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Non-Peptide $\alpha_v\beta_3$ Antagonists. Part 6: Design and Synthesis of $\alpha_v\beta_3$ Antagonists Containing a Pyridone or Pyrazinone Central Scaffold

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Abstract—Two novel series of small-molecule RGD mimetics containing either a substituted pyridone or pyrazinone central constraint were prepared. Modification of the β-alanine 3-substituent produced compounds that are potent and selective $\alpha_v\beta_3$ antagonists and exhibit a range of physicochemical properties.

Osteoporosis is a disease that affects a large proportion of the elderly population. In particular, it strikes postmenopausal women resulting in fractures which can lead to other significant health problems.[1] One approach to combatting this disease is to reduce osteoclast activity by antagonism of the integrin $\alpha_v\beta_3$.[2] This receptor is found predominantly in osteoclasts and is thought to be involved in the adhesion and migration of osteoclasts on the bone surface. $\alpha_v\beta_3$ has been shown to bind to a number of proteins including osteopontin, vitronectin and fibrinogen through the recognition of the RGD triad.[3] Small molecule mimetics of RGD have been reported as $\alpha_v\beta_3$ antagonists and have been shown to inhibit bone resorption in rats.[4,5] In this paper, we describe an extension of our work resulting in a series of potent compounds which contain a pyridone or pyrazinone as a rigid central core.

Previous reports from this laboratory have disclosed the 1,3-disubstituted pyrrolidinone **1** as a novel $\alpha_v\beta_3$ antagonist.[6,7] Common to compounds in this series is a 5,6,7,8-tetrahydro[1,8]naphthyridine (which functions as a guanidine mimic), a pyrrolidinone central constraint and a 3-aryl β-alanine. Although these compounds are potent antagonists of $\alpha_v\beta_3$, they generally suffer poor pharmacokinetics due to low oral bioavailability and high clearance. We sought to explore the structure–activity relationships of new central scaffolds with alternate β-alanines in order to modify the physical properties and, hopefully, improve the pharmacokinetic profiles.

Results and Discussion

Analogues of **1** containing different central cores were prepared and evaluated for their ability to bind to the receptor and they are described in Table 1. The binding to $\alpha_v\beta_3$ was measured by the ability of the compound to displace a non-peptide radio-ligand from Scintillation Proximity Beads coated with the human $\alpha_v\beta_3$ receptor (SPAV3 assay).[8] Parenthetically, all compounds were also tested for their ability to bind to the $\alpha_{IIB}\beta_3$ integrin

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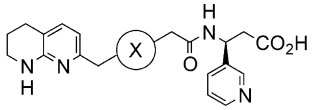
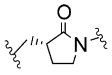
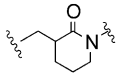
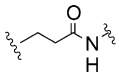
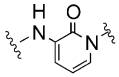
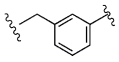
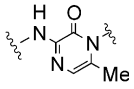
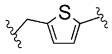
Table 1. Central constraints

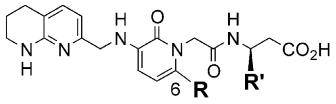


Compd	X	SPAV3 IC_{50} (nM)	Compd	X	SPAV3 IC_{50} (nM)
1		0.4	**5**		1.2
2		1.3	**6**		1.4
3		21	**7**		0.8
4		246			

using a platelet aggregation assay and all were found to have an IC_{50} of greater than 3 μM.[9] As can be seen from Table 1, compound **1** is very potent with an IC_{50} of 0.4 nM in the SPAV3 assay. Removal of the cyclic constraint to give the amide **2** leads to a modest 3-fold decrease in potency while the installation of planar aromatic groups, such as phenyl (**3**) or thiophene (**4**), was particularly detrimental. Clearly, simple aryl ring replacements of the pyrrolidinone ring are not well tolerated. Ring expansion of **1** provided the six-membered lactam **5** (racemic) with an IC_{50} of 1.2 nM.[6] We hypothesized that removal of the chiral center in **5** by utilizing a planar carbonyl-containing group would afford a potent compound. Thus, the incorporation of a pyridone to give **6** did afford a potent antagonist (IC_{50} = 1.4 nM) in contrast to the reduction in potency that was seen with compounds **3** or **4**. Moreover, the pyrazinone **7** was also shown to be very potent (IC_{50} = 0.8 nM). The carbonyl present in the ring of both **6** and **7** appears to play a major role in the binding to $\alpha_v\beta_3$. Since both the pyridone and pyrazinone containing analogues are of comparable potency to the starting pyrrolidinone **1**, but without the additional chiral center, they were selected for further SAR studies.

