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Bioorganic & Medicinal Chemistry Letters
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Bioorganic & Medicinal Chemistry Letters 14 (2004) 1049–1052

Non-peptide $\alpha_v\beta_3$ antagonists. Part 7: 3-Substituted tetrahydro-[1,8]naphthyridine derivatives☆

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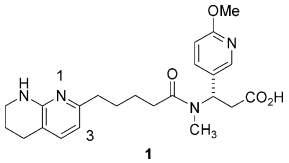
Received 14 May 2003; accepted 13 November 2003

Abstract—A series of 3-substituted tetrahydro-[1,8]naphthyridine containing $\alpha_v\beta_3$ antagonists was prepared. A comparison of their in vitro IC_{50} values to the electron properties of the 3-substituents revealed a good linear Hammett correlation ($\rho = -1.96$, $R^2 = 0.959$). Electron-withdrawing groups at the 3-position of the tetrahydro-[1,8]naphthyridine decreased potency while electron-donating groups enhanced potency.

Osteoporosis is a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue, leading to increase in bone fragility and susceptibility to fracture.[2,3] Osteoporosis due to estrogen deficiency is caused by increase in osteoclast-mediated bone resorption. It is well known that the integrin receptor $\alpha_v\beta_3$, a heterodimeric cell-surface adhesion receptor, is highly expressed in osteoclasts (bone resorbing cells) but not in osteoblasts (bone-forming cells).[4,5] Antibodies against $\alpha_v\beta_3$ and the RGD-containing peptide echistatin have been shown to inhibit bone resorption in vitro and in vivo.[6–8] More recently, non-peptide $\alpha_v\beta_3$ antagonists have been reported to prevent bone loss in ovariectomized rats.[9–12] These results suggest that antagonists of the $\alpha_v\beta_3$ receptor may have clinical utility for the prevention and treatment of osteoporosis.



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Potent non-peptide $\alpha_v\beta_3$ antagonists reported to date all contain a guanidine mimetic and a carboxylic acid that are linked together by various tethers and constraining elements.[13,14] Previously, we have reported the tetrahydro-[1,8]naphthyridine (THN) moiety to be a moderately basic, lipophilic N-terminus that provides both potency and selectivity for $\alpha_v\beta_3$.[15] Compound **1**, a member of the 'chain-shortened' class[16] of RGD mimetics, was identified in these laboratories as a potent $\alpha_v\beta_3$ antagonist that displays excellent pharmacokinetics in dogs ($F = 76\%$, $t_{1/2} = 5.8$ h). In this paper, we report our efforts to further improve the potency of **1** by exploring the effects of electron- withdrawing and electron-donating substituents at the 3-position of the THN group.

The synthetic sequence for preparing *N*-methyl-β-alanine **8** in high optical purity is depicted in Scheme 1. Treatment of 5-bromo-2-methoxypyridine **2** with ethyl acrylate under Heck coupling conditions provided **3** in good yield. Michael addition of *N*-Benzyl-(*R*)-α-methylbenzylamine to the acrylate **3** provided β-alanine **4** with good diastereoselectivity (de > 94%).[17] Selective removal of the benzyl groups under catalytic hydrogenation conditions furnished amine **5**, which was treated with 2,4-dinitrobenzenesulfonyl chloride to afford sulfonamide **6**.[18] Methylation of the amino group under Mitsunobu conditions followed by deprotection using mercaptoacetic acid furnished the desired *N*-methyl-β-alanine **8**.

