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Piperidine-containing β-arylpropionic acids as potent antagonists of $\alpha_v\beta_3/\alpha_v\beta_5$ integrins

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This paper is dedicated to the memory of Barry C. Lange (deceased April 2003), who touched our lives briefly, but memorably, with his positive spirit

Abstract—The synthesis and SAR of a new class of piperidine-based $\alpha_v\beta_3/\alpha_v\beta_5$ integrin antagonists is described. Replacement of an amide bond in a prototype isonipecotamide by a C–C isostere, and adjustment of the spacer length between the carboxylic acid and basic moieties, led to low nanomolar antagonists of $\alpha_v\beta_3$ and/or $\alpha_v\beta_5$ integrins with excellent selectivity versus $\alpha_{IIb}\beta_3$.

Integrins are a family of heterodimeric transmembrane glycoproteins that are involved in cell–cell interactions and communication between cells and the extracellular matrix. These receptors have been implicated in a variety of diseases, such as cancer, osteoporosis, restenosis, and macular degeneration.[1–6] The integrins $\alpha_{IIb}\beta_3$, $\alpha_v\beta_3$, $\alpha_v\beta_5$, $\alpha_v\beta_6$, and $\alpha_5\beta_1$ recognize adhesive proteins that contain the Arg-Gly-Asp (RGD) tripeptide sequence,[7,8] which is critical for binding to the integrin extracellular domain. Hence, selective and bioavailable nonpeptide mimics of the RGD recognition motif have been pursued in attempts to modulate integrin-mediated biological processes, such as cell adhesion, migration, and proliferation.[1,2,4,9–15]

A drug discovery program in our laboratory that targeted the platelet fibrinogen (Fg) receptor, $\alpha_{IIb}\beta_3$ (GPIIb/IIIa), produced elarofiban (RWJ-53308), a potent, selective, orally bioavailable antagonist, which was selected for human clinical evaluation (Scheme 1).[16] In the course of structure–activity relationship studies, we found that replacement of the basic piperidine by other basic groups and exchange of the nipecotamide for an isonipecotamide core causes a reversal of integrin binding selectivity.[17] Whereas elarofiban is a potent antagonist of $\alpha_{IIb}\beta_3$ ($IC_{50} = 0.15\,nM$) with little activity against the $\alpha_v\beta_3$ integrin ($IC_{50} > 50\,\mu M$), related isonipecotamide **1** is a potent antagonist of $\alpha_v\beta_3$ ($IC_{50} = 19\,nM$) with weak activity against $\alpha_{IIb}\beta_3$ ($IC_{50} = 1.8\,\mu M$). This observation prompted us to explore the potential of the isonipecotamide scaffold as a template for selective antagonists of the $\alpha_v\beta_3$ integrin.

Diverse isonipecotamide analogues were prepared via solid-phase chemistry (Scheme 2)[18] with a variety of basic moieties and aryl substituents being introduced. Some of the basic groups were inspired by literature reports, such as tetrahydronaphthyridine,[19] aminopyridyl,[20] and cyclic guanidines,[21] which are guanidine isosteres that have yielded potent $\alpha_v\beta_3$ integrin antagonists. Wang resin-bound Fmoc-protected β-amino acids **2** were deprotected by treatment with piperidine in DMF and reacted with Fmoc-protected isonipecotic acid under standard peptide coupling conditions to yield **3**. After removal of the protecting group (viz. **4**), the resin-bound isonipecotamides were coupled with a variety

