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Design and Synthesis of 1,5- and 2,5-Substituted Tetrahydrobenzazepinones as Novel Potent and Selective Integrin $\alpha_V\beta_3$ Antagonists

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Abstract—The design and synthesis of novel integrin $\alpha_V\beta_3$ antagonists based on a 1,5- or 2,5-substituted tetrahydrobenzaezpinone core is described. In vitro activity of respective compounds was determined via $\alpha_V\beta_3$ binding assay, and selected derivatives were submitted to further characterization in functional cellular assays. SAR was obtained by modification of the benzazepinone core, variation of the spacer linking guanidine moiety and core, and modification of the guanidine mimetic. These efforts led to the identification of novel $\alpha_V\beta_3$ inhibitors displaying potency in the subnanomolar range, selectivity versus $\alpha_{IIb}\beta_3$ and functional efficacy in relevant cellular assays. A method for the preparation of enantiomerically pure derivatives was developed, and respective enantiomers evaluated in vitro. Compounds **31** and **37** were assessed for metabolic stability, resorption in the Caco-2 assay and pharmacokinetics.
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Introduction

The integrin $\alpha_V\beta_3$, the so-called vitronectin receptor, is a member of the integrin superfamily of cell adhesion receptors.[1] $\alpha_V\beta_3$ is a 160/85 kDa non-covalently associated heterodimer mediating cell adhesion to various extracellular matrix and serum proteins (e.g., vitronectin, fibrinogen, fibronectin, von Willebrand factor, osteopontin, and thrombospondin) via the RGD motif[2] as well as the interaction with various non-RGD containing ligands like PECAM-1,[3] Cyr61,[4] MMP-2,[5] and ADAM23.[6] $\alpha_V\beta_3$ is expressed on proliferative endothelial and smooth muscle cells, on macrophages, on activated platelets and on metastatic tumour 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.[7–9] Overexpression of $\alpha_V\beta_3$ has been observed in different processes like angiogenesis and neovascularization,[10] occurring in diseases such as rheumatoid arthritis,[11] diabetic retinopathy and age-related macular degeneration,[12] tumor growth and metastasis,[13] osteoporosis,[14] acute renal failure,[15] and restenosis after PTCA (percutaneous transluminal coronary angioplasty).[16] Monoclonal $\alpha_V\beta_3$ antibodies, peptidic and non-peptidic antagonists have shown beneficial effects in vitro and in vivo.[17–20] Therefore pharmacological modulation of integrin $\alpha_V\beta_3$ mediated processes is expected to have a therapeutic benefit in these indications. Clinical studies using $\alpha_V\beta3$ antagonists already have been initiated. Cilengitide (EMD 121974, Merck KGaA), a peptide-based $\alpha_V\beta_3$ inhibitor, has shown promising results in

Abbreviations: DIEA, diisopropylethylamine; EDC, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide; Et_3N, triethylamine; EtOAc, EtOAc; HOAc, acetic acid; HATU, *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; MTBE, *tert*-butyl methylether; NMM, *N*-methylmorpholine; PPA, *n*-propylphosphonic acid cyclic anhydride; sat., saturated; TFA, trifluoroacetic acid, TOTU, *O*-[(cyano-ethoxycarbonylmethylene)-amino]-*N*,*N*,*N*′,*N*′-tetramethyluronium tetrafluoroborate.

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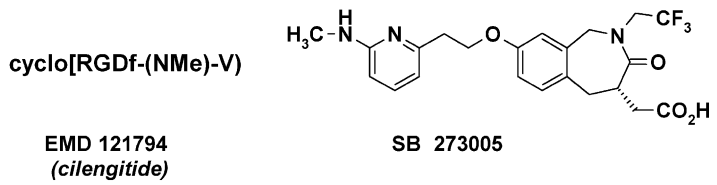


Chart 1. $\alpha_V\beta_3$ Antagonists in clinical development.

phase I/II clinical trials for anti-tumor therapy, whereas SB 273005 (GSK), an orally active non-peptide inhibitor, is in development for the potential treatment of rheumatoid arthritis and osteoporosis (Chart 1).[21,22] During the last years several non-peptide RGD derived $\alpha_V\beta_3$ antagonists have been described, however, most compounds reported suffer from poor pharmacokinetics and limited oral availability.[23–25]

Our interest in this area was prompted by the finding that $\alpha_V\beta_3$ mediated migration of activated smooth muscle cells into the neointima plays a key role in the development of restenosis after PTCA. This process was found to be alleviated or blocked by the application of respective antagonists.[26]

Recently we reported the discovery of *N*-substituted dibenzazepinone derivatives as new $\alpha_V\beta_3$ antagonists.[27] Although displaying high potencies in vitro and in functional assays, the compounds featured some unfavourable properties preventing further development. 1,5-Disubstituted dibenzazepinones comprise a stereogenic center, and inversion of the bis-annelated azepinone part is hindered. Thus dibenzazepinones like **1** were obtained as mixture of diastereomers. In addition most derivatives showed poor solubility in aqueous solutions which exacerbated further screening. Following up these initial studies, our objective was the identification of simplified analogues with improved properties. We figured that the analogous tetrahydrobenzazepinones should exhibit facilitated ring inversion, thereby avoiding the problem of diastereomerism (Fig. 1). Furthermore, omitting a benzene ring should result in a significant reduction in lipophilicity and molecular weight.

Herein we describe the synthesis of 1,5-substituted 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-2-ones and 2,5-substituted 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-1-ones (subsequently referred to as 1,5- and 2,5-benzazepinones, respectively) as novel and potent $\alpha_v\beta_3$ antagonists. We will also present the structure activity relationships (SAR) for this class and similar derivatives obtained by variation of the guanidine pharmacophore, scaffold modification and variation of the spacer linking core and guanidine part. A method for the preparation of enantiomerically pure 1,5-benzazepinones was elaborated and applied in the synthesis of key representatives. Assignment of the absolute configuration was achieved via X-ray structure analysis. Selected examples were examined for functional efficacy in cellular assays, metabolic stability, resorption, and pharmacokinetic behaviour.

Chemistry

Scheme 1 outlines the general synthesis of 1,5- and 2,5-substituted benzazepinones **31**–**47**. Starting from an anthranilic acid ester reaction with ethyl 4-chloro-4-oxobutanoate followed by Dieckmann condensation and decarboxylation led to the corresponding substituted 3,4-dihydro-1*H*-1-benzo[*b*]azepine-2,5-diones **3a**–**d** in good to high yields.[28] Subsequent Wittig–Horner

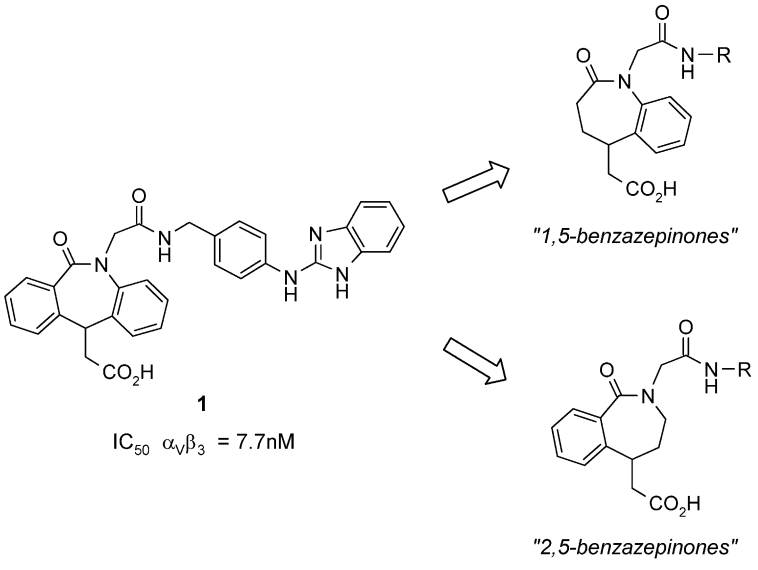
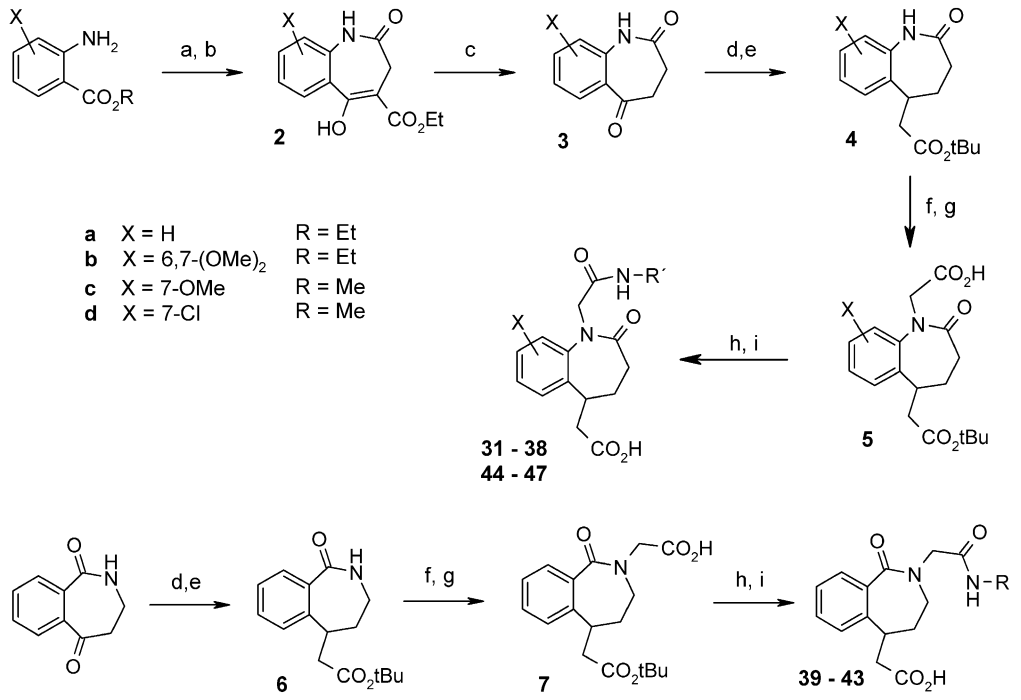


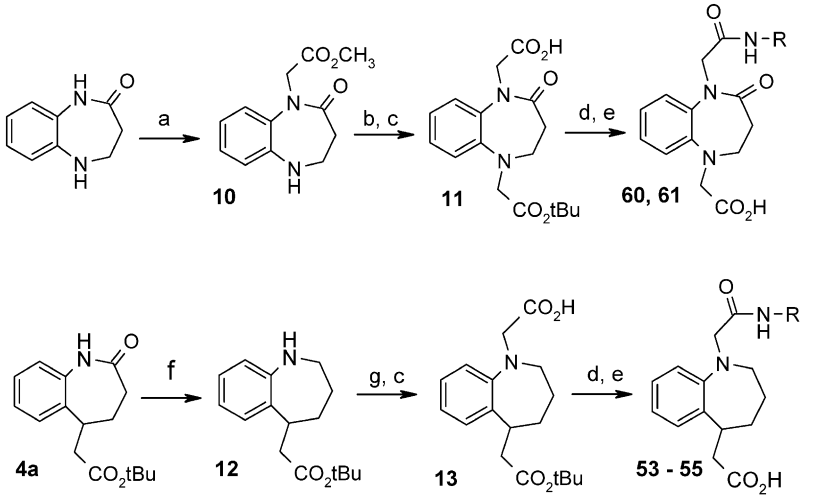
Figure 1. Design of benzazepinone-based $\alpha_V\beta_3$ inhibitors.



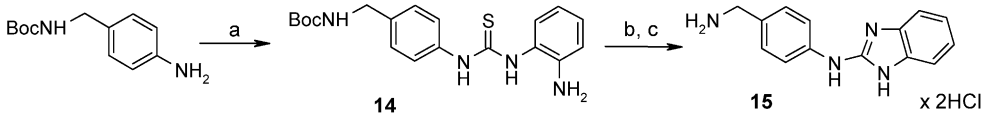
Scheme 1. Reagents: (a) ethyl 4-chloro-4-oxobutanoate, pyridine, THF; (b) NaH, DMSO, THF; (c) H_2O, DMSO, 150 °C; (d) *tert*-butyl (diethoxyphosphoryl)acetate, NaH, DMF, 0 °C–rt; (e) H_2, Pd–C (or Pt–C), EtOH; (f) methyl bromoacetate, NaH, DMF; (g) NaOH, dioxane, H_2O; (h) R′NH_2, TOTU, NMM, DMF, 0 °C–rt (or: HATU, DIEA, DMF/CH_2Cl_2, 0 °C–rt); (i) HCl, dioxane (or: TFA, CH_2Cl_2).

olefination, hydrogenation, *N*-alkylation and cleavage of the methyl ester yielded compounds **5a–d** as central intermediates. Although in case of the 7-chloro-substituted analogue **4d** hydrogenation was carried out in the presence of 5% Pt–C to suppress dechlorination, a mixture of target compound and respective dechlorinated product was obtained, and separation was performed on the last step of the synthesis. Conversion into the final products **31–38** and **44–47** was achieved by condensation of acids **5a–d** with various building blocks applying either TOTU[29] or HATU[30] as coupling reagents and subsequent saponification. 2,5-Substituted benzazepinones **39–43** and thienyl derivative **56** were prepared analogously starting either from 3,4-dihydro-2*H*-benzo[*c*]azepin-1,5-dione or 6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-dione.[31] Synthesis of analogous 2,5-tetrahydrobenzodiazepinones **60** and **61** follows standard methods using 1,3,4,5-tetrahydro-benzo[*b*][1,4]diazepine-2-one[32] as starting material (Scheme 2). 1,5-Tetrahydrobenzazepines **53–55** were prepared by diborane reduction of **4a**, alkylation and subsequent saponification.

Scheme 3 depicts exemplarily the synthesis of *N*-[4-(aminomethyl)phenyl]-1*H*-benzimidazol-2-amine for the general preparation of 2-aminobenzimidazoles.[33] Reaction of an amine with thiocarbonyldiimidazole and 1,2-phenylenediamine yielded thiourea **14**, which was



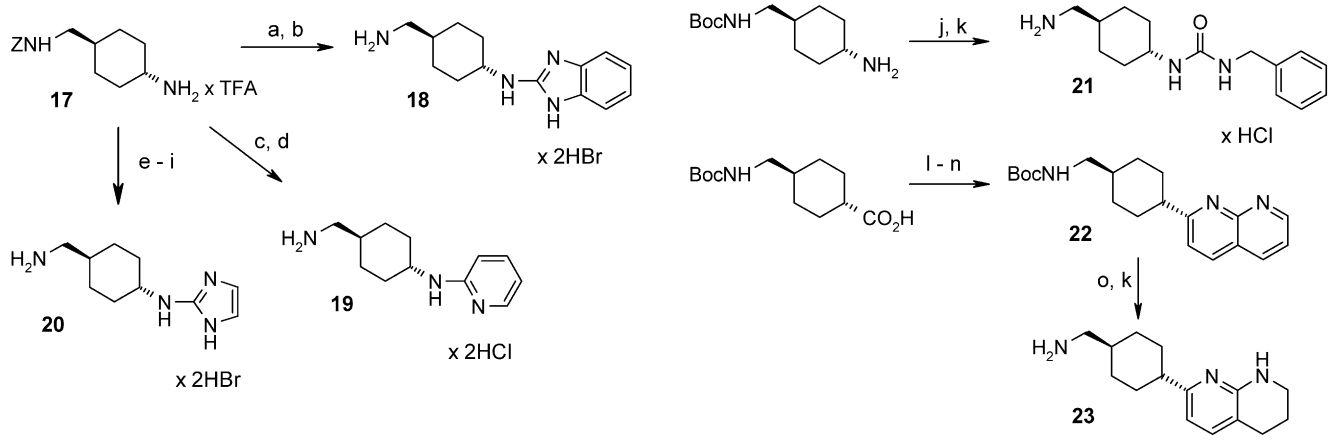
Scheme 2. Reagents: (a) NaH, methyl bromo acetate, DMF, 0 °C–rt; (b) K_2CO_3, *tert*-butyl bromo acetate, DMF; (c) KOH (or NaOH), dioxane, H_2O; (d) RNH_2, TOTU, NMM, DMF, 0 °C–rt (or: HATU, DIEA, DMF/CH_2Cl_2, 0 °C–rt); (e) HCl, dioxane (or: TFA, CH_2Cl_2); (f) B_2H_6, THF; (g) methyl bromo acetate, K_2CO_3, KI, DMF.



