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Review Article

De novo design, discovery and development of cyclic urea HIV protease inhibitors

George V. De Lucca* and Patrick Y.S. Lam
DuPont Pharmaceuticals Company, Experimental Station, P.O. Box 80500, Wilmington, DE 19880-0500, USA.
**Correspondence*

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Introduction

Since the identification of HIV as the causative agent of AIDS there has been a worldwide effort to find effective therapies for this disease. One of the most intense areas of research has been the effort to find effective inhibitors of the essential aspartic protease (PR) of HIV that processes the viral *gag* and *gag-pol* polyproteins into structural and functional proteins. Inhibition of HIV-PR *in vitro* results in the production of progeny virions which are immature and noninfectious (1). The abundance of structural information available on HIV-PR has made the enzyme an attractive target for computer-aided drug design strategies (2).

Clinical studies show that HIV-PR inhibitors are effective in reducing the viral load and increasing the number of $CD4^+$ lymphocytes of HIV-infected patients (3). Saquinavir, ritonavir, indinavir and nelfinavir have been approved by the FDA and are being used in AIDS therapy in combination with reverse transcriptase (RT) inhibitors. However, the daunting ability of the virus to rapidly generate resistant mutants (4) suggests that there is an ongoing need for new HIV-PR inhibitors with superior pharmacokinetic and efficacy profiles.

The different approaches to the discovery of the various types of HIV-PR inhibitors have been extensively reviewed (5). Leads have been identified through random screening and rational drug design. Regardless of how the leads were generated, the main feature of the research on HIV protease inhibitors has been the extensive use of structural information and computational/computer modeling techniques to optimize initial lead structures.

Design of cyclic ureas

When we started to design new structures as HIV protease inhibitors there were two important components that were available. First, high resolution X-ray structures of linear inhibitors complexed with HIV-1-PR were available, which revealed the presence of a tetracoordinated structural water molecule linking the bound inhibitor to the flexible glycine-rich beta strands or “flaps” of the HIV-PR dimer. This structural water molecule accepts two hydrogen bonds from the backbone amide hydrogens of residues Ile 50 and Ile 50’ and donates two hydrogen bonds to the carbonyl oxygens flanking the transition state mimetic of the inhibitor molecule.

At the same time, a promising computational methodology that became available was the technique of searching databases containing 3D molecular structures using a 3D pharmacophore model. This technique has been used to identify synthetic frameworks that can serve as the starting point for the design of nonpeptide inhibitors (6).

The use of this 3D database searching technique and the incorporation of the structural water molecule into the inhibitor became important criteria in our design strategy (7) and is summarized in Figure 1.

Using the available structural information and the SAR we had established for the linear C_2 symmetric diols (8) we were able to generate several pharmacophore models. Searching 3D databases using our pharmacophore model yielded the hit **1C** (Fig. 1), which incorporated a mimic for the structural water molecule.

Because the phenyl ring of **1C** might not properly position all the substituents of the inhibitor for maximum interaction with the enzyme, a cyclohexanone ring **1D** was chosen as the initial synthetic scaffold with the ketone oxygen as the structural water mimic. Since the SAR established for linear C_2 symmetric diols indicated that the diol imparts significant potency compared to corresponding mono-ol transition state analogs (8, 9), the cyclohexanone ring was enlarged to the 7-membered ring **1E** to incorporate a diol functionality. This synthetic target

