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# Design, Synthesis and Biological Evaluation of Nonpeptide Integrin Antagonists

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**Abstract**—Recent studies demonstrated that peptide and antibody antagonists of integrin $\alpha_v\beta_3$ block angiogenesis and tumor growth. In this article, the design, synthesis and biological evaluation of a series of nitroaryl ether-based, nonpeptide mimetics are described. The design of these compounds was based on Merck's arylether/α-aminoacid/guanidine framework and incorporates a novel nitroaryl system. The synthesized mimetics were tested against a variety of integrins ($\alpha_v\beta_3$, $\alpha_{IIb}\beta_3$, and $\alpha_v\beta_5$) in order to determine their binding selectivity and ability to inhibit cell adhesion. Selected compounds were also tested for their ability to inhibit angiogenesis in vivo in the CAM (chick chorioallantoic membrane) assay. From the generated compound library, compounds **16** and **19** proved to be potent and selective inhibitors of $\alpha_{IIb}\beta_3$ ($IC_{50} = 14$ nM) whereas compound **11** showed excellent in vivo inhibition of angiogenesis (at 30 μg/embryo). 

## Introduction

The integrins are a class of cell surface proteins that facilitate cell–cell and cell–matrix adhesion.[1] These important biological targets are membrane bound, heterodimeric glycoproteins made up of an α-subunit and a β-subunit. The relative affinity and specificity for ligand binding is determined by the unique combination of the different α- and β-subunits. Of the members of this family of receptors, $\alpha_{IIb}\beta_3$, $\alpha_5\beta_1$, $\alpha_v\beta_3$ and $\alpha_v\beta_5$ are extensively studied. A number of known natural ligands to these integrins, such as fibronectin (binds to $\alpha_5\beta_1$ and $\alpha_v\beta_3$), fibrinogen (binds to $\alpha_{IIb}\beta_3$ and $\alpha_v\beta_3$) and vitronectin (binds to $\alpha_v\beta_3$ and $\alpha_v\beta_5$), contain common peptide sequence within their native sequence, which are recognized by several integrins. The $\alpha_{IIb}\beta_3$ integrin was shown to be an excellent target for the inhibition of platelet aggregation and several groups have already disclosed the design and synthesis of potent binders with peptide and nonpeptidal structures.[2] Within the context of angiogenesis, the functions of $\alpha_v\beta_3$ and $\alpha_v\beta_5$ have been shown to be vital.[3] Cheresh and co-workers have shown that in vivo inhibition of binding of these integrins to their native ligands by antibodies or cyclic peptides interferes with angiogenesis and induces tumor regression.[4] In addition to its relevance to angiogenesis, $\alpha_v\beta_3$ has also been shown to play a role in mediating adhesion of osteoclasts to the bone matrix[5] and in the migration of vascular smooth muscle cells.[6] Antagonists of $\alpha_v\beta_3$ are, therefore, envisioned as potential therapeutic agents for the treatment of numerous disease states such as diabetic retinopathy,[7] cancer,[4] osteoporosis[5] and restenosis.[6]

The first small molecule antagonists of $\alpha_v\beta_3$ were reported by Kessler et al.[8] (e.g. **1**, Fig. 1). Subsequently, groups from Dupont-Merck[9a] (e.g. **2**, Fig. 1) and

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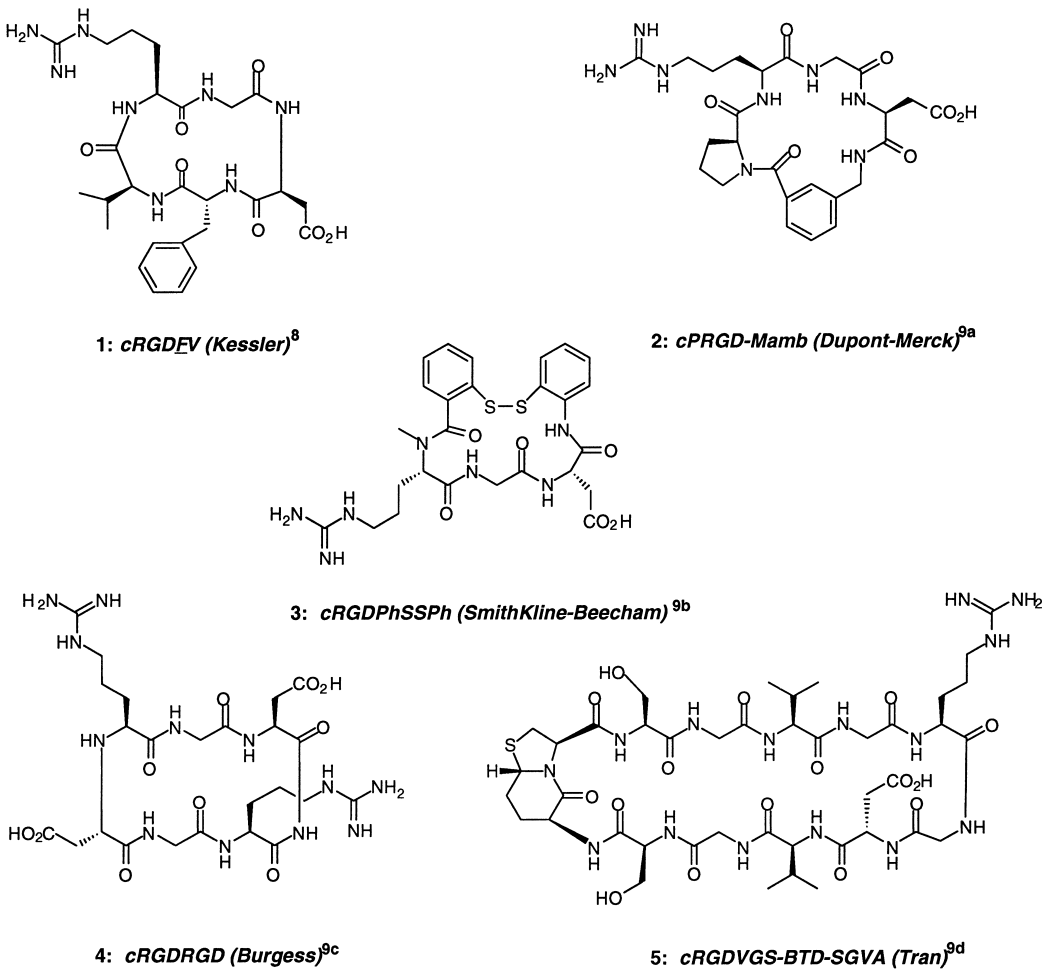



**Figure 1.** Selected structures of $\alpha_v\beta_3$ antagonists.

SmithKline Beecham[9b] (SKB) (e.g. **3**, Fig. 1) published their results in the field. In addition, cyclic peptides such as **4** and **5** (Fig. 1) were synthesized and shown to be active by Burgess et al.[9c] and Tran et al.,[9d] respectively.

More recently a number of groups reported their results with high affinity ligands for $\alpha_v\beta_3$ possessing structures significantly deviating from classical peptide frameworks (e.g. **6**–**9**, Fig. 2). These structures contain a central scaffold (e.g. benzene,[10a] benzodiazepine-type,[10b,d] or urea[10c] backbone) onto which appendages carrying carboxylate and guanidino groups are attached. In our group we have previously utilized carbohydrate frameworks[11] as scaffolds for the design and synthesis of potential $\alpha_v\beta_3$ antagonsists.[12] In this article we describe the design, chemical synthesis and biological evaluation of a series of nitroaryl-based integrin antagonists and their use as anti-angiogenic agents.

## Results and Discussion

### Design and retrosynthetic analysis

Figure 3 shows the targeted compounds (**10**–**22**) for the present study. Amongst the considerations that led to their design were: (a) the Merck[10a] findings pointing to the importance of the guanidine/aryl sulfonamide functionalities; and (b) the facile entry into such structures from *o*-nitro-arylfluorides as shown in Fig. 4. The designed molecules fall within the general structure I (Fig. 4), which can be derived by coupling the central nitrofluoroaromatic system II with fragments III (nucleophile) and IV (aminoacid component).

### Chemical synthesis

For the synthesis of compounds **10**–**22** (Fig. 3), the amino acid derivatives **26**, **29a**, and **29b** were required. These intermediates were obtained from L-asparagine

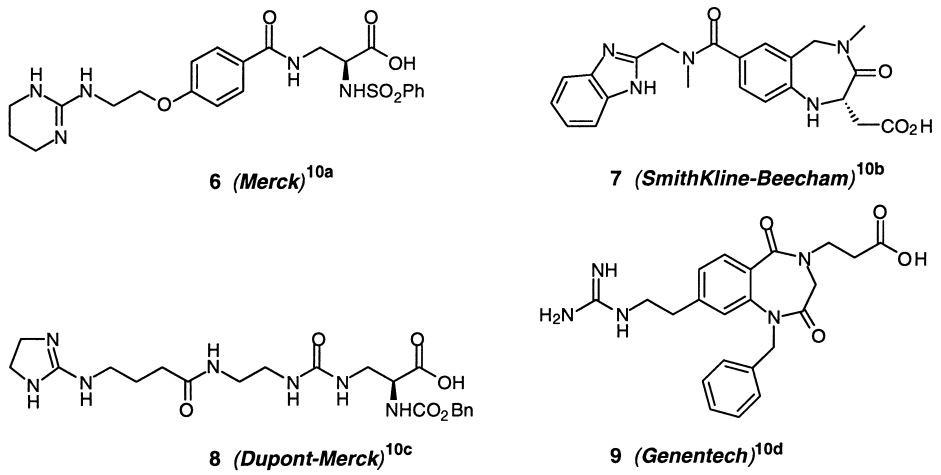



**Figure 2.** Selected nonpeptide mimetics with high affinity for $\alpha_v\beta_3$.

(**23**) as outlined in Scheme 1. Thus, conversion of **23** to its Boc derivative (**24**, 88%) under standard conditions was followed by benzyl ester formation ($Cs_2CO_3$–BnBr)[13a] to afford **25** (88% yield). Conversion of the amide to the amine by a decarboxylative rearrangement with $PhI(OCOCF_3)_2$ furnished derivative **26** in 41% yield.[13b,c] The sulfonamides **29a** and **29b** were prepared by sulfonylation of the amino group of **23** to afford **27a** and **27b**, followed by Hoffmann rearrangement and esterification of the resulting aminoacids (**28a** and **28b**) with isobutylene (Scheme 1). Details and yields for these transformations can be found in Scheme 1.[14]

Scheme 2 summarizes the initial approach to compounds **10**–**13**. Thus, 4-fluoro-*o*-nitrobenzoic acid (**30**) was converted to its methyl ester (**31**, 98%) by treatment with trimethylorthoacetate[15] at 80 °C, and thence reacted with $N_3(CH_2)_2OTBS$ in DMF[16] in the presence of catalytic amounts of TBAF resulting in the formation of compound **32** (73%). Saponification of **32** (LiOH, 99% yield) furnished carboxylic acid **33** which was condensed with building block **26** in the presence of DCC and 4-DMAP to give key intermediate **34** (82% yield). For the synthesis of **10**, compound **34** was reduced with $Ph_3P$ in the presence of $H_2O$, to afford amine **35a**, together with the rearranged product **35b** (80% combined yield) in which the side chain heteroatoms have interchanged positions (via an internal nucleophilic attack, see structure **35a**).[17] On standing at ambient temperature, primary amine **35a** underwent quantitative conversion to primary alcohol **35b**. However, it was possible to rapidly manipulate the compound through basic hydrolysis (LiOH) and guanylation (1*H*-pyrazole-1-carboxamidine·HCl)[18] and obtain the targeted compound **10**, albeit in low yield (15% after RP-HPLC purification).

For the synthesis of the sulfonamide compounds **11**–**13**, the common intermediate **34** was deprotected (TFA, 84%) and the liberated amine (**37**) was reacted with the appropriate sulfonyl chloride to afford compounds **38a** (78%) and **38b** (57%). Reduction of the azide functionality in **38a** and **38b** with $Ph_3P$–$H_2O$, again resulted in a mixture of the corresponding primary amine (**39a** and **39b**) and its rearranged primary alcohol (**41a** and **41b**) in 80% total yield. Basic hydrolysis of **39a** and **39b** resulted in the formation of the corresponding carboxylic acids (**40a** and **40b**, 93–99% yield), guanylation of which as described above furnished the desired compounds **11** and **13** (13–15% yield, unoptimized) respectively. Similarly, hydrolysis of **41a** (LiOH, 96% yield) followed by guanylation furnished compound **12** in low yield, via compound **42a**.

The rearrangement observed during the reduction of the side-chain azido group led us to explore an alternative strategy for the construction of the targeted nitroaryl ether compounds. According to the new plan, a nucleophilic species containing a fully protected guanidine moiety was to be employed in the displacement of the fluoride from the central nitroaryl system. To this end, the nucleophiles **51**–**56**[19–21] were prepared from readily available starting materials and by standard chemistry as outlined in Scheme 3. The incorporation of these fragments into the main-frame of the molecule via nucleophilic aromatic substitution,[16,17] and the synthesis of the final targets are shown in Scheme 4 (**11**, **14**–**19**) and Scheme 5 (**20** and **21**). Thus, the acid chloride **57** (derived from carboxylic acid **30**) was coupled with amines **29a** and **29b** in the presence of $Et_3N$ to afford amides **58** (98%) and **59** (96%), respectively. Coupling of **58** with nucleophile **51** was effected in the presence of

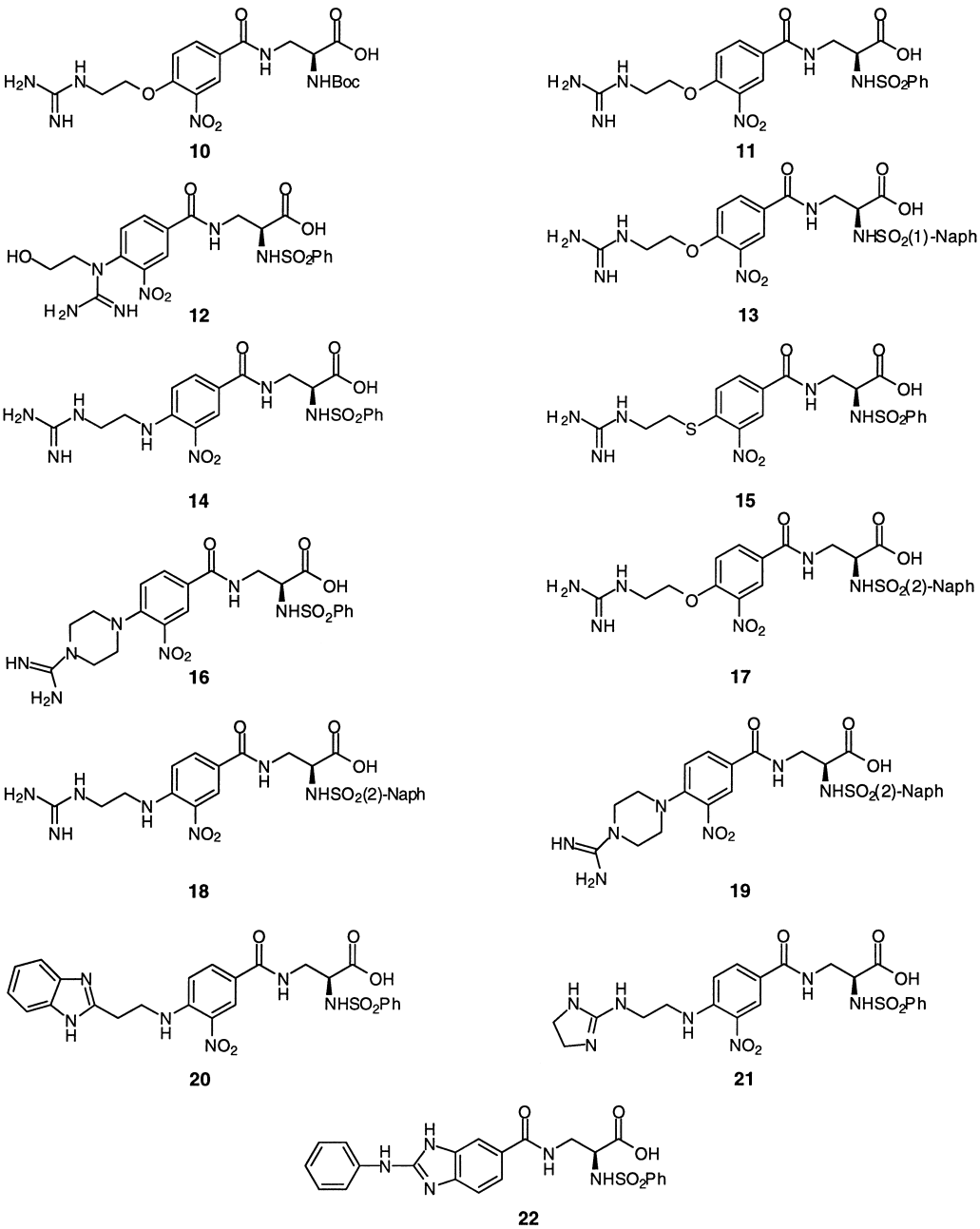



**Figure 3.** Targeted nitroaryl ethers (**10**–**21**) and benzimidazole **22**.

NaH in DMF to afford product **60** in 66% yield. Similarly, **63** was obtained by coupling **59** with **51** (69% yield). The amino compounds **61** and **64** were obtained from **58** and **59** in 73 and 99% yield, respectively, by reaction with amine **53** in DMF at ambient temperature. Thioether **62** was obtained by exposure of **58** to thiol **54** and NaH (DMF, 25 °C, 23% yield). Treatment of compounds **60**–**64** with TFA in $CH_2Cl_2$ at room temperature resulted in concomitant deprotection of both the guanidine and carboxyl groups in excellent yield (90–99%, after RP-HPLC purification). The piperazine compounds **16** and **19** were prepared in a similar fashion from **58** and **59** respectively by first displacing the fluoride with nucleophile **52**, followed by TFA-induced deprotection of the resulting derivatives **65** and **66** as summarized in Scheme 4.