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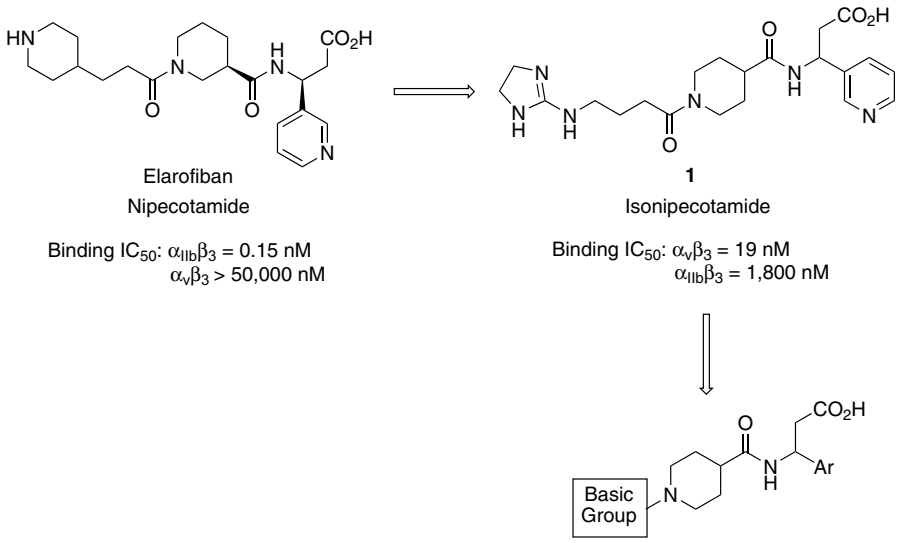
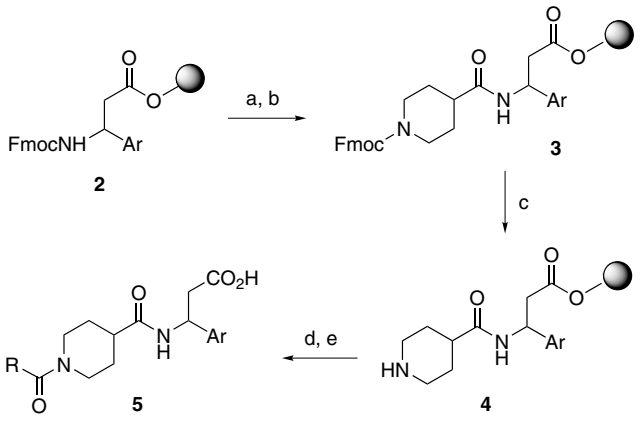


Scheme 1. Design of an isonipecotamide-based $\alpha_v\beta_3$ antagonist library.



Scheme 2. Solid-phase synthesis of an isonipecotamide integrin antagonist library. Reagents and conditions: (a) piperidine, DMF; (b) Fmoc-protected isonipecotic acid, $(i\text{-Pr})_2$NEt, *O*-(7-azabenzotriazol-1-yl-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), DMF; (c) piperidine, DMF; (d) RCO_2H, $(i\text{-Pr})_2$NEt, HATU, DMF; (e) CF_3CO_2H, CH_2Cl_2.

of acids. Cleavage from the support yielded target compounds **5**.

Some representative compounds are depicted in Table 1. The combination of the tetrahydronaphthyridine or cyclic guanidine basic group with a 5-methylenedioxyphenyl or 3-quinolinyl substituent for Ar (**5c**, **5d**–**f**) gave the most potent $\alpha_v\beta_3$ integrin antagonists in the isonipecotamide series. The selectivity versus $\alpha_{IIb}\beta_3$ was variable, however. Unfortunately, the desired potency and selectivity of these compounds was not accompanied by an acceptable pharmacokinetic (PK) profile; in particular, the oral bioavailability of these compounds in rats never exceeded 4% (data not shown). We hypothesized that the poor oral bioavailability was, at least in part, due to the amide bond at the 4-position of the piperidine ring. On the basis of this rationale, the isonipecotamide amide bond was replaced by a C–C isostere to reduce polarity.

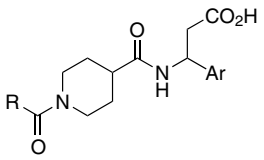
Two synthetic strategies for the synthesis of the C–C isosteres were employed. The first approach was based on the Claisen rearrangement of a trimethylsilyl ketene acetal derived from malonate **8** (Scheme 3).[24] Boc-protected isonipecotic acid **6** was converted to piperidine aldehyde **7**,[25] which was reacted with arylacetylides to form the corresponding propargyl alcohols. After partial reduction to the *cis*-olefins, the alcohols were converted to malonates **8**. Their corresponding trimethylsilyl ketene acetals rearranged smoothly on heating and the accompanying desilylation/decarboxylation provided methyl esters **9**.