In the pyridone series, compounds were prepared to examine the potency effects of C-6 substituents in conjunction with a variety of β-alanine substituents.[7,10] The compounds synthesized are detailed in Table 2. Comparisons of compounds containing a 3-pyridyl-β-alanine show that small alkyl substituents are tolerated in the C-6 position of the pyridone. The methyl (**8**) and propyl (**10**) groups are equipotent to the unsubstituted compound **6**. Interestingly, compound **9** containing a cyclopropyl substituent shows a 7-fold boost in potency when compared to **6** (IC_{50}s of 0.2 and 1.4 nM, respectively, in the SPAV3 assay). It is noteworthy that these analogues are all very polar as shown by their negative measured log*P* values. In an attempt to enhance oral absorption for these very polar and

Table 2. Pyridones

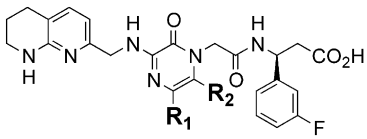


Compd	R	R′	SPAV3 IC_{50} (nM)	LogP
6	H		1.4	−1.55
8	Me		1.0	−1.46
9	c-Pr		0.2	−0.8
10	Pr		1.4	−0.48
11	c-Pr		9	−0.97
12	c-Pr		0.2	0.28
13	c-Pr		0.8	0.54

zwitterionic compounds, lipophilic β-alanine substituents were evaluated in the 6-cyclopropyl-pyridone series. The acetylene analogue **11** was considerably less potent (IC_{50} = 9 nM) and still very polar. The addition of larger, more lipophilic groups was successful in raising the logP value above zero. Thus, the dihydrobenzofuran **12** and the 3-fluorophenyl analogue **13** are both potent $\alpha_v\beta_3$ antagonists with log*P* values of 0.28 and 0.54 compared to −1.55 for **6**.

The SAR of the pyrazinone-based antagonists was explored using a 3-fluorophenyl-β-alanine (Table 3). As with the pyridone series, small alkyl substituents such as methyl (**14**), ethyl (**16**) and cyclopropyl (**18**) are well tolerated however, the large phenyl substituent of **20** results in a significant loss (100-fold) in potency.

Table 3. Pyrazinones

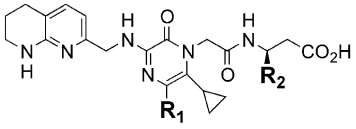


Compd	R1	R2	SPAV3 IC_{50} (nM)	LogP
14	H	Me	1.1	−0.31
15	Cl	Me	2.1	0.61
16	H	Et	1.9	−0.47
17	Cl	Et	9.3	1.3
18	H	cPr	1.4	0.15
19	Cl	cPr	2.7	1.1
20	Cl	Ph	112	1.6

The addition of a chloro substituent at C-5 has only a modest 2- to 4-fold negative effect on $\alpha_v\beta_3$ binding affinity but was found to raise the log*P* by a full log unit (compare **14** to **15**, **16** to **17** and **18** to **19**). Different 3-substituted β-alanines were incorporated into the 6-cyclopropyl-pyrazinone series (see Table 4). These were made with and without a 5-chloro substituent to obtain compounds with high intrinsic $\alpha_v\beta_3$ binding potency and a range of polarity. The 3-pyridyl substitution on the β-alanine produced potent compounds (**21**, $IC_{50} = 0.2$ nM and **22**, $IC_{50} = 0.3$ nM) with low log*P* values. The 6-benzodioxazolyl derivative **23** had a similar potency and polarity to the pyridine analogues. However, the non-polar β-alanines such as 3-fluorophenyl (**19**), 3-quinolinyl (**24**) and 6-dihydrobenzofuranyl (**25**) in conjunction with a 5-chloro substituent afforded lipophilic antagonists with log*P* values ranging from 0.9 to 1.12.

Compounds representing a range of lipophilicities were selected for protein binding determinations using human plasma and for PK evaluation in the dog. The compounds chosen are given in Table 5 and they are arranged in order of increasing lipophilicity with the starting pyrrolidinone **1** given for reference. As can be seen from Table 5, increases in protein binding for both the pyridone and pyrazinone series mirror increases in log*P*. These protein binding values are higher than the value for the pyrrolidinone **1**. Unfortunately, all of the compounds tested exhibited half-lives of approximately 1 h with moderate to high clearance values. The oral bioavailability values were low, and in some cases (e.g., **8** and **14**) the plasma levels following oral dosing were undetectable.

Table 4.