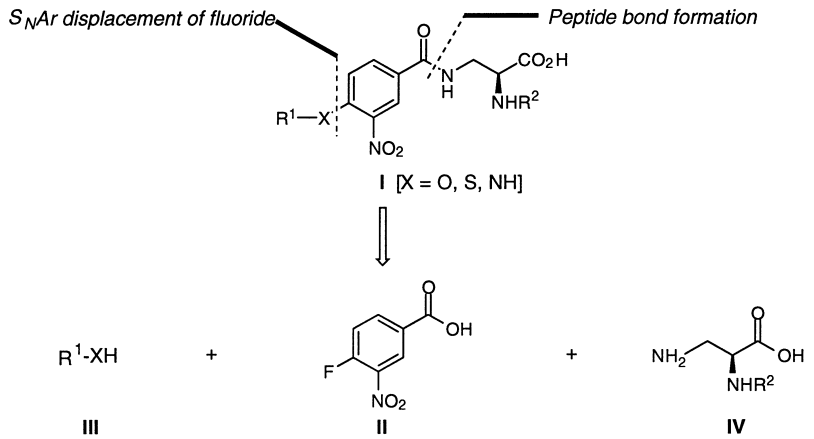
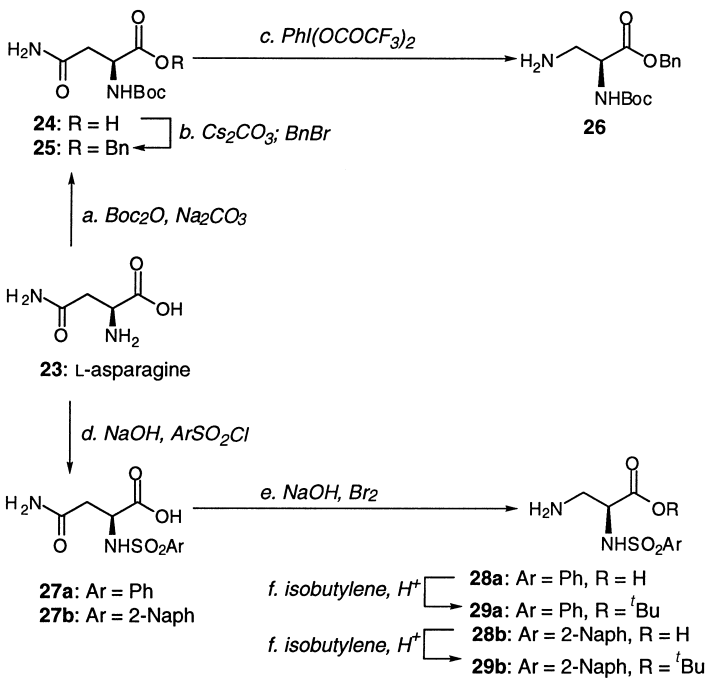


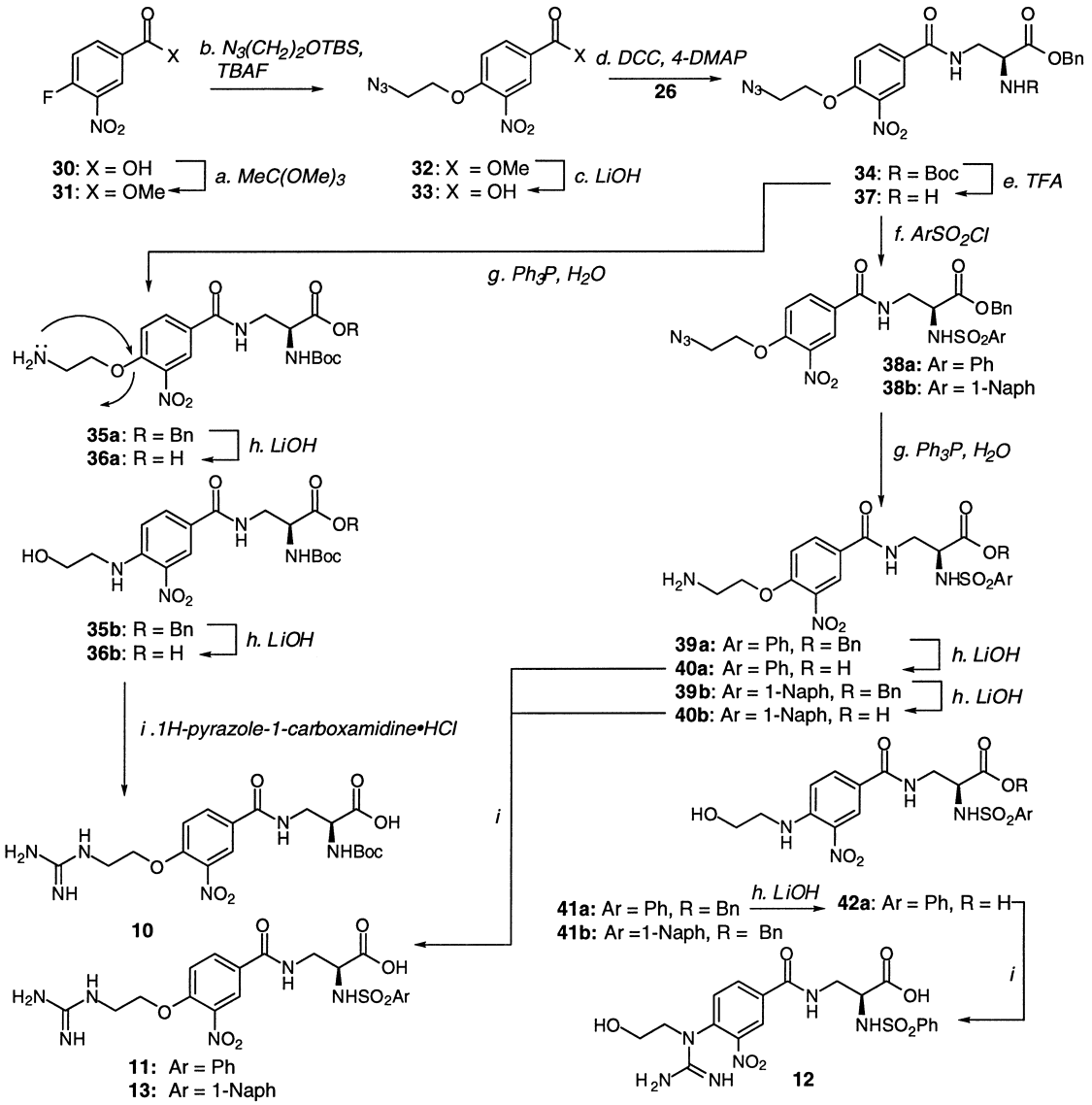

**Figure 4.** General structures of nitroaryl ether peptide mimetics and retrosynthetic analysis.




**Scheme 1.** Synthesis of amino esters **26**, **29a**, and **29b**. Reagents and conditions: (a) 1.1 equiv of $Boc_2O$, 1.0 equiv of $Na_2CO_3$, 1,4-dioxane, $H_2O$, 25 °C, 88%; (b. i.) 20% aq solution of $Cs_2CO_3$, $H_2O$:MeOH (1:2.5), 25 °C, 4 h, 100%; (ii) 1.1 equiv of BnBr, DMF, 25 °C, 14 h, 88%; (c) 1.5 equiv of $PhI(OCOCF_3)_2$, DMF:$H_2O$ (1:1), 2.0 equiv of pyridine, 25 °C, 3.5 h, 41%; (d) 1.1 equiv of $ArSO_2Cl$, 2.25 equiv of NaOH, dioxane:$H_2O$ (1:2), 0→25 °C, 3 h, [71% for **27a**, 66% for **27b**]; (e) 1.3 equiv of $Br_2$, 9.2 equiv of NaOH, $H_2O$, 0→90 °C, [75% for **28a**, 81% for **28b**]; (f) isobutylene, 2.8 equiv of concd $H_2SO_4$, DME, −78→25 °C, 48 h, [55% for **29a**, 51% for **29b**]. DME = dimethoxyethane; DMF = dimethylformamide; 2-Naph = 2-naphthyl.

The synthesis of compounds **20** and **21** is shown in Scheme 5. Thus, reaction of **58** with **55** in the presence of $Et_3N$ at 25 °C in DMF resulted in the formation of compound **67** (92% yield) which was exposed to TFA:$CH_2Cl_2$ (1:1) at 25 °C to afford targeted benzimidazole **20** (97% yield). In a similar fashion, compound **21** was prepared via the intermediacy of **68** by reaction of **58** with **56** ($Et_3N$, DMF, 25 °C) followed by deprotection (83% after RP-HPLC purification).

Finally, the preparation of compound **22** is shown in Scheme 6. Thus, key intermediate **57** was reacted with ammonia in DMF to afford nitroaniline **69** in 93% yield. Reduction of **69** with $H_2$ in the presence of 10%

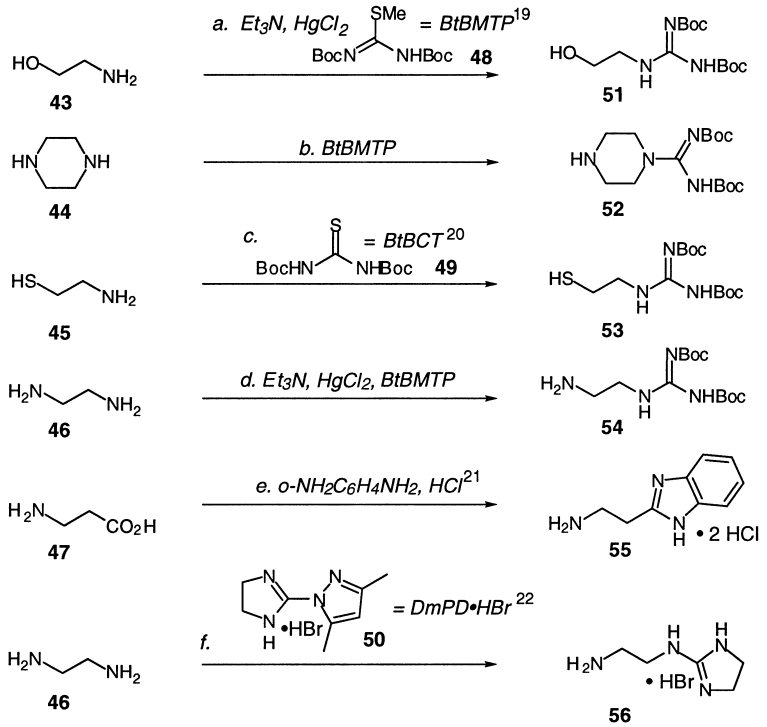



**Scheme 2.** Synthesis of compounds **10**–**13**. Reagents and conditions: (a) 5.0 equiv of $MeC(OMe)_3$, PhMe, 80 °C, 8 h, 98%; (b) 1.1 equiv of $N_3(CH_2)_2OTBS$, 0.1 equiv of TBAF, 4 Å MS, DMF, 25 °C, 4 h, 73%; (c) 2.0 equiv of $LiOH{\cdot}H_2O$, dioxane:$H_2O$ (3:1), 25 °C, 4 h 99%; (d) 1.0 equiv of DCC, 0.2 equiv of 4-DMAP, $CH_2CL_2$, 25 °C, 4 h, 82%; (e) 50% TFA in $CH_2Cl_2$, 25 °C, 2 h, 84%; (f) 1.1 equiv of $PhSO_2Cl$ or 1-$NaphSO_2Cl$, 1.3 equiv of *i*-$Pr_2NEt$, $CH_2Cl_2$, 25 °C, 4 h, **38a** (78%), or **38b** (57%); (g) 2.0 equiv of $Ph_3P$, 44 equiv of $H_2O$, THF, 25 °C, 12 h, 80%, ca. 1:1 of **35a**:**35b**; 80%, ca. 1:1 of **39a**:**41a**: 81%, ca. 1:1 of **39b**:**41b**; (h) 2.0 equiv of $LiOH{\cdot}H_2O$, THF:$H_2O$ (3:1), 25 °C, 4 h, 93–99% for **36ab**, **40ab**, **42a**; (i) 1.1 equiv of 1*H*-pyrazole-1-carboxamidine·HCl, 1.1 equiv of *i*-$Pr_2NEt$, DMF, 25 °C, 16 h, 13–15% for **10**, **11**, **13**: 50 °C, 16 h, 5% for **12**, after RP-HPLC. TFA = trifluoroacetic acid; TBAF = tetra-*n*-butyl-ammonium fluoride; DCC = 1,3-dicyclohexylcarbodiimide.

Pd/C catalyst in MeOH led to 1,2-diamine **70** (90%), which reacted with phenylisothiocyanate in EtOH to afford thiourea **71** (69% yield). Treatment of **71** with $HgCl_2$ and $Et_3N$ in DMF at ambient temperature gave guanidine **72** in 81% yield. Cleavage of the *tert*-butyl ester in **72** with TFA in $CH_2Cl_2$ then led to the targeted compound **22** (88% yield, after RP-HPLC purification).

## Biological evaluation

In integrin inhibition assays, the nitroaryl ether mimetics revealed high activity and selectivity (Table 1). Compound **1** had an $IC_{50}$ of 3 nM on $\alpha_v\beta_3$, 1.8 mM on $\alpha_v\beta_5$ and 6.4 mM on $\alpha_{IIb}\beta_3$. The nitroaryl compounds **10**–**21** (Fig. 3) were all essentially inactive on



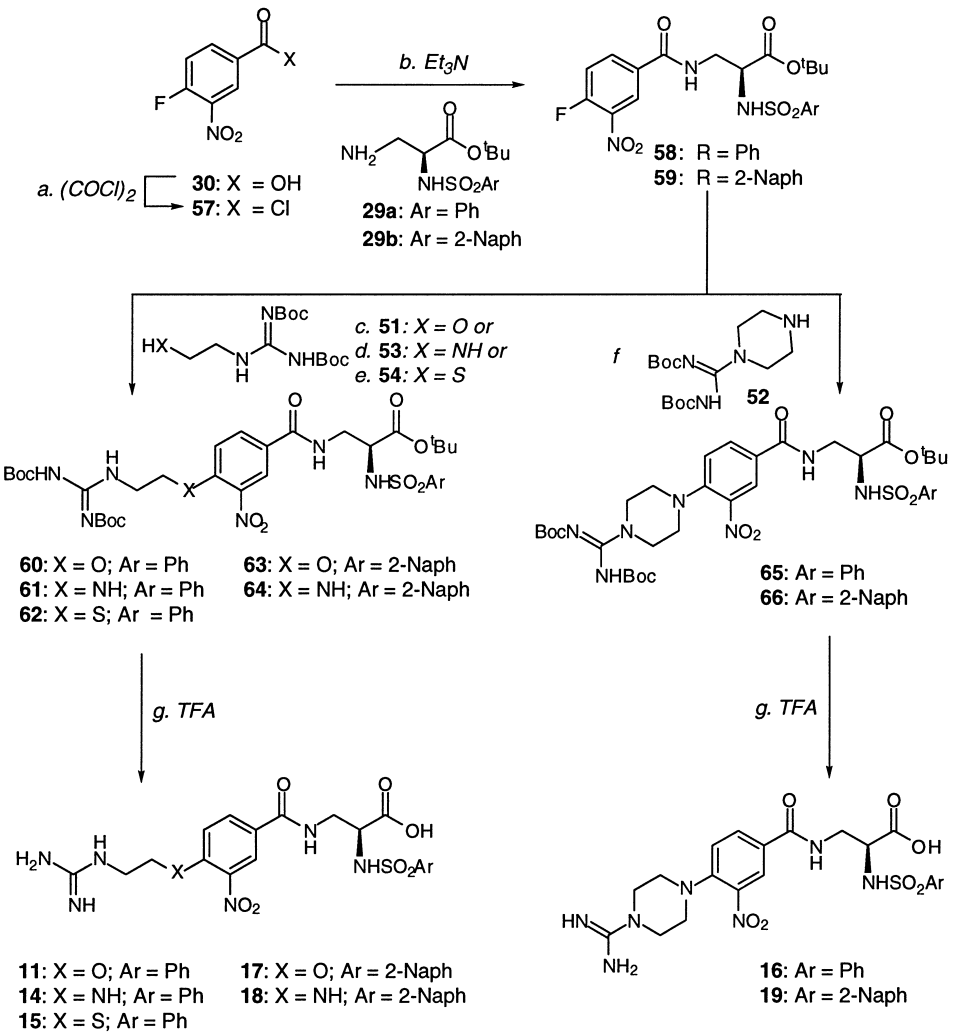

**Scheme 3.** Synthesis of guanidine derivatives **51**–**56**. Reagents and conditions: (a) 1.0 equiv of B*t*BMTP, 2.0 equiv of $Et_3N$, 1.0 equiv of $HgCl_2$, DMF, 25 °C, 4 h, 98%; (b) 1.0 equiv of B*t*BMTP, DMF, 25 °C, 14 h, 95%; (c) 1.0 equiv of B*t*BCT, 2.0 equiv of $Et_3N$, DMF, 25 dC, 14 h, 60%; (d) 0.2 equiv of B*t*BMTP, 0.4 equiv of $Et_3N$, 0.2 equiv of $HgCl_2$, DMF, 25 °C, 4 h, 51%; (e) 0.66 equiv of *o*-$NH_2C_6H_4NH_2$, 5.5 N aq HCl, reflux, 24 h, 73%; (f) 1.0 equiv of DmPD·HBr, *i*-$Pr_2NEt$, DMF, 25 °C, 11 h, 51%. Boc = *tert*-butoxycarbonyl; B*t*BCT = *N,N'*-bis-*tert*-butoxycarbonylthiourea; BtBMTP = 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea; DmPD·HBr-2-(3,5-dimethylpyrazolyl)-4,5-dehydroimidazole hydrobromide.

$\alpha_v\beta_5$, none having an $IC_{50}$ of below 1 μM. Some were specific inhibitors of $\alpha_v\beta_3$ (e.g. compound **20**), others were mixed inhibitors of both $\alpha_v\beta_3$ and $\alpha_{IIb}\beta_3$ (e.g. compounds **15** and **18**) or $\alpha_{IIb}\beta_3$-specific inhibitors (e.g. compound **19**). The degree of selectivity for $\alpha_v\beta_3$ over $\alpha_{IIb}\beta_3$ was up to two orders of magnitude (compound **20**), and thus comparable with selective peptidic inhibitors of $\alpha_v\beta_3$ (e.g. compound **1**), while monospecific $\alpha_{IIb}\beta_3$ inhibitors were also found (compound **12**). The activity of the compounds was high, the most potent (compound **20**) being a mixed $\alpha_v\beta_3/\alpha_{IIb}\beta_3$ inhibitor with an $IC_{50}$ in the picomolar range, more active than the highly active peptidic compound **1**.

The nitroaryl ether mimetics showed high activity and selectivity in the isolated integrin receptor assay and were, therefore, tested in a cell adhesion assay (Table 2). The $IC_{50}$ value for compound **1** as standard was 6.6 μM for M21 cell adhesion to vitronectin (mediated predominantly by $\alpha_v\beta_3$[24]). Inhibition of UCLA-P3 adhesion to vitronectin (mediated by $\alpha_v\beta_5$[24]) resulted in an $IC_{50}$ value of 1.7 μM. Inhibition of $\alpha_{IIb}\beta_3$-mediated adhesion of M21-L-IIb cells to fibrinogen did not reach an $IC_{50}$ value at 100 μM inhibitor.

Compounds **16** and **19** specifically inhibited $\alpha_{IIb}\beta_3$-mediated adhesion ($IC_{50} = 0.014$ μM) and had essentially no effect on $\alpha_v\beta_3$- and $\alpha_v\beta_5$-mediated adhesion ($IC_{50} = 33$–$95$ μM). Compounds **12** and **14** showed moderate $IC_{50}$ values on $\alpha_{IIb}\beta_3$ (0.13 and 0.2 μM) and were at least two orders of magnitude less active in inhibiting $\alpha_v\beta_3$- and $\alpha_v\beta_5$-mediated adhesion. Compounds **15**, **17**, **18**, and **21** had the highest activity on $\alpha_v\beta_3$- and $\alpha_v\beta_5$-mediated adhesion but also inhibited $\alpha_{IIb}\beta_3$-mediated adhesion very effectively. Compounds **10**, **11**, **13**, **20** and **22** showed low or no activity on all three cell lines. Thus, the compounds found to be more active on isolated integrins were, in general, more active in whole cell assays. The difference in magnitude of concentration dependency can be ascribed to multivalent interactions in the case of the cells.

