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Synthesis and evaluation of inhibitors of cytochrome P450 3A (CYP3A) for pharmacokinetic enhancement of drugs

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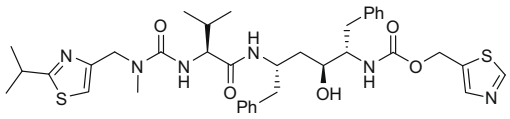
ABSTRACT

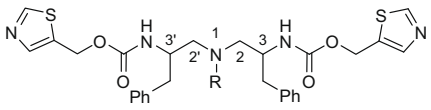
The HIV protease inhibitor ritonavir (RTV) is also a potent inhibitor of the metabolizing enzyme cytochrome P450 3A (CYP3A) and is clinically useful in HIV therapy in its ability to enhance human plasma levels of other HIV protease inhibitors (PIs). A novel series of CYP3A inhibitors was designed around the structural elements of RTV believed to be important to CYP3A inhibition, with general design features being the attachment of groups that mimic the P2–P3 segment of RTV to a soluble core. Several analogs were found to strongly enhance plasma levels of lopinavir (LPV), including **8**, which compares favorably with RTV in the same model. Interestingly, an inverse correlation between in vitro inhibition of CYP3A and elevation of LPV was observed. The compounds described in this study may be useful for enhancing the pharmacokinetics of drugs that are metabolized by CYP3A.

The cytochrome P450 3A (CYP3A) group of enzymes is largely responsible for the metabolic clearance of many important classes of therapeutic agents, including immunosuppressants (i.e., cyclosporin, FK506, rapamycin),[1] the taxane derived chemotherapeutic agents (e.g., taxotere),[2] macrolide antibiotics (e.g., clarithromycin and azithromycin),[3] and the protease inhibitor class of antiretroviral agents (i.e., ritonavir (RTV), indinavir, saquinavir, amprenavir, nelfinavir, lopinavir (LPV), tipranavir, atazanavir and darunavir).[4] Compounds that inhibit CYP3A can increase the plasma levels of these drugs through drug–drug interactions which may result in adverse complications.[3b,4a,5] However, when properly controlled, pharmacokinetic enhancement of drugs can be beneficial to therapy. Nowhere is this more evident than in the pharmacokinetic boosting of inhibitors of HIV-1 aspartyl protease by RTV to treat HIV infection.[6] The antiretroviral agent Kaletra™ is a co-formulation of a second-generation protease inhibitor (PI), LPV[7] with RTV, itself a first generation PI. RTV is also a potent inhibitor of CYP3A (K_i = 3.2 nM) and is administered at a sub-therapeutic dose sufficient to inhibit the CYP3A-mediated metabolism of LPV, thereby greatly enhancing exposure of LPV.[4c] The pharmacokinetic enhancement of LPV by RTV allows for convenient dosing regimens (both BID and QD are approved in the US) that maintain mean LPV plasma levels >75-fold in excess of the EC_{50} for wild-type virus, thereby improving the overall effectiveness of therapy by greatly reducing the risk of resistance development.[8] Pharmacokinetic enhancement by RTV of other marketed HIV PIs also provides significant clinical benefit.[9]

An analysis of RTV (Fig. 1) and close structural analogs identified three important elements responsible for CYP binding and inhibition: (1) direct heme interaction via an unhindered electron-rich atom (5-thiazole group), (2) extensive hydrophobic interactions with the CYP active site and (3) stability toward CYP-mediated oxidative chemistry.[6] Spectroscopic studies have shown that one of the structural features of RTV responsible for CYP binding and inhibition is the unhindered nitrogen atom within the unsubstituted 5-thiazolyl group, which is believed to bind directly to the CYP heme iron.[6] Metabolism of RTV by CYP3A occurs by hydroxylation of the



Ritonavir



CYP3A inhibitor structure

Figure 1. Design of novel CYP3A inhibitors.