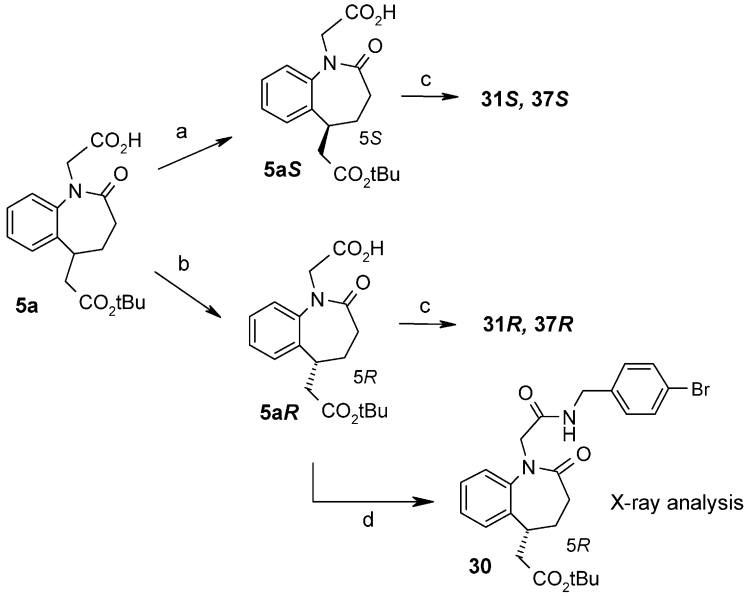
Scheme 3. Reagents: (a) 1. thiocarbonyldiimidazole, imidazole; 2. 1,2-phenylenediamine, CH_3CN; (b) HgO (yellow), cat. S, EtOH/rflx.; (c) HCl, dioxane.

subjected to cyclodesulfurization using HgO. Final deprotection afforded intermediate **15** in good yield; the other aminobenzimidazoles were prepared analogously. Building blocks **18–23** all comprise different guanidine mimetics in combination with the methylcyclohexyl residue as spacer element, and were prepared according to general methods described in the literature (Scheme 4).[34–36]

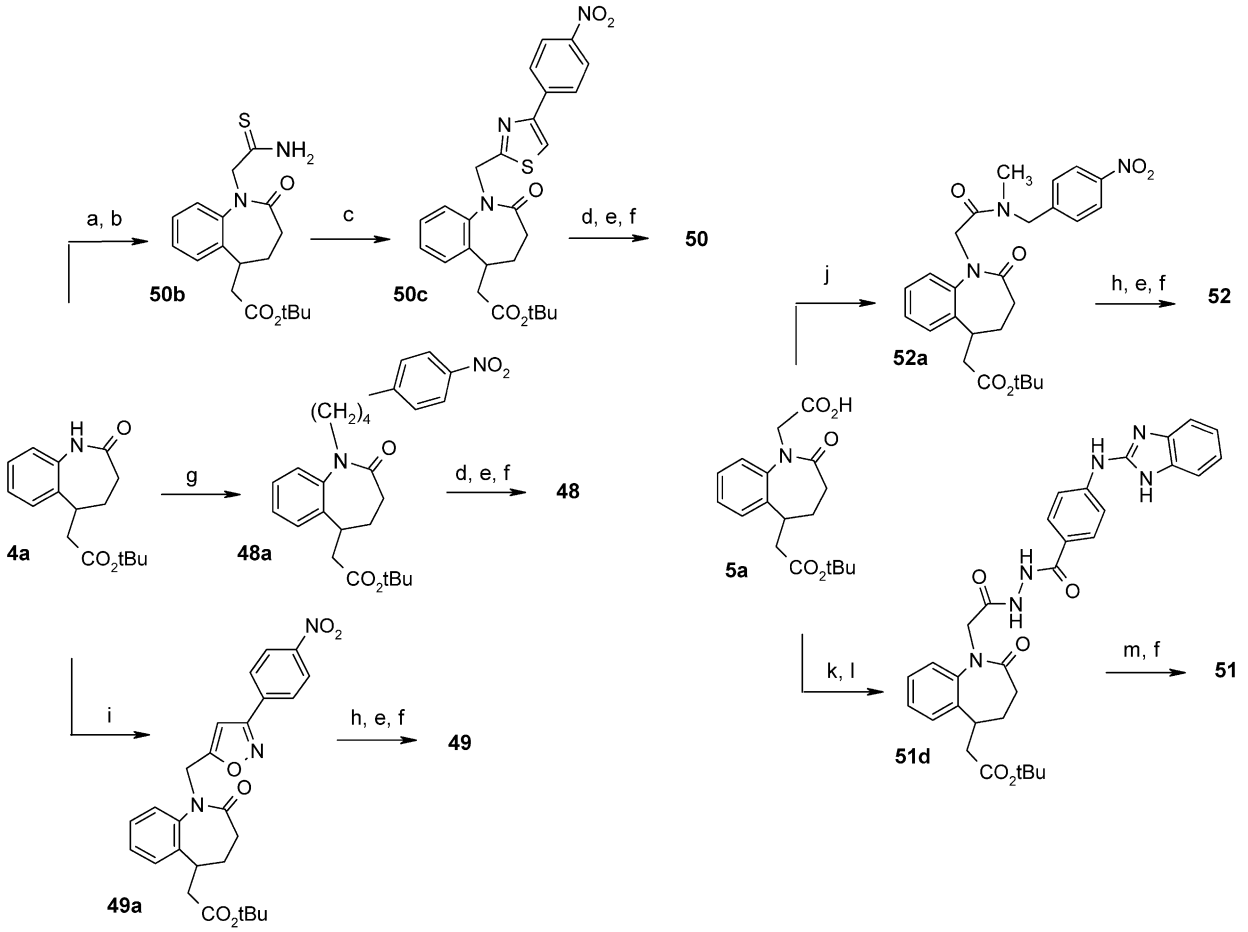
Enantiomerically pure 1,5-benzazepinones were prepared by resolution of intermediate acid **5a** by formation of diastereomeric salts using either (1*S*)-(−)- or (1*R*)-(+)-1-naphtylethylamine as base (Scheme 5), and then converted into the target products as described above. The absolute configuration of intermediate **5a*R*** was determined via X-ray structure of the respective 4-bromobenzamide **30**, which in consequence enabled us to assign the absolute configuration for the final products **31** and **37**.[37] Synthesis of 1,5-benzazepinones (**48–52**) with modified or replaced acetamide linker was accomplished via the corresponding nitrophenyl derivatives (Scheme 6). Alkylation of **4a** with bromoaceto-



Scheme 4. Reagents: (a) cf. general method Scheme 3; (b) HBr, glacial acetic acid; (c) 2-fluoropyridine, DIEA, rflx.; (d) H_2, Pd–C, MeOH; (e) BrCN, NaOAc, MeOH; (f) H_2S, Et_3N, pyridine; then CH_3I, CH_2Cl_2; (g) 2,2-diethoxyethylamine, CH_3CN/rflx.; (h) 6 N HCl, CH_3CN/0 °C, then 25% NaOH, rt; (i) HBr, glacial acetic acid; (j) benzylisocyanate, Et_3N, toluene, DMF/rflx.; (k) HCl, dioxane (or: TFA, CH_2Cl_2); (l) *N*,*O*-dimethylhydroxylamine×HCl, NMM, EDC, CH_3CN, 0 °C–rt; (m) MeMgBr, THF, 0 °C–rt; (n) 2-aminonicotinealdehyde, KOH, H_2O, rt; (o) H_2, Pd–C, EtOH.



Scheme 5. Reagents: (a) (1*R*)-(+)-1-(napthyl)ethylamine; (b) (1*S*)-(−)-1-(napthyl)ethylamine; (c) RNH_2, TOTU, NMM, DMF, 0 °C–rt; then: HCl, dioxane; (d) 4-bromobenzylamine, PPA, Et_3N, CH_2Cl_2, 0 °C–rt.



Scheme 6. Reagents: (a) NaH, bromoacetonitrile, DMF; (b) H_2S, Et_3N, pyridine; (c) 2-bromo-(4-nitrophenyl)ethanone, dioxane; (d) $N_2H_4 \times H_2O$, cat. $FeCl_3$/C, MeOH, rflx.; (e) cf. general method Scheme 3; (f) TFA; (g) 1-(4-bromobutyl)-4-nitrobenzene, NaH, DMF; (h) H_2, Pd–C, EtOH; (i) 5-chloromethyl-3-(4-nitrophenyl)-isoxazole, NaH, DMF, 0 °C–rt; (j) *N*-methyl-(4-nitrophenyl)-methane amine, HATU, DIEA, DMF, 0 °C–rt; (k) 4-(1H-benzimidazol-2-ylamino)benzohydrazide, EDC, NMM, DMF/CH_2Cl_2, 0 °C–rt; (m) Lawesson's reagent, THF/rflx.

nitrile, conversion into the thioamide, formation of the thiazole using 2-bromo-(4-nitrophenyl)ethanone, hydrogenation, conversion into the 2-aminobenzimidazole and cleavage of the *tert*-butyl ester afforded compound **50**. Analogously, compounds **48** and **49** were prepared applying either 4-(4-nitrophenyl)butylmethanesulfonate[38] or 5-chloromethyl-3-(4-nitro-phenyl)-isoxazole[39] as alkylating agents. Condensation of **5a** with *N*-methyl-(4-nitrophenyl)-methylamine or 4-(1H-benzimidazol-2-ylamino)benzohydrazide, conversion of the latter into the thiadiazole and further reaction as described above afforded compounds **51** and **52**, respectively.

Analysis of compounds **31–61** via HPLC and NMR did not reveal any evidence for the existence of diasteromers, thereby confirming our original concept for the design and preparation of benzazepinone-based structures.

Results and Discussion

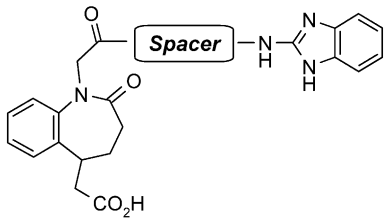
Screening

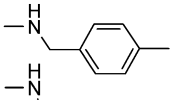
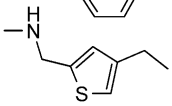
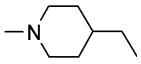
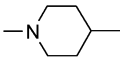
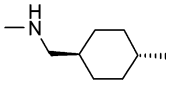
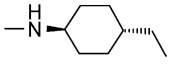
Compounds **31–61** were evaluated regarding $\alpha_V\beta_3$ inhibition by means of competitive ELISA using vitronectin as natural ligand. Compounds displaying IC_{50} values $>10\,\mu M$ were considered as 'not active'. Specificity versus $\alpha_{IIb}\beta_3$ was examined routinely for compounds displaying an IC_{50} $\alpha_V\beta_3$ $<100\,nM$. All compounds discussed showed at least 1000-fold selectivity. If not indicated otherwise, compounds were screened as racemic mixtures.

SAR

First, we wanted to asses the general applicability of the tetrahydrobenzazepinone core as scaffold for $\alpha_V\beta_3$ antagonists. Table 1 presents the SAR data obtained employing the 1,5-benzazepinone core in combination with 2-aminobenzimidazole as guanidine replacement and variation of spacer structure and length. The selection of spacer residues applied was based on the information gained previously in the dibenzazepinone series.[27] Benzyl derivative **31** already exhibited an IC_{50} of 4.4 nM, thus showing an improvement of nearly a factor of 2 compared to dibenzazepinone **1**. In contrast, replacement of benzyl by thienyl in **32** led to 3- to 4-fold increase in IC_{50} versus **31**. Introduction of a piperidine moiety as spacer resulted in a dramatic decrease in potency (**33**, **34**). We consider this effect to be caused by switching from secondary to tertiary amide (cf. amide

Table 1. Effect of spacer variation within 1,5-tetrahydrobenzazepinone series



Compd	Spacer	$\alpha_V\beta_3$ ELISA IC_{50}, nM[a]
31		4.4
32		16.0
33		5000
34		1000
35	–NH–$(CH_2)_4$–	56.1
36	–NH–$(CH_2)_5$–	7.2
37		**1.5**
38		5000

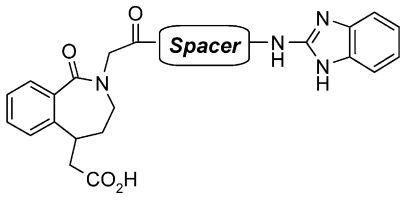
[a]Values are means of three experiments; intra-assay variation <10%, inter-assay variation <factor 2.

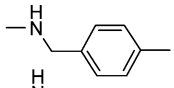
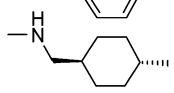
modification, Table 4) and increased constraint in the spacer unit. Replacement of the benzyl residue by linear C4- and C5-alkyl spacer resulted in 12- and about 2-fold reduction in activity (**35**, **36**), respectively. Incorporation of methylcyclohexyl residue as spacer led to derivative **37** displaying improved potency with an IC_{50} of 1.6 nM, whereas incorporation of the same moiety in 'reversed' form in **38** led to a dramatic decrease of activity.

Table 2 summarizes the results obtained employing the 2,5-benzazepinone core. Benzyl derivative **39** displayed a 16-fold reduction in activity compared to dibenzazepinone **1**, and a 27-fold reduction versus the corresponding 1,5-analogue **31**. Similar results were obtained using methylcyclohexyl and C5-alkyl as spacer (**40**, **41**), whereas the respective linear C4-alkyl derivative **42** showed a 2- to 3-fold improved potency compared to its 1,5-benzazepinone analogue **35**. Additional reduction in spacer length did not lead to a further improvement in potency, C3-alkyl derivative **43** showed retained activity. Up to now, **40** represents the most active compound from the 2,5-series with an IC_{50} of 10.6 nM.

It is well accepted that the distance between acidic and basic group has a major influence on the activity of $\alpha_V\beta_3$ antagonists.[40] Therefore, although comprising the same spacer moieties, a direct comparison of 1,5- and 2,5-

Table 2. Effect of spacer variation within 2,5-tetrahydrobenzazepinone series



Compd	Spacer	$\alpha_V\beta_3$ ELISA IC_{50}, nM[a]
39		122.0
40		**10.6**
41	–NH–$(CH_2)_5$–	52.7
42	–NH–$(CH_2)_4$–	20.4
43	–NH–$(CH_2)_3$–	28.1

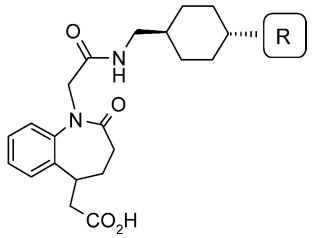
[a]cf. Table 1.

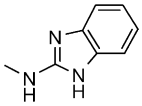
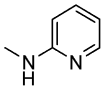
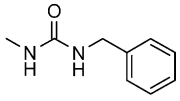
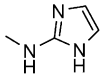
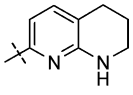
benzazepinones from Table 1 and 2 is not legitimate as the overall length from acid to guanidine mimetic differs between these two series. Nevertheless, according to the results obtained so far, the 1,5-benzazepinone core appeared more promising, hence we focused our efforts on this series.

Subsequently, we evaluated the SAR related to the guanidine mimetic. Table 3 presents exemplarily the results we obtained by employing guanidine mimetics of different basicity in combination with methylcyclohexyl as spacer. As already observed in the dibenzazepinone series, highest activity was found for compound **37** containing 2-aminobenzimidazole as basic pharmacophore. Introduction of a benzylurea as non-basic guanidine mimetic resulted in considerable loss in potency with **45** exhibiting an IC_{50} of 500 nM. 2-Aminopyridine and -imidazole derivatives **44** and **46** exhibited a ca. 30-fold reduction in activity. Although described as excellent guanidine replacement in other structural classes,[41] incorporation of tetrahydronaphtyridine (THN) also led to diminished potency with **47** showing an IC_{50} of 10 nM. Presumably the combination of cyclohexyl-based spacer and THN is too constrained and results in an unfavorable alignment within this part of the molecule. Based on these results, we decided to retain the 2-aminobenzimidazole as guanidine mimetic during the following studies.

Table 4 summarizes the SAR for the acetamide linker. Replacement of the amide by ethylene in **48** resulted in a nearly 100-fold reduction in potency, the same was observed in the case of the corresponding isosteric thiazole **50**. Incorporation of oxazole and thiadiazole as linker in **49** and **51** led to totally inactive derivatives, whereas *N*-methylation of the amide resulted in a 4-fold decrease (**52**). These results clearly demonstrate the requirement for the acetamide linkage in this part of the structure, a finding which was also observed in the dibenzazepinone series. Probably the

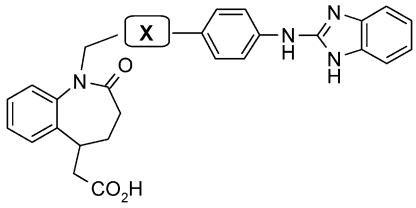
Table 3. Variation of guanidine mimetic

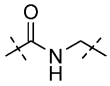
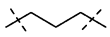
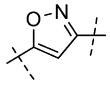
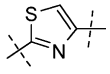
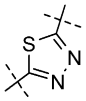
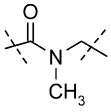


Compd	R	$\alpha_V\beta_3$ ELISA IC_{50}, nM[a]
37		**1.6**
44		58.6
45		500
46		44.4
47		10.0

[a]cf. Table 1.

Table 4. Amide modification



Compd	X	$\alpha_V\beta_3$ ELISA IC_{50}, nM[a]
31		4.4
48		500
49		na
50		500
51		na
52		16.7

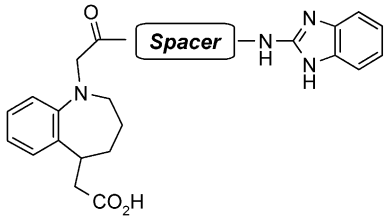
[a]cf. Table 1.

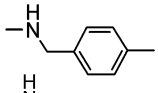
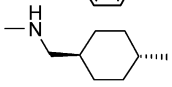
amide interacts with the integrin receptor, thus contributing substantially to the overall binding of the molecule.

1,5-Tetrahydrobenzazepines (**53**–**55**) were prepared to asses SAR around the benzazepinone core. Generally, derivatives from this series showed improved solubility versus the tetrahydrobenzazepinones, certainly due to the presence of an additional basic center in these structures. Table 5 highlights the results obtained employing those spacer residues which previously had shown the 'best' results. Whereas introduction of C5-alkyl in **55** resulted in a ca. 13-fold reduction in activity, the respective benzyl and cyclohexyl derivatives **53** and **54** showed retained potency. However, although displaying favorable properties, this series was discontinued due to the poor functional activity in cellular assays (cf. **54**, Table 9).

Table 6 presents the results for modification of the annelated benzene ring. Replacement of benzyl by thienyl in **56** led to a 3-fold reduction in potency. Introduction of additional substituents in the benzene part had a pronounced effect. 7-Chloro analogue **57** exhibited slightly improved activity, whereas introduction of a 7-methoxy group displayed a 6-fold improvement in potency. Compound **59** showed an IC_{50} of 0.26 nM and thus represents the most potent derivative from this series with respect to in vitro activity.