Selected compounds (**11**, **14** and **16**) were tested in the chick chorioallantoic membrane (CAM) angiogenesis assay using bFGF as a cytokine.[23] The effects of these

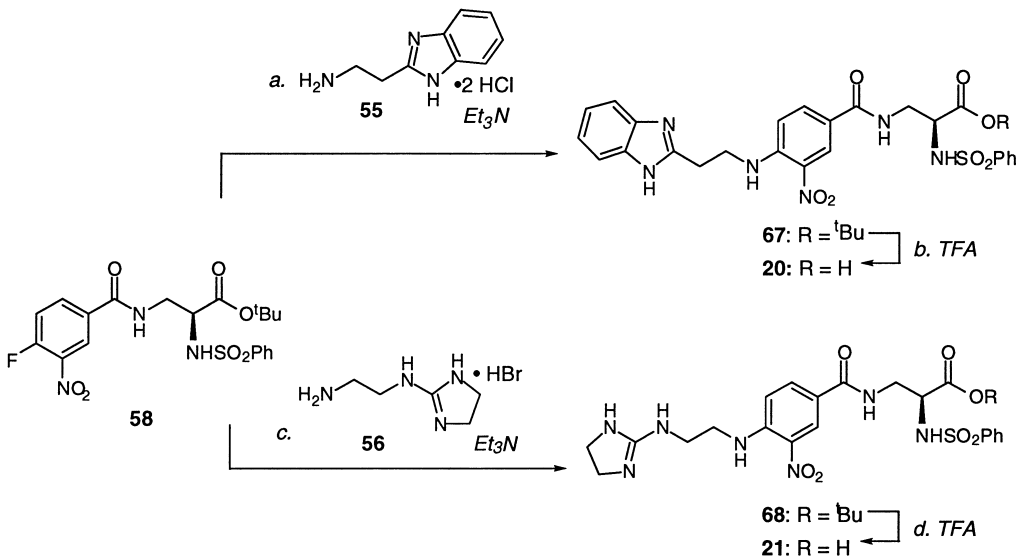



**Scheme 4.** Synthesis of compounds **11** and **14**–**19**. Reagents and conditions: (a) 1.2 equiv of $(COCl)_2$, PhH, DMF, 0 °C. 6 h, 99%; (b) 1.0 equiv of **29a** or **29b**, 1.2 equiv of $Et_3N$, $CH_2Cl_2$, 0 °C, 2 h, **58** (98%), or **59** (96%); (c) for **60**: 2.2 equiv of NaH, 2.2 equiv of **51**, DMF, 25 °C, 8 h, 66%; for **63**: 4.0 equiv of NaH, 1.2 equiv of **51**, DMF, 25 °C, 4 h, 69% (d) 1.1 equiv of **53**, DMF, 25 °C, 4 h, 73%; for **64**: 1.9 equiv of **53**, NMP, 25 °C, 99%; (e) for **65**: 2.2 equiv of NaH, 2.5 equiv of **54**, DMF, 25 °C, 12 h, 23%; (f) 1.1 equiv of **52**, DMF, 25 °C, 6 h, 83%; for **66**: 2.0 equiv of **52**, DMF, 25 °C, 20 h, 99%; (g) 50% TFA in $CH_2Cl_2$, 25 °C, 30 min, 90–99% for **11**, **14**–**19** after RP-HPLC. Boc = *tert*-butoxycarbonyl: TFA = trifluoroacetic acid; NMP = *N*-methyl-2-pyrrolidinone; DMF = dimethylformamide.

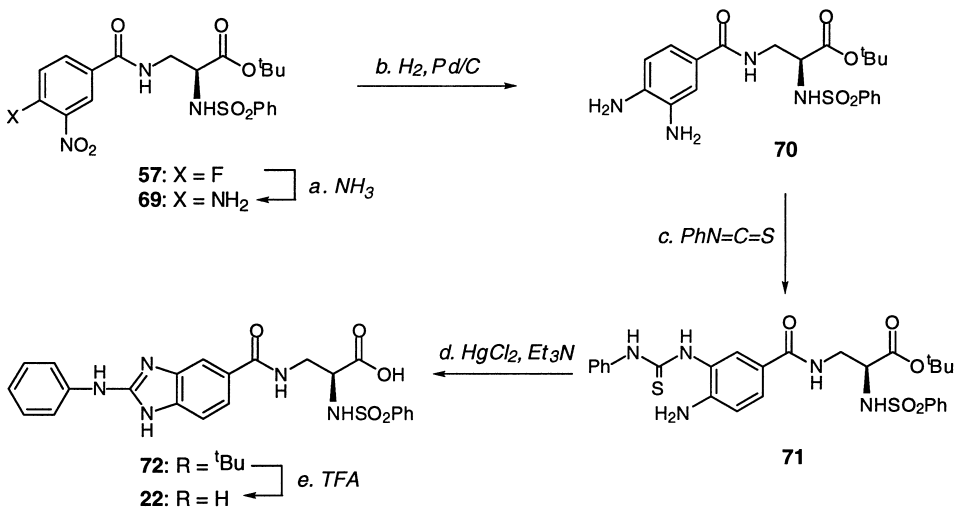
compounds, compound **1** and the inactive peptide *c*RBADFV (EM-601)[4] are shown in Fig. 5. As seen from these data, compound **11** exhibited excellent inhibition at 30 μg/embryo, while **14** and **16** exhibited minimal inhibition of angiogenesis. Further details regarding these biological studies are included in the experimental section.

## Conclusion

In this article we described the molecular design, chemical synthesis and biological investigation of a series of small organic molecules based on a nitroaryl ether scaffold. The synthesis of these compounds relied on a displacement of a fluoride from a nitroaryl system by nucleophiles carrying oxygen, sulfur or nitrogen atoms, followed by side-chain construction through amide and sulfonamide bond formations. The synthesized compounds exhibited varying degrees of inhibition of integrin-mediated cell adhesion with compounds **16** and **19** showing the most potent and selective preference for $\alpha_{IIb}\beta_3$- versus $\alpha_v\beta_3$- and $\alpha_v\beta_5$-mediated adhesion. Furthermore, compound **11** proved to be an excellent inhibitor or angiogenesis at 30 μg/embryo in the chick




**Scheme 5.** Synthesis of compounds **20** and **21**. Reagents and conditions: (a) 1.0 equiv of **55**, 2.2 equiv of $Et_3N$, DMF, 25 °C, 16 h, 92%; (b) 50% TFA in $CH_2Cl_2$, 25 °C, 4 h, 97%; (c) 1.0 equiv of **56**, 2.2 equiv of $Et_3N$, DMF, 12 h, 110% (crude yield); (d) 50% TFA in $CH_2Cl_2$ 25 °C, 4 h, 83% after RP-HPLC; TFA = trifluoroacetic acid; DMF = dimethylformamide.




**Scheme 6.** Synthesis of compound **22**. Reagents and conditions: (a) $NH_3$, DMF, 25 °C, 5 h, 93%; (b) 10% Pd/C, $H_2$, MeOH, 25 °C, 8 h, 90%; (c) 1.1 equiv of PhNCS, EtOH, 14 h, 69%; (d) 1.0 equiv of $HgCl_2$, 1.0 equiv of $Et_3N$, DMF, 4 h, 81%; (e) 50% TFA in $CH_2Cl_2$, 30 min, 88% yield, after RP-HPLC. TFA = trifluroacetic acid; DMF = dimethylformamide.

chorioallantoic membrane (CAM) assay. It is expected that the use of some of these compounds as delivery systems may result in the beneficial localization of anticancer drugs to the tumor vasculature.[24] Further studies with these compounds is warranted and continued investigations in the field may prove beneficial in biology and medicine.

## Experimental

### Chemistry general techniques

All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Tetrahydrofuran (THF) and diethyl ether (ether) were distilled from

**Table 1.** Effect of compounds (**10**–**21**) on ligand interaction with integrins[a]

| | $\alpha_v\beta_3$ | | $\alpha_v\beta_5$ | | $\alpha_{IIb}\beta_3$ | |
|---|---|---|---|---|---|---|
| Compd | $IC_{50}$ (M) | cQ | $IC_{50}$ (M) | cQ | $IC_{50}$ (M) | cQ |
| **GRGDSPK** | 3.2E-07 | 1.0E + 02 | > | 9.9E + 01 | 6.0E-06 | 9.3E-01 |
| **1** | 3.1E-09 | 1.0E + 00 | 1.8E-06 | 1.0E + 00 | 6.4E-06 | 1.0E + 00 |
| **20** | 8.10E-10 | 2.06E-01 | > | | 2.40E-08 | 3.70E-03 |
| **18** | 1.30E-09 | 4.00E-01 | 1.3E-06 | 7.00E-01 | 1.70E-11 | 2.70E-06 |
| **15** | 3.00E-09 | 9.80E-01 | 3.50E-06 | 1.90E + 00 | 1.30E-10 | 2.00E-05 |
| **17** | 3.80E-09 | 1.20E + 00 | 2.10E-06 | 1.20E + 00 | 3.60E-10 | 5.60E-05 |
| **21** | 9.5E-09 | 3.10E + 00 | 5.00E-06 | 2.80E + 00 | 9.00E-10 | 1.40E-04 |
| **14** | 3.90E-08 | 1.2E + 01 | 8.30E-06 | 4.60E + 00 | 6.7E-10 | 1.10 E-04 |
| **13** | 4.40E-08 | 1.40E + 01 | > | | 1.40E-08 | 2.10E-03 |
| **16** | 9.30E-08 | 3.00E + 01 | > | | 8.70E-10 | 1.40E-04 |
| **11** | 1.00E-07 | 3.30E + 01 | > | | 1.20E-08 | 1.90E-03 |
| **10** | 4.00E-07 | 1.30E + 02 | 9.00E-06 | 5.00E + 00 | 2.10E-06 | 3.30E-01 |
| **19** | 4.80E-07 | 1.50E + 02 | > | | 3.60E-11 | 5.60E-06 |
| **22** | 1.50E-06 | 4.70E + 02 | > | | 6.50E-08 | 1.00E-02 |
| **12** | 1.90E-06 | 6.00E + 02 | > | | 4.90E-10 | 7.60E-05 |

[a]Biotinylated ligands vitronectin ($\alpha_v\beta_3$ and $\alpha_v\beta_5$) or fibrinogen ($\alpha_{IIb}\beta_3$) were allowed to bind to immobilized integrins in the presence of the compounds **10**–**21** (Fig. 3). The concentration necessary for half-maximal inhibition of ligand binding is shown. The peptide GRGDSPK and compound **1** were included for reference. The data were sorted by $IC_{50}$ (low to high) on $\alpha_v\beta_3$. The 'cQ' value designates the activity of the compound relative to the activity of compound **1**. The sign '>', indicates that the $IC_{50}$ had not been reached at the maximum concentration tested, (10 μM).

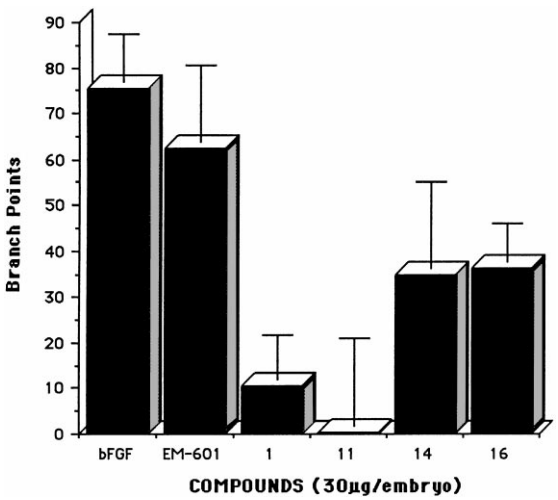



**Figure 5.** Effect of compounds on bFGF induced CAM angiogenesis.

sodium-benzophenone, and methylene chloride ($CH_2Cl_2$), benzene (PhH), and toluene from calcium hydride. Anhydrous solvents were also obtained by passing them through commercially available activated alumina columns. Yields refer to chromatographically and spectroscopically ($^1H$ NMR) homogeneous materials, unless otherwise stated. All solutions used in workup procedures were saturated unless otherwise noted. All reagents were purchased at highest commercial quality and used without further purification unless otherwise stated.

All reactions were monitored by thin-layer chromatography carried out on 0.25 mm E. Merck silica gel plates (60F-254) using UV light as visualizing agent and 7% ethanolic phosphomolybdic acid or *p*-anisaldehyde solution and heat as developing agents. E. Merck silica gel (60, particle size 0.040–0.063 mm) was used for flash column chromatography. Preparative thin-layer chromatography separations were carried out on 0.25, 0.50 or 1 mm E. Merck silica gel plates (60F-254). Reverse-phase HPLC was performed on a Waters Model 600E HPLC instrument utilizing a Vydac 218TP1022 column with detection at 254 nm using a 90:10→40:60 $H_2O$:$CH_3CN$ + 0.1% TFA gradient over 40 min.

NMR spectra were recorded on Bruker DRX-600, AMX-500, AMX-400 or AC-250 instruments and calibrated using residual undeuterated solvent as an internal reference. The following abbreviations were used to explain the multiplicities: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; band, several overlapping signals; b, broad. IR spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. High resolution mass spectra (HRMS) were recorded on a VG ZAB-ZSE mass spectrometer under fast atom bombardment (FAB) conditions. Electrospray mass spectra were recorded on a Perkin Elmer Science API III mass spectrometer.

**Table 2.** Effect of compounds (**10**–**21**) on cell adhesion[a]

| Compd | M21/VN[b] $IC_{50}$ (M) | UCLA-P3/VN[b] $IC_{50}$ (M) | M21-L-IIb/Fg[b] $IC_{50}$ (M) |
|---|---|---|---|
| **GRGDSPK** | 3.3E-05 | 4.0E-05 | 7.5E-05 |
| **1** | 6.6E-06 | 1.7E-06 | > 1.0E-04 |
| **15** | 1.3E-06 | 8.3E-07 | 1.5E-07 |
| **21** | 2.0E-06 | 6.0E-06 | 5.0E-07 |
| **18** | 3.3E-06 | 3.5E-06 | 2.0E-08 |
| **17** | 8.7E-06 | 1.8E-06 | 4.4E-08 |
| **14** | 1.1E-05 | 9.0E-06 | 1.3E-07 |
| **20** | 1.4E-05 | 4.0E-05 | 1.0E-05 |
| **13** | 4.0E-05 | 1.5E-05 | 2.5E-06 |
| **16** | 4.5E-05 | 3.3E-05 | 1.4E-08 |
| **10** | 6.0E-05 | 1.5E-05 | 4.5E-05 |
| **11** | 7.5E-05 | 4.5E-05 | 2.5E-06 |
| **19** | 9.5E-05 | 4.7E-05 | 1.4E-08 |
| **22** | > 1.0E-04 | > 1.0E-04 | 3.5E-05 |
| **12** | > 1.0E-04 | 5.0E-05 | 2.0E-07 |

[a]Cells (25000) were allowed to adhere to immobilized ligands in the presence of the compounds as described in the text. The concentration resulting in half-maximal inhibition of cell adhesion ($IC_{50}$) is shown. The data were sorted by $IC_{50}$ (low to high) on $\alpha_v\beta_3$ mediated adhesion of M21 cells.
[b]M21 cell line expresses $\alpha_v\beta_3/\alpha_v\beta_5$ (10:1), UCLA-P3 expresses $\alpha_v\beta_5$, M21-L-IIb expresses $\alpha_{IIb}\beta_3$, VN = vitronectin; Fg = fibrinogen.

### Preparation of amino acid derivatives 26, 29a, and 29b

**Compound 25**. To a solution of *t*-butoxycarbonyl-(L)-asparagine **24** (12.6 g, 50 mol) in MeOH (200 mL) was added water (20 mL). The solution was neutralized with a 20% aqueous solution of $Cs_2CO_3$ (57 mL) and then evaporated to dryness. The resulting residue was taken up in DMF (50 mL) and then azeotropically dried by evaporation to dryness. The cesium salt was then taken up in DMF (125 mL) followed by addition of benzyl bromide (6.5 mL, 55 mmol). The mixture was stirred at room temperature for 6 h, evaporated to dryness and the residue triturated with water (500 mL). The solid was dissolved in ethyl acetate (150 mL) and the organic phase was washed with water (75 mL), dried over $Na_2SO_4$ and the solvent was removed under reduced pressure. The crude ester was recrystallized from ethyl acetate/hexane to give **25** (15.1 g, 88%) as a colorless solid. IR (KBr): $V_{max}$ 3401, 3349, 3204, 2982, 2935, 1741, 1688, 1657, 1524, 1293, 1169, 1055 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.36–7.32 (m, 5H, Ph), 5.73 (d, $J$ = 8.5 Hz, 1H, $NHCO_2$), 5.59 (bs, 1H, CONH*H*), 5.40 (bs, 1H, CON*H*H), 5.20 (d, $J$ = 12.5 Hz, 1H, C*H*HPh), 5.17 (d, $J$ = 12.5 Hz, 1H, CH*H*Ph), 4.56 (ddd, $J$ = 4.0, 5.0, 8.5 Hz, 1H, C*H*$CH_2$), 2.95 (dd, $J$ = 5.0, 16.5 Hz, 1H, CHCH*H*), 2.76 (dd, $J$ = 4.0, 16.5 Hz, 1H, CHC*H*H), 1.42 (s, 9H, $^t$Bu); $^{13}C$ NMR (150 MHz, $CDCl_3$): δ 171.9, 171.2, 155.7, 135.4, 128.5, 128.3, 128.2, 80.1, 67.4, 50.3, 37.4, 28.3; FAB-HRMS ($M + Na^+$) calcd 345.1426, found 345.1421.

**Compound 26**. To a stirred solution of bis[trifluoroacetoxy]phenyl iodine (2.0 g, 4.7 mmol) in DMF:$H_2O$ (12 mL:12 mL) compound **25** (1.0 g, 3.1 mmol) was added at room temperature. After 15 min, pyridine (0.5 mL, 6.2 mmol) was added and stirring was continued for 3 h. The solvent was removed under reduced pressure and the residue dissolved in water (30 mL). The solution was washed with ether and the aqueous layer was basified with 1 N NaOH and extracted with dichloromethane. The solvent was removed under reduced pressure to give an oily residue. Purification by flash column chromatography (10% MeOH in $CH_2Cl_2$) gave amine **26** as a yellow oil (0.37 g, 41%). $R_f$ = 0.11 (2.5% methanol in ethyl acetate); IR (thin film): $V_{max}$ 3366, 3313, 3064, 2979, 2934, 1688, 1518, 1501, 1456, 1393, 1368, 1324, 1254, 1204, 1166, 1055, 1002, 838, 800, 743, 692 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.36–7.28 (m, 5H, Ph), 6.36 (bm, 2H, $NH_2$), 6.06 (d, $J$ = 7.5 Hz, 1H, $NHCO_2$), 5.18 (d, $J$ = 12.0 Hz, 1H, C*H*HPh), 5.13 (d, $J$ = 12.0 Hz, 1H, CH*H*Ph), 4.52–4.43 (bm, 1H, C*H*$CH_2$), 3.35 (bdd, $J$ = 12.5 Hz, 1H, CHC*H*H), 3.24 (bdd, $J$ = 6.5, 12.5 Hz, 1H, CHC*H*H), 1.32 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 170.0, 155.9, 134.8, 128.5, 128.4, 128.3, 80.6, 67.7, 52.9, 41.6, 28.0; FAB-HRMS ($M + H^+$) calcd 295.1658, found 295.1650.