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isopropyl group on the 4-thiazole (at the opposite end of the molecule) to give the 2-hydroxyisopropyl derivative as the only major metabolite found in human plasma.[10] In this study, we used these principles to design novel CYP inhibitors that are structurally less complex, easier to prepare, more soluble than RTV, and devoid of antiviral activity. These compounds are bi-functional inhibitors in that they bear a 5-thiazole group at the terminus of two hydrophobic chains symmetrically positioned about a central amine. These novel CYP inhibitors provide insight into strategies for designing second-generation CYP inhibitors for enhancing and sustaining levels of PIs, as well as other therapeutic CYP3A substrates.

Novel CYP inhibitors were designed (see Fig. 1) to take advantage of these features by introducing two heterocycles containing an unhindered nitrogen atom (e.g., 5-thiazole) that can be presented to the CYP heme iron while avoiding any alkylated heterocycle which could possibly be oxidized by CYP3A. The heme-iron binding heterocycle is presented at the terminus of a chain containing groups designed to maintain good hydrophobic interactions with the CYP active site. Since RTV has very low aqueous solubility and requires extensive formulation to achieve oral absorption,[11] the heterocyclic groups were symmetrically placed around a basic nitrogen to increase aqueous solubility.

The compounds were synthesized as shown in Schemes 1 and 2. The protected amino alcohol **1** was oxidized to aldehyde **2**, which was subsequently allowed to react with amine and sodium triacetoxyborohydride to give the tertiary amine **3**. This reductive amination reaction resulted in epimerization of the chiral centers, such that **3** was obtained as a mixture of all possible stereoisomers. Deprotection of **3**, followed by reaction with the 4-nitrophenylester of 5-hydroxymethyl thiazole (or other heterocycle) provided a mixture of isomers, which could be separated by column chromatography to give a 1:1 mixture of *SS* and *RR* isomers along with the *SR* isomer.

Stereochemistry could be controlled by treating compound **1** with methanesulfonyl chloride to provide mesylate **4**, which was then converted to the corresponding azide and reduced by hydrogenation with Lindlar's catalyst to give amine **5**. Aziridine **6**, synthesized from **1** by the action of triphenylphosphine and diethyl azodicarboxylate, was treated with amine **5** to give the secondary amine product **7** as a single diastereomer. Using this strategy, other stereoisomers of **7** were readily prepared from the appropriate enantiomer of **1**.

Compound **7** was utilized in two separate synthetic pathways to provide the target inhibitors as shown. Deprotection, followed by bis-acylation gave **8**, which was allowed to react with aldehyde under reductive amination conditions to provide final compounds. Alternatively, **7** was first converted to tertiary amine, followed by deprotection and bis-acylation to give final compounds.

These compounds were evaluated for their abilities to inhibit the CYP3A4-mediated oxidation of 7-benzyloxyquinoline (7-BQ) using cDNA-expressed CYP3A4 (supersomes).[12] Tables 1–3 present SAR for these compounds as inhibitors of recombinant human CYP3A4. Table 1 shows SAR for compounds with different alkyl substituents on the central nitrogen (N-1). All of these analogs were potent CYP3A4 inhibitors, with only a threefold IC_{50} range (0.05–0.15 μM) for groups ranging in size from hydrogen (**8–10**) to the large chain present in the C_3-symmetric inhibitor **11**. The stereochemistry of the benzyl side-chains at C-3 did not have a large effect on activity, as can be seen by comparing the stereoisomers of *N*-neopentyl (**12** and **13**), ethyl (**15–17**), and isobutyl (**18–20**) analogs. *N*-Arylmethyl analogs (see **23–30**) offered no potency advantage over aliphatic analogs.