☆See ref 1.
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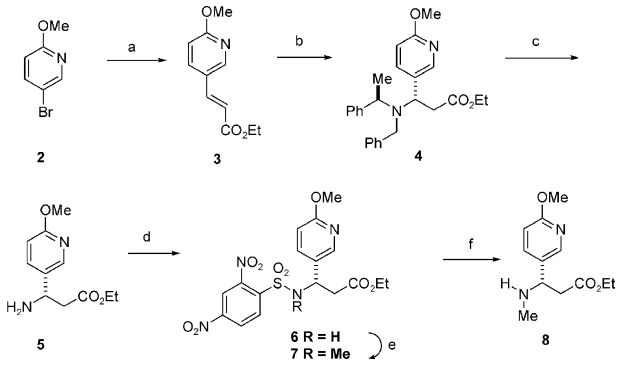
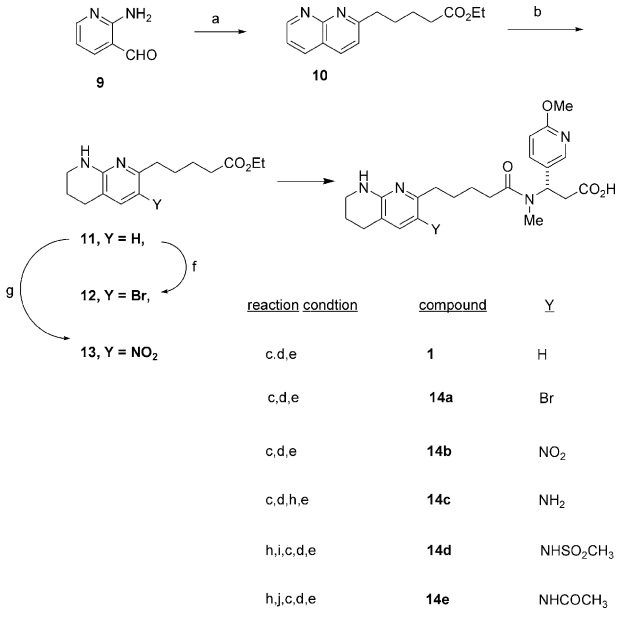
doi:10.1016/j.bmcl.2003.11.036

The synthetic strategy used to prepare compounds **1** and **14a–e** is illustrated in Scheme 2. Preparation of the naphthyridine **10** was achieved via a Friedlander condensation using the aminopyridinylaldehyde **9**[19] and ethyl oxoheptanoate. Regioselective hydrogenation afforded the desired tetrahydro-[1,8]naphthyridinyl pentanoate **11** in good yield. Following saponification, the corresponding acid was treated with EDC, HOAt and **8** in DMF and the resulting ethyl ester was hydrolyzed to furnish **1**. Alternatively, intermediate **11** was functionalized at the 3-position of the THN ring and converted to compounds **14b–e**. For example, bromination of **11** in acetic acid proceeded instantaneously and the resulting 3-bromo THN intermediate **12** converted into **14a**. On the other hand, treatment of **11** with a mixture of concentrated H_2SO_4 and KNO_3 provided in good yield the desired nitro product **13**, which served as an intermediate for the preparation of **14b–e**.



Scheme 1. Preparation of *N*-methyl 3-(*S*)-(2-methoxypyrid-5-yl)-β-alanine ethyl ester (**8**): (a) $Pd(OAc)_2$, Et_3N, tri-*o*-tolylphosphine, ethylacrylate, CH_3CN, 77%; (b) *N*-benzyl (*R*)-α-methylbenzyl amine/BuLi, −78 °C, then NH_4Cl, 80%; (c) $Pd(OH)_2$, H_2, EtOH/EtOAc, 83%; (d) 2,4-dinitrobenzenesulfonyl chloride, $NaHCO_3$, 81%; (e) MeOH, Ph_3P, DEAD, 51%; (f) mercaptoacetic acid, Et_3N, 78%.

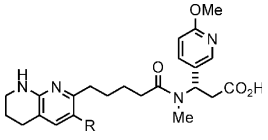


Scheme 2. Preparation of **1** and 3-substituted THN derivatives **14a–e**: (a) $CH_3CO(CH_2)_4CO_2Et$, EtOH, proline, 87%; (b) Pd/C, H_2, 82%; (c) LiOH/THF/H_2O, then HCl, 93%; (d) EDC, HOAt, Et_3N, DMF, **1–7**; (e) LiOH/THF/H_2O, then HCl; (f) Br_2, acetic acid, 100%; (g) concd H_2SO_4, KNO_3, 10 min, 85%; (h) H_2, Pd/C, EtOH; (i) $MeSO_2Cl$, Et_3N, THF; (j) CH_3COCl, Et_3N, THF.