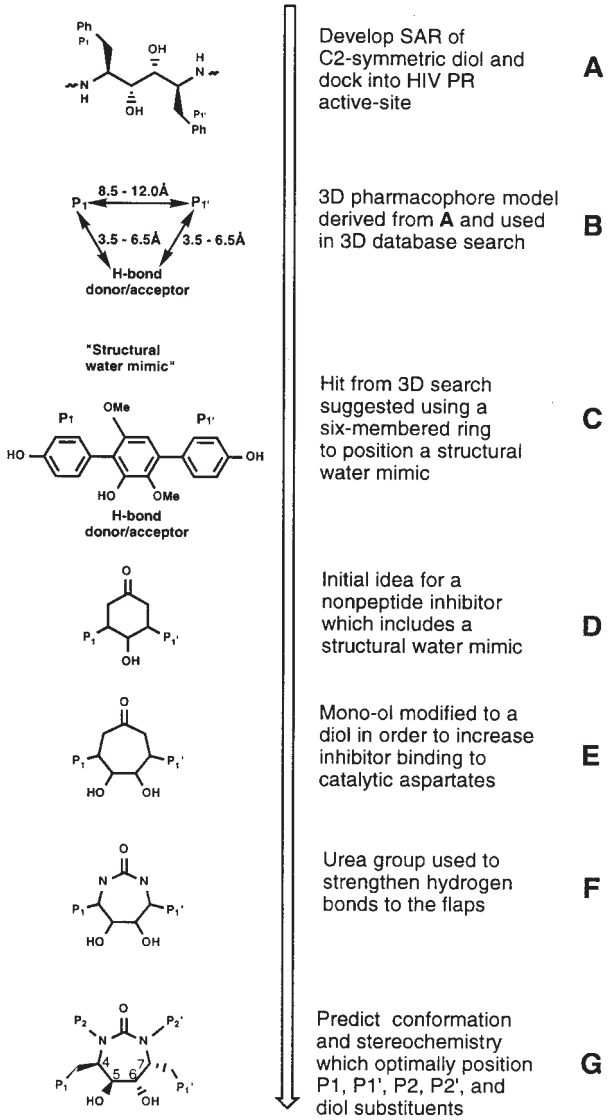


Fig. 1. Strategy and steps involved in the design of cyclic urea inhibitors of HIV-PR.

was further modified to a cyclic urea **1F** in order to strengthen the hydrogen bonds to the flap residues.

Of critical importance for proper modeling studies was the prediction of the preferred conformations of the cyclic urea. The 7-membered cyclic urea can exist in two pseudo chair conformations. When the nitrogens are unsubstituted, 1,3-diaxial strain causes the conformer with pseudo diequatorial benzyl groups to be preferred. When the two nitrogens are substituted the allylic 1,2-strain between the benzylic groups and the nitrogen substituents causes the conformer with pseudo diaxial benzyl groups to be preferred. This conformational prediction was subsequently confirmed by X-ray analysis (10). With this type of conformational analysis, the modeling predicted the optimal stereochemistry for cyclic ureas to be 4*R*, 5*S*, 6*S*, 7*R* (Fig. **1G**), which is derived from unnatural (D) phenylalanine. It is only with this stereochemistry that the substituents on N are directed towards the S2/S2′ sites of HIV-PR. This is in contrast to the linear C_2 symmetric diol inhibitors where natural (L) phenylalanine provides the optimal stereochemistry (8, 11).

Cyclic urea **2** (XK216), with allyl substituents, was the first D-phenylalanine-based cyclic urea synthesized and was found to be a potent inhibitor with a K_i of 5.2 nM (Table I). XK216 binds 1000x tighter than its enantiomer **3**. In addition to its high affinity, XK216 was also found to be orally bioavailable in rats (F = 49%). The high oral bioavailability of XK216 is probably attributable to its low molecular weight.

X-ray structures of HIV-1-PR revealed that the S2/S2′ pockets are essentially lipophilic. The SAR of the cyclic ureas is consistent with this observation (10). As the size of the N-substituent is increased incrementally from methyl to n-heptyl the potency increases. The optimal size is the n-butyl (**6**) with a K_i of 1.4 nM (Table I). In the cycloalkyl series, cyclobutylmethyl analog **10** was found to have the best K_i among the cycloalkylmethyl cyclic ureas. The hydrophobic nature of the S2/S2′ pockets was further demonstrated by the 2-3 orders of magnitude decrease in binding when hydrophilic oxygen and nitrogen atoms are inserted into short alkyl side chains as in **7** and **8**, or into small cycloalkyls as in 11 (Table I).

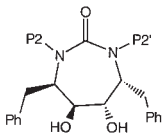
Models showed that the S2/S2′ pockets are very large and should accommodate large N-substituents. The benzyl analog 12 had a K_i of 3.0 nM, and the larger 2-naphthylmethyl analog **14** was found to be a subnanomolar inhibitor with a K_i of 0.31 nM. Modeling revealed that the 2-naphthylmethyl could fit in only one orientation, and that there is more space available at the *meta* position compared with the *ortho* or *para* positions of the P2/P2′ benzyl substituent. A series of regioisomeric fluoro substituents were synthesized and showed that the *para* and *meta* positions are preferred over the *ortho* position. On the other hand, 3,5 disubstitution, as in **16**, gave poorer binders. Models suggest that since one side of the P2 benzyl ring interacts with the wall of the S2 pocket, only one *meta* position can be substituted.