**Compound 27a**. To a solution of (L)-asparagine (**23**) (10.00 g, 75.7 mmol) in $H_2O$:dioxane (50 mL:50 mL) was added NaOH (3.40 g, 85.0 mmol) at 0 °C. After 15 min at 0 °C, phenylsulfonylchloride (10.6 mL, 84.0 mmol) was added followed by addition of a solution of NaOH (3.40 g, 85.0 mmol) in $H_2O$ (50 mL) at 0 °C. After 30 min, the cooling bath was removed and the solution was concentrated to *ca.* 50 mL under reduced pressure. The aqueous phase was extracted with ethyl acetate (2 × 50 mL). The aqueous layer was acidified at 0 °C with concd aqueous HCl (pH ≈ 1) while the protected amino acid precipitated. The resulting solid was collected by filtration and washed with $H_2O$ (20 mL). Overnight drying in an oven at ca. 50 °C gave **27a** as a colorless solid (14.6 g, 71%). The crude product was used without further purification. IR (KBr): $V_{max}$ 3495, 3338, 3260, 1723, 1648, 1578, 1449, 1325, 1261, 1202, 1166, 1086 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d_4$): δ 7.88–7.86 (m, 2H, Ph), 7.60–7.57 (m, 1H, Ph), 7.54–7.51 (m, 2H, Ph), 4.23 (t, 1H, $J$ = 6.0 Hz, C*H*$CO_2$H), 2.66 (dd, 1H, $J$ = 6.0, 15.5 Hz, C*H*H(C=O)$NH_2$), 2.60 (dd, $J$ = 6.0, 15.5 Hz, CH*H*(C=O)$NH_2$); $^{13}C$ NMR (125 MHz, methanol-$d_4$): δ 174.3, 173.6, 142.1, 133.7, 130.0, 128.2, 53.9, 39.6; FAB-HRMS ($M + H^+$) calcd 273.0545, found 273.0540.

**Compound 27b**. Compound **27b** was prepared by the same procedure as for **27a**. Crude yield: 16.06 g (66%). IR (KBr): $V_{max}$ 3424, 3289, 2925, 1851, 1713, 1673, 1502, 1399, 1333, 1258, 1223, 1191, 1159, 1127, 1075, 1023, 964, 866, 822, 794, 714, 669, 638, 548, 477 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 8.40 (d, $J$ = 1.0 Hz, 1H, naphthyl), 8.15 (d, $J$ = 9.0 Hz, 1H, $NHSO_2$), 8.12 (d, $J$ = 8.0 Hz, 1H, naphthyl), 8.07 (d, $J$ = 9.0 Hz, 1H, naphthyl), 8.01 (d, $J$ = 8.0 Hz, 1H, naphthyl), 7.81 (dd, $J$ = 1.5, 8.8 Hz, 1H, naphthyl), 7.68 (ddd, $J$ = 1.5, 6.8, 7.5 Hz, 1H, naphthyl), 7.64 (ddd, $J$ = 1.5, 6.8, 7.5 Hz, 1H, naphthyl), 7.33 (bs, 1H, CONH*H*), 6.87 (bs, 1H, CON*H*H), 4.16 (bm, 1H, C*H*$CH_2$), 2.47 (dd, $J$ = 7.0, 15.5 Hz, 1H, CHCH*H*) 2.28 (dd, $J$ = 6.5, 15.5 Hz, 1H, CHC*H*H); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 172.0, 170.5, 138.4, 134.1, 131.6, 129.2, 129.0, 128.6, 127.8, 127.4, 127.1, 122.6, 52.5, 38.0; FAB-HRMS ($M+H^+$) calcd 323.0702, found 323.0708.

**Compound 28a**. To a round-bottom flask equipped with a magnetic stirring bar was added an aqueous solution of NaOH (11.15 g, 280.0 mmol) in water (50 mL) and cooled to 0 °C. Bromine (2.60 mL, 50.0 mmol) was added dropwise within 5 min and the reaction mixture was stirred for a further 5 min at this temperature. A solution of the protected amino acid **27a** (10.44 g, 38.0 mmol) in a solution of NaOH (3.10 g, 70.0 mmol, 30 mL $H_2O$) was added in one portion at 0 °C. Stirring was continued at this temperature for 20 min and upon removal of the cooling bath the reaction mixture was heated to 90 °C for an additional 30 min. After cooling to 0 °C the pH of the reaction mixture was adjusted to 7 with concentrated and 1 M aqueous HCl. The resulting colourless precipitate was collected by filtration. The residue was washed with water, dried overnight in an oven at ca. 50 °C to give **28a** as a colorless solid (6.95 g, 75%). The crude product was used without further purification. IR (KBr): $V_{max}$ 3509, 3299, 3058, 2936, 1636, 1596, 1522, 1446, 1413, 1355, 1340, 1300, 1246, 1163, 1094, 1028, 924 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 7.84–7.82 (m, 2H, Ph), 7.66–7.63 (m, 1H, Ph), 7.60–7.56 (m, 2H, Ph), 7.58 (bm, 1H, $NHSO_2$Ph), 3.35 (bs, 2H, $NH_2$), 3.17 (dd, $J$ = 4.5, 9.5 Hz, 1H, C*H*$CH_2$), 3.01 (dd, $J$ = 2.5, 12.0 Hz, 1H, C*H*H), 2.80 (dd, $J$ = 9.5, 12.0 Hz, 1H, CH*H*); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 169.4, 139.1, 132.7, 129.2, 126.8, 52.7, 41.7; FAB-HRMS ($M+Na^+$) calcd 245.0596, found 245.0599.

**Compound 28b**. Compound **28b** was prepared by the same procedure as for **28a**. Crude yield (11.88 g, 81%) as a beige-coloured solid. IR (KBr): $V_{max}$ 3338, 3241, 3056, 2831, 2601, 1651, 1604, 1513, 1463, 1404, 1382, 1335, 1151, 1076, 1039, 985, 955, 931, 913, 855, 814, 787, 749, 657, 618, 550, 480 $cm^{-1}$; $^1H$ NMR (500 MHz, DMSO-$d_6$): δ 8.48 (bs, 1H, naphthyl), 8.16–8.10 (2 bd, 2H, naphthyl), 8.04 (d, $J$ = 8.5 Hz, 1H, naphthyl), 7.85 (dd, $J$ = 2.0, 8.5 Hz, 1H, naphthyl), 7.70 (ddd, $J$ = 1.5, 7.0, 8.0 Hz, 1H, naphthyl), 7.66 (ddd, $J$ = 1.0, 7.0, 8.0 Hz, 1H, naphthyl), 7.45 (bm, 1H, $NHSO_2$), 3.54–3.19 (bm, 2H, $NH_2$), 3.23 (dd, superimposed, $J$ = 4.5, 9.5 Hz, 1H, C*H*$CH_2$), 3.04 (dd, $J$ = 4.5, 12.0 Hz, 1H, CHC*H*H), 2.83 (dd, $J$ = 9.5, 12.0 Hz, 1H, CHCH*H*); $^{13}C$ NMR (125 MHz, DMSO-$d_6$): δ 169.3, 136.1, 134.3, 131.6, 129.4, 129.2, 128.9, 128.0, 127.8, 127.6, 122.5, 52.7, 41.6; FAB-HRMS ($M+H^+$) calcd 295.0753, found 295.0761

**Compound 29a**. A sealed tube equipped with a magnetic stirring bar was charged with **28a** (4.88 g, 20.0 mmol) and 75 mL of anhydrous dimethoxyethane. After addition of 3.0 mL of concd $H_2SO_4$ the reaction mixture was cooled to −78 °C under an atmosphere of argon and 40 mL of isobutylene was condensed into the sealed tube. After sealing the cooling bath was removed and the reaction mixture was stirred for 48 h at room temperature. The reaction mixture was poured into 100 mL of ice water. The aqueous solution was extracted with diethyl ether (40 mL) and then the pH of the aqueous phase adjusted to 12–13 with 6 N aqueous NaOH. The free amine was extracted with ethyl acetate (4×50 mL) and the combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ solution (50 mL), 5% aqueous $KHSO_4$ solution (50 mL) and brine (50 mL). The organic phase was dried over $MgSO_4$, filtrated and the solvent removed in vacuo to give **29a** (3.32 g, 55.5%) as an off-white solid. The crude product was used without further purification. $R_f$ = 0.27 (silica gel, ethyl acetate); IR (KBr): $V_{max}$ 3372, 3295, 2981, 2932, 1726, 1452, 1337, 1261, 1161, 1094, 945, 898, 845, 753 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 7.86–7.84 (m, 2H, Ph), 7.58–7.54 (m, 1H, Ph), 7.51–7.48 (m, 1H, Ph), 3.76 (dd, $J$ = 4.0, 5.5 Hz, 1H, C*H*$CH_2$), 3.02 (dd, $J$ = 9.0, 13.0 Hz, 1H, C*H*H), 2.88 (dd, $J$ = 5.5, 13.0 Hz, 1H, CH*H*), 1.27 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 169.3, 139.7, 132.8, 129.1, 127.2, 82.8, 58.8, 44.9, 27.7; FAB-HRMS ($M+H^+$) calcd 301.1222, found 301.1211.

**Compound 29b**. Compound **29b** was prepared by the same procedure as for **29a**. Crude yield: 4.56 g (51%) as an off-white solid. $R_f$ = 0.25 (silica gel, ethyl acetate + 2% $Et_3N$); IR (KBr): $V_{max}$ 3360, 3264, 3057, 2981, 2935, 2873, 2747, 1731, 1588, 1501, 1455, 1339, 1254, 1220, 1157, 1076, 952, 926, 823, 782, 747, 663, 619, 552, 481 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.40 (bs, 1H, naphthyl), 7.92 (bd, $J$ = 8.5 Hz, 2H, naphthyl), 7.86 (d, $J$ = 8.0 Hz, 1H, naphthyl), 7.82 (dd, $J$ = 1.5, 8.5 Hz, 1H, naphthyl), 7.64–7.55 (2×ddd, superimposed, $J$ = 1.0, 7.0, 8.5 Hz, 2H, naphthyl), 3.84 (dd, $J$ = 4.2, 5.8 Hz, 1H, C*H*$CH_2$), 3.30–2.60 (bm, superimposed, 2H, $NH_2$), 3.03 (dd, $J$ = 4.2, 13.4 Hz, 1H, CHC*H*H), 2.88 (dd, $J$ = 5.8,

13.4 Hz, 1H, CHCH*H*), 1.08 (s, 9H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.2, 136.3, 134.9, 132.0, 129.5, 129.2, 128.9, 128.6, 127.8, 127.5, 122.4, 82.9, 58.6, 44.6, 27.5; FAB-HRMS ($M+H^+$) calcd 351.1379, found 351.1371.

### Preparation of compounds 10–13

**Compound 31**. To a suspension of the acid **30** (5.0 g, 27 mmol) in toluene was added trimethylorthoacetate (17 mL, 135 mmol). The mixture was heated to 80 °C for 12 h and the solvent removed under reduced pressure to give **31** as a colorless solid (5.26 g, 98%). $R_f$ = 0.46 (silica gel, 25% ethyl acetate in hexane); IR (KBr): $V_{max}$ 3061, 2960, 1714, 1614, 1542, 1438, 1351, 1297, 1262, 1233, 1130, 871, 755 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.74 (dd, $^4J$ ($^1$H-$^1$H) = 2.0 Hz, $^4J$ ($^1$H-$^{19}$F) = 7.0 Hz, 1H, Ar), 8.32 (ddd, $^4J$($^1$H-$^1$H) = 2.0 Hz, $^4J$ ($^1$H-$^{19}$F) = 4.5 Hz, $^3J$($^1$H-$^1$H) = 9.0 Hz, 1H, Ar), 7.39 (dd, $^3J$($^1$H-$^1$H) = 9.0 Hz, $^3J$($^1$H-$^{19}$F) = 10.5 Hz, 1H, Ar); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 164.1, 159.1, 156.9, 136.5, 127.8, 118.8, 118.7, 52.9; FAB-HRMS ($M+H^+$) calcd 200.0281, found 200.0286.

**Compound 32**. To a solution of **31** (4.0 g, 20 mmol) in DMF (10 mL) were added ca. 4 g of 4 Å molecular sieves and 4.46 g (0.22 mmol) of $N_3(CH_2)_2OTBS$ at room temperature. After 10 min, 2 mL (2.0 mmol) of a 1 M solution of TBAF in THF was added. The mixture was stirred for 4 h at room temperature and then filtered through a short path of celite®. The filtrate was taken up in ethyl acetate (100 mL) and successively washed with water, saturated aqueous $NaHCO_3$-solution and brine. The organic extract was dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give a yellow oil. Flash column chromatography (silica gel, 40% ethyl acetate in hexanes) gave **32** as a yellow solid (3.85 g, 73%). $R_f$ = 0.35 (silica gel, 40% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 2950, 2938, 2114, 1713, 1620, 1536, 1438, 1349, 1303, 1276, 1247, 1161, 1136, 918, 760 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.54 (d, $J$ = 2.0 Hz, 1H, Ar), 8.22 (dd, $J$ = 2.0, 9.0 Hz, 1H, Ar), 7.13 (d, $J$ = 9.0 Hz, 1H, Ar), 4.32 (t, $J$ = 5.0 Hz, 2H, $OCH_2$), 3.94 (s, 3H, $OCH_3$), 3.71 (t, $J$ = 5.0 Hz, 2H, $CH_2N_3$); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 164.7, 154.7, 135.3, 127.3, 123.3, 114.0, 68.8, 52.5, 49.7; FAB-HRMS ($M+Na^+$) calcd 289.0549, found 289.0553.

**Compound 33**. To a solution of **32** (3.85 g, 14.0 mmol) in 1,4-dioxane:water (90 mL:30 mL) was added $LiOH\cdot H_2O$ (1.2 g, 28 mmol). The reaction mixture was stirred at room temperature for 4 h and then 40 mL of a saturated aqueous $NH_4Cl$-solution was added. The organic solvent was removed under reduced pressure to give a yellow slush. The slush was taken up in water and acidified with aqueous 1 M $KHSO_4$-solution. The aqueous layer was then extracted with $CH_2Cl_2$ (3×70 mL). The combined organic extracts were dried over $MgSO_4$, filtered and the solvent removed under reduced pressure to give **33** as a yellow solid (3.50 g, 99%). $R_f$ = 0.10 (silica gel, 60% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3087, 2964, 2877, 2659, 2539, 2120, 1699, 1616, 1534, 1429, 1359, 1282, 1163, 1138, 1079, 1039, 1002, 929, 847, 763, 687, 642, 546 cm$^{-1}$; $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.40 (d, $J$ = 2.0 Hz, 1H, Ar), 8.22 (dd, $J$ = 2.0, 9.0 Hz, 1H, Ar), 7.37 (d, $J$ = 9.0 Hz, 1H, Ar), 4.37 (t, $J$ = 4.5 Hz, 2H, $OCH_2$), 3.67 (t, $J$ = 5.0 Hz, 2H, $CH_2N_3$); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 167.4, 156.0, 140.9, 136.4, 127.9, 124.9, 115.7, 70.3, 51.1; FAB-HRMS ($M+Na^+$) calcd 275.0392, found 275.0395.

**Compound 34**. To a solution of amine **26** (0.33 g, 1.10 mmol) and acid **33** (0.286 g, 1.10 mmol) in $CH_2Cl_2$ (30 mL) was added a catalytic amount of 4-DMAP (0.03 g, 0.22 mol) and DCC (0.26 g, 1.1 mol) at room temperature. The reaction mixture was stirred for 4 h at this temperature and the precipated dicyclohexyl urea was then filtered and the filtrate washed successively with water, saturated aqueous $NaHCO_3$-solution and brine. The organic solvent was removed under reduced pressure to give an oil which after purification by flash column chromatography (silica gel, 60% ethyl acetate in hexanes) gave amide **34** as a yellow solid (2.48 g, 82%). $R_f$ = 0.28 (silica gel, 60% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3343, 2977, 2933, 2112, 1738, 1710, 1619, 1531, 1498, 1366, 1333, 1280, 1161, 1084, 1047 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.23 (d, $J$ = 2.0 Hz, 1H, Ar), 7.98 (dd, $J$ = 2.0, 11.0 Hz, 1H, Ar), 7.40 (bt, 1H, NHCO), 7.39–7.31 (m, 5H, Ph), 7.09 (d, $J$ = 11.0 Hz, 1H, Ar), 5.67 (d, $J$ = 8.0 Hz, 1H, $NHCO_2$), 5.21 (s, 2H, $CH_2Ph$), 4.60–4.50 (bm, 1H, C*H*$CH_2$), 4.30 (t, $J$ = 6.0 Hz, 2H, $OCH_2$), 3.95–3.85 (bm, 1H, CHC*H*H), 3.78–3.70 (bm, superimposed, 1H, CHCH*H*), 3.70 (t, $J$ = 6.0 Hz, 2H, $CH_2N_3$), 1.43 (s, 9H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 170.0, 164.9, 153.8, 139.8, 135.0, 133.0, 128.7, 128.6, 126.9, 124.6, 114.3, 81.0, 68.8, 67.9, 49.8, 33.8, 28.2, 25.5, 24.8; FAB-HRMS ($M+Cs^+$) calcd 661.1023, found 661.1050.

**Compounds 35ab**. To a solution of the azide **34** (50 mg, 0.095 mmol) in a mixture of THF:$H_2O$ (8 mL THF: 0.04 mL $H_2O$) was added triphenylphosphine (50 mg, 0.19 mmol). The reaction mixture was stirred at room temperature for 14 h and the solvent was removed under reduced pressure. Purification of the crude residue by flash column chromatography (silica gel, 20% methanol in dichloromethane) gave two major fractions (total yield 80%). Fraction 1: 17 mg (yellowish oil, 40%); fraction 2: 17 mg (yellowish oil, 40%). Fraction 1 was positive in ninhydrin test while fraction 2 was negative. Fraction 1 **35a** $R_f$ = 0.48 (silica gel, 20% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.22

(m, 1H, Ar), 7.94 (d, $J=9.0$ Hz, 1H, Ar), 7.43–7.30 (m, 6H), 7.07 (d, $J=9.0$ Hz, 1H, Ar), 5.80 (d, $J=6.0$ Hz, 1H, NHBoc), 5.19 (s, 2H, C$H_2$Ph), 4.54 (bm, 1H, C*H*NHBoc), 4.21 (bm, 2H, C$H_2$OAr), 3.87–3.76 (m, 2H), 3.19 (s, 2H, C$H_2$NH$_2$), 2.75 (bs, 2H, NH$_2$), 1.41 (s, 9H, $^t$Bu); FAB-HRMS (M + H$^+$) calcd 503.2142, found 503.2162. Fraction 2 **35b**: $R_f=0.86$ (silica gel, 20% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.46 (m, 1H, Ar), 8.42 (t, $J=6.5$ Hz, 1H, NHAr), 7.79 (dd, $J=2.5$, 11.0 Hz, 1H, Ar), 7.38–7.28 (m, 5H, Ar), 7.21 (m, 1H, N*H*CO), 6.80 (d, $J=11.0$ Hz, 1H, Ar), 5.85 (d, $J=9.0$ Hz, 1H, N*H*Boc), 5.19 (s, 2H, C$H_2$Ph), 4.53 (m, 1H, C*H*NHBoc), 3.92 (t, $J=6.5$ Hz, 2H, C$H_2$OH), 3.88–3.73 (m, 2H, C$H_2$NH(CO)), 3.52–3.38 (m, 2H, C$H_2$NHAr), 1.41 (s, 9H, $^t$Bu); FAB-HRMS (M + Cs$^+$) calcd 635.118, found 635.110.

