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Bioorganic & Medicinal Chemistry Letters 16 (2006) 839–844
Bioorganic & Medicinal Chemistry Letters

Convergent, parallel synthesis of a series of β-substituted 1,2,4-oxadiazole butanoic acids as potent and selective $\alpha_v\beta_3$ receptor antagonists

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Received 22 September 2005; revised 3 November 2005; accepted 3 November 2005
Available online 17 November 2005

Abstract—We describe a series of 1,2,4-oxadiazoles, which are potent antagonists of the integrin $\alpha_v\beta_3$ and, in addition, show selectivity relative to the other β_3 integrin $\alpha_{IIb}\beta_3$. In whole cells, the majority of these analogs also demonstrated modest selectivity against other α_v integrins such as $\alpha_v\beta_1$ and $\alpha_v\beta_6$.

The integrin $\alpha_v\beta_3$ is a non-covalently linked, heterodimeric transmembrane receptor, which is found on the surface of activated endothelial cells, smooth muscle cells, and many tumor cells. The $\alpha_v\beta_3$ receptor recognizes the arginine–glycine–aspartic acid (RGD) tripeptide sequence contained within various extracellular matrix proteins. Through this interaction endothelial cells and tumor cells are able to unite with a wide variety of extracellular matrix components such as vitronectin, fibronectin, fibrinogen, thrombospondin, osteopontin, bone sialoprotein, and denatured collagen.[1] Antagonists of $\alpha_v\beta_3$ have been demonstrated to inhibit angiogenesis, the process of new blood vessel growth from pre-existing vasculature, and thereby have potential utility in inhibiting tumor growth.[2] The $\alpha_v\beta_3$ receptor is also the prevalent integrin found on the surface of osteoclasts, which are responsible for cellular attachment and subsequent bone resorption.[3] Antagonists of $\alpha_v\beta_3$ have been shown to inhibit bone loss in animal models of osteoporosis[4] and have shown efficacy in animal models of rheumatoid arthritis.[5] In addition, $\alpha_v\beta_3$ is believed to play a significant role in several other pathophysiological conditions, including restenosis after angioplasty[6] and ocular neovascularization.[4,7] Antagonists of this integrin may prove to be beneficial in the treatment of these diverse disease states.

Peptidomimetic $\alpha_v\beta_3$ antagonists based on the RGD sequence, such as SC-68448, which demonstrated antitumor efficacy in a mouse Leydig cell tumor model[8] have been reported previously. Other $\alpha_v\beta_3$ antagonists in which the central glycine linker have been replaced with

Keywords: Integrin; Vitronectin; $\alpha_v\beta_3$; Antagonist; 1,2,4-Oxadiazole; RGD; Peptidomimetic.
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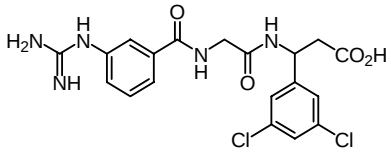
doi:10.1016/j.bmcl.2005.11.008

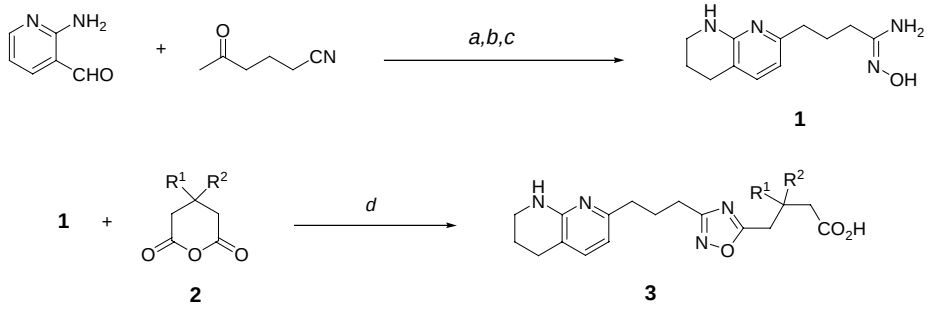
non-peptidic moieties have subsequently been reported. In addition, reduced basicity guanidine isosteres have been incorporated. These efforts have resulted in compounds with improved pharmacokinetic properties.[9]



