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Synthesis and SAR of *N*-Substituted Dibenzazepinone Derivatives as Novel Potent and Selective $\alpha_V\beta_3$ Antagonists

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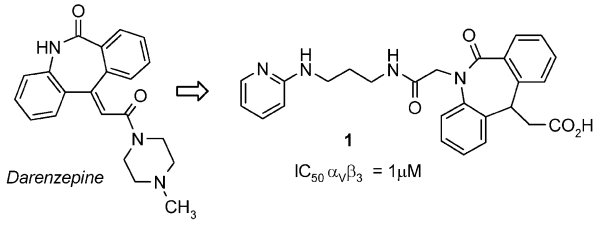
Abstract—Synthesis and SARs of new integrin $\alpha_V\beta_3$ antagonists based on an *N*-substituted dibenzazepinone scaffold are described. Variation of spacer and guanidine mimetic led to potent compounds exhibiting an IC_{50} towards $\alpha_V\beta_3$ in the nanomolar range, high selectivity versus integrin $\alpha_{IIb}\beta_3$ and efficacy in functional cellular assays.

Integrins are a widely expressed family of heterodimeric transmembrane receptors mediating cell–cell and cell–matrix adhesion, migration and signaling. They are formed by various combinations of the currently known 17 α- and nine β-subunits which determine affinity and specificity towards different extracellular adhesive matrix proteins like fibrinogen, fibronectin, vitronectin, osteopontin and laminin.[1] Pharmacological modulation of integrin mediated processes in general is of considerable interest,[2] and especially the platelet fibrinogen receptor $\alpha_{IIb}\beta_3$ has attracted much interest in the search for new antithrombotic agents.[3]

More recently, the integrin $\alpha_V\beta_3$, the so-called vitronectin receptor, has received increasing attention. $\alpha_V\beta_3$ is expressed on proliferative endothelial cells and smooth muscle cells, on macrophages, on activated platelets and on metastatic tumor cells, and was shown to be involved in bone resorption by osteoclasts, migration of activated endothelial and vascular smooth muscle cells, angiogenesis and tumor progression.[4–6] Monoclonal anti-integrin $\alpha_V\beta_3$ antibodies, peptidic and non-peptidic antagonists already have shown beneficial effects in vitro and in vivo.[7–9] Therefore it is expected that selective $\alpha_V\beta_3$ antagonists offer new therapeutic opportunities for the treatment of several human pathologies like osteoporosis,[10] restenosis after percutaneous transluminal coronary angioplasty (PTCA)[11] and diseases involving neovascularization such as rheumatoid arthritis,[12] tumor-induced angiogenesis[13] and metastasis.[14]

Like many integrins $\alpha_V\beta_3$ recognizes the tripeptide sequence RGD as common binding motif in its target proteins.[15] In early studies Kessler et al. disclosed cyclic RGD peptides as selective $\alpha_V\beta_3$ antagonists,[16] and deduced a general model for inhibitors suggesting a fixed alignment of a basic as well as an acidic group (distance between 650 and 700 pm) separated by a spacer unit. In the meantime several groups have reported non-peptidic $\alpha_V\beta_3$ inhibitors employing various scaffolds.[17,18]

Herein we describe the synthesis of new $\alpha_V\beta_3$ inhibitors based on an *N*-substituted dibenzazepinone core. We also present the structure–activity relationship (SAR) for this class of compounds derived from modification of the spacer between core and guanidine part and variation of the guanidine pharmacophore. Selected examples were examined for functional efficacy in cellular assays, metabolic stability and resorption in the Caco-2 model.



Scheme 1. Design of dibenzazepinone based $\alpha_V\beta_3$ antagonists.

