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Phenylbutyrates as Potent, Orally Bioavailable Vitronectin Receptor (Integrin αvβ3) Antagonists

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Abstract—In our continuing efforts to identify small molecule vitronectin receptor antagonists, we have discovered a series of phenylbutyrate derivatives, exemplified by **16**, which have good potency and excellent oral bioavailability (approximately 100% in rats). This new series is derived conceptually from opening of the seven-membered ring of SB-265123.

Integrin αvβ3, also referred to as the vitronectin receptor, is a member of the integrin family of heterodimeric transmembrane glycoprotein complexes that function in cellular adhesion events and signal transduction processes.[1] Integrin αvβ3 is expressed on a variety of cell types, including osteoclasts, vascular smooth muscle cells, and endothelial cells, and is known to mediate several biologically-relevant processes, including adhesion of osteoclasts to the bone matrix, migration of vascular smooth muscle cells, and angiogenesis. As a result, antagonists of integrin αvβ3 are expected to have utility in the treatment of several human diseases, including osteoporosis, restenosis following percutaneous transluminal coronary angioplasty (PTCA), rheumatoid arthritis, cancer, diabetic retinopathy, and macular degeneration.

The identification of small molecule vitronectin receptor antagonists is a vigorous area of research, and a wide variety of potent antagonists have been identified.[1] In a previous report from these laboratories, we described the discovery of SB-265123,[2] a potent vitronectin receptor antagonist with very good pharmacokinetics in rats, including oral bioavailability of approximately 100%.[3] In following up on this lead, we envisioned opening the seven-membered ring to afford a 4-phenylbutyrate derivative. This modification would allow us to determine if the conformational constraint provided by the seven-membered ring in SB-265123 is required for potent biological activity. In addition, if 4-phenylbutyrates were found to be potent vitronectin receptor antagonists with good pharmacokinetic properties, they would be structurally simpler leads that might be more readily amenable to rapid and thorough investigation. In this communication, we report the results of our preliminary studies in this area.

The phenylbutyrate derivatives **7**–**10** (Table 1) were prepared as described in Scheme 1. Reaction of 2-(4-methoxyphenyl)-1-phenylethanone (**1**)[4] with the enolate of ethyl acetate gave the β-hydroxyester **2**, which on treatment with Et_3SiH and boron trifluoride etherate[5] gave a mixture of **3** and the corresponding α,β-unsaturated ester (from dehydration of **2**). This mixture was hydrogenated to afford pure **3**. Methyl ether deprotection with etha-

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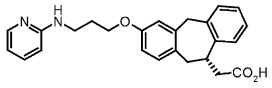
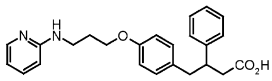
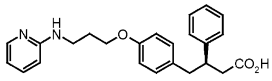
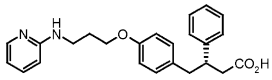
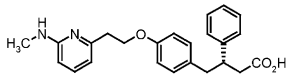
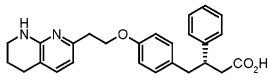
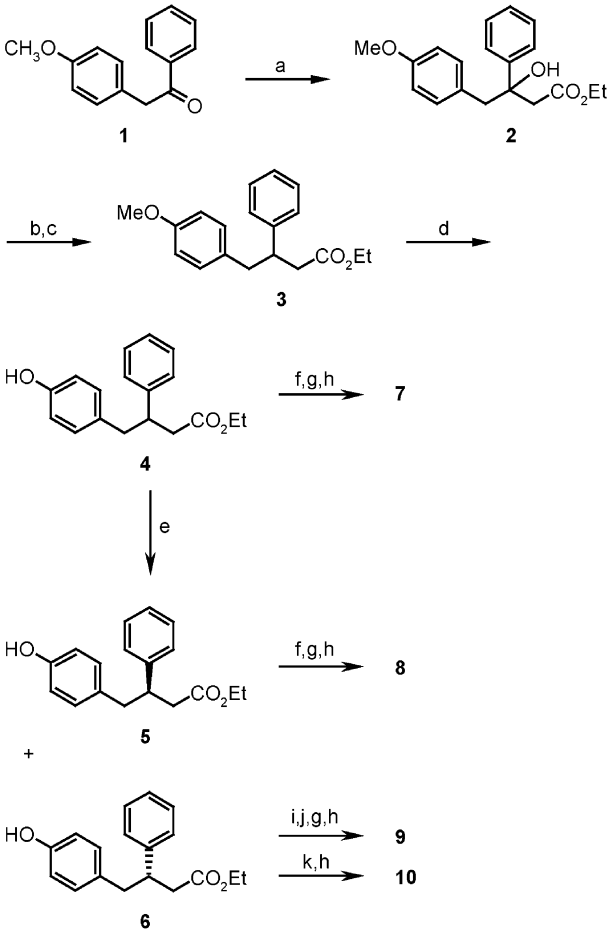
Table 1. In vitro activity and rat pharmacokinetics of phenylbutyrate-based vitronectin receptor antagonists

