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Antibiotics

Synthetic and Biologic Studies on New Urea and Triazole Containing Cystobactamid Derivatives

Therese Planke,[a] Katarina Cirnski,[b], Jennifer Herrmann,[b] Rolf Müller,[b] and Andreas Kirschning*[a]

Abstract: The cystobactamids belong to the group of arene-based oligoamides that effectively inhibit bacterial type IIa topoisomerases. Cystobactamid 861-2 is the most active member of these antibiotics. Most amide bonds present in the cystobactamids link benzoic acids with anilines and it was found that some of these amide bonds undergo chemical and enzymatic hydrolysis, especially the one linking ring C with ring D. This work reports on the chemical synthesis and biological evaluation of thirteen new cystobactamids that still contain the methoxyaspartate hinge However, we exchanged selected amide bonds either by the urea or the triazole groups and modified ring A in the latter case. While hydrolytic stability could be improved with these structural substitutes, the high antibacterial potency of cystobactamid 861-2 could only be preserved in selected cases. This includes derivatives, in which the urea group is positioned between rings A and B and where the triazole is found between rings C and D.

[a] *T. Planke, Prof. Dr. A. Kirschning*
Institut für Organische Chemie und Biomolekulares Wirkstoffzentrum (BMWZ), Leibniz Universität Hannover
Schneiderberg 1B, 30167 Hannover (Germany)
Fax: (+49) 511-762-3011
E-mail: andreas.kirschning@oci.uni-hannover.de and gerald.draeger@oci.uni-hannover.de

[b] *Prof. Dr. R. Müller, Dr. J. Herrmann, K. Cirnski*
Abteilung Mikrobielle Naturstoffe, Helmholtz Institut für Pharmazeutische Forschung Saarland, Helmholtz Zentrum für Infektionsforschung und Universität des Saarlandes, Campus E8.1, 66123 Saarbrücken, Germany

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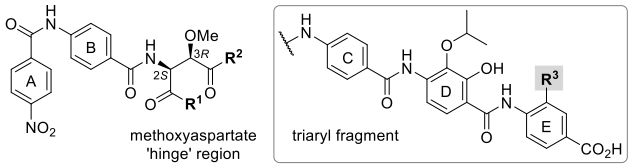
Introduction

The cystobactamids, an unusual group of oligoamides from *Cystobacter sp*. Cbv34, were first reported in 2014.[1] The extracts inhibited the growth of several Gram-negative and Gram-positive bacteria and HPLC-assisted bioactivity-guided screening provided cystobactamids 919-1 (**1**) and 919-2 (**2**) as active compounds (Figure 1). These oligoamides contain *p*-aminobenzoic acid building blocks and either an *iso*-β-methoxyasparagine or a β-methoxyasparagine unit. Later, additional derivatives such as the cystobactamids 920-1 (**3**), 920-2 (**4**) and 862-1 (**5**) were reported that structurally differ in the E-ring and the asparate hinge region. [2a]

Cystobactamid 862-1 (**5**) was found to be the most active natural member. It inhibits several clinically relevant Gram-positive and Gram-negative strains (*Acinetobacter baumannii:* MIC = 0.5 µg/mL, *Citrobacter freundii*: MIC = 0.06 µg/mL, carbapenem-resistant *E. coli* WT-III *marR*Δ74bp: MIC = 0.5 µg/mL, fluoroquinolone-resistant *P. aeruginosa* CRE: MIC = 1.0 µg/mL, and *Proteus vulgaris:* MIC = 0.25 µg/mL)[2] by inhibiting bacterial type IIa topoisomerases. It has to be stressed, that the cystobactamids are structurally related to albicidin with similar antibacterial properties, which has extensively been studied by Süssmuth *et al*.[3]



cystobactamid:	R^1	R^2	R^3
919-1 (**1**)	NH_2	triaryl	O*i*Pr
919-2 (**2**)	triaryl	NH_2	O*i*Pr
920-1 (**3**)	OH	triaryl	O*i*Pr
920-2 (**4**)	triaryl	OH	O*i*Pr
861-2 (**5**)	triaryl	NH_2	H

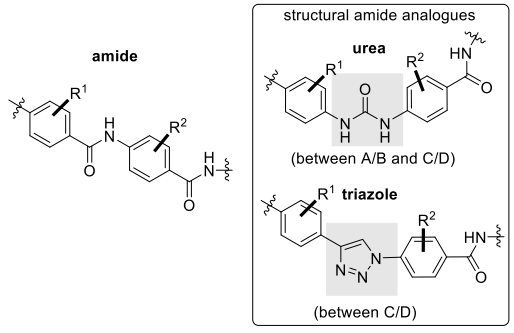


Figure 1. Structures of selected cystobactamids 919-1 (**1**), 919-2 (**2**), 920-1 (**3**), 920-2 (**4**) and 861-2 (**5**) and the urea as well as triazole groups as structural substitutes for amide group (rings are labelled with letters A-E).

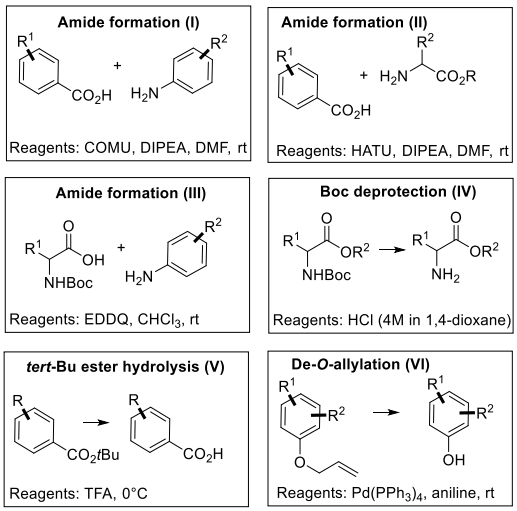
Several total syntheses of cystobactamids 861-2, 919-2 and 920-1 have been published by the Trauner group and by us.[2a,4,5] These endeavours were essential to revise and prove the constitutions as well as the 2*S*, 3*R* configurations of cystobactamids.[5] Both, the synthetic programmes and the cystobactamid isolation protocols revealed, that the amide bonds between benzoic acids and anilines are prone to hydrolysis with the amide bond that links rings C and D being the most labile one.

As part of a medicinal chemistry programme on cystobactamids, we therefore envisaged to prepare a library of methoxyaspartate containing cystobactamids. One aspect of this programme covers the substitution of the amide group by supposedly chemically more stable functional elements such as urea and triazole (figure 1). Besides 1,2,4-triazoles, a cis amide bond surrogate,[6] the 1,2,3-triazole ring has recently been found to be a prominant amide bond bioisostere.[7,8]

Here, we report on our recent total synthetic endeavours towards new cystobactamide derivatives with improved chemical stability and the determination of their antibacterial properties. This includes the direct comparison with ciprofloxacin (CP).

Chemical Syntheses

General considerations: The cystobactamids are natural products with a modular architecture. The key structural elements are amide bonds, that are composed of combinations of benzoic acids, anilines and carboxylate and amino group in the methoxyasparate unit. In addition, protecting groups for the carboxylates, amines and phenols have to be chosen. Substantial search and optimisation led to a toolbox of reactions listed in Scheme 1 (cases I-VI), that also repeatedly served to prepare the new cystobactamids reported here. Three principal types of amide forming processes have been developed, that combine two aromatic building blocks (case I), a benzoic acid with an amine (case II), and an aniline with a carboxylate (case III).



Scheme 1. Reagents employed for principal reaction for constructing cystobactamids (COMU = (1-cyano-2-ethoxy-2-oxoethylidene-aminooxy)dimethylaminomorpholinocarbenium-hexa-fluorophosphate; EEDQ = *N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline; HATU = [*O*-(7-azabenzotriazole-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium-hexa-fluorophosphate]; DIPEA = di*iso*propyl-ethylamine, DMF = dimethylformamide, TFA = trifluoroacetic acid).

Boc-deprotection of the methoxyaspartate hinge region was achieved under mildly acidic conditions (case IV), avoiding the hydrolysis of the *tert*-butyl ester in ring E. This ester was commonly cleaved under stronger acidic conditions in neat TFA, routinely the final step of our chemical syntheses (case V). Finally,

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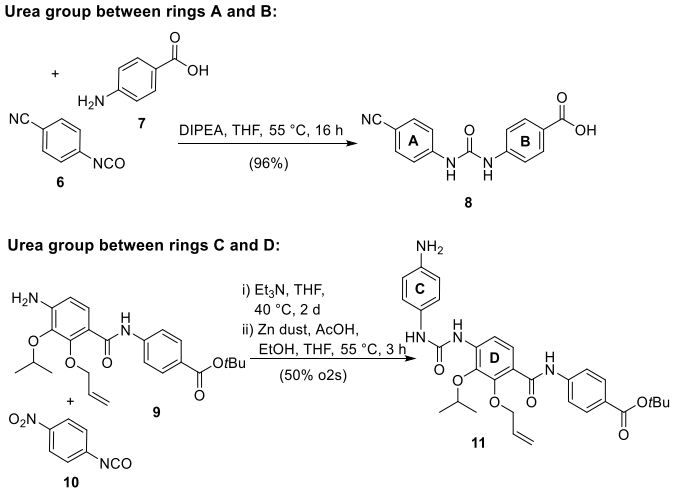
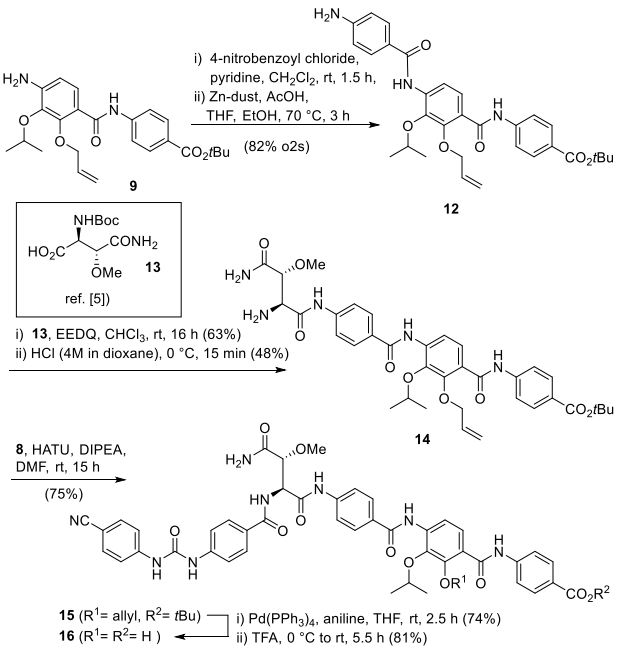
the allyl deprotection of the phenol function was achieved under Pd(0)-catalised conditions (case VI).

Syntheses of urea-modified cystobactamids: For exchanging the amide group by urea one of the coupling partners was chosen to contain the isocyanate group as in 4-isocyanato-benzonitrile **6** and 1-isocyanato-4-nitrobenzene **10** (Scheme 2). These building blocks were flexibly used to prepare cystobactamid derivatives containing an urea bridge between rings A and B as well as rings C and D. Several coupling partners **9**, **19** and **20** were at hand from our previously published syntheses of cystobactamids 861-2 (**5**) and 920-1 (**3**).[2a,5]

4-Isocyanato-benzonitrile (**6**) was efficiently coupled with 4-aminobenzoic acid **7** to yield disubstituted urea **8** resembling the linkages between rings A and B.



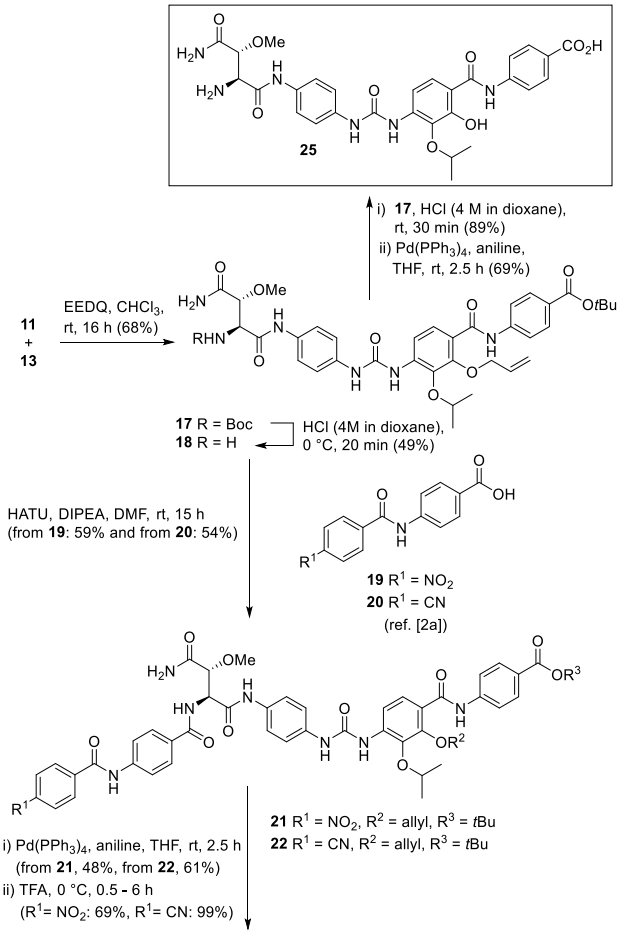
Scheme 2. Synthesis of urea-containing building blocks **8** and **11**.



Scheme 3. Synthesis of cystobactamid derivative **16** bearing an urea group between rings A and B.

Diamide **9** was coupled with 1-isocyanato-4-nitrobenzene **10** followed by reduction of the nitro group yielded urea derivative **11** in which the urea group is located between rings C and D. We first prepared cyano derivative **16** in which the urea group is located between the A and B rings (Scheme 3). The cyano derivative was chosen, because it has been established that exchange of the nitro group by cyanide leads to improved antibacterial properties.[8]

The synthesis commenced with the coupling of amide **9** with 4-nitrobenzoic acid and reduction of the resulting nitroarene to yield the aniline **12**. Next the aniline was linked to the (2*S*,3*R*)-methoxyasparate derivative **13**.[2a] Then, the Boc group was hydrolised under mildly acidic conditions circumventing cleavage of the *tert*-butyl ester. Next, the resulting tetramide **14** was coupled with the urea derivative **8** and the resulting product **15** was transformed into the cystobactamid derivative **16** after *O*-deallylation and ester hydrolysis.



Scheme 4. Synthesis of cystobactamid derivatives **23** - **25** bearing an urea group between rings C and D.

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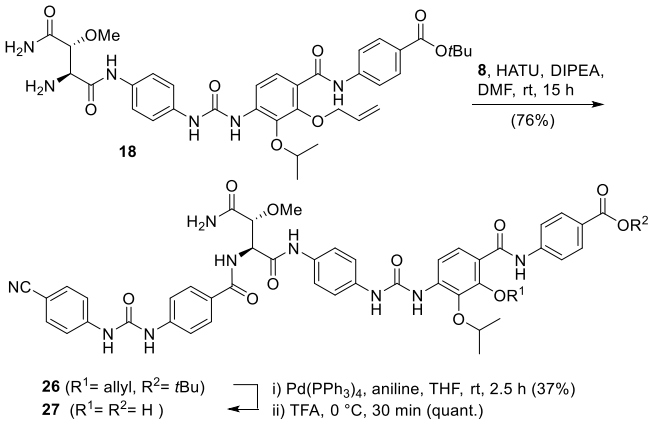
Next, we installed the urea group between rings C and D (Scheme 4). For that, urea derivative **11** was coupled with methoxyasparate derivative **13** to yield Boc-amide **17**, which was transformed into amine **18** under mildly acidic conditions. Amide formation with diamides **19** and **20**, respectively, yielded cystobactamid precursors **21** and **22**, that underwent the common two-step protocol for removing the allyl- and *tert*-butyl groups. The two urea-bearing cystobactamid derivatives **23** and **24** were purified by RP-HPLC. The truncated derivative **25** was prepared from Boc-protected tetramide **17** under harsher acidic conditions, that led to hydrolysis of both the Boc-group as well as the *tert*-butyl ester. This was followed by cleavage of the allylether group. In order to remove any traces of the transition metal the crude product was also purified by RP-HPLC.