Synthesis of THN derivatives **14f–i**, possessing a carbon-substituent at C-3, utilized the general route outlined in Scheme 3. Various substituents were incorporated at the beginning of the synthesis, using the 3-bromo tetrahydronaphthyridine **12** as the starting material. A Suzuki coupling with phenylboronic acid provided **12a**. Similarly, a Stille coupling using vinylstannane afforded the desired vinyl-substituted intermediate **12b**.[20] Intermediates **12c** and **12d** were obtained from **12** upon treatment with $Zn(CN)_2$ or MeZnCl in the presence of palladium, respectively. All four esters (**12a–d**) were converted to analogues **14f–i** in three steps.

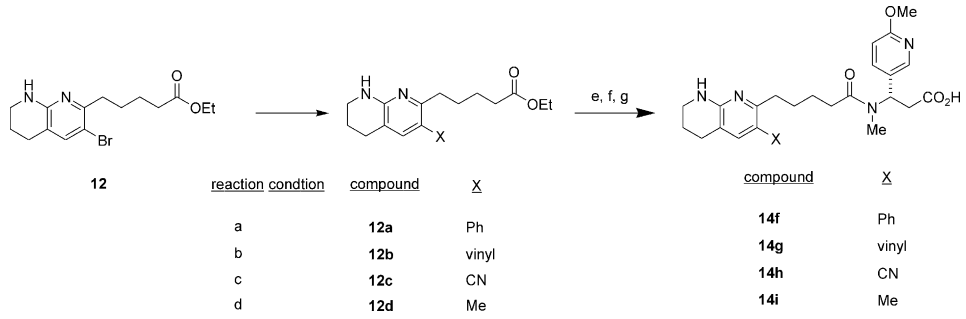
Compounds **14a–i** were evaluated for their ability to displace a non-peptide ligand from human recombinant $\alpha_v\beta_3$ using a scintillation proximity bead displacement assay (SPAV3).[15] The SPAV3 IC_{50} values are compared in Table 1 to the Hammett constant of *para*-substituents (σ_p), a measure of the substituent's ability to donate or withdraw electrons.[21] Analogues that possess electron donating groups at the 3-position of the THN ring, NH_2 (**14c**), Me (**14i**), and vinyl (**14g**) increased potency less than 2-fold. An analogue with OMe at the 3-position would also be a good example to further examine the electron donating effect. However, it could not be prepared easily. Compounds with electron-withdrawing 3-substituents were less potent than **1** in the displacement assay. A good correlation was observed between potency loss and the electron withdrawing capability of the 3-substituent. Analogues with moderate electron withdrawing group Br (**14a**) decreased potency by 3-fold. Strong electron-withdrawing groups such as CN (**14h**) and NO_2 (**14b**) decreased potency significantly, resulting in a 24- and 52-fold potency loss, respectively. Analogues with weak electron-withdrawing substituents Ph (**14f**), $NHCOCH_3$ (**14e**) and $NHSO_2Me$ (**14d**) showed no significant potency changes.