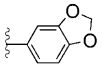
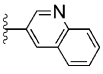
Compd	R1	R2	SPAV3 IC_{50} (nM)	LogP
18	H		1.4	0.15
19	Cl		2.7	1.1
21	H		0.2	−0.25
22	Cl		0.3	−0.26
23	H		0.2	−0.1
24	Cl		0.7	1.12
25	Cl		0.2	0.9

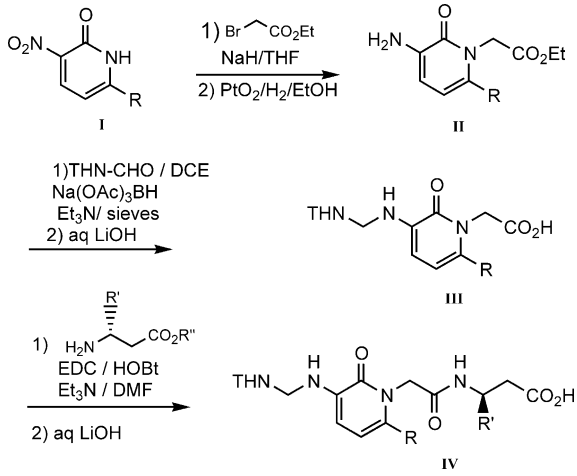
Table 5. Physical properties and in vivo parameters

Compd	LogP	%PB	Dog PK[a]		
			$t_{1/2}$	Cl (mg/mL/kg)	%F
1	−0.61	55.4	1.0	42	—
8	−1.46	91.2	0.8	21	—
16	−0.47	97.2	1.4	22	4.3
23	−0.11	97.5	1.1	26	0.3
18	0.15	97.5	1.0	18	1.5
13	0.54	99.4	0.8	20	3
15	0.61	98.5	2.1	28	—

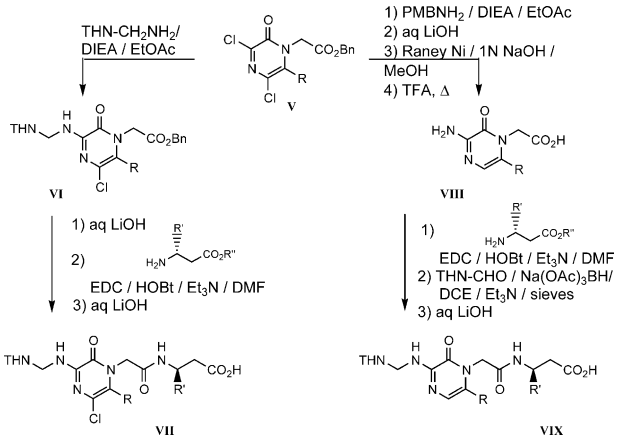
[a]Dosed at 0.2 mpk iv and 1 mpk po in water.

Chemistry

Compounds illustrated in Table 1 were prepared as previously described.[6,11] Pyridone containing analogues were prepared as shown in Scheme 1 commencing with the appropriate 6-alkyl-3-nitro-2-(1H)-pyridone **I**.[12] *N*-Alkylation was achieved by heating **I** at 55 °C for 15 h with NaH and ethylbromoacetate. The nitro group was reduced to give **II** using PtO_2 and H_2 in ethanol. This amine was subjected to reductive amination with 5,6,7,8-tetrahydro[1,8]naphthyridine-2-aldehyde (THN-CHO) followed by a basic hydrolysis to yield **III**.[11] EDC coupling with the appropriate β-alanine ester was then followed by a second hydrolysis to give the final compound **IV**. Scheme 2 describes the synthesis of the



Scheme 1.



Scheme 2.

5-chloropyrazinone and the pyrazinone containing antagonists both of which start with a common intermediate **V**.[13] The chlorine at position 3 of **V** can be displaced readily by amines. Thus chloropyrazinones were produced by displacement with $THNCH_2NH_2$ to give **VI**. After saponification, an EDC coupling with the desired β-alanine ester followed by a second hydrolysis gave the desired acid **VII**. The synthesis of compounds in the pyrazinone series began with a similar displacement with *p*-methoxy benzylamine and then hydrolysis of the ester. Treatment with Raney–Ni in equal parts methanol and 1 N NaOH removed the chlorine in the 5-position and then the PMB group was removed with TFA. Standard methodology (as described above) was used to convert **VIII** into the target compounds **IX**.

In conclusion, we have been successful in finding new scaffolds to use as central constraints to the replace pyrrolidinone present in our initial series of small-molecule $\alpha_v\beta_3$ integrin antagonists. 1,3-Disubstituted pyridones and pyrazinones containing small alkyl substituents at the 6-position were found to be equipotent to the pyrrolidinone **1**. All the compounds prepared were selective when tested against the related platelet receptor $\alpha_{IIB}\beta_3$. Combination of different 3-substituted β-alanines and ring substituents on the central scaffold were found to give highly potent compounds with a range of physical properties. However, as with compound **1** from the pyrrolidinone series, these antagonists suffer from low $t_{1/2}$, moderate to high clearance and low oral bioavailability in dog.

Acknowledgements

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