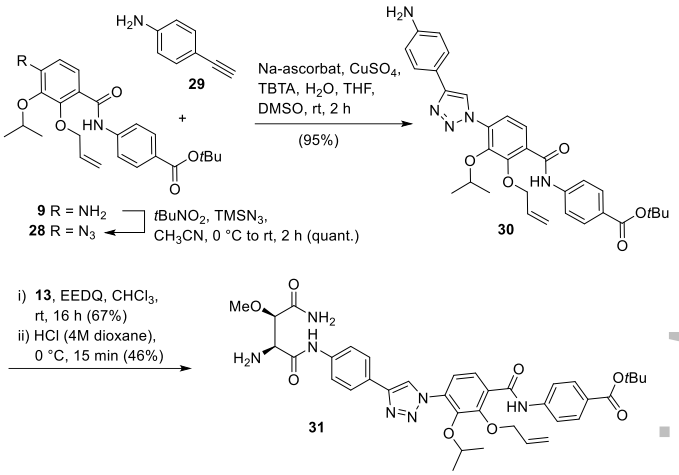
Finally, urea derivative **18** also served as starting point to prepare cystobactamid **27** with two urea groups between rings A/B and C/D (Scheme 6). Coupling with urea derivative **8** yielded compound **26** which was transformed into the cystobactamid derivative **27** in two steps under our standard conditions.



Scheme 5. Synthesis of cystobactamid derivative **27** that contains two urea linkages between rings A/B and C/D.

With a set of new urea-modified cystobactamids in hand we tested the chemical stability of derivative **24** representing the group of urea cystobactamids prepared here. It was dissolved in DMSO-d_6, triethyl amine (12 eq.) was added and a series of ^{1}H-NMR spectra were recorded over a period of 27 h. Careful inspection revealed no degradation products derived from urea derivative **24**. As expected exchange of the amide group by urea leads to enhanced stability under basic conditions.

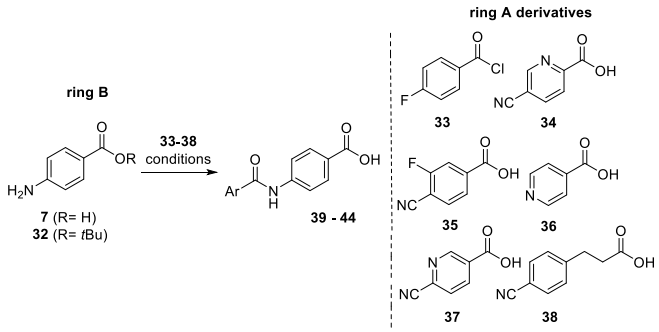
Syntheses of triazole-modified cystobactamids: A second structural element for amide substitution is the triazole ring that is straifgthforwardly been prepared from an alkyne and an azide.[7,8] We pursued to substitute the most labile amide group between rings C and D. Thus, we chose 4-ethynylaniline **29** as alkyne building block and consequently arylazide **28** as second component. The latter was prepared from aniline **9** and reacted under classical Sharpless conditions to yield triazole **30**. Amide coupling with methoxyasparate **13** provided amine **31** after Boc-deprotection under mildly acidic conditions (Scheme 6).



Scheme 6. Synthesis of the central triazole derivative **31**.

Having installed the triazole ring between rings C and D, we turned our attention to prepare several A/B-ring fragments that vary in ring A (Table 1).

Table 1. Preparation of diamides **39**-**44** (COMU= 1-cyano-2-ethoxy-2-oxoethylideneaminooxy) di-methylamino-morpholino-carbenium-hexafluorophosphate).



building block ring A	building block ring B	conditions	yields (%)
33	**7**	Na_2CO_3, THF, H_2O, rt, 3 h	**39** (98)
34	**32**	for **34**-**38**: COMU, DIPEA, DMF, rt, 16 h, then TFA, rt, 30 min	**40** (75)
35	**32**		**41** (66)
36	**32**		**42** (94)
37	**32**		**43** (83)
38	**32**		**44** (79)

We mainly focussed on modifications in the 4-position and exchange of the benzene by the pyridine ring (Table 1; building blocks **33**-**37**). In one case, we used a benzoyl chloride (**33**) which was directly reacted with the aminobenzoic acid (**7**). In most cases, however, the *tert*-butyl ester **32** which was coupled with A-ring derivatives **34**-**37** by *in situ* activation of their carboxylic function. Finally, also 3-(4-isocyanophenyl)propanoic acid (**38**) was chosen as elongated bishomo analogue of 4-cyanobenzoic acid. Consequently, we had a small library of A/B-ring fragments (**39**-**44**) at hand that was used to access triazole-bearing cystobactamids **45**-**52** in a three step sequence (coupling of A/B fragments to triazole-containing aspartate building block **31**, de-*O*-allylation and *tert*-butyl ester hydrolysis) (Scehem 8).

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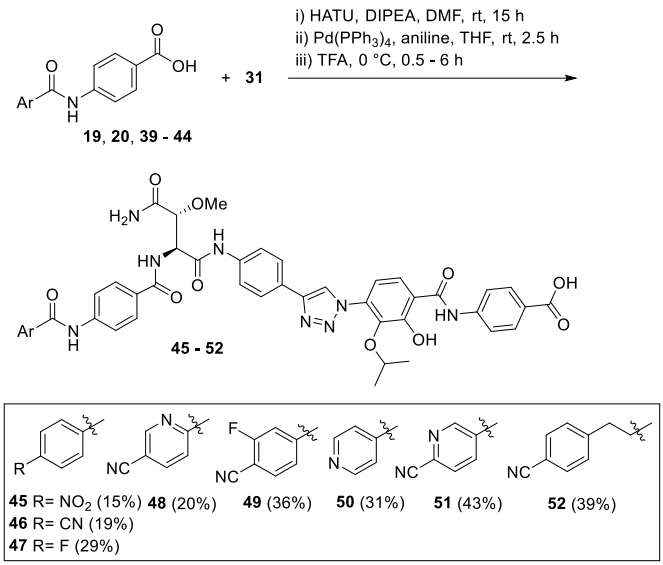

Scheme 8. Synthesis of triazole-modified cystobactamids **45**-**52** (yields refer to the three step sequence).

Evaluation of antibacterial properties

The new urea-modified cystobactamids **16**, **23**-**25** and **27** were tested against a panel of different Gram-negative and Gram-positive pathogens, including intrinsically multidrug-resistant *P. aeruginosa* (Table 2) and directly compared with cystobactamid 861-2 (**5**). Incorporation of the urea group between rings C and D as in derivatives **23**-**25** and **27** leads to substantial and even complete loss of antibacterial activity. This also includes truncation that is represented by cystobactamid derivative **25**. In essence, although chemical stabilisation of the cystobactamids can be achieved by exchanging the amide group with urea, this approach fails for connecting rings C and D due to loss of antibacterial activity. However, when the urea group is positioned between rings A and B as in cystobactamid derivative **16**, biological activity is almost completely preserved compared to cystobactamid 861-2 (**5**) and even considerably higher for strain *E. coli BW25113*.

Table 2. Biological activity of urea derivatives **16**, **23**-**25** and **27** compared to cystobactamid 861-2 (**5**) (MIC values in µg/ml; nd = not determined).[a]

strain	**16**	**23**	**24**	**25**	**27**	**5**
S. aureus Newmann	16	> 64	> 64	> 64	> 64	1
E. coli BW25113	≤ 0.03	nd	1	nd	> 64	0.25
E. coli ΔacrB	≤ 0.03	nd	≤ 0.03	nd	>64	≤ 0.003
E. coli ΔtolC	nd	> 64	nd	> 64	nd	≤0.003
E. coli DSM-1116	nd	> 64	nd	> 64	nd	0.2
P. aeruginosa Pa14	1	>64	>64	>64	>64	1
Pa14ΔmexAB	1	>64	>64	>64	>64	0.25

[a] Values for ciprofloxacin (CP) are listed in table 3.

Likewise, antibacterial properties of triazole-modified cystobactamid derivatives **45**-**52** were evaluated (Table 3). Principally, exchange of the amide group by a triazole ring does not lead to loss of antibacterial activity, so that this modification can be regarded to be a successful strategy to generate cystobactamid derivatives with enhanced chemical and biological stabilities between rings C and D.[9] Furthermore, this set of new analogues reveals finetuning of antibacterial activities by structural changes in ring A. Interestingly, when ring A represents a pyridine ring with N positioned in the *para* and *meta* positions relative to ring B as in compounds **50** and **51** substantial reduction of antibacterial activity against *S. aureus* and *P. aeruginosa* is observed. This is not the case for pyridine derivative **48**, in which the nitrogen atom is located in the *ortho* position. When extending the length between rings A and B by insertion of an ethylene unit as in derivative **52** reduced antibiotic activity is also observed. On the other hand triazole derivatives **45**-**47** as well as fluoro derivative **49** bearing a cyanide group in the *para* position are still highly active in a comparable range to cystobactamid 861-2 (**5**). Importantly, the activity spans across all four strains tested. The important finding of this study is, that the triazole group is a good substitute for the amide linkage between rings C and D.

Table 3. Biological activity of triazole derivatives **45**-**52** compared to cystobactamid 861-2 (**5**) and CP (MIC values in µg/ml).

strain	**45**	**46**	**47**	**48**	**49**	**50**	**51**	**52**	**5**	**CP**
E. coli BW25113tolC	<0.03	<0.03	<0.03	0.125	<0.03	1	<0.03	0.25	<0.03	0.03
E. coli ΔacrB	<0.03	<0.03	<0.03	<0.03	<0.03	0.25	0.25	0.125	0.06	<0.003
S. aureus Newmann	1	1	8	4	1	>64	64	>64	0.125	0.2
P. aeruginosa Pa14	4	4	8	8	4	>64	32	>64	1	0.2
Pa14ΔmexAB	4	4	8	4	4	>64	32	>64	0.125	0.01

Conclusions

In summary, we report on the chemical synthesis of thirteen new analogues derived from cystobactamid 861-2 (**5**). These derivatives differ from the most potent natural member of the cystobactamids by exchange of the amide groups by either the urea group or by a triazole ring. These first structure activity studies (SAR) for natural methoxyaspartate bearing cystobactamids reveal, that the urea function can be introduced between rings A and B but not rings D and E for preserving antibacterial activity. We also show, that the triazole ring can serve as a substitute for the amide group in cystobactamids. Finally, ring A can be modified in various manners without substantial loss of acticvity. This work provides a first information on future directions of medicinal chemistry programmes on the cystobactamids and matches recent findings on the albicidines.[10]

Experimental Section

The experimental section below covers synthetic key protocols for preparing cystobactamids, lists of analytic and spectroscopic data and protocols to

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evaluate their biological properties.General experimental information as well as copies of NMR spectra are found in the supporting information.

General procedure I for amide formation (according to Scheme 1)
DIPEA (4.0 eq) was added to a stirred solution of acid (2.0 eq), amine (1.0 eq) and COMU (2.0 eq) in DMF (0.15 M) at 0 °C. The mixture was stirred at rt for 15 h. The reaction was terminated by diluting with EtOAc, washed with sat. $NaHCO_3$ solution (4x), brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure.

General procedure II for amide formation (according to Scheme 1)
DIPEA (12.7 eq) was added dropwise to a stirred solution of acid (2.5 eq) and HATU (2.5 eq) in DMF (0.11 M) at rt and stirring was continued at rt for five minutes. The mixture was transferred dropwise to a stirred solution of amine (1.0 eq) in DMF (0.07 M) at rt and the mixture was stirred at rt for 15 h. The reaction was concentrated under reduced pressure.

General procedure III for amide formation (according to Scheme 1)
Precooled chlouroform (0.33 M) was added to amine (1.0 eq) and acid (1.7 eq). A solution of EEDQ (1.6 eq) in precooled chloroform (0.75 M) was added dropwise to the acid-amine-mixture at 0 °C. After the mixture was warmed up to rt stirring was continued at rt for 16 h, it was dry loaded onto silica and purified by column chromatography (PE/EtOAc = 2:1 → 1:4).

General procedure IV for Boc deprotection (according to Scheme 1)
Ester (1.0 eq) was added in small portions to 4 N HCl in 1,4-dioxane (100 eq) at 0 °C over five minutes, then the mixture was warmed up to rt over a period of 15 min. The mixture was slowly transferred to a mixture of EtOAc and a 80 % sat. aq. $NaHCO_3$ solution (400 mL, 1:1), the layers were separated, the aq. layer was extracted with EtOAc (3x 100 mL), the combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*.

General procedure V for *tert*-Bu ester hydrolysis (according to Scheme 1)
Precooled TFA (0.02 M) was added slowly to ester (1.0 eq) at 0 °C. The mixture was warmed up to rt over a period 30 min, then it was stirred between 30 min and 6 h. The reaction was terminated by addition of Et_2O. The precipitate was filtered, washed with an excess of Et_2O and dried under high vacuum.

General procedure VI for de-*O*-allylation (according to Scheme 1)
$Pd(PPh_3)_4$ (0.25 eq) was added in one portion to a stirred mixture of allyl ether (1.0 eq) and aniline (2.0 eq) in THF (0.04 M) and stirring was continued at rt for 2.5 h. The mixture was terminated by addition of HCl. The reaction was concentrated under reduced pressure.

Chemical Syntheses

4-(3-(4-Cyanophenyl)ureido)-benzoic acid (8): DIPEA (3.50 mL, 20.8 mmol, 3.0 eq) was added to a solution of 4-aminobenzoic acid (**7**, 952 mg, 6.94 mmol, 1.0 eq) and 4-cyanophenyl isocyanate (**6**, 1.00 g, 6.94 mmol, 1.0 eq) in THF (30 mL). The reaction was stirred at 55 °C for 16 h. The precipitate was filtered and washed with Et_2O (200 mL). Column chromatography (CH_2Cl_2/MeOH, 5-10% MeOH) yielded the title compound **8** (1.87 g, 6.66 mmol, 96%) as colourless solid.T_M = 290 °C (decomposition); ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.7 (1H, br. s, CO_2H), 9.31 (1H, s, H-6/H-8), 9.23 (1H, s, H-6/H-8), 7.88 (2H, m, H-3, H-3‘), 7.74 (2H, m, H-10, H-10‘), 7.64 (2H, m, H-11, H-11‘), 7.57 (2H, m, H-4, H-4‘) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 167.0 (q, C-1), 151.9 (q, C-7), 143.9 (q, C-9), 143.4 (q, C-5), 133.3 (2C, t, C-11, C-11‘), 130.5 (2C, t, C-3, C-3‘), 124.2 (q, C-2), 119.2 (q, CN), 118.2 (2C, t, C-10, C-10‘), 117.6 (2C, t, C-4, C-4‘), 103.6 (q, C-12) ppm; HRMS (ESI): *m/z* calc. for $C_{15}H_{10}N_3O_3$ $[M - H]^-$: 280.0722; found 280.0723.