Table 5. In vitro activity of 1,5-tetrahydrobenzazepines

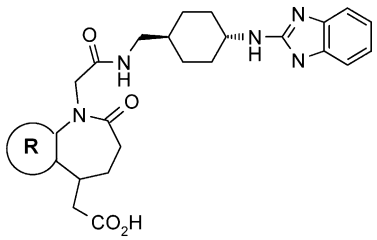


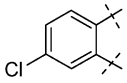
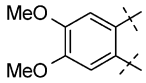
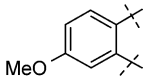
Compd	Spacer	$\alpha_V\beta_3$ ELISA IC_{50}, nM[a]
53		10.0
54		2.4
55	–NH–$(CH_2)_5$–	100

[a]cf. Table 1.

Due to their potency in functional assays (cf. Table 9) compounds **31** and **37** were selected for in vitro evaluation of the corresponding enantiomers (Table 8). In case of benzyl derivative **31**, the *(R)*-enantiomer was more active than the corresponding *(S)*-enantiomer, a result which is in agreement with the natural Asp configuration and comparable structures from SmithKline-Beecham.[42,43] However, the difference in activity

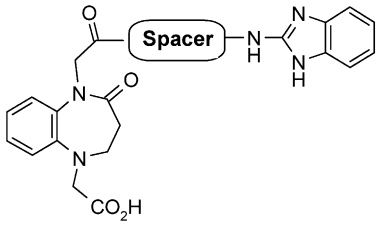
Table 6. Core modification

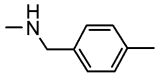
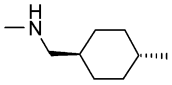


Compd	R	$\alpha_V\beta_3$ ELISA IC_{50}, nM[a]
37		1.6
56		4.9
57		0.99
58		100
59		**0.26**

[a]cf. Table 1.

Table 7. 1,5-Substituted tetrahydrobenzodiazepines



Compd	Spacer	$\alpha_V\beta_3$ ELISA IC_{50}, nM[a]
60		500
61		100

[a]cf. Table 1.

Table 8. Activity of enantiomerically pure **31** and **37**

Compd	$\alpha_V\beta_3$/VN ELISA[a] IC_{50}, nM	$\alpha_V\beta_3$/OPN ELISA[a] IC_{50}, nM
31R	3.4	3.7
31S	20.0	16.4
37R	1.5	1.9
37S	1.7	2.1

[a]cf. Table 1, VN = vitronectin, OPN = osteopontin.

between the enantiomers amounts only to a factor of 5–6, and is not as pronounced as reported for the SKB structures. Surprisingly, in case of cyclohexyl analogue **37** we did not observe a significant difference in the potencies of *(R)*- and *(S)*-enantiomers. This finding was confirmed in a second binding assay using osteopontin as natural ligand.

For completion of our studies we also examined the corresponding 1,5-disubstituted tetrahydrobenzodiazepines featuring nitrogen as replacement of the chiral center. Compounds **60** and **61** were found to exhibit ca. 100-fold reduction in potency relative to their corresponding 1,5-benzazepinone analogues (Table 7).

Functional efficacy and early ADME

Selected compounds were subjected to further characterization with respect to specificity versus other integrins, potency in functional cellular assays and early ADME (Table 9), the selection being based on in vitro potency and structural criteria.

All derivatives exhibited high selectivity versus integrins $\alpha_{IIb}\beta_3$ and $\alpha_4\beta_1$. Primary functional efficacy was tested by inhibition of recombinant $\alpha_V\beta_3$ transfected CHO-K1 cell adhesion. Compounds showing an inhibitory activity of larger than 80% at 10 μM were subjected to IC_{50} determination. For some compounds in vitro potency did not correlate with functional efficacy in cell adhesion. In principle this discrepancy could be attributed to the possibility that some of the compounds might have different functional properties acting as (partial) agonists, however, extended studies to examine these findings were not conducted in this stage. Altogether, from all derivatives tested, compounds **31** and **37** were identified as most active analogues in inhibition of cellular adhesion with IC_{50} values of 500 and 40 nM, respectively.

The integrins $\alpha_V\beta_3$ and $\alpha_V\beta_5$ have both been shown to mediate cell adhesion to vitronectin, but they trigger different post ligand binding events.[44] Although recent reports suggest that selectivity of an $\alpha_V\beta_3$ antagonist versus $\alpha_V\beta_5$ is not a pre-requisite,[45] a definite answer to this question is not possible at the moment. On one hand selectivity might be crucial to prevent possible side effects like retinal degeneration,[46] on the other hand simultaneous inhibition of both $\alpha_V\beta_3$ and $\alpha_V\beta_5$ by dual antagonists might be essential to provoke a beneficial effect in certain diseases. Especially in the case of restenosis the latter view is supported by a recent paper which describes the involvement of $\alpha_V\beta_5$ in rat neointima formation.[47] Therefore interesting compounds were also checked for efficacy against $\alpha_V\beta_5$-mediated adhesion of recombinant $\alpha_V\beta_5$ transfected CHO-K1 cells. Again, although structurally closely related, compounds **31** and **37** exhibited a very different profile with IC_{50} values $\alpha_V\beta_5$ of 0.1 and 4.5 μM, respectively.

According to early ADME evaluation all derivatives displayed medium to good absorption in the Caco-2 model.[48] Calculated log*P*s range from 3 to 5 which is highly lipophilic relative to most $\alpha_V\beta_3$ antagonists

Table 9. Potency, efficacy and ADME parameter of selected compounds

Compd	$\alpha_V\beta_3$/VN ELISA[a] IC_{50}, nM	$\alpha_{IIb}\beta_3$ /Fg ELISA[a] IC_{50}, nM	$\alpha_4\beta_1$/FN[b] Inh. @ 10^{-5} M	$\alpha_V\beta_3$/OPN Adhesion[b] Inh. @ 10^{-5} M	$\alpha_V\beta_3$/OPN Adhesion[b] IC_{50}, μM	$\alpha_V\beta_5$/OPN Adhesion[b] Inh. @ 10^{-5} M	$\alpha_V\beta_5$/OPN Adhesion[b] IC_{50}, μM	ClogP	Caco-2 permeation assay P_{app}[c], cm/s × 10^{-6}
31	4.4	>10.000	0%	>80%	0.5	>80%	0.1	4.1	1.50
36	7.2	>10.000	0%	61%		>80%		3.3	nd
37	1.6	>10.000	4%	>80%	0.04	>80%	4.5	3.7	2.06
40	10.6	>10.000	12%	39%		58%		3.4	2.85
54	2.4	>10.000	25%	55%		25%		5.1	2.37
56	4.9	>10.000	0%	34%		99%		3.4	2.99
57	0.99	>10.000	16%	>80%	2.9	79%		4.5	1.71
59	0.26	>10.000	0%	>80%	1.3	nd		3.7	2.50

[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; $n=2$, intra-assay variation <20% (P_{app} values >2e–7 cm/s are considered as medium, >2e–6 cm/s as high transport rate). Abbreviations: nd = not determined, VN = vitronectin, Fg = fibrinogen, FN = fibronectin, OPN = osteopontin.

reported to date. Compounds **31** and **37** were examined for metabolic stability versus rat and human liver microsomes. Both derivatives showed no metabolism in rat. Compound **37** was stable in human matrix, whereas **31** was glucuronidated to about 10% after 1 h indicating that an inadequate availibility in humans is to be expected. Assessment of pharmacokinetic behaviour for **31** and **37** demonstrated low clearance in rats (0.02 and 0.15 L/h/kg), but high clearance in pigs (1.6 and 2.2 L/h/kg) after iv-application. Oral bioavailability in rats (4.64 mg/kg) was low with both derivatives (up to 2%) but was substantially enhanced when compound **37** was administered as ethyl ester prodrug (16%). When administered subcutaneously to mice (0.1 mg/kg) or rats (1 mg/kg), compound **31** demonstrated high and stable plasma levels for up to 8 h reaching peak levels of 500 and 3000 ng/L.

Conclusions

In summary, we identified the tetrahydrobenzazepinone scaffold as useful core for the synthesis of new integrin $\alpha_V\beta_3$ antagonists. Starting from dibenzazepinone based $\alpha_V\beta_3$ inhibitors, respective 1,5- and 2,5-substituted tetrahydrobenzazepinones were designed and prepared as simplified analogues with reduced lipophilicity. According to in vitro screening 1,5-substituted tetrahydrobenzazepinones showed improved biological activity relative to their 2,5-analogues and lead **1**. SAR involving the benzazepinone core, spacer unit and guanidine pharmacophore were established and led to new inhibitors with high potency and selectivity. 7-Methoxy analogue **59** was identified as representative displaying highest in vitro potency with an IC_{50} of 0.26 nM in the $\alpha_V\beta_3$ binding assay. In vitro evaluation of enantiomerically pure **31** and **37** showed that in case of **31** the *(R)*-enantiomer was more active, whereas for **37** no significant difference between the enantiomers was observed. Characterization of selected analogues in secondary screening assays revealed **31** and **37** as derivatives displaying the highest functional efficacy in inhibition of $\alpha_V\beta_3$-mediated cell adhesion. Assessment in early ADME and pharmacokinetic behaviour showed a satisfactory profile for iv-application in rat. Both compounds will be subjected into efficacy screening in different disease models in vivo.

Experimental

Chemistry

Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers and used without further purification. Starting materials were either commercially available or were prepared according to the literature methods indicated. All reactions were conducted under nitrogen atmosphere, chemical yields are not optimized. All final products gave satisfactory ^{1}H NMR, HRMS and HPLC results.

Melting points were determined using a Büchi 530 apparatus and are uncorrected. TLC was performed using silica gel plates (Merck silica gel 60 F_{254}), preparative chromatography was performed either by conventional flash chromatography (Merck 60 230–400 mesh ASTM) or using pre-packed silica gel cartridges supplied by Macherey Nagel (Chromabond) or Biotage (KP-SiL, 60 Å, 23–63 μm). MPLC separations were carried out on a Büchi system (688 pump, 687 gradient former and 684 fraction collector) using Bischoff columns (250×20, 500×32 mm; Prontoprep 2025/3250; 60-2540-C18) and gradients from H_2O and CH_3CN containing 0.1% acetic acid. Generally all compounds were shown to be homogenous by HPLC on an Agilent 1100 system with UV- (DAD) and MSD-detection (ESI, Single Quad, *m/z* 100–700), GROM columns (GROM-SIL 80 ODS-7pH, 4 μ, 40×2 mm; 60 °C, flowrate 0.5 mL/min) employing different gradients from H_2O and CH_3CN containing 0.1% TFA. Purity of final products was determined separately using MN Nucleosil columns (C18PPN, 100 Å, 5 μm, 100×2 mm, 40 °C), flowrate 0.2 mL/min in two different gradients (0–100%; 5–40%; 35 min).

^{1}H NMR spectra were recorded using Bruker DPX (360 MHz) or Varian Inova (400 MHz) spectrometers, all values are reported as chemical shifts in δ units (ppm) relative to TMS as internal standard. Mass

spectral analysis was performed on a Micromass Q-TOF or LCT for high resolution MS (HRMS). Optical rotation was determined on a Perkin–Elmer 241 polarimeter. Log*P* values were calculated using the ACD software.

Ethyl 5-hydroxy-7,8-dimethoxy-2-oxo-2,3-dihydro-1*H*-benzo[*b*]azepine-4-carboxylate (2b). (a) To a solution of ethyl 2-amino-4,5-dimethoxybenzoate (20 g, 88.8 mmol) and pyridine (7.17 mL) in THF (300 mL) at room temperature was added dropwise ethyl 4-chloro-4-oxobutanoate (18.99 g, 164.59 mmol). The mixture was stirred for 2 h, then poured into H_2O, extracted with EtOAc (3×) and the combined organic phases washed with 2 N HCl, $NaHCO_3$ (sat.) and brine. The organic layer was dried ($MgSO_4$), evaporated and stirred with *n*-pentane to yield a yellow solid: 30.4 g (96%); MS (ESI) *m*/*z* 354.1 [M + H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.65 (s, 1H), 8.10 (s, 1H), 7.40 (s, 1H), 4.30 (q, 2H), 4.10 (q, 2H), 3.85 (s, 3H), 3.80 (s, 3H), 2.70 (m, 4H), 1.30 (t, 3H), 1.20 (t, 3H).

(b) To a suspension of NaH (5.95 g, 60%, deoiled) in DMSO (100 mL) and THF (15 mL) at room temperature a solution of the above amide (25 g, 70.75 mmol) in DMSO (100 mL) was added dropwise over 1 h and the mixture stirred for 1 h. A cooled solution (0 °C) of HOAc (40 mL) was added, and the resulting solution was stirred for 30 min. H_2O (250 mL) was added dropwise and the resulting white precipitate filtered off, dissolved in CH_2Cl_2/MeOH (90:1), washed with brine, dried ($MgSO_4$), and concentrated. The resulting residue was stirred with *n*-pentane and diethyl ether to afford a white amorphous solid: 19.5g, 89.7%; MS (ESI) *m*/*z* 308.0 [M + H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.3 (s, 1H), 10.10 (s, 1H), 7.25 (s, 1H), 6.75 (s, 1H), 4.30 (q, 2H), 3.80 (s, 6H), 2.95 (s, 2H), 1.35 (t, 3H).

Methyl/ethyl 5-hydroxy-7-methoxy-2-oxo-2,3-dihydro-1*H*-benzo[*b*]azepine-4-carboxylate (2c). Analogously to **2b**, methyl 2-amino-5-methoxybenzoate (10.01 g, 90 mmol) afforded methyl 2-[(4-ethoxy-4-oxobutanoyl)amino]-5-methoxybenzoate: 15.9 g, 54%; MS (ESI) *m*/*z* 310.1 [M + H$^+$]. Subsequent treatment with NaH in DMSO yielded 5.95 g of a white solid as mixture of the corresponding methyl and ethyl ester (1:1) which were not separated at this stage; MS (ESI) *m*/*z* 286.0 (methyl), 278.0 (ethyl) [M + H$^+$].

Methyl/ethyl 7-chloro-5-hydroxy-2-oxo-2,3-dihydro-1*H*-benzo[*b*]azepine-4-carboxylate (2d). (a) Analogously to **2b**, methyl 2-amino-5-chlorobenzoate (23 g, 123.9 mmol) afforded the desired amide. Recrystallization from MeOH gave methyl 4-chloro-2-[(4-ethoxy-4-oxobutanoyl)amino]benzoic acid as white solid: 34.1 g, 87%; MS (ESI) *m*/*z* 352.0 [M + H$^+$]. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 11.06 (s br., 1H), 8.68 (d, 1H), 7.99 (m, 1H), 7.47 (dd, 1H), 4.16 (q, 2H), 3.92 (s, 3H), 2.74 (m, 4H), 1.24 (t, 3H).

(b) Subsequent treatment of 4-chloro-2-[(4-ethoxy-4-oxobutanoyl)amino]benzoic acid (50.2 g, 160 mmol) with NaH in DMSO yielded the title compound (32 g) as white solid consisting of a mixture of the corresponding ethyl and methyl ester (6:4) which were not separated at this stage; MS (ESI) *m*/*z* 268.0 (methyl), 282.0 (ethyl) [M + H$^+$].

7,8-Dimethoxy-3,4-dihydro-1*H*-benzo[*b*]azepine-2,5-dione (3b). To a solution of **2b** (17 g, 55.32 mmol) in DMSO (300 mL) was added H_2O (3 mL). The resulting solution was heated to 150 °C and stirred for 2 h. The mixture was cooled to room temperature and poured into 10% brine, and the resulting yellow precipitate was filtered off, washed with brine and dried: 10.5 g, 80.7%; MS (ESI) *m*/*z* 236.1 [M + H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.90 (s, 1H), 7.35 (s, 1H), 6.80 (s, 1H), 3.80 (s, 3H), 3.75 (s, 3H), 2.85 (m, 2H), 2.65 (m, 2H).

7-Methoxy-3,4-dihydro-1*H*-benzo[*b*]azepine-2,5-dione (3c). Analogously to **3b**, **2c** (5.95 g) was converted into the title compound affording, after chromatography (CH_2Cl_2/MeOH 5%), a white amorphous solid: 3.0 g, 28.5% based on methyl 2-[(4-ethoxy-4-oxobutanoyl)amino]-5-methoxybenzoate); MS (ESI) *m*/*z* 206.0 [M + H$^+$].

7-Chloro-3,4-dihydro-1*H*-benzo[*b*]azepine-2,5-dione (3d). Analogously to **3b**, crude **2d** (32 g) was converted into the title compound as a white solid: 19.0 g, 57% based on methyl 2-[(4-ethoxy-4-oxobutanoyl)amino]-5-chlorobenzoate.

***tert*-Butyl (2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)acetate (4a).** (a) To a suspension of NaH (3.27 g, 60% deoiled) in DMF (35 mL) at 0 °C was added dropwise a solution of *tert*-butyl (diethoxyphosphoryl)acetate (22.3 g, 80 mmol) in DMF (35 mL). The mixture was stirred for 1 h. To this solution 3,4-dihydro-1*H*-benzo[*b*]azepine-2,5-dione **3a** (12.4 g, 70.9 mmol) in DMF (90 mL) at 0 °C was added dropwise, and the mixture then stirred at room temperature for 3 days. The mixture was poured into 700 mL of cold 5% brine, and the resulting yellow precipitate was filtered, washed with H_2O, dissolved in CH_2Cl_2, washed with 5% $NaHCO_3$ and dried (Na_2SO_4). The resulting residue was recrystallised from cyclohexane (150 mL) yielding white crystals: 17.5 g, 90.5%; mp 136–138 °C.