First clinical candidate DMP 323

The conformational stability of the N-substituted cyclic ureas is invaluable in structure-based design because it makes the interactions of the added substituents with the enzyme more predictable. This scaffold also provides a synthetic advantage in structure-activity relationship studies, since cyclic ureas with symmetric P2/P2′ substituents can be prepared easily and the optimal side chains can rapidly be identified. Although synthetically much more challenging, extensive analog studies focused on P1/P1′ have been carried out (12). However, due to lipophilicity, pharmacokinetic and cost considerations, simple benzyl groups at P1/P1′ are generally preferred.

Using the N-benzyl substituted cyclic urea as a rigid scaffold, modeling (based on the complex of **14**/HIV-PR)

Table I: P2/P2′ SAR of symmetric cyclic urea inhibitors of HIV protease.



cpd	P2/P2′	K_i[a] (nM)	IC_{90}[a] (μM)	Rat P.O. bioavail[b] C_{max} (μM)	Rat P.O. bioavail[b] F%
1	H	4500	>100	-	-
2	allyl (XK216)	5.2	4.7	2.7	49
3	allyl (enantiomer of **2**)	4500	>100	-	-
4	methyl	5700	>141	-	-
5	n-ethyl	100	>132	-	-
6	n-butyl	1.4	0.68	-	-
7	2-dimethylaminoethyl	2660	106	-	-
8	$CH_2CH_2OCH_3$	800	>114	-	-
9	cyclopropylmethyl	2.1	1.8	4.3 9.2 (dog)	100 48 (dog)
10	cyclobutylmethyl	1.3	1.0	-	-
11	3-methylisoxazolin-3-yl	3800	96	-	-
12	benzyl	3.0	0.83	1.3	-
13	1-naphthylmethyl	86	16	-	-
14	2-naphthylmethyl	0.31	3.9	0.38	-
15	3-fluorobenzyl	3.0	0.71	-	-
16	3,5-difluorobenzyl	24	4.3	-	-
17	4-hydroxymethylbenzyl (DMP 323)	0.34	0.057	0.78 2.8 (dog)	27 37 (dog)
18	3-hydroxymethylbenzyl	0.14	0.038	0.83	18
19	4-hydroxybenzyl	0.12	0.032	0.39	22
20	3-hydroxybenzyl	0.12	0.054	0.81 2.0 (dog)	30 16 (dog)
21	3-aminobenzyl•$2CH_3SO_3H$ (DMP 450)	0.28	0.13	2.25 11.2 (dog)	71 79 (dog)
22	3-aminomethylbenzyl	980	78	-	-
23	3-acetylbenzyl	0.07	0.04	0.28	-
24	3-carboxybenzyl	0.43	34	-	-
25	3-hydrazidobenzyl	0.018	10	-	-
26	3-(carboxamido oxime)benzyl	<0.01	0.30	-	-
27	3-aminoindazol-5-yl-methyl	<0.01	2.0	-	-
29	3-(carboxamido)benzyl	0.040	0.71	-	-
30	3-(N-methylcarboxamido)-benzyl	0.066	0.081	0.12	-
31	3-(N-ethylcarboxamido)-benzyl	0.21	0.139	0.06	-
32	3-(N-2-pyridylcarboxamido)-benzyl	0.043	0.003	<0.1	-
33	3-(N-thiazolylcarboxamido)-benzyl	0.027	0.004	<0.1	-
34	3-(N-2-imidazolyl-carboxamido)-benzyl	0.014	0.060	-	-
35	3-(N-2-benzimidazolylcarboxamido)-benzyl	0.024	0.005	<0.02	-
36	3-aldoximebenzyl	0.010	0.005	0.35	-
37	3-acetoximebenzyl	0.018	0.002	0.08 0.51 (in gelucire)	-
38	indazol-5-yl-methyl	0.014	0.007	<0.10 1.0 (dog)	- 13 (dog
39	3-aminobenzyl/indazol-5-yl-methyl	0.042	0.011	7.9 (dog)	93 (dog)
40	4-aminobenzyl/indazol-5-yl-methyl	0.036	0.011	12 (dog)	100 (dog)
41	n-butyl/3-aminoindazol-5-yl-methyl	0.026	0.062	11 (dog)	63 (dog)
42	benzyl/3-aminoindazol-5-yl-methyl	0.031	0.075	10 (dog)	60 (dog
43	3-amino-4-fluorobenzyl/ 3-(N-2-imidazolylcarboxamido)-benzyl	0.012	0.018	0.2 (dog)	-