***tert*-Butyl-4-(2-(allyloxy)-3-isopropoxy-4-(3-(4-nitrophenyl)ureido)-benz-amido)benzoate (S1):** DIPEA (36 µL, 211 µmol, 2.0 eq) was added to a solution of amine **9** (45 mg, 106 µmol, 1.0 eq) and 4-nitrophenyl isocyanate (**10**, 52 mg, 317 µmol, 3.0 eq) in THF (2 mL). The reaction mixture was stirred at 55 °C for 6 h. Additional 4-nitrophenyl isocyanate (**9**, 52 mg, 317 µmol, 3.0 eq) was added and the reaction was stirred at 55 °C for another 14 h. The reaction mixture was concentrated *in vacuo* and the residue was purified by preparative HPLC (RP-18; run time 100 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 53 min) which provided compound **S1** as a colourless solid (44.7 mg, 76.4 mmol, 72%). T_M = 202 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.4 (1H, s, H-8), 10.3 (1H, s, H-23), 8.55 (1H, s, H-21), 8.22 (2H, m, H-26, H-26‘), 8.09 (1H, d, *J* = 8.7 Hz, H-11), 7.88 (2H, m, H-5, H-5‘), 7.81 (2H, m, H-6, H-6‘), 7.73 (2H, m, H-25, H-25‘), 7.42 (1H, d, *J* = 8.7 Hz, H-12), 6.08 – 5.98 (1H, m, H-19), 5.40 (1H, dq, *J* = 1.6, 17.2 Hz, H-20$_{trans}$), 5.22 (1H, dq, *J* = 1.4, 10.4 Hz, H-20$_{cis}$), 4.66 – 4.59 (3H, m, H-16, H-18), 1.54 (9H, s, H-1), 1.33 (6H, d, *J* = 6.2 Hz, H-17) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 164.6 (q, C-3), 164.3 (q, C-9), 151.6 (q, C-22), 149.3 (q, C-15), 146.0 (q, C-27), 143.0 (q, C-7), 141.3 (q, C-24), 138.9 (q, C-13), 136.8 (q, C-10), 133.6 (t, C-19), 130.1 (2C, t, C-5, C-5’), 126.0 (q, C-4), 125.3 (2C, t, C-26, C-26’), 124.4 (t, C-12), 124.1 (q, C-14), 118.8 (2C, t, C-6, C-6’), 117.9 (s, C-20), 117.6 (2C, t, C-25, C-25’), 114.0 (t, C-11), 80.3 (q, C-2), 76.2 (t, C-16), 74.2 (s, C-18), 27.9 (3C, p, C-1), 22.0 (2C, p, C-17) ppm; HRMS (ESI): *m/z* calc. for $C_{31}H_{34}N_4O_8Na$ $[M + Na]^+$: 613.2274; found 613.2278.

***tert*-Butyl-4-(2-(allyloxy)-4-(3-(4-aminophenyl)ureido)-3-isopropoxy-benzamido)benzoate (11):** Zinc (78.5 mg, 1.20 mmol, 2.0 eq) was added in one portion at rt to a stirred solution of nitro compound **S1** (352 mg, 0.60 mmol, 1.0 eq) in THF (1 mL), EtOH (1 mL) and glacial acetic acid (0.2 mL). After stirring vigorously at rt for 30 min, a 3rd and 4th equivalent of zinc were added and the mixture was stirred at rt for another 30 min. This step was repeated twice, after which time the reaction mixture was heated at 70 °C for a period of 30 min and the 9th and 10th equivalent of zinc were added and the mixture was stirred at 70 °C for additional 30 min. The reaction mixture was cooled to rt, diluted with Et_2O and terminated by addition of a sat. aq. $NaHCO_3$ solution. The precipitate was filtered and washed with an excess of Et_2O, the layers were separated, the aq. layer was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc= 3:1) yielded the title compound **11** (234 mg, 0.42 mmol, 70%) as a yellow solid. T_M = 134 °C; ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 10.4 (1H, s, H-8), 9.05 (1H, s, H-21), 8.10 (1H, s, H-23), 8.08 (1H, s, H-11), 7.88 (2H, m, H-5, H-5‘), 7.80 (2H, m, H-6, H-6‘), 7.39 (1H, d, *J* = 8.8 Hz, H-12), 7.10 (2H, m, H-25, H-25‘), 6.53 (2H, m, H-26, H-26‘), 6.07 – 5.98 (1H, m, H-19), 5.40 (1H, dq, *J* = 1.6, 17.2 Hz, H-20$_{trans}$), 5.22 (1H, dq, *J* = 1.4, 9.3 Hz, H-20$_{cis}$), 4.83 (2H, br. S, NH_2), 4.62 – 4.57 (3H, m, H-16, H-18), 1.54 (9H, s, H-1), 1.29 (6H, d, *J* = 6.1 Hz, H-17) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 174.7 (q, C-3), 164.6 (q, C-9), 164.3 (q, C-22), 152.5 (q, C-13), 149.3 (q, C-15), 144.3 (q, C-27), 143.1 (q, C-7), 138.5 (q, C-10), 138.2 (q, C-14), 133.6 (t, C-19), 130.1 (2C, t, C-5, C-5’), 128.4 (q, C-24) 125.9 (q, C-4), 124.4 (t, C-12), 122.2 (2C, t, C-25, C-25’), 118.8 (2C, t, C-6, C-6’), 117.9 (s, C-20), 114.2 (2C, t, C-26, C-26’), 113.6 (t, C-11), 80.3 (q, C-2), 75.7 (t, C-16), 74.0 (s, C-18), 27.9 (3C, p, C-1), 21.9 (2C, p, C-17) ppm; HRMS (ESI): *m/z* calc. for $C_{31}H_{37}N_4O_6$ $[M + H]^+$: 561.2713; found 561.2705.

***tert*-Butyl-4-(2-(allyloxy)-3-isopropoxy-4-(4-nitrobenzamido)-benzamido)-benzoate (S2):** 4-Nitrobenzoyl chloride (3.48 g, 18.7 mmol, 1.6 eq) was added in small portions to a solution of amine **9** (5.00 g, 11.7 mmol, 1.0 eq) and pyridine (3.78 mL, 46.8 mmol, 4.0 eq) in CH_2Cl_2 (80 mL). The reaction was terminated after stirring 1.5 h at rt by addition of an aq. $NaHSO_4$ solution (1 M). The layers were separated and the aq. layer was extracted with CH_2Cl_2 (3x). The combined organic phases were dried over Na_2SO_4, filtered and concentrated *in vacuo* to yield crude nitro compound **S2** (6.66 g, 11.6 mmol, 99%) as a brown oil which was used without further purification in the next step.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-aminobenzamido)-3-isopropoxybenzamido)-benzoate (12):** Zinc (757 mg, 11.6 mmol, 2.0 eq) was added in one portion at rt to a stirred solution of nitro compound **S2** (3.33 g, 5.79 mmol, 1.0 eq) in THF (9.7 mL), EtOH (9.7 mL) and glacial acetic acid (2.0 mL). After stirring vigorously at rt for 30 min, a 3rd and 4th equivalent of zinc were added and the mixture was stirred at rt for another 30 min. This step was repeated twice, after which time the reaction was heated to 70 °C for a period of 30 min and the 9th and 10th equivalent of zinc were added. The mixture was stirred at 70 °C for additional 30 min. The reaction mixture was cooled to rt, diluted with Et_2O and terminated by addition of a sat. aq. $NaHCO_3$ solution. The precipitate was filtered and washed with an excess of Et_2O, the layers were separated, the aq. layer was extracted with Et_2O (3x), washed with brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc= 3:1) yielded the title compound **12** (2.59 g, 4.75 mmol, 82% over two steps) as a yellow solid. T_M = 90 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.2 (1H, s, H-8), 8.65 (1H, s, H-21), 8.49 (1H, d, *J* = 8.9 Hz, H-11), 8.05 (1H, d, *J* = 8.9 Hz, H-12), 7.98 (2H, m, H-5, H-5‘), 7.74 (2H, m, H-24, H-24‘), 7.73 (2H, m, H-6, H-6‘), 6.73 (2H, m, H-25, H-25‘), 6.19 – 6.09 (1H, m, H-19), 5.49 (1H, dq, *J* = 1.4, 17.1 Hz, H-20$_{trans}$), 5.40 (1H, dq, *J* = 1.1, 10.4 Hz, H-20$_{cis}$), 4.73 (1H, hept, *J* = 6.2 Hz, H-16), 4.69 (2H, dt, *J* = 1.2, 5.9 Hz, H-18), 4.11 (2H, br. s, NH_2), 1.60 (9H, s, H-1), 1.38 (6H, d, *J* = 6.2 Hz, H-17) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.6 (q, C-3), 164.8 (q, C-22), 162.9 (q, C-9), 150.5 (q, C-26), 149.4 (q, C-15), 142.4 (q, C-7), 138.9 (q, C-14), 138.2 (q, C-4), 132.4 (t, C-19), 130.8 (2C, t, C-5, C-5’), 129.1 (2C, t, C-24, C-24’), 127.6 (q, C-13), 127.3 (t, C-12), 123.8 (q, C-23), 121.1 (q, C-10), 120.1 (s, C-20), 119.1 (2C, t, C-6, C-6’), 115.7 (t, C-11),

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114.5 (2C, t, C-25, C-25'), 80.9 (q, C-2), 76.7 (t, C-16), 75.0 (s, C-18), 28.4 (3C, p, C-1), 23.0 (2C, p, C-17) ppm; HRMS (ESI): *m/z* calc. for $C_{31}H_{36}N_3O_6$ [M + H]$^+$: 546.2604; found 546.2600.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-((*tert*-butoxycarbonyl)-amino)-3-methoxy-4-oxobutanamido)benzamido)-3-isopropoxybenz-amido)benzoate (S3):** Following to the general procedure III using amine **12** (1.50 g, 2.75 mmol, 1.0 eq) and acid **13** (1.23 g, 4.68 mmol, 1.7 eq) compound **S3** (1.37 g, 1.73 mmol, 63%) was obtained as a yellow amorphous solid. $[\alpha]_D^{22}$ = -0.9° (*c* 1.3, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.5 (1H, s, N*H*), 10.4 (1H, s, N*H*), 9.51 (1H, s, N*H*), 7.98 (2H, m, Ar*H*), 7.90 (2H, m, Ar*H*), 7.84 – 7.80 (5H, m, Ar*H*), 7.45 – 7.40 (3H, m, Ar*H*, NH_2), 6.80 (1H, d, *J* = 8.4 Hz, N*H*Boc), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.37 (1H, dd, *J* = 1.6, 17.1 Hz, C$H_{allyl\text{-}trans}$), 5.20 (1H, dd, *J* = 1.4, 9.8 Hz, C$H_{allyl\text{-}cis}$), 4.61 (2H, d, *J* = 5.4 Hz, OCH_2allyl), 4.50 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.41 (1H, t, *J* = 7.9 Hz, C*H*NH), 3.86 (1H, d, *J* = 7.4 Hz, C*H*OMe), 3.26 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.38 (9H, s, C(CH_3)$_3$), 1.26 (6H, d, *J* = 6.2 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 170.6 (q, CONH$_2$), 168.9 (q, *C*ONH), 164.6 (q, *C*ONH), 164.5 (q, *C*ONH), 164.3 (q, CO$_2$*t*Bu), 154.8 (q, CO$_2$*t*Bu), 149.5 (q, C-Ar), 143.0 (q, C-Ar), 142.5 (q, C-Ar), 142.2 (q, C-Ar), 135.7 (q, C-Ar), 133.6 (t, *C*Hallyl), 130.1 (2C, t, C-Ar), 128.4 (2C, t, C-Ar), 127.0 (q, C-Ar), 126.0 (q, C-Ar), 123.6 (t, C-Ar), 118.9 (t, C-Ar), 118.8 (4C, t, C-Ar), 117.8 (s, *C*H$_2$allyl), 80.3 (t, *C*HOMe), 80.1 (q, *C*(CH$_3$)$_3$), 78.7 (q, *C*(CH$_3$)$_3$), 76.3 (t, *C*H(CH$_3$)$_2$), 74.3 (s, OCH_2allyl), 57.6 (p, OCH$_3$), 56.6 (t, *C*HNH), 28.1 (3C, p, C(CH$_3$)$_3$), 27.8 (3C, p, C(CH$_3$)$_3$), 22.3 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{41}H_{51}N_5O_{11}$Na [M + Na]$^+$: 812.3483; found 812.3480.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutan-amido)-benzamido)-3-isopropoxybenzamido)benzoate (14):** Following the general procedure IV with **S3** (200 mg, 0.25 mmol, 1.0 eq) preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN = 80 : 20 → 0 : 100 in 80 min; t$_r$ = 32 min) provided amine **14** as a yellow amorphous solid (83 mg, 0.12 mmol, 48%). $[\alpha]_D^{23}$ = +3.8° (*c* 1.1, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.5 (1H, s, N*H*), 9.53 (1H, s, N*H*), 7.98 (2H, m, Ar*H*), 7.89 (2H, m, Ar*H*), 7.84 – 7.80 (5H, m, Ar*H*), 7.47 (2H, d, *J* = 70 Hz, NH$_2$), 7.41 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, dd, *J* = 1.7, 17.1 Hz, C$H_{allyl\text{-}trans}$), 5.20 (1H, dd, *J* = 1.5, 9.8 Hz, C$H_{allyl\text{-}cis}$), 4.61 (2H, d, *J* = 5.5 Hz, OCH_2allyl), 4.50 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 3.86 (1H, d, *J* = 6.6 Hz, C*H*OMe), 3.79 (1H, d, *J* = 6.6 Hz, C*H*NH$_2$), 3.31 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.26 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.1 (q, CONH$_2$), 164.6 (q, *C*ONH), 164.5 (q, *C*ONH), 164.3 (q, *C*ONH), 163.0 (q, CO$_2$*t*Bu), 149.5 (q, C-Ar), 143.0 (q, C-Ar), 142.5 (q, C-Ar), 142.0 (q, C-Ar), 135.6 (q, C-Ar), 133.6 (t, *C*Hallyl), 130.1 (2C, t, C-Ar), 128.5 (q, C-Ar), 128.4 (2C, t, C-Ar), 127.1 (q, C-Ar), 126.0 (q, C-Ar), 123.6 (t, C-Ar), 119.0 (t, C-Ar), 118.8 (2C, t, C-Ar), 118.8 (2C, t, C-Ar), 117.8 (s, *C*H$_2$allyl), 82.1 (t, *C*HOMe), 80.3 (q, *C*(CH$_3$)$_3$), 76.2 (t, *C*H(CH$_3$)$_2$), 74.3 (s, OCH_2allyl), 58.0 (p, OCH$_3$), 56.6 (t, *C*HNH$_2$), 27.9 (3C, p, C(CH$_3$)$_3$), 22.3 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{36}H_{43}N_5O_9$Na [M + Na]$^+$: 712.2958; found 712.2960.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-((2*S*,3*R*)-4-amino-2-(4-(3-(4-cyanophenyl)-ureido)-benz-amido)-3-methoxy-4-oxobutanamido)benzamido)-3-iso-propoxybenzamido)benzoate (15):** Following the general procedure II acid **8** (41.8 mg, 149 µmol, 2.5 eq) and amine **14** (41.0 mg, 59.4 µmol, 1.0 eq). provided compound **15** as a colourless solid after preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN = 60 : 40 → 0 : 100 in 80 min; t$_r$ = 67 min) (42.7 mg, 44.8 µmol, 75%).T$_M$ = 226 °C (decomposition); $[\alpha]_D^{22}$ = +34.0° (*c* 4.2, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.5 (1H, s, N*H*), 10.5 (1H, s, N*H*), 9.52 (1H, s, N*H*), 9.51 (1H, s, N*H*$_{Urea}$), 9.38 (1H, s, N*H*$_{Urea}$), 8.37 (1H, d, *J* = 8.1 Hz, N*H*CH), 7.98 (2H, m, Ar*H*), 7.89 (2H, m, Ar*H*), 7.84 – 7.82 (7H, m, Ar*H*), 7.74 (2H, m, Ar*H*), 7.66 (2H, m, Ar*H*), 7.59 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 27.1 Hz, CON*H*$_2$), 7.41 (1H, d, *J* = 8.5 Hz, Ar*H*), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, dq, *J* = 1.6, 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.20 (1H, dq, *J* = 1.3, 10.5 Hz, C$H_{allyl\text{-}cis}$), 4.90 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.61 (2H, d, *J* = 5.4 Hz, OCH_2allyl), 4.50 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.01 (3H, s, OCH_3), 1.54 (9H, s, C(CH_3)$_3$), 1.26 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 170.9 (q, CONH$_2$), 168.8 (q, *C*ONH), 165.5 (q, *C*ONH), 164.6 (q, *C*ONH), 164.5 (q, CO$_2$*t*Bu), 164.3 (q, *C*ONH), 152.0 (q, NH*C*ONH), 149.5 (q, C-Ar), 144.0 (q, C-Ar), 143.0 (q, C-Ar), 142.5 (q, C-Ar), 142.5 (q, C-Ar), 142.2 (q, C-Ar), 135.7 (q, C-Ar), 133.6 (t, *C*Hallyl), 133.3 (2C, t, C-Ar), 130.1 (2C, t, C-Ar), 128.5 (2C, t, C-Ar), 128.5 (t, C-Ar), 128.4 (2C, t, C-Ar), 127.1 (q, C-Ar), 126.0 (q, C-Ar), 123.6 (t, C-Ar), 119.3 (q, CN), 118.9 (2C, t, C-Ar), 118.8 (2C, t, C-Ar), 118.2 (2C, t, C-Ar), 117.8 (s, *C*H$_2$allyl), 117.5 (2C, t, C-Ar), 103.5 (q, C-Ar), 80.3 (q, *C*(CH$_3$)$_3$), 80.0 (t, *C*HOMe), 76.3 (t, *C*H(CH$_3$)$_2$), 74.3 (s, OCH_2allyl), 57.7 (p, OCH$_3$), 55.7 (t, *C*HNH), 27.9 (3C, p, C(CH$_3$)$_3$), 22.3 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{51}H_{52}N_8O_{11}$Na [M + Na]$^+$: 975.3653; found 975.3633.