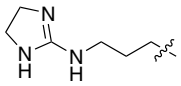
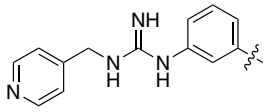
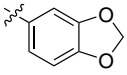
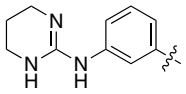
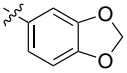
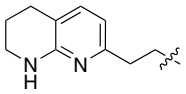
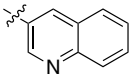
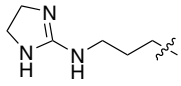
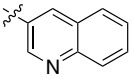
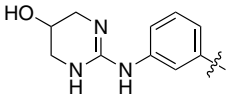
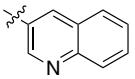
The Boc-protecting group was removed under standard conditions and the resulting piperidines were coupled with different acids to yield amides **10**. Hydrolysis of the methyl ester, followed by catalytic hydrogenation, yielded the desired C–C bioisosteres **11**.

Alternatively, the target compounds were prepared according to Scheme 4.[26] Piperidine acids **12** ($n=2$) were converted into the corresponding Weinreb amides and transformed into aryl ketones **13** via condensation with an in situ generated aryl lithium species. Horner–Emmons chemistry, followed by hydrogenation and hydrolysis of the Boc group, gave piperidines **14**. Coupling of **14** with a desired carboxylic acid, followed by basic hydrolysis of the ester, provided target compounds **15**.

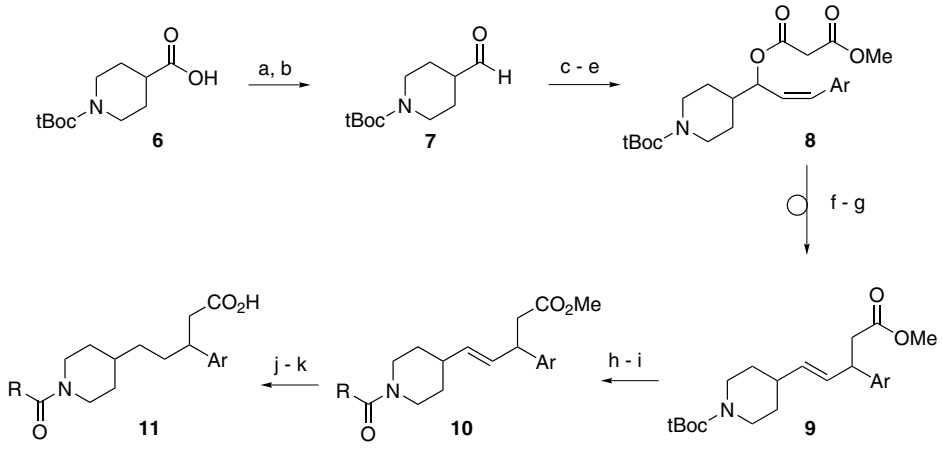
We were gratified that some target molecules, such as **11a**, possessed potent $\alpha_v\beta_3$ integrin binding (Table 2).[27] The combination of the methylenedioxyphenyl group with the tetrahydronaphthyridine (**11b**) or aminopyridyl groups (**11c**) resulted in considerably weaker antagonists. When the PK profile of some of these compounds was evaluated, only **11b** and **11c** were found to exhibit desirable oral bioavailability. A head-to-head comparison between C–C isostere **11c** and amide **5g** in a rat PK study validated our working hypothesis that a less

Table 1. Effect of basic group and aryl substitution on integrin binding activity



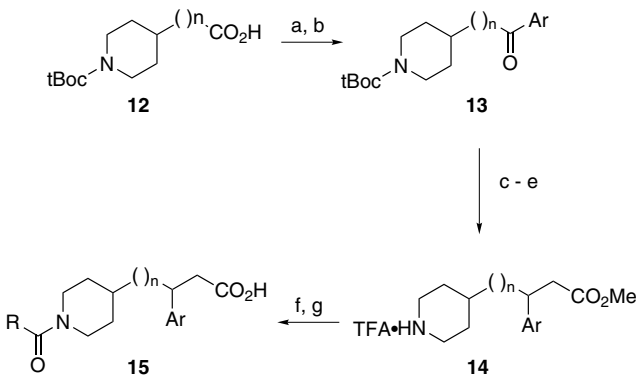
Compd	R	Ar	IC_{50} (nM)	
			$\alpha_v\beta_3$[a]	$\alpha_{IIb}\beta_3$[b]
5a			45.7 ± 16	1810 ± 86
5b			25.3 ± 12	56.4 ± 20
5c			10.4 ± 2.0	209 ± 93
5d			2.6 ± 0.5	2850 ± 314
5e			2.8 ± 0.6	79.3 ± 15
5f			5.5 ± 2.4	177 ± 3.8