(b) A suspension of 10% Pd–C (3 g) in EtOH (50 mL) was flushed with H_2. To this suspension was added a solution of (2-oxo-2,3-dihydro-1H-1-benzo[b]azepin-5-yl)-acetic acid *tert*-butyl ester (14.7 g, 53.8 mmol) in EtOH (125 mL) and dioxane (75 mL). The mixture was hydrogenated at room temperature and atmospheric pressure until the absorption of hydrogen was complete. Filtration and subsequent washing afforded an oily residue that was crystallized from diethyl ether/*n*-hexane yielding **4b** as white crystals: 14.2 g, 96%; mp 101–103 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.58 (s, 1H), 7.28.10 (m, 3H), 6.98 (d, 1H), 3.25 (m, 1H), 2.75 (dd, 1H). 2.70 (dd, 1H), 2.30 (m, 1H), 2.12 (m, 2H), 1.71 (m, 1H), 1.35 (s, 9H).

***tert*-Butyl (7,8-dimethoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)acetate (4b).** Analogously to **4a** and **3b** (10.5 g, 44.63 mmol) afforded, after treatment

with *n*-pentane, **4b**, as a white solid: 8.16 g, 55%; MS (ESI) *m*/*z* 280.1 [M + H$^+$–^{t}Bu].

***tert*-Butyl (7-methoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo*[b]*azepin-5-yl)acetate (4c).** Analogously to **4a** and **3c** (3.0 g, 14.62 mmol) afforded, after chromatography (EtOAc/MeOH), **4c** as yellowish oil: 3.32 g, 63.9%; MS (ESI) *m*/*z* 251.0 [M + H$^+$–^{t}Bu].

***tert*-Butyl (7-chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo*[b]*azepin-5-yl)acetate (4d).** Analogously to **4a** and **3d** (19.0 g, 90.63 mmol) afforded, after Wittig–Horner olefination and recrystallisation from diisopropyl ether, the desired product: 23.5 g, 84.2%; MS (ESI) *m*/*z* 615.2 [2M + H$^+$]. Hydrogenation using 5% Pt–C (4.1 g) as catalyst in a mixture of EtOH (250 mL) and dioxane (100 mL) at room temperature and atmospheric pressure for 4 days afforded 23.5 g of a beige solid as a mixture of target product (**4d**) and the corresponding de-chlorinated compound; the mixture was used directly in the next step without further purification).

[5-(2-*tert*-Butoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo*[b]*azepin-1-yl]acetic acid (5a). (a) To a suspension of NaH (2.6 g; 60%, deoiled) in DMF (35 mL) at 10–20 °C was added dropwise a solution of **4a** (16.8 g, 61.1 mmol) in DMF (60 mL). The mixture was stirred for 1 h. To this solution methyl bromoacetate (10 g, 63.4 mmol) at 10–20 °C was added dropwise, and the mixture stirred for an additional 12 h. The solution was poured into 5% cold brine (400 mL) and extracted with a mixture of diethyl ether/*n*-hexane (3× 100 mL each). The combined extracts were washed with H_2O, 10% $NaHCO_3$ and brine, and dried (Na_2SO_4). Filtration and evaporation afforded a yellowish oil which was used in the next step without further purification; MS (FAB) *m*/*z*: 348 [M + H$^+$].

(b) To a solution of the above crude product in dioxane (100 mL) at room temperature 1 N NaOH (65 mL) was added dropwise. After 45 min, the reaction mixture was adjusted to pH 7 using 1 N $KHSO_4$ solution, dioxane largely distilled off, and the residue diluted with H_2O, adjusted to pH 9 using 1 N NaOH and extracted with diethyl ether (3×). The aqueous phase was rendered acidic using 1 N $KHSO_4$ solution, the precipitating acid extracted with a mixture of diethyl ether/*n*-hexane 4:1. The organic phase was washed with H_2O, 1 N NaOH, brine and dried (Na_2SO_4). Filtration and evaporation afforded an oily residue that was crystallised by using diethyl ether/*n*-hexane 1:4 (H_2O-sat.). Filtration and drying afforded the title compound as white crystals: 17.5 g, 87.5%; mp 117–119 °C. MS (ESI) *m*/*z* 278.0 [M + H$^+$–^{t}Bu]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.25 (m, 4H), 4.35 (m, 2H), 3.58 (m, 1H), 2.70 (m, 2H), 2.31 (m, 2H), 2.10 (m, 1H), 1.65 (m, 1H), 1.35 (s, 9H).

[5-(2-*tert*-Butoxy-2-oxoethyl)-7,8-dimethoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo*[b]*azepin-1-yl]acetic acid (5b). Analogously to **5a** and **4b** (4.0 g, 11.93 mmol) afforded **5b** as white foam: 2.6 g, 56.2%; MS (ESI) *m*/*z* 338.1 [M + H$^+$–^{t}Bu]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 6.85 (s, 1H), 6.75 (s, 1H), 4.35 (s br., 2H), 3.80 (s, 3H), 3.75 (s, 3H), 3.60 (s, 2H), 2.70 (m, 2H), 2.25 (m, 1H), 2.15 (m, 2H),1.60 (m, 1H), 1.35 (s, 9H).

[5-(2-*tert*-Butoxy-2-oxoethyl)-7-methoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo*[b]*azepin-1-yl]acetic acid (5c). Analogously to **5a** and **4c** (2.0 g, 6.55 mmol) afforded **5c** as white amorphous solid: 2.0 g, 95%; MS (ESI) *m*/*z* 308.0 [M + H$^+$–^{t}Bu]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.15 (d, 1H), 6.80 (dd, 1H), 6.70 (d, 1H), 4.60 (m, 1H), 4.35 (m, 1H), 3.80 (s, 3H), 3.68 (m, 1H), 2.70 (m, 1H), 2.65 (dd, 1H), 2.45 (m, 1H), 2.30 (m, 2H), 1.65 (m, 1H), 1.35 (s, 9H).

[5-(2-*tert*-Butoxy-2-oxoethyl)-7-chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo*[b]*azepin-1-yl]acetic acid (5d). Analogously to **5a**, crude **4d** (18.6 g) was converted into *tert*-butyl methyl 2,2′-(7-chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1,5-diyl)diacetate which was used in the next step without further purification. To a solution of the above methyl ester in dioxane (250 mL) at room temperature was added KOH (4.51 g, 80.45 mmol) as an aqueous solution (H_2O 150 mL). The mixture was stirred for 1 h at room temperature and then concentrated. The resulting residue was dissolved in H_2O (100 mL) and the solution was extracted with EtOAc (2×). After evaporation, the residue was taken up in diethyl ether and precipitated by addition of *n*-pentane. Recrystallisation from diisopropyl ether (2×) afforded **4d**: 4.8 g (comprising about 15% of the dechlorinated product according to HPLC/MS); MS (ESI) *m*/*z* 390.0 [M + Na$^+$].

***tert*-Butyl-(1-oxo-2,3,4,5-tetrahydro-1*H*-benzo*[c]*azepin-5-yl)acetate (6).** Analogously to **4a**, 3,4-dihydro-1*H*-2-benzazepin-1,5-(2H)-dione (5.2 g, 29.7 mmol) afforded **6** as white crystals after crystallization from diethyl ether/*n*-hexane: 6.8 g, 83.4%; mp 126–127 °C; MS (FAB) *m*/*z* 276 [M–H$^+$].

[5-(2-*tert*-Butoxy-2-oxoethyl)-1-oxo-1,3,4,5-tetrahydro-2*H*-benzo*[c]*azepin-2-yl]acetic acid (7). Analogously to **5a** and **6** (6.28 g, 22.8 mmol) afforded **7** as white crystals after crystallisation from *n*-hexane (H_2O-sat.): 5.2 g, 68%; mp 135–137 °C; MS (FAB) *m*/*z* 334 [M–H$^+$].

***tert*-Butyl (5-oxo-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepine-8-yl)acetate (8).** A mixture of 6,7-dihydro-4*H*-thieno[3,2-*b*]azepine-5,8-dione (5.3 g, 29.2 mmol) and *tert*-butoxycarbonylmethylene-triphenyl phosphorane (12 g, 32.2 mmol) in toluene (15 mL) was heated to reflux for 10 h. Toluene was distilled off and the black residue purified by chromatography (EtOAc/cyclohexane 7:3). The consistent fraction was subjected to boiling cyclohexane (40 mL, cooled and filtered to afford yellowish crystals: 3 g; 36.7%; MS (ESI) *m*/*z* 280.0 [M + H$^+$]. Analogously to **5a**, hydrogenation and purification by chromatography (EtOAc/cyclohexane 7:3) afforded the title compound as yellowish crystals: 1.4 g, 47%; MS (ESI) *m*/*z* 282.1 [M + H$^+$].

[8-(2-*tert*-Butoxy-2-oxoethyl)-5-oxo-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepin-4-yl]acetic acid (9). Analogously to **5a** and **8** (2.92 g, 10.38 mmol) afforded **9** as yellow crystals: 1.2 g, 34%; MS (ESI) *m*/*z* 340.1 [M + H$^+$].

Methyl (2-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]diazepin-1-yl)acetate (10). To a solution of 1,3,4,5-tetrahydro-2*H*-1,5-benzodiazepine-2-one[49] (12.2 g, 75.3 mmol) in DMF (350 mL) at 5 °C was added NaH (1.9 g, 79.8 mmol; 60% dispersion in mineral oil), and the resulting slurry stirred at 5 °C for 30 min and at room temperature for 10 min. To this solution methyl bromo acetate (11.5 g) was added dropwise, and stirred at 5 °C for another 30 min. The reaction mixture was poured into ice water (600 mL) and extracted with EtOAc (3×). The organic phase was washed with brine, dried ($MgSO_4$). Evaporation and chromatography (CH_2Cl_2/MeOH 9:1) afforded **10** as yellow oil: 9.6 g, 54.5%; MS (ESI) *m*/*z* 235.1 [M + H$^+$].

[5-(2-*tert*-Butoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-benzo[*b*][1,4]benzodiazepin-1-yl]acetic acid (11). To a solution of **10** (9.6 g, 41 mmol) and *tert*-butyl bromo acetic acid (8.0 g, 41 mmol) in DMF (90 mL) at 5 °C was added K_2CO_3 (14.2 g, powdered). The mixture was stirred at 5 °C for 1 h and at room temperature for 14 h. The reaction mixture was poured into ice water (300 mL) and extracted with MTBE (100 mL each, 3×) The combined organic phases were washed with brine, dried ($MgSO_4$) and concentrated. The obtained residue was purified by chromatography (EtOAc/cyclohexane 7:3) affording the corresponding ester as slightly yellowish oil: 7.0 g, 49%; MS (ESI) *m*/*z* 349.1 [M + H$^+$]. Analogously to **5a** alkaline saponification yielded the title compound as white crystals: 3.8 g, 57%; mp 140–142 °C; MS (ESI) *m*/*z* 335.1 [M + H$^+$].

***tert*-Butyl 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl-acetate (12).** (a) To a solution of **4a** (10 g, 36.32 mmol) in THF (100 mL) at room temperature was added dropwise B_2H_6 (1 N in THF, 75 mL). The mixture was stirred for 12 h. To this solution H_2O was added, extracted with diethyl ether (2×), the combined organic phases washed with H_2O (3×) and brine, dried ($MgSO_4$) and concentrated to yield 7.45 g of the crude product as yellow oil (78%) which was used in the next step without further purification; MS (ESI) *m*/*z* 262.1 [M + H$^+$].

[5-(2-*tert*-Butoxy-2-oxoethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl]acetic acid (13). To a solution of crude **12** (12 g) in DMF (100 mL) was added K_2CO_3 (6.98 g), KI (0.15 g) and methyl bromoacetate (21.1 g, 137.93 mmol). The mixture was heated to 100 °C for 2 h, then concentrated and the obtained residue taken up in CH_2Cl_2. Washing with brine, drying ($MgSO_4$), evaporation and chromatography (CH_2Cl_2/MeOH 0–2%) afforded the corresponding ester as yellow oil: 12.17 g, 79.5%; MS (ESI) *m*/*z* 334.1 [M + H$^+$]. After dissolution in dioxane (100 mL) and H_2O (40 mL) KOH (3 g, 53.47 mmol) was added and stirred overnight. The mixture then was concentrated, the remainder dissolved in H_2O and adjusted to pH 3 using 2 N HCl. Extraction with CH_2Cl_2, washing with H_2O, drying ($MgSO_4$) and evaporation yielded **13** as orange oil which was used without further purification: 11.0 g, 95%; MS (ESI) *m*/*z* 320.1 [M + H$^+$].

Synthesis of *N*-substituted 2-amino-benzimidazoles, general method:

***Tert*-butyl 4-({[(2-aminophenyl)amino]carbonothioyl}amino)benzylcarbamate (14).** To a mixture of thiocarbonyldiimidazole (24.5 g, 137.5 mmol) and imidazole (1.56 g, 22.9 mmol) in CH_3CN (100 mL) at 0 °C was added dropwise a solution of *tert*-butyl-4-amino-benzylcarbamate (20 g, 89.97 mmol) in CH_3CN (600 mL). The mixture was stirred at room temperature for 12 h, 1,2-phenylenediamine (19.5 g, 180.32 mmol) added and stirred at room temperature for an additional 2 h. The mixture was evaporated, the residue taken up in CH_2Cl_2, and the solution washed thoroughly with 10% citric acid and brine, dried (Na_2SO_4), filtered and concentrated. The resulting brown foam was used in the next step without further purification; MS (ESI) *m*/*z* 373.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.50 (s, 1H), 9.05 (s, 1H), 7.45 (d, 2H), 7.35 (m, 1H), 7.20 (m, 2H), 7.15 (m, 1H), 6.95 (m, 1H), 6.75 (m, 1H), 6.60 (m, 1H), 4.85 (s br., 2H), 4.10 (d, 2H), 1.35 (s, 9H).

***N*-[4-(Aminomethyl)phenyl]-1*H*-benzimidazol-2-amine bishydrochloride (15).** To a mixture of crude **14** in EtOH (750 mL) was added HgO (yellow, 36.7 g) and sulfur (0.4 g). The resulting mixture was heated to reflux for 2 h. Double filtration through Celite and evaporation afforded a brown amorphous solid: 20.7 g, 68%; MS (ESI) *m*/*z* 339.1 [M + H$^+$]. Cleavage of Boc was achieved by first dissolving the solid (8 g, 23.7 mmol) in CH_2Cl_2 (70 mL) and adding a solution of HCl in diethyl ether (sat. at 0 °C). The resulting mixture was stirred at room temperature for 2 h. The resulting precipitate was filtered, washed with CH_2Cl_2, and dried to afford **15** as brown amorphous solid: 6.7 g, 90.8%; MS (ESI) *m*/*z* 239.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 11.6 (s br., 1H), 8.4 (s br., 3H), 8.25 (s br., 1H), 7.65 d, 2H), 7.55 (d, 2H), 7.45 (m, 2H), 7.3 (m, 2H), 4.19 (m, 2H).

***trans*-Benzyl {4-[(*tert*-butoxycarbonyl)amino]cyclohexyl}-methylcarbamate (16).** *trans*-4-({[(Benzyloxy)carbonyl]-amino}methyl)cyclohexanecarboxylic acid (90.4 g, 310 mmol) was converted into the title compound following the previously published method.[50] Treating the resulting crude product with EtOAc afforded **16** as white solid: 68.2 g, 60.6%. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 7.35 (5H, m), 5.15 (s, 2H), 5.00 (t, 1H), 4.45 (s br., 1H), 3.35 (m, 1H), 3.05 (m, 2H), 1.98 (m, 2H), 1.75 (m, 2H), 1.40 (s, 9H), 1.35 (m, superposed by Boc), 1.05 (m, 4H).

***trans*-Benzyl (4-aminocyclohexyl)methylcarbamate trifluoroacetate (17).** To a solution of **16** (20 g, 55.18 mmol) in CH_2Cl_2 (200 mL) at room temperature was added TFA (90 mL) and the resulting mixture stirred for 5 h. Evaporation, azeotropic removal of TFA with toluene, and treatment of obtained residue with MTBE afforded **17** as white solid: 19.9 g, 95.8%, MS (ESI) *m*/*z* 263.1 [M + H$^+$].

***trans*-*N*-{[4-(Aminomethyl)cyclohexyl]}-1*H*-benzimidazol-2-amine bishydrobromide (18).** Analogously to **14** and **17** (5 g, 13.28 mmol) afforded the corresponding amino-benzimidazole (4.5 g, beige foam) which was

used without further purification. Treatment with HBr in glacial acetic acid for 1 h at room temperature, evaporation and azeotropic removal of acetic acid with acetone gave a solid residue which was treated with acetone, filtered and dried to afford **18** as slightly beige solid: 4 g; 84%; MS (ESI) *m/z* 245.2 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.10 (d, 1H), 7.80 (s br., 3H), 7.35 (m, 2H), 7.25 (m, 2H), 3.51 (m, 1H), 2.70 (m, 2H), 2.05 (m, 2H), 1.80 (m, 2H), 1.65 (m, 1H), 1.35 (m, 2H), 1.15 (m, 2H).