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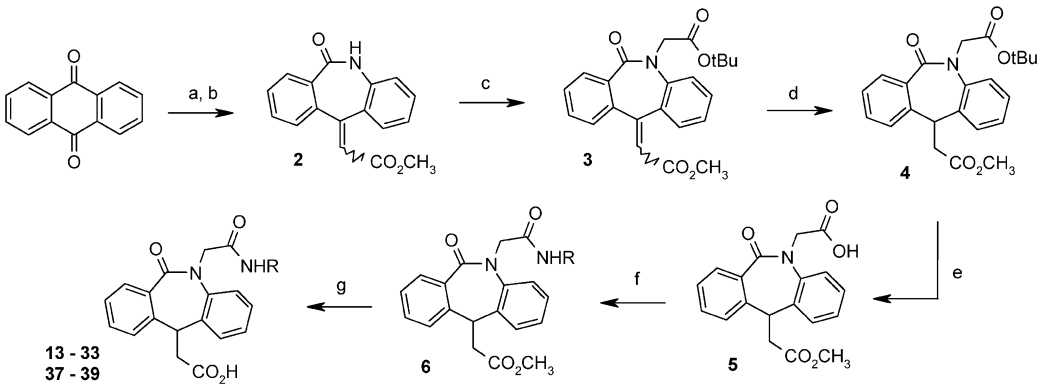
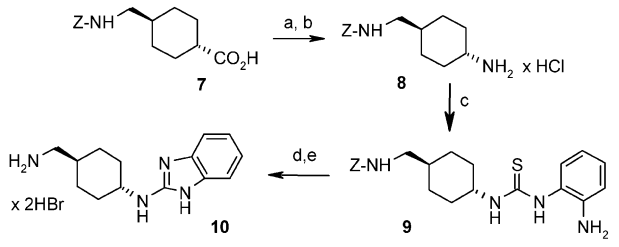
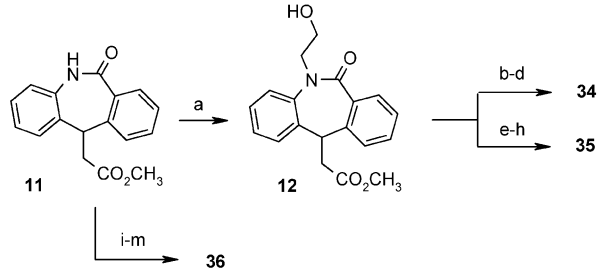
PII: S0960-894X(01)00773-9



Scheme 2. Reagents and conditions: (a) NaN_3, H_2SO_4 (85%); (b) methyl diethylphosphonoacetate, NaH, DMF (70%); (c) NaH, $BrCH_2CO_2tBu$, DMF/60 °C (83%); (d) H_2, Pd/C; CH_3OH/120 bar, 50 °C; (e) TFA, CH_2Cl_2 (56% from **3**); (f) R-NH_2, EDC or HATU, DIPEA, CH_2Cl_2, DMF/0 °C–rt; (g) LiOH, dioxane/H_2O 4:1.



Scheme 3. Reagents and conditions: (a) DPPA, Et_3N, Li*O*t*Bu*, toluene (65%); (b) HCl/dioxane (60%); (c) thiocarbonyldiimidazole, imidazole, 1,2-phenylenediamine, CH_3CN (85%); (d) HgO (yellow), cat. S, EtOH; (e) HBr, HOAc (90% from **9**).



Scheme 4. Reagents and conditions: (a) ethylene oxide, LDA, THF (40%); (b) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2 (55%); (c) *N*-[4-(aminomethyl)phenyl]-*N*′-benzylurea,[26] cat. HCl, $NaBH_3CN$, CH_3OH (20%); (d) NaOH, CH_3OH/H_2O/80 °C (79%); (e) 4-(4-nitrophenyl)butyl methanesulfonate, NaH, DMF/75 °C (40%); (f) H_2, Pd/C, EtOH/EtOAc (92%); (g) benzylisocyanate, Et_3N, DMF (6%); (h) KOH, CH_3OH (90%); (i) 4-nitrobenzyl bromide, NaH, DMF; (k) H_2, Pd/C, CH_3OH; (l) benzylisocyanate, Et_3N, DMF; (m) KOH, CH_3OH (6% from **11**).

Based on published data we established a pharmacophore model as 3D-template for the assessment of novel $\alpha_V\beta_3$ antagonists which was used to design and apply various new scaffolds in the synthesis of $\alpha_V\beta_3$ antagonists. Comparison of $\alpha_V\beta_3$ antagonists comprising a tricyclic core[19] and Darenzepine, a compound which had been in development at Knoll/BASF Pharma,[20] prompted us to examine the dibenzazepinone moiety as a new scaffold for integrin antagonists. Compound **1** was prepared as first example of this series, and its affinity in the μM range (Scheme 1) encouraged us to investigate this type of structure further.