[a]Values were measured as described previously (10). [b]Bioavailability was determined in groups of rats, unless otherwise indicated (n = 4 per group), dosed with compound in formulations containing propylene glycol, polyethylene glycol 400 and water at 10 mg/kg. The maximum plasma concentration (C_{max}) is the observed peak plasma concentration after an oral dose. Oral bioavailability (F%) was determined by the ratio AUC_{PO}/AUC_{IV}, where AUC is the area under the plasma concentration-time curve from time zero to infinity and is normalized for dose.

revealed that the N-benzyl group serves two very important functions. First, it contributes an important hydrophobic interaction with the lipophilic S2 enzyme pocket. Second, it can serve as a scaffold for directing substituents from the *meta* and *para* positions towards the S2/S3 subsites, where there are several H-bond donors/acceptors, namely, the side chains and/or backbone amides of Asp-29, Asp-30 and Gly-48.

To take advantage of these potential H-bond possibilities, hydroxy and hydroxymethyl groups were incorporated, as in **17-20** (Table I). These compounds have K_i values in the subnanomolar range. Moreover, because of the reduced lipophilicity, the translation from K_i to IC_{90} is greatly improved. For example, cyclic urea **17** (clogP and HPLC logP are 4.8 and 3.6, respectively) translates 2 orders of magnitude better than other subnanomolar inhibitors like **14** (clogP 9.2). The IC_{90}s of these cyclic ureas (**17-20**) are in the range of 0.032-0.057 μM.

While increasing the potency of the cyclic ureas by an order of magnitude, these analogs maintained the oral bioavailability of earlier compounds. The oral and i.v. pharmacokinetic profiles of these cyclic ureas were examined in the rat. At a dose of 10 mg/kg they exhibited good pharmacokinetics with a C_{max} of 0.39-0.83 μM (F = 18-30%) (13). We carried out additional studies in the dog with **17** and **20** and both compounds showed higher blood levels and lower clearance values than in the rat. In the case of the *p*-hydroxymethyl cyclic urea, blood levels exceeded the IC_{90} for wild type HIV (0.057 mcM) for 6 h. Based on these data, **17** (DMP 323) was selected for clinical development.

DMP 323 was examined in seronegative male volunteers with single doses ranging from 60-1200 mg. Disappointingly, blood levels at each dose in man showed a high degree of intersubject variation. For example, after a single dose of 750 mg, the values for C_{max} in μM for 5 individual subjects were: 2.50, 0.28, 0.51, 0.57 and undetectable, resulting in a mean value of 0.77 ± 0.99 μM. Therefore, further development of DMP 323 was discontinued.

At least two factors likely contributed to the variable and low plasma levels observed in man with DMP 323. First, the very poor solubility (6 μg/ml) of DMP 323 in aqueous media suggests that it may have precipitated on dosing, although this variability was not observed in other species dosed with cosolvent formulations. Second, metabolism of DMP 323 is both rapid and extensive (14). Thus, rapid metabolism combined with poor absorption of the compound due to precipitation in the stomach resulted in low C_{max} and short apparent half-life.

Second clinical candidate DMP 450

While the development of DMP 323 was in progress, we intensified our analog synthesis and design program to identify a second clinical candidate. In order to take advantage of several H-bond donors/acceptors residues near the S2/S3 subsites, numerous functional groups, many with multiple H-bond donor and acceptor possibilities, were examined in order to increase potency and water solubility (Table I). Analogs with P2/P2′ substituents capable of multiple H-bonding interactions, such as **24-29**, are more potent enzyme inhibitors. However, many of them are too polar and the translation to antiviral potency is poor. Moreover, the oral bioavailability in rats of many of these compounds is less than that of DMP 323.