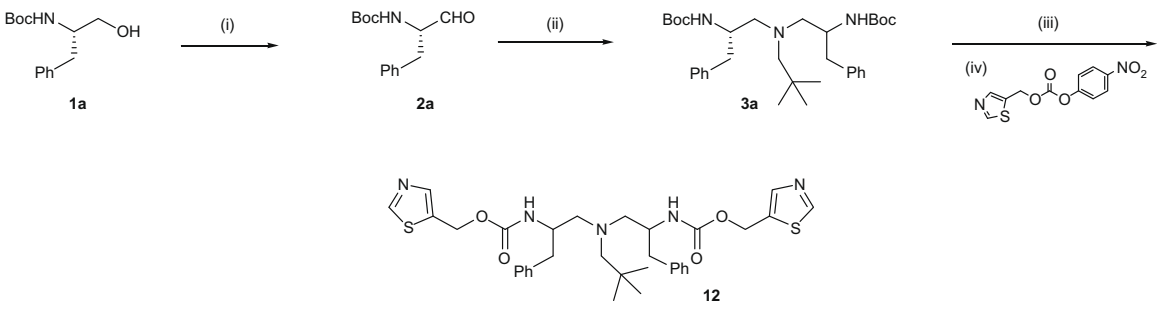
Table 2 presents SAR for various hydrophobic side-chains at C-3. Compounds with smaller C-3 substituents such as compounds **31** (R = H) and **32–34** (R = methyl) showed markedly weaker CYP inhibition, clearly demonstrating the importance of this group to the activity of these compounds. The benzyl side-chain found in compound **15** could be replaced with a group of similar or larger size (for example, isobutyl analog **35**) with little effect on the CYP3A4 inhibitory potency.

The results in Table 3 indicate that replacement of the 5-thiazolyl group at the chain terminus with other heterocycles resulted in loss of activity against CYP3A4. The 5-oxazole **41**, 5-imidazole **42**, and 4-pyrazole **45** analogs were each ~2-fold less active than **15**. Removal of the nitrogen from the thiazole ring **43** resulted in a fivefold loss in activity. Replacement of the thiazole with a basic pyridyl group **44** resulted in a greater than 20-fold loss in activity.

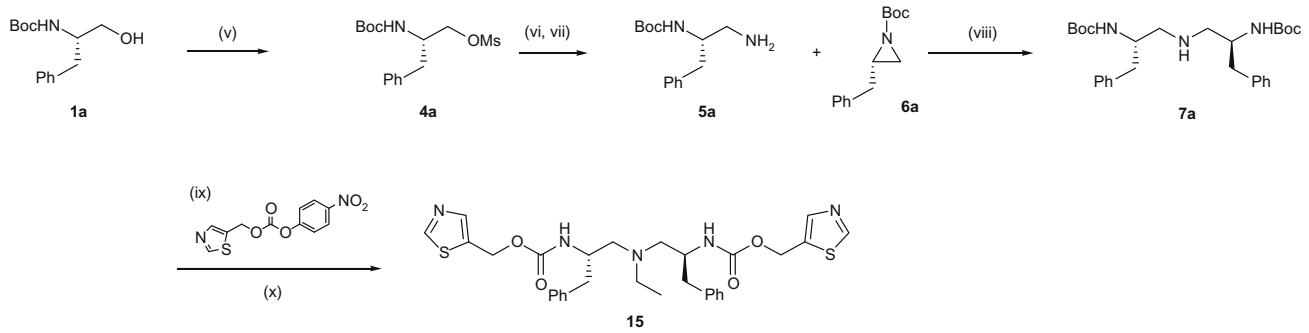
Selected analogs were also evaluated for their ability to inhibit the CYP3A4-mediated oxidation of 7-BQ in human liver microsomes (HLM).[12] The inhibition data of the comparator compounds is shown in Table 4. Inhibition in HLM was highly correlated to inhibition in CYP3A supersomes ($r^2 = 0.78$) (Fig. 2). The excellent correlation between the data suggests that screening in cDNA-expressed CYP3A4 supersomes is a useful method for identification of novel CYP3A inhibitors.

The inhibitory potencies of the CYP inhibitors against purified recombinant HIV protease were evaluated following previously described procedures.[13] All CYP inhibitors prepared were found to have activity (IC_{50}) against HIV-1 protease >10 μM, which is >50,000-fold weaker than RTV. These CYP inhibitors would therefore be expected to be devoid of antiviral activity.