Table 1. Structure–activity relationships



Compd	*R*	SPAV3 (IC_{50}, nM)[a]	Log ($1/IC_{50}$)[b]	σ_p[c]
1	H	0.7 (2)±0.2	0.15	0
14c	NH_2	0.4	0.40	−0.30
14i	Me	0.3 (3)±0.1	0.52	−0.14
14g	Vinyl	0.3	0.52	−0.08
14f	Ph	0.9	0.05	0.05
14e	$NHCOCH_3$	0.6	0.22	0
14d	$NHSO_2Me$	0.9	0.05	0.03
14a	Br	2.3	−0.36	0.26
14h	CN	16.5	−1.22	0.71
14b	NO_2	36.7	−1.56	0.81

[a] Displacement of [^{125}I]L-775,219 from purified human $\alpha_v\beta_3$ bound to wheatgerm agglutinin scintillation proximity beads;[15] data in parentheses indicates the number of repeated assays.
[b] For relationship of log ($1/IC_{50}$) and log ($1/K_i$), see ref 22 for detail.
[c] Hammett constants from ref 21.



Scheme 3. Preparation of 3-substituted THN derivatives **14f–i**; (a) $C_6H_5B(OH)_2$, $(Ph_3P)_4Pd$, Na_2CO_3, DME, 80 °C, 16 h, 71%; (b) $Bu_3SnCHCH_2$, $(Ph_3P)_4Pd$, DMF, 120 °C, 49%; (c) $Zn(CN)_2$, $(Ph_3P)_4Pd$, DMF, 120 °C; (d) MeZnCl, $PdCl_2(Ph_3P)_2$, THF, 36%; (e) LiOH/THF/H_2O, then HCl; (f) EDC, HOAt, Et_3N, DMF, **8**; (g) LiOH/THF/H_2O, then HCl.

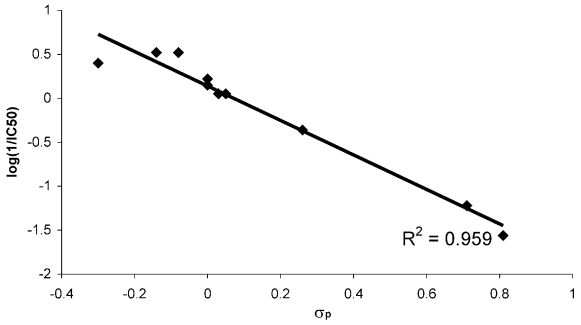


Figure 1. Correlation of potency and 3-substituent effect.

The Hammett plot in Figure 1 further illustrates the relationship between in vitro potency and the electronic properties of the 3-substituents.[21,22] A good correlation was obtained between the SPAV3 IC_{50} values of compounds **14a–i** and their electronic properties ($R^2 = 0.959$). The plot revealed a significant negative ρ value of −1.96, indicating that the binding affinity is sensitive to the effect of the electronic perturbation of the tetrahydro-[1,8]naphthyridine bicycle. The electronic effect of the 3-substituent on potency is likely mediated through the basicity of the THN nitrogens. With 3-substituted pyridines, increased basicity is observed with electron donating substituents and decreased basicity with electron withdrawing substituents.[23] Increase in basicity of the THN nitrogens may enhance the binding interactions between the THN nitrogens and the receptor. To evaluate the pharmacokinetics, compound **14i** was selected to study in dogs. It showed a good PK profile ($F = 65\%$, $t_{1/2} = 4.9$ h, Cl = 2.4 mL/min/kg), comparable to that of compound **1**. The methyl substituent at the 3-position did not improve the dog PK profile of the lead compound.

A series of 3-substituted THN $\alpha_v\beta_3$ antagonists was prepared and evaluated for their ability to bind to human recombinant $\alpha_v\beta_3$. A good correlation was established between ligand binding affinity and the electronic properties of the THN 3-substituent. It was observed that electron-withdrawing groups at 3-position of the THN decrease potency and electron-donating groups can enhance potency. The 3-substituents of the THN ring may control the binding affinity to $\alpha_v\beta_3$ integrins by modulating the pK_a of the THN nitrogen atoms. Among the compounds studied, less than 2-fold increase of potency was observed with electron donating 3-substituents (**14i** and **14g**).

Acknowledgements

The authors would like to thank Audrey Wallace, Yuan Meng, Carmen Fernandez-Metzler, Thomayant Prueksaritanont for the pharmacokinetic studies.

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