To address the poor physical property limitations observed with DMP 323, we examined a number of substituents with basic and acidic (**24**) functionalities. Attempts to introduce very highly basic groups (**22**) were not successful with regard to inhibitory potency (K_i), probably because of the introduction of a formal charge and the associated high desolvation penalty.

A number of symmetrical cyclic ureas containing aniline substituents at the P2/P2′ position were synthesized, including aminobenzyl, N-methylaminobenzyl and N,N-dimethylaminobenzyl substituted cyclic ureas. The aniline **21** (DMP 450) combined potency similar to DMP 323 with substantial water solubility (>130 mg/ml as the bis-mesylate salt) (15).

DMP 450 was then studied extensively in rat, dog, rhesus monkey and chimpanzee to define its pharmacokinetics (15). Bioavailability was substantial in all species, with F ranging from 24% in the chimpanzee to 80% in the dog. Based on its potency, excellent pharmacokinetics and acceptable safety profile, DMP 450 was selected for clinical development.

In phase I clinical studies in HIV seronegative male volunteers, DMP 450 showed substantial blood levels. With a single dose of 11 mg/kg (750 mg dose) the C_{max} was 6.5 μM and the level at 6 h remained above 1 μM. The measured half-life in man (5.7 h) is consistent with some degree of potential accumulation with multiple dosing every 6-8 h. A multiple-dose study using 1000 mg q.i.d. did, indeed, indicate an increase in trough level from 1.73 μM on day 2, to 3.2 μM by day 4. DMP 450 was well tolerated with no adverse effects noted in these studies (15).

Early clinical trial results of other protease inhibitors identified the potential for rebound in plasma RNA levels with concomitant emergence of HIV variants with multiple mutations in the protease coding regions (4), probably due to inadequate blood levels at trough to cover wild-type or mutant virus strains. The importance of adequate blood levels and, in particular, free drug concentration was accentuated by the clinical failure of SC-52151 (16), which was ascribed to high plasma protein binding. These clinical results suggested that it was the relationship between the plasma level of free drug and the inherent drug potency against wild-type and mutant viruses that were the likely predictors of clinical efficacy.

To assess the binding of DMP 450 to human plasma protein, equilibrium dialysis experiments using ^{14}C-labeled compound were conducted. These showed that DMP 450 was 90-93% protein bound. The effect of this plasma protein binding on the antiviral potency of DMP 450 was examined by conducting antiviral assays in the

Table II: Resistance of mutant viruses to cyclic urea analogs.

Inhibitor	K_i (nM)[a]	IC_{90} (nM)[b]	Resistance of mutant viruses (IC_{90} mutant/IC_{90} WT) 84V[c]	82F[d]	84V/82F[c]	Ritonavir[d] virus	Indinavir[d] virus
DMP 323	0.34	57	28	7.1	97	93	18
DMP 450	0.28	130	10	5.3	100	49	27
26	<0.01	300	1.0	-	0.7	-	-
33	0.027	4.2	1.2	0.9	28	24	8.7
34	0.014	60	0.7	1.6	0.7	0.2	0.4
35	0.024	5.1	0.6	0.3	1.0	1.2	0.7
39	0.042	11	6.8	2.0	200	75	20
41	0.026	62	4.0	2.0	17	18	12
42	0.031	75	2.8	1.6	28	15	7.8
43	0.012	18	1.0	-	1.0	2.5	1.0

[a]Values were measured by the assay described previously (10, 25). [b]Values were measured using the RNA assay described previously (10, 26). [c]Values were measured using the yield reduction assay described previously (15, 27, 28). [d]The viruses were constructed and the IC_{90} values were measured using the ICC assay as described previously (15, 18a, 29).

presence of human serum proteins. In the presence of 45 mg/ml serum albumin plus 1 mg/ml α_1-acid glycoprotein, the apparent antiviral potency (IC_{90}) of DMP 450 decreased 4.5- to 8.4-fold (15).