Also in Table 4 are results for in vivo studies evaluating the abilities of CYP inhibitors to enhance the plasma levels of LPV in dogs. For these studies, equal doses of LPV and the CYP inhibitor (5 mg/kg each) were administered by oral gavage in adult beagle dogs ($n = 3$), and the concentrations of both compounds were simultaneously measured over time (12 time points over 12 h).[6] In the absence of a CYP inhibitor, LPV gave no measurable plasma levels in this model. The effect of all but one of the CYP inhibitors on boosting plasma levels of LPV either equaled or exceeded the perfor-

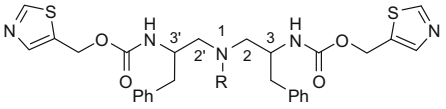


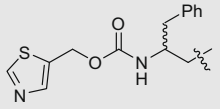
Scheme 1. Reagents and conditions: (i) (a) DMSO, ClC(O)C(O)Cl, CH_2Cl_2, −78 °C, 30 min; (b) Et_3N, CH_2Cl_2, −78 °C—rt, 1 h; (ii) $(CH_3)_3CCH_2NH_2$, $NaHB(OAc)_3$, AcOH, $Cl(CH_2)_2Cl$, rt, 18 h; (iii) 1:2 TFA/CH_2Cl_2; (iv) EtOAc, 60 °C, 16 h.



Scheme 2. Reagents and conditions: (v) MsCl, Et_3N, CH_2Cl_2, 0 °C, 2 h; (vi) NaN_3, DMF, 80 °C, 2 h; (vii) H_2, Lindlar's catalyst, EtOH, 1 atm, rt, 3 h; (viii) 2-PrOH, 100 °C, 18 h; (ix) (a) 1:2 TFA/CH_2Cl_2, rt, 2 h; (b) EtOAc, 60 °C, 16 h; (x) CH_3CHO, $Cl(CH_2)_2Cl$, AcOH, $NaHB(OAc)_3$, rt, 2 h.

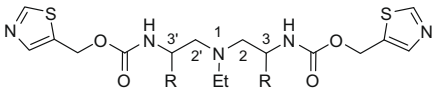
Table 1
SAR for substitution at N-1



Compd	Stereo 3,3′	R	CYP3A4[a] IC_{50} (μM)
RTV			0.05
8	*SS*	H	0.148
9	*SR*	H	0.09
10	*RR*	H	0.099
11			0.065
12	*SS,RR*	$CH_2C(CH_3)_3$	0.11
13	*SR*	$CH_2C(CH_3)_3$	0.1
15	*SS*	CH_2CH_3	0.15
16	*SR*	CH_2CH_3	0.11
17	*RR*	CH_2CH_3	0.11
18	*SS*	$CH_2CH(CH_3)_2$	0.11
19	*SR*	$CH_2CH(CH_3)_2$	0.09
20	*RR*	$CH_2CH(CH_3)_2$	0.067
21	*SS*	CH_2(*c*Pr)	0.052
22	*RR*	$(CH_2)_2CH(CH_3)_2$	0.05
23	*SS*	CH_2Ph	0.135
24	*SR*	CH_2Ph	0.087
25	*RR*	CH_2Ph	0.06
26	*SR*	CH_2(3-MeO)Ph	0.05
27	*SS*	CH_2(3-Pyr)	0.066
28	*SS*	CH_2(4-Pyr)	0.049
29	*SS*	CH_2(5-imidazole)	0.066
30	*SR*	CH_2(3-quinoline)	0.07

[a] Inhibition of 7-BQ (CYP3A4).

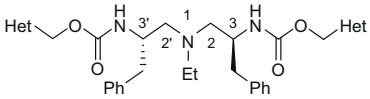
Table 2
SAR for hydrophobic side-chain substituents at C-3



Compd	Stereo 3,3′	R	CYP3A4[a] IC_{50} (μM)
15	*SS*	CH_2Ph	0.15
31		H	>3
32	*SS*	CH_3	>3
33	*SR*	CH_3	1.79
34	*RR*	CH_3	1.33
35	*SS*	$CH_2CH(CH_3)_2$	0.136
36	Mixture	$CH_2CO_2CH_3$	0.088
37	Mixture	CH_2(*c*-Hex)	0.066
38	Mixture	CH_2OCH_2Ph	0.135
39	Mixture	CH_2(4-OH)Ph	0.091
40	Mixture	CH_2(4-OBn)Ph	0.3

[a] Inhibition of 7-BQ (CYP3A4).