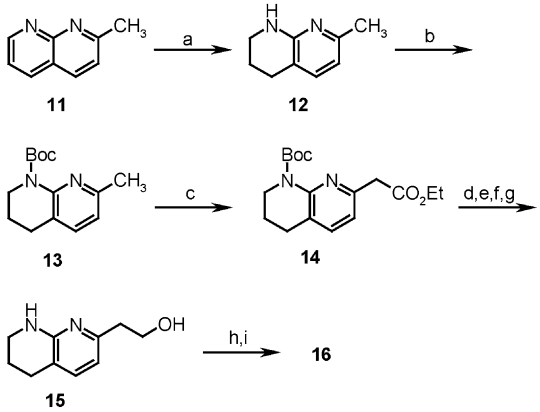
Entry	Compd	$\alpha_v\beta_3$ K_i (nM)	$\alpha_v\beta_3$/HEK IC_{50} (nM)	$T_{1/2}$ (min)	Clp (mL/min/kg)	Oral F (%)
SB-265123		4±1	60	181–378	3±1	≈100
7		32±6	500	—	—	—
8		170±36	—	—	—	—
9		12±3	470	144±27	7.2±0.9	≈100
10		7±2	330	310±167	4.9±1.3	≈100
16		2.5±0.6	30	95±8	6.0±1.7	≈100



Scheme 1. (a) EtOAc/$LiN(TMS)_2$, THF (96%); (b) Et_3SiH, $BF_3{\cdot}OEt_2$, CH_2Cl_2; (c) H_2, 10% Pd/C, EtOH (91% for two steps); (d) EtSH, $AlCl_3$, CH_2Cl_2 (96%); (e) chiral HPLC; (f) 2-[(3-hydroxy-1-propyl)-amino]pyridine-*N*-oxide, DIAD, $(Ph)_3P$, DMF (68% for **7**; 51% for **8**); (g) cyclohexene, 10% Pd/C, 2-propanol (77% for **7**; 87% for **8**; 43% for **9**;); (h) 1.0 N LiOH, THF, H_2O, then acidification (74% for **7**; 43% for **8**; 43% for **9**; 41% for **10**); (i) 2-[*N*-(3-methanesulfonyloxy-1-propyl)-*N*-(*tert*-butoxycarbonyl)amino]pyridine-*N*-oxide, NaH, DMSO (38%); (j) TFA, CH_2Cl_2 (quantitative); (k) 6-(methylamino)-2-pyridylethanol, DIAD, $(Ph)_3P$, DMF (93%).

nethiol and $AlCl_3$[6] gave **4**, which was resolved by chiral HPLC[7] to give **5** and **6**. The absolute configuration of the phenols was determined by X-ray crystallographic analysis of the (4-bromophenyl)urethane derivative of the (*S*)-phenol **6**.[8] Compounds **7** and **8** were prepared from **4** and **5**, respectively, according to established methods.[2] For the synthesis of **9**, the (*S*)-phenylbutyrate phenol **6** was treated with 2-[*N*-(3-methanesulfonyloxy-1-propyl)-*N*-(*tert*-butoxycarbonyl)amino]pyridine-*N*-oxide[9] in the presence of sodium hydride. Acidic removal of the Boc group, reduction of the *N*-oxide, and saponification gave **9**. Compound **10** was prepared from **6** according to established methods.[10]

The preparation of phenylbutyrate **16** is shown in Scheme 2. 2-Methyl-[1,8]naphthyridine (**11**)[11] was selectively hydrogenated[12] to afford the tetrahydronaphthyridine **12**, which was then protected as its *tert*-butyl carbamate (**13**). Deprotonation of **13** with LDA at 0 °C



Scheme 2. (a) H_2, 10% Pd/C, EtOH (99%); (b) LiHMDS, $(Boc)_2O$, THF (83%); (c) LDA, $(EtO)_2C{=}O$, THF, 0 °C (100%); (d) $LiBH_4$, THF, reflux; (e) 4 N HCl/dioxane, CH_2Cl_2, then 1.0 N NaOH; (f) HCO_2H, Et_2O; (g) 1.0 N NaOH (48% for four steps); (h) compound **6**, DIAD, $(Ph)_3P$, THF (71%); (i) 1.0 N LiOH, THF, H_2O, then acidification (74%).

in the presence of diethyl carbonate gave ester **14** in quantitative yield. Reduction and deprotection gave crude **15**, which was conveniently purified by crystallization of the formate salt. Coupling of **15** with **6** followed by saponification gave **16**.