[a] Inhibition of human vitronectin binding to immobilized $\alpha_v\beta_3$ ($N \geqslant 3$ when $IC_{50} < 1\,\mu M$).[22]
[b] Inhibition of biotinylated Fg binding to immobilized $\alpha_{IIb}\beta_3$ ($N \geqslant 2$ when $IC_{50} < 1\,\mu M$).[23]



Scheme 3. Synthesis of C–C bioisosteres. Reagents and conditions: (a) *i*-BuOCOCl, MeNHOMe·HCl, *N*-methylmorpholine, THF; (b) $LiAlH_4$, Et_2O; (c) BuLi/HCCAr, THF; (d) H_2, Lindlar's catalyst, pyridine; (e) $ClCOCH_2CO_2Me$, Et_3N, CH_2Cl_2; (f) NaH, TMSCl, THF; (g) heat; (h) CF_3CO_2H, CH_2Cl_2; (i) RCO_2H, $(i\text{-}Pr)_2NEt$, HATU, DMF; (j) NaOH, 1,4-dioxane; (k) H_2, Pd/C, MeOH.

polar core is conducive to an improved PK profile. Despite the disappointing binding affinity for **11b** and **11c**, it is apparent that the combination of a methylenedioxyphenyl with a less basic moiety such as



Scheme 4. Alternative synthesis of C–C isosteres ($n=2$) and truncated analogues ($n=0$, 1). Reagents and conditions: (a) *i*-BuOCOCl, MeNHOMe·HCl, NMM, THF; (b) BuLi/ArX (X = Br or I), THF; (c) $(MeO)_2POCH_2CO_2Me$, $NaN(TMS)_2$, THF; (d) H_2, Pd/C, MeOH; (e) CF_3CO_2H, CH_2Cl_2; (f) RCO_2H, $(i\text{-Pr})_2NEt$, HATU, DMF; (g) NaOH, 1,4-dioxane.

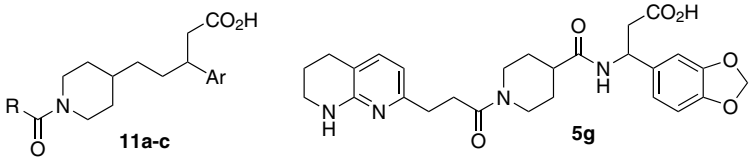
tetrahydronaphthyridine is useful for obtaining oral bioavailability. We realized that the spacer length between the basic moiety and the carboxylic terminus was not optimal, as it is greater than the length generally contained in potent antagonist series reported in the literature. Consequently, we tried to regain integrin affinity while maintaining good bioavailability by reducing this distance.

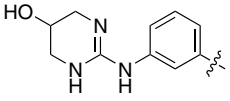
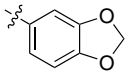
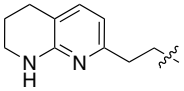
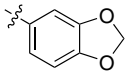
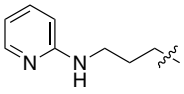
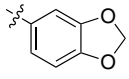
Several truncated combinations ($n=0$, 1) with equivalent structural features were synthesized (Scheme 4).[26] This approach furnished a compound with the desired profile, in that **15a** turned out to be a low-nanomolar antagonist of $\alpha_v\beta_3$ with excellent selectivity versus $\alpha_{IIb}\beta_3$ (Table 3). A potential benefit of **15a** and **19** is their improved binding potency for $\alpha_v\beta_5$, since dual $\alpha_v\beta_3/\alpha_v\beta_5$ integrin antagonists have been reported to block tumor-induced angiogenesis.[28,29]

We investigated the oral bioavailability of **15a** in rats and we were pleased to discover that its pharmacokinetic profile is quite satisfactory (Table 4). Replacement of the methylenedioxyphenyl group with various aryl groups (**15b–f**) indicated that the 3-(4-piperidinylmethyl)-3-arylpropionic acid scaffold is an excellent template for the design of nanomolar inhibitors of both the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins (Table 4). The oral bioavailability of these analogues is highly dependent on the nature of the aryl substituent.