**Compound 10**. To a solution of **35a** (0.023 g, 0.046 mmol) in a mixture of THF:$H_2O$ (6 mL:2 mL) was added LiOH·$H_2O$ (4 mg, 0.092 mmol) at room temperature. The mixture was stirred for 4 h and then acidified with acetic acid. The solvent was removed under reduced pressure and the residue used in the next step without further purification. To a solution of the crude acid in 2 mL of anhydrous DMF was added *N*,*N*-diisopropylethylamine (9 mL, 0.05 mmol) and 1*H*-pyrazole carboxamidine·HCl (8 mg, 0.05 mmol). After 16 h, the solvent was removed under reduced pressure and the residue was purified by RP-HPLC (C-18) to give **10** (3.25 mg, 13%) as a yellowish solid. $t_R=20.5$ min; $^1$H NMR (500 MHz, $D_2O$): δ 8.33 (d, 1H, $J=2.0$ Hz, Ar), 7.98 (dd, 1H, $J=2.0$, 9.0 Hz, Ar), 7.30 (d, $J=9.0$ Hz, 1H, Ar), 4.42 (m, 1H, C*H*NHBoc), 4.34 (t, $J=4.0$ Hz, 2H, C$H_2$NH(CO)), 3.82 (m, 2H, NH$_2$ (C=NH) NHC$H_2$), 3.63 (t, 2H, $J=4.0$ Hz, 2H, C$H_2$O); FAB-HRMS (M + Cs$^+$) calcd 587.0866, found 587.0895.

**Compound 37**. To a solution of **34** (0.10 g, 0.019 mmol) in $CH_2Cl_2$ (4 mL) at room temperature was added trifluoroacetic acid (4 mL). The mixture was stirred for 2 h. The solvent was removed in vacuo to give a yellowish oil, which after flash chromatography (silica, 5% methanol in dichloromethane) gave **37** as an oil (0.07 g, 84%). $R_f=0.19$ (silica, 5% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.21 (d, $J=2.0$ Hz, 1H, Ar), 7.95 (dd, $J=2.0$, 11.0 Hz, 1H, Ar), 7.39–7.29 (m, 5H, Ar), 7.21 (bm, 1H), 7.05 (d, $J=9.0$ Hz, 1H), 5.16 (s, 2H, $CH_2$Ph), 4.27 (t, $J=5.0$ Hz, 2H, C$H_2$OAr), 3.67 (t, $J=5.0$ Hz, 2H, C$H_2$N$_3$), 3.95–3.78 (bm, 1H, C*H*NH$_2$), 3.65–3.52 (bm, 1H, CHC*H*H), 4.32–4.31 (bm, 1H, CHCH*H*); $^{13}$C (125 MHz, $CDCl_3$): δ 164.9, 153.7, 139.2, 135.1, 133.1, 128.6, 128.5, 128.4, 127.0, 124.6, 114.2, 68.7, 67.4, 49.7, 33.8, 25.5; FAB-HRMS (M + Cs$^+$) calcd 561.0499, found 561.0507.

**Compound 38a**. To a solution of **37** (0.13 g, 0.30 mmol) in $CH_2Cl_2$ (10 mL) was added *N*,*N*-diisopropylethylamine (0.07 mL, 0.39 mmol) and benzenesulfonyl chloride (0.034 mL, 0.33 mmol) at room temperature. After 4 h, the reaction mixture was diluted with $CH_2Cl_2$ (10 mL) and water (10 mL). The layers were seperated and the organic layer washed with a saturated solution of sodium bicarbonate and brine and dried ($MgSO_4$). The solvent was removed in vacuo to give an oil, which after preparative thin-layer chromatography (silica, 60% ether in hexanes) gave **38a** as an oil (0.13 g, 78%). $R_f=0.43$ (silica, 60% ether in hexane); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.26 (d, $J=2.0$ Hz, 1H, Ar), 7.98 (dd, $J=2.0$, 9.0 Hz, 1H, Ar), 7.81 (d, $J=8.0$ Hz, 2H, Ar), 7.53 (t, $J=8.0$ Hz, 1H, Ph), 7.42 (t, $J=8.0$ Hz, 2H, Ph), 7.31–7.30 (m, 3H, Ar), 7.22–7.21 (m, 2H, Ar), 7.08 (d, $J=9.0$ Hz, 1H, Ar), 7.03 (t, $J=5.5$ Hz, 1H), 5.03 (d, $J=12.0$ Hz, 1H, PhC*H*H), 4.99 (d, $J=12.0$ Hz, 1H, PhCH*H*), 4.29 (t, $J=4.5$ Hz, 2H, C$H_2$O), 4.16 (dd, $J=4.0$, 7.5 Hz, 1H, CHC*H*H), 3.92–3.87 (m, 1H, C*H*CH$_2$), 3.72–3.67 (m, superimposed, 3 H , CHCH*H*, C$H_2$N$_3$); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.2, 165.2, 153.7, 139.3, 138.7, 134.3, 133.1, 132.9, 129.1, 128.4, 128.3, 126.9, 126.5, 124.9, 114.1, 68.7, 68.1, 55.4, 49.7, 42.4; FAB-HRMS (M + Cs$^+$) calcd 701.0431, found 701.0442.

**Compound 38b**. Compound **38b** was prepared by the same procedure as for **38a**. Yield (0.031 g, 57%) as an oil. $R_f=0.18$ (5% methanol in dichloromethane); IR (thin film): $V_{max}$ 3277, 2930, 2112, 1740, 1652, 1618, 1523, 1496, 1348, 1280, 1162, 1125, 984, 910, 772 cm$^{-1}$. $^1$H NMR (500 MHz, $CDCl_3$): δ 8.60 (d, $J=11.0$ Hz, 1H, naphthyl), 8.21 (dd, $J=2.0$, 9.3 Hz, 1H, naphthyl), 8.03 (d, $J=2.9$ Hz, 1H, Ar), 8.01 (d, $J=10.4$ Hz, 1H, naphthyl), 7.87 (d, $J=9.3$ Hz, 1H, naphthyl), 7.81 (dd, $J=2.9$, 11.0 Hz, 1H, Ar), 7.62 (ddd, $J=1.7$, 8.7, 8.7 Hz, 1H, naphthyl), 7.54 (ddd, $J=1.3$, 8.8, 8.8 Hz, 1H, naphthyl), 7.47 (dd, $J=9.4$, 10.1 Hz, 1H, naphthyl), 7.28–7.22 (m, 3H, Ph), 7.12–7.07 (m, 2H, Ph), 6.98 (d, $J=11.0$ Hz, 1H, Ar), 6.69 (dd, $J=7.5$ Hz, 1H, NHCO), 6.22 (d, $J=9.5$ Hz, 1H, NHSO$_2$), 4.89 (d, $J=15.0$ Hz, 1H, C*H*HPh), 4.83 (d, $J=15.0$ Hz, 1H, CH*H*Ph), 4.25 (t, $J=6.0$ Hz, 2H, OCH$_2$), 4.13 (ddd, $J=5.4$, 9.4, 9.5 Hz, 1H, C*H*CH$_2$), 3.74 (ddd, $J=5.4$, 7.4, 17.5 Hz, 1H, CHC*H*H), 3.69 (t, $J=6.1$ Hz, 2H, CH$_2$N$_3$), 3.67 (ddd, superimposed, $J=7.5$, 9.0, 17.5 Hz, 1H, CHCH*H*); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.3, 165.1, 153.7, 139.1, 134.8, 134.4, 134.0, 133.5, 132.9, 129.9, 129.0, 128.6, 128.5, 128.3, 127.7, 126.3, 124.8, 124.1, 114.0, 68.7, 67.9, 55.7, 49.8, 42.2; FAB-HRMS(M + Cs$^+$) calcd 751.0587, found 751.0599.

**Compounds 39a and 41a**. Compounds **39a** and **41** were prepared by the same procedure as for **35ab**. Yield: (F1 = 0.029 g, F2 = 0.028 g), total yield (80%). F2 was

positive in ninhydrin test while F1 was not. $R_f$ (F1) **41a** = 0.39 (silica, 10% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.35 (bs, 1H, Ar), 8.31 (bs, 1H, $CH_2NH$Ar), 7.76–7.60 (m, superimposed, 3H, Ar), 7.50 (bs, 1H), 7.38 (t, $J$ = 9.0 Hz, 1H, Ar), 7.28 (t, $J$ = 9.0 Hz, 2H, Ar), 7.26–7.13 (m, 5H, Ar), 6.86 (d, $J$ = 11.0 Hz, 1H, Ar), 6.64 (d, $J$ = 11.0 Hz, 1H, $NHSO_2$), 4.92 (d, $J$ = 15.0 Hz, 1H, PhC$H$H), 4.86 (d, $J$ = 15.0 Hz, 1H, PhCH$H$), 4.26–4.23 (m, 1H, C$H$CH$_2$), 3.80–3.67 (m, superimposed, 4H, HO$CH_2$, CHC$H_2$), 3.34–3.31 (bm, C$H_2$NHAr), 2.92 (bs, $CH_2OH$) ; $R_f$ (F2) **39a** = 0.16 (silica, 20% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): δ 8.24 (bs, 1H, Ar), 7.94 (d, $J$ = 9.0 Hz, 1H, Ar), 7.80 (d, $J$ = 8.0 Hz, 2H), 7.49 (t, $J$ = 8.0 Hz, 1H, Ph), 7.40 (t, $J$ = 8.0 Hz, 2H, Ph), 7.30–7.28 (m, 3H, Ar), 7.19–7.18 (m, superimposed, 3H, Ar, N$H$(CO)), 7.02 (d, $J$ = 9.0 Hz, 1H, Ar), 5.01 (d, $J$ = 12.5 Hz, 1H, PhC$H$H), 4.97 (d, $J$ = 12.5 Hz, 1H, PhCH$H$), 4.18–4.15 (m, superimposed, 3H, C$H$CH$_2$, OCH$_2$), 3.86–3.84 (m, 1H, CHC$H$H), 3.70–3.68 (m, 1H, CHCH$H$), 3.15–3.13 (bm, 2H, OC$H_2$NH$_2$), 2.82 (bm, 2H, N$H_2$); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.5, 165.4, 154.4, 139.9, 138.8, 134.4, 133.0, 132.8, 129.0, 138.5, 128.4, 127.0, 126.3, 125.0, 114.1, 71.4, 68.0, 55.4, 42.3, 40.7; FAB-HRMS ($M + Cs^+$) calcd 675.0526, found 675.0546.

**Compound 11**. Compound **11** was prepared by the same procedure as for **10**. Yield: (3.31 mg, 13%). $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.26 (d, $J$ = 2.0 Hz, 1H, Ar), 8.04 (dd, $J$ = 2.0, 8.5 Hz, 1H, Ar), 7.82–7.80 (m, 2H, Ph), 7.47–7.36 (m, 4H, Ar, Ph), 4.35 (t, $J$ = 5.0 Hz, 2H, OCH$_2$), 4.19 (dd, $J$ = 4.0, 14.0 Hz, 1H, C$H$CH$_2$), 3.75 (dd, $J$ = 4.0, 14.0 Hz, 1H, CHC$H$H), 3.68 (t, $J$ = 5.0 Hz, 2H, C$H_2$NH(C = N)), 3.47 (dd, $J$ = 11.0, 14.0 Hz, 1H, CHCH$H$).

**Compound 12**. To a solution of the benzyl ester **41a** (0.10 g, 0.22 mmol) in THF:$H_2O$ (3 mL:1 mL) was added LiOH·$H_2O$ (18.5 mg, 0.44 mmol) at room temperature. After stirring for 4 h, the reaction mixture was acidified with acetic acid and the solvent removed in vacuo to give the crude acid **42a**. To a solution of the acid **42a** in DMF (5 mL) was added *N*,*N*-diisopropylethylamine (38 mL, 0.22 mmol). After stirring at 50 °C for 16 h, the solvent was removed in vacuo to give an oil, which after RP-HPLC (C-18) gave **12** (5.4 mg, 5%) as a yellowish solid. $t_R$ = 14.9 min; $^1$H NMR (600 MHz, $CDCl_3$): δ 8.26 (d, $J$ = 2.0 Hz, 1H, Ar), 7.67–7.65 (m, 2H, Ph), 7.64 (dd, $J$ = 2.0, 9.0 Hz, Ar), 7.24–7.18 (m, 3H, Ph), 7.06 (d, $J$ = 9.0 Hz, Ar), 4.49 (t, $J$ = 4.0 Hz, 2H, C$H_2$OH), 4.15 (dd, $J$ = 6.0, 10.0 Hz, 1H, C$H$CH$_2$), 3.86 (t, $J$ = 4.0 Hz, 2H, C$H_2$N(C = NH)NH$_2$), 3.70 (dd, $J$ = 6.0, 14.0 Hz, 1H, CHC$H$H), 3.35 (dd, $J$ = 10.0, 14.0 Hz, 1H, CHCH$H$); $^{13}$C NMR (150 MHz, $CDCl_3$): δ 167.6, 164.9, 147.2, 141.7, 132.4, 130.5, 129.6, 127.7, 126.8, 125.6, 125.5, 122.2, 112.5, 70.4, 42.6, 28.7, 23.2. Electrospray mass spectrum ($M + H^+$) calcd 495, found 495.

**Compound 39b**. To a solution of the azide **38b** (0.031 g, 0.05 mmol) in THF:$H_2O$ (8 mL:0.04 mL) was added triphenylphosphine (0.026 g, 0.1 mmol). After stirring at room temperature for 12 h, the solvent was removed in vacuo to give a white solid. The solid was purifed by preparative thin-layer chromatography (silica, 20% methanol in dichloromethane) to give **39b** as an oil (0.013 g, 44%). $R_f$ = 0.1 (silica gel, 10% methanol in dichloromethane); IR (thin film): $V_{max}$ 3361, 3282, 3070, 2922, 2851, 1742, 1650, 1620, 1527, 1456, 1349, 1322, 1280, 1162, 1126, 989, 910 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, $J$ = 10.8 Hz, 1H, naphthyl), 8.17 (dd, $J$ = 1.0, 9.1 Hz, 1H, naphthyl), 8.02 (d, $J$ = 2.5 Hz, 1H, Ar), 7.92 (d, $J$ = 10.3 Hz, 1H, naphthyl), 7.77 (d, $J$ = 10.3 Hz, 1H, naphthyl), 7.72 (dd, $J$ = 2.6, 11.0 Hz, 1H, Ar), 7.58 (dd, $J$ = 8.3, 8.3 Hz, 1H, naphthyl), 7.49 (dd, $J$ = 7.3, 7.3 Hz, 1H, naphthyl), 7.41 (dd, $J$ = 7.5, 7.5 Hz, 1H, naphthyl), 7.23–7.16 (m, 3H, Ph), 7.09–7.04 (m, 2H, Ph), 6.84 (d, $J$ = 11.1 Hz, 1H, Ar), 4.83 (d, $J$ = 15.2 Hz, 1H, C$H$HPh), 4.76 (d, $J$ = 15.2 Hz, 1H, CH$H$Ph), 4.23 (dd, $J$ = 5.8, 9.1 Hz, 1H, C$H$CH$_2$), 4.10–4.04 (bm, 2H, OCH$_2$), 3.95–3.61 (bm, 5H, C$H_2$N$H_2$, CHC$H$H), 3.18–3.05 (bm, 1H, CHC$H$H); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 169.6, 165.3, 154.2, 146.9, 134.6, 134.5, 134.0, 133.9, 133.2, 129.8, 129.0, 128.6, 128.5, 128.4, 128.2, 127.8, 127.0, 125.9, 124.9, 124.2, 124.1, 114.3, 67.6, 55.9, 42.0, 40.5, 29.6; FAB-HRMS ($M + Cs^+$) calcd 725.0682, found 725.0695.

**Compound 13**. Compound **13** was prepared by the same procedure as for **10**. Yield: (1.8 mg, 15%) as a yellowish solid. $t_R$ = 21.2 min; $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.63 (d, $J$ = 9.0 Hz, 1H, naphthyl), 8.17 (dd, $J$ = 1.5, 7.5 Hz, 1H, naphthyl), 7.94 (d, $J$ = 8.5 Hz, 1H, naphthyl), 7.88 (d, $J$ = 2.5 Hz, 1H, Ar),7.76–7.70 (m, superimposed, 2H, Ar, naphthyl), 7.57 (ddd, $J$ = 1.0, 6.5, 9.3 Hz, 1H, naphthyl), 7.47 (dd, $J$ = 7.5, 8.0 Hz, 1H, naphthyl), 7.42 (ddd, $J$ = 1.0, 7.0, 7.5 Hz, 1H, naphthyl), 7.25 (d, $J$ = 9.0 Hz, 1H, Ar), 4.36 (t, $J$ = 5.0 Hz, 1H, $CH_2O$), 4.18 (dd, $J$ = 4.5, 9.5 Hz, 1H, C$H$CHH), 3.72 (t, $J$ = 5.0 Hz, 2H, C$H_2$NH), 3.65 (dd, $J$ = 4.5, 13.5 Hz, 1H, CHC$H$H), 3.41 (dd, $J$ = 9.5, 13.5 Hz, 1H, CHCH$H$); Electrospray mass spectrum calcd ($M + H^+$) 545, found 545.

### Preparation of compounds 51–56

**Compound 51**. To a solution of aminoethanol (**43**) (1.0 mL, 16.0 mmol) in DMF (30 mL) was added 1,3-bis-(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (**48**) (4.81 g, 16.0 mmol), triethylamine (4.63 mL, 32.0 mmol) and mercury(II) dichloride (4.48 g, 16.0 mmol) at room temperature. After 4 h, the reaction mixture was diluted with ethyl acetate and filtered over a short path of

celite®. The filtrate was succesively washed with water (2×20 mL), brine (20 mL) and dried over $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure the crude compound was purified by flash column chromatography to give **51** as a colourless solid (4.95 g, 98%). $R_f$=0.43 (silica gel, 50% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3329, 3142, 2977, 2934, 2870, 1724, 1644, 1443, 1412, 1360, 1299, 1103, 1052, 1027, 864, 809, 778 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 11.48 (bs, 1H, $NHCO_2$), 8.66 (m, 1H, $CH_2NH$), 4.54 (bs, 1H, OH), 3.74 (t, $J$=4.5 Hz, 2H, $CH_2OH$), 3.54 (dt, $J$=5.5, 5.5 Hz, 2H, $CH_2NH$), 1.47 (s, 9H, $^t$Bu), 1.45 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 162.8, 157.4, 153.1, 83.5, 79.2, 63.1, 44.4, 28.2, 28.0; FAB-HRMS ($M+H^+$) calcd 304.1872, found 304.1878.

**Compound 52**. To a solution of piperazine (**44**) (3.45 mL, 12.0 mmol) in DMF (10 mL) was added 1,3-bis-(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (**48**) (0.87 g, 3.00 mmol) at room temperature. After 14 h, the reaction mixture was diluted with ethyl acetate and water. The layers were separated and the organic layer was washed succesively with water (2×20 mL), brine (20 mL) and dried over $Na_2SO_4$. The solvent was removed under reduced pressure to give **52** as a colorless solid (0.93 g, 95%). $R_f$=0.34 (silica gel, 10% methanol in dichloromethane); IR (KBr): $V_{max}$ 3294, 2980, 2931, 2856, 1749, 1664, 1605, 1527, 1448, 1367, 1305, 1230, 1149, 1116, 1019, 893, 842, 730, 682 $cm^{-1}$. $^1H$ NMR (500 MHz, methanol-$d_4$): δ 3.48 (t, $J$=5.0 Hz, 4H, $(CH_2)_2N(C=N)$), 2.83 (t, $J$=5.0 Hz, 4H, $(CH_2)_2NH$), 1.46 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, methanol-$d_4$): δ 154.4, 81.4, 48.2, 46.0, 28.6; FAB-HRMS ($M+Na^+$) calcd 341.1226, found 341.1235.