The phenylbutyrate derivatives prepared as described above were evaluated in our standard integrin binding assays (Table 1).[13–15] In the interest of synthetic efficiency, we first prepared the racemic phenylbutyrate derivative **7**. In the αvβ3 binding assay,[13] **7** ($K_i = 32$ nM) is 8-fold less potent than SB-265123 ($K_i = 4$ nM). In accord with this level of affinity for the isolated receptor, **7** is a moderate inhibitor ($IC_{50} = 500$ nM) in the αvβ3/HEK cell adhesion assay,[14] which measures affinity for αvβ3 in a cellular context. Compound **7** is a potent antagonist of the related vitronectin receptor αvβ5 ($K_i = 6$ nM),[13] but selectivity against integrin αIIbβ3 is very good ($K_i > 10{,}000$ nM).[15] This selectivity profile is very similar to that of SB-265123, which has αvβ5 $K_i = 2.6$ nM and αIIbβ3 $K_i = 9000$ nM.[2]

Considering the encouraging overall activity and selectivity of **1**, we prepared the pure enantiomers **8** and **9**. In accord with previous observations,[2,10] the (*S*)-enantiomer **9** is more active than the (*R*)-enantiomer **8**. In the αvβ3 binding assay, **9** ($K_i = 12$ nM) is approximately 3-fold less potent than SB-265123 ($K_i = 4$ nM). However, despite this relatively good affinity for isolated αvβ3, **9** has $IC_{50} = 470$ nM in the αvβ3/HEK assay, which is approximately 8-fold less potent than SB-265123 ($IC_{50} = 60$ nM). These results suggest that the conformational constraint provided by the seven-membered ring in SB-265123 contributes significantly to potency against cellular αvβ3. In pharmacokinetic studies[16] in rats, phenylbutyrate **9** has a half life of 2.4 h, clearance of 7.2 mL/min/kg, and very high oral bioavailability (approximately 100%). This pharmacokinetic profile is very similar to that of SB-265123,[2,3] and shows that the seven-membered ring is not required for good pharmacokinetic properties.

The combined results of biological and pharmacokinetic evaluation indicate that phenylbutyrate **9** is a promising new lead, with moderate potency and excellent pharmacokinetics, including very high oral bioavailability. Our next objective was to determine if potency in this series could be improved without significantly compromising the pharmacokinetic profile. Therefore, we initiated a brief investigation towards this end, focused primarily on the guanidine mimetic.

We surveyed several guanidine mimetics that are known to confer good affinity for αvβ3, and found that two aminopyridine-based derivatives gave promising results. One of these derivatives, **10**, which contains the 2-(methylamino)pyridine subunit,[10,17] has $K_i = 7$ nM in the αvβ3 binding assay and is slightly more potent than **9** in the αvβ3/HEK assay ($IC_{50} = 330$ nM). Furthermore, **10** has very good pharmacokinetics in rats, with a half life of 5.2 h, clearance of 4.9 mL/min/kg, and very high oral bioavailability (approximately 100%). The other derivative, **16**, which contains the 5,6,7,8-tetrahydro[1,8]naphthyridine guanidine mimetic,[12b] has much improved affinity for αvβ3, both in the isolated receptor assay ($K_i = 2.5$ nM) as well as in the cell adhesion assay ($IC_{50} = 30$ nM). Compound **16** is also a potent antagonist of integrin αvβ5 ($K_i = 2.5$ nM), but has good selectivity against integrin αIIbβ3 ($K_i = 36{,}000$ nM). The increased activity of **16** against αvβ3 may be related to the increased lipophilicity of the 5,6,7,8-tetrahydro[1,8]naphthyridine guanidine mimetic,[12b] which might allow for a more favorable interaction with the receptor. In addition, the conformational restriction imposed by the piperidine ring, which causes the amidine-like nitrogens of **16** to be more exposed than in aminopyridines **9** and **10**, may also contribute to the increased activity. Significantly, **16** has very good pharmacokinetic properties in rats, with a half life of 1.5 h, clearance of 6.0 mL/min/kg, and very high oral bioavailability (approximately 100%).

