysis afforded azido acid **30**.[26] In addition to a mono-fluorinated P3 substituent, we were also interested in a difluoro substituted P3. Unfortunately the 3,5-difluorophenyl Grignard reagent was insufficiently reactive to undergo copper catalyzed Grignard addition to **27**. Accordingly, we used the route shown in Scheme 6 whereby the more reactive Grignard of the P1 substituent was utilized.

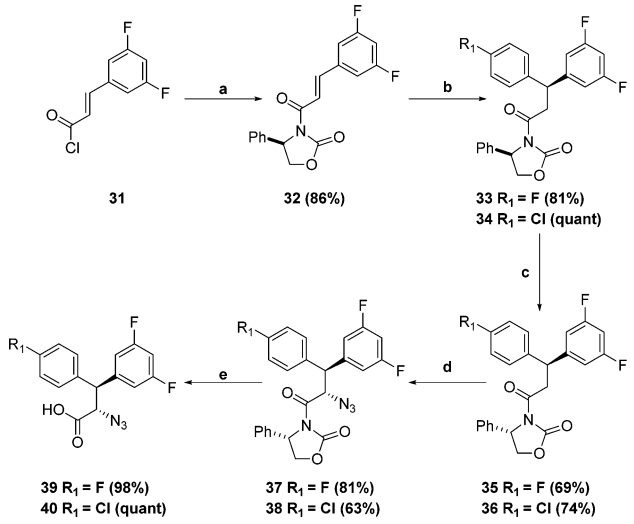
3,5-Difluoro substituted acryloyl chloride **31** was treated with the anion of (*R*)-4-phenyloxazolidin-2-one to afford the desired acrylooxazolidinone **32**. Copper-catalyzed Grignard addition afforded acryloyloxazolidinones **33** and **34**. Switching of the chiral auxiliaries afforded **35** and **36**, which underwent

Scheme 5[a]



[a]Reagents and conditions: (a) ^{n}BuLi, (*S*)-4-phenyloxazolidin-2-one, THF, −78 °C; (b) (3-Fluorophenyl)magnesium bromide, CuBr.SMe_2, THF, −20 °C; (c) NaHMDS, trisyl azide, THF, −78 °C; (d) H_2O_2, LiOH, $NaHCO_3$, THF/H_2O, 0 °C.

Scheme 6[a]



[a]Reagents and conditions: (a) ^{n}BuLi, (*R*)-4-phenyloxazolidin-2-one, THF, −78 °C; (b) (4-fluoro or chlorophenyl)magnesium bromide, CuBr·SMe_2, THF, −20 °C; (c) H_2O_2, LiOH, $NaHCO_3$, THF/H_2O, 0 °C; (d) $SOCl_2$, CH_2Cl_2, reflux; (d) ^{n}BuLi, (*S*)-4-phenyloxazolidin-2-one, THF, −78 °C; (d) NaHMDS, trisyl azide, THF, −78 °C; (d) H_2O_2, LiOH, $NaHCO_3$, THF/H_2O, 0 °C.

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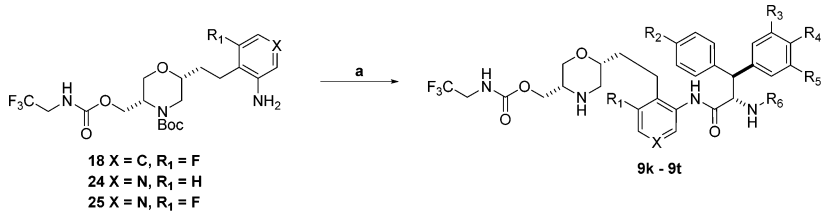
Scheme 7[a]



[a]Reagents and conditions: (a) (i) (*S*)-2-((methoxycarbonyl)amino)-3,3-diphenylpropa-noic acid or (*S*)-2-((*tert*-butoxycarbonyl)amino)-3,3-diphenylpropanoic acid, $POCl_3$, pyridine, 0 °C; (ii) 4 M HCl, dioxane, RT; (b) (i) **30**, **39**, or **40**, $POCl_3$, pyridine, 0 °C; (ii) Pd/C, 1 atm H_2, MeOH, RT, or PPh_3, THF/H_2O, reflux; (iii) 4 M HCl, dioxane, RT.

electrophilic azide transfer to give α-azidocarboximides **37** and **38**. Hydrogen peroxide mediated hydrolysis liberated azido acids **39** and **40**. As depicted in Scheme 7 anilines **18** and **25** were coupled to azido acids **30**, **39**, and **40**. Azide reduction, followed by Boc-removal, afforded the desired targets **9p**−**9t**.

The relevant data for this set of compounds is shown in Table 2. The combination of *para*-fluorophenyl as the P1 substituent and a *meta*-fluorophenyl as the P3 substituent improved cell based antiviral activity (**9p** vs **9l**). Adding a second fluorine to the P3 phenyl served to maintain cell based activity while lowering rat clearance (**9p** vs **9q**). Incorporation of a P2 pyridyl substituent further improved rat clearance relative to the P2 phenyl, while maintaining cell based activity (**9r** vs **9p**). Finally, replacing the P1 *para*-fluoro of **9r** with a *para*-chloro substituent afforded **9t**. This compound offered improvements in binding affinity, cell-based antiviral activity, rat clearance, and oral bioavailability. Additional preclinical evaluation of **9s**−**9t** showed that **9t** had the most favorable overall profile. Based on these desirable attributes **9t** was designated as **MK-8718** and was chosen for further studies to enable entry into the clinic for assessment of human pharmacokinetic properties.

In summary, a series of HIV protease inhibitors were designed containing a novel morpholine based aspartate binding group. Structure based optimization of the P1, P1′, P2, and P3 substituents was carried out to improve cell based antiviral activity and rat pharmacokinetic properties. This resulted in the identification of **MK-8718**, a potent HIV protease inhibitor with a favorable pharmacokinetic profile with potential for further development.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acsmedchem-lett.6b00135.

Synthetic experimental details for the synthesis of **MK-8718** and **9b** − **9j** along with descriptions of primary biological assays. Experimental details for the remaining compounds can be found in the following patent: WO 2014043019 A1 (PDF)

Accession Codes

X-ray crystallographic data for **2**, **8**, **9a**, and **MK-8718** bound to HIV protease have been deposited in the RCSB protein data bank (pdb codes 5IVQ, 5IVR, 5IVS, and 5IVT).

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Notes

The authors declare no competing financial interest.

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