**Compound 53**. To a solution of aminoethanethiol (**45**) (114 mg, 1.00 mmol) in DMF (5 mL) was added *N*,*N*′-bis-*tert*-butoxycarbonylthiourea (**49**) (276 mg, 1.00 mmol) and triethylamine (2.79 mL, 2.0 mmol) at room temperature. After 14 h, the reaction mixture was diluted with 5 mL of $H_2O$ and extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed with brine and dried over $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure the crude compound was purified by flash column chromatography (silica gel, 25% diethyl ether in hexanes) to give **53** as an airsensitive colorless solid (191 mg, 59.8%). $R_f$=0.16 (silica, 25% diethyl ether in hexanes); IR (KBr): $V_{max}$ 3327, 3132, 2978, 2931, 1726, 1643, 1565, 1431, 1363, 1329, 1280, 1227, 1133, 1088, 1058, 855, 809, 760, 606 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 11.45 (bs, 1H, $(C=N)NH(C=O)$), 8.61 (bt, $J$=5.9 Hz, 1H, $CH_2NH$), 3.74 (bdt, $J$=6.0, 6.5 Hz, 2H, $CH_2NH$), 2.85 (t, $J$=6.5 Hz, 2H, $CH_2SH$), 1.47 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 163.4, 156.1, 153.1, 83.2, 79.3, 39.2, 37.0, 28.3, 28.1; FAB-HRMS calcd only *S*-*S*-dimer.

**Compound 54**. To a solution of ethylenediamine (**54**) (3.45 mL, 51.6 mmol) in DMF (50 mL) was added 1,3-bis-(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (**48**) (3.00 g, 10.33 mmol), triethylamine (2.88 mL, 20.7 mmol) and mercury(II)chloride (2.81 g, 10.3 mmol) at room temperature. After 4 h, the reaction mixture was diluted with 20 mL of ethyl acetate and filtered over a short path of celite®. The filtrate was succesively washed with $H_2O$ (2×50 mL), brine (50 mL) and dried over $MgSO_4$. Flash column chromatography (silica gel, 20% MeOH in ethyl acetate + 2% $Et_3N$) gave **54** as a colourless solid (1.60 g, 51.2%). $R_f$=0.30 (silica gel, 20% MeOH in ethyl acetate + 2% $Et_3N$); IR (KBr): $V_{max}$ 3446, 3389, 3259, 2978, 2819, 1728, 1706, 1656, 1626, 1521, 1485, 1365, 1253, 1171, 1093, 1049, 888, 802, 738, 699, 562 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 11.38 (bs, 1H, $(C=N)NH(C=O)$), 8.61 (bt, 1H, $CH_2NH(C=N)$), 3.45 (bdt, $J$=5.5, 5.5 Hz, 2H, $CH_2NH$), 2.85 (t, $J$=5.5 Hz, 2H, $CH_2NH_2$), 1.46 (s, 9H, $^t$Bu) ; $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 163.4, 156.4, 153.1, 83.1, 79.2, 41.8, 40.9, 28.2; FAB-HRMS ($M+H^+$) calcd 303.2032, found 303.2037.

**Compound 55**. To a solution of phenylenediamine (1.08 g, 0.01 mol) in 5.5 N HCl (10 mL) was added β-alanine (**47**) (1.125 g, 0.015 mol) at room temperature. The reaction mixture was refluxed for 24 h and then allowed to cool to room temperature. The solvent was removed in vacuo to give a precipitate, which was filtered and washed with ether (1.70 g, 73%). $R_f$=0.12 (20% methanol in dichloromethane); $^1H$ NMR (500 MHz, $D_2O$): δ 7.73–7.72 (m, 2H, Ar), 7.55–7.53 (m, 2H, Ar), 3.61–3.55 (m, 4H, $CH_2CH_2$); FAB-HRMS ($M+H^+$) calcd 162.1031, found 162.1029.

**Compound 56**. To a solution of ethylenediamine (**46**) (1.0 mL, 0.015 mol) in DMF (10 mL) was added 2-(3,5-dimethylpyrazolyl)-4,5-dehydroimidazole hydrobromide (**50**) (3.67 g, 0.015 mol) and *N*,*N*-diisopropylethylamine (2.61 mL, 0.015 mol) at room temperature. After stirring for 11 h, ether (12 mL) was added to the reaction mixture and a white precipitate formed. The precipitate was filtered and washed with ether to give **56** (1.59 g, 51%). IR (KBr): $V_{max}$ 3164, 1681, 1599, 1484, 1287, 1211, 1137, 1069, 952 $cm^{-1}$; $^1H$ NMR (500 MHz, $D_2O$): δ 3.54 (bs, 4H, $NHCH_2CH_2NH$), 3.17 (t, $J$=6.0 Hz, $CH_2NH$), 2.65 (t, $J$=6.0 Hz, $CH_2NH_2$); $^{13}C$ NMR (125 MHz, $D_2O$): δ 160.9, 45.3, 43.6, 40.3; FAB-HRMS ($M+H^+$) calcd 129.1140, found 129.1134.

### Preparation of compounds 11 and 14–19

**Compound 58**. To a solution of 3-nitro-4-fluoro benzoic acid (**30**) (1.59 g, 8.57 mmol) in benzene (40 mL) was added DMF (0.03 mL, 0.40 mmol) and oxalylchloride (3.73 mL, 20.2 mmol) at 0 °C. After 6 h, the solvent was

removed in vacuo. The resulting yellow viscous oil (1.73 g, 8.57 mmol) was dissolved in $CH_2Cl_2$ (20 mL). The solution was cooled to 0 °C and triethylamine (1.28 mL, 9.20 mmol) was added. A solution of the protected 2-amino alanine *tert*-butylester **29a** (2.32 g, 7.70 mmol) in $CH_2Cl_2$ (40 mL) was added. After 4 h, the reaction mixture was diluted with water and the aqueous phase was extracted with dichloromethane (2×50 mL) after phase separation. The combined organic extracts were washed with saturated aqueous $NaHCO_3$-solution and dried over $MgSO_4$. After filtration and evaporation of the solvent under reduced pressure the crude compound was purified by flash column chromatography (silica gel, 45% ethyl acetate in hexanes) to give **58** as a yellow foam (3.90 g, 98%). $R_f$ = 0.19 (silica gel, 40% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3286, 2980, 2936, 1730, 1653, 1619, 1537, 1493, 1448, 1349, 1314, 1159, 1131, 1092 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.56 (dd, $^4J(^1H\text{-}^1H)$ = 2.5 Hz, $^4J(^1H\text{-}^{19}F)$ = 7.5 Hz, 1H, Ar), 8.12 (ddd, $^4J(^1H\text{-}^1H)$ = 2.5 Hz, $^4J$ ($^1H\text{-}^{19}F$) = 4.0 Hz, $^3J$ ($^1H\text{-}^1H$) = 9.0 Hz, 1H, Ar), 7.84 (d, $J$ = 7.5 Hz, 2H, Ph), 7.58 (d, $J$ = 7.5 Hz, 1H, Ph), 7.50 (t, $J$ = 7.5 Hz, 2H, m-Ar), 7.34 (dd, $^3J$ ($^1H\text{-}^1H$) = 9.0 Hz, $^3J$ ($^1H\text{-}^{19}F$) = 10.0 Hz, Ar), 7.13 (t, $J$ = 5.5 Hz, 1H, (C=O)N*H*), 5.89 (d, $J$ = 8.0 Hz, 1H, CHN*H*$SO_2$Ph), 3.97–3.92 (m, 2H, C*H*H, C*H*$CH_2$), 3.60–3.54 (m, 1H, CH*H*), 1.29 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 168.1, 164.5, 158.1, 156.0, 138.6, 134.2, 134.1, 133.2, 130.9, 129.2, 127.2, 125.6, 118.9, 118.7, 84.2, 55.8, 42.5, 27.6; FAB-HRMS ($M + Cs^+$) calcd 600.0217, found 600.0195.

**Compound 59**. Compound **59** was prepared by the same procedure as for compound **58**. Yield (985 mg, 96%) as an off-white solid. $R_f$ = 0.24 (silica gel, 50% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3395, 3297, 3083, 2981, 2937, 1734, 1671, 1620, 1534, 1494, 1460, 1345, 1264, 1156, 1128, 1079, 977, 918, 833, 750, 661, 617, 549, 479 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.46 (dd, $^4J(^1H\text{-}^1H)$ = 2.5 Hz, $^4J(^1H\text{-}^{19}F)$ = 7.0 Hz, 1H, Ar), 8.38 (d, $J$ = 2.0 Hz, 1H, naphthyl), 8.02 (ddd, $^4J(^1H\text{-}^1H)$ = 2.5 Hz, $^4J(^1H\text{-}^{19}F)$ = 4.0 Hz, $^3J(^1H\text{-}^1H)$ = 8.8 Hz, 1H, Ar), 7.90 (bd, superimposed, $J$ = 8.5 Hz, 1H, naphthyl), 7.88 (bd, superimposed, $J$ = 8.5 Hz, 1H, naphthyl), 7.83 (bd, $J$ = 8.0 Hz, 1H, naphthyl), 7.79 (dd, $J$ = 2.0, 8.0 Hz, 1H, naphthyl), 7.62 (ddd, $J$ = 1.0, 7.5, 8.5 Hz, 1H, naphthyl), 7.58 (ddd, $J$ = 1.0, 7.5, 8.5 Hz, 1H, naphthyl), 7.27 (br, dd, $J$ = 6.0, 8.5 Hz, 1H, CONH), 7.18 (bdd, $^3J(^1H\text{-}^1H)$ = 9.0 Hz, $^3J(^1H\text{-}^{19}F)$ = 10.0 Hz, 1H, Ar), 6.15 (d, $J$ = 8.0 Hz, 1H, $NHSO_2$), 4.06 (ddd, $J$ = 4.0, 5.5, 8.0 Hz, 1H, C*H*$CH_2$), 3.93 (ddd, $J$ = 4.0, 6.0, 11.0 Hz, 1H, CHCH*H*), 3.57 (ddd, $J$ = 5.5 Hz, 8.5 Hz, 1H, CHC*H*H), 1.17 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 168.3, 164.3, 158.0, 155.8, 135.5, 134.7, 134.1, 134.0, 131.8, 130.5, 129.5, 129.1, 128.6, 127.7, 125.4, 122.0, 118.6, 118.4, 83.9, 55.9, 42.3, 27.4; FAB-HRMS ($M + Cs^+$) calcd 650.0373, found 650.0358.

**Compound 60**. To a round bottom flask equipped with a magnetic stirring bar was placed NaH (60% suspension in mineral oil) (0.16 g, 3.96 mmol) and THF (10 mL) at 0 °C . To the stirred suspension was added a solution of **51** (0.55 g, 1.80 mmol) in THF (5 mL). Stirring was continued at this temperature for an additional 30 min and the resulting grey suspension was ready for use. A round bottom flask equipped with a magnetic stirring bar was charged with the aromatic fluoride **58** (0.1 g, 0.30 mmol) and DMF (10 mL). The solution was cooled to 0 °C and 5.5 mL of the previously prepared suspension was added by means of a syringe. After 8 h at 0 °C the reaction was stopped by addition of water (10 mL) and diluted with ethyl acetate. The aqueous phase was separated and extracted with ethyl acetate (3×25 mL) The combined organic extracts were washed successively with $H_2O$ (2×10 mL) and brine (10 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica, 60% ethyl acetate in hexanes) to give **60** as a yellowish foam (0.15 g, 66%). $R_f$ = 0.18 (silica gel, 50% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3331,2978, 2951, 1733, 1645, 1619, 1532, 1367, 1319, 1277, 1144, 1051, 1025 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 11.43 (bs, 1H, (C=N)NH (C=O)), 8.76 (bt, $J$ = 5.5 Hz, 1H, $CH_2$N*H*(C=N)), 8.32 (d, $J$ = 2.5 Hz, 1H, Ar), 8.00 (dd, $J$ = 2.5, 9.0 Hz, 1H, Ar), 7.85–7.84 (m, 2H, Ph), 7.58 (t, $J$ = 8.0 Hz, 1H, Ph), 7.49 (t, $J$ = 8.0 Hz, 2H, Ph), 7.20 (d, $J$ = 9.0 Hz, 1H, Ar), 6.95 (t, $J$ = 8.0 Hz, 1H, NHCO), 5.84 (d, $J$ = 7.5 Hz, 1H, $HNSO_2$), 4.28 (t, $J$ = 5.5 Hz, 2H, $CH_2O$), 3.96–3.87 (m, superimposed, 4H, CHC$H_2$, C$H_2$NH(C=N)), 3.60–3.54 (m, 1H, C*H*$CH_2$), 1.50 (s, 9H, $^t$Bu), 1.48 (s, 9H, $^t$Bu), 1.28 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ 168.2, 165.0, 163.3, 156.5, 154.5, 154.1, 150.9, 139.4, 138.8, 133.1, 132.7, 129.2, 127.2, 126.5, 125.0, 114.5, 84.0, 83.4, 68.1, 55.9, 42.4, 39.4, 28.3, 28.0, 27.6; FAB-HRMS ($M + Cs^+$) calcd 883.1949, found 883.1970.

**Compound 11**. To a solution of **60** (30.0 mg, 0.04 mmol) in $CH_2Cl_2$ (2 mL) trifluoroacetic acid (2 mL) was added dropwise. The reaction mixture was stirred at 25 °C for 2 h. The solvents were removed under reduced pressure and the residue was purified by RP-HPLC (C-18) to give **11** as yellowish solid (22.0 mg, 92%). $t_R$ = 12.2 min; IR (KBr): $V_{max}$ 3418, 1679, 1529, 1433, 1354, 1319, 1278, 1198, 1161, 1092, 1046, 932, 837, 802, 756, 688 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d_4$): δ 8.26 (d, $J$ = 2.0 Hz, 1H, Ar), 8.04 (dd, $J$ = 2.0, 8.5 Hz, 1H, Ar), 7.82–7.80 (m, 2H, Ph), 7.47–7.36 (m, 4H, Ar), 4.35 (t, $J$ = 5.0 Hz, 2H, $OCH_2$), 4.19 (dd, $J$ = 4.0, 14.0 Hz, 1H, C*H*$CH_2$), 3.75 (dd, $J$ = 4.0, 14.0 Hz, 1H, CHC*H*H), 3.68 (t, $J$ = 5.0 Hz, 2H, C$H_2$NH(C=N)), 3.47 (dd, $J$ = 11.0, 14.0 Hz, 1H,

CHCH*H*); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 167.7, 155.0, 142.2, 140.7, 134.5, 133.6, 130.0, 128.2, 125.9, 115.7, 69.8, 43.3, 41.8, 25.2; FAB-HRMS ($M+H^+$) calcd 495.1298, found 495.1311.

**Compound 61**. To a solution of **58** (100 mg, 0.20 mmol) in DMF (10 mL) was added **53** (68 mg, 0.22 mmol). After stirring at room temperature for 4 h, the reaction mixture was diluted with water (10 mL) and the aqueous phase extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed succesively with water (2×10 mL) and brine (20 mL) and dried over $Na_2SO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in hexanes) to give **61** as a yellowish foam (110 mg, 73%). $R_f$=0.48 (silica gel, 60% ethyl acetate in hexanes); IR (film): $V_{max}$ 3318, 2925, 1723, 1623, 1517, 1412, 1324, 1158 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 11.47 (bs, 1H, (C=N)NH(C=O)), 8.59 (d, $J$=2.5 Hz, 1H, Ar), 8.56 (t, $J$=10.0 Hz, 1H, NH), 8.43 (t, $J$=10.0 Hz, 1H, NH), 7.93 (dd, $J$=2.5 Hz, 10.0 Hz, 1H, Ar), 7.84 (d, $J$=9.0 Hz, 2H, Ph), 7.53 (t, $J$=10.0 Hz, 1H, Ph), 7.46 (t, $J$=10.0 Hz, 2H, Ph), 7.21 (d, $J$=10.0 Hz, 1H, Ar), 6.81 (t, $J$=10.0 Hz, 1H, CONH), 5.87 (d, $J$=10.0 Hz, 1H, $NHSO_2$), 3.98–3.93 (m, 1H, $CHCH_2$), 3.87–3.82 (m, 1H, CHC*H*H), 3.72–3.55 (m, 5H, CHCH*H*, NHC$H_2$, C$H_2$NH(C=N)), 1.52 (s, 9H, $^t$Bu), 1.47 (s, 9H, $^t$Bu), 1.27 (s, 9H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 168.4, 165.7, 163.3, 156.6, 153.2, 146.9, 139.1, 134.7, 133.0, 131.4, 129.1, 127.2, 126.2, 121.0, 114.4, 83.7, 83.5, 79.5, 56.2, 42.4, 42.2, 39.0, 28.3, 28.0, 27.6; FAB-HRMS ($M+Cs^+$) calcd 882.2109, found 882.2129.

**Compound 14**. Compound **14** was prepared by the same procedure as **11**. Yield (33.2 mg, 92%) as a yellow solid. $t_R$=15.9 min; IR (KBr): $V_{max}$ 3364, 3245, 2998, 2584, 1669, 1624, 1555, 1520, 1433, 1313, 1198, 1161, 923, 756, 722 cm$^{-1}$; $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.61 (d, $J$=2.5 Hz, 1H, Ar), 7.92 (dd, $J$=2.5, 9.0 Hz, 1H, Ar), 7.81 (d, $J$=7.0 Hz, 2H, Ph), 7.47–7.40 (m, 3H, Ph), 7.11 ( d, $J$=9.0 Hz, 1H, Ar), 4.19 (dd, $J$=5.0, 9.0 Hz, 1H, C*H*CH$_2$), 3.72 (dd, $J$=5.0, 13.5 Hz, 1H, CHC*H*H), 3.67 (t, $J$=6.0 Hz, 2H, NHC$H_2$), 3.52 (t, $J$=6.0 Hz, 2H, NHC$H_2$), 3.46 (dd, $J$=9.0, 13.5 Hz, 1H, CHCH*H*); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 168.3, 159.0, 148.0, 142.1, 135.8, 133.6, 132.9, 130.0, 127.8, 125.0, 122.3, 114.8 43.2, 42.5, 41.1, 31.1; FAB-HRMS ($M+H^+$) calcd 494.1458, found 494.1444.