***tert*-Butyl-4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(3-(4-cyanophenyl)ureido)-benz-amido)-3-methoxy-4-oxobutanamido)benzamido)-2-hydroxy-3-isopropoxy-benzamido)benzoate (S4):** Following to the general procedure VI compound **15** (42.0 mg, 44.1 µmol, 1.0 eq) was used. Preparative HPLC (RP-18; run time 80 min; H$_2$O/MeCN = 70 : 30 → 0 : 100 in 70 min; t$_r$ = 56 min) provided Phenol **S4** as a colourless amorphous solid (29.8 mg, 32.6 µmol, 74%). $[\alpha]_D^{21}$ = +29.3° (*c* 1.2, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.4 (1H, br. s, O*H*), 10.8 (1H, br. s, N*H*), 10.6 (1H, s, N*H*), 9.40 (1H, s, N*H*), 9.38 (1H, s, N*H*$_{Urea}$), 9.28 (1H, s, N*H*$_{Urea}$), 8.38 (1H, d, *J* = 8.1 Hz, N*H*CH), 7.96 (2H, m, Ar*H*), 7.92 (2H, m, Ar*H*), 7.86 – 7.82 (7H, m, Ar*H*), 7.74 (2H, m, Ar*H*), 7.70 (1H, d, *J* = 8.9 Hz, Ar*H*), 7.66 (2H, m, Ar*H*), 7.59 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 26.5 Hz, CON*H*$_2$), 4.91 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.56 (1H, hept, *J* = 6.2 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.31 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.27 (6H, d, *J* = 6.2 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 170.9 (q, CONH$_2$), 168.8 (q, *C*ONH), 168.4 (q, *C*ONH), 165.5 (q, *C*ONH), 164.6 (q, CO$_2$*t*Bu), 164.2 (q, *C*ONH), 154.5 (q, C-Ar), 152.0 (q, NH*C*ONH), 144.0 (q, C-Ar), 142.4 (q, C-Ar), 142.3 (q, C-Ar), 142.1 (q, C-Ar), 137.0 (q, C-Ar), 136.3 (q, C-Ar), 133.3 (2C, t, C-Ar), 129.9 (2C, t, C-Ar), 128.5 (2C, t, C-Ar), 128.3 (2C, t, C-Ar), 127.1 (q, C-Ar), 126.7 (q, C-Ar), 122.9 (t, C-Ar), 120.6 (2C, t, C-Ar), 119.3 (q, CN), 119.0 (2C, t, C-Ar), 118.2 (2C, t, C-Ar), 117.5 (2C, t, C-Ar), 112.5 (t, C-Ar), 111.8 (q, C-Ar), 103.5 (q, C-Ar), 80.5 (q, *C*(CH$_3$)$_3$), 80.0 (t, *C*HOMe), 74.7 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.8 (t, *C*HNH), 27.9 (3C, p, C(CH$_3$)$_3$), 22.3 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{48}H_{48}N_8O_{11}$Na [M + Na]$^+$: 935.3340; found 935.3342.

4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(3-(4-cyanophenyl)ureido)benzamido)-3-methoxy-4-oxo-butanamido)benzamido)-2-hydroxy-3-isopropoxybenz-amido)benzoic acid (16): Following to the general procedure V phenol **S4** (29.8 mg, 32.6 µmol, 1.0 eq) was stirred for 5.5 h. Acid **16** was obtained as a colourless amorphous solid (22.5 mg, 26.3 µmol, 81%). $[\alpha]_D^{22}$ = +23.1° (*c* 1.1, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.3 (1H, br. s, O*H*), 10.6 (1H, br. s, N*H*), 10.6 (1H, s, N*H*), 9.40 (1H, s, N*H*), 9.38 (1H, s, N*H*$_{Urea}$), 9.26 (1H, s, N*H*$_{Urea}$), 8.37 (1H, d, *J* = 8.1 Hz, N*H*CH), 7.98 – 7.95 (4H, m, Ar*H*), 7.88 – 7.82 (7H, m, Ar*H*), 7.76 – 7.70 (3H, m, Ar*H*), 7.66 (2H, m, Ar*H*), 7.58 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 26.7 Hz, CON*H*$_2$), 4.90 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.55 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.31 (3H, s, OCH_3), 1.27 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 170.9 (q, CONH$_2$), 168.8 (q, *C*ONH), 168.5 (q, *C*ONH), 166.9 (q, *C*O$_2$H), 165.5 (q, *C*ONH), 164.2 (q, *C*ONH), 154.1 (q, C-Ar), 151.9 (q, NH*C*ONH), 144.0 (q, C-Ar), 142.4 (q, C-Ar), 142.3 (q, C-Ar), 142.0 (q, C-Ar), 137.0 (q, C-Ar), 136.3 (q, C-Ar), 133.3 (2C, t, C-Ar), 130.2 (2C, t, C-Ar), 128.5 (2C, t, C-Ar), 128.5 (q, C-Ar), 128.3 (2C, t, C-Ar), 127.1 (q, C-Ar), 126.3 (q, C-Ar), 122.8 (t, C-Ar), 120.7 (2C, t, C-Ar), 119.3 (q, CN), 119.0 (2C, t, C-Ar), 118.2 (2C, t, C-Ar), 117.5 (2C, t, C-Ar), 112.4 (t, C-Ar), 112.2 (q, C-Ar), 103.5 (q, C-Ar), 80.0 (t, *C*HOMe), 74.9 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.7 (t, *C*HNH), 22.3 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{44}H_{41}N_8O_{11}$ [M + H]$^+$: 857.2895; found 857.2896.

***tert*-Butyl-4-(2-(allyloxy)-4-(3-(4-((2*S*,3*R*)-4-amino-2-((*tert*-butoxycarbonyl)-amino)-3-methoxy-4-oxobutanamido)phenyl)ureido)-3-isopropoxybenz-amido)benzoate (17):** Following the general procedure III using amine **11** (234 mg, 417 µmol, 1.0 eq) and acid **13** (186 mg, 710 µmol, 1.7 eq) compound **17** (229 mg, 284 mmol, 68%) was obtained as a yellow solid. T$_M$ = 168 °C; $[\alpha]_D^{21}$ = -7.0° (*c* 0.9, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.4 (1H, s, N*H*), 9.94 (1H, s, N*H*), 9.52 (1H, s, N*H*$_{Urea}$), 8.30 (1H, s, N*H*$_{Urea}$), 8.11 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.88 (2H, m, Ar*H*), 7.81 (2H, m, Ar*H*), 7.57 (2H, m, Ar*H*), 7.42 – 7.38 (5H, m, Ar*H*, NH$_2$), 6.70 (1H, d, *J* = 8.3 Hz, N*H*Boc), 6.05 – 5.98 (1H, m, CH_{allyl}), 5.40 (1H, dd, *J* = 1.6, 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.22 (1H, dd, *J* = 1.4, 9.3 Hz, C$H_{allyl\text{-}cis}$), 4.64 – 4.58 (3H, m, OCH_2allyl, C*H*Me$_2$), 4.35 (1H, t, *J* = 8.5 Hz, C*H*NH), 3.83 (1H, d, *J* = 7.4 Hz, C*H*OMe), 3.25 (3H, s, OCH_3), 1.54 (9H, s, C(CH_3)$_3$), 1.38 (9H, s, C(CH_3)$_3$), 1.33 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 170.8 (q, CONH$_2$), 167.8 (q, *C*ONH), 164.6 (2C, q, *C*ONH), 164.3 (q, CO$_2$*t*Bu), 152.0 (q, NH*C*ONH), 149.3 (q, C-Ar), 143.1 (q, C-Ar), 138.4 (q, C-Ar), 137.8 (q, C-Ar), 135.0 (q, C-Ar), 133.6 (t, *C*Hallyl), 130.1 (2C, t, C-Ar), 125.9 (q, C-Ar), 124.5 (t, C-Ar), 124.4 (q, C-Ar), 123.0 (q, C-Ar), 120.1 (2C, t, C-Ar), 118.8 (2C, t, C-Ar), 118.6 (2C, t, C-Ar), 117.9 (s, *C*H$_2$allyl), 113.7 (t, C-Ar), 80.3 (t, *C*HOMe), 78.6 (2C, q, *C*(CH$_3$)$_3$), 75.9 (t, *C*H(CH$_3$)$_2$), 74.1 (s, OCH_2allyl), 57.6 (p, OCH$_3$), 56.5 (t, *C*HNH), 28.1 (3C, p, C(CH$_3$)$_3$), 27.9 (3C, p, C(CH$_3$)$_3$), 21.9 (2C, p, CH(CH$_3$)$_2$) ppm; **HRMS** (ESI): *m/z* calc. for $C_{41}H_{53}N_6O_{11}$ [M + H]$^+$: 805.3772; found 805.3772.

***tert*-Butyl-4-(2-(allyloxy)-4-(3-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido)-phenyl)ureido)-3-isopropoxybenzamido)benzoate (18):** Following to the general procedure IV compound **17** (178 mg, 0.22 mmol, 1.0 eq) was used. Preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN =

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70 : 30 → 0 : 100 in 80 min; t_r = 26 min) provided amine **18** as a yellow amorphous solid (76.2 mg, 0.11 mmol, 49%). $[\alpha]_D^{21}$ = +4.1° (*c* 1.1, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.4 (1H, s, N*H*), 9.87 (1H, br. s, N*H*), 9.59 (1H, s, NH_{Urea}), 8.33 (1H, s, NH_{Urea}), 8.11 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.88 (2H, m, Ar*H*), 7.81 (2H, m, Ar*H*), 7.58 (2H, m, Ar*H*), 7.43 – 7.41 (3H, m, Ar*H*), 7.36 (2H, d, *J* = 80.3 Hz, CONH_2), 6.07 – 5.98 (1H, m, CH_{allyl}), 5.40 (1H, dd, *J* = 1.6, 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.22 (1H, dd, *J* = 1.4, 9.3 Hz, C$H_{allyl\text{-}cis}$), 4.65 – 4.59 (3H, m, OCH_2allyl, C*H*Me$_2$), 3.76 (1H, d, *J* = 6.8 Hz, C*H*OMe), 3.59 (1H, d, *J* = 6.8 Hz, C*H*NH$_2$), 3.37 (2H, br. s, NH_2), 3.28 (3H, s, OCH_3), 1.54 (9H, s, C(CH_3)$_3$), 1.33 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.7 (q, CONH_2), 170.7 (q, *C*ONH), 164.6 (q, CO$_2$*t*Bu), 164.3 (q, *C*ONH), 152.1 (q, NH*C*ONH), 149.3 (q, C-Ar), 143.1 (q, C-Ar), 138.4 (q, C-Ar), 137.8 (q, C-Ar), 134.9 (q, C-Ar), 133.7 (q, C-Ar), 133.6 (t, *C*Hallyl), 130.1 (2C, t, C-Ar), 125.9 (q, C-Ar), 124.5 (t, C-Ar), 122.9 (q, C-Ar), 119.9 (2C, t, C-Ar), 118.8 (2C, t, C-Ar), 118.7 (2C, t, C-Ar), 117.9 (s, CH$_2$allyl), 113.7 (t, C-Ar), 83.2 (t, *C*HOMe), 80.3 (q, *C*(CH$_3$)$_3$), 75.9 (t, *C*H(CH$_3$)$_2$), 74.1 (s, OCH_2allyl), 57.8 (p, OCH$_3$), 57.1 (t, *C*HNH$_2$), 27.9 (3C, p, C(CH_3)$_3$), 21.9 (2C, p, CH(CH_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{36}H_{45}N_6O_9$ [M + H]$^+$: 705.3248; found 705.3242.

4-(2-(Allyloxy)-4-(3-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido)-phenyl)-ureido)-3-isopropoxybenzamido)benzoic acid (S5): Ester **17** (80 mg, 99.4 µmol, 1.0 eq) was added in small portions to 4 N HCl in 1,4-dioxane (2.48 mL, 9.94 mmol, 100 eq) and stirred for 30 min at rt. The mixture was slowly transferred to a mixture of EtOAc and a 80 % sat. aq. $NaHCO_3$ solution (400 mL, 1:1). The layers were separated, the aq. layer was extracted with EtOAc (3x 100 mL), the combined organic phases were washed with brine (150 mL), dried over Na_2SO_4, filtered and concentrated *in vacuo*. Preparative HPLC (RP-18; run time 100 min; H_2O/MeCN = 95 : 05 → 0 : 100 in 90 min; t_r = 30 min) provided acid **S5** as a yellow amorphous solid (57.3 mg, 88.4 µmol, 89%). $[\alpha]_D^{22}$ = +7.0° (*c* 0.9, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.4 (1H, s, N*H*), 9.87 (1H, br. s, N*H*), 9.56 (1H, s, NH_{Urea}), 8.31 (1H, s, NH_{Urea}), 8.11 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.92 (2H, m, Ar*H*), 7.81 (2H, m, Ar*H*), 7.58 (2H, m, Ar*H*), 7.42 – 7.40 (3H, m, Ar*H*), 7.37 (2H, d, *J* = 80.7 Hz, CONH_2), 6.08 – 5.99 (1H, m, CH_{allyl}), 5.40 (1H, dd, *J* = 1.7, 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.23 (1H, dd, *J* = 1.4, 10.4 Hz, C$H_{allyl\text{-}cis}$), 4.64 – 4.59 (3H, m, OCH_2allyl, C*H*Me$_2$), 3.76 (1H, d, *J* = 6.8 Hz, C*H*OMe), 3.60 (1H, d, *J* = 6.8 Hz, C*H*NH$_2$), 3.27 (3H, s, OCH_3), 1.33 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.7 (q, *C*ONH$_2$), 170.7 (q, *C*ONH), 167.1 (q, *C*O$_2$H), 164.3 (q, *C*ONH), 152.1 (q, NH*C*ONH), 149.3 (q, C-Ar), 142.9 (q, C-Ar), 138.5 (q, C-Ar), 137.8 (q, C-Ar), 134.9 (q, C-Ar), 133.7 (q, C-Ar), 133.6 (t, *C*Hallyl), 130.4 (2C, t, C-Ar), 125.8 (q, C-Ar), 124.5 (t, C-Ar), 123.1 (q, C-Ar), 119.9 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.7 (2C, t, C-Ar), 117.9 (s, *C*H$_2$allyl), 113.7 (t, C-Ar), 83.2 (t, *C*HOMe), 76.0 (t, *C*H(CH$_3$)$_2$), 74.1 (s, OCH_2allyl), 57.8 (p, OCH$_3$), 57.1 (t, *C*HNH$_2$), 22.0 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{32}H_{37}N_6O_9$ [M + H]$^+$: 649.2622; found 649.2624.