Table 3
SAR for heterocycles at chain terminus



Compd	Het	CYP3A4[a] IC_{50} (μM)
15	5-Thiazole	0.15
41	5-Oxazole	0.274
42	5-Imidazole	0.348
43	2-Thiophene	0.741
44	3-Pyridyl	3
45	4-Pyrazole	>0.3

[a] Inhibition of 7-BQ (CYP3A4).

mance of RTV (LPV AUCs ranged from 10.23 to 22.95 μg h/mL vs 11.26 μg h/mL for RTV). Overall plasma levels of the novel CYP inhibitors were somewhat lower than that observed with RTV in this model (RTV AUC = 2.19 μg h/mL vs AUC <2 μg h/mL for all compounds tested). The large C_3-symmetric compound **11** gave poor plasma levels, and was significantly less effective at enhancing plasma levels of LPV. The effect of the two stereoisomeric compounds **12** and **13** on LPV levels was comparable to that for RTV. Compounds **8** and **16** were the most effective at enhancing LPV levels. Plasma levels of the secondary amine derivative **8** were higher than other compounds tested (AUC = 1.78 μg h/mL) and provided the greatest increase in the plasma levels of LPV (C_{max} = 5.02 μg/mL, AUC = 22.95 μg h/mL).

The plasma exposures of this series appear to be related to the substituent at the central nitrogen. As can be seen from the data in Table 4, compounds bearing a larger alkyl group (i.e., neohexyl analogs **12** and **13**) were more potent inhibitors in vitro than those bearing a smaller group (i.e., ethyl analog **16**) or those lacking an alkyl substituent (i.e., **8**). In vivo, compounds bearing a smaller group at this central nitrogen achieved higher plasma levels, with the greatest overall exposure being achieved with the secondary amine analog, **8**.

A comparison between in vitro activity of CYP inhibitors and their ability to boost LPV reveals an apparent inverse correlation (Fig. 3a), such that the more potent inhibitors in vitro were less effective at elevating LPV levels in vivo. The reason for this observation may be twofold. Presumably, the relative potencies against human CYP3A may not reflect the corresponding activities against the canine enzyme. Alternatively, CYP inhibition

Table 4
Effect of CYP inhibitors on plasma concentration of LPV in dog[a]

Compd	CYP3A4[b] IC_{50} (μM)	HLM IC_{50} (μM)	Mean (SEM) PK parameters[c]			
			LPV		CYP inhibitor	
			C_{max}	AUC	C_{max}	AUC
RTV	0.05	0.04	2.5	11.26	1.32	2.19
8	0.15	0.13	5.02	22.95	0.83	1.78
11	0.065	0.054	0.95	3.09	0.03	0.06
12	0.11	0.15	2.27	11.69	0.3	0.68
13	0.1	0.09	1.7	10.23	0.29	1.1
15	0.15	0.15	3.2	12.14	0.61	1.38
16	0.11	0.09	3.47	15.95	0.57	1.3

[a] Oral co-dose of inhibitor and LPV (5 mg/kg each, $n = 3$).
[b] Inhibition of 7-BQ (CYP3A4).
[c] AUC (μg h/mL); C_{max} (μg/mL).

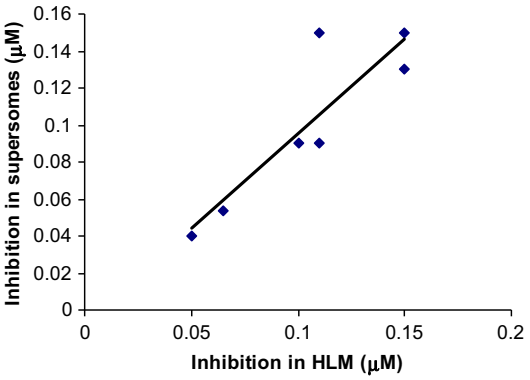


Figure 2. Correlation of CYP3A4 inhibition in HLM and recombinant CYP3A supersomes.