Scheme 2 highlights the general synthesis of dibenzazepinone based derivatives. Starting from anthraquinone, Schmidt rearrangement and Wittig–Horner olefination gave methyl (6-oxo-5,6-dihydro-11*H*-dibenzo-[*b*,*e*]azepin-11-ylidene)-acetate **2**. Subsequent *N*-alkylation, hydrogenation and cleavage of the *t*-butyl ester yielded **5** as central intermediate, which was converted into the final products by coupling with various building blocks comprising the desired guanidine mimetics and subsequent saponification.[21]

The building blocks carrying the guanidine pharmacophores applied in the synthesis were prepared according to methods already described in the literature.[22] Scheme 3 depicts the preparation of *N*-[4-(aminomethyl)cyclohexyl]-1*H*-benzimidazol-2-amine as an example. Starting from Z-protected *trans*-aminomethylcyclohexanecarboxylic acid **7**,[23] introduction of the amino group via Curtius degradation and cleavage of Boc led to compound **8** in high yield. Conversion into the aminobenzimidazole[24] and deprotection using HBr in acetic acid afforded compound **10**.

Derivatives with modified acetamide linker were prepared as outlined in Scheme 4. Alkylation of **11** using 4-(4-nitrophenyl)butyl methanesulfonate[25] and introduction of the benzyl urea after hydrogenation of the nitro group afforded alkyl analogue **36** (Table 4). Reaction of **11** with ethyleneoxide gave alcohol **12**, which was converted into the corresponding amino and ether derivatives **34** and **35** as described (Scheme 4).

The *N*-substituted dibenzazepinone derivatives described in this communication feature a stereogenic center, and in addition inversion of the bis-annelated azepinone was found to be hindered.[27] Therefore compounds **1** and **13**–**39** were obtained as diastereomeric mixtures. In the case of compounds **28** and **32** separation of diastereomers was performed via column chromatography; however, interconversion was observed within 24–48 h at room temperature which prevented us from studying the isomers separately. The screening results presented in this paper therefore refer to the corresponding mixtures of diastereomers.

Compounds **13**–**39** were evaluated regarding $\alpha_V\beta_3$ affinity via competitive ELISA using vitronectin as natural ligand.[21] Compounds displaying IC_{50} values >10 μM were considered as 'not active'.

Table 1 displays SAR data on the influence of both spacer structure and length and benzimidazole as guanidine mimetic. The corresponding benzyl derivative **15** displayed the highest affinity within the benzimidazole series. Elongation to phenethyl (**16**) or replacement by pyridylmethyl (**17**) resulted in a 3- to 5-fold reduction in potency. Incorporation of phenyl (**14**) or *meta*-substituted benzyl (**18**) led to a dramatic decrease in activity which we consider as a result of alteration in spacer orientation leading to an unfavorable alignment of acidic and basic groups. Replacement of benzyl by thienyl resulted in retention of activity for the 2,4-substituted thienyl derivative (**19**) and a 5-fold decrease for the 2,5-thienyl analogue (**20**), whereas introduction of the 2,4-substituted thiazole (**21**) led to about 10-fold decrease in potency.

Based on these results we started to investigate SAR of the guanidine pharmacophore employing either the 2,4-thienyl or the benzyl residue as spacer (Tables 2 and 3).

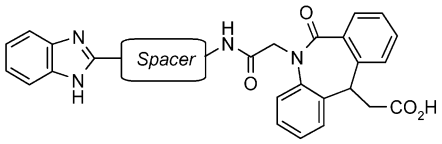
Table 2 presents the results obtained in the thienyl series. Only the pyridylaminomethyl derivative **23** showed an activity comparable to benzimidazole **19**, whereas the aza-benzimidazole analogue **22** and the amidine **24** exhibited 5- and 10-fold reduction in activity, respectively.