The combined results for **16** demonstrate that phenylbutyrate derivatives can be potent vitronectin receptor (αvβ3 and αvβ5) antagonists with excellent pharmacokinetics. In fact, the overall profile of phenylbutyrate **16** is very similar to that of SB-265123. In further biological testing, phenylbutyrate **16** was found to be a potent inhibitor of human vascular smooth muscle cell migration ($IC_{50} = 26$ nM),[18] suggesting that this compound may have utility in the treatment of restenosis following PTCA.

In conclusion, we have described a new series of potent, orally bioavailable, nonpeptide vitronectin receptor (αvβ3 and αvβ5) antagonists based on a phenylbutyrate template, which is derived conceptually from opening of the seven-membered ring of SB-265123. A representative of this series, compound **16**, has very good affinity for αvβ3 and αvβ5, good selectivity against αIIbβ3, and excellent pharmacokinetics in rats, with oral bioavailability of approximately 100%. Furthermore, compound **16** is a potent inhibitor of vascular smooth muscle cell migration in vitro, suggesting that this compound may have utility in the treatment of restenosis following PTCA. The results of further investigations in this new series, including further lead optimization studies as well as additional biological characterization of selected derivatives, will be reported in due course.

References and Notes

1. (a) For recent reviews on integrin αvβ3, see: Coleman, P. J.; Duong, L. T. *Exp. Opin. Ther. Patents* **2002**, *12*, 1009. (b) Hölzemann, G. *Idrugs* **2001**, *4*, 72. (c) Miller, W. H.; Keenan, R. M.; Willette, R. N.; Lark, M. W. *Drug Disc. Today* **2000**, *5*, 397. (d) Duggan, M. E.; Hutchinson, M. E. *Exp. Opin. Ther. Patents* **2000**, *10*, 1367. (e) Hartman, G. D.; Duggan, M. E. *Exp. Opin. Invest. Drugs* **2000**, *9*, 1281.
2. Miller, W. H.; Bondinell, W. E.; Cousins, R. D.; Erhard, K. F.; Jakas, D. R.; Keenan, R. M.; Ku, T. W.; Newlander, K. A.; Ross, S. T.; Haltiwanger, R. C.; Bradbeer, J.; Drake, F. H.; Gowen, M.; Hoffman, S. J.; Hwang, S.-M.; James, I. E.; Lark, M. W.; Lechowska, B.; Rieman, D. J.; Stroup, G. B.; Vasko-Moser, J. A.; Zembryki, D. L.; Azzarano, L. M.; Adams, P. C.; Salyers, K. L.; Smith, B. R.; Ward, K. W.;

