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Non-peptidic $\alpha_v\beta_3$ antagonists containing indol-1-yl propionic acids

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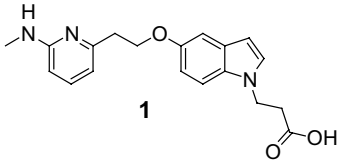
Abstract—We describe the synthesis and structure/activity relationship of RGD mimetics that are potent inhibitors of the integrin $\alpha_v\beta_3$. Indol-1-yl propionic acids containing a variety of basic moieties at the 5-position, as well as substitutions alpha and beta to the carboxy terminus were synthesized and evaluated. Novel compounds with improved potency have been identified.

The integrin family is a group of heterodimeric transmembrane glycoproteins that are involved in cell adhesion, signal transduction, and migration.[1] The vitronectin receptor, $\alpha_v\beta_3$ is a member of the integrin family and is predominantly involved in adhesion of osteoclasts to bone matrix, migration of vascular smooth muscle cells and angiogenesis of proliferating endothelium.[2] Therefore, inhibitors of $\alpha_v\beta_3$ are thought to be useful in the treatment of many diseases including osteoporosis, restenosis, cancer, and ocular disease.[3]

We have recently reported an original series of N-substituted indoles such as compound **1** (Fig. 1) that possess a number of favorable characteristics including good oral bioavailability.[4] In view of these promising preliminary results, we maintained the indole scaffold of our first-generation inhibitor, which provided a good PK profile, and further explored a structure/activity relationship study around this series. To this end, we explored replacing the basic moieties at the *N*-terminus, substituting at positions alpha and beta to the carboxylic acid terminus and replacing the linker region between the termini (Fig. 2).



1

Figure 1. First-generation inhibitor of $\alpha_v\beta_3$.

The synthetic routes to various indol-1-yl propionic acid analogues are outlined in Schemes 1–6. Several different basic endings were prepared by the procedures outlined in Scheme 1. Commercially available 2-aminopyridine was protected with *tert*-butylchloride and treated with LDA and DMF, followed by deprotection to give aldehyde **2**. This was then treated with acetone and base to give 2-methyl-[1,8]naphthyridine **3**, which was hydrogenated and subsequently protected with Boc_2O to give **4a**.[5] Alternatively, commercially available 6-methyl-2-nitropyridin-3-ol was reduced by hydrogenation and then treated with chloro-acetyl chloride to give lactam **5**,[6] which was reduced with lithium aluminum hydride, followed by protection of the amine with Boc_2O to give **4b**. Compounds **4** were then treated with base and diethyl carbonate to give the esters **6a**,**b**. Treatment of ester **6a** with selenium dioxide, followed by treatment

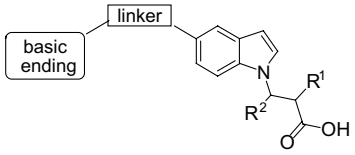


Figure 2. Second-generation inhibitors of $\alpha_v\beta_3$.

Keywords: Integrins; RGD mimetic; $\alpha_v\beta_3$ antagonists.
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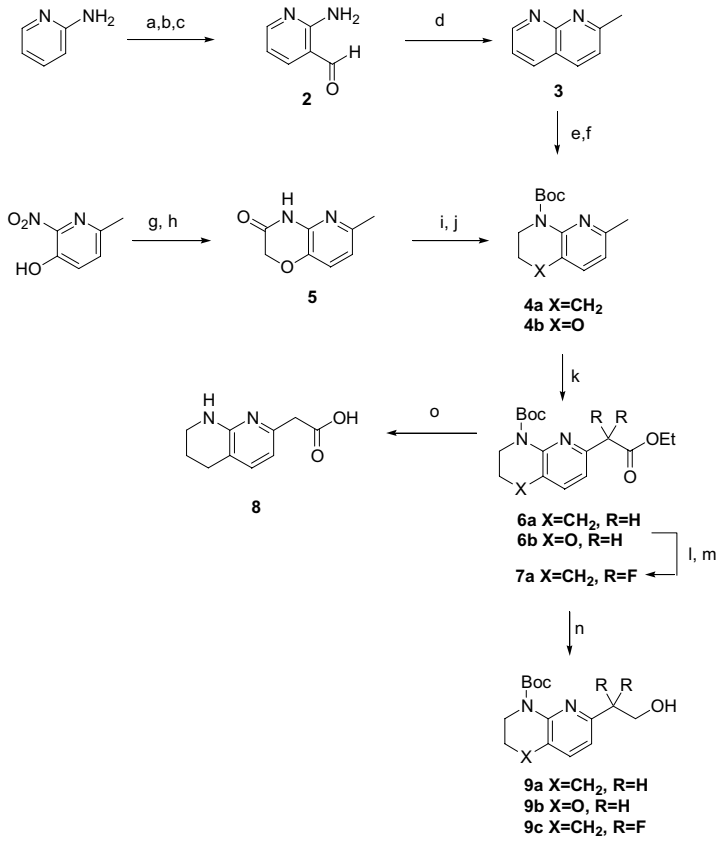