4-(4-(3-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido)phenyl)-ureido)-2-hydroxy-3-isopropoxybenzamido)benzoic acid (25): Following to the general procedure VI compound **S5** (10.0 mg, 15.4 µmol, 1.0 eq) provided phenol **25** as a colourless amorphous solid (6.5 mg, 10.7 µmol, 69%). Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 95 : 05 → 0 : 100 in 60 min; t_r = 21 min). $[\alpha]_D^{23}$ = +24.1° (*c* 0.7, MeOH); ^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 9.83 (1H, br. s, CO$_2$*H*), 9.55 (1H, s, N*H*), 8.34 (2H, br. s, NH_{Urea}), 8.09 (1H, s, N*H*), 7.87 (2H, m, Ar*H*), 7.76 (2H, m, Ar*H*), 7.57 – 7.54 (3H, m, Ar*H*), 7.46 – 7.43 (2H, m, Ar*H*, CONH_2), 7.40 (2H, m, Ar*H*), 7.24 (1H, s, CONH_2), 4.79 (1H, hept, *J* = 6.5 Hz, C*H*Me$_2$), 3.74 (1H, d, *J* = 7.0 Hz, C*H*OMe), 3.57 (1H, d, *J* = 7.0 Hz, C*H*NH$_2$), 3.27 (3H, s, OCH_3), 1.25 (6H, d, *J* = 6.5 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.8 (q, *C*ONH$_2$), 170.8 (q, *C*ONH), 168.0 (q, *C*O$_2$H), 164.8 (q, *C*ONH), 152.2 (q, NH*C*ONH), 143.5 (q, C-Ar), 137.4 (q, C-Ar), 135.3 (q, C-Ar), 134.5 (q, C-Ar), 133.9 (q, C-Ar), 133.9 (q, C-Ar), 130.4 (q, C-Ar), 130.2 (2C, t, C-Ar), 123.4 (t, C-Ar), 119.8 (2C, t, C-Ar), 119.2 (2C, t, C-Ar), 118.5 (2C, t, C-Ar), 112.0 (q, C-Ar), 104.0 (t, C-Ar), 83.3 (t, *C*HOMe), 72.0 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 57.1 (t, *C*HNH$_2$), 22.1 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{29}H_{32}N_6O_9Na$ [M + Na]$^+$: 631.2128; found 631.2127.

***tert*-Butyl-4-(2-(allyloxy)-4-(3-(4-((2*S*,3*R*)-4-amino-3-methoxy-2-(4-(4-nitro-benzamido)-benzamido)-4-oxobutanamido)phenyl)ureido)-3-isopropoxy-benzamido)benzoate (21):** Following the general procedure II acid **19** (31.0 mg, 108 µmol, 2.5 eq) and amine **18** (31.0 mg, 44.0 µmol, 1.0 eq) provided phenol **S7** as a grey amorphous solid (15.8 mg, 17.3 µmol, 61%). Preparative HPLC (RP-18; run time 100 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 57 min) provided compound **21** as a colourless solid (25.2 mg, 25.9 µmol, 59%). T_M = 230 °C (decomposition); $[\alpha]_D^{21}$ = +46.1° (*c* 0.9, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.8 (1H, s, N*H*), 10.4 (1H, s, N*H*), 10.2 (1H, s, N*H*), 9.67 (1H, s, NH_{Urea}), 8.43 – 8.35 (4H, m, Ar*H*, NH_{Urea}, N*H*CH), 8.22 (2H, m, Ar*H*), 8.11 (1H, d, *J* = 8.7 Hz, Ar*H*), 7.91 – 7.87 (6H, m, Ar*H*), 7.81 (2H, m, Ar*H*), 7.61 – 7.55 (3H, m, Ar*H*, CONH_2), 7.44 – 7.40 (4H, m, Ar*H*, CONH_2), 6.06 – 5.98 (1H, m, CH_{allyl}), 5.40 (1H, dd, *J* = 1.4, 17.3 Hz, C$H_{allyl\text{-}trans}$), 5.22 (1H, dd, *J* = 1.1, 9.2 Hz, C$H_{allyl\text{-}cis}$), 4.89 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.63 – 4.59 (3H, m, OCH_2allyl, C*H*Me$_2$), 4.09 (1H, d, *J* = 7.9 Hz, C*H*OMe), 3.31 (3H, s, OCH_3), 1.54 (9H, s, C(CH_3)$_3$), 1.33 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.1 (q, CONH_2), 167.6 (q, *C*ONH), 165.3 (q, *C*ONH), 164.6 (q, CO$_2$*t*Bu), 164.3 (q, *C*ONH), 164.2 (q, *C*ONH), 152.1 (q, NH*C*ONH), 149.3 (q, C-Ar), 143.1 (q, C-Ar), 141.7 (q, C-Ar), 140.7 (q, C-Ar), 138.4 (q, C-Ar), 137.9 (q, C-Ar), 135.1 (q, C-Ar), 133.6 (t, *C*Hallyl), 130.1 (2C, t, C-Ar), 129.4 (2C, t, C-Ar), 129.1 (q, C-Ar), 128.3 (2C, t, C-Ar), 125.9 (q, C-Ar), 124.5 (t, C-Ar), 123.6 (2C, t, C-Ar), 122.9 (q, C-Ar), 120.1 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.8 (2C, t, C-Ar), 118.6 (2C, t, C-Ar), 117.9 (s, *C*H$_2$allyl), 113.7 (t, C-Ar), 80.3 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 75.9 (t, *C*H(CH$_3$)$_2$), 74.1 (s, OCH_2allyl), 57.7 (p, OCH$_3$), 55.6 (t, *C*HNH), 27.9 (3C, p, C(CH_3)$_3$), 21.9 (2C, p, CH(CH_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{50}H_{52}N_8O_{13}Na$ [M + Na]$^+$: 995.3552; found 995.3553.

***tert*-Butyl-4-(2-(allyloxy)-4-(3-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)ureido)-3-isopropoxy-benzamido)benzoate (22):** Following the general procedure II acid **20** (34.5 mg, 129 µmol, 2.5 eq) and amine **18** (36.5 mg, 51.8 µmol, 1.0 eq) provided compound **22** as a colourless solid (26.6 mg, 27.9 µmol, 54%). Preparative HPLC (RP-18; run time 100 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 56 min). T_M = 239 °C (decomposition); $[\alpha]_D^{23}$ = +24.4° (*c* 1.2, MeOH); ^{1}H-NMR (600 MHz, DMSO-d$_6$): δ = 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 10.1 (1H, s, N*H*), 9.54 (1H, s, NH_{Urea}), 8.39 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.31 (1H, s, NH_{Urea}), 8.13 – 8.10 (3H, m, Ar*H*), 8.04 (2H, m, Ar*H*), 7.94 – 7.81 (6H, m, Ar*H*), 7.81 (2H, m, Ar*H*), 7.60 (2H, m, Ar*H*), 7.53 (1H, s, CONH_2), 7.44 – 7.40 (4H, m, Ar*H*, CONH_2), 6.05 – 6.00 (1H, m, CH_{allyl}), 5.40 (1H, dq, *J* = 1.6, 17.1 Hz, C$H_{allyl\text{-}trans}$), 5.22 (1H, dq, *J* = 1.3, 10.4 Hz, C$H_{allyl\text{-}cis}$), 4.88 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.63 – 4.59 (3H, m, OCH_2allyl, C*H*Me$_2$), 4.07 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.30 (3H, s, OCH_3), 1.54 (9H, s, C(CH_3)$_3$), 1.33 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.1 (q, CONH_2), 167.6 (q, *C*ONH), 165.3 (q, *C*ONH), 164.6 (q, CO$_2$*t*Bu), 164.5 (q, *C*ONH), 164.3 (q, *C*ONH), 152.0 (q, NH*C*ONH), 149.3 (q, C-Ar), 143.1 (q, C-Ar), 141.7 (q, C-Ar), 138.7 (q, C-Ar), 138.4 (q, C-Ar), 137.8 (q, C-Ar), 135.0 (q, C-Ar), 133.6 (t, *C*Hallyl), 132.5 (2C, t, C-Ar), 130.1 (2C, t, C-Ar), 129.0 (q, C-Ar), 128.6 (2C, t, C-Ar), 128.2 (2C, t, C-Ar), 125.9 (q, C-Ar), 124.5 (t, C-Ar), 123.0 (q, C-Ar), 120.1 (2C, t, C-Ar), 119.6 (2C, t, C-Ar), 118.8 (2C, t, C-Ar), 118.6 (2C, t, C-Ar), 118.3 (q, C-Ar), 117.9 (s, *C*H$_2$allyl), 117.3 (q, CN), 114.0 (q, C-Ar), 113.7 (t, C-Ar), 80.3 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 75.9 (t, *C*H(CH$_3$)$_2$), 74.1 (s, OCH_2allyl), 57.7 (p, OCH$_3$), 55.5 (t, *C*HNH), 27.9 (3C, p, C(CH$_3$)$_3$), 22.0 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{51}H_{53}N_8O_{11}$ [M + H]$^+$: 953.3834; found 953.3840.

***tert*-Butyl-4-(4-(3-(4-((2*S*,3*R*)-4-amino-3-methoxy-2-(4-(4-nitrobenzamido)-benzamido)-4-oxobutanamido)phenyl)ureido)-2-hydroxy-3-isopropoxy-benzamido)benzoate (S6):** Following the general procedure VI compound **21** (25.0 mg, 25.7 µmol, 1.0 eq) provided phenol **S6** as a yellow amorphous solid (11.5 mg, 12.3 µmol, 48%). Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 90 : 10 → 0 : 100 in 70 min; t_r = 61 min). $[\alpha]_D^{24}$ = +130.6° (*c* 0.9, MeCN); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.5 (1H, s, O*H*), 10.8 (1H, s, N*H*), 10.6 (1H, s, N*H*), 10.2 (1H, s, N*H*), 9.61 (1H, s, NH_{urea}), 8.39 – 8.37 (3H, m, Ar*H*, N*H*CH), 8.33 (1H, s, NH_{urea}), 8.21 (2H, m, Ar*H*), 7.92 – 7.79 (10H, m, Ar*H*), 7.60 (2H, m, Ar*H*), 7.53 (1H, s, CONH_2), 7.44 – 7.41 (3H, m, Ar*H*, CONH_2), 4.89 (1H, t, *J* = 8.0 Hz, C*H*NH), 4.63 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.07 (1H, d, *J* = 8.0 Hz, C*H*OMe), 3.31 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.30 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.1 (q, CONH_2), 169.0 (q, *C*ONH), 167.6 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO$_2$*t*Bu), 164.2 (q, *C*ONH), 151.9 (q, NH*C*ONH), 149.3 (q, C-Ar), 142.1 (q, C-Ar), 141.7 (q, C-Ar), 140.3 (q, C-Ar), 139.0 (q, C-Ar), 135.0 (q, C-Ar), 133.6 (q, C-Ar), 132.9 (q, C-Ar), 129.9 (2C, t, C-Ar), 129.4 (2C, t, C-Ar), 129.1 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.7 (q, C-Ar), 123.6 (2C, t, C-Ar), 123.0 (t, C-Ar), 120.7 (2C, t, C-Ar), 120.2 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.7 (2C, t, C-Ar), 109.3 (t, C-Ar), 80.5 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 74.2 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.5 (t, *C*HNH), 27.9 (3C, p, C(CH$_3$)$_3$), 22.0 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{47}H_{47}N_8O_{13}$ [M – H]$^-$: 931.3268; found 931.3262.

***tert*-Butyl-4-(4-(3-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)phenyl)ureido)-2-hydroxy-3-isopropoxybenz-amido)benzoate (S7):** Following the general procedure VI compound **22** (26.0 mg, 27.3 µmol, 1.0 eq) was used. Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 26 min) $[\alpha]_D^{25}$ = +66.7° (*c* 0.8, MeOH); ^{1}H-NMR (600 MHz, DMSO-d$_6$): δ = 12.5 (1H, br. s, O*H*), 10.7 (1H, s, N*H*), 10.5 (1H, s, N*H*), 10.1 (1H, s, N*H*), 9.62 (1H, s, NH_{urea}), 8.39 (1H, d,

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J = 8.1 Hz, N*H*CH), 8.34 (1H, s, N*H*$_{urea}$), 8.13 (2H, m, Ar*H*), 8.04 (2H, m, Ar*H*), 7.93 – 7.87 (7H, m, Ar*H*), 7.84 (2H, m, Ar*H*), 7.81 (1H, d, *J* = 9.3 Hz, Ar*H*), 7.60 (2H, m, Ar*H*), 7.53 (1H, s, CON*H*$_2$), 7.44 – 7.42 (3H, m, Ar*H*, CON*H*$_2$), 4.89 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.63 (1H, hept, *J* = 6.2 Hz, C*H*Me$_2$), 4.07 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.31 (3H, s, OC*H*$_3$), 1.55 (9H, s, C(C*H*$_3$)$_3$), 1.30 (6H, d, *J* = 6.2 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.1 (q, CONH$_2$), 169.0 (q, *C*ONH), 167.6 (q, *C*ONH), 165.3 (q, *C*ONH), 164.6 (q, CO$_2$*t*Bu), 164.5 (q, *C*ONH), 154.4 (q, C-Ar), 151.9 (q, NH*C*ONH), 142.1 (q, C-Ar), 141.7 (q, C-Ar), 139.1 (q, C-Ar), 138.7 (q, C-Ar), 135.0 (q, C-Ar), 133.6 (q, C-Ar), 132.8 (q, C-Ar), 132.5 (2C, t, C-Ar), 129.9 (2C, t, C-Ar), 129.0 (q, C-Ar), 128.6 (2C, t, C-Ar), 128.2 (2C, t, C-Ar), 126.7 (q, C-Ar), 123.0 (t, C-Ar), 120.7 (2C, t, C-Ar), 120.1 (2C, t, C-Ar), 119.6 (2C, t, C-Ar), 118.6 (2C, t, C-Ar), 118.3 (q, CN), 114.0 (q, C-Ar), 109.2 (q, C-Ar), 108.1 (t, C-Ar), 80.5 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 74.2 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.5 (t, *C*HNH), 27.8 (3C, p, C(CH$_3$)$_3$), 21.9 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{48}H_{48}N_8O_{11}Na$ [M + Na]$^+$: 935.3340; found 935.3339.

4-(4-(3-(4-((2*S*,3*R*)-4-Amino-3-methoxy-2-(4-(4-nitrobenzamido)benzamido)-4-oxobutan-amido)phenyl)ureido)-2-hydroxy-3-isopropoxybenzamido)-benzoic acid (23): Following the general procedure V phenol **S6** (9.0 mg, 9.64 µmol, 1.0 eq) was stirred for 6 h. Acid **23** was obtained as a colourless amorphous solid (5.8 mg, 6.62 µmol, 69%). $[\alpha]_D^{24}$ = +38.7° (*c* 0.6, DMSO); ^{1}H-NMR (500 MHz, DMSO-d$_6$ +2 µL DCO$_2$D): δ = 10.8 (1H, s, N*H*), 10.6 (1H, br. s, N*H*), 10.2 (1H, s, N*H*), 9.61 (1H, s, N*H*$_{Urea}$), 8.40 – 8.37 (3H, m, Ar*H*, N*H*CH), 8.33 (1H, s, N*H*$_{Urea}$), 8.20 (2H, m, Ar*H*), 7.96 (2H, m, Ar*H*), 7.92 – 7.84 (5H, m, Ar*H*), 7.84 (2H, m, Ar*H*), 7.80 (1H, d, *J* = 8.5 Hz, Ar*H*), 7.60 (2H, m, Ar*H*), 7.49 (2H, d, *J* = 46.1 Hz, CON*H*$_2$), 7.42 (2H, m, Ar*H*), 4.89 (1H, t, *J* = 8.5 Hz, C*H*NH), 4.63 (1H, hept, *J* = 6.0 Hz, C*H*Me$_2$), 4.07 (1H, d, *J* = 7.3 Hz, C*H*OMe), 3.30 (3H, s, OC*H*$_3$), 1.30 (6H, d, *J* = 6.0 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$ +2 µL DCO$_2$D): δ = 171.1 (q, CONH$_2$), 169.0 (q, *C*ONH), 167.6 (q, *C*ONH), 167.0 (q, *C*O$_2$H), 165.4 (q, *C*ONH), 164.3 (q, *C*ONH), 154.5 (q, C-Ar), 152.0 (q, NH*C*ONH), 149.3 (q, C-Ar), 142.1 (q, C-Ar), 141.7 (q, C-Ar), 140.4 (q, C-Ar), 139.1 (q, C-Ar), 135.0 (q, C-Ar), 133.7 (q, C-Ar), 132.9 (q, C-Ar), 130.2 (2C, t, C-Ar), 129.4 (2C, t, C-Ar), 129.2 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.2 (q, C-Ar), 123.6 (2C, t, C-Ar), 123.1 (t, C-Ar), 120.8 (2C, t, C-Ar), 120.2 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.7 (2C, t, C-Ar), 109.3 (q, C-Ar), 108.2 (t, C-Ar), 80.2 (t, *C*HOMe), 74.2 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.6 (t, *C*HNH), 22.0 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{43}H_{40}N_8O_{13}Na$ [M + Na]$^+$: 899.2613; found 899.2613.