**Compound 62**. To a solution of **54** (1.60 mg, 5.0 mmol) in THF (50 mL) was added NaH (60% suspension in mineral oil) (200 mg, 5.00 mmol) at 0 °C. After 15 min the resulting thiolate solution was ready for use. To a solution of **58** (100 mg, 0.20 mmol) in DMF (10 mL) was added the thiolate solution (5.0 mL, 0.5 mmol) by syringe. After 12 h at room temperature the reaction was stopped by addition of water (10 mL) and diluted with ethyl acetate. After phase seperation the aqueous phase was extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed succesively with water (2×10 mL) and brine (10 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 40% ethyl acetate in hexanes) to give **62** as a yellowish foam (35 mg, 23%). $R_f$=0.32 (silica gel, 40% ethyl acetate in hexanes); $^1$H NMR (500 MHz, $CDCl_3$): δ 11.45 (bs, 1H, (C=N)NH (C=O)), 8.65 (bt, superimposed, $J$=4.5 Hz, 1H, $CH_2NH$(C=N)), 8.63 (d, superimposed, $J$=2.0 Hz, 1H, Ar), 8.22 (d, $J$=8.5 Hz, 1H, Ar), 8.15 (dd, $J$=2.0, 8.5 Hz, 2H, Ar), 7.84 (d, $J$=8.0 Hz, 2H, Ph), 7.56 (t, $J$=7.5 Hz, 1H, Ph), 7.48 (bdd, $J$=7.0, 8.0 Hz, 2H, Ph), 6.98 (t, $J$=5.5 Hz, 1H, CONH), 5.72 (d, $J$=7.0 Hz, 1H, $NHSO_2$), 3.99–3.93 (bm, 1H, $CHCH_2$), 3.88 (ddd, $J$=4.5, 5.5, 13.5 Hz, 1H, CHC*H*H), 3.70–3.58 (m, 3H, CHCH*H*, C$H_2$NH(C=N)), 3.26 (t, $J$=8.0 Hz, 2H, $SCH_2$), 1.57 (s, 9H, $^t$Bu), 1.50 (s, 9H, $^t$Bu), 1.30 (s, 9H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 168.2, 165.1, 163.4, 156.3, 153.1, 145.3, 141.0, 138.9, 133.1, 132.3, 130.3, 129.2, 127.7, 127.2, 124.7, 84.0, 83.5, 79.6, 55.9, 42.4, 39.2, 30.1, 28.4, 28.0, 27.6; FAB-HRMS ($M+Cs^+$) calcd 899.1720, found 899.1753.

**Compound 15**. Compound **15** was prepared by the same procedure as for **11**. Yield: (23.0 mg, 92%) as a yellow solid. $t_R$=16.0 min; $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.58 (d, $J$=2.0 Hz, 1H, Ar), 8.06 (dd, $J$=2.0, 8.5 Hz, 1H, Ar), 7.82 (d, $J$=7.0 Hz, 2H, Ph), 7.71 (d, $J$=8.5 Hz, 1H, Ph), 7.48–7.41 (m, 3H, Ar), 4.23 (dd, $J$=5.0, 9.0 Hz, 1H, C*H*CH$_2$), 3.80–3.76 (m, 1H, CHC*H*H), 3.56 (t, $J$=6.5 Hz, 2H, C$H_2$NH(C=N)), 3.50–3.43 (m, 1H, CHCH*H*), 3.34 (t, $J$=6.5 Hz, 2H, $SCH_2$); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 167.6, 155.2, 142.1, 140.7, 133.5, 133.3, 132.5, 128.3, 128.0, 126.0, 43.4, 40.7, 32.3; FAB-HRMS(M+H+) calcd 511.1070, found 511.1058.

**Compound 65**. To a solution of **58** (100 mg, 0.20 mmol) in DMF (10 mL) was added **52** (68 mg, 0.22 mmol). After 6 h, the reaction mixture was diluted with water (25 mL) and ethyl acetate. After phase separation the aqueous phase was extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed succesively with water (2×20 mL) and brine (20 mL) and dried over $Na_2SO_4$ After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 40→50% ethyl acetate in hexanes) to give **65** as a yellowish foam (120 mg, 83%). $R_f$=0.30 (silica gel, 40% ethyl acetate in hexanes); IR (film): $V_{max}$ 3266, 2977, 1743, 1621, 1520, 1451, 1367, 1304, 1158, 1130, 1094, 1014 cm$^{-1}$; $^1$H

NMR (500 MHz, $CDCl_3$): δ 10.22 (bs, 1H, (C=N) *H*N(C=O)), 8.29 (d, $J$=2.5 Hz, 1H, Ar), 7.92 (dd, $J$=2.5, 9.0 Hz, 1H, Ar), 7.85–7.84 (m, 2H, Ph), 7.83–7.82 (m, 1H), 7.56 (t, $J$=7.0 Hz, 1H, Ph), 7.48 (t, $J$=7.0 Hz, 2H, Ar), 7.08 (d, $J$=9.0 Hz, 1H, Ar), 6.93 (t, $J$=6.0 Hz, 1H, CO(*NH*)), 5.85 (d, $J$=8.0 Hz, 1H, N*H*$SO_2$), 3.96–3.87 (m, 2H, C*H*$CH_2$, CHC*H*H), 3.80–3.70 (bm, 4H, NH(C*H*$_2$)$_2$), 3.59–3.54 (m, 1H, $CHCH_H$), 3.23–3.21 (m, 4H, N($CH_2$)$_2$), 1.48 (s, 18 H, $^t$Bu), 1.26 (s, 9H, $^t$Bu); $^{13}$C NMR (500 MHz, $CDCl_3$): δ 168.3, 165.3, 155.2, 147.5 140.9, 138.8, 133.1, 132.0, 129.2, 127.2, 126.3, 126.0, 119.9, 84.0, 56.0, 50.3, 42.2, 28.1, 27.6; FAB-HRMS (M+$Cs^+$) calcd 908.2265, found 908.2233.

**Compound 16**. Compound **16** was prepared by the same procedure as for **11**. Yield: (15.0 mg, 93%) as a yellowish solid. $t_R$=15.3 min; IR (KBr): $V_{max}$ 3367, 3239, 2925, 2857, 1662, 1613, 1523, 1449, 1388, 1320, 1199, 1173, 1135, 1093, 992, 837, 802, 721 $cm^{-1}$; $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.22 (d, $J$=2.0 Hz, 1H, Ar), 7.95 (dd, $J$=2.0, 8.5 Hz, 1H, Ar), 7.79 (m, 2H, Ph), 7.47–7.38 (m, 3H, Ph), 7.32 (d, $J$=8.5 Hz, 1H, Ar), 4.21 (dd, $J$=5.0, 9.0 Hz, 1H, C*H*$CH_2$), 3.74 (dd, $J$=5.0, 10.0 Hz, 1H, CHC*H*H), 3.67–3.65 (m, 4H, N($CH_2$)$_2$), 3.49–3.44 (m, 1H, CHCH*H*), 3.31–3.29 (m, 4H, N($CH_2$)$_2$); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 172.6, 167.9, 158.4, 148.3, 142.8, 142.2, 129.9, 56.6, 50.9, 46.3, 43.3; FAB-HRMS (M+$H^+$) calcd 520.1614, found 520.1630.

**Compound 63**. To a solution of **51** (130 mg, 0.43 mmol) in THF (5.0 mL) was added NaH (60% suspension in mineral oil) (70 mg, 1.74 mmol) at 0 °C. Stirring was continued at this temperature for additional 15 min and the resulting grey suspension was ready for use. To a solution of **59** (200 mg, 0.39 mmol) in DMF (20 mL) was added the alkoxide (2.5 mL). After stirring for 1 h at 0 °C the remaining 2.5 mL of the alkoxide was added. After 3 h at 0 °C the reaction was stopped by addition of saturated aqueous $NH_4Cl$-solution (10 mL) and diluted with ethyl acetate. After phase separation the aqueous phase was extracted with ethyl acetate (3×25 mL). The combined organic extracts were washed succesively with $H_2O$ (2×10 mL) and brine (10 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in hexanes) to give **63** as a yellow solid (211 mg, 69%). $R_f$=0.16 (silica gel, 50% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3330, 2979, 2934, 1728, 1620, 1570, 1531, 1416, 1329, 1281, 1156, 1079, 1023, 970, 916, 816, 753, 660, 618, 552, 477 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 11.45 (bs, 1H, (C=N)NH(C=O)), 8.78 (bt, 1H, $CH_2$N*H*(C=N)), 8.37 (s, 1H, Ar), 8.26 (d, $J$=2.0 Hz, 1H, naphthyl), 7.92–7.87 (2×d, $J$=8.0 Hz, 2H, naphthyl), 7.90 (d, $J$=8.5 Hz, 1H, Ar), 7.83 (d, $J$=8.5 Hz, 1H, naphthyl), 7.79 (dd, $J$=2.0, 8.5 Hz, 1H, naphthyl), 7.64–7.55 (2×br, dd, 2H, naphthyl), 7.07 (d, $J$=8.5 Hz, 1H, Ar), 6.90 (dd, $J$=5.5, 5.5 Hz, 1H, $CH_2$N*H*(C=O)), 5.95 (d, $J$=7.5 Hz, 1H, N$HSO_2$), 4.22 (t, $J$=5.3 Hz, 2H, O$CH_2$), 4.02 (ddd, $J$=4.0, 7.5, 8.5 Hz, 1H, C*H*$CH_2$), 3.93–3.83 (m, superimposed, 3H, CHC*H*H, $CH_2$NH (C=N)), 3.55 (ddd, $J$=5.5, 8.5, 13.5 Hz, 1H, CHCH*H*), 1.50 (s, 9H, $^t$Bu), 1.47 (s, 9H, $^t$Bu), 1.17 (s, 9H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 168.3, 164.9, 156.4, 154.0, 152.9, 139.3, 135.6, 134.9, 132.6, 132.0, 129.6, 129.2, 129.1, 128.7, 127.8, 127.7, 127.6, 126.3, 125.0, 122.1, 114.4, 84.0, 83.5, 68.0, 56.1, 42.3, 39.5, 28.3, 28.0, 27.5; FAB-HRMS (M+$Cs^+$) calcd 933.2105, found 933.2116

**Compound 17**. Compound **17** was prepared by the same procedure as for **11**. Yield: (32.7 mg, 99%) as an off-white to brownish solid. $t_R$=14.5 min. IR (KBr): $V_{max}$ 3421, 2999, 2898, 1657, 1635, 1528, 1383, 1351, 1322, 1276, 1198, 1157, 1132, 1080, 1046, 979, 823, 754, 660, 550 $cm^{-1}$; $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.15 (s, 1H, naphthyl), 7.93 (d, $J$=2.0 Hz, 1H, Ar), 7.72 (d, $J$=8.0 Hz, 1H, naphthyl), 7.69–7.58 (m, 4H, naphthyl, Ar), 7.42–7.35 (2×ddd, superimposed, 2H, naphthyl), 6.92 (d, $J$=9.0 Hz, 1H, Ar), 4.21 (dd, $J$=4.5, 9.8 Hz, 1H, C*H*$CH_2$), 4.13 (t, $J$=5.0 Hz, 2H, O$CH_2$), 3.61 (dd, $J$=4.5, 13.5 Hz, 1H, CHC*H*H), 3.57 (t, $J$=4.5 Hz, 2H, C*H*$_2$NH(C=N)), 3.28 (dd, $J$=9.8 Hz, 13.5 Hz, 1H, CHCH*H*); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 172.8, 167.1, 159.3, 154.9, 140.1, 139.5, 135.9, 134.1, 133.4, 130.3, 130.2, 129.5, 128.8, 128.7, 128.4, 127.3, 125.7, 123.5, 115.3, 69.7, 56.8, 43.1, 41.8; FAB-HRMS (M+$H^+$) calcd 545.1455, found 545.1471.

**Compound 64**. To a solution of **59** (50 mg, 0.10 mmol) in 1-methyl-2-pyrrolidinone (1 mL) was added **53** (58 mg, 0.19 mmol) at room temperature. After 4 h, the reaction mixture was diluted with water (10 mL) and the aqueous phase extracted with ethyl acetate (3×10 mL). The combined organic extracts were washed succesively with water (2×5 mL) and brine (5 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 50% ethyl acetate in hexanes) to give **64** as a yellow solid (76 mg, 99%). $R_f$=0.22 (silica gel, 50% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3300, 3065, 2975, 2931, 1734, 1660, 1620, 1535, 1497, 1347, 1261, 1159, 1129, 1079, 972, 917, 817, 751, 661, 551, 477 $cm^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 11.49 (bs, 1H, (C=N)NH(C=O)), 8.58 (bt, 1H, $CH_2$N*H*(C=N)), 8.47 (d, $J$=2.0 Hz, 1H, Ar), 8.41 (dd, $J$=5.5 Hz, 1H, N*H*$CH_2$), 8.37 (d, $J$=2.0 Hz, 1H, naphthyl), 7.90–7.84 (m, superimposed, 3H, naphthyl), 7.86 (dd, $J$=2.0, 9.0 Hz, 1H, Ar), 7.79 (dd, $J$=2.0, 8.5 Hz, 1H, naphthyl), 7.59 (ddd, $J$=1.5, 7.0, 7.0 Hz, 1H, naphthyl), 7.54 (ddd,

$J$ = 1.5, 7.0, 7.0 Hz, 1H, naphthyl), 7.12 (d, $J$ = 9.0 Hz, 1H, Ar), 6.69 (t, $J$ = 5.5 Hz, 1H, $CH_2NH(C=O)$), 5.89 (d, $J$ = 8.0 Hz, 1H, $NHSO_2$), 4.03 (ddd, $J$ = 4.0, 8.0, 8.5 Hz, 1H, $CHCH_2$), 3.85 (ddd, $J$ = 4.0, 6.0, 14.0 Hz, 1H, CHCHH), 3.70 (bdt, $J$ = 5.5, 5.5 Hz, 2H, $NHCH_2$), 3.61–3.50 (m, 3H, CHCHH, $CH_2NH(C=N)$), 1.52 (s, 9H, $^t$Bu), 1.47 (s, 9H, $^t$Bu), 1.18 (s, 9H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 168.5, 165.6, 156.6, 153.2, 146.9, 136.0, 134.8, 134.6, 132.0, 131.3, 129.6, 129.2, 128.9, 128.6, 127.8, 127.6, 126.0, 122.2, 120.8, 114.3, 83.8, 83.6, 56.4, 42.4, 42.2, 39.1, 28.3, 28.0, 27.6; FAB-HRMS ($M+Cs^+$) calcd 932.2265, found 932.2285.

**Compound 18**. Compound **18** was prepared by the same procedure as **11**. Yield (81.7 mg, 90%) as an orange yellow solid. $t_R$ = 12.4 min; IR (KBr): $V_{max}$ 3364, 1676, 1624, 1556, 1520, 1426, 1315, 1241, 1200, 1158, 1133, 1076, 1025, 999, 824, 757, 719, 660, 549, 479 cm$^{-1}$; $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.17 (bs, 1H, naphthyl), 8.14 (d, $J$ = 2.0 Hz, 1H, Ar), 7.72 (d, $J$ = 8.0 Hz, 1H, naphthyl), 7.68–7.65 (m, 2H, naphthyl), 7.57 (bd, superimposed, $J$ = 9.5 Hz, 1H, naphthyl), 7.55 (dd, superimposed, $J$ = 2.0, 9.0 Hz, 1H, Ar), 7.41 (ddd, $J$ = 1.5, 7.0, 8.0 Hz, 1H, naphthyl), 7.36 (ddd, $J$ = 1.5, 7.0, 8.0 Hz, 1H, naphthyl), 6.74 (d, $J$ = 9.0 Hz, 1H, Ar), 4.25 (dd, $J$ = 4.5, 10.0 Hz, 1H, $CHCH_2$), 3.62 (dd, $J$ = 4.5, 14.0 Hz, 1H, CHCHH), 3.52 (t, $J$ = 6.0 Hz, 2H, $NHCH_2$), 3.41 (t, $J$ = 6.0 Hz, 2H, $NHCH_2$), 3.30 (dd, $J$ = 10.0, 14.0 Hz, 1H, CHCHH); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 173.0, 167.8, 147.8, 139.5, 135.9, 135.3, 133.4, 130.3, 130.2, 129.3, 128.7, 128.6, 128.3, 127.2, 123.5, 121.5, 114.5, 57.0, 42.9, 42.5, 41.5; FAB-HRMS ($M+Na^+$) calcd 566.1434, found 566.1453.

**Compound 66**. To a solution of **59** (150 mg, 0.29 mmol) in DMF (5 mL) was added **52** (190 mg, 0.58 mmol) at room temperature. After 20 h, the reaction mixture was diluted with water (25 mL) and ethyl acetate. After phase seperation, the aqueous phase extracted with ethyl acetate (3×30 mL). The combined organic extracts were washed succesively with water (2×20 mL) and brine (20 mL) and dried over $MgSO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash column chromatography (silica gel, 40% ethyl acetate in hexanes) to give **66** as a yellow solid (240 mg, 99%). $R_f$ = 0.33 (silica gel, 50% ethyl acetate in hexanes); IR (KBr): $V_{max}$ 3397, 2979, 2933, 1741, 1610, 1524, 1454, 1367, 1303, 1239, 1157, 1015, 975, 834, 752, 661, 615, 552, 477 cm$^{-1}$; $^1$H NMR (500 MHz, $CDCl_3$): δ 11.49 (bs, 1H, (C=N)NH(C=O), 8.38 (bs, 1H, naphthyl), 8.24 (d, $J$ = 2.0 Hz, 1H, Ar), 7.90 (bd, $J$ = 7.5 Hz, 1H, naphthyl), 7.87 (bd, $J$ = 9.0 Hz, 1H, naphthyl), 7.83 (dd, superimposed, $J$ = 2.0, 8.5 Hz, 1H, Ar), 7.82 (d, superimposed, $J$ = 8.0 Hz, 1H, naphthyl), 7.79 (dd, $J$ = 2.0, 8.5 Hz, 1H, naphthyl), 7.64–7.55 (2×bddd, superimposed, 2H, naphthyl), 7.13 (bm, 1H, NH(C=O)), 6.98 (d, $J$ = 9.0 Hz, 1H, Ar), 4.01 (ddd, $J$ = 3.5, 8.0, 9.0 Hz, 1H, $CHCH_2$), 3.88 (ddd, $J$ = 4.0, 6.0, 13.5 Hz, 1H, CHCHH), 3.73 (bm, 4H, $NCH_2$), 3.55 (ddd, $J$ = 5.5, 8.5, 13.5 Hz, 1 H CHCHH), 3.18 (bm, 4H, $NCH_2$), 1.48 (s, 18 H, $^t$Bu), 1.15 (s, 9H, $^t$Bu); $^{13}$C NMR (125 MHz, $CDCl_3$): δ 168.6, 165.1, 155.2, 147.3, 140.9, 135.6, 134.9, 132.0, 129.6, 129.2, 129.0, 128.7, 127.8, 127.7, 126.2, 126.0, 122.1, 119.8, 119.7, 83.9, 56.1, 50.3, 42.2, 28.2, 28.0, 27.3; FAB-HRMS ($M+Cs^+$) calcd 958.2422, found 958.2458.

