Available online at www.sciencedirect.com
SCIENCE DIRECT®
Bioorganic & Medicinal Chemistry Letters 14 (2004) 4411–4415
Bioorganic & Medicinal Chemistry Letters

Nonpeptide $\alpha_v\beta_3$ antagonists. Part 9: Improved pharmacokinetic profile through the use of an aliphatic, des-amide backbone

David B. Whitman,[a,*] Ben C. Askew,[a,†] Le T. Duong,[b] Carmen Fernandez-Metzler,[d] Wasyl Halczenko,[a] George D. Hartman,[a] John H. Hutchinson,[a] Chih-Tai Leu,[b] Thomayant Prueksaritanont,[c] Gideon A. Rodan,[b] Sevgi B. Rodan[b] and Mark E. Duggan[a]

[a]*Department of Medicinal Chemistry, Merck Research Laboratories, West Point, PA 19486, USA*
[b]*Department of Bone Biology and Osteoporosis Research, Merck Research Laboratories, West Point, PA 19486, USA*
[c]*Department of Drug Metabolism, Merck Research Laboratories, West Point, PA 19486, USA*
[d]*Department of Pharmacology, Merck Research Laboratories, West Point, PA 19486, USA*

Received 23 February 2004; accepted 21 June 2004

Abstract—A series of $\alpha_v\beta_3$ receptor antagonists lacking the amide bond of previously-reported 'chain-shortened' compounds is described. Replacement of the lone amide bond with two methylene groups in this series yields more lipophilic compounds that have longer half-lives, lower clearance, and greater oral bioavailability when administered to dogs.