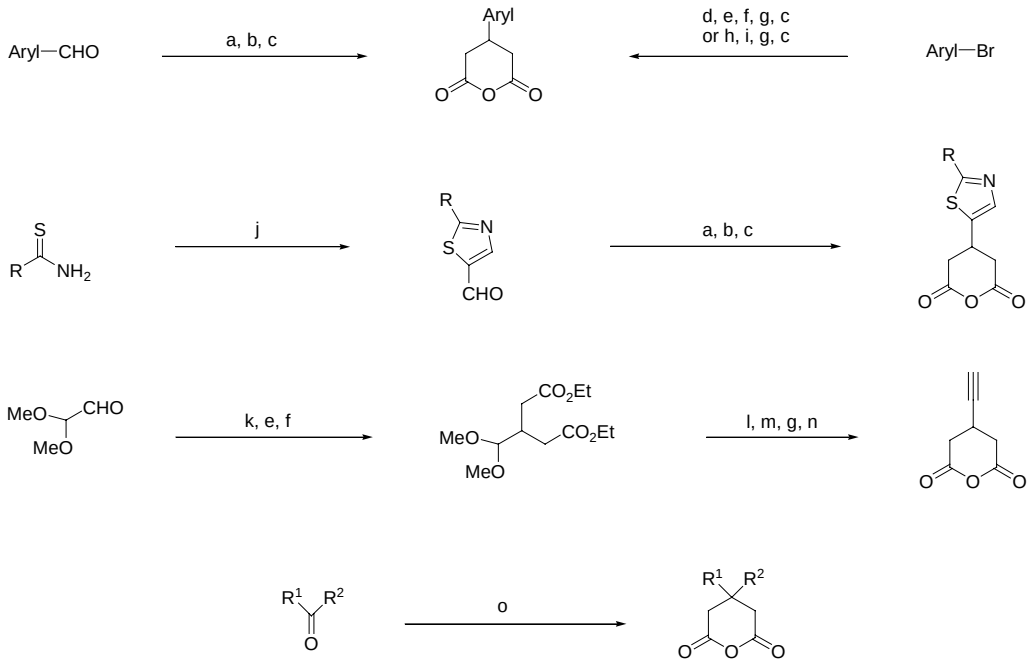
SC-68448

We now report some of our own efforts directed toward non-peptidic analogs.[10] We chose to incorporate the readily constructed 1,2,4-oxadiazole ring, a known ester/amide isostere, as a central core. The synthesis exploited the hydroxyamidine intermediate **1**.[11] The 1,8-tetrahydronaphthyridine moiety was incorporated, which was known to be an effective guanidine mimetic when applied to $\alpha_v\beta_3$ antagonists.[12] Reaction of the hydroxyamidine **1** with 3-substituted or 3,3-disubstituted glutaric anhydrides **2** allowed construction of the 1,2,4-oxadiazole ring with concomitant introduction of a substituted butanoic acid chain (Scheme 1).[13] This allowed for the rapid parallel synthesis of a series of analogs in racemic form. The limiting factor was thus the accessibility of the glutaric anhydrides. Fortunately, we were able to exploit various established methods to generate these intermediates (Scheme 2).[14]

In particular, the condensation of an aromatic aldehyde with ethyl acetoacetate mediated by piperidine and subsequent basic digestion of the resulting carbocyclic intermediate to give a 3-aryl glutaric diacid (Scheme 2) proved particularly convenient.[15] The diacids could readily be converted to the cyclic anhydrides by heating with excess acetic anhydride. Other substituted glutaric anhydrides were prepared via established procedures



Scheme 1. Reagents and conditions: (a) i—Proline, EtOH, Δ, ii—isomer separation (b) H_2/Pd; (c) NH_2OH, EtOH, Δ; (d) 1,4-dioxane, Δ.