4-(4-(3-(4-((2*S*,3*R*)-4-Amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxo-butanamido)phenyl)ureido)-2-hydroxy-3-isopropoxybenz-amido)benzoic acid (24): Following the general procedure V phenol **S7** (14.0 mg, 15.3 µmol, 1.0 eq) was stirred for 30 min. Acid **24** was obtained as a yellow amorphous solid (13.0 mg, 15.2 µmol, 99%). $[\alpha]_D^{23}$ = +37.2° (*c* 0.3, DMSO); ^{1}H-NMR (500 MHz, DMSO-d$_6$ +2 µL DCO$_2$D): δ = 12.5 (1H, s, O*H*), 10.7 (1H, s, N*H*), 10.5 (1H, s, N*H*), 10.1 (1H, s, N*H*), 9.61 (1H, s, N*H*$_{Urea}$), 8.38 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.34 (1H, s, N*H*$_{Urea}$), 8.13 (2H, m, Ar*H*), 8.04 (2H, m, Ar*H*), 7.96 (2H, m, Ar*H*), 7.91 – 7.83 (7H, m, Ar*H*), 7.81 (1H, d, *J* = 9.2 Hz, Ar*H*), 7.60 (2H, m, Ar*H*), 7.52 – 7.41 (4H, m, Ar*H*, CON*H*$_2$), 4.88 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.62 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.06 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.30 (3H, s, OC*H*$_3$), 1.30 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$ +2 µL DCO$_2$D): δ = 171.1 (q, CONH$_2$), 169.0 (q, *C*ONH), 167.6 (q, *C*ONH), 166.9 (q, *C*O$_2$H), 165.3 (q, *C*ONH), 164.5 (q, *C*ONH), 154.3 (q, C-Ar), 151.9 (q, NH*C*ONH), 142.0 (q, C-Ar), 141.7 (q, C-Ar), 139.1 (q, C-Ar), 138.7 (q, C-Ar), 134.9 (q, C-Ar), 133.7 (q, C-Ar), 132.5 (2C, t, C-Ar), 130.2 (2C, t, C-Ar), 129.0 (q, C-Ar), 128.6 (2C, t, C-Ar), 128.3 (2C, t, C-Ar), 126.1 (q, C-Ar), 123.0 (t, C-Ar), 120.8 (2C, t, C-Ar), 120.6 (q, C-Ar), 120.1 (2C, t, C-Ar), 119.6 (2C, t, C-Ar), 118.7 (2C, t, C-Ar), 118.3 (q, CN), 114.1 (q, C-Ar), 109.2 (q, C-Ar), 108.2 (t, C-Ar), 80.1 (t, *C*HOMe), 74.3 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.5 (t, *C*HNH), 21.9 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{44}H_{40}N_8O_{11}Na$ [M + Na]$^+$: 879.2714; found 879.2714.

***tert*-Butyl-4-(2-(allyloxy)-4-(3-(4-((2*S*,3*R*)-4-amino-2-(4-(3-(4-cyanophenyl)-ureido)-benz-amido)-3-methoxy-4-oxobutanamido)phenyl)ureido)-3-iso-propoxybenzamido)-benzoate (26):** Following the general procedure II acid **8** (26.0 mg, 92.2 µmol, 2.5 eq) and amine **18** (26.0 mg, 36.9 µmol, 1.0 eq) provided compound **26** as a colourless solid (27.0 mg, 27.9 µmol, 76%). Preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN = 70 : 30 → 0 : 100 in 80 min; t$_r$ = 56 min). T$_M$ = 203 °C (decomposition); $[\alpha]_D^{24}$ = +40.0° (*c* 0.8, MeOH); ^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 10.4 (1H, s, N*H*), 10.1 (1H, s, N*H*), 9.52 (1H, s, N*H*$_{urea}$), 9.43 (1H, s, N*H*$_{urea}$), 9.30 (1H, s, N*H*$_{urea}$), 8.31 – 8.30 (2H, m, N*H*$_{urea}$, N*H*CH), 8.11 (1H, d, *J* = 8.8 Hz, Ar*H*), 7.88 (2H, m, Ar*H*), 7.82 – 7.80 (4H, m, Ar*H*), 7.74 (2H, m, Ar*H*), 7.65 (2H, m, Ar*H*), 7.60 – 7.57 (4H, m, Ar*H*), 7.51 (1H, s, CON*H*$_2$), 7.43 – 7.40 (4H, m, Ar*H*, CON*H*$_2$), 6.07 – 5.99 (1H, m, C*H*$_{allyl}$), 5.40 (1H, dd, *J* = 1.7, 17.2 Hz, C*H*$_{allyl\text{-}trans}$), 5.22 (1H, dd, *J* = 1.5, 10.5 Hz, C*H*$_{allyl\text{-}cis}$), 4.86 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.64 – 4.59 (3H, m, OC*H*$_2$allyl, C*H*Me$_2$), 4.06 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.30 (3H, s, OC*H*$_3$), 1.54 (9H, s, C(C*H*$_3$)$_3$), 1.32 (6H, d, *J* = 6.2 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.1 (q, CONH$_2$), 167.7 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, *C*ONH), 164.3 (q, CO$_2$*t*Bu), 152.0 (q, NH*C*ONH), 152.0 (q, NH*C*ONH), 149.3 (q, C-Ar), 144.0 (q, C-Ar), 143.1 (q, C-Ar), 142.4 (q, C-Ar), 138.4 (q, C-Ar), 137.8 (q, C-Ar), 135.0 (q, C-Ar), 133.6 (q, C-Ar), 133.6 (t, *C*Hallyl), 133.3 (2C, t, C-Ar), 130.1 (2C, t, C-Ar), 128.5 (2C, t, C-Ar), 127.2 (q, C-Ar), 125.9 (q, C-Ar), 124.4 (t, C-Ar), 123.0 (q, C-Ar), 120.1 (2C, t, C-Ar), 119.3 (q, CN), 118.8 (2C, t, C-Ar), 118.6 (2C, t, C-Ar), 118.2 (2C, t, C-Ar), 117.9 (s, *C*H$_2$allyl), 117.5 (2C, t, C-Ar), 113.7 (t, C-Ar), 103.5 (q, C-Ar), 80.3 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 75.9 (t, *C*H(CH$_3$)$_2$), 74.1 (s, OC*H*$_2$allyl), 57.7 (p, OCH$_3$), 55.5 (t, *C*HNH), 27.9 (3C, p, C(*C*H$_3$)$_3$), 21.9 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{51}H_{53}N_9O_{11}Na$ [M + Na]$^+$: 990.3762; found 990.3769.

***tert*-Butyl-4-(4-(3-(4-((2*S*,3*R*)-4-amino-2-(4-(3-(4-cyanophenyl)ureido)-benz-amido)-3-methoxy-4-oxobutanamido)phenyl)ureido)-2-hydroxy-3-iso-propoxybenzamido)benzoate (S8):** Following the general procedure VI compound **26** (26.0 mg, 26.8 µmol, 1.0 eq) was used. Preparative HPLC (RP-18; run time 80 min; H$_2$O/MeCN = 70 : 30 → 0 : 100 in 70 min; t$_r$ = 61 min) provided phenol **S8** as a colourless amorphous solid (9.3 mg, 10.0 µmol, 37%). $[\alpha]_D^{22}$ = +43.6° (*c* 0.9, MeOH); ^{1}H-NMR (600 MHz, DMSO-d$_6$): δ = 12.5 (1H, br. s, O*H*), 10.6 (1H, br. s, N*H*), 10.1 (1H, s, N*H*), 9.61 (1H, s, N*H*$_{urea}$), 9.50 (1H, s, N*H*$_{urea}$), 9.36 (1H, s, N*H*$_{urea}$), 9.32 (1H, s, N*H*$_{urea}$), 8.30 (1H, d, *J* = 8.1 Hz, N*H*CH), 7.91 (2H, m, Ar*H*), 7.88 – 7.79 (6H, m, Ar*H*), 7.73 (2H, m, Ar*H*), 7.66 (2H, m, Ar*H*), 7.60 – 7.56 (4H, m, Ar*H*), 7.52 – 7.38 (4H, m, Ar*H*, CON*H*$_2$), 4.86 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.63 (1H, hept, *J* = 6.2 Hz, C*H*Me$_2$), 4.06 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.30 (3H, s, OC*H*$_3$), 1.55 (9H, s, C(C*H*$_3$)$_3$), 1.30 (6H, d, *J* = 6.2 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.1 (q, CONH$_2$), 169.0 (q, *C*ONH), 167.7 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO$_2$*t*Bu), 154.6 (q, C-Ar), 152.0 (q, NH*C*ONH), 151.9 (q, NH*C*ONH), 144.0 (q, C-Ar), 142.4 (q, C-Ar), 142.2 (q, C-Ar), 139.0 (q, C-Ar), 135.0 (q, C-Ar), 133.6 (q, C-Ar), 133.3 (2C, t, C-Ar), 132.9 (q, C-Ar), 129.9 (2C, t, C-Ar), 128.5 (2C, t, C-Ar), 127.2 (q, C-Ar), 126.6 (q, C-Ar), 123.0 (t, C-Ar), 120.6 (2C, t, C-Ar), 120.1 (2C, t, C-Ar), 119.3 (q, CN), 118.6 (2C, t, C-Ar), 118.2 (2C, t, C-Ar), 117.5 (2C, t, C-Ar), 109.3 (q, C-Ar), 107.9 (t, C-Ar), 103.5 (q, C-Ar), 80.4 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 74.1 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.5 (t, *C*HNH), 27.8 (3C, p, C(CH$_3$)$_3$), 21.9 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{48}H_{49}N_9O_{11}Na$ [M + Na]$^+$: 950.3449; found 950.3447.

4-(4-(3-(4-((2*S*,3*R*)-4-Amino-2-(4-(3-(4-cyanophenyl)ureido)benzamido)-3-methoxy-4-oxobutanamido)phenyl)ureido)-2-hydroxy-3-isopropoxybenz-amido)benzoic acid (27): Following the general procedure V phenol **S8** (9.0 mg, 9.70 µmol, 1.0 eq) was stirred for 30 min. Acid **27** was obtained as a colourless amorphous solid (8.4 mg, 9.70 µmol, 99%). $[\alpha]_D^{23}$ = +12.7° (*c* 1.1, MeOH); ^{1}H-NMR (600 MHz, DMSO-d$_6$ +2 µL DCO$_2$D): δ = 12.5 (1H, br. s, O*H*), 10.5 (1H, br. s, N*H*), 10.1 (1H, s, N*H*), 9.61 (1H, s, N*H*$_{Urea}$), 9.37 (1H, s, N*H*$_{Urea}$), 9.25 (1H, s, N*H*$_{Urea}$), 8.34 (1H, s, N*H*$_{Urea}$),8.30 (1H, d, *J* = 8.1 Hz, N*H*CH), 7.96 (2H, m, Ar*H*), 7.89 (1H, d, *J* = 9.0 Hz, Ar*H*), 7.85 – 7.80 (5H, m, Ar*H*), 7.74 (2H, m, Ar*H*), 7.65 (2H, m, Ar*H*), 7.60 – 7.55 (4H, m, Ar*H*), 7.52 – 7.41 (4H, m, Ar*H*, CON*H*$_2$), 4.86 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.62 (1H, hept, *J* = 6.2 Hz, C*H*Me$_2$), 4.06 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.30 (3H, s, OC*H*$_3$), 1.30 (6H, d, *J* = 6.2 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$ +2 µL DCO$_2$D): δ = 171.1 (q, CONH$_2$), 169.0 (q, *C*ONH), 167.7 (q, *C*ONH), 166.9 (q, *C*O$_2$H), 165.4 (q, *C*ONH), 154.3 (q, C-Ar), 152.0 (q, NH*C*ONH), 151.9 (q, NH*C*ONH), 144.0 (q, C-Ar), 142.3 (q, C-Ar), 142.0 (q, C-Ar), 139.1 (q, C-Ar), 134.9 (q, C-Ar), 133.7 (q, C-Ar), 133.3 (2C, t, C-Ar), 132.8 (q, C-Ar), 130.2 (2C, t, C-Ar), 128.5 (2C, t, C-Ar), 127.3 (q, C-Ar), 126.2 (q, C-Ar), 123.0 (t, C-Ar), 120.8 (2C, t, C-Ar), 120.1 (2C, t, C-Ar), 119.3 (q, CN), 118.7 (2C, t, C-Ar), 118.2 (2C, t, C-Ar), 117.5 (2C, t, C-Ar), 109.2 (q, C-Ar), 108.2 (t, C-Ar), 103.5 (q, C-Ar), 80.1 (t, *C*HOMe), 74.3 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.5 (t, *C*HNH), 21.9 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{44}H_{42}N_9O_{11}$ [M + H]$^+$: 872.3004; found 872.3004.