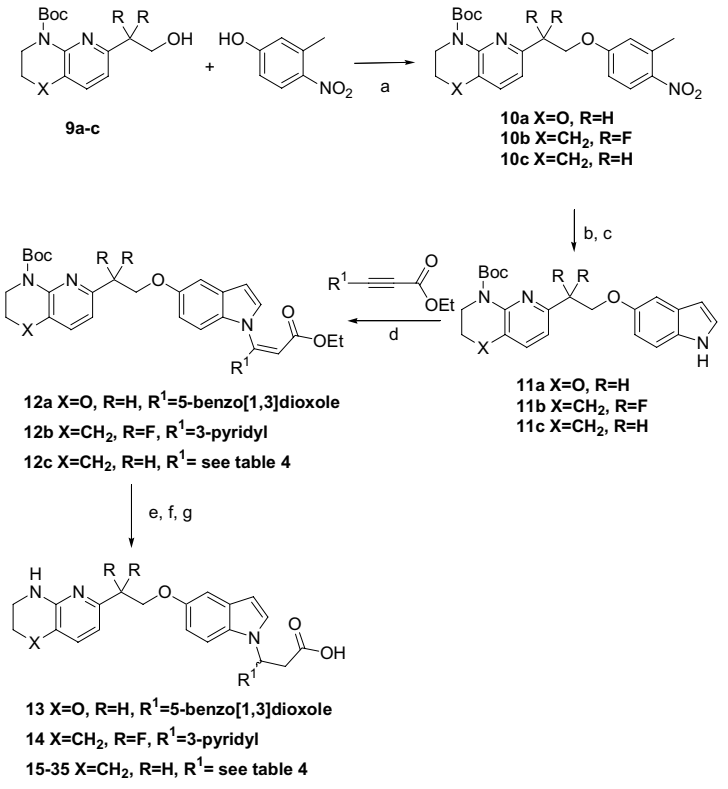
Scheme 1. Reagents and conditions: (a) *tert*-butylchloride, DIEA, DCM, 67%; (b) LDA, DMF, 95%; (c) 3 N HCl, H_2O, 52%; (d) L-proline, acetone, 99%; (e) H_2, Pd/C, EtOH, 74%; (f) Boc_2O, NaH, THF, 50%; (g) H_2, Pd/C, EtOAc, 99%; (h) $NaHCO_3$, 2-butanone, H_2O, $ClCOCH_2Cl$, 79%; (i) LAH, THF, rt, 3 h, 99%; (j) Boc_2O, neat, 60 °C, 80%; (k) LDA, $(EtO)_2CO$, THF, 0 °C, 49–75%; (l) selenium dioxide, dioxane, rt, 24 h, 81%; (m) DAST, DCM, −78 °C, 1 h, 40%; (n) $LiBH_4$, THF, −78 °C, 3 h, 25–94%; (o) (a) NaOH, MeOH, (b) TFA, DCM, 99%.

with DAST yielded the difluoro derivative **7a**.[7] Alternatively, **6a** was saponified with sodium hydroxide followed by Boc deprotection with TFA to give compound **8**. Esters **6a**,**b** and **7a** were reduced in the presence of lithium borohydride to give alcohols **9a**–**c**.

