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1,2,3,4-Tetrahydroquinoline-containing $\alpha_V\beta_3$ integrin antagonists with enhanced oral bioavailability

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Abstract—Reduction of the quinoline ring in an $\alpha_v\beta_3$ antagonist yielded a 1,2,3,4-tetrahydro derivative as two diastereomers, the four isomers of which were separated by sequential chiral HPLC. Two isomers had significant $\alpha_V\beta_3$ antagonist activity with improved oral bioavailability, relative to the corresponding quinoline derivative.

Interactions between the $\alpha_V\beta_3$ integrin and its extracellular matrix ligands are a basis of cell adhesion events, leading to the migration, invasion, proliferation, and survival of cells. The $\alpha_V\beta_3$ integrin is expressed in several cell types, such as osteoclasts, endothelial cells, vascular smooth muscle cells, and some tumor cells. Although the normal level of expression is typically low, expression is greatly enhanced in pathological conditions involving tissue remodeling and growth. Hence, this integrin has attracted attention as a therapeutic target for the treatment of cancer, osteoporosis, rheumatoid arthritis, and diabetic retinopathy.[1] Monoclonal antibodies to $\alpha_V\beta_3$ (Vitaxin, CNTO 95) and peptide antagonists based on the Arg-Gly-Asp (RGD) motif have been the most studied to date and have shown good efficacy in various animal models.[1,2] Interesting efficacy for orally bioavailable, small-molecule $\alpha_V\beta_3$ integrin antagonists[3] in models of osteoporosis[4] and arthritis[5] has been reported.

Starting from the nipecotamide-based $\alpha_{IIb}\beta_3$ antagonist, elarofiban (**1**, Fig. 1),[6] we identified the isonipecotamide structure **2** ($\alpha_V\beta_3$ IC_{50} = 3.6 nM, $\alpha_{IIb}\beta_3$ IC_{50} = 170 nM)

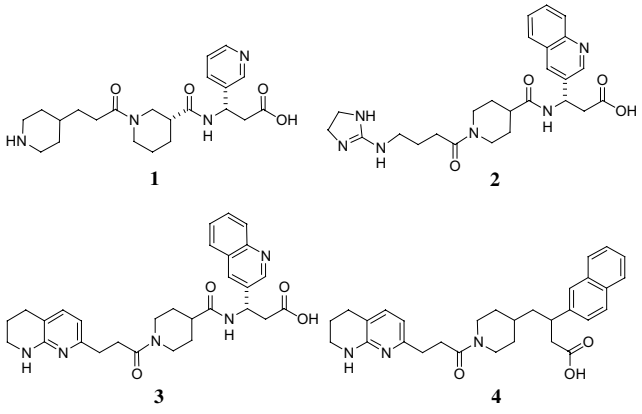

Figure 1. Evolution of series from nipecotamide (**1**) to isonipecotamides (**2** and **3**) to carba-analog (**4**).

with reversed selectivity for $\alpha_V\beta_3$ relative to $\alpha_{IIb}\beta_3$.[7,8] This compound represented a good starting point, but it was deficient in showing only moderate selectivity and low oral bioavailability (F = 4%, Table 1). In this case, antagonism of the integrin $\alpha_{IIb}\beta_3$ would be an undesirable activity as it causes blockade of platelet aggregation. Recently, we reported[8] the introduction of the tetrahydronaphthyridine group[9] in **3** and the

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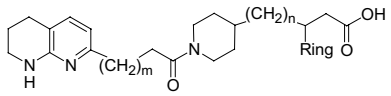
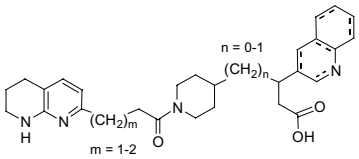
Table 1. Binding studies at $\alpha_V\beta_3$, $\alpha_V\beta_5$, and $\alpha_{IIb}\beta_3$ integrins by quinoline based derivatives (IC_{50})[a]