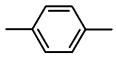
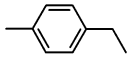
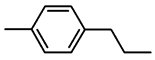
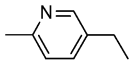
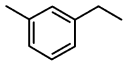
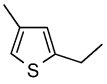
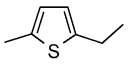
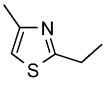
Table 3 summarizes the results obtained employing the benzyl spacer in combination with different guanidine mimetics. Introduction of additional substituents into the benzimidazole moiety of **19** led to a decrease in potency (**25**, **26**), whereas the use of guanidine itself as pharmacophore (**27**) showed retained activity. In line with recent studies[28] we found about 4-fold enhanced potency upon incorporation of benzyl urea as non-basic guanidine mimetic (**28**). Exchange of nitrogen in compounds **29**–**31** resulted in a dramatic loss of potency and proved both nitrogens to be essential in the urea part. Highest activity in this series was found using 2-aminobenzimidazole as guanidine mimetic; compound **32** displayed an IC_{50} of 7.3 nM. To our surprise, the corresponding 2-aminopyridine **33** showed a dramatic reduction in activity, which is in contrast to our experiences in using this guanidine mimetic in another series of $\alpha_V\beta_3$ antagonists.[29]

Table 4 presents the SAR with regard to the acetamide spacer in compound **28**. Compounds **34**–**36** showed a dramatic loss in potency; similar results were obtained by elongation to the analogous propionyl amide (data not shown). These findings clearly demonstrate an absolute requirement for the acetamide linkage in this part of the structure.

In view of the results obtained we aimed at further optimization using the aminobenzimidazole as guanidine pharmacophore (Table 5). Replacement of the benzyl residue by linear C4- and C5-alkyl (**37**, **38**) led to

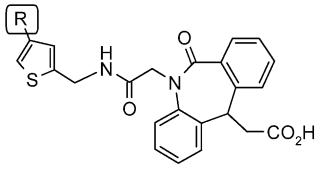
Table 1. Effect of spacer variation within the benzimidazole series

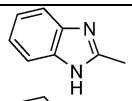
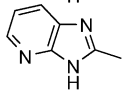
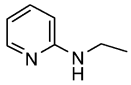


Compd	Spacer	$\alpha_V\beta_3$ ELISA IC_{50}, μM[a]
13		1.0
14		5.0
15		**0.074**
16		0.38
17		0.2
18		10
19		0.1
20		0.5
21		1.0

[a]Values are means of three experiments; intra-assay variation $<10\%$, inter-assay variation $<$ factor 2.

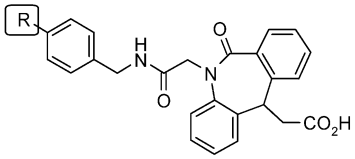
Table 2. 2,4-Disubstituted thienyl analogues

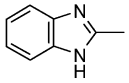
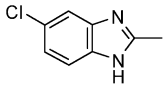
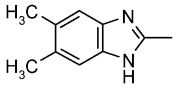
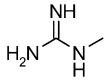
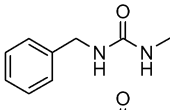
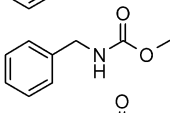
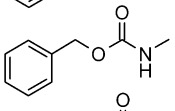
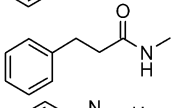
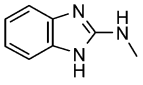
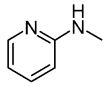


Compd	R	$\alpha_V\beta_3$ ELISA IC_{50}, μM[a]
19		0.1
22		0.5
23		**0.22**
24		1.0

[a]Values are means of three experiments; intra-assay variation $<10\%$, inter-assay variation $<$ factor 2.

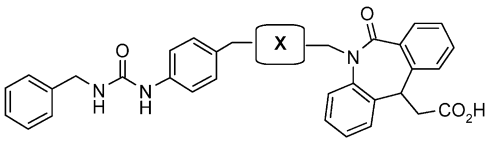
Table 3. Influence of the guanidine pharmacophore



Compd	R	$\alpha_V\beta_3$ ELISA IC_{50}, μM[a]
15		0.074
25		0.62
26		0.22
27		0.084
28		0.023
29		10
30		10
31		na
32		**0.007**
33		5.0

[a]Values are means of three experiments; intra-assay variation < 10%, inter-assay variation < factor 2.
na, not active.