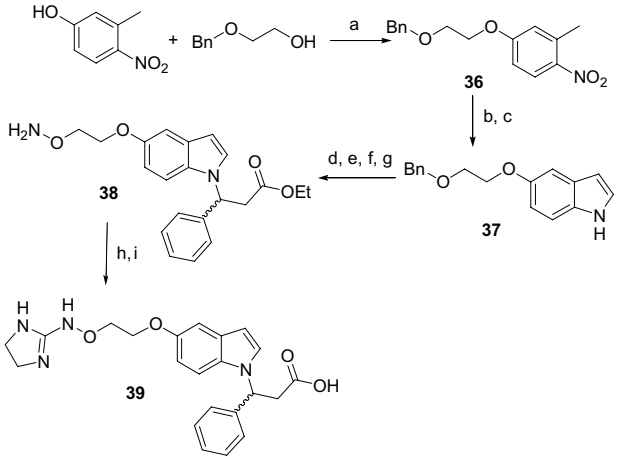
Indoles **13**–**35** were synthesized from the coupling of commercially available 3-methyl-4-nitrophenol and alcohols **9a**–**c** in a Mitsunobu reaction to give nitrophenol esters **10a**–**c**, as depicted in Scheme 2. Subsequent treatment with *N*,*N*-dimethylformamide dimethyl acetal and pyrrolidine followed by hydrogenation afforded intermediates **11a**–**c**.[8] Michael addition with substituted aryl ethyl propiolates and cesium fluoride gave ethyl acrylates **12a**–**c**, which were reduced by hydrogenation, followed by deprotection of the Boc group with copper(I) triflate. Finally, the target compounds **13**–**35** were obtained by the saponification of the corresponding esters **12a**–**c**.

A second approach that lead to the synthesis of the O-guanidine basic endings is shown in Scheme 3. Commercially available 3-methyl-4-nitrophenol and 2-benzyloxyethanol were coupled in a Mitsunobu reaction to give **36**, followed by treatment with *N*,*N*-dimethylformamide dimethyl acetal and pyrrolidine, followed by selective hydrogenation to give **37**. Michael addition with ethyl phenylpropiolate and TBAF, followed by hydrogenation gave the corresponding alcohol, which was coupled with *N*-hydroxyphthalimide in a Mitsunobu reaction and then deprotected with methylamine to give the O-amino derivative **38**. This amine was treated with 2-(3,5-dimethylpyrazolyl)-4,5-dihydroimidazole hydrobromide and then saponified with LiOH to give **39**.

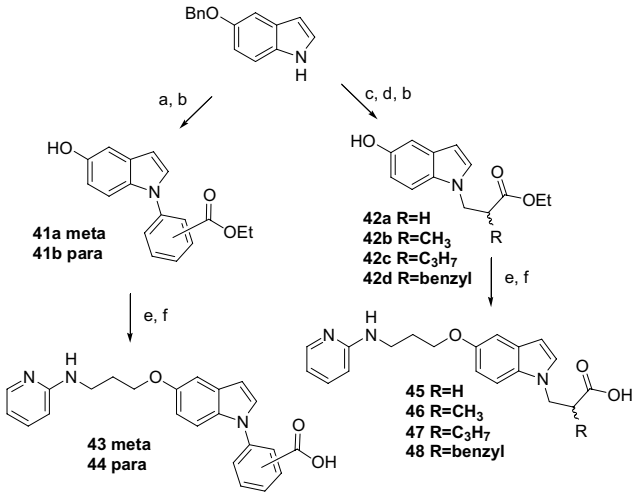
The synthesis of compounds with substitution on the propionic acid are shown in Scheme 4. Commercially available 5-benzyloxy-1*H*-indole was alkylated with 3-bromopropionic acid ethyl ester followed by treatment with lithium diisopropylamide and the corresponding substituted bromide, followed by hydrogenation to give the corresponding 5-hydroxyindoles **42a**–**d**. Compound **42a**–**d** was coupled with 3-(2-pyridylamino)-propan-1-ol in a Mitsunobu reaction, followed by saponification with lithium hydroxide to give the target compounds **45**–**48**. Alternatively, 5-benzyloxy-1*H*-indole was coupled with either *meta*- or *para*-bromobenzoic acid ethyl ester in the presence of a palladium catalyst[9] followed by hydrogenation to give hydroxyindoles **41a**,**b**. The Mitsunobu coupling reaction with 3-(2-pyridylamino)-propan-1-ol followed by subsequent saponification with sodium hydroxide afforded the target compounds **43** and **44**.



Scheme 2. Reagents and conditions: (a) PPh_3, DIAD, THF, 60–88%; (b) *N*,*N*-dimethylformamide dimethyl acetal, pyrrolidine, DMF, 16 h, 120 °C; (c) EtOAc, MeOH, H_2, Pd/C, 27–54% (2 steps); (d) CsF, DMF, 60 °C, 4 h, 40–80%; (e) EtOAc, MeOH, H_2, Pd/C, 70–80%; (f) Cu(OTf), 10% DMF/toluene, 80–90%; (g) LiOH, 70% MeOH/H_2O, 40–80%.