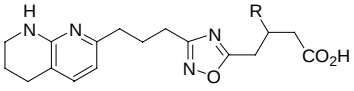
Scheme 2. Representative methods for forming 3-substituted glutaric anhydrides. Reagents and conditions: (a) ethyl acetoacetate, piperidine; (b) i—NaOH, H_2O, EtOH, Δ, ii—HCl; (c) Ac_2O, Δ; (d) ethyl acrylate, $Pd(OAc)_2$, $P(o\text{-}tol)_3$, Et_3N; (e) diethyl malonate, NaOEt, EtOH; (f) DMSO, H_2O, NaCl, Δ; (g) i—NaOH, ii—HCl; (h) $MeO_2CCHCHCH_2CO_2Me$, Pd(OAc)2, $P(o\text{-}tol)_3$, Et_3N; (i) H_2, Pd; (j) $CHCl(CHO)_2$, $MgCO_3$; (k) $EtO_2CCHPO(OEt)_2$, MeCN, DBU, LiCl; (l) AcOH, H_2O; (m) $(EtO)_2POCN_2COCH_3$, K_2CO_3, EtOH; (n) i—NaOH, ii—$(CF_3CO)_2O$, 50 °C; (o) See Ref. 14.

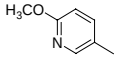
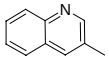
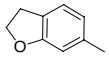
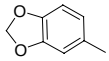
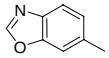
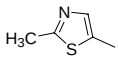
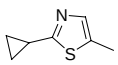
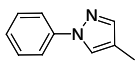
or as outlined in Scheme 2. For examples **13** and **14–28**, the single enantiomers (S) were prepared via coupling of the resolved glutaric half ester with the hydroxyamidines. The resolved half ester was obtained by chromatographic separation of the enantiomers or via an enzymatic hydrolysis of the glutaric di-ester.[10]

A series of β-substituted 1,2,4-oxadiazolyl butanoic acids were prepared (Table 1) and tested in both the $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ solid-phase receptor binding assays (SPRA).[4] Most analogs demonstrated at least 100-fold selectivity over the related platelet integrin, $\alpha_{IIb}\beta_3$. Introduction of a β-substituent imparted considerable potency with a methyl group giving an order of magnitude increase in potency over a hydrogen atom (compounds **4** and **5**). Aromatic, substituted aromatic, and heteroaromatic substituents gave the best potency (compounds **7–17**). The quinoline and benzoxazole analogs (**11**, **14**) gave sub-nanomolar activity, $\alpha_v\beta_3$ for although the selectivity versus $\alpha_{IIb}\beta_3$ was decreased for compound **11**.

A number of β,β-disubstituted analogs were also prepared. Data for a selection of these analogs are shown in Table 2. In general, the potency was reduced from the mono-substituted analogs. However, the 3-pyridyl, methyl analog **20** did retain low single digit potency for $\alpha_v\beta_3$ and was approximately 300-fold selective for $\alpha_{IIb}\beta_3$.

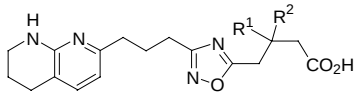
Table 1. SPRA data for β-substituted analogs



Compound	R	IC_{50} (nM)[a]	
		$\alpha_v\beta_3$ SPRA	$\alpha_{IIb}\beta_3$ SPRA
4	H	160	32,466
5	Me	12	9298
6	C≡CH	8.7	1217
7	Ph	1.8	747
8	3-Fluoro-Ph	1.75	419
9	3-Pyridyl	1.6	474
10		1.0	187
11		0.65	18
12		2.1	224
13[b]		0.4	27
14		0.50	65.4
15		1.28	423
16		1.43	168
17		1.2	216

[a] Average of at least three determinations.
[b] Single enantiomer (S).