The dosing regimen of 1000 mg q.i.d. would be sufficient to provide for 90% inhibition of wild-type HIV (929 nM, when adjusted for protein binding). These plasma levels, however, may not provide for adequate inhibition of mutant variants of HIV carrying multiple amino acid substitutions within protease (17). Thus, we focused our resources on the identification of a third-generation cyclic urea with approximately a 10-fold improvement over DMP 450.

Future cyclic urea clinical candidates

To discover superior inhibitors of HIV-PR, we have focused on simultaneous optimization of multiple properties. Our goal is to design an inhibitor which combines potency to wild-type and mutant strains of HIV, pharmacokinetic behavior, plasma protein binding propensity and physical properties such that we can provide sufficient free drug at trough to inhibit both wild type and mutant variants of HIV with b.i.d. or t.i.d. dosing.

Potency

Using the N-benzyl analog as a scaffold for directing substituents towards the S2/S3 sites with its array of H-bond donors and acceptors, inhibitors were designed to H-bond to the backbone residues of the enzyme in order to increase potency. While functional groups having multiple H-bond donor and acceptor possibilities are more potent enzyme inhibitors, many are polar and the translation to antiviral potency is poor. For example, the amide **29**, the amidoxime **26** and the aminoindazole **27** analogs were extremely potent inhibitors of the enzyme but showed only low to modest antiviral activity.

However, adjusting the lipophilicity of these compounds resulted in better translation and more potent antiviral activity. Of particular note are the amides **29-35** which show increasingly better translation as lipophilicity increases. Several lipophilic heterocyclic amides were evaluated and showed exceptionally potent antiviral activity (18).

Besides heterocyclic amides, other compounds with the ability to translate enzyme potency into excellent antiviral potency were the oxime analogs **36** and **37** and the heterocyclic indazole analog **38** (19), which had antiviral potency down to 5 nM.

Resistance profile

Several cyclic urea amides were evaluated against a panel of drug-resistant mutant viruses (Table II). Cyclic urea containing heterocyclic amides **34** and **35** exhibited excellent profiles against the panel of drug-resistant mutants (18a). This remarkable resistance probably stems from its ability to form a large number of H-bonds with the backbone atoms of the enzyme. This relationship between the number of H-bonds to backbone atoms and resistance profile (as well as enzyme potency) has also been observed in other cyclic urea analogs (**26**) (20). However, in many cases substituents that are capable of forming multiple H-bonds are also very polar and are unable to translate their enzyme potency into antiviral potency. Some of the heterocyclic amides are exceptional in their ability to form many H-bonds while being lipophilic enough to have excellent antiviral potency.

Pharmacokinetics

Unfortunately, because of its extreme insolubility, no formulation of the symmetrical amide **35** could be developed for oral or intravenous administration to animals. Similarly, the potent but symmetrical cyclic urea oxime **37** and indazole **38** analogs also showed low oral bioavailability.

Factors reducing oral bioavailability include poor solubility or dissolution in the aqueous gastrointestinal fluids, poor diffusion through the intestinal membrane and metabolism. Chemical characteristics known to be associated with poor intestinal permeation include high molecular weight (21) and the number of H-bonding functional groups (22).

While the symmetric cyclic urea is an extremely rigid scaffold complementary to HIV-PR that provides significant synthetic and cost advantages, the symmetrical structure also proved to have significant limitations in producing orally bioavailable compounds. Nonsymmetric cyclic ureas, on the other hand, offer the advantages of better solubility, flexibility in adjusting the physical chemical properties and greater flexibility in designing enzyme interactions. These potential benefits prompted us to concentrate our efforts on nonsymmetrical analogs. In this way, we can better address the often conflicting issues of solubility, potency, protein binding, resistance profile and oral bioavailability. In particular, we focused our efforts on the synthesis of three classes of nonsymmetrically substituted P2/P2′ analogs.

The first class centered on analogs containing an indazole as one of the P2 groups, since this substituent showed excellent enzyme and antiviral potency (example **38**, Table I). We used the other P2 group to adjust the physical and chemical properties of the compound in order to optimize oral bioavailability (20).

The second approach used a heterocyclic-benzamide substituent as one of the P2 groups, since this group showed the best resistance profile against mutant viruses (examples **34** and **35** Table II). We used the second P2 group to adjust the physical and chemical properties of the compound in order to optimize oral bioavailability.