***tert*-Butyl-4-(2-(allyloxy)-4-azido-3-isopropoxybenzamido)benzoate (28):** *tert*-Butylnitrite (1.13 mL, 9.50 mmol, 1.5 eq) and trimethylsilyl azide (1.26 mL, 9.50 mmol, 1.5 eq) were added dropwise to a solution of amine **9** (2.70 g, 6.34 mmol, 1.0 eq) in acetonitrile (127 mL) at 0 °C. After 2 h at rt all volatiles were removed *in vacuo*. Column chromatography (PE/EtOAc = 20:1 → 10:1) yielded azide **28** (2.86 g, 6.34 mmol, quant.) as a yellow solid. T$_M$ = 78 °C; ^{1}H-NMR (400 MHz, CDCl$_3$): δ = 10.2 (1H, s, H-8), 8.00 – 7.96 (3H, m, H-5, H-5', H-11), 7.71 (2H, m, H-6, H-6'), 6.95 (1H, d, *J* = 8.7 Hz, H-12), 6.17 – 6.08 (1H, m, H-19), 5.48 (1H, dq, *J* = 1.4, 17.2 Hz, H-20$_{trans}$), 5.40 (1H, dq, *J* = 1.2, 10.3 Hz, H-20$_{cis}$), 4.73 (2H, dt, *J* = 1.2, 6.0 Hz, H-18), 4.60 (1H, hept, *J* = 6.2 Hz, H-16), 1.60 (9H, s, H-1), 1.36 (6H, d, *J* = 6.2 Hz, H-17) ppm; ^{13}C-NMR (100

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MHz, $CDCl_3$): δ = 165.5 (q, C-3), 162.5 (q, C-9), 151.4 (q, C-15), 143.1 (q, C-14), 142.2 (q, C-7), 139.2 (q, C-13), 132.3 (t, C-19), 130.8 (2C, t, C-5, C-5'), 127.6 (q, C-4), 127.1 (t, C-11), 123.3 (q, C-10), 120.3 (s, C-20), 119.2 (2C, t, C-6, C-6'), 116.4 (t, C-12), 81.0 (q, C-2), 76.9 (t, C-16), 75.3 (s, C-18), 28.4 (3C, p, C-1), 22.3 (2C, p, C-17) ppm; HRMS (ESI): *m/z* calc. for $C_{24}H_{28}N_4O_5Na$ [M + Na]$^+$: 475.1957; found 475.1959; IR (neat): $\tilde{\nu}$ = 3318, 2980, 2118, 1708, 1672, 1589, 1528, 1252, 1101, 978, 770 cm^{-1}.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-aminophenyl)-1*H*-1,2,3-triazol-1-yl)-3-isopropoxy-benzamido)benzoate (30):** Azide **28** (2.98 g, 6.58 mmol, 1.0 eq) and 4-ethynylaniline (**29**, 771 mg, 6.56 mmol, 1.0 eq) were dissolved in a mixture of THF (55 mL) and DMSO (110 mL). Sodium ascorbate (782 mg, 3.95 mmol, 0.6 eq) was dissolved in water (5.5 mL) and added to the reaction mixture. After addition of tris[(1-benzyl-1*H*-1,2,3-triazol-4-yl)methyl]amine (1.40 g, 2.63 mmol, 0.4 eq) and $CuSO_4$ (105 mg, 0.66 mmol, 0.1 eq), the reaction was stirred at rt for 2 h. Half of the solvent was removed under reduced pressure. The residue was extracted with EtOAc (3x). The combined organic phases were washed with NH_4Cl-solution, water and brine, dried over Na_2SO_4, filtered and concentrated *in vacuo*. Column chromatography (PE/EtOAc = 20:1) yielded the desired product **30** (3.56 g, 6.25 mmol, 95%) as yellow solid. T_M = 75 °C; ^{1}H-NMR (400 MHz, $CDCl_3$): δ = 10.2 (1H, s, H-8), 8.36 (1H, s, H-21), 8.16 (1H, d, *J* = 8.7 Hz, H-11), 8.00 (2H, m, H-5, H-5'), 7.80 (1H, d, *J* = 8.7 Hz, H-12), 7.76 – 7.72 (4H, m, H-6, H-6', H-24, H-24'), 6.38 (2H, m, H-25, H-25'), 6.22 – 6.12 (1H, m, H-19), 5.53 (1H, dq, *J* = 1.2, 17.1 Hz, H-20$_{trans}$), 5.44 (1H, dq, *J* = 1.0, 10.4 Hz, H-20$_{cis}$), 4.83 (2H, d, *J* = 6.0 Hz, H-18), 4.36 (1H, hept, *J* = 6.2 Hz, H-16), 1.60 (9H, s, H-1), 1.12 (6H, d, *J* = 6.2 Hz, H-17) ppm; ^{13}C-NMR (100 MHz, $CDCl_3$): δ = 165.4 (q, C-3), 162.0 (q, C-9), 151.4 (q, C-15), 148.1 (q, C-22), 146.0 (q, C-26), 142.9 (q, C-14), 141.9 (q, C-7), 135.8 (q, C-13), 132.1 (t, C-19), 130.8 (2C, t, C-5, C-5'), 127.8 (q, C-4/C-10), 127.3 (q, C-4/C-10), 127.3 (t, C-11), 127.2 (2C, t, C-24, C-24'), 121.3 (q, C-23), 120.8 (t, C-12), 120.6 (s, C-20), 120.3 (t, C-21), 119.3 (2C, t, C-6, C-6'), 115.9 (2C, t, C-25, C-25'), 81.0 (q, C-2), 77.9 (t, C-16), 75.6 (s, C-18), 28.4 (3C, p, C-1), 22.3 (2C, p, C-17) ppm; HRMS (ESI): *m/z* calc. for $C_{32}H_{36}N_5O_5$ [M + H]$^+$: 570.2716; found 570.2714.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-2-((*tert*-butoxycarbonyl)-amino)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxybenzamido)-benzoate (S9):** Following the general procedure III using amine **30** (2.83 g, 4.97 mmol, 1.0 eq) and acid **13** (2.22 g, 8.45 mmol, 1.7 eq) compound **S9** (2.72 g, 3.34 mmol, 67%) was obtained as a yellow amorphous solid. [*α*]$_D^{24}$ = -3.9° (*c* 2.0, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.7 (1H, s, N*H*), 10.2 (1H, s, N*H*), 8.89 (1H, s, C*H*$_{Triazol}$), 7.93 – 7.91 (4H, m, Ar*H*), 7.84 (2H, m, Ar*H*), 7.76 (2H, m, Ar*H*), 7.61 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.54 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.43 (2H, d, *J* = 17.8 Hz, N*H*$_2$), 6.76 (1H, d, *J* = 8.4 Hz, N*H*Boc), 6.07 – 5.97 (1H, m, C*H*$_{allyl}$), 5.38 (1H, dq, *J* = 1.6, 17.3 Hz, C*H*$_{allyl\text{-}trans}$), 5.20 (1H, dd, *J* = 1.4, 9.6 Hz, C*H*$_{allyl\text{-}cis}$), 4.69 (2H, d, *J* = 5.5 Hz, OC*H*$_2$allyl), 4.40 (1H, t, *J* = 7.5 Hz, C*H*NH), 4.28 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 3.86 (1H, d, *J* = 7.4 Hz, C*H*OMe), 3.26 (3H, s, OC*H*$_3$), 1.55 (9H, s, C(C*H*$_3$)$_3$), 1.39 (9H, s, C(C*H*$_3$)$_3$), 1.01 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 170.7 (q, CONH$_2$), 168.4 (q, *C*ONH), 168.1 (q, CO$_2$*t*Bu), 164.6 (q, *C*ONH), 164.3 (q, CO$_2$*t*Bu), 150.3 (q, *C*-Ar), 146.3 (q, C-Ar$_{Triazol}$), 143.9 (q, C-Ar), 142.8 (q, C-Ar), 138.9 (q, C-Ar), 133.6 (q, C-Ar), 133.5 (t, *C*Hallyl), 132.9 (q, C-Ar), 130.1 (2C, t, C-Ar), 126.3 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.3 (q, C-Ar), 123.9 (t, C-Ar), 122.8 (t, C-H$_{Triazol}$), 120.9 (t, C-Ar), 119.8 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.0 (s, *C*H$_2$allyl), 80.4 (t, *C*HOMe), 80.2 (q, *C*(CH$_3$)$_3$), 78.6 (q, *C*(CH$_3$)$_3$), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OC*H*$_2$allyl), 57.6 (p, OC*H*$_3$), 56.5 (t, *C*HNH), 28.1 (3C, p, C(C*H*$_3$)$_3$), 27.8 (3C, p, C(C*H*$_3$)$_3$), 21.8 (2C, p, CH(C*H*$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{42}H_{51}N_7O_{10}Na$ [M + Na]$^+$: 836.33595; found 836.3596.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-2,4-diamino-3-methoxy-4-oxobutanamido)-phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxybenzamido)-benzoate (31):** Following the general procedure IV compound **S9** (420 mg, 0.52 mmol, 1.0 eq) was used. Preparative HPLC (RP-18; run time 100 min; H_2O/MeCN = 80 : 20 → 0 : 100 in 80 min; t_r = 31 min) provided amine **31** as a yellow amorphous solid (131 mg, 0.18 mmol, 36%). **[*α*]$_D^{24}$** = +27.7° (*c* 1.1, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.7 (1H, s, N*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.14 – 7.73 (10H, m, N*H*, Ar*H*), 7.66 – 7.53 (3H, m, Ar*H*, N*H*$_2$), 6.07 – 5.99 (1H, m, C*H*$_{allyl}$), 5.39 (1H, d, *J* = 17.2 Hz, C*H*$_{allyl\text{-}trans}$), 5.20 (1H, d, *J* = 10.3 Hz, C*H*$_{allyl\text{-}cis}$), 4.69 (2H, d, *J* = 5.5 Hz, OC*H*$_2$allyl), 4.31 – 4.13 (3H, m, C*H*NH$_2$, C*H*OMe, C*H*Me$_2$), 3.39 (3H, s, OC*H*$_3$), 1.55 (9H, s, C(C*H*$_3$)$_3$), 1.00 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 170.0 (q, CONH$_2$), 164.6 (q, *C*ONH), 164.3 (q, *C*ONH), 163.0 (q, CO$_2$*t*Bu), 150.3 (q, *C*-Ar), 146.2 (q, C-Ar$_{Triazol}$), 143.9 (q, C-Ar), 142.8 (q, C-Ar), 138.2 (q, C-Ar), 133.6 (q, C-Ar), 133.5 (t, *C*Hallyl), 133.0 (q, C-Ar), 130.1 (2C, t, C-Ar), 126.3 (q, C-Ar), 126.0 (2C, t, C-Ar), 125.9 (q, C-Ar), 123.9 (t, C-Ar), 122.9 (t, C-H$_{Triazol}$), 120.9 (t, C-Ar), 120.0 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.0 (s, *C*H$_2$allyl), 80.4 (q, *C*(CH$_3$)$_3$), 78.7 (t, *C*HOMe), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OC*H*$_2$allyl), 58.6 (p, OC*H*$_3$), 54.3 (t, *C*HNH$_2$), 27.9 (3C, p, C(C*H*$_3$)$_3$), 21.9 (2C, p, CH(C*H*$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{37}H_{44}N_7O_8$ [M + H]$^+$: 714.3251; found 714.3250.

4-(4-Fluorobenzamido)-benzoic acid (39): 4-Fluorbenzoyl chloride (**33**, 3.5 mL, 29.2 mmol, 4.0 eq) was dropped to a solution of 4-aminobenzoic acid (**7**, 1.0 g, 7.29 mmol, 1.0 eq) and Na_2CO_3 (1.55 g, 14.6 mmol, 2.0 eq) in water/THF (47 mL, 1:1). After stirring vigorously at rt for 3 h, the filtrate was filtered and washed with hot water (1.5 L). Acid **39** (1.85 g, 7.15 mmol, 98%) was obtained after drying at high vacuum as colourless solid. T_M = 301 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.8 (1H, s, CO$_2$*H*), 10.5 (1H, s, H-6), 8.07 – 8.03 (2H, m, H-9, H-9'), 7.95 – 7.89 (4H, m, H-3, H-3', H-4, H-4'), 7.41 – 7.36 (2H, m, H-10, H-10') ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 166.9 (q, C-1), 164.8 (q, C-7), 164.2 (d, *J* = 249.4 Hz, C-11), 143.2 (q, C-5), 131.1 (d, *J* = 2.9 Hz, C-8), 130.6 (d, *J* = 9.2 Hz, C-9, C-9'), 130.2 (2C, t, C-3, C-3'), 125.5 (q, C-2), 119.5 (2C, t, C-4, C-4'), 115.4 (d, *J* = 21.8 Hz, C-10, C-10') ppm; HRMS (ESI): *m/z* calc. for $C_{14}H_9NO_3F$ [M – H]$^-$: 258.0566; found 258.0564.

4-(5-Cyanopicolinamido)-benzoic acid (40): Following the general procedure I using amine **32** (32.6 mg, 0.17 mmol) and acid **34** (50 mg, 0.34 mmol) intermediate was isolated and used directly for *t*Bu-saponification following to general procedure V**.** Acid **40** (33.7 mg, 0.13 mmol, 75%) was obtained as a beige solid.T_M = 354 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.8 (1H, s, CO$_2$*H*), 11.1 (1H, s, H-6), 9.22 (1H, d, *J* = 1.7 Hz, H-12), 8.60 (1H, dd, *J* = 1.7, 8.1 Hz, H-10), 8.31 (1H, d, *J* = 8.1 Hz, H-9), 8.06 (2H, m, H-4, H-4'), 7.95 (2H, m, H-3, H-3') ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 166.9 (q, C-1), 161.8 (q, C-7), 152.3 (q, C-8), 151.5 (t, C-10), 142.3 (t, C-12), 142.1 (q, C-5), 130.2 (2C, t, C-3, C-3'), 126.2 (q, C-2), 122.6 (t, C-9), 120.0 (2C, t, C-4, C-4'), 116.6 (q, CN), 111.8 (q, C-11) ppm; HRMS (ESI): *m/z* calc. for $C_{14}H_8N_3O_3$ [M – H]$^-$: 266.0566; found 266.0564.

4-(4-Cyano-3-fluorobenzamido)-benzoic acid (41): Following the general procedure I using amine **32** (58.5 mg, 0.30 mmol) and acid **35** (100 mg, 0.61 mmol) intermediate was isolated and used directly for *t*Bu-saponification following to general procedure V. Acid **41** (57.0 mg, 0.20 mmol, 66%) was obtained as a colourless solid.T_M = 298 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.8 (1H, s, CO$_2$*H*), 10.8 (1H, s, H-6), 8.16 – 8.13 (1H, m, H-9), 8.08 – 8.05 (1H, m, H-13), 7.98 – 7.95 (3H, m, H-4, H-4', H-10), 7.91 – 7.88 (2H, m, H-3, H-3') ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 166.8 (q, C-1), 163.5 (q, C-7), 162.1 (d, *J* = 238.1 Hz, C-12), 142.6 (q, C-5), 141.5 (d, *J* = 7.3 Hz, C-8), 134.3 (t, C-9), 130.3 (2C, t, C-3, C-3'), 126.1 (q, C-2), 124.7 (d, *J* = 3.5 Hz, C-10), 119.7 (2C, t, C-4, C-4'), 115.8 (d, *J* = 21.4 Hz, C-13), 113.6 (q, CN), 102.9 (d, *J* = 15.3 Hz, C-11) ppm; HRMS (ESI): *m/z* calc. for $C_{15}H_8N_2O_3F$ [M – H]$^-$: 283.0519; found 283.0516.

4-(Isonicotinamido)-benzoic acid (42): Following to general procedure I using amine **32** (78.4 mg, 0.41 mmol) and acid **36** (100 mg, 0.81 mmol) the intermediate was isolated and directly used for *t*Bu-saponification following the general procedure V. Acid **42** (92.3 mg, 0.38 mmol, 94%) was obtained as a beige solid. T_M = 381 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.8 (1H, s, CO$_2$*H*), 10.8 (1H, s, H-6), 8.82 (2H, m, H-10, H-10'), 7.97 (2H, m, H-4, H-4'), 7.92 – 7.91 (2H, m, H-3, H-3'), 7.90 – 7.89 (2H, m, H-9, H-9') ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 166.9 (q, C-1), 164.3 (q, C-7), 149.9 (2C, t, C-10, C-10'), 142.6 (q, C-5), 142.1 (q, C-8), 130.3 (2C, t, C-4, C-4'), 126.1 (q, C-2), 121.9 (2C, t, C-9, C-9'), 119.7 (2C, t, C-3, C-3') ppm; HRMS (ESI): *m/z* calc. for $C_{13}H_9N_2O_3$ [M – H]$^-$: 241.0613; found 241.0608.

4-(6-Cyanonicotinamido)-benzoic acid (43): Following the general procedure I using amine **32** (65.2 mg, 0.34 mmol) and acid **37** (100 mg, 0.68 mmol) intermediate was isolated and used directly for *t*Bu-saponification following the general procedure V**.** Acid **43** (75.0 mg, 0.28 mmol, 83%) was obtained as a beige solid.T_M = 289 °C (decomposition); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.7 (1H, s, CO$_2$*H*), 10.9 (1H, s, H-6), 9.23 (1H, d, *J* = 1.9 Hz, H-12), 8.53 (1H, dd, *J* = 1.9, 8.0 Hz, H-9), 8.26 (1H, d, *J* = 8.0 Hz, H-10), 7.97 (2H, m, H-4, H-4'), 7.90 (2H, m, H-3, H-3') ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 166.8 (q, C-1), 163.1 (q, C-7), 150.2 (t, C-12), 142.5 (q, C-5), 137.3 (t, C-9), 134.5 (q, C-8), 133.4 (q, C-11), 130.4 (2C, t, C-4, C-4'), 128.8 (t, C-10), 126.2 (q, C-2), 119.6 (2C, t, C-3, C-3'), 117.1 (q, CN) ppm; HRMS (ESI): *m/z* calc. for $C_{14}H_8N_3O_3$ [M – H]$^-$: 266.0566; found 266.0565.