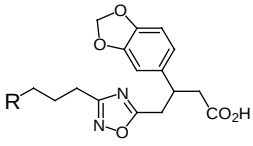
Table 2. SPRA data for β,β-di-substituted analogs

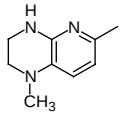
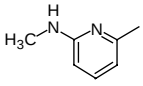
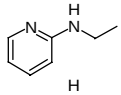
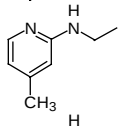
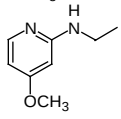
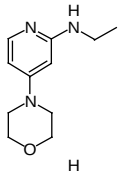
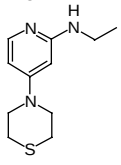


Compound	R^1	R^2	IC_{50} (nM)[a]	
			$\alpha_v\beta_3$ SPRA	$\alpha_{IIb}\beta_3$ SPRA
18	Me	Me	20	12,607
19	Ph	Me	116	35,774
20	3-Pyridyl	Me	3.6	950
21	$-(CH_2)_4-$		9.5	8130

[a] Average of at least three determinations.

Table 3. SPRA data for alternate guanidine mimetic analogs



Compound	R	IC_{50} (nM)[a]	
		$\alpha_v\beta_3$SPRA	$\alpha_{IIb}\beta_3$ SPRA
22		1.7	Not tested
23		2.1	278
24[b]		2.4	126
25[b]		2.0	91
26[b]		1.1	64
27[b]		0.78	17
28[b]		0.26	22

[a] Average of at least three determinations.
[b] Single enantiomer (S).

Table 4. Cell assay selectivity data

Compound	IC_{50} (nM)[a]			
	$\alpha_v\beta_1$ 293 cell	$\alpha_v\beta_3$ 293 cell	$\alpha_v\beta_5$ 293 cell	$\alpha_v\beta_6$ HT29 cell
6	[b]	4.0	4.0	6240
8	[b]	1.1	3.7	3730
9	[b]	0.77	3.3	2420
12	9.7	0.63	[b]	3020
13	2.6	0.65	1.7	2660
14	2.7	0.32	[b]	486
16	[b]	0.60	1.2	1590
23	[b]	3.2	16	>10,000
27	[b]	0.74	4.6	4360
28	[b]	0.62	2.9	2670

[a] Average of at least three determinations.
[b] Not tested.

The 1,8-tetrahydronaphthyridine moiety was clearly an effective guanidine mimetic for these oxadiazole based $\alpha_v\beta_3$ antagonists, which is in line with the findings of other researchers.[12] Some structural variation of this part of the molecule was investigated however to determine if further optimization were possible. A selection of guanidine mimetic variants is shown in Table 3. The β-substituent was held constant as the 3,4-methylenedioxyphenyl group.

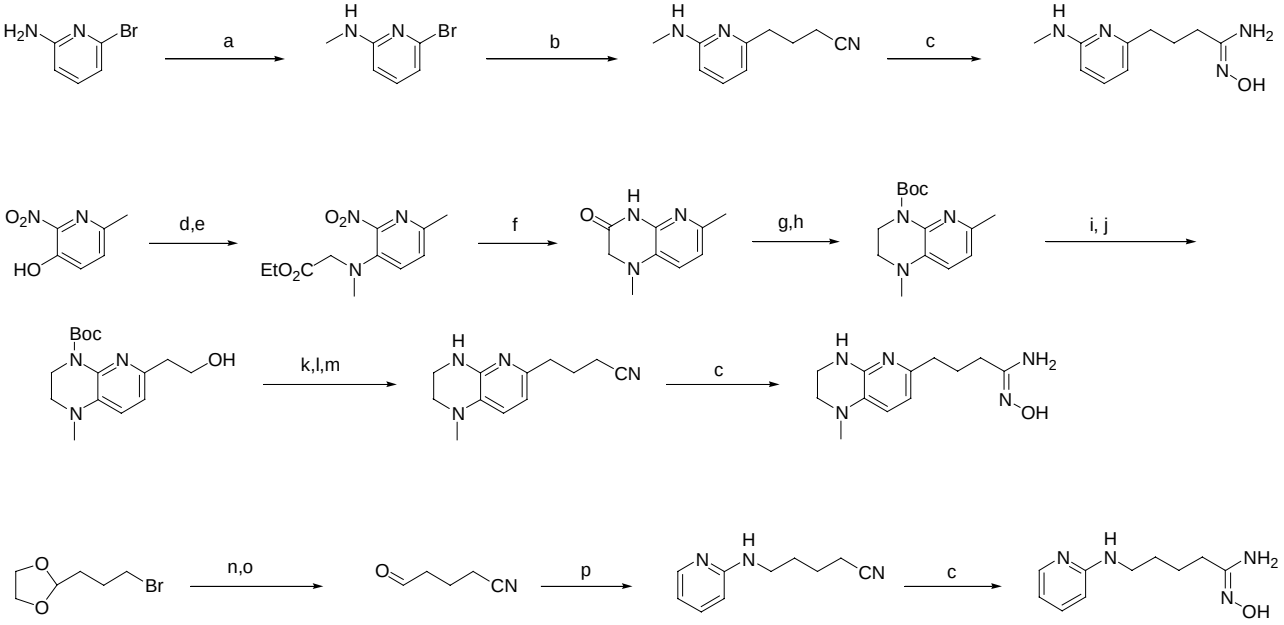
The aminopyridine **24** and reversed aminopyridine **23** were slightly less potent than the corresponding tetrahydronaphthyridine analog **13**. This may be due at least in part to increased conformational freedom. Substitution of electron-donating groups on or within the pyridine or naphthyridine nucleus tended to increase potency with the 4-thiomorpholine-substituted analog **28** being notable. We speculate that an increase in the pK_a of the guanidine surrogate was, in part, contributing to the increased potency of these analogs.