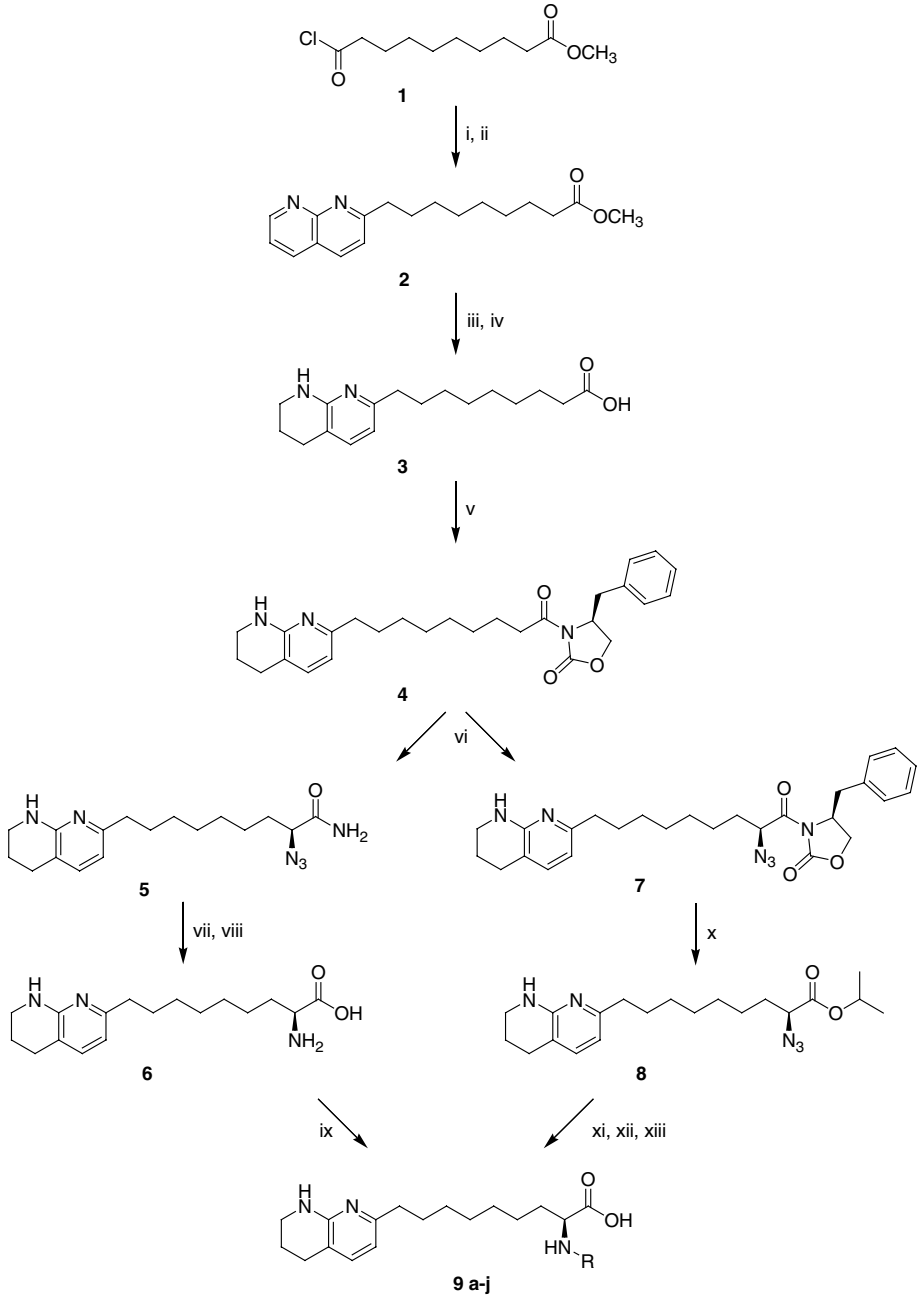
In the constant process of remodeling bone, cells called osteoclasts are responsible for bone resorption. Osteoblasts balance this process by forming new bone. The skeletal disease known as osteoporosis occurs when the activity of osteoclasts increases relative to the activity of osteoblasts. This leads to a net decrease in bone density, which makes affected individuals more susceptible to fractures. Osteoporosis affects primarily postmenopausal women, because increased bone resorption is associated with a decrease in estrogen levels.[1] The integrin $\alpha_v\beta_3$ receptor, which is highly expressed on osteoclasts, plays an essential role in the attachment and migration of these cells during bone resorption. Compounds that bind to the $\alpha_v\beta_3$ receptor have been shown to inhibit bone resorption in vivo.[2]

Previous reports from this laboratory have detailed the progression of $\alpha_v\beta_3$ antagonists from proteins containing an arginine-glycine-aspartic acid (RGD) sequence, to 'full-length' analogs containing two amide linkages, to 'chain-shortened' molecules with a single amide bond.[3–6] These studies showed that the optimal distance between the *N*-terminal tetrahydronaphthyridine nitrogen and the *C*-terminal carboxylic acid is eight atoms.[6] Certain aryl substituents on the carbon atoms alpha and beta to the carboxylic acid, as well as sulfonamides at the alpha position, have been shown to significantly increase affinity for the $\alpha_v\beta_3$ receptor in other series.[3,7] In this paper we describe the identification of a new class of chain-shortened compounds that combine some of these potency-enhancing, alpha-amino substitutions with replacement of the single remaining amide bond to further improve the pharmacokinetic characteristics of the series.

The pathway used to prepare the compounds discussed here is shown in Scheme 1. Commercially available methyl sebacoyl chloride was treated with CuCN and MeMgBr to form the methyl ketone, which was then subjected to a Friedlander condensation with 2-amino-3-formylpyridine.[8] The resulting 1,8-naphthyridine **2** was then hydrogenated and the ester hydrolyzed, yielding the 5,6,7,8-tetrahydro-1,8-naphthyridine **3**. Formation of the mixed anhydride of this carboxylic acid followed by treatment with the lithium anion of (*S*)-4-benzyl-2-oxazolidinone gave the chiral intermediate **4**.[9]

* Corresponding author. Tel.: +1-215-652-4533; fax: +1-215-652-7310; e-mail: david_whitman@merck.com
† Present address: Amgen, Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA.