No.	Isomer designation ($[\alpha]_D^{23}$)	Structural description			$\alpha_V\beta_3$ (nM)[b]	$\alpha_V\beta_5$ (nM)[b]	$\alpha_{IIb}\beta_3$ (nM)[c]	F[d] (%)
		m	*n*	Ring				
2	*S*			See figure	3.6 ± 0.9	470 ± 110	170 ± 30	4
3	*S*			See figure	2.6 ± 0.6	270 ± 50	2900	
27	*R*, *S*	1	1	3-Quinoline	0.8 ± 0.2	2.2 ± 0.7	1100	4
28	*R*, *S*	1	1	3-(5,6,7,8-THQ)[e]	1.6 ± 0.7	11 ± 4	3000	0
29	[f]	1	1	3-(1,2,3,4-THQ)	2.5 ± 0.4	17 ± 2	14,000	
29a	a (+16°)	1	1	3-(1,2,3,4-THQ)	26 ± 8	1000	>50,000	
29d	d (−15°)	1	1	3-(1,2,3,4-THQ)	2.7 ± 0.7	8.7 ± 2.1	4700	22
29b	b (+24°)	1	1	3-(1,2,3,4-THQ)	1.2 ± 0.1	7.8 ± 1.4	13,000	8
29c	c (−25°)	1	1	3-(1,2,3,4-THQ)	52 ± 14	2200	>50,000	
33	[f]	1	1	3-(1-Me-1,2,3,4-THQ)	49 ± 2	180 ± 20	>50,000	
34	*R*, *S*	1	1	3-(6-MeOPy)[g]	0.7 ± 0.2	2.7 ± 0.8	6100	8
34a	a (−22°)[h]	1	1	3-(6-MeOPy)	0.4 ± 0.1	3.1 ± 1.5	1800	2
34b	b (+22°)[h]	1	1	3-(6-MeOPy)	16 ± 6	98 ± 39	>50,000	
30	*R*, *S*	2	0	3-Quinoline	0.5 ± 0.1	36 ± 9	870	1
31	[f]	2	0	3-(1,2,3,4-THQ)	3.7 ± 1.5	260 ± 60	15,000	100
31a	a (+20°)[i]	2	0	3-(1,2,3,4-THQ)	1.6 ± 0.5	44 ± 12	13,000	46
31d	d (−20°)[j]	2	0	3-(1,2,3,4-THQ)	5.4 ± 0.2	160 ± 60	17,000	52
31b	b (+17°)[i]	2	0	3-(1,2,3,4-THQ)	70 ± 7	2500	>50,000	
31c	c (−26°)[j]	2	0	3-(1,2,3,4-THQ)	100 ± 40	1500	>50,000	
SB 265123[k]					4.0 ± 1.3	2.9 ± 0.5	1200	100[k]

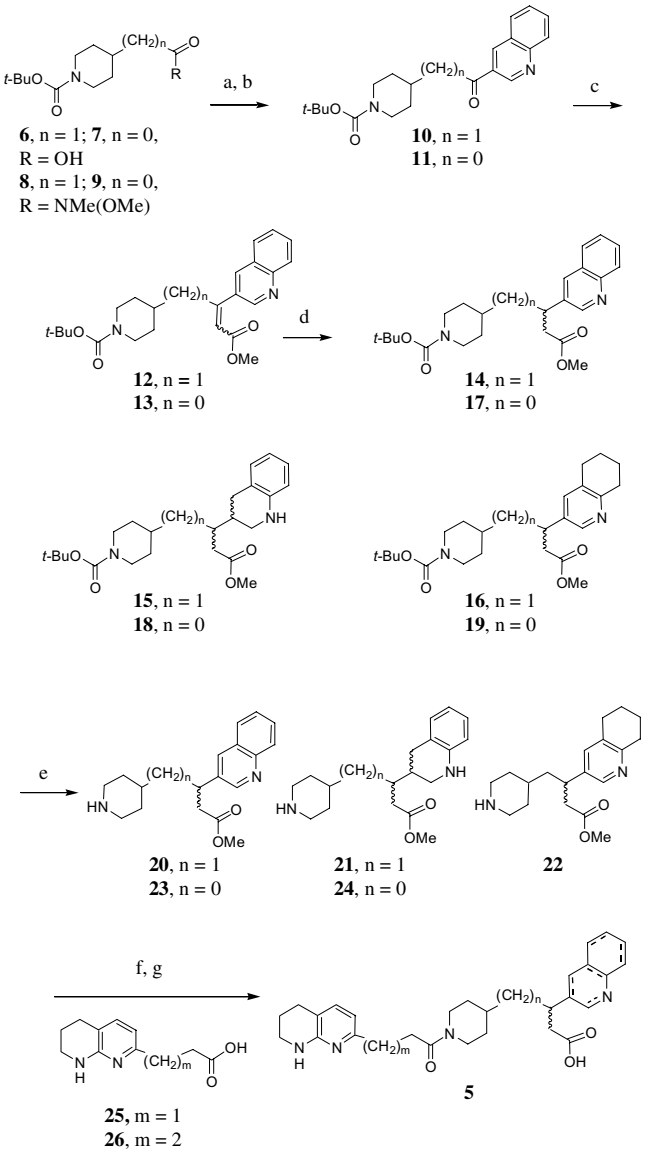
[a] **29a** and **29d**, **29b** and **29c**, **34a** and **34b**, **31a** and **31d**, **31b** and **31c** are enantiomeric pairs.
[b] Inhibition of human vitronectin binding to immobilized $\alpha_V\beta_3$ and $\alpha_V\beta_5$ ($N \geqslant 3$).[15]
[c] Inhibition of biotinylated fibrinogen binding to immobilized $\alpha_{IIb}\beta_3$ ($N \geqslant 2$).[16]
[d] See Ref. 18.
[e] THQ = tetrahydroquinoline.
[f] Mixture of two diastereomers (four isomers).
[g] MeOPy = methoxypyridine.
[h] Separated by chiral HPLC on Chiralcel® OJ (96/4 hexane/EtOH elution) at same Boc-protected intermediate stage as **15**.
[i] Prepared from isomers **18a** ($[\alpha]_D^{23}$ +43) and **18b** ($[\alpha]_D^{23}$ +53), which were separated from **18c/18d** on a Chiralpak® OD column (MeOH elution), and from each other on Chiralpak® AD column (EtOH elution) as described above.[13]
[j] Prepared from isomers **18c** ($[\alpha]_D^{23}$ −62) and **18d** ($[\alpha]_D^{23}$ −46), which were separated on the initial Chiralpak® OD column from the mixture of **18a/18b**.
[k] See Ref. 4a