Selected analogs were also tested for binding to $\alpha_v\beta_1$-, $\alpha_v\beta_3$-, and $\alpha_v\beta_5$-expressing 293 cells[16] and $\alpha_v\beta_6$-expressing HT29 cells[10] to probe selectivity against other α_v integrins (Table 4). In general, whole cell $\alpha_v\beta_3$ potencies were similar to those obtained in the SPRA. The $\alpha_v\beta_1$ and $\alpha_v\beta_5$ potencies were slightly lower than, but mostly within an order of magnitude of $\alpha_v\beta_3$, while $\alpha_v\beta_6$ potencies were significantly less (generally 500- to 1500-fold).

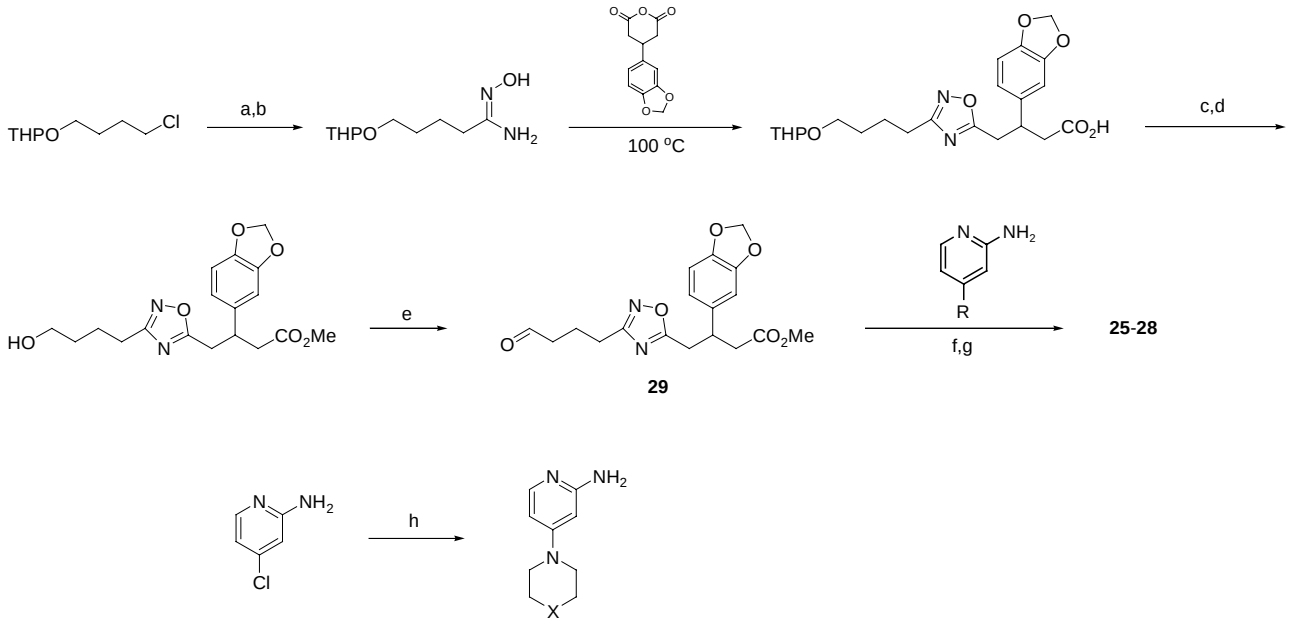
Representative synthetic protocols for analogs **22**–**28** are shown in Schemes 3 and 4 . For analogs **22**–**24**, alternate hydroxyamidines were prepared (Scheme 3) and were combined with the obligatory glutaric anhydride as in Scheme 1. For analogs **25**–**28**, a reductive amination of the aldehyde intermediate **29** with a requisite aminopyridine offered an alternate and efficient mode of synthesis (Scheme 4).