0960-894X/$ - see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmcl.2004.06.068



Scheme 1. Reagents and conditions: (i) CuCN, MeMgBr, THF; (ii) 2-amino-3-formylpyridine, L-(−)-proline, EtOH, (66% yield over two steps); (iii) 10% Pd/C, H_2 (1 atm), EtOH, (97%); (iv) NaOH, MeOH, (88%); (v) NEt_3, trimethyl acetyl chloride, then *n*-BuLi + (*S*)-4-benzyloxazolidinone, THF; (vi) KHMDS, 2,4,6-triisopropylbenzenesulfonyl azide; (vii) 10% Pd/C, H_2 (1 atm), EtOH, (84%); (viii) 6 N HCl, (90%); (ix) NaOH, R–Cl or R–NCO, 2:1 H_2O–dioxane, (17–57%); (x) Ti(O*i*-Pr)$_4$, *i*-PrOH, (14%); (xi) Ph_3P, 3:1 THF–H_2O, (62%); (xii) NMM, R–Cl, DCM, (28–98%); (xiii) 6 N HCl, dioxane, (51–99%).

Treatment of **4** with KHMDS and 2,4,6-triisopropylbenzenesulfonyl azide gave the desired 2(*S*)-azido-4(*S*)-benzyloxazolidinone **7** with high diastereoselectivity. Unexpectedly, the reaction also yielded the primary amide **5** in a ratio of approximately 1:1 with compound **7**. The azide **5** was reduced with palladium on carbon and the primary amide hydrolyzed to the carboxylic acid **6** by mild heating in 6 N HCl. Alkylations of **6** were performed under typical Schotten–Baumann conditions using the appropriate sulfonyl chloride, acid chloride, chloroformate, or isocyanate to yield the target compounds.

Alternately, the 2-azido-1-benzyloxazolidinone **7** was treated with titanium isopropoxide in isopropanol to form the isopropyl ester **8**. After Staudinger reduction of the azide, the resulting amine was treated with the appropriate alkylating agent and *N*-methylmorpholine in dichloromethane. Hydrolysis of the ester was then accomplished by heating with 6 N HCl to generate the compounds obtained through this variation of the synthetic scheme.

Table 1 shows the key data for several alpha-amino substitutions in the chain-shortened series of com-

pounds.[10–12] Although some of these compounds achieved the desired sub-nanomolar potency in the SPAV3 assay, their pharmacokinetic profiles were less than optimal. When dosed to dogs, half-lives of the compounds were generally short, and oral bioavailability was very low.

It was hypothesized that deletion of the lone amide bond, while maintaining the overall length of the molecule, might improve the pharmacokinetic profile of the chain-shortened compounds. A comparison of the Log *P* values of the compounds in Tables 1 and 2 shows that this modification causes a significant increase in lipophilicity, but in both series, all of the compounds tested had human protein binding values >97%. The des-amide analogs shown in Table 2 were less potent in the SPAV3 assay than their amide counterparts; however, the pharmacokinetic profiles in dogs were significantly improved. The phenylsulfonamide compound **9d** exhibited a plasma half-life of 9.3 h, with low clearance (7 mL/min/kg). When dosed orally, the bioavailability (*F*) was 55%, approximately an eightfold improvement over the analogous amide **10c**. The CBZ-amine **9c** showed a similar increase in oral bioavailability, but its half-life was only slightly better than the comparable amide **10b**. The aliphatic *n*-butyl sulfonamide **9f**, although not quite as potent, had an excellent half-life of 8.1 h and the highest oral bioavailability of the series (91%).