'evolved' carba-analogs (e.g., **4**) that lack the amide group beta to the carboxylic acid. These derivatives had improved selectivity relative to $\alpha_{IIb}\beta_3$ and in the case of some β-aryl substituted carba-analogs, such as **4**, significant improvements in oral bioavailability were observed. However, no β-heterocyclic groups were found to exhibit good oral bioavailability (e.g., pyridyl) initially. This paper focuses on quinoline-containing structures of general formula **5**. The structure was modified by varying the spacer units and taking advantage of the selective reduction of the quinoline ring that occurred during hydrogenation.



5

The syntheses of targets **5** are described in Scheme 1. A strategy was required that would allow variation of the spacer between the piperidine and the quinoline substituent so that the optimum arrangement could be determined.[10] Boc-protected piperidine carboxylic acids **6** and **7** were converted to their corresponding Weinreb amides **8** and **9**, which were reacted with the lithium reagent derived from 3-bromoquinoline to yield the ketones **10** and **11**. The latter reaction was best performed by premixing the Weinreb amide and aryl bromide in THF, followed by the addition of butyl lithium.[11] The resultant ketones were elaborated to the unsaturated esters **12** and **13** by reaction with the sodium salt of trimethyl phosphonoacetate. The mixture of *E*- and *Z*-isomers of **12** was hydrogenated in the presence of 10% palladium on carbon to give three different products, depending on the reduction conditions. One could produce quinoline **14** by conducting the hydrogenation at low pressure (8 psig). Over-reduced products **15** and **16** resulted from using intermediate pressure (30 psig) for two days. The optimal conditions for producing the 1,2,3,4-tetrahydroquinoline **15** were to hydrogenate in toluene with triethylamine present at higher pressure and temperature.[12] The stereoisomers of **15** (four isomers) were separated at this stage by chiral HPLC.[13] The isomer lettering order is based on the elution order



Scheme 1. (a) MeONHMe·HCl, NMM (6 mol equiv), HOBt (0.5 mol equiv), HBTU (1.2 mol equiv), MeCN, 6–8 h, 85–95%. (b) 3-Bromoquinoline (2 mol equiv), THF, BuLi (2 mol equiv), −90 °C (**10** or **11**, 62%). (c) $(MeO)_2P(O)CH_2$–CO_2Me (4 mol equiv), NaHMDS (3 mol equiv), THF, −50 °C, reflux after ketone addn., 4 h (**12**, 100%; **13**, 65%). (d) Equal wt of 10% Pd/C, MeOH, H_2, at 0–8 psig for 24 h (**14**, 50%; **17**, 68%); at 30 psig for 48 h (**15**, 37%, **16**, 28%; **18**, 49%, **19**, 18%); or half wt of 10% Pd/C, toluene, Et_3N, 50 °C, 50 psig, 28 h (**15**, 73%, **16**, 3%). (e) 2 N HCl in dioxane, anisole (cat.), 2 h, 100%. (f) For **20**–**23**, NMM (5 mol equiv), HOBT (0.5 mol equiv), HBTU (1.2 mol equiv), MeCN, DMF, 8–12 h (87–93%); for **24**, PyBroP, DMF, CH_2Cl_2, *i*-Pr_2NEt, 0 °C, 1.5 h (80–94%). (g) 3 N NaOH, MeOH, 24 h (79–97%) or 4 N HCl, 48 h (75–95%).