Johanson, K. O.; Huffman, W. F. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1807.
3. Ward, K. W.; Azzarano, L. M.; Bondinell, W. E.; Cousins, R. D.; Huffman, W. F.; Jakas, D. R.; Keenan, R. M.; Ku, T. W.; Lundberg, D.; Miller, W. H.; Mumaw, J. A.; Newlander, K. A.; Pirhalla, J. L.; Roethke, T. J.; Salyers, K. L.; Souder, P. R.; Stelman, G. J.; Smith, B. R. *Drug Metab. Dispos.* **1999**, *27*, 1232.
4. Drefahl, G.; Hartmann, M.; Grosspietsch, H. *Chem. Ber.* **1958**, *91*, 755.
5. Orphanopoulos, M.; Smonu, I. *Synth. Commun.* **1988**, 833.
6. Node, M.; Nishide, K.; Fuji, K.; Fujita, E. *J. Org. Chem.* **1980**, *45*, 4275.
7. Racemic phenol **4** was resolved into its enantiomers by chiral HPLC using the following conditions: Daicel Chiralcel AD® column (21.2×250 mm), 5% ethanol in hexane mobile phase, 15 mL/min flow rate, uv detection at 254 nm, 40 mg injection; t_R for ethyl (*S*)-(−)-4-(4-hydroxyphenyl)-3-phenylbutyrate = 19.8 min.; t_R for ethyl (*R*)-(+)-4-(4-hydroxyphenyl)-3-phenylbutyrate = 23.0 min.
8. Tables of crystal data, fractional atomic coordinates, anisotropic thermal parameters for non-hydrogen atoms, bond distances and angles have been included with the deposited supplementary material (deposition number CCDC 186477) sent to the Cambridge Crystallographic Data Centre, Lensfield Road, Cambridge CB2 1EW, United Kingdom. Listings of structure factors are available from the authors upon request.
9. 2-[*N*-(3-methanesulfonyloxy-1-propyl)-*N*-(*tert*-butoxycarbonyl)amino]pyridine-*N*-oxide was prepared from 2-[(3-hydroxy-1-propyl)amino]pyridine-*N*-oxide by the following sequence: (a) $(Boc)_2O$, *tert*-BuOH (98%); (b) methanesulfonyl chloride, pyridine, $CHCl_3$ (64%).
10. Miller, W. H.; Alberts, D. P.; Bhatnagar, P. K.; Bondinell, W. E.; Callahan, J. F.; Calvo, R. R.; Cousins, R. D.; Erhard, K. F.; Heerding, D. A.; Keenan, R. M.; Kwon, C.; Manley, P. J.; Newlander, K. A.; Ross, S. T.; Samanen, J. M.; Uzinskas, I. N.; Venslavsky, J. W.; Yuan, C. C. K.; Haltiwanger, R. C.; Gowen, M.; Hwang, S.-M.; James, I. E.; Lark, M. W.; Rieman, D. J.; Stroup, G. B.; Azzarano, L. M.; Salyers, K. L.; Smith, B. R.; Ward, K. W.; Johanson, K. O.; Huffman, W. F. *J. Med. Chem.* **2000**, *43*, 22.
11. Hawes, E. M.; Wibberley, D. G. *J. Chem. Soc.(C)* **1966**, *315*.
12. (a) Duggan, M. E.; Hartman, G. D.; Hoffman, W. F.; Meissner, R. S.; Perkins, J. J.; Askew, B. C.; Coleman, P. J.; Hutchinson, J. H.; Naylor-Olsen, A. M. International Patent Application WO 98/08840, 1998. (b) Duggan, M. E.; Duong, L. T.; Fisher, J. F.; Hamill, T. G.; Hoffman, W. F.; Huff, J. R.; Ihle, N. C.; Leu, C.-T.; 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.
13. Binding affinity for human αvβ3 and human αvβ5 was determined in a competitive binding assay employing ^{3}H-SK&F-107260 as the displaced ligand. The K_i values represent the means of values determined in two to three separate experiments. See: Wong, A.; Hwang, S. M.; McDevitt, P.; McNulty, D.; Stadel, J. M.; Johanson, K. *Mol. Pharm.* **1996**, *50*, 529.
14. Affinity for human αvβ3 in a cellular context was determined by measuring the inhibition of the adhesion of purified human vitronectin to HEK 293 cells transfected with human αvβ3. The IC_{50} values represent the means of values determined in two experiments in triplicate with an internal standard. Kumar, C. S.; James, I. E.; Wong, A.; Mwang, V.; Field, J. A.; Nuthulaganti, P.; Conner, J. R.; Eichman, C.; Ali, F.; Hwang, S. M.; Rieman, D. J.; Drake, F. H.; Gowen, M. *J. Biol. Chem.* **1997**, *272*, 16390.
15. Binding affinity for human αIIbβ3 was determined in a competitive binding assay employing ^{3}H-SK&F 107260 as the displaced ligand. The K_i values represent the means of values determined in two to three separate experiments. See: Ali, F. E.; Bennett, D. B.; Calvo, R. R.; Elliott, J. D.; Hwang, S.-M.; Ku, T. W.; Lago, M. A.; Nichols, A. J.; Romoff, T. T.; Shah, D. H.; Vasko, J. A.; Wong, A. S.; Yellin, T. O.; Yuan, C.-K.; Samanen, J. M. *J. Med. Chem.* **1994**, *37*, 769.
16. Pharmacokinetic parameters were determined using noncompartmental analysis of plasma concentration of test compound versus time data determined in three rats. Oral bioavailability was calculated from the dose-normalized iv and po. AUC values, where AUC is the area under the plasma concentration versus time curve. See: Gibaldi, M., Perrier, D. In *Pharmacokinetics*, 2nd ed.; Swarbrick, J., Ed.; Marcel Dekker: New York, 1982; Vol. 15, pp 145–198.
17. Keenan, R. M.; Miller, W. H.; Barton, L. S.; Bondinell, W. E.; Cousins, R. D.; Eppley, D. F.; Hwang, S.-M.; Kwon, C.; Lago, M. A.; Nguyen, T. T.; Smith, B. R.; Uzinskas, I. N.; Yuan, C. C. K. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1801.
18. See: Yue, T. L.; Wang, S. K.; Song, C. P.; Olson, B.; Mckenna, P. J.; Feuerstein, G. Z. *Circ. Res.* **1994**, *75*, 1.