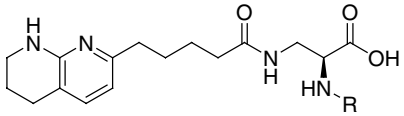
Acylation of the amine to generate the phenylacetylamino (**9i**) and benzoylamino (**9j**) compounds produced analogs with extremely long half-lives of 19.2 and 17.9 h, respectively. However, these compounds had reduced affinity for the $\alpha_v\beta_3$ receptor compared to the sulfonamides. A similar effect was seen in the series of compounds with the amide-containing backbone.

The use of a camphorsulfonyl group in $\alpha_v\beta_3$ antagonists has been reported previously.[1] In both the amide and the des-amide series shown here, the camphorsulfonamide compounds (**9a** and **10a**) were the most potent in the SPAV3 assay. Unfortunately, this functionality also caused a reduction in both half-life and bioavailability in this series.

The prepared compounds were also tested in a platelet aggregation assay and found to be selective against the fibrinogen receptor, $\alpha_{IIB}\beta_3$, which is a related integrin that shares the same β subunit as $\alpha_v\beta_3$.

In conclusion, we have identified a new class of potent $\alpha_v\beta_3$ receptor antagonists that possesses an improved pharmacokinetic profile over an earlier series of chain-shortened compounds. By replacing the amide bond with two methylene groups, the overall length is maintained, permitting favorable binding interactions with the receptor. This substitution makes the resulting des-amide compounds more lipophilic and leads to longer

Table 1. Chain-shortened $\alpha_v\beta_3$ receptor antagonists: potency, Log *P*, and pharmacokinetic parameters in dogs[10–12]



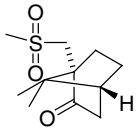
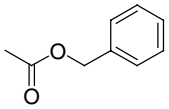
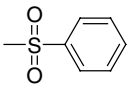
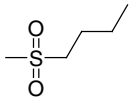
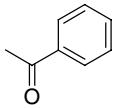
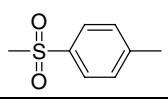
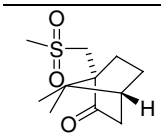
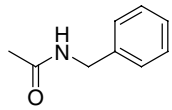
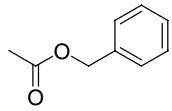
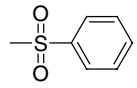
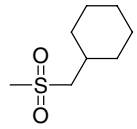
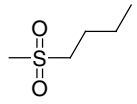
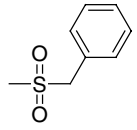
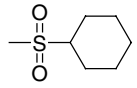
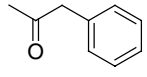
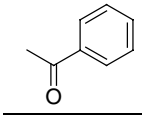
R	Compound	SPAV3 (IC_{50}, nM)	Log *P*	$T_{1/2}$ (h)	Cl (mL/min/kg)	*F* (%)
	**10a**	0.1	—	0.4	22	1
	**10b**	1.8	0.32	1.2	10	5
	**10c**	0.3	−0.38	0.7	29	7
	**10d**	2.3	−0.44	—	—	—
	**10e**	73.8	−0.23	—	—	—
	**10f**	0.4	0.08	1.2	13	<1

Table 2. Chain-shortened, des-amide $\alpha_v\beta_3$ receptor antagonists: potency, Log *P*, and pharmacokinetic parameters in dogs[10,11]

R	Compound	SPAV3 (IC_{50}, nM)	Log *P*	$T_{1/2}$ (h)	Cl (mL/min/kg)	*F* (%)
	**9a**	0.8	1.18	0.4	12	2
	**9b**	4.7	1.44	1.8	10	31
	**9c**	6.1	1.89	1.8	5	61
	**9d**	11.2	1.05	9.3	7	55
	**9e**	18.1	1.69	1.9	7	77
	**9f**	21.3	0.95	8.1	4	91
	**9g**	34.5	1.16	3.2	11	33
	**9h**	49.8	—	—	—	—
	**9i**	51.6	1.13	19.2	13	17
	**9j**	71.7	1.29	17.9	1	36

half-lives, lower clearance, and increased oral bioavailability when administered to dogs.