***trans*-*N*-[4-(Aminomethyl)cyclohexyl]pyridine-2-amine bishydrochloride (19).** A mixture of **17** (5 g; 13.28 mmol), DIEA (1.7 g) and 2-fluoropyridine (50 mL) was heated to reflux for 18 h. After concentration, the remainder was taken up in EtOAc, washed with 10% citric acid, brine, dried ($MgSO_4$) and concentrated. Crystallization from MTBE/MeOH 1:1 afforded a white solid (4.15 g, 92%); MS (ESI) *m/z* 340.3 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.75 (d, 1H), 7.85 (m, 2H), 7.35 (m, 5H), 7.05 (d, 1H), 6.85 (m, 1H), 5.05 (s, 2H), 2.90 (m, 2H), 1.95 (m, 2H), 1.75 (m, 2H), 1.45.90 (m, 6H). Hydrogenation in the presence of 10% Pd–C (0.4 g) in MeOH (115 mL) at room temperature at atmospheric pressure afforded a yellowish oil which was converted into the corresponding hydrochloride using 4 N HCl in diethyl ether. The resulting precipitate was filtered off and dried to yield an amorphous solid: 1.5 g, 45%; MS (ESI) *m/z* 206.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.05 (s, 1H), 8.20 (s, 3H), 7.85 (m, 2H), 6.80 (m, 1H), 3.80 (m, 1H), 2.72 (m, 2H), 2.02 (m, 2H), 1.80 (m, 2H), 1.65 (m, 1H), 1.30 (m, 2H), 1.15 (m, 2H).

***trans*-*N*-[4-(Aminomethyl)cyclohexyl]-1*H*-imidazole-2-amine bishydrobromide (20).** (a) To a mixture of **17** (3.0 g, 7.97 mmol) and 2.75 g sodium acetate in MeOH (40 mL) at 0 °C was added dropwise a solution of BrCN (1.26 g,14.73 mmol) in MeOH (10 mL). The mixture was stirred at 0 °C for 3 h and at room temperature for an additional 12 h and concentrated. The obtained residue was taken up in H_2O, extracted twice with MTBE, dried ($MgSO_4$) and evaporated. Chromatography (EtOAc/heptane 50%) afforded **20a** as a white solid (1.52 g, 66%); MS/ESI) *m/z* 288.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.45.25 (m, 6H), 6.75 (d, 1H), 5.05 (d, 2H), 2.85 (m, 3H), 1.85 (m, 2H), 1.70 (m, 2H), 1.35 (m, 1H), 1.20 (m, 2H), 0.95 (m, 2H).

(b) Through a solution of **20a** (1.52 g) and Et_3N (5.35 g) in pyridine (50 mL) at 0 °C was passed H_2S for 1 h. The mixture was allowed to stand at room temperature for 3 days, then evaporated affording the corresponding thiourea as beige foam: 0.77 g. The foam was dissolved in CH_2Cl_2 (15 mL), CH_3I (0.68 g) was added at room temperature, and the mixture stirred for 2 days. Evaporation afforded an orange oil: 1.48 g; MS (ESI) *m/z* 336.1 [M + H$^+$]. Reaction with 2,2-diethoxyethanamine (0.44 g) in CH_3CN (20 mL) for 5 h under reflux and concentration afforded 1.7 g of a yellow oil (MS (ESI) *m/z* 421.2 [M + H$^+$]) that was dissolved in 6 N HCl (40 mL) and stirred at 0 °C for 4 h. A pH of 12 was maintained using a 25% NaOH solution and stirring continued for an additional 12 h. The reaction mixture was extracted with EtOAc (4×), the combined organic phases were dried ($MgSO_4$) and concentrated to afford **20b**: 0.8 g, 77% (based on the corresponding thiourea); MS/ESI) *m/z* 329.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.45.25 (m, 6H), 6.45 (s, 2H), 5.35 (d, 1H), 5.05 (s, 2H), 3.25 (m, 1H, superposed by H_2O), 2.90 (m, 2H), 1.95 (m, 2H), 1.70 (m, 2H), 1.35 (m, 1H), 1.15 (m, 2H), 0.95 (m, 2H).

(c) The mixture of **20b** (0.7 g, 2.13 mmol) and HBr in HOAc (30 mL) was stirred at room temperature for 3 h. The solution was then evaporated and the resulting residue stirred with MTBE to afford **20**: 0.98 g, 95%; MS (ESI) *m/z* 195.1 [M + H$^+$].

***trans*-*N*-[4-(Aminomethyl)cyclohexyl]-*N'*-benzylurea hydrochloride (21).** To a solution of *tert*-butyl-(4-aminocyclohexyl)methylcarbamate[51] (2.7 g, 6.55 mmol) and Et_3N (1.3 g) in toluene (50 mL) and DMF (10 mL) was added dropwise benzylisocyanate (1.3 g) and the mixture heated to reflux for 3 h. After evaporation, the resulting residue was dissolved in EtOAc, washed with 10% citric acid (3×), $NaHCO_3$ (sat., 1×), brine, dried ($MgSO_4$) and concentrated. Treatment of the resulting solid with MTBE afforded the desired urea as white solid: 2.1 g, 88%; MS (ESI) *m/z* 306.1 [M + H$^+$–^{t}Bu]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.30 (m, 2H), 7.25 (m, 3H), 6.80 (t, 1H), 6.15 (t, 1H), 5.75 (d, 1H), 4.20 (d, 2H), 2.72 (m, 2H), 1.80 (m, 2H), 1.65 (m, 2H), 1.40 (s, 9H), 1.28 (m, 1H), 1.05.80 (m, 5H). A solution of the above urea (2 g) in dioxane (30 mL) was treated with 4 N HCl in dioxane at room temperature for 4 h. The resulting white precipitate was filtered off, washed with MTBE and dried to afford **21** as white solid: 1.1 g, 67%; MS (ESI) *m/z* 262.1 [M + H$^+$].

***trans-tert*-Butyl [4-(1,8-naphthyridin-2-yl)cyclohexyl]methylcarbamate (22).** (a) A mixture of 4-{[(*tert*-butoxycarbonyl)amino]methyl}cyclohexanecarboxylic acid (10.1 g, 40 mmol), *N*,*O*-dimethylhydroxylamine hydrochloride (3.8 g, 40 mmol), NMM (27.6 g, 0.27 mol) and EDC (9.44 g, 50.0 mmol) in CH_3CN (200 mL) was stirred at room temperature for 2 days. The solution was concentrated, the residue taken up in EtOAc, washed subsequently with H_2O, 10% $KHSO_4$, $NaHCO_3$ (sat.), brine, dried ($MgSO_4$) and filtered. Evaporation afforded **22a** as a yellow oil: 5.8 g, 49.6%; MS (ESI) *m/z* 245.1 [M + H$^+$-tBu].

(b) To a solution of **22a** (5.8 g, 20 mmol) in THF (80 mL) at 0 °C was added dropwise methyl magnesium bromide (40 mmol, 12 mL of 3 M solution in diethyl ether), and the resulting solution was stirred for 2 h at the 0 °C and overnight at room temperature. The mixture was acidified cautiously using a 10% $KHSO_4$ solution and extracted with EtOAc. The organic phase was washed with $NaHCO_3$ (sat.), brine, dried ($MgSO_4$) and evaporated to afford **22b**: 4.12 g, 83.4%; MS (ESI) *m/z* 278.1 [M + Na$^+$].

(c) A mixture of **22b** (4.0 g, 15.66 mmol), 2-aminonicotinaldehyde[52] (2.18 g, 17.86 mmol) and KOH (0.6 mL,

20% aqueous solution) was heated to reflux for 5 h. Concentration and chromatography of the obtained residue (MTBE/MeOH) afforded the title compound: 4.25 g, 80%; MS (ESI) *m/z* 342.1 [M + H$^+$]. ^{1}H NMR (360 MHz, $CDCl_3$) δ: 9.09.04 (m, 1H), 8.14 (dd, 1H), 8.09 (d, 1H), 7.45.40 (m, 1H), 7.38 (d, 1H), 4.61 (s br., 1H), 3.05 (t, 1H), 2.95 (m, 1H), 2.12 (d, 2H), 1.95 (d, 2H), 1.79 (m, 2H), 1.63 (s, 2H), 1.46 (s, 9H), 1.15 (m, 2H).

***trans*-[4-(5,6,7,8-Tetrahydro-1,8-naphthyridin-2-yl)cyclohexyl]methylamine bishydrochloride (23).** (a) A suspension of **22** (1.5 g, 4.39 mmol) and 10% Pd–C (0.25 g) in EtOH (20 mL) was hydrogenated at room temperature and atmospheric pressure. Filtration through Celite and concentration afforded **23a** as white solid: 1.43 g, 94%; MS (ESI) *m/z* 346.2 [M + H$^+$].

(b) Treatment of **23a** (2.5 g, 83.8 mmol) in CH_2Cl_2 (50 mL) with TFA (5.6 mL) and concentration afforded a crude oil which was dissolved in H_2O and extracted with EtOAc (3×). Evaporation of the combined organic layers afforded **23** a white solid: 1.48 g, 82.4%; MS (ESI) *m/z* 246.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 14.35 (s, 1H), 8.35 (s, 1H), 8.10 (s br., 3H), 7.60 (d, 1H), 6.55 (d, 1H), 3.55.30 (m, superposed by H_2O), 2.80.55 (m, 5H), 2.0.75 (m, 6H), 1.70.50 (m, 3H), 1.05 (m, 2H).

***N*-{[5-(Aminomethyl)thien-3-yl]methyl}-1*H*-benzimidazol-2-amine bishydrochloride (24).** (a) Through a solution of *tert*-butyl-(4-cyanothien-2-yl)methylcarbamate[53] (13.5 g, 56.65 mmol) in EtOH (240 mL) NH_3 was passed. After addition of Ra-Ni (18 g aqueous suspension; decanted with EtOH) the mixture was hydrogenated at room temperature and atmospheric pressure. Filtration of the mixture, evaporation and chromatography of the obtained residue (CH_2Cl_2/MeOH + 1% Et_3N) afforded a yellowish oil which was converted into the corresponding hydrochloride by addition of HCl in diethyl ether. Filtration and drying afforded **24a** as white amorphous solid: 9.8 g, 62%. ^{1}H NMR ('free' amine) (360 MHz, DMSO-d_6) δ: 7.48 (t, 1H), 7.05 (s, 1H), 6.85 (s, 1H), 4.20 (d, 2H), 3.60 (s, 2H), 2.40 (s br., 2H), 1.40 (s, 9H).

(b) Analogously to **14** and **15**, amine **24a** (6.5 g, 23.31 mmol) afforded the desired amino-benzimidazole: 1.6 g; MS (ESI) *m/z* 359.2 [M + H$^+$]. Cleavage of Boc using 4 N HCl in dioxane and treatment with MTBE afforded **24** as slightly yellowish solid: 1.3 g, 15.6%; MS (ESI) *m/z* 259.0 [M + H$^+$].

***trans*-*N*-[(4-Aminocyclohexyl)methyl]-1*H*-benzimidazol-2-amine bishydrochloride (25).** Analogously to **15**, *tert*-butyl 4-(aminomethyl)cyclohexylcarbamate[54] (5.4 g, 23.65 mmol) afforded the desired amino-benzimidazole. Cleavage of Boc by treatment with 4 N HCl in dioxane afforded **25** as white solid: 3.3 g, 44.2%; MS (FAB) *m/z* 245 [M + H$^+$]. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 13.1 (s br., 2H), 9.42 (t, 1H), 8.25 (s, 3H), 7.40 (m, 2H), 7.20 (m, 2H9, 3.34 (m, 2H), 2.95 (m, 1H), 2.03 (m, 2H), 1.95 (m, 2H), 1.63 (m, 1H), 1.38 (m, 2H), 1.09 (m, 2H).

***N*-(Piperidin-4-ylmethyl)-1*H*-benzimidazol-2-amine trifluoracetate (26).** (a) To a mixture of thiocarbonyldiimidazole (6.75 g, 37.88 mmol) and imidazole (0.5 g, 7.34 mmol) in CH_3CN (100 mL) at room temperature was added dropwise a solution of *tert*.-butyloxycarbonyl-4-(aminomethyl)-1-piperidine (5.38 g, 25 mmol) in CH_3CN (25 mL). The mixture was stirred for 3 h at room temperature. 1,2-Phenylenediamine (5.5 g, 50.86 mmol) was added and the mixture heated to 60 °C for 1 h. Upon cooling a solid precipitated which was filtered off and dried: 6.8 g, 74.5%; MS (ESI) *m/z* 309.1 [M + H$^+$].

(b) Analogously to **15**, cyclodesulfurization of **26a** (5 g, 13.72 mmol) and subsequent chromatography (CH_2Cl_2/MeOH 5–25%) afforded the amino-benzimidazole as beige foam: 2.65 g, 75.6%; MS (ESI) *m/z* 331.2 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO) δ ppm: 7.15 (m, 2H), 6.9 (m, 2H), 3.95 (d, 2H), 3.2 (m 2H), 2.7 (m; 2H), 1.8 (m, 1H), 1.7 (m, 2H), 1.35 (s, 9H), 1.05 (m, 2H). Stirring with TFA (50 mL), evaporation and treatment of the obtained residue with *n*-pentane afforded **26** as slightly beige amorphous solid: 2.3 g, 63%; MS (ESI) *m/z* 231.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 13.25 (s, 1H), 9.35 (m, 1H), 8.80 (s br., 1H), 8.50 (s br., 1H), 7.40 (m, 2H), 7.20 (m, 2H), 3.30 (m, 4H), 2.85 (m, 2H), 1.9 (m, 3H), 1.35 (m, 2H).

***N*-(1*H*-Benzimidazol-2-yl)butane-1,4-diamine trifluoracetate (27).** Analogously to **15**, *N*-Boc-1,4-diaminobutane (9.87 g, 52.3 mmol) afforded the amino-benzimidazole. Stirring with TFA (60 mL), evaporation, treatment with *n*-pentane and recrystallization from MeOH/MTBE 1:1 afforded **27** as amorphous solid: 14.35 g, 65.8%; MS (ESI) *m/z* 205.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO) δ: 9.20 (t, 1H), 7.80 (s br., 3H), 7.35 (m, 2H), 7.20 (m, 2H), 3.40 (m, 2H partially superposed with H_2O-peak), 2.80 (m, 2H), 1.65 (m, 4H).

***N*-(1*H*-Benzimidazol-2-yl)pentane-1,5-diamine hydrochloride (28).** Analogous to **27**, *N*-Boc-1,5-diaminopentane×HCl (7.0 g, 29.3 mmol) afforded the amino-benzimidazole, subsequent stirring with TFA (30 mL), conversion into the corresponding hydrochloride by precipitation with sat. HCl in diethyl ether and treatment with a mixture of MeOH/MTBE afforded **28** as reddish amorphous solid: 5.7 g, 81%; MS (ESI) *m/z* 219.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.30 (t, 1H), 8.15 (s br., 3H), 7.40 (m, 2H), 7.25 (m, 2H), 3.35 (m, 2H partially superposed with H_2O), 2.80 (m, 2H), 1.65 (m, 4H), 1.45 (m, 2H).

***N*-(1*H*-Benzimidazol-2-yl)propane-1,3-diamine trifluoracetate (29).** Analogously to **15**, *N*-Boc-1,3-diaminopropane (4.99 g, 28.64 mmol) afforded the amino-benzimidazole. After stirring with TFA (60 mL) and concentration a brown oil was obtained that was refluxed with charcoal (2 g) in CH_3OH, filtrated and concentrated again. Treatment with MTBE afforded **29** as brownish solid: 6.0 g, 89.6%; MS (ESI) *m/z* 191.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.85 (s br., 3H), 7.43 (m, 2H), 7.22 (m, 2H), 3.45 (m, 2H), 2.90 (m, 2H), 1.87 (m, 2H).

[(5*R*)-5-(2-*tert*-Butoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-1-yl]acetic acid (5a*R*). **5a** (14.2 g, 42.6 mmol) was suspended in diethyl ether (170 mL) and dissolved by addition of (1*S*)-(−)-1-(naphtyl)ethylamine (7.3 g, 42.64 mmol). The yellow solution was treated with (1*S*)-1-naphtyl)ethaneaminium[(5*R*)-5-(2-*tert*-butoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzazepin-1-yl]acetate prepared previously by preparative HPLC-separation of compound **5a** using a chiral column (Chiralpak AD 500×; 50 mm; 20 μm) and subsequent conversion into the respective salt. The solution was stirred for 3 h, the resulting precipitate filtered off and recrystallized three times from a mixture of EtOAc/isopropanole. Purity of the obtained enantiomers was checked by chiral HPLC. To a suspension of the hydrochloride salt (3.5 g) in a mixture of diethyl ether/*n*-hexane (10:3; 30 mL) was added an aqueous solution of amidosulfonic acid and the mixture stirred until occurrence of a clear phase. The organic layer was washed with amidosulfonic acid (3×), brine, dried (Na_2SO_4) and evaporated yielding **5a*R*** as amorphous solid: 2.25 g, 15.8%.

A sample of above acid was reacted with 4-bromobenzylamine and crystallized. The absolute configuration was determined by single crystal X-ray structural analysis.

tert*-Butyl ((5*R*)-1-{2-[(4-bromobenzyl)amino]-2-oxoethyl}-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)acetate (30).** To a solution of **5a*R (2.0 g, 6 mmol), 4-bromobenzylamine (1.4 g), Et_3N (3.5 g) in CH_2Cl_2 (30 mL) at 0 °C was added a solution of PPA (6.5 mL, 50% in EtOAc) and the mixture stirred for 1 h. After addition of H_2O (50 mL) the organic layer was washed with 5% NaHCO3 (2×), 5% citric acid, H_2O and dried ($MgSO_4$). After evaporation the amorphous solid was treated with diethyl ether to afford a fine-cristalline solid that was recrystallized from MeOH (40 mL), filtered and dried. X-ray analysis proved the *R*-configuration. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.65 (t, 1H), 7.48 (d, 2H), 7.30 (m, 2H), 7.20 (m, 4H), 4.40 (m, 1H), 4.28 (m, 3H), 3.55 (m, 1H), 2.71 (m, 2H), 2.27 (m, 1H), 2.15 (m, 2H), 1.68 (m, 1H), 1.30 (s, 9H).