(isomer-a is faster eluting) of intermediate **15**. The related intermediates **17**–**19** were prepared similarly from **13**. Intermediates **14**–**19** were converted to targets **5** by similar methods. The Boc-group was removed with HCl to give the piperidines, which were individually coupled with tetrahydronaphthyridine acids **25**[14] or **26**.[10] Conditions using *O*-benzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HBTU), 1-hydroxybenzotriazole (HOBT), and *N*-methylmorpholine (NMM) were effective with **20**–**23**. For **24**, the usual coupling conditions were unacceptable because of oxidation to the quinoline. The coupling reagent, bromotrispyrrolidinophosphonium hexafluorophosphate (PyBroP), was found to be suitable, without accompanying oxidation. Hydrolysis of the methyl ester was performed under acidic or basic conditions to afford targets of type **5** (**27**–**31**, Table 1).

The N–Me derivative **33** was produced by alkylation of the intermediate 1,2,3,4-tetrahydroquinoline **15** (2,6-di-(*t*-butyl)pyridine (1.2 mol equiv), MeI (1.2 mol equiv), DMF, 20 h, 31%) to give the *N*-methyl intermediate **32**, which was converted to **33** as described above. Compound **34** (Table 1) was prepared by the same method as described in Scheme 1, beginning with 5-bromo-2-methoxypyridine. The isonipecotamide structures (**2**, **3**) were prepared as described earlier.[8] Full experimental methods for the preparation and chiral HPLC separation of a related series are discussed elsewhere.[15]

The target compounds were evaluated as antagonists of vitronectin binding to $\alpha_V\beta_3$ and $\alpha_V\beta_5$, and fibrinogen binding to $\alpha_{IIb}\beta_3$ (Table 1). SB 265123, included as a reference compound, is reported to be a potent antagonist of both α_V integrins and to be selective relative to α_{IIb} (300-fold).[4a] The original quinoline-substituted isonipecotamide lead **2** was a potent antagonist of $\alpha_V\beta_3$, but was weakly active against $\alpha_V\beta_5$ and not selective relative to $\alpha_{IIb}\beta_3$. It was thought that dual antagonism of $\alpha_V\beta_3$ and $\alpha_V\beta_5$ might be an advantage in certain disease states.[2] Replacement of the cyclic guanidine group with the tetrahydronaphthyridine group in **3** led to a great improvement in selectivity, which was first observed by Coleman et al.[9] and noted by us in other series.[15,17] When the amide of **3** was replaced by a carbon linker in **27**, good dual potency at $\alpha_V\beta_3$ and $\alpha_V\beta_5$ was achieved, along with excellent selectivity (1400-fold). Compound **27** was compared to **2** in a rat pharmacokinetics (PK) study,[18] but there was no improvement in oral bioavailability for **27** ($F = 4\%$, $C_{max} = 0.5\,\mu M$, $t_{1/2} = 3\,h$) versus **2** ($F = 4\%$, $C_{max} = 0.8\,\mu M$, $t_{1/2} = 7\,h$, dosed 30 mg/kg po). This result was surprising since a related $\alpha_V\beta_3$ antagonist containing the tetrahydronaphthyridine and quinoline groups was orally bioavailable in dogs.[9] Analogs of **27** with the quinoline reduced to 5,6,7,8- and 1,2,3,4-tetrahydroquinolines (THQ), **28** and **29**, were obtained as byproducts. Compounds **28** and **29** have potency and selectivity comparable to **27**, so it was of interest to test their PK properties. Although 5,6,7,8-THQ **28** was not detectable following oral administration, 1,2,3,4-THQ **29** was observed at high levels in the plasma in a pilot rat PK experiment (21 μM at 2 h; 15 mg/kg, po). Therefore, the four isomers of **29** (two *dl* pairs) were prepared and evaluated. Two of the isomers, **29b** and **29d** had good potency in binding assays, so they were examined in rat PK experiments.[19] A dramatic improvement in oral absorption was noted with **29d** ($F = 22\%$, $C_{max} = 3\,\mu M$, $t_{1/2} = 2\,h$) versus quinoline **27**. Although the quinolinyl group has been used extensively in integrin antagonists, the THQ-group has not yet been described. The N–Me analog **33** showed decreased potency relative to **29**.