The third class centered on analogs containing a 3-amino-5-indazole as one of the P2 groups, since this substituent showed the most potent enzyme activity (example **27**, Table I). In this case, we used the other P2 group to adjust the lipophilicity to optimize the translation of enzyme potency into antiviral potency.

Many nonsymmetrical mono-indazole substituted analogs were prepared and tested and several showed good potency and oral bioavailability (20). For example, the anilines **39** and **40** both showed potent antiviral activity (IC_{90} = 11 nM) and excellent oral bioavailability in the dog (F = 93-100%). Unfortunately, these analogs had a very poor resistance profile, especially against the double mutant (I84V/V82F) and the related ritonavir selected virus (example **39**, Table II).

Many attempts to improve the oral bioavailability of the heterocyclic-benzamides were not very successful. One of the best compounds, **43**, while having good antiviral potency (IC_{90} = 18 nM) and an excellent resistance profile (Table II), had only a very modest C_{max} of 0.2 μM in the dog (Table I).

In general, the use of a 3-amino-5-indazole as one of the P2 groups was more successful in providing compounds with good antiviral potency, excellent pharmacokinetics and adequate resistance profiles. Some of the best were the more lipophilic N-butyl **41** (23) and N-benzyl **42** (24) analogs (Table I). Both compounds showed excellent oral bioavailability in dogs with a C_{max} of 11-10 μM (Table I). In addition, they showed a much better resistance profile than DMP 323 (example **17**), DMP 450 (example **21**) or the indazole analog **39** (Table II).

A major factor contributing to the low oral bioavailability of many compounds with good resistance profiles appeared to be their higher molecular weights. The oral bioavailability of cyclic urea analogs have been examined in dogs and the results are summarized as a scatter plot of C_{max} as a function of molecular weight (Fig. 2). The use of the C_{max} as an approximate surrogate for oral bioavailability is used for convenience, since the determination of F% is not always possible for many poorly bioavailable compounds due to detection difficulties. Our experience with cyclic ureas has shown that C_{max} is an adequate surrogate for F%. The data shows an apparent cut-off of oral bioavailability at a molecular weight (MW) of about 610. Most of the compounds with low bioavailability, that have a MW below 610, are either symmetrical or have low aqueous solubility. To improve the resistance profile, analogs need to be larger in order to have the multiple H-bonding interactions with residues Asp-29, Asp-30 and Gly-48. However, in doing so, the molecular weight of the resulting analogs often exceeds the 610 MW limit that seems to be important for oral bioavailability of HIV-PR inhibitors in the cyclic urea class.

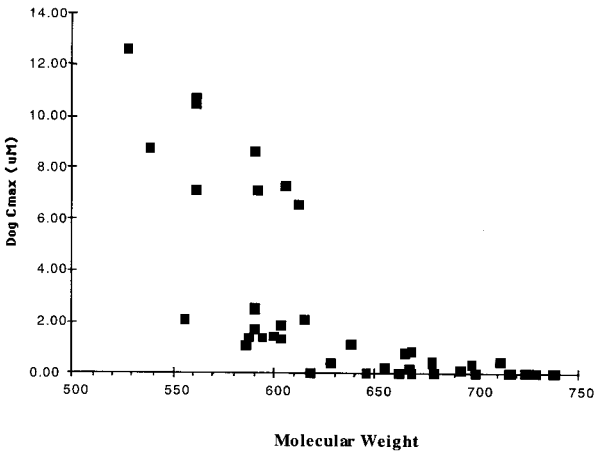


Fig. 2. Oral bioavailability of cyclic urea analogs in dogs at a dose of 10 mg/kg.

Conclusions

Combining the antiviral testing against wild-type and mutant variants, antiviral testing in the presence of human plasma proteins and dog pharmacokinetic assessment on selected compounds, we define the overall quality of a given compound. Working within the constraints imposed by molecular weight and lipophilicity, we can then select compounds with the best balance of properties for further preclinical evaluation. Using this strategy we have been able to identify the 3-amino-5-indazole analog **41**, designated DMP 851, as a drug candidate which has good potency, resistance profile and physical and chemical properties, while maintaining excellent oral pharmacokinetics. Based on these favorable characteristics, DMP 851 is under further development and is currently undergoing phase I clinical trials (30).

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