[(5*S*)-5-(2-*tert*-Butoxy-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-1-yl]acetic acid (5a*S*). Taking the combined mother liquors of **5a*R*** the acid (8 g) was isolated as a yellowish amorphous residue as described for the preparation of **5a*R***. The acid was converted into the diasteromeric salt using (1*R*)-(+)-1-naphtyl)ethylamin which was recrystallized. Analogously to **5a*R*** the title compound was obtained as amorphous solid: 2.5 g, 17.6%.

General procedure for the synthesis of compounds 31–47 and 52–60:

Method A

[1-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-5-yl]acetic acid (31). To a mixture of **5a** (4.78 g, 14.35 mmol) and **15** (3.4 g, 14.4 mmol) in DMF (20 mL) at 5 °C was added dropwise NMM (1.5 g). TOTU (4.7 g, 14.5 mmol) was then introduced in portions over the course of 30 min, the resulting yellow solution stirred for 1 h and evaporated. The residue was treated with H_2O, dissolved in a mixture of EtOAc and diethyl ether 1:1, washed with 10% K_2CO_3, brine, dried (Na_2SO_4), and concentrated. Purification by chromatography (CH_2Cl_2/MeOH + 0.1% NH_3) afforded the desired *tert*-butyl ester as white amorphous solid: 5.8 g, 73%. To a solution of the above *tert*-butyl ester (5.4 g, 9.8 mmol) in CH_2Cl_2 (80 mL) at room temperature was added 4 N HCl in dioxane (100 mL) and the mixture stirred for 12 h. Evaporation, treatment with CH_2Cl_2 and drying afforded the title compound as slightly yellowish amorphous residue: 4.5 g; 92.6%. Mp 188–190 °C; ^{1}H NMR (360 MHz, DMSO-d_6) δ: 10.89 (s, 1H), 9.37 (s, 1H), 8.48 (t, 1H), 7.68 (d, 2H), 7.33.19 (m, 8H), 6.97 (m, 2H), 4.50 (m, 1H), 4.26.17 (m, 3H), 3.60.45 (1H, superposed by H_2O), 2.75.63 (m 2H), 2.32 (m, 1H), 2.11 (m, 2H), 1.59 (m, 1H). Anal. ($C_{28}H_{27}N_5O_4\times$HCl) C (calcd 62.01, found 63.05), H, N. HRMS (ESI) calcd, 496.1985; found, 496.1985 [M–H$^+$].

Method B

(1-{2-[({4-[(1*H*-Benzimidazol-2-ylamino)methyl]thien-2-yl}methyl)amino]-2-oxoethyl}-2-oxo-2,3,4,5-tetrahydro-1*H*-benz[*b*]azepine-5-yl)acetic acid (32). To a solution of **5a** (0.23 g, 0.78 mmol) in CH_2Cl_2 (10 mL) at 10 °C were added HATU (0.3 g, 0.94 mmol) and 0.13 mL DIEA and the solution stirred for 1 h. After cooling to 0 °C, **24** (0.25 g, 0.78 mmol) and DIEA (0.13 mL) were added, and the mixture stirred for an additional 5 min. The solution was then adjusted to pH 7–8 by dropwise addition of DIEA, stirred for 1 h at 0 °C and additional 12 h at room temperature. The mixture was concentrated, taken up in EtOAc, washed with 5% citric acid, 5% $NaHCO_3$, brine, dried (Na_2SO_4) and evaporated again. The resulting residue was then stirred with TFA (5 mL) at room temperature for 1 h. Evaporation and azeotropic removal of TFA using toluene afforded a brown oil which was purified by MPLC. Concentration and lyophilizing afforded **32** as slightly yellowish amorphous solid: 90 mg, 23%. For elemental analysis a sample was converted into the corresponding hydrochloride. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.15 (s br., 1H), 8.69 (m, 1H), 7.34 (m, 3H), 7.27 (m, 2H), 7.19 (m, 4H), 6.99 (s, 1H), 4.51 (d, 2H), 4.46 (m, 1H), 4.42 (d, 2H), 4.16 (m, 1H), 3.50.35 (1H, superposed by H_2O), 2.72 (m, 1H), 2.64 (m, 1H), 2.32 (m, 1H), 2.09 (m, 2H), 1.65 (m, 1H). HRMS (ESI) for $C_{27}H_{27}N_5O_4S$: calcd, 516.1706; found, 516.1710 [M–H$^+$].

The following compounds were prepared analogously.

[1-(2-{4-[(1*H*-Benzimidazol-2-ylamino)methyl]piperidin-1-yl}-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*4*]azepine-5-yl]acetic acid (33). Reaction of **5a** (0.25 g, 0.75 mmol) with **26** (0.46 g, 0.82 mmol) using method B and purification by MPLC afforded **33** as amorphous white solid: 134 mg, 36.5%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.85 (m br., 1H), 7.35 (m, 2H), 7.30.15 (m, 6H), 4.75 (m, 1H), 4.50.28 (m, 2H), 3.90 (m, 1H),

3.65.50 (m, 2H), 3.05 (m, 1H), 2.71 (m, 2H), 2.32 (m, 1H), 2.13 (m, 2H), 1.90 (m, 1H), 1.76 (m, 2H), 1.58 (m, 1H), 1.3.0 (m, 4H). HRMS (ESI) for $C_{27}H_{31}N_5O_4$: calcd, 488.2298; found, 488.2327 [M–H$^+$].

(1-{2-[4-(1*H*-Benzimidazol-2-ylamino)piperidin-1-yl]-2-oxoethyl}-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-5-yl)acetic acid×HOAc (34). Reaction of **5a** (0.6 g, 1.8 mmol) with *N*-piperidin-4-yl-1*H*-benzimidazol-2-amine bistrifluoroacetate[55] (0.8 g, 1.8 mmol) using method A and work up as described afforded **34** as white amorphous solid: 0.45 g, 46.8%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.32.23 (m, 4H), 7.12 (m, 2H), 6.92 (m, 1H), 6.85 (m, 2H), 4.90 (m, 1H), 4.49 (m, 1H), 4.18 (m, 1H), 4.78 (m, 2H), 4.60 (m, 1H), 3.20 (m, 1H), 2.92 (m, 1H), 2.65 (m, 2H), 2.30 (m, 1H), 2.13 (m, 2H), 1.97 (m, 1H), 1.89 (s, 3H), 1.71.35 (m, 4H). HRMS (ESI) for $C_{26}H_{29}N_5O_4\times C_2H_4O_2$: calcd, 474.2141; found, 474.2144 [M−H$^+$].

[1-(2-{[4-(1*H*-Benzimidazol-2-ylamino)butyl]amino}-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-5-yl]acetic acid×HOAc (35). Reaction of **5a** (1.04 g, 3.1 mmol) with **27** (1.0 g, 3.28 mmol) using method A yielded **35** as slightly yellowish amorphous solid: 0.5 g, 36.3%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.98 (t br., 1H), 7.54 (s br., 1H), 7.29 (m, 2H), 7.19 (m, 4H), 6.97 (m, 2H), 4.38 (m, 1H), 4.22 (m, 1H), 3.70.25 (3H, superposed by H_2O), 3.12 m, (2H), 2.63 (m, 2H), 2.30 (m, 1H), 2.06 (s, 2H), 1.90 (s, 3H), 1.55.47 (m, 5H). HRMS (ESI) for $C_{25}H_{30}N_5O_4\times C_2H_4O_2$: calcd, 462.2141; found, 496.2148 [M–H$^+$].

[1-(2-{[5-(1*H*-Benzimidazol-2-ylamino)pentyl]amino}-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-5-yl]acetic acid (36). Reaction of **5a** (1.04 g, 3.1 mmol) with **28** (0.75 g, 3.1 mmol) using method A afforded **36** as slightly yellowish amorphous solid: 0.48 g, 8.8%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.13 (s br., 1H), 8.04 (m br., 1H), 7.28 (m, 4H), 7.22 (m, 2H), 7.09 (m, 2H), 4.39 (m, 1H), 4.13 (m, 1H), 3.70.25 (2H, superposed by H_2O), 3.10 (m, 2H), 2.76.65 (m, 3H), 2.70 (m, 2H), 2.31 (m, 1H), 2.11 (m, 2H), 1.63 (m, 3H), 1.46 (m, 2H), 1.34 (m, 2H). HRMS (ESI) for $C_{26}H_{31}N_5O_4$: calcd, 476.2298; found, 476.2294 [M–H$^+$].

***trans*-{1-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-5-yl}acetic acid (37).** Reaction of **5a** (0.6 g, 1.8 mmol) with **18** using method A afforded **37** as slightly yellowish amorphous solid: 0.5 g, 55.2%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.00 (t, 1H), 7.28 (m, 2H), 7.23 (m, 2H), 7.10 (m, 2H), 6.84 (m, 2H), 6.70 (d, 1H), 4.45 (m, 1H), 4.12 (m, 1H), 3.40 (m, 2H), 2.97 (m, 2H), 2.61 (m, 2H), 2.31 (m, 1H), 2.13 (m, 2H), 2.02 (m, 2H), 1.75 (m, 2H), 1.54 (m, 1H), 1.38 (m, 1H), 1.21 (m, 2H), 1.09 (m, 2H). Anal. ($C_{28}H_{33}N_5O_4\times$HCl) C, H, N. HRMS (ESI) calcd, 502.2454; found, 502.2454 [M–H$^+$].

***trans*-{1-[2-({4-[(1*H*-Benzimidazol-2-ylamino)methyl]-cyclohexyl}amino)-2-oxoethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-5-yl}acetic acid×HOAc (38).** Reaction of **5a** (0.6 g, 1.8 mmol) with **25** (0.5 g, 1.8 mmol) using method A afforded **38** as slightly yellowish amorphous solid: 0.7 g, 52.4%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.87 (d, 1H), 7.28 (m, 2H), 7.26 (m, 2H), 7.08 (m, 2H), 6.84 (m, 3H), 4.42 (m, 1H), 4.03 (m, 1H), 3.75.25 (2H, superposed by H_2O), 3.11 (m, 2H), 2.62.52 (m, 2H), 2.32 (m, 1H), 2.10 (m, 2H), 1.89 (s, 3H), 1.82 (m, 4H), 1.53 (m, 2H), 1.15 (m, 2H), 1.00 (m, 2H). HRMS (ESI) for $C_{28}H_{33}N_5O_4\times C_2H_4O_2$: calcd, 502.2454; found, 502.2449 [M–H$^+$].

[2-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-1-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl]acetic acid (39). Reaction of **7** (0.57 g, 1.8 mmol) with **15** using method A afforded **39** as white amorphous solid: 0.5 g, 55.8%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.81 (s, 1H), 8.48 (t, 1H), 7.64 (d, 2H), 7.51 (m, 2H), 7.49.14 (m, 6H), 7.05 (m, 2H), 4.29 (m, 2H), 4.21 (s, 2H), 3.50.30 (1H, superposed by H_2O), 3.28 (m, 1H), 3.12 (m, 1H), 2.80 (dd, 1H), 2.70 (dd, 1H), 2.34 (m, 1H), 1.48 (m, 1H). HRMS (ESI) for $C_{28}H_{27}N_5O_4$: calcd, 496.1985; found, 496.1993 [M–H$^+$].

***trans*-{2-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-1-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl}acetic acid×HCl (40).** Reaction of **7** (0.6 g, 1.8 mmol) with **18** (0.57 g, 1.8 mmol) using method A and lyophilizing the resulting oil afforded **40** of a white amorphous solid: 0.35 g, 36.5%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.87 (d, 1H), 8.03 (t, 1H), 7.46 (m, 2H), 7.35 (m, 2H), 7.21 (m, 4H), 4.15 (m, 2H), 3.55.20 (3H, superposed by H_2O), 3.18.99 (m, 3H), 2.82 (dd, 1H), 2.76 (dd, 1H), 2.35 (m, 1H), 2.02 (m, 2H), 1.81 (m, 2H), 1.45.20 (m, 4H), 1.05 (m, 2H). HRMS (ESI) for $C_{28}H_{33}N_5O_4\times$HCl: calcd, 502.2454; found, 502.2454 [M–H$^+$].

[2-(2-{[5-(1*H*-Benzimidazol-2-ylamino)pentyl]amino}-2-oxoethyl)-1-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl]acetic acid×HCl (41). Analogously by reaction of **7** (0.87 g, 2.6 mmol) with **28** (0.79 g, 3.1 mmol) afforded **41** as white solid: 0.67 g, 50.2%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.05 (t, 1H), 8.04 (t, 1H), 7.45 (m, 2H), 7.36 (m, 2H), 7.32 (m, 1H), 7.21 (m, 3H), 4.12 (s, 2H), 3.50.30 (3H, superposed by H_2O), 3.17 (dd, 1H), 3.11 (m, 2H), 3.05 (m, 1H), 2.75 (dd, 1H), 2.65 (dd, 1H), 2.32 (m, 1H), 1.64 (m, 2H), 1.50.35 (m, 5H). HRMS (ESI) for $C_{26}H_{31}N_5O_4\times$HCl: calcd, 478.2454; found, 478.2435 [M + H$^+$].

[2-(2-{[4-(1*H*-Benzimidazol-2-ylamino)butyl]amino}-2-oxoethyl)-1-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl]acetic acid×HCl (42). Reaction of **7** (0.87 g, 2.6 mmol) with **27** (1.0 g, 2.6 mmol) and cleavage of the *tert*-butyl ester with 4 N HCl in dioxane using HOAc as solvent afforded **42** as white amorphous solid: 0.65 g, 50.1%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.05 (t, 1H), 8.09 (t, 1H), 7.46 (m, 2H), 7.35 (m, 2H), 7.28 (m, 1H), 7.21 (m, 3H), 4.13 (s, 2H), 3.50.35 (m, 3H), 3.16 (m, 3H), 3.05 (m, 1H), 2.79 (dd, 1H), 2.65 (dd, 1H), 2.31 (m, 1H), 1.64 (m, 2H), 1.54 (m, 2H), 1.43 (m, 1H). HRMS

(ESI) for $C_{25}H_{29}N_6O_4\times HCl$: calcd, 464.2298; found, 464.2291 [M + H$^+$].

[2-(2-{[4-(1*H*-Benzimidazol-2-ylamino)propyl]amino}-2-oxoethyl)-1-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepin-5-yl]acetic acid×HCl (43). Reaction of **7** (0.87 g, 2.6 mmol) with **29** (1.05 g, 3.1 mmol) and standard cleavage of the *tert*-butyl ester with 4 N HCl in dioxane using HOAc as solvent afforded **43** as white amorphous solid: 0.72 g, 57.4%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.94 (t, 1H), 8.17 (t, 1H), 7.46 (m, 2H), 7.36 (m, 2H), 7.32 (m, 1H), 7.21 (m, 3H), 4.16 (m, 2H), 3.50.35 (4H, superposed by H_2O), 3.23 (m, 2H), 3.05 (m, 1H), 2.77 (dd, 1H), 2.64 (dd, 1H), 2.31 (m, 1H), 1.91 (m, 2H), 1.44 (m, 1H). HRMS (ESI) for $C_{24}H_{27}N_6O_4\times HCl$: calcd, 450.2141; found, 450.2152 [M + H$^+$].

***trans*-{2-Oxo-1-[2-oxo-2-({[4-(pyridin-2-ylamino)cyclohexyl]methyl}amino)ethyl]-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl}acetic acid (44).** Reaction of **5a** (0.5 g, 1.5 mmol) with **19** (0.5 g, 1.6 mmol) using method B afforded 0.5 g of the corresponding *tert*-butyl ester. The ester (0.4 g, 0.77 mmol) was treated with TFA (15 mL), chromatography of the obtained residue via Chromabond-RP18 afforded **44** as white solid: 85 mg, 23%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.02 (m, 1H), 7.94 (d, 1H), 7.87 (m, 1H), 7.31 (m, 2H), 7.21 (m, 2H), 6.93 (d, 1H), 6.78 (m, 1H), 4.45 (m, 1H), 4.19 (m, 1H), 3.51 (m, 2H), 2.97 (m, 2H), 2.94 (m, 2H), 2.31 (m, 1H), 2.12 (m, 2H), 1.95 (m, 2H), 1.74 (m, 2H), 1.56 (m, 1H), 1.40 (m, 1H), 1.27 (m, 2H), 1.03 (m, 2H). HRMS (ESI) for $C_{26}H_{32}N_4O_4$: calcd, 463.2345; found, 463.2345 [M–H$^+$].

***trans*-[1-(2-{[(4-{[(Benzylamino)carbonyl]amino}cyclohexyl)methyl]amino}-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl]acetic acid (45).** Reaction of **5a** (0.165 g, 0.5 mmol) with **21** (0.13 g, 0.5 mmol) using method A afforded 0.32 g of the corresponding *tert*-butyl ester; MS (ESI) *m*/*z* 577.1 [M + H$^+$]. The ester (0.1 g, 0.17 mmol) was treated with TFA (10 mL), and the obtained crude product partitioned between EtOAc and H_2O. The aqueous layer was adjusted to pH 10 by addition of a 0.1 N NaOH solution, extracted with EtOAc and then the pH adjusted to 4 by adding 1 N HCl. After extraction with CH_2Cl_2 the organic layer was washed again, dried (Na_2SO_4) and evaporated to afford **45** as white solid: 80 mg, 88.6%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.96 (t, 1H), 7.30 (m, 4H), 7.20 (m, 5H), 6.15 (t, 1H), 5.76 (d, 1H), 4.40 (m, 1H), 4.18 (m, 2H), 4.13 (m, 1H), 3.49 (m, 1H), 2.92 (m, 2H), 2.65 (m, 1H), 2.35 (m, 1H), 2.13 (m, 2H), 1.90 (m, 2H), 1.65 (m, 2H), 1.31 (m, 1H); 1.20.83 (m, 5H). HRMS (ESI) for $C_{29}H_{36}N_5O_4$: calcd, 519.2607; found, 519.2608 [M–H$^+$].