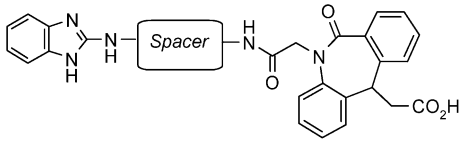
Table 4. Acetamide modification

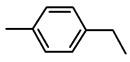
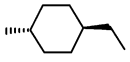


Compd	Spacer	$\alpha_V\beta_3$ ELISA IC_{50}, μM[a]
28		0.023
34		na
35		na
36		10

[a]Values are means of three experiments; intra-assay variation < 10%, inter-assay variation < factor 2 (na = not active).

Table 5. Spacer modification within aminobenzimidazole series



Compd	Spacer	$\alpha_V\beta_3$ ELISA IC_{50}, nM[a]
32		7.3
37	-$(CH_2)_4$-	14.9
38	-$(CH_2)_5$-	12.9
39		**1.6**

[a]Values are means of three experiments; intra-assay variation < 10%, inter-assay variation < factor 2.

a 1.5- and 2-fold reductions of activity, respectively. Compound **39** showed an IC_{50} of 1.6 nM and thus represents the most potent derivative within the whole dibenzazepinone series obtained so far.

Specificity versus $\alpha_{IIb}\beta_3$ was examined routinely for compounds displaying an IC_{50} $\alpha_V\beta_3$ < 100 nM. All compounds discussed in this paper showed at least 1000-fold selectivity.

Compounds **32** and **39**, which had been identified as most potent representatives from this series, were submitted to further characterization with respect to specificity versus other integrins, potency in functional cellular assays and early ADME (Table 6). Both derivatives exhibited high selectivity versus integrin $\alpha_5\beta_1$ and $\alpha_4\beta_1$, and medium to high efficacy in inhibition of recombinant $\alpha_V\beta_3$ transfected CHO-K1 cell adhesion and primary human smooth muscle cell migration. The observation that in vitro potencies were not fully reflected in cellular adhesion assays has already been reported for other $\alpha_V\beta_3$ antagonists.[31] Both **32** and **39** displayed good absorption in the Caco-2 model[32] and satisfactory metabolic stability versus human liver microsomes. Pharmacokinetic studies will show whether these compounds are suitable for efficacy testing in in vivo models.

In summary, we have shown that the *N*-substituted dibenzazepinone scaffold can be successfully employed in the synthesis of new integrin $\alpha_V\beta_3$ antagonists. SARs involving spacer and guanidine pharmacophore were

Table 6. Profile of compounds **32** and **39**

Compd	$\alpha_V\beta_3$/VN ELISA[a] IC_{50}, nM	$\alpha_{IIb}\beta_3$ /Fg ELISA[a] IC_{50}, nM	$\alpha_5\beta_1$/FN[b] inh. @ 10^{-5} M	$\alpha_4\beta_1$/FN[b] inh. @ 10^{-5} M	$\alpha_V\beta_3$/OPN adhesion[b] IC_{50}, nM	SMC migration[b] inh. @ 10^{-5} M (%)	Caco-2 permeation assay P_{app}[c], cm/s$\times10^{-6}$
32	7.3	>100,000	na	na	100	67	1.6
39	1.6	>100,000	na	na	40	100	2.7

[a]Values are means of three experiments; intra-assay variation < 10%, inter-assay variation < factor 2.
[b]Cell adhesion and migration: values are means of four experiments; intra-assay variation < 20%, inter-assay variation < factor 2.
[c]P_{app} = apparent permeability coefficient,[30] $n=2$, intra-assay variation < 20%. na, not active; VN, vitronectin; FN, fibronectin; Fg, fibrinogen; OPN, osteopontin.

established and led to novel potent and highly selective inhibitors. Characterization of selected analogues in secondary screening showed good efficacy in cellular systems and promising profile in early ADME.

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