In summary, we have identified a novel series of potent $\alpha_v\beta_3/\alpha_v\beta_5$ integrin antagonists based on a piperidine template. Replacement of an amide bond in isonipecotamide lead **5g** by a C–C isostere, and adjustment of the spacer length between the carboxylic acid and basic moieties, led to low-nanomolar inhibitors of the $\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins with excellent selectivity versus $\alpha_{IIb}\beta_3$.

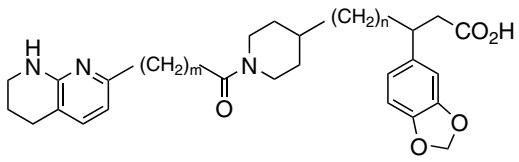
Table 2. Structure–activity relationship of selected C–C isosteres **11a–c** and comparison with isonipecotamide **5g**



Compd	R	Ar	IC_{50} (nM)		Rat PK[c]			
			$\alpha_v\beta_3$[a]	$\alpha_{IIb}\beta_3$[b]	Oral F (%)	$t_{1/2}$ (po) (h)	Cl (iv) (mg/kg μM h)	AUC (po) (μM h)
11a			1.7 ± 0.5	1578 ± 1056	2.6	5.4	0.04	21.2
11b			142 ± 27	4362 ± 2558	88	3.0	0.09	304
11c			233 ± 101	10,882 ± 3670	96	6.6	0.2	142
5g	—	—	21.7 ± 6.6	15,719 ± 1319	2.4	6.7	0.09	7.9

[a] Inhibition of human vitronectin binding to immobilized $\alpha_v\beta_3$ ($N \geqslant 3$ when $IC_{50} < 1\,\mu M$).[22]
[b] Inhibition of biotinylated Fg binding to immobilized $\alpha_{IIb}\beta_3$ ($N \geqslant 3$ when appropriate).[23]
[c] PK experiments were performed in rats dosed po (10 mg/kg, $N=4$) versus iv (2 mg/kg, $N=4$). The drug levels in plasma were determined by LC/MS. Oral dosing was done in 5% dextrose in water at pH 2.

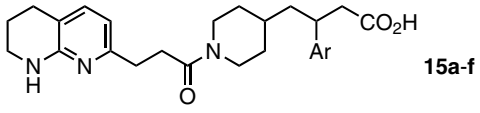
Table 3. Effect of spacer length on integrin binding affinity



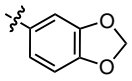
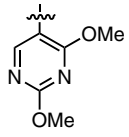
Compd	*m*	*n*	IC_{50} (nM)		
			$\alpha_v\beta_3$[a]	$\alpha_{IIb}\beta_3$[b]	$\alpha_v\beta_5$[a]
16	1	0	281[c]	>10,000[c]	775[c]
17	1	2	75±16	>10,000	405±126
18	2	0	28.1±8	6195±1155	95.7±23
15a	2	1	1.1±0.2	2515±295	2.3±0.9
19	3	0	1.9±0.2	4030±430	33.5±6.3
20	3	1	20.6±5.8	4260±1660	220±95

[a] Same as Table 2.
[b] Same as Table 2.
[c] $N=1$.

Table 4. Structure–activity relationship of **15a–f**



15a-f

Compd	Ar	IC_{50} (nM)			Rat PK[c]			
		$\alpha_v\beta_3$[a]	$\alpha_v\beta_5$[a]	$\alpha_{IIb}\beta_3$[b]	Oral F (%)	$t_{1/2}$ (po) (h)	Cl (iv) (mg/kg μM h)	AUC (po) (μM h)
15a		1.1±0.2	2.3±0.9	2515±295	31	2.1	0.1	97
15b	3-Fluorophenyl	1.0±0.2	2.8±0.1	>10,000	14	1.7	0.5	2.7
15c	3-Pyridyl	0.8±0.1	1.7±0.3	6610±2850	0	nd[d]	1.1	nd[d]
15d	2-Me-pyrimidin-5-yl	0.7±0.3	0.7±0.2	965±75	4	2.6	10.4	<0.1
15e		1.5±0.8	4.6±1.7	1470±369	1	nd[d]	1	0.1
15f	2-Naphthyl	1.9±0.6	24.5±6.5	>10,000	47	5.65	0.02	286

[a] Same as Table 2.
[b] Same as Table 2.
[c] Same as Table 2.
[d] nd = not determined.

Acknowledgements

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