The rat pharmacokinetics (PK) of some representative examples is shown in Table 5. In general, the compounds had high bioavailability with short $t_{1/2}$ and moderate clearance. The thiomorpholine analog **28** had relatively high clearance probably due to the higher pK_a. The analog **16** containing the cyclopropylthiazole β-substituent had the highest oral exposures in this series, while retaining reasonable potency. It was considered that improved half-life in rat would probably be needed in order to translate to a suitable half-life in human for once or twice a day dosing.

In summary, we have developed a series of readily accessible 1,2,4-oxadiazole butanoic acid analogs, and by appropriate substitution at the β-position and by the



Scheme 3. Synthesis of alternate hydroxyamidines for the preparation of compounds **22**–**24**. Reagents: (a) NaH, MeI; (b) $NC(CH_2)_3ZnBr$, $Pd(PPh_3)_4$; (c) NH_2OH; (d) $(CF_3SO_2)_2O$, Et3N; (e) $MeNHCH_2CO_2Et$; (f) H_2, Pd/C; (g) $LiAlH_4$; (h) Boc_2O, Et_3N; (i) LDA, diethylcarbonate; (j) $LiBH_4$; (k) Ph_3P, imidazole, I_2; (l) ethylcyanoacetate, NaH, DMF; (m) KOH, ethylene glycol, Δ; (n) NaCN, DMF; (o) *p*-TsOH, Me_2CO, H_2O, $NaIO_4$; (p) 2-aminopyridine, $NaBH(OAc)_3$.



Scheme 4. Synthesis of compounds **25**–**28**. Reagents and conditions: (a) NaCN, NaI, DMF; (b) NH_2OH; (c) MeI, K_2CO_3; (d) *p*-TsOH, MeOH; (e) TPAP, NMO, sieves; (f) $NaBH(OAc)_3$, R=Me, OMe, morpholine, thiomorpholine; (g) LiOH; (h) morpholine or thiomorpholine (X=O, S); dimethylacetamide, 200 °C, Microwave.

Table 5. Rat PK data for select analogs

Compound	*F* (%)	$t_{1/2}$ (h)	AUC (po)/Dose (h * μg/mL/mg/kg)	Cl (mL/min/kg)	Vz (mL/kg)
10	100	1.1	1.91	12.0	694
11	66	1.1	0.60	19.1	622
12	63	1.2	0.97	17.3	803
13	95	1.4	1.50	10.9	733
16	96	1.8	3.05	5.56	497
22	77	0.93	0.71	18.2	447
28	29	0.40	0.06	78	897

Calculated from 5 mg/kg IV and 10 mg/kg po dosing.

incorporation of an appropriate guanidine mimetic have obtained a number of analogs with low to sub-nanomolar $\alpha_v\beta_3$ potency and 100-fold selectivity over $\alpha_{IIb}\beta_3$. In general, this class of molecules shows good oral bioavailability with select analogs showing promising pharmacokinetic properties. Further development of the SAR along with improvements in the in vivo characteristics of this series of heterocyclic compounds will be reported in due course.

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