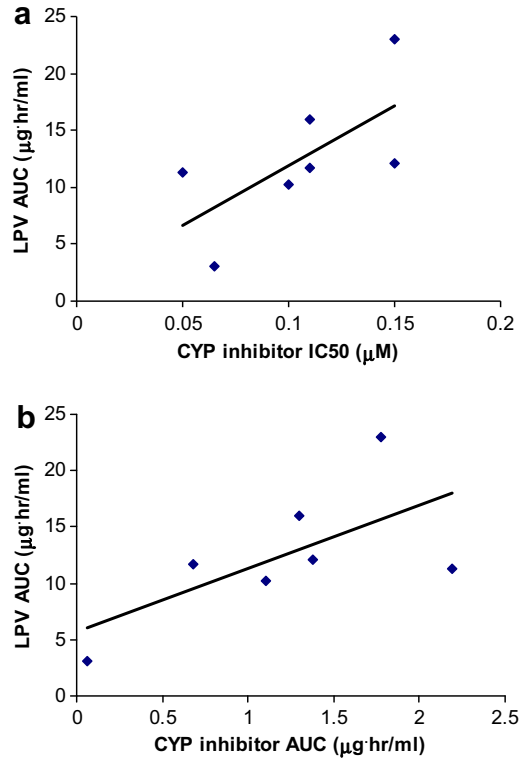


Figure 3. (a) Comparison of CYP inhibitor in vitro activity and LPV plasma level achieved when co-dosed with the CYP inhibitor (5 mg/kg) in dog. (b) Comparison of plasma levels achieved with co-dosing a CYP inhibitor and LPV (5 mg/kg) in dog.

may be relatively complete at concentrations achieved by each inhibitor, and LPV exposure may depend on the exposure of the boosting agent. This is supported by the high correlation of CYP inhibitor exposure and LPV exposure (Fig. 3b). Thus, the CYP inhibitors that achieved better exposure in vivo were more effective at boosting LPV levels. These results reveal that CYP inhibitors with relatively modest in vitro potency (in comparison to the potent inhibitor RTV) can be very effective at boosting LPV in vivo , provided they have favorable pharmacokinetic properties.

This study has several limitations. In vivo screening was conducted in dogs, while in vitro screening utilized human systems. While the dog has proven to be a useful model for pharmacokinetic enhancement of lopinavir, prediction of pharmacokinetic enhancement in humans would require extensive additional in vitro studies in both canine and human systems. Nonetheless, the results described here provide proof-of-concept that alternate CYP3A inhibitors can be designed that may be useful for therapeutic boosting.

In this report, we have described the design and synthesis of a series of compounds that are potent inhibitors of cytochrome P450 enzymes, based on structural elements found in the potent CYP3A inhibitor RTV. These compounds are structurally less complex than RTV and they have no activity towards HIV aspartyl protease. Potent analogs in this series inhibit CYP3A with IC_{50} <0.1 μM, comparing favorably to inhibition by RTV (IC_{50} = 0.05 μM). Pharmacokinetic studies in dog demonstrate the ability of these compounds to enhance plasma levels of LPV to an extent that is equal to or greater than that achieved with RTV. Two compounds, **8** and **16**, co-dosed with LPV at 5 mg/kg each in dog, gave the greatest pharmacokinetic enhancement of LPV, with LPV AUC = 22.95 and 15.95 μg h/mL, respectively. Results with these two compounds exceed that achieved with RTV, even though plasma levels for **8** and **16** were both less than plasma levels of RTV.

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Supplementary data

Supplementary data (General experimental section: synthetic procedures for preparation of compounds **2**–**45**; cytochrome P450 inhibition testing; pharmacokinetic analysis) associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2009.07.118.

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