***trans*-{1-[2-({[4-(1*H*-Imidazol-2-ylamino)cyclohexyl]methyl}amino)-2-oxoethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine-5-yl}acetic acid×HOAc (46).** Reaction of **5a** (0.5 g, 1.5 mmol) with **20** (0.44 g, 1.95 mmol) using method B afforded **46** as slightly brownish solid: 0.57 g, 68.3%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.98 (t, 1H), 7.29 (m, 2H), 7.21 (m, 2H), 6.64 (s, 2H), 6.47 (s br., 1H), 4.37 (m, 1H), 4.31 (m, 1H), 3.45.10 (2H, superposed by H_2O), 2.95 (m, 2H), 2.69 (m, 2H), 2.31 (m, 1H), 2.11 (m, 2H), 1.99 (m, 2H), 1.89 (s, 3H), 1.70 (m, 2H), 1.55 (m, 1H), 1.35 (m, 1H), 1.12 (m, 2H), 0.98 (m, 2H). HRMS (ESI) for $C_{24}H_{31}N_5O_4\times C_2H_4O_2$: calcd, 452.2298; found, 452.2302 [M-H$^+$].

***trans*-{2-Oxo-1-[2-oxo-2-({[4-(5,6,7,8-tetrahydro-1,8-naphthyridin-2-yl)cyclohexyl]methyl}amino)ethyl]-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl}acetic acid-×TFA (47).** Reaction of **5a** (0.26 g, 0.78 mmol) with **23** (0.3 g, 0.94 mmol) using method B yielded the corresponding *tert*-butyl ester as white solid: 0.31 g, 71.1%; MS (ESI) *m*/*z* 561.3 [M + H$^+$]. The ester (0.2 g, 0.36 mmol) in CH_2Cl_2 (30 mL) was treated with TFA (0.8 mL) affording 47 as amorphous solid: 0.21 g, 95.6%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.07 (t, 1H), 7.8 (s, 1H), 7.63 (d, 1H), 7.31 (m, 2H), 7.22 (m, 2H), 6.62 (d, 1H), 4.43 (m, 1H), 4,16 (m, 1H), 3.50.25 (2H, superposed by H_2O), 2.98 (m, 2H), 2.75.63 (m, 4H), 2.56 (m, 2H), 2.32 (m, 1H), 2.11 (m, 2H), 1.95.81 (m, 6H), 1.65.55 (m, 3H), 1.43 (m, 2H), 0.98 (m, 2H). HRMS (ESI) for $C_{29}H_{36}N_4O_4\times C_2HF_3O_2$: calcd, 505.2787; found, 525.2787 [M + H$^+$].

[1-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl]-acetic acid (53). Reaction of **13** (0.5 g, 1.57 mmol) with **15** (0.7 g, 1.72 mmol) using method A, chromatography (CH_2Cl_2/MeOH 2–5%) and treatment of the corresponding *tert*-butyl ester with TFA afforded **53** as white foam: 0.41 g, 44.4%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 10.85 (s br., 1H), 8.29 (t, 1H), 7.40 (m, 4H), 7.31 (m, 2H), 7.23 (m, 2H), 7.09 (m, 2H), 6.89 (m, 2H), 4.34 (m, 2H), 3.87 (d, 1H), 3.82 (d, 1H), 3.51 (1H, superposed by H_2O), 2.98 (m, 2H), 2.71 (m, 2H), 1.70 (m, 1H), 1.64 (m, 2H), 1.46 (m, 1H). HRMS (ESI) for $C_{28}H_{29}N_5O_3$: calcd, 484.2349; found, 484.2348 [M + H$^+$].

***trans*-{1-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl}acetic acid (54).** Reaction of **13** (0.5 g, 1.57 mmol) with **18** (0.7 g, 1.72 mmol) using method B, chromatography (CH_2Cl_2/MeOH 2–5%) and treatment of the corresponding *tert*-butyl ester with TFA afforded **54** as white solid: 0.42 g, 44.5%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.97 (d, 1H), 7.64 (t, 1H), 7.36 (m, 2H), 7.25 (m, 2H), 7.07 (m, 2H), 6.84 (m, 2H), 3.78 (d, 1H), 3.72 (d, 1H), 3.44 (m, 2H, overlapping with H_2O), 2.97 (m, 4H), 2.70 (m, 2H), 1.99 (m, 2H), 1.64 (m, 5H), 1.45 (m, 1H), 1.36 (m, 1H), 1.28 (m, 2H), 0.98 (m, 2H). HRMS (ESI) for $C_{28}H_{35}N_5O_3$: calcd, 490.2818; found, 490.2825 [M + H$^+$].

[1-(2-{[5-(1*H*-Benzimidazol-2-ylamino)pentyl]amino}-2-oxoethyl)-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl]-acetic acid hydrochloride (55). Reaction of **13** (0.5 g, 1.57 mmol) with **28** (0.4 g, 1.57 mmol) using method A, chromatography (CH_2Cl_2/MeOH 2%) and treatment of the corresponding *tert*-butyl ester with 4 N HCl in dioxane afforded **55** as brownish solid: 0.3 g, 36.5%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 12.6 (s, 1H), 9.10 (t, 1H), 7.38 (m, 2H), 7.21 (m, 2H), 7.08 (m, 2H), 6.86 (m,

2H), 3.75.50 (2H, superposed by H_2O), 3.46 (m, 1H), 3.35 (m, 2H), 3.11 (m, 2H), 2.93 (m, 2H), 2.71 (m, 2H), 1.67 (m, 1H), 1.59 (m, 4H), 1.44 (m, 3H), 1.29 (m, 2H). HRMS (ESI) for $C_{26}H_{33}N_5O_3\times HCl$: calcd, 464.2649; found, 464.2662 [$M+H^+$].

***trans*-{4-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-5-oxo-5,6,7,8-tetrahydro-4*H*-thieno[3,2-*b*]azepin-8-yl}acetic acid×HCl (56).** Reaction of **9** (0.6 g, 1.8 mmol) with **18** (0.56 g, 1.8 mmol) using method A and chromatography (CH_2Cl_2/MeOH + conc. NH_3) yielded 100 mg of the *tert*-butyl ester as white amorphous solid. Deprotection by treatment with 4 N HCl in dioxane and evaporation afforded **56** as white solid: 65 mg, 6.6%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.83 (m, 1H), 8.03 (t, 1H), 7.37 (m, 3H), 7.08 (m, 2H), 7.02 (d, 1H), 4.22 (dd, 2H), 3.70 (m, 1H), 3.49 (m, 1H), 2.96 (m, 2H), 2.74 (m, 1H), 2.60 (m, 1H), 2.30.15 (m, 3H), 2.02 (m, 2H), 1.76 (m, 3H), 1.37.03 (m, 3H), 0.96 (m, 2H). HRMS (ESI) for $C_{26}H_{31}N_5O_4S\times HCl$: calcd, 508.2019; found, 508.2018 [$M-H^+$].

***trans*-{1-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-7-chloro-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl}acetic acid (57).** Reaction of **5d** (1.0 g, 2.72 mmol) with **18** (0.95 g, 2.99 mmol) using method B, treatment with TFA and purification by MPLC afforded **57** as white solid: 0.4 g, 27.4%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.03 (t, 1H), 7.35 (m, 2H), 7.23 (s, 1H), 7.18 (m, 2H), 6.96 (m, 2H), 4.39 (m, 1H), 4.18 (m, 1H), 3.48 (m, 2H, superposed with H_2O), 2.97 (m, 2H), 2.68 (m, 2H), 2.31 (m, 1H), 2.13 (m, 2H), 2.02 (m, 2H), 1.74 (m, 2H), 1.61 (m, 1H), 1.38 (m, 1H), 1.26 (m, 2H), 1.02 (m, 2H). HRMS (ESI) for $C_{28}H_{32}ClN_5O_4\times C_2H_4O_2$: calcd, 536.2065; found, 536.2058 [M-H^+].

***trans*-{1-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-7,8-dimethoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl}acetic acid×HOAc (58).** Reaction of **5b** (1.0 g, 2.54 mmol) with **18** (0.91 g, 2.8 mmol) using method B, treatment with TFA and chromatography (CH_2Cl_2/MeOH 10% + 0.1% acetic acid) afforded **58** as white amorphous solid: 0.8 g, 52%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.68 (broad, 1H), 8.03 (t, 1H), 7.34 (m, 2H), 7.18 (m, 2H), 6.97 (s, 1H), 6.76 (s, 1H), 4.43 (m, 1H), 4.16 (m, 1H), 3.77 (s, 3H), 3.73 (s, 3H), 3.46 (m, 2H), 2.99 (m, 2H), 2.69 (m, 2H), 2.31 (m, 1H), 2.14.99 (m, 4H), 1.77 (m, 1H), 1.56 (m, 1H), 1.40 (m, 1H), 1.31 (m, 2H), 1.01 (m, 2H). HRMS (ESI) for $C_{30}H_{37}N_5O_6\times C_2H_4O_2$: calcd, 562.2666; found, 562.2666 [$M-H^+$].

***trans*-{1-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-7-methoxy-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl}acetic acid × HOAc (59).** Reaction of **5c** (0.2 g, 0.55 mmol) with **18** (0.19 g, 0.61 mmol) using method B, treatment with TFA and purification by MPLC afforded **59** as white amorphous solid: 0.12g, 51.7%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 12.60 (s, 1H), 8.98 (d, 1H), 8.01 (br., 1H), 7.37 (m, 2H), 7.25 (m, 3H), 6.87 (m, 1H), 6.73 (s, 1H), 4.37 (m, 1H), 4.12 (m, 1H), 3.75 (s, 3H), 3.50.25 (2H, superposed by H_2O), 2.98 (m, 2H), 2.69 (m, 2H), 2.31 (m, 1H), 2.10.99 (m, 4H), 1.80 (m, 2H), 1.56 (m, 1H), 1.41.18 (m, 4H), 1.04 (m, 1H). HRMS (ESI) for $C_{29}H_{35}N_5O_5\times C_2HF_3O_2$: calcd, 532.2560; found, 532.2560 [$M-H^+$].

[5-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]amino}-2-oxoethyl)-4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-1-yl]acetic acid×HCl (60). Reaction of **11** (0.65 g, 2 mmol) with **15** using method A, chromatography of the corresponding *tert*-butyl ester (CH_2Cl_2/MeOH + conc. NH_3) and subsequent treatment with 4 N HCl in dioxane afforded **60** as white solid: 0.4 g, 37.4%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 11.17 (br., 1H), 8.32 (t, 1H), 7.43.16 (m, 12H), 4.42 (s, 2H), 4.28 (m, 2H), 3.78 (s, 2H), 3.43 (m, 2H, overlapping with H_2O), 2.38 (m, 2H). HRMS (ESI) for $C_{27}H_{26}N_6O_4\times HCl$: calcd, 497.1937; found, 497.1938 [$M-H^+$].

***trans*-{5-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-4-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*][1,4]diazepin-1-yl}acetic acid×HCl (61).** Reaction of **11** (0.65 g, 2 mmol) with **18** using method A, chromatography (CH_2Cl_2/MeOH + 50% acetic acid 12/3/1) and treatment with 4 N HCl afforded **61** as white solid: 0.35 g, 32.3%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 9.00 (m, 1H), 7.90/7.69 (t, 1H), 7.38 (m, 2H), 7.28.15 (m, 6H), 4.32 (s, 2H), 4.27 (s, 2H), 3.94 (s, 2H), 3.61.25 (3H, superposed by H_2O), 2.96 (m, 2H), 2.36 (m, 2H), 1.98 (m, 2H), 1.64 (m, 2H), 1.33.05 (m, 3H), 0.91 (m, 2H). HRMS (ESI) for $C_{27}H_{32}N_6O_4\times HCl$: calcd, 503.2407; found, 503.2424 [$M-H^+$].

[(5*R*)-1-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]-amino}-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl]acetic acid (31*R*). Analogously to **31**, conversion of **5a*R*** (1.0 g, 3.0 mmol) afforded **31*R*** as white solid: 0.82 g, 55%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 10.87 (s, 1H), 9.36 (s br., 1H), 8.47 (t, 1H), 7.68 (m, 2H), 7.34.19 (m, 8H), 6.98 (m, 2H), 4.49 (m, 1H), 4.31.17 (m, 3H), 3.51 (m, 1H), 2.73.65 (m, 2H), 2.35 (m, 1H), 2.14 (m, 2H), 1.59 (m, 1H). $[\alpha]_D^{20} = -109.3$ (K-salt; $c = 2.35$ in H_2O). HRMS (ESI) calcd, 496.1985; found, 496.1986 [$M-H^+$]. Anal. ($C_{28}H_{27}N_5O_4$) calcd: C 67.59, H 5.47, N 14.01; found: C 67.6, H 5.4, N 13.9.

[(5*S*)-1-(2-{[4-(1*H*-Benzimidazol-2-ylamino)benzyl]-amino}-2-oxoethyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl]acetic acid (31*S*). Analogously to **31**, conversion of **5a*S*** (1.0 g, 3.0 mmol) afforded **31*S*** as white solid: 0.79 g, 53%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 10.87 (s, 1H), 9.36 (s br., 1H), 8.46 (m, 1H), 7.68 (m, 2H), 7.34.19 (m, 8H), 6.98 (m, 2H), 4.49 (m, 1H), 4.31.17 (m, 3H), 3.50 (m, 1H), 2.73.65 (m, 2H), 2.35 (m, 1H), 2.14 (m, 2H), 1.59 (m, 1H). $[\alpha]_D^{20} = +105.4$ (K-salt; $c = 2.35$ in H_2O). HRMS calcd, 496.1985; found, 496.1981 [$M-H^+$]. Anal. ($C_{28}H_{27}N_5O_4$) calcd: C: 67.59, H: 5.47, N: 14.01; found: C 67.1, H 5.4, N 14.0.

{(5*R*)-*trans*-1-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]methyl}amino)-2-oxoethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl}acetic acid (37*R*). Analogously to **37**, conversion of **5a*R*** (1.0 g, 3.0 mmol)

afforded **37*R*** as white solid: 0.67 g, 44.3%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.03 (t, 1H), 7.31 (s, 2H), 7.21 (s, 2H), 7.12 (m, 2H), 6.84 (m, 2H), 6.54 (d, 1H), 4.42 (m, 1H), 4.18 (m, 1H), 3.50.35 (2H, superposed by H_2O), 2.96 (m, 2H), 2.73.63 (m, 2H), 2.34 (m, 1H), 2.12 (m, 2H), 1.99 (m, 2H), 1.73 (m, 2H), 1.56 (m, 1H), 1.37 (m, 1H), 1.19 (m, 2H), 1.01 (m, 2H). $[\alpha]_D^{20} = -104°$ (K-salt, $c = 1$ in H_2O). Anal. ($C_{28}H_{33}N_5O_4 \times HCl$) calcd: C 62.37, H 5.6.35, N 12.97; found: C 62.4, H 6.5, N 12.6. HRMS (ESI) calcd, 504.2611; found, 504.2619 [M + H$^+$].

{(5*S*)-1-[2-({[4-(1*H*-Benzimidazol-2-ylamino)cyclohexyl]-methyl}amino)-2-oxoethyl]-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl}acetic acid (37*S*). Analogously to **37**, conversion of **5a*S*** (1.0 g, 3.0 mmol) afforded **37*S*** as white solid: 0.56 g, 37%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.05 (t, 1H), 7.31 (s, 2H), 7.21 (s, 2H), 7.12 (m, 2H), 6.84 (m, 2H), 6.50 (d, 1H), 4.43 (m, 1H), 4.18 (m, 1H), 3.50.35 (2H, superposed by H_2O), 2.97 (m, 2H), 2.72 (m, 1H), 2.62 (m, 1H), 2.31 (m, 1H), 2.12 (m, 2H), 1.95 (m, 2H), 1.75 (m, 2H), 1.60 (m, 1H), 1.40 (m, 1H), 1.20 (m, 2H), 1.00 (m, 2H). $[\alpha]_D^{20} = +101.6°$ (K$^+$-salt, $c = 1$ in H_2O). Anal. ($C_{28}H_{33}N_5O_4 \times HCl$) calcd: C 62.37, H 6.35, N 12.97; found: C 62.5, H 6.3, N 12.8. HRMS (ESI) calcd, 504.2611; found, 504.2589 [M + H$^+$].

(1-{4-[4-(1*H*-Benzimidazol-2-ylamino)phenyl]butyl}-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl)acetic acid (48). (a) To a suspension of NaH (0.16 g, 60% deoiled) in DMF (10 mL) at 4 °C was added dropwise a solution of **4a** (0.8 g, 2.91 mmol) in DMF (20 mL). The mixture was stirred for 1 h. A catalytic amount of KI and 1-(4-bromobutyl)-4-nitrobenzene (1.0 g, 3.87 mmol) in DMF (10 mL) were added at room temperature, and the mixture stirred for another 2 h. H_2O was added, the mixture diluted with CH_2Cl_2, washed several times with brine, dried ($MgSO_4$) and evaporated. The obtained crude product was purified by column chromatography (CH_2Cl_2/MeOH 2–3%) affording **48a** as yellow oil: 0.42 g, 32%; MS (ESI): *m*/*z* 397.1 [M + H$^+$–tBu]. (b) A solution of **48a** (0.4 g, 0.88 mmol) in MeOH (75 mL) was hydrogenated in the presence of 10% Pd–C (0.1 g) at room temperature and atmospheric pressure. Removal of the catalyst by filtration through Celite and evaporation of the solvent gave the corresponding amine as oil which was used in the next step without further purification: 0.36 g, 96.5%; MS (ESI) *m*/*z*: 397.1 [M + H$^+$]. Analogously to **15**, the amine was converted into the corresponding amino-benzimidazole, chromatography of the crude product (CH_2Cl_2/MeOH 4%) afforded a white foam: 0.22 g, 50%; MS (ESI) *m*/*z*: 539.2 [M + H$^+$]. Treatment with TFA (10 mL) at room temperature for 30 min, concentration and lyophilizing the obtained oil afforded **48** as amorphous solid: 0.21 g, 96%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 10.55 (broad, 1H), 7.40.19 (m, 12H), 4.21 (m, 1H), 3.47 (m, 1H), 2.77 (m, 1H), 2.71 (m, 1H), 2.55 (m, 2H), 2.27 (m, 1H), 2.03 (m, 2H), 1.87 (s, 3H), 1.55 (m, 6H). HRMS (ESI) for $C_{29}H_{30}N_4O_3$: calcd, 481.2240; found, 481.2246 [M−H$^+$].