Acknowledgements

The authors would like to thank the mass spectrometry and analytical groups for their assistance and also the Pharmacology Department staff of Dr. Joseph J. Lynch for administering the compounds to dogs.

References and notes

1. Duggan, M. E.; Hutchinson, J. H. *Exp. Opin. Ther. Patents* **2000**, *10*, 1367–1383.
2. Coleman, P. J.; Duong, L. T. *Exp. Opin. Ther. Patents* **2002**, *12*, 1009–1021.
3. Duggan, M. E.; Duong, L. T.; Fisher, J. E.; Hamill, T. G.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.; Nagy, R. M.; Perkins, J. J.; Rodan, S. B.; Wesolowski, G.; Whitman, D. B.; Zartman, A. E.; Rodan, G. A.; Hartman, G. D. *J. Med. Chem.* **2000**, *43*, 3736–3745.
4. Meissner, R. S.; Perkins, J. J.; Duong, L. T.; Hartman, G. D.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.; Nagy, R. M.; Naylor-Olsen, A.; Rodan, G. A.; Rodan, S. G.; Whitman, D. B.; Wesolowski, G. A.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 25–29.
5. Coleman, P. J.; Brashear, K. M.; Hunt, C. A.; Hoffman, W. F.; Hutchinson, J. H.; Breslin, M. J.; McVean, C. A.; Askew, B. C.; Hartman, G. D.; Rodan, S. G.; Rodan, G. A.; Leu, C.; Prueksaritanont, T.; Fernandez-Metzler, C.; Ma, B.; Libby, L. A.; Merkle, K. M.; Stump, G. L.; Wallace, A. A.; Lynch, J. J.; Lynch, R.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 31–34.
6. Coleman, P. J.; Askew, B. C.; Hutchinson, J. H.; Whitman, D. B.; Perkins, J. J.; Hartman, G. D.; Rodan, G. A.; Leu, C.; Prueksaritanont, T.; Fernandez-Metzler, C.; Merkle, K. M.; Lynch, R.; Lynch, J. J.; Rodan, S. B.; Duggan, M. E. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2463–2465.

7. Brashear, K. M.; Hunt, C. A.; Kucer, B. T.; Duggan, M. E.; Hartman, G. D.; Rodan, G. A.; Rodan, S. B.; Leu, C.; Prueksaritanont, T.; Fernandez-Metzler, C.; Barrish, A.; Homnick, C.; Hutchinson, J. H.; Coleman, P. J. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 3483–3486.
8. The 2-methyl-1,8-naphthyridine regioisomer (methyl 8-(2-methyl-1,8-naphthyridin-3-yl)octanoate, in this case) typically generated in these Friedlander condensations was formed in a ratio of approximately 1:3 to desired product. It was easily separable by flash chromatography on silica gel.
9. Evans, D. A.; Britton, T. C.; Ellman, J. A.; Dorow, R. L. *J. Am. Chem. Soc.* **1990**, *112*, 4011–4030.
10. Dogs were dosed at 1 mpk po and 0.2 mpk iv. All animal studies described in this report were approved by the Merck Research Laboratories Institutional Animal Care and Use Committee.
11. SPAV3 is a scintillation-proximity assay, which measures the ability of a compound to bind to the $\alpha_v\beta_3$ receptor by displacing 3-{4-[2-(6-aminopyridin-6-yl)ethyl]benzoyl-amino}-2(*S*)-4-^{125}iodobenzenesulfonylaminopropionic acid from purified recombinant human $\alpha_v\beta_3$. The procedure is described in Refs. 3,12.
12. A representative synthesis of the chain-shortened compounds listed in Table 1 is described in Merck and Co., Inc. U.S. Patent 6,048,861; 2000.