It was of interest to compare the 2-methoxypyridine analog **34**, as this group has displayed good PK properties.[4b] In our series, neither the racemate **34** ($F = 8\%$, $C_{max} = 0.9\,\mu M$, $t_{1/2} = ND$) nor the active isomer **34a** ($F = 2\%$, $C_{max} = 0.1\,\mu M$, $t_{1/2} = 2\,h$) had the oral bioavailability seen for **29d**. However, the $\alpha_V\beta_3$ potency of **34a** was noteworthy.

The quinoline and THQ compounds **30** and **31** ($m = 2$, $n = 0$, Table 1), which lack a carbon atom between the piperidine and β-position of the carboxylic acid, were evaluated; they have one additional linker carbon attached to the tetrahydronaphthyridine group. Racemic **30** and **31** had good potency against $\alpha_V\beta_3$, but lesser potency against $\alpha_V\beta_5$ as compared to **27** and **29**. The most active THQ isomer, **31a**, was 30-fold more potent against $\alpha_V\beta_3$ than $\alpha_V\beta_5$. Both of the active THQ isomers, **31a** ($F = 46\%$, $C_{max} = 8\,\mu M$, $t_{1/2} = 2\,h$) and **31d** ($F = 52\%$, $C_{max} = 58\,\mu M$, $t_{1/2} = 1\,h$), showed even better oral bioavailability than what was seen above. The corresponding quinoline, **30**, was not well absorbed ($F = 1\%$).

The relationship of stereochemistry to biological activity is different in the THQ analogs **29** and **31**. The enantiomeric pairing of isomers was determined by measuring optical rotations of the intermediates (**15**, **18**) and final products (**29**, **31**; Table 1). The absolute values of the four optical rotations were not that different for the four isomers of **31**, making it more difficult to pair the final-product isomers. For this reason, ^1H and ^{13}C NMR studies were done (D_2O, 600 MHz) on the four isomers of **31**. The spectra of **31a** and **31d** were identical to each other and distinct from the spectra of **31b** and **31c**; the spectra of **31b** and **31c** were also identical. From this analysis, the two more potent isomers of **29** (**b** and **d**) have a diastereomeric relationship, whereas the two more potent isomers of **31** (**a** and **d**) are enantiomers of each other. Therefore, the absolute stereochemistry at the β-position is different for the more potent isomers of **31**, which is not commonly the case with aryl substituents.

Conclusion

The quinoline containing carba-analog **27** was modified by hydrogenation, which improved its oral bioavailability. Conditions were developed to selectively reduce the quinoline to the 1,2,3,4-tetrahydroquinoline unit. These 1,2,3,4-THQ-containing α_V antagonists had good potency and the highest oral bioavailability in this series thus far. The four individual isomers of the THQ-analogs **29** and **31** were obtained by using chiral HPLC. Biological activity resided primarily in two of the isomers in each case.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2004.08.067.

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11. To a rapidly stirred, cold (−90 °C) solution of the Weinreb amide **8** (51.2 g, 179 mmol) and 3-bromo-quinoline (74.7 g, 358 mmol) in THF (205 mL) was added a 1.6 M solution BuLi in hexanes (225 mL, 358 mmol), maintaining the internal temperature ⩽−84 °C. The mixture was stirred at −90 °C for 1.5 h and the cold bath was removed. The mixture was stirred for 1 h and placed in an ice/water bath until the internal temperature rose to −6 °C. Saturated aqueous NH_4Cl (500 mL) was added at such a rated that the internal temperature was ⩽10 °C and the resulting