[1-({3-[4-(1*H*-Benzimidazol-2-ylamino)phenyl]isoxazol-5-yl}methyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl]acetic acid×HOAc (49). (a) To a suspension of NaH (0.16 g, 60% deoiled) in DMF (5 mL) at 0–4 °C was added dropwise a solution of **4a** (2 g, 7.26 mmol) in DMF (10 mL) and stirred for 1 h. A catalytic amount of KI and 5-chloromethyl-3-(4-nitro-phenyl)-isoxazole[37] (2.37 g, 9.44 mmol) in DMF (10 mL) was added and the mixture stirred for another 30 min. H_2O was added, the mixture extracted with CH_2Cl_2, the collected organic layers washed with brine and dried ($MgSO_4$). After evaporation the obtained crude oil was stirred with n-pentane to afford **49a** as beige amorphous solid: 3.4 g, 98%; MS (ESI) *m*/*z*: 477.8 [M + H$^+$].

(b) A solution of **49a** (2.5 g, 5.24 mmol) in EtOH (50 mL) was hydrogenated in the presence of 10% Pd–C (0.8 g) at room temperature and atmospheric pressure. Removal of the catalyst by filtration through Celite and evaporation of the solvent afforded a red-yellow oil which was reacted directly without further purification: 2.47 g; MS (ESI) *m*/*z*: 448.0 [M + H$^+$]. Analogously to **15**, the amine was converted into the corresponding amino-benzimidazole, chromatography of the crude product (CH_2Cl_2/MeOH 5–7%) afforded **49b** as yellow foam: 1.2 g, 40.8%; MS (ESI) *m*/*z*: 564.2 [M + H$^+$].

(c) **49b** (1 g, 1.77 mmol) was treated with TFA (50 mL) and the crude product purified by MPLC. Lyophilizing afforded **49** as slightly beige amorphous solid: 0.58 g, 57.6%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 10.37 (broad, 1H), 7.92 (m, 2H), 7.84 (m, 2H), 7.47 (m, 1H), 7.30 (m, 5H), 7.07 (m, 2H), 6.85 (s, 1H), 5.26 (m, 1H), 5.07 (m, 1H), 3.45 (m, 1H, overlapping with H_2O), 2.65.45 (2H, superposed by DMSO), 2.35 (m, 1H), 2.19 (m, 2H), 1.60 (m, 1H). HRMS (ESI) for $C_{29}H_{25}N_5O_4 \times C_2H_4O_2$: calcd, 508.1985; found, 508.1978 [M + H$^+$].

[1-({4-[4-(1*H*-Benzimidazol-2-ylamino)phenyl]-1,3-thiazol-2-yl}methyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl]acetic acid (50). (a) To a suspension of NaH (1.28 g, 60% deoiled) in DMF (10 mL) at 5 °C was added dropwise a solution of **4a** (8.0 g, 29.05 mmol) in DMF (10 mL) and the mixture stirred for 1 h. Bromoacetonitrile (3.49 g, 31.96 mmol) in DMF (20 mL) was added dropwise and the mixture stirred at room temperature for an additional 4 h. H_2O was added, the mixture diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and evaporated. Purification of the crude product by chromatography (CH_2Cl_2/MeOH 5%) afforded **50a** as yellow oil: 7.61 g, 83%; MS (ESI): *m*/*z* 259.0 [M + H$^+$–tBu].

(b) A solution of **50a** (5 g, 15.9 mmol) in pyridine (70 mL) was saturated with H_2S for 1 h and then allowed to stand at room temperature overnight. Evaporation and treatment of the obtained residue with n-pentane afforded the corresponding thioamide **50b** (5.5 g) as pink solid which was used without further purification.

(c) The solution of **50b** (1.5 g, 4.3 mmol) and 2-bromo-(4-nitrophenyl)ethanone (1.36 g, 5.6 mmol) in dioxane (30 mL) was stirred at room temperature for 12 h. The mixture was diluted with CH_2Cl_2, washed with brine, dried (Na_2SO_4) and evaporated. Treatment of the resulting residue with *n*-pentane afforded **50c** as brown

solid: 2.1 g, 98%; MS (ESI) *m/z*: 494.1 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 8.40 (s, 1H), 8.30 (m, 2H), 8.20 (m, 2H), 7.60 (m, 1H), 7.35 (m, 1H), 7.25 (m, 2H), 5.50 (d, 1H), 5.30 (d, 1H), 2.70 (m, 2H), 2.30 (m, 1H), 2.20 (m, 3H), 1.65 (m, 1H), 1.25 (s, 9H).

(d) To a solution of **50c** (1.5 g, 3.04 mmol), 0.03 g $FeCl_3 \times 6H_2O$ and 1 g activated carbon in MeOH (30 mL) at 60 °C was added dropwise $N_2H_4 \times H_2O$ (6.1 g). The mixture was stirred for 1 h. Filtration through Celite and evaporation of the solvent afforded 1.4 g of the crude amine which was used without further purification; MS (ESI) *m/z*: 464.1 [M + H$^+$]. Analogously to **15**, the amine (0.9 g) was converted into the corresponding amino-benzimidazole affording, after chromatography (CH_2Cl_2/MeOH 2–4%), a slightly yellow foam: 0.33 g, 29.4%; MS (ESI) *m/z*: 580.3 [M + H$^+$]. Treatment with TFA (40 mL), purification of the crude product by MPLC and lyophilizing afforded **50** as slightly yellow solid: 40 mg, 13.8%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 10.93 (s, 1H), 9.54 (s, 1H), 7.89 (m, 4H), 7.57 (d, 1H), 7.39.30 (m, 6H), 7.00 (m, 2H), 5.41.30 (m, 2H), 3.51 (m, 1H), 2.70 (m, 2H), 2.58 (m, 1H), 2.21 (m, 2H), 1.64 (m, 1H). HRMS (ESI) for $C_{29}H_{25}N_5O_3S$: calcd, 522.1600; found, 522.1605 [M–H$^+$].

[1-({5-[4-(1*H*-Benzimidazol-2-ylamino)phenyl]-1,3,4-thiadiazol-2-yl}methyl)-2-oxo-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-yl]acetic acid (51). (a) Analogously to **15**, 4-amino benzoic acid methyl ester (8.3 g, 54.9 mmol) was converted into the corresponding amino-benzimidazole. Treatment with MTBE afforded a slightly yellow amorphous solid: 8.14 g, 55.8%; MS (ESI) *m/z*: 268.0 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 11.60 (s broad, 1H), 9.95 (s, 1H), 7.80 (m, 4H), 7.45 (m, 1H), 7.35 (m, 1H), 7.05 (m, 2H), 3.85 (s, 3H).

(b) A mixture of 4-(1*H*-benzimidazol-2-ylamino)-benzoic acid methyl ester (4 g, 14.97 mmol) and LiOH (0.6 g) in dioxane/H_2O 1:1 (120 mL) at 35 °C was stirred for 24 h. After evaporation, dilution with H_2O and acidification by addition of 2 N HCl, the resulting white precipitate was filtered off and dried affording **51b**: 3.9 g, 96.8%; MS (ESI) *m/z*: 254.0 [M + H$^+$].

(c) Condensation of **51b** (2.0 g, 7.9 mmol) with hydrazinecarboxylic *tert*-butyl ester (1.05 g, 7.9 mmol) using EDC as coupling reagent, chromatography (CH_2Cl_2/acetone 1:1) and treatment with CH_2Cl_2 afforded a white amorphous solid: 65 g, 56.9%; MS (ESI) *m/z*: 368.1 [M + H$^+$]. Treatment of 1 g with 4 N HCl in dioxane and thorough evaporation afforded the corresponding deprotected hydrazide hydrochloride **51c** as white solid: 1.0 g, 97.2%.

(d) Condensation of **51c** (0.81 g, 2.4 mmol) and **5a** (1.0 g, 2.62 mmol) in CH_2Cl_2/DMF 5:1 (25 mL) using EDC as coupling reagent and NMM as base, standard work up and chromatography afforded **51d** as white foam: 0.5 g, 35.8%; MS (ESI) *m/z*: 583.2 [M + H$^+$].

(e) To a solution of **51d** (0.2 g, 0.34 mmol) in THF (20 mL) under reflux was added Lawesson's reagent (0.5 g) in several portions. After evaporation the obtained crude product was purified by chromatography (CH_2Cl_2/MeOH 0–5%) affording a white foam: 50 mg, 25.1%; MS (ESI) *m/z*: 583.2 [M + H$^+$]. Treatment with TFA (5 mL), evaporation, chromatography using Chromabond-C18 (H_2O/CH_3CN + 0.1% acetic acid, 0–100%) and lyophilizing afforded **51** as white solid: 5 mg, 11.1%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 7.90 (m, 4H), 7.72 (m, 2H), 7.55 (m, 1H), 7.35 (m, 2H), 7.28 (m, 1H), 7.06 (m, 2H), 5.48 (d, 1H), 5.30 (d, 1H), 4.81 (m, 1H), 2.80.65 (m, 2H), 2.35 (m, 1H), 2.20 (m, 1H), 1.75.60 (m, 2H). HRMS (ESI) for $C_{28}H_{24}N_6O_3S$: calcd, 525.6109; found, 525.6195 [M + H$^+$].

2-(4-{[{[5-(Carboxymethyl)-2-oxo-2,3,4,5-tetrahydro- 1*H*- benzo[*b*]azepin - 5 - yl]acetyl}(methyl)amino]methyl}-anilino)-1*H*-benzimidazol×TFA (52). (a) Reaction of **5a** (2.2 g, 6.6 mmol) with *N*-methyl-(4-nitrophenyl)-methane amine (1.32 g) in CH_2Cl_2 (40 mL) using method B and chromatography of the crude product (CH_2Cl_2/MeOH 2–4%) afforded **52a** as a slightly yellow oil: 2.26 g, 71%; MS (ESI) *m/z*: 580.3 [M + H$^+$]. ^{1}H NMR (360 MHz, DMSO-d_6) δ (rotamers): 8.25/8.20 (d, 2H), 7.60/7.50 (d, 2H), 7.35.20 (m, 4H), 4.85.5 (m, 4H), 3.05/2.85 (s, 3H), 2.70 (m, 1H), 2.30 (m, 1H), 2.15 (m, 2H), 1.65 (m, 1H), 1.30 (s, 9H). b.) To a solution of **52a** (1.26 g, 2.62 mmol),), $FeCl_3 \times 6H_2O$ (0.015 g) and activated carbon (0.41 g) in MeOH (20 mL) at 60 °C were added $N_2H_4 \times H_2O$ (5.25 g) and the resulting mixture stirred for 1 h. The mixture was filtrated through Celite and evaporated to afford a white foam: 1.1 g, 99%; MS (ESI) *m/z*: 452.2 [M + H$^+$]. (c) Analogously to **15**, preparation of the respective amino-benzimidazole and chromatography (CH_2Cl_2/MeOH 2–4%) afforded a slightly beige foam: 0.9 g, 50%; MS (ESI) *m/z*: 568.2 [M + H$^+$]. Treatment with TFA (50 mL) and subsequent purification by chromatography (CH_2Cl_2/MeOH 8–10%) afforded **52** as amorphous solid: 0.88 g, 88.7%. ^{1}H NMR (360 MHz, DMSO-d_6) δ: 10.88 (broad, 1H), 7.55.23 (m, 12H), 4.85 (m, 1H), 4.71.51 (m, 3H), 4.56 (m, 1H), 3.03/2.85 (s, 3H, N–CH_3), 2.71 (m, 2H), 2.32 (m, 1H), 2.16 (m, 2H), 1.60 (m, 1H). HRMS (ESI) for $C_{29}H_{29}N_5O_4 \times C_2HF_3O_2$: calcd, 510.2141; found, 510.2136 [M–H$^+$].

Biological assays

Receptor and ligand purification. Receptors and ligands were purified according to published procedures.[56] Briefly, integrin $\alpha_v\beta_3$ was purified starting from NP-40 solubilized human placenta by peptide-affinity chromatography (GRGDSPK affinity column) and ion exchange chromatography on a Mono Q column. Vitronectin was purified from outdated human plasma by precipitation, affinity chromatography on a heparin column and size exclusion chromatography. Human fibrinogen was purchased from Calbiochem, the human integrin $\alpha_{IIb}\beta_3$ from Kordia and human fibronectin was purchased from Roche.

1. $\alpha_V\beta_3$ ELISA. The primary screening assay is based on a competitive ELISA format: after coating of the microtiter plates overnight at 4 °C with the human

integrin $\alpha_V\beta_3$ in 0.05 M $NaHCO_3$, pH 9.2 and blocking with 1% milk powder in assay buffer (50 mM Tris pH 7.5; 100 mM NaCl; 1 mM $CaCl_2$; 1 mM $MgCl_2$; 10 μM $MnCl_2$) the plates were washed three times with 0.05% Tween 20/assay buffer. For competition the test compounds were co-incubated in serial dilutions together with or without the ligand vitronectin or osteopontin (1 μg/mL) in assay buffer/0.1% milk powder. After washing, the bound vitronectin was detected with a peroxidase-labeled polyclonal anti-human vitronectin or osteopontin antibody and TMB-substrate (detection at 450 nm). The assay was performed in triplicate for each concentration, the intra-assay variation of the resulting IC_{50} values is in the range of less than 10% and the inter-assay variation is in general less than a factor of 2.

2. $\alpha_{IIb}\beta_3$ ELISA. The microtiter plates were coated overnight at 4 °C with fibrinogen, 10 μg/mL in 0.05 M $NaHCO_3$ pH 9.2. After blocking with 1% BSA/PBS and washing with 0.05% Tween 20/PBS the test compounds were incubated in the presence of the integrin $\alpha_{IIb}\beta_3$ (Kordia) 100 μg/mL PBS/0.1% BSA. The bound integrin was detected with a biotinylated anti-integrin $\alpha_{IIb}\beta_3$ antibody (Dianova), streptavidin-peroxidase-complex (Roche) and TMB-substrate.

3. $\alpha_V\beta_3$ Cell adhesion assay. A whole-cell assay with recombinant cells was used to measure the functional potency of the integrin $\alpha_V\beta_3$ antagonists in RGD-dependent $\alpha_V\beta_3$ cell adhesion. 24-well plates were coated with vitronectin 5 μg/mL in 0.05 M $NaHCO_3$ pH 9.2 overnight at 4 °C and washed with medium CHO-S-SFMII (Gibco). A stable human integrin $\alpha_V\beta_3$ co-transfected CHO-K1 cell line was preincubated in serumfree medium (CHO-S-SFMII) with test compounds in various concentrations for 1 h at 37 °C and transferred to the assay plate (2.5×10^5 cells/well). After incubation for 3 h the plates were washed to remove non-adherent cells with medium and bound cells could be quantified by XTT (Roche) in medium.

4. $\alpha_v\beta_5$ Cell adhesion assay. The integrin $\alpha_v\beta_5$ assay is similar to the integrin $\alpha_v\beta_3$ assay. Instead of the recombinant $\alpha_v\beta_3$ cell line a stable cotransfected human integrin $\alpha_v\beta_5$ CHO-K1 cell line was used.

5. $\alpha_4\beta_1$ Cell adhesion assays. The assay formats are analogous to the integrin $\alpha_v\beta_3$ cell adhesion assay. The plates were coated with fibronectin (Roche). Jurkat cells (ATCC) were incubated in RPMI medium.

6. Metabolic stability with microsomes. Human and rat liver microsomes as well as 100 μmol of test compound were incubated with and without UDPGA and NADPH for 1 h at 37 °C. For detection of glucuronides 100 μL of the UDPGA/NADPH incubation were separated from the original vials. Glucuronidase was added and incubation continued for another h, then stopped by addition of acetonitrile. Analysis was done by means of HPLC.

7. Caco-2 assay. Caco-2 cells (passage 47-60/ Dulbecco's modified Eagle's medium (DMEM)) were seeded onto a filter membrane (Transwell/0.4 μm pore size/ Costar) at a density of 30,000 cells/cm^2. The cells were grown in culture medium consisting of DMEM supplemented with 20% FCS, 1% nonessential amino acids and 1% glutamine. The culture medium was replaced every two days and the cells were maintained at 37 °C, 90% relative humidity, and 5% CO_2. Permeability studies were conducted with the monolayers after 14 days in culture. The transport medium was modified with Hank's balanced salt solution (MHBS) containing 25 mM MES, pH 6.0. Each monolayer was washed with DMEM (without phenol red and FCS) and 1.5 mL of DMEM (without phenol red and FCS) was placed on the basolateral side of the monolayer and 0.5 mL MHBS at the apical side. MHBS was removed 3 h later. The permeability studies were initiated by adding the drugs (10 μM) to the apical or basolateral side of the monolayer. The barrier integrity was evaluated by measuring TEER (trans epithelial electrical resistance) during growth and at the beginning and end of the transport studies of the compounds. The monolayers were incubated 24 h at 37 °C. Samples were taken from each donor and receiver compartment. The concentration of the drugs were analyzed by HPLC.

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