**Compound 19**. Compound **19** was prepared by the same procedure as for **11**. Yield (31.9 mg, 93%) as a yellowish solid. $t_R$ = 11.1 min; IR (KBr): $V_{max}$ 3401, 3297, 3251, 2996, 2928, 1659, 1613, 1523, 1451, 1385, 1323, 1199, 1157, 1138, 1078, 992, 808, 753, 720, 660, 549 cm$^{-1}$; $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.19 (bs, 1H, naphthyl), 7.93 (d, $J$ = 2.0 Hz, 1H, Ar), 7.76 (bd, $J$ = 9.0 Hz, 1H, naphthyl), 7.71–7.61 (m, superimposed, 3H, naphthyl, Ar), 7.55 (dd, $J$ = 2.0 Hz, 8.8 Hz, 1H, naphthyl), 7.44–7.36 (2×ddd, superimposed, 2H, naphthyl), 6.91 (d, $J$ = 8.5 Hz, 1H, Ar), 4.21 (dd, $J$ = 4.5, 9.5 Hz, 1H, $CHCH_2$), 3.61 (dd, $J$ = 4.5, 13.5 Hz, 1H, CHCHH), 3.55 (m, 4H, $NCH_2$), 3.29 (dd, $J$ = 9.5, 13.5 Hz, 1H, CHCHH), 3.15–3.09 (m, 4H, $NCH_2$); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 167.6, 158.5, 148.2, 142.1, 139.4, 136.0, 133.5, 133.3, 130.4, 130.3, 129.7, 128.9, 128.5, 127.3, 126.7, 123.6, 121.2, 50.9, 49.6, 48.6, 46.4; FAB-HRMS ($M+Cs^+$) calcd 702.0747, found 702.0784.

### Preparation of compounds 20 and 21

**Compound 67**. To a solution of **57** (0.10 g, 0.20 mmol) in DMF (8 mL) was added **55** (0.038 g, 0.22 mmol) and triethylamine (0.06 mL, 0.44 mmol) at room temperature. After stirring at 25 °C for 16 h, the reaction mixture was diluted with ethyl acetate (10 mL) and water (10 mL). The layers were seperated and the aqueous layer was extracted with ethyl acetate (2×10 mL). The organic extracts were collected and washed with water (2×10 mL) and brine (20 mL) and dried over $Na_2SO_4$. After filtration and evaporation under reduced pressure the residue was purified by flash chromatography (silica, ethyl acetate) to give **67** as a yellowish solid (110 mg, 92%). $R_f$ = 0.43 (silica, ethyl acetate); $^1$H NMR (500 MHz, methanol-$d_4$): δ 8.57 (d, $J$ = 2.0 Hz, 1H, Ar), 7.96 (bm, 1H, Ar), 7.83 (dd, $J$ = 2.0, 9.0 Hz, 1H, Ar), 7.80–7.78 (m, 2H, Ar), 7.48–7.39 (m, 4H, Ar), 7.18 (dd, $J$ = 4.0, 6.0 Hz, 2H), 7.06 (d, $J$ = 9.0 Hz, 1H, Ar), 4.12 (dd, $J$ = 6.0, 8.0 Hz, 1H, $CH_2CH$), 3.89 (t, $J$ = 7.0 Hz, 2H, $CH_2Ar$), 3.65 (dd, $J$ = 6.0, 14.0 Hz, 1H, CHHCH), 3.46 (dd, $J$ = 8.0, 14.0 Hz, 1H, CHHCH), 3.26 (t, $J$ = 7.0 Hz, 2H, $CH_2NH$), 1.22 (s, 9H, $^t$Bu); $^{13}$C NMR (125 MHz, methanol-$d_4$): δ 170.4, 168.1, 164.8, 153.6,

147.9, 142.2, 135.6, 133.6, 132.6, 132.4, 130.1, 128.1, 127.7, 123.5, 121.8, 114.9, 83.3, 57.3, 43.2, 42.3, 27.9; Electrospray mass spectrum ($M+H^+$) calcd 609, observed 609.

**Compound 20**. To a solution of **57** (0.068 g, 0.11 mmol) in $CH_2Cl_2$ (2 mL) was added trifluoroacetic acid (2 mL) at room temperature. After 4 h, the solvent was removed in vacuo to give an oil which after RP-HPLC (C-18) gave **20** as a yellow solid (0.056, 97%). $^1H$ NMR (500 MHz, methanol-$d_4$): δ 8.65 (d, $J=1.0$ Hz, 1H, Ar), 7.93 (dd, $J=1.0$, 9.0 Hz, 1H, Ar), 7.81 (d, $J=8.0$ Hz, 2H, Ph), 7.74 (dd, $J=3.0$, 6.0 Hz, 2H, Ar), 7.58 (dd, $J=3.0$, 6.0 Hz, Ar), 7.48 (t, $J=7.0$ Hz, 1H, Ph), 7.43 (t, $J=8.0$ Hz, 2H, Ph), 7.16 (d, $J=9.0$ Hz, 1H, Ar), 4.20 (dd, $J=5.0$, 9.0 Hz, 1H, C*H*CHH), 4.04 (t, $J=6.5$ Hz, 2H, C$H_2$Ar), 3.74 (dd, $J=5.0$, 14.0 Hz, 1H, CHC*H*H), 3.54 (t, $J=6.5$ Hz, 2H, $CH_2NH$), 3.45 (dd, $J=9.0$, 14.0 Hz, 1H, CHCH*H*); $^{13}C$ NMR (125 MHz, methanol-$d_4$): δ 172.6, 168.1, 152.6, 147.3, 142.0, 135.7, 133.5, 133.1, 132.4, 132.3, 130.0, 127.9, 127.8, 127.4, 122.5, 114.8, 114.6, 56.8, 43.2, 41.2, 27.2; FAB-HRMS ($M+Cs^+$) calcd 685.0482, found 685.0461.

**Compound 68**. To a solution of **57** (0.06 g, 0.13 mmol) in DMF (10 mL) was added **56** (0.03 g, 0.14 mmol) and triethylamine (0.04 mL, 0.29 mmol) at room temperature. After 12 h, the solvent was removed in vacuo to give **68** as a crude yellow oil (0.09 g, 110%). $R_f=0.23$ (40% methanol in dichloromethane); $^1H$ NMR (500 MHz, methanol-$d_4$): δ 8.63 (d, $J=2.0$ Hz, 1H, Ar), 7.93 (dd, $J=2.0$, 9.0 Hz, 1H, Ar), 7.82 (d, $J=6.5$ Hz, 2H, Ph), 7.48–7.42 (m, 3H, Ph), 7.09 (d, $J=9.0$ Hz, 1H, Ar), 4.08–4.06 (m, 1H, C*H*CHH), 3.68–3.62 (m, superimposed, 5H, $NHCH_2CH_2NH$, CHC*H*H), 3.50–3.44 (m, 1H, CHCH*H*), 3.30 (t, $J=3.5$ Hz, 2H, C$H_2$NHAr), 1.24 (s, 9H, $^t$Bu); Electrospray mass spectrum calcd ($M+H^+$) 573, found 573.

**Compound 21**. To a solution of **68** (0.09 g, 0.14 mmol) in $CH_2Cl_2$ (5 mL) was added trifluoroacetic acid (5 mL) at room temperature. After 4 h, the solvent was removed in vacuo to give an oil which after RP-HPLC (C-18) gave **21** as a yellow solid (0.07 g, 83%) $t_R=14.0$ min; $^1H$ NMR (500 MHz, methanol-$d_4$): δ 8.64 (bs, 1H, Ar), 7.94 (d, $J=9.0$ Hz, 1H, Ar), 7.82 (d, $J=7.0$ Hz, 2H, Ph), 7.48 (t, $J=7.0$ Hz, 1H, Ph), 7.43 (t, $J=7.0$ Hz, 1H, Ph), 7.12 (d, $J=9.0$ Hz, 1H, Ar), 4.20 (dd, $J=5.0$, 9.0 Hz, 1H, C*H*$CH_2$), 3.73 (dd, $J=5.0$, 14.0 Hz, 1H, CHC*H*H), 3.70–3.66 (m, superimposed, 7H, $NCH_2$ $CH_2N$, $CH_2N(C=N)$), 3.52 (t, $J=6.0$ Hz, 2H, $CH_2NHAr$), 3.45 (dd, $J=9.0$, 14.0 Hz, 1H, CHCH*H*); $^{13}C$ NMR (125 MHz, methanol-$d_4$): δ 172.7, 168.3, 161.6, 148.0, 142.1, 135.8, 133.5, 132.9, 130.0, 128.0, 127.7, 122.3, 114.9, 56.7, 44.1, 43.2, 42.9, 42.7; FAB-HRMS ($M+H^+$) calcd 520.1614, found 520.1630.

**Preparation of compound 22**

**Compound 69**. To a solution of the fluoride **57** (0.10 g, 0.20 mmol) in dry DMF (10 mL) at room temperature a stream of $NH_3$ (g) was bubbled through for 1 h. After stirring for 4 h, the reaction mixture was diluted with ethyl acetate and water. The layers were separated and the organic layer was washed with water (2×10 mL), brine (20 mL) and dried ($Na_2SO_4$). The solvent was removed in vacuo to give **61** as a yellowish oil (0.09 g, 93%). $R_f=0.25$ (silica, 50% ethyl acetate in hexane); IR (thin film): $V_{max}$ 3359, 1729, 1631, 1516, 1308, 1258, 1158, 1093 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d_4$): δ 8.54 (d, $J=2.0$ Hz, 1H, Ar), 7.83–7.81 (m, 2H, Ar), 7.74 (dd, $J=2.0$, 9.0 Hz, 1H, Ar), 7.52–7.43 (m, 3H, Ar), 6.97 (d, $J=9.0$ Hz, 1H, Ar), 4.12 (dd, $J=6.0$, 8.0 Hz, 1H, CH), 3.64 (dd, $J=6.0$, 13.5 Hz, 1H, C*H*H), 3.47 (dd, $J=8.0$, 13.5 Hz, 1H, CH*H*), 1.25 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, methanol-$d_4$): δ 170.5, 168.3, 149.4, 142.2, 134.8, 133.6, 131.7, 130.1, 128.1, 127.1, 122.2, 119.9, 83.4, 57.3, 43.2, 27.9; FAB-HRMS calcd ($M+Cs^+$) 597.0420, found 597.0439.

**Compound 70**. To a solution of amine **69** (0.23 g, 0.50 mmol) in methanol (15 mL) at room temperature was added 10% Pd/C (0.10 g) under argon. The flask was then equipped with a balloon containing $H_2$ (g). After 8 h, the reaction mixture was filtered through a pad of celite and the solvent removed in vacuo to give **70** as a brownish-reddish oil (0.19 g, 90%). $R_f=0.11$ (silica, 80% ethyl acetate in hexane); IR (thin film): $V_{max}$ 3360, 2979, 1729, 1625, 1582, 1542, 1508, 1447, 1369, 1310, 1248, 1160, 1093, 758, 721, 688, 590 $cm^{-1}$; $^1H$ NMR (500 MHz, methanol-$d_4$): δ 7.82–7.80 (m, 2H, Ar), 7.53–7.49 (m, 1H, Ar), 7.46–7.43 (m, 2H, Ar), 7.11 (d, $J=2.0$ Hz, 1H, Ar), 7.05 (d, $J=2.0$ Hz, 1H, Ar), 6.64 (d, $J=8.5$ Hz, 1H, Ar), 4.08 (dd, $J=7.5$, 14.5 Hz, 1H, CH), 3.61 (dd, $J=6.0$, 13.5 Hz, 1H, C*H*H), 3.47 (dd, $J=8.0$, 13.5 Hz, 1H, CH*H*), 1.22 (s, 9H, $^t$Bu); $^{13}C$ NMR (125 MHz, methanol-$d_4$): δ 170.8, 170.6, 142.1, 141.2, 134.8, 133.7, 130.1, 128.1, 124.5, 120.6, 116.5, 115.5, 83.3, 57.5, 43.1, 28.0; FAB-HRMS calcd ($M+Na^+$) 435.1702, found 434.1727.

**Compound 71**. To a solution of the diamine **70** (0.092 g, 0.20 mmol) in ethanol (20 mL) was added triethylamine (0.032 mL, 0.22 mmol) and phenyl isothiocyanate (0.028 mL, 0.22 mmol). After 14 h, the solvent was removed in vacuo to give a brown residue which was purified by preparative thin-layer chromatography (silica, 5% methanol in dichloromethane) to give **71** as a brown solid (0.082 g, 69%). $R_f=0.16$ (silica, 5% methanol in dichloromethane); IR (thin film): $V_{max}$ 3316, 3061, 2978, 1729, 1624, 1504, 1448, 1368, 1309, 1252, 1159, 1092, 837, 733 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$): δ 8.15 (bs, 1H, NH), 7.81 (d, $J=7.5$ Hz, 2H, Ar), 7.56–7.03

(m, 14 H), 6.78 (bs, 1H, NHC=O), 6.58 (d, $J$=8.0 Hz, 1H, $H$NSO$_2$Ph), 4.51 (bs, 1H), 4.05 (bs, 1H), 3.67 (bs, 1H), 1.20 (s, 9H, $^t$Bu); $^1$H NMR (500 MHz, $CDCl_3$): δ 180.3, 168.6, 167.4, 147.0, 143.3, 139.6, 137.6, 132.7, 129.0, 128.4, 127.1, 126.6, 125.4, 123.5, 116.1, 83.2, 60.3, 56.5, 42.0, 27.5; FAB-HRMS calcd ($M+Cs^+$) 702.0821, found 702.0797.

**Compound 72**. To a solution of the thiourea **71** (0.077 g, 0.14 mmol) in DMF (10 mL) at room temperature was added triethylamine (0.02 mL, 0.14 mmol) and mercury (II) chloride (0.04 g, 0.14 mmol). After 4 h, the reaction mixture was filtered through celite and rinsed with ethyl acetate. The solvent was removed in vacuo to give **72** as a brown residue (0.05 g, 81%) which was carried onto the next step. $R_f$=0.32 (silica, 5% methanol in dichloromethane); $^1$H NMR (500 MHz, $CDCl_3$): δ 7.98 (m, 2H, Ar), 7.53–6.90 (m, 15 H, Ar), 4.16 (m, 1H, CH), 3.83 (bs, 1H, C$H$H), 3.62 (bs, 1H, CH$H$), 1.25 (bs, 9H, $^t$Bu); FAB-HRMS calcd ($M+Cs^+$) 668.0944, found 668.0923.

**Compound 22**. Compound **22** was prepared by the same procedure as for **10**. Yield: (0.04 g, 88%). $t_R$=14.8 min; $^1$H NMR (500 MHz, methanol-$d_4$): δ 7.85–7.82 (m, 3H, Ar), 7.75 (dd, $J$=1.5, 8.5 Hz, 1H, Ar), 7.56–7.41 (m, 9H, Ar), 4.22 (dd, $J$=5.0, 9.0 Hz, 1H, CH), 3.78 (dd, $J$=5.0, 13.5 Hz, C$H$H), 3.48 (dd, $J$=9.0, 13.5 Hz, CH$H$); $^{13}$C NMR (150 MHz, methanol-$d_4$): δ 171.9, 169.2, 150.7, 141.6, 136.2, 133.1, 131.2, 130.9, 130.6, 129.5, 128.3, 127.5, 124.6, 124.1, 111.9, 111.8, 56.1, 42.8; FAB-HRMS calcd ($M+H^+$) 480.1342, found 480.1352.

### Receptor and cell adhesion assays

Human integrins and vitronectin and fibrinogen from human plasma were prepared as previously detailed;[25] $\alpha_{IIb}\beta_3$ was purified from outdated thrombocytes,[26] $\alpha_v\beta_3$ and $\alpha_v\beta_5$ were from term human placenta.[27] The integrins were >95% pure as judged by SDS–PAGE and by ELISA. Receptor inhibition assays[28] and cell attachment[25] were performed as previously described.

Human cell lines and culture and the adhesive characteristics of the cells have been described in full elsewhere.[25,29] The melanoma cell line M21 attach to vitronectin predominantly over $\alpha_v\beta_3$ with a small contribution from $\alpha_v\beta_5$. M21-L lack $\alpha_v$ expression and were transfected with full length cDNA of $\alpha_{IIb}$ gene to establish a line M21-L-IIb[30] which adhere to fibrinogen using expressed cell surface $\alpha_{IIb}\beta_3$. The carcinoma line UCLA-P3 expresses $\alpha_v\beta_5$ as a vitronectin receptor.[25,31]

Cell adhesion assays were detailed previously,[25,32] limiting integrin usage by selecting the appropriate substrate. Briefly, nontissue culture treated 96-well plates were coated with purified fibrinogen or vitronectin (5–10 mg/mL). Cells were harvested, resuspended and washed once in adhesion buffer (RPMI with 1% BSA, 50 mM HEPES (pH 7.4)) before being allowed to adhere (25,000 cells: 1 h, 37 °C) in the presence of test compounds to the immobilized ligands. Non-adherent cells were removed by aspiration followed by three rapid washes with adhesion buffer and remaining cells were detected using hexosaminidase substrate.

### Chick chorioallantoic membrane (CAM) assay

**Animals.** Ten day old chick embryos were purchased from McIntyre Poultry (Lakeside, CA, USA) and incubated at 37 °C with 60% humidity and 51% relative humidity.

**Preparation of filter discs.** The filter discs for placement on the chick CAM were cut out from Whatman grade 1 filter paper using a paper punch (6 mm diameter). The discs were then soaked in 1 mL of a 3.0 mg/mL cortisone acetate in absolute ethanol solution. The discs were air dried for 45–60 min in a sterile laminar flow hood.

**Candling.** To locate the optimal position for the placement of the filter disc on the CAM and to identify potential blood vessels for intravenous injections, the eggs were candled. The broad end of the egg was placed up to the candlelight to determine the position of the air sac. To prepare the egg for intravenous injection, the egg was rotated close to the light to determine the position of the prominent blood vessels on the lateral sides of the egg that were well anchored and close to the surface. The vessel selected for injection was as straight as possible and from medium to small in size.

**Dropping the CAM.** To separate the CAM from the shell membrane the broad end of the eggs where the air sac was located was swabbed with 70% ethanol. A small hole was drilled through the broad end of the egg. Another hole, through the shell only, was drilled at the position where the CAM will separate from the eggshell, approximately 90° from the preselected blood vessel. Curved tip forceps were used to push down on the shell membrane at the sight of filter disc placement. This pressure allowed the CAM to separate from the shell. Gentle suction was applied to the hole at the broad end of the egg which helped create the false air sac directly over the CAM. To create a window through the eggshell immediately over the dropped CAM, a 1 cm×1 cm box was drawn directly over the newly created false air sac and then cut with a model cutting wheel.

**Cytokine stimulation of angiogenesis.** The dried filter discs were coated in 1–2 mL of a 1–2 μg/mL cytokine solution (bFGF). The cytokine coated filter discs were then placed on their respective CAMS in an area with

low density of preexisting vessels. The window was sealed with transparent tape and the embryos were placed in the incubator.

**Administration of angiogenesis inhibitors.** The embryos were incubated undisturbed for 18–20 h to facilitate adherence of filter discs to the CAM tissue and to induce the early stages of angiogenesis. The shell around the preselected vessel was then removed and a window was created. A drop of paraffin oil was placed around the cut borders of the window to loosen the shell from the membrane. The shell window was then removed using a pair of dissecting forceps and 100 mL total volume of the antagonist solution was injected into the preselected blood vessel. The embryos were then incubated for 48 h.

**Quantification of angiogenesis.** In order to quantify angiogenesis within the chick CAMs, embryos were removed from the incubator and CAMs harvested. Using dissecting scissors, the shell immediately surrounding the window was removed to expose the underlying filter disc. Using dissecting forceps and scissors, the portion of CAM tissue containing the cytokine filter disc was removed from the rest of the CAM and placed in a 35×10 mm sterile petri dish. Each CAM was individually rinsed with 2 mL of sterile PBS pH 7.40 prior to its analysis. A stereo microscope was used to count the number of blood vessel branch points directly beneath the applied filter disc. The relative number of blood vessel branch points is indicative of the number of new blood vessel sprouts arising from pre-existing blood vessels. Quantification of the number of branch points was performed in a double blind fashion.

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