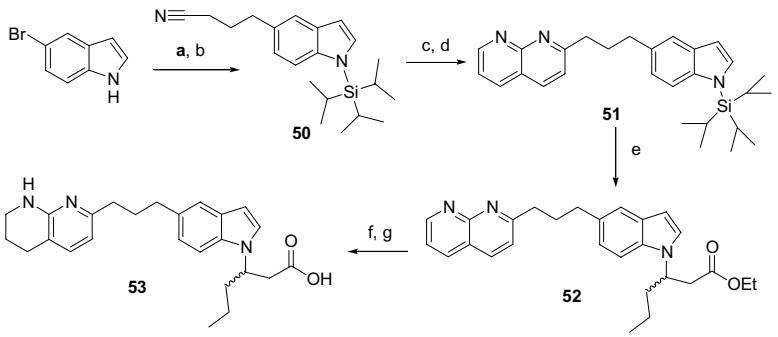


Scheme 3. Reagents and conditions: (a) PPh_3, DIAD, THF, rt, 75%; (b) *N*,*N*-dimethylformamide dimethyl acetal, pyrrolidine, DMF, 120 °C, 16 h; (c) EtOAc, MeOH, H_2, Pd/C, 22%; (d) ethyl phenylpropiolate, TBAF, 70 °C, 16 h, 69%; (e) EtOAc, MeOH, H_2, Pd/C, 80%; (f) *N*-hydroxyphthalimide, PPh_3, DIAD, THF, 96%; (g) methylamine, rt, 16 h, 73%; (h) 2-(3,5-dimethylpyrazolyl)-4,5-dihydroimidazole hydrobromide, MeOH, 5 days, 99%; (i) LiOH, 70% MeOH/H_2O, rt, 16 h; 74–80%.

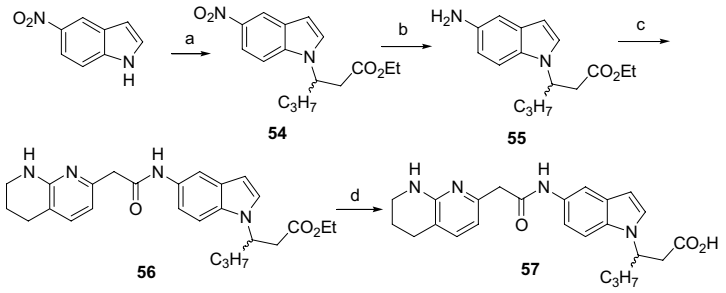


Scheme 4. Reagents and conditions: (a) P(*t*-Bu)$_3$, Cs_2CO_3, *m*- or *p*-Br–$C_6H_4CO_2Et$, $Pd_2(dba)_3$, toluene, 16–30%; (b) H_2, Pd/C, MeOH, 98%; (c) (i) NaH, DMF, rt; (ii) 3-bromopropionic acid ethyl ester, reflux, 71%; (d) LDA, THF, RBr, −78 °C, 50–90%; (e) *n*-Bu_3P, ADDP, 3-(pyridin-2-ylamino)-propan-1-ol, THF, rt, 15–54%; (f) (i) NaOH, MeOH (ii) HCl, 70–85%.

The synthesis of molecules with a modified linker region between the basic ending and the indole core are shown in Schemes 5 and 6. Commercially available 5-bromoindole was coupled to 3-cyanopropylzinc bromide in the presence of a palladium catalyst to give the corresponding cyano derivative, which was protected with TIPS-Cl in the presence of base to give **50**. Compound **50** was reacted with methyl magnesium bromide followed by treatment with 2-amino-benzaldehyde and L-proline to give compound **51**. Alkylation with 3-bromohexanoic



Scheme 5. Reagents and conditions: (a) $PdCl_2(dppf)_2$, 3-cyanopropylzinc bromide [0.5 M THF], THF, 18 h, 93%; (b) LHMDS, TIPSCl, THF, −78 °C to rt, 4 h, 99%; (c) CH_3MgBr, THF, −78 °C to rt, 18 h, 95%; (d) 2-amino-benzaldehyde, L-proline, EtOH, 57%; (e) (i) THF, TBAF, rt; (ii) THF, NaH, rt; (iii) 3-bromohexanoic acid ethyl ester, 17%; (f) H_2, Pd/C, MeOH, 80%; (g) LiOH, THF, MeOH, 50 °C, 24 h, 65%.