mixture was stirred under nitrogen for 18 h. The aqueous phase was extracted with EtOAc and the organic extracts were combined, dried over Na_2SO_4, filtered, and evaporated to give 105 g of a dark oil, which was purified by column chromatography (1.7 kg of flash grade silica gel; eluant: toluene 3 L, 15% EtOAc in toluene 14 L, 22% EtOAc in toluene 9 L, 28% EtOAc in toluene 7 L and finally 60% EtOAc in toluene 1.8 L). Evaporation of appropriate fractions gave 40.57 g of a solid, which was triturated with 12:1 hexane/EtOAc (130 mL) and allowed to stand for 18 h. The resulting solid was collected by filtration and washed with portions of hexane to give 37.8 g of the product as a yellow solid. The mother liquors were concentrated, treated with hexane, EtOAc, and acetone and filtered to give 2.06 g of the product as a yellow solid. The two batches were combined to give 39.8 g of **10** (62% yield, mp 114–116 °C). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.17–1.34 (m, 2H), 1.46 (s, 9H), 1.74–1.84 (m, 2H), 2.16–2.33 (m, 1H), 2.69–2.84 (m, 2H), 3.04 (d, J = 7.6 Hz, 2H), 4.03–4.23 (m, 2H), 7.61–7.68 (m, 1H), 7.83–7.89 (m, 1H), 7.97 (dd, J = 1.5, 9.1 Hz, 1H), 8.16 (d, J = 9.1 Hz, 1H), 8.70 (d, J = 1.2 Hz, 1H), 9.43 (d, J = 1.2 Hz, 1H). MS (ES+) m/z 396.1 (M+MeCN+H$^+$). Anal. Calcd for $C_{21}H_{26}N_2O_3 \cdot 0.2\ C_6H_{14}$: C, 71.74; H, 7.84; N, 7.54. Found: C, 71.77; H, 7.55; N, 7.98.

12. A solution of **12** (17.1 g, 41.7 mmol) was combined with 10% Pd/C (8.6 g) in toluene (210 mL) with Et_3N (2.1 mL). The reaction mixture was shaken on a Parr apparatus at 50 °C and 50 psig for about 28 h. It was stopped when the hydrogen uptake slowed. The reaction mixture was filtered through Celite® and evaporated. After purification by flash chromatography on silica gel (11-cm diameter, gradient elution with 20–30% EtOAc in heptane), **15** was isolated as a gum (12.5 g, 72%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.0–1.6 (m, 6H), 1.45 (s, 9H), 2.0–2.7 (m, 8H), 3.00 (m, 1H), 3.26 (m, 1H), 3.67 (s, 3H), 3.83 (m, 1H), 4.11 (m, 2H), 6.49 (d, J = 8 Hz, 1H), 6.62 (t, J = 7 Hz, 1H), 6.97 (m, 2H). MS (ES+) m/z 417.1 (M+H$^+$). HRMS (FAB$^+$) m/z (M$^+$) Calcd for $C_{24}H_{36}N_2O_4$: 416.2675. Found: 416.2662.
13. The four isomers of **15** were separated by sequential chiral chromatography. Isomers (lettered based on elution order, with isomer-**a** eluting first) **15a** and **15b** were separated from isomers **15c** and **15d** using a Chiralpak® OD column [cellulose tris-(3,5-dimethyl-phenylcarbamate) coated on 20-μm silica gel, 41 × 5 cm; using methanol as eluant: 100 vol% at 80 mL/min; 220 nM]. The isomers **15a** ($[\alpha]_D^{23}$ +30, c 0.59, MeOH) and **15b** ($[\alpha]_D^{23}$ +62, c 0.54, MeOH) were separated using a Chiralpak® AD column [amylose tris-(3,5-dimethyl-phenylcarbamate) coated on 20-μm silica gel, using ethanol as eluant under the same conditions as above]. The isomers **15c** ($[\alpha]_D^{23}$ −65, c 0.68, MeOH) and **15d** ($[\alpha]_D^{23}$ −31, c 0.55, MeOH) were separated similarly on a Chiralpak® AD column. The purity of each isomer was greater than 99% by HPLC.
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18. Rat PK experiments were done in animals dosed po at 10 mg/kg (N = 4) versus iv at 2 mg/kg (N = 4), unless otherwise noted. The drug levels in plasma were compared by LC/MS. Oral dosing was done in D5W (5% Dextrose Injection USP, Baxter) adjusted to pH 2 with 0.1 N HCl solution. All compounds were fully soluble in this formulation.
19. As a precaution, analytical reference and plasma samples of **29** and **31** were treated with acidified (0.1% CF_3CO_2H) MeCN during the protein precipitation step, because significant oxidation to the quinoline occurs in neutral MeCN.