Scheme 6. Reagents and conditions: (a) (i) NaH, DMF, rt; (ii) 3-bromo-hexanoic acid ethyl ester, 34%; (b) H_2, 10% Pd/C, MeOH, 78%; (c) **8**, BOP, DIEA, DMF, rt, 67%; (d) (i) NaOH, MeOH (ii) HCl, 81%.

acid ethyl ester gave **52**, which was reduced with hydrogenation and saponified with lithium hydroxide to give **53** (Scheme 5).

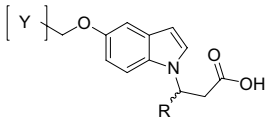
The synthesis of the amide linker derivative is shown in Scheme 6. Commercially available 5-nitroindole was alkylated with 3-bromohexanoic acid ethyl ester to give nitroindole **54**, which was reduced by hydrogenation to give aminoindole **55**. This was coupled with **8** using BOP and DIEA to give amide **56**, which was saponified with sodium hydroxide to give **57**.

Compounds described above were evaluated in a standard integrin binding assay,[4] and the results are outlined in Tables 1–4.

The crystal structure of $\alpha_v\beta_3$ has recently been reported[10] and we were able to build a model of this series of compounds, which explains the SAR observed.[11] It has previously been reported that compounds containing a tetrahydronaphthyridine (THN) moiety have been potent $\alpha_v\beta_3$ inhibitors and that this basic ending has improved pharmacokinetic properties.[5] We attempted to replace the existing methylaminopyridine of our first-generation compound with several different basic endings, including the THN, to increase potency and improve pharmacokinetic properties. Compounds with various basic ending groups are shown in Table 1. The replacement of a pyridylamino group (**45**) for a methylaminopyridine (**1**) led to a 13-fold increase in potency. This increase in potency is due to the increased rigidity obtained by placing a phenyl ring in the linker region between the basic ending and the indole scaffold.[12] A further 6-fold increase in potency can be obtained with the THN compound **15**, which has a piperidine ring that fixes the position of the hydrogen in the methylamine of compound **1** by incorporating it into a ring. This cyclic structure is also more lipophilic.[3c] Modification of the THN basic ending with difluoromethylene (**14**) led to a decrease in activity due to an unfavorable change in the pK_a of the pyridyl nitrogen. Placing an oxygen in the THN cyclic structure (**13**) does not negatively effect the pK_a of the pyridyl nitrogen, but there is an unfavorable contact with a carbonyl of a protein residue in this region, which lowers the potency.[11] Finally, the O-amidine derivative **39** exhibited lower potency, similar to **45**, possibly due to the increased flexibility of the guanidine mimetic.

It is well known that many scaffolds can be used as peptidomimetic inhibitors of $\alpha_v\beta_3$,[12] since the glycine of RGD and the peptide backbone do not make any interactions with the protein.[10] The importance of the scaffold appears to be the ability to present the aspartate and guanidine mimetics in the correct orientation for recognition by $\alpha_v\beta_3$ and to modulate the PK profile of the $\alpha_v\beta_3$ antagonist. We have found, however, that subtle changes in the linker region have profound effect on the activity (Table 2). Substitution of an oxygen (**16**) for a carbon (**53**) led to a greater than 4-fold decrease in

Table 1. Antagonists with modification of the N-terminus basic moiety



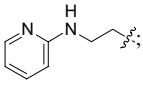
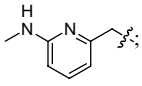
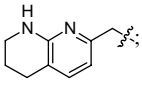
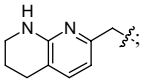
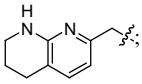
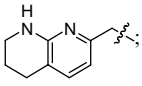
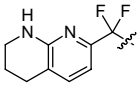
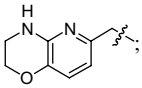
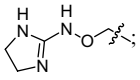
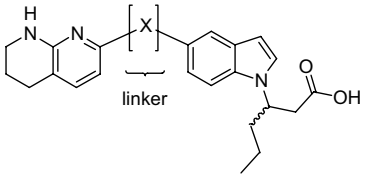
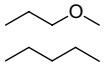
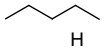
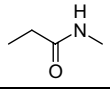
Compd	Y; R	IC_{50} (nM) $\alpha_v\beta_3$
45	 ; H	470
1	 ; H	36
15	 ; H	6
17	 ; Ph	1
30	 ; 3-pyridyl	0.25
21	 ; 5-benzo-[1,3]dioxole	0.38
14	 ; 3-pyridyl	130
13	 ; 5-benzo-[1,3]dioxole	8
39	 ; Ph	200

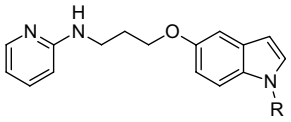
Table 2. Antagonists with varying linkers

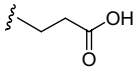
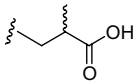
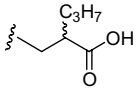
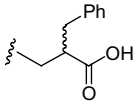
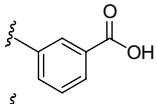
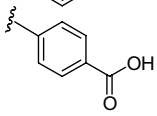


Compd	X	IC_{50} (nM) $\alpha_v\beta_3$
16		5
53		23
57		78

activity. It is theorized[11] that the oxygen and carbon prefer different conformations and the ethoxy linker is able to place the basic ending in the correct orientation for interaction with the protein aspartic acid while maintaining a low energy conformation. Although the amide linker (**57**) can adopt a similar low energy conformation

Table 3. Antagonists with propionic acid substitutions



Compd	R	IC_{50} (nM) $\alpha_v\beta_3$
45		470
46		460
47		2000
48		1900
43		>20,000
44		>20,000

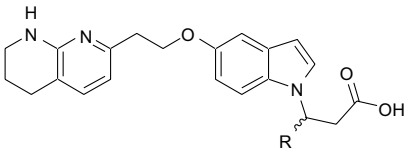
to the ethoxy linker, there is an unfavorable interaction of the amide carbonyl with a tyrosine residue in this region, which significantly decreases its activity.

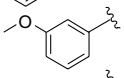
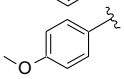
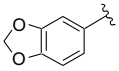
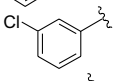
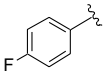
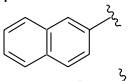
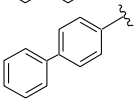
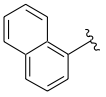
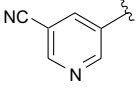
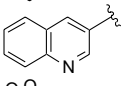
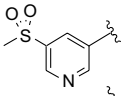
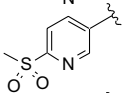
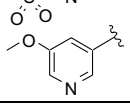
Compounds with substituents alpha to the carboxylic acid as well as compounds replacing the propionic acid with more rigid groups are shown in Table 3. A small substitution at the alpha position, such as replacement of a hydrogen (**45**) with a methyl (**46**) was tolerated, but larger substitutions such as *n*-propyl (**47**) and benzyl (**48**) led to a loss of activity. Also, replacing the propionic acid of compound **45** with more rigid groups such *meta* and *para* benzoic acids **43** and **44** led to the complete loss of activity.

Although we were unable to significantly affect the potency of these molecules by substitutioning alpha to the carboxy terminus or by replacing the propionic acid with other acid derivatives, compounds with substitution beta to the carboxy terminus did show a significant increase in potency, as shown in Table 4. Substitutions beta to the carboxylic acid have been described by other groups[13] and our results indicate that various betasubstituents can have a significant impact on potency. Substituents that were particularly potent were the substituted 3-pyridyl compounds such as **28**, **30**, **34**, and **35**, whereas bulky substituents such as **26** and **27** significantly reduced potency.

In conclusion, several compounds were identified with superior activity to our first-generation compound **1**. We were able to maintain the indole scaffold and significantly increase potency by replacing the methylamino-

Table 4. Antagonists with substitution beta to the carboxy terminus



Compd	R	IC_{50} (nM) $\alpha_v\beta_3$
15	H	6.0
16		3.0
17		1.0
18		1.1
19		0.8
20		0.7
21		0.38
22		55
23		0.5
24		0.7
25		37
26		40
27		37
28		0.26
29		1.2
30		0.25
31		0.9
32		0.38
33		0.46
34		0.3
35		0.25

pyridine basic ending with the THN moiety, as well as making substitutions beta to the carboxy terminus. Several of these indol-1-yl propionic acids were of interest to our group. In particular, compound **21**, which was dosed orally and intravenously to mice to give a half-life of 1.5 h, an *F* value of 73% and clearance of 13 mL/min/kg.

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