4-(3-(4-Cyanophenyl)-propanamido)-benzoic acid (44): Following the general procedure I using amine **32** (55.1 mg, 0.29 mmol) and acid **38** (100 mg, 0.57 mmol) the intermediate was isolated and directly used for the next step,

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the *t*Bu-saponification following the general procedure V**.** Acid **44** (66.0 mg, 0.22 mmol, 79%) was obtained as a colourless solid. T_M = 280 °C; ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.7 (1H, br. s, CO_2H), 10.3 (1H, s, H-6), 7.87 (2H, m, H-3, H-3‘), 7.76 (2H, m, H-12, H-12‘), 7.67 (2H, m, H-4, H-4‘), 7.47 (2H, m, H-11, H-11‘), 3.00 (2H, t, *J* = 7.5 Hz, H-9), 2.71 (2H, t, *J* = 7.5 Hz, H-8) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 170.5 (q, C-7), 166.9 (q, C-1), 147.2 (q, C-10), 143.1 (q, C-5), 132.2 (2C, t, C-12, C-12‘), 130.4 (2C, t, C-3, C-3‘), 129.4 (2C, t, C-11, C-11‘), 125.0 (q, C-2), 119,0 (q, CN), 118,3 (2C, t, C-4, C-4‘), 108.9 (q, C-13), 37.1 (s, C-8), 30.5 (s, C-9) ppm; HRMS (ESI): *m/z* calc. for $C_{17}H_{13}N_2O_3$ [M – H]$^-$: 293.0926; found 293.0924.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-3-methoxy-2-(4-(4-nitrobenzamido)-benzamido)-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxybenzamido)-benzoate (S10):** Following the general procedure II acid **19** (32.0 mg, 112 µmol, 2.5 eq) and amine **31** (32.0 mg, 44.9 µmol, 1.0 eq) provided compound **S10** as a colourless amorphous solid (20.1 mg, 20.5 µmol, 45%). Preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 58 min). $[\alpha]_D^{24}$ = +48.6° (*c* 2.0, DMSO); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.8 (1H, s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.50 (1H, d, *J* = 7.9 Hz, N*H*CH), 8.39 (2H, m, Ar*H*), 8.21 (2H, m, Ar*H*), 7.94 – 7.92 (8H, m, Ar*H*), 7.84 (2H, m, Ar*H*), 7.80 (2H, m, Ar*H*), 7.62 – 7.60 (2H, m, Ar*H*, CONH_2), 7.54 (1H, d, *J* = 8.4 Hz, Ar*H*), 7.48 (1H, s, CONH_2), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, d, *J* = 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.21 (1H, d, *J* = 10.3 Hz, C$H_{allyl\text{-}cis}$), 4.92 (1H, t, *J* = 7.9 Hz, C*H*NH), 4.69 (2H, d, *J* = 4.8 Hz, OCH_2allyl), 4.28 (1H, hept, *J* = 6.0 Hz, C*H*Me$_2$), 4.11 (1H, d, *J* = 7.9 Hz, C*H*OMe), 3.32 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.0 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.1 (q, CONH_2), 168.2 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 164.3 (q, *C*ONH), 164.3 (q, *C*ONH), 150.3 (q, C-Ar), 149.3 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 144.0 (q, C-Ar), 142.9 (q, C-Ar), 141.7 (q, C-Ar), 140.3 (q, C-Ar), 138.9 (q, C-Ar), 133.7 (q, C-Ar), 133.5 (q, C-Ar), 133.0 (t, *C*Hallyl), 130.2 (q, C-Ar), 129.4 (2C, t, C-Ar), 129.1 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.3 (2C, t, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (2C, t, C-Ar), 123.9 (t, C-Ar), 123.6 (2C, t, C-Ar), 122.8 (t, C-Ar$_{Triazol}$), 120.9 (t, C-Ar), 119.8 (q, C-Ar), 119.7 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.0 (s, *C*H$_2$allyl), 80.4 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 76.9 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OCH_2allyl), 57.8 (p, OCH_3), 55.7 (t, *C*HNH), 27.9 (3C, p, C(CH_3)$_3$), 21.9 (2C, p, CH(CH_3)$_2$) ppm; **HRMS** (ESI): *m/z* calc. for $C_{51}H_{51}N_9O_{12}Na$ [M + Na]$^+$: 1004.3555; found 1004.3553.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxybenzamido)-benzoate (S11):** Following the general procedure II acid **20** (30.0 mg, 112 µmol, 2.5 eq) and amine **31** (32.0 mg, 44.9 µmol, 1.0 eq) provided compound **S11** as a colourless amorphous solid (19.2 mg, 20.0 µmol, 44%). Preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 56 min). $[\alpha]_D^{25}$ = +53.4° (*c* 1.9, DMSO); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.8 (1H, s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.51 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.13 (2H, m, Ar*H*), 8.04 (2H, m, Ar*H*), 7.94 – 7.90 (8H, m, Ar*H*), 7.84 (2H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.61 – 7.60 (2H, m, Ar*H*, CONH_2), 7.53 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.47 (1H, s, CONH_2), 6.05 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, d, *J* = 17.3 Hz, C$H_{allyl\text{-}trans}$), 5.20 (1H, d, *J* = 10.5 Hz, C$H_{allyl\text{-}cis}$), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.69 (2H, d, *J* = 5.0 Hz, OCH_2allyl), 4.28 (1H, hept, *J* = 6.0 Hz, C*H*Me$_2$), 4.11 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.31 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.0 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 168.2 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 164.5 (q, *C*ONH), 164.3 (q, *C*ONH), 150.3 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 144.0 (q, C-Ar), 142.9 (q, C-Ar), 141.8 (q, C-Ar), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 133.6 (q, C-Ar), 133.5 (q, C-Ar), 133.0 (t, *C*Hallyl), 132.5 (2C, t, C-Ar), 130.2 (q, C-Ar), 129.0 (q, C-Ar), 128.7 (2C, t, C-Ar), 128.3 (2C, t, C-Ar), 126.3 (2C, t, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (2C, t, C-Ar), 123.9 (t, C-Ar), 122.8 (t, C-Ar$_{Triazol}$), 120.9 (t, C-Ar), 119.8 (q, C-Ar), 119.6 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.3 (q, CN), 118.0 (s, *C*H$_2$allyl), 114.1 (q, C-Ar), 80.4 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OCH_2allyl), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 27.9 (3C, p, C(CH_3)$_3$), 21.9 (2C, p, CH(CH_3)$_2$) ppm; **HRMS** (ESI): *m/z* calc. for $C_{52}H_{51}N_9O_{10}Na$ [M + Na]$^+$: 984.3657; found 984.3649.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-fluorobenzamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxybenzamido)-benzoate (S12):** Following the general procedure II acid **39** (43.6 mg, 168 µmol, 2.5 eq) and amine **31** (48.0 mg, 67.2 µmol, 1.0 eq) provided compound **S12** as a beige solid (33.9 mg, 35.5 µmol, 53%). Preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 59 min). T_M = 231 °C (decomposition); $[\alpha]_D^{22}$ = +87.8° (*c* 0.5, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.7 (1H, s, N*H*), 10.5 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.45 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.08 – 8.05 (2H, m, Ar*H*), 7.94 – 7.88 (8H, m, Ar*H*), 7.85 (2H, m, Ar*H*), 7.80 (2H, m, Ar*H*), 7.62 – 7.47 (4H, m, Ar*H*, CONH_2), 7.41 – 7.32 (2H, m, Ar*H*), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, dd, *J* = 1.5, 17.1 Hz, C$H_{allyl\text{-}trans}$), 5.21 (1H, d, *J* = 10.6 Hz, C$H_{allyl\text{-}cis}$), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.69 (2H, d, *J* = 5.3 Hz, OCH_2allyl), 4.28 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.10 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 168.2 (q, *C*ONH), 165.4 (q, *C*ONH), 164.7 (q, CO_2*t*Bu), 164.6 (q, *C*ONH), 164.3 (q, *C*ONH), 164.2 (d, *J* = 254.2 Hz, *C*-F), 150.3 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 143.9 (q, C-Ar), 142.8 (q, C-Ar), 142.1 (q, C-Ar), 138.9 (q, C-Ar), 133.6 (q, C-Ar), 133.5 (t, *C*Hallyl), 132.9 (q, C-Ar), 131.1 (d, *J* = 2.8 Hz, C-Ar), 130.5 (2C, d, *J* = 9.2 Hz, C-Ar), 130.1 (2C, t, C-Ar), 128.6 (q, C-Ar), 128.2 (2C, t, C-Ar), 126.3 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.9 (t, C-Ar), 122.8 (t, C-Ar$_{Triazol}$), 120.9 (t, C-Ar), 119.8 (2C, t, C-Ar), 119.5 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.0 (s, *C*H$_2$allyl), 115.4 (2C, d, *J* = 21.9 Hz, C-Ar), 80.4 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OCH_2allyl), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 27.8 (3C, p, C(CH$_3$)$_3$), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{51}H_{51}N_8O_{10}FNa$ [M + Na]$^+$: 977.3610; found 977.3611.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(5-cyanopicolinamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxy-benzamido)benzoate (S13):** Following the general procedure II acid **40** (31.8 mg, 119 µmol, 2.5 eq) and amine **31** (34.0 mg, 47.6 µmol, 1.0 eq) provided compound **S13** as a beige amorphous solid (23.0 mg, 23.9 µmol, 50%). Preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 56 min). $[\alpha]_D^{22}$ = +27.7° (*c* 0.3, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 11.0 (1H, s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 9.22 (1H, br. s, Ar*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.60 (1H, dd, *J* = 1.7, 8.1 Hz, Ar*H*), 8.49 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.31 (1H, d, *J* = 8.1 Hz, Ar*H*), 8.06 (2H, m, Ar*H*), 7.94 – 7.89 (6H, m, Ar*H*), 7.85 (2H, m, Ar*H*), 7.80 (2H, m, Ar*H*), 7.61 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.54 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.53 (2H, d, *J* = 40.9 Hz, CONH_2), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, d, *J* = 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.20 (1H, d, *J* = 10.4 Hz, C$H_{allyl\text{-}cis}$), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.69 (2H, d, *J* = 5.1 Hz, OCH_2allyl), 4.28 (1H, hept, *J* = 6.0 Hz, C*H*Me$_2$), 4.11 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.0 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 168.2 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 164.3 (q, *C*ONH), 161.7 (q, *C*ONH), 152.3 (q, C-Ar), 151.5 (q, C-Ar), 150.3 (t, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 143.9 (q, C-Ar), 142.8 (q, C-Ar), 142.3 (t, C-Ar), 141.1 (q, C-Ar), 138.9 (q, C-Ar), 133.6 (q, C-Ar), 133.5 (q, C-Ar), 132.9 (t, *C*Hallyl), 130.2 (2C, t, C-Ar), 129.3 (q, C-Ar), 128.2 (2C, t, C-Ar), 126.3 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.9 (t, C-Ar), 122.8 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.9 (t, C-Ar), 119.9 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.0 (s, *C*H$_2$allyl), 116.6 (q, CN), 111.8 (q, C-Ar), 80.4 (q, *C*(CH$_3$)$_3$), 80.0 (t, *C*HOMe), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OCH_2allyl), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 27.8 (3C, p, C(CH_3)$_3$), 21.8 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{51}H_{50}N_{10}O_{10}Na$ [M + Na]$^+$: 985.3609; found 985.3609.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyano-3-fluoro-benzamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxy-benzamido)benzoate (S14):** Following the general procedure II acid **41** (47.7 mg, 168 µmol, 2.5 eq) and amine **31** (48.0 mg, 67.2 µmol, 1.0 eq) provided compound **S14** as a colourless amorphous solid (56.2 mg, 57.4 µmol, 85%). Preparative HPLC (RP-18; run time 100 min; H$_2$O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 59 min). $[\alpha]_D^{23}$ = +36.7° (*c* 0.3, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.8 (1H, s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.47 (1H, d, *J* = 8.4 Hz, N*H*CH), 8.17 – 8.13 (1H, m, Ar*H*), 8.09 – 8.06 (1H, m, Ar*H*), 7.99 – 7.96 (1H, m, Ar*H*), 7.94 – 7.90 (8H, m, Ar*H*), 7.84 (2H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.61 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.56 – 7.47 (3H, m, Ar*H*, CONH_2), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, dd, *J* = 1.5, 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.21 (1H, dd, *J* = 1.2, 10.4 Hz, C$H_{allyl\text{-}cis}$), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.69 (2H, d, *J* = 5.4 Hz, OCH_2allyl), 4.28 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 7.9 Hz, C*H*OMe), 3.31 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 168.1 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 164.3 (q, *C*ONH), 163.5 (q, *C*ONH), 162.1 (d, *J* = 223.0 Hz, *C*-F), 150.3 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 143.9 (q, C-Ar), 142.8 (q, C-Ar), 141.5 (d, *J* = 5.5 Hz, *C*CONH), 138.9 (q, C-Ar), 134.3 (t, C-Ar), 133.6 (q, C-Ar), 133.5 (t, *C*Hallyl), 132.9 (q, C-Ar), 130.1 (2C, t, C-Ar), 129.2 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.3 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 124.7 (d, *J* = 3.3 Hz, CH*C*HCCONH), 123.9 (t, C-Ar), 122.7 (t, C-Ar$_{Triazol}$), 120.9 (t, C-Ar), 120.7 (q, CN), 119.8 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.0 (s, *C*H$_2$allyl), 115.8 (d, *J* = 21.8 Hz, *C*HCF), 113.6 (q, C-Ar), 102.9 (d, *J* = 15.3 Hz, *C*CN), 80.4 (q, *C*(CH$_3$)$_3$), 80.0 (t, *C*HOMe), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6

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(s, OCH_2allyl), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 27.8 (3C, p, C(CH_3)$_3$), 21.8 (2C, p, CH(CH_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{52}H_{51}N_9O_{10}F$ [M + H]$^+$: 980.3743; found 980.3753.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(isonicotinamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxybenzamido)-benzoate (S15):** Following to the general procedure II acid **42** (32.2 mg, 133 µmol, 2.5 eq) and amine **31** (38.0 mg, 53.2 µmol, 1.0 eq) provided compound **S15** as a colourless amorphous solid (26.7 mg, 28.5 µmol, 54%). Preparative HPLC (RP-18; run time 100 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 50 min). $[\alpha]_D^{24}$ = +32.4° (*c* 2.3, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.8 (1H, s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.81 (2H, d, *J* = 5.8 Hz, Ar*H*), 8.51 (1H, d, *J* = 8.1 Hz, N*H*CH), 7.94 – 7.88 (10H, m, Ar*H*), 7.85 (2H, m, Ar*H*), 7.80 (2H, m, Ar*H*), 7.62 – 7.47 (4H, m, Ar*H*, CONH_2), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, dd, *J* = 1.6, 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.21 (1H, dd, *J* = 1.5, 10.5 Hz, C$H_{allyl\text{-}cis}$), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.69 (2H, d, *J* = 5.4 Hz, OCH_2allyl), 4.28 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.11 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 168.2 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 164.3 (q, *C*ONH), 164.3 (q, *C*ONH), 150.3 (2C, t, C-Ar), 150.3 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 143.9 (q, C-Ar), 142.8 (q, C-Ar), 141.7 (q, C-Ar), 141.6 (q, C-Ar), 138.9 (q, C-Ar), 133.6 (q, C-Ar), 133.5 (t, *C*Hallyl), 132.9 (q, C-Ar), 130.1 (2C, t, C-Ar), 129.1 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.3 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (2C, t, C-Ar), 123.9 (t, C-Ar), 122.8 (t, C-Ar$_{Triazol}$), 121.6 (2C, t, C-Ar), 120.9 (t, C-Ar), 119.8 (q, C-Ar), 119.7 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.0 (s, CH_2allyl), 80.4 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OCH_2allyl), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 27.8 (3C, p, C(CH$_3$)$_3$), 21.8 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{50}H_{51}N_9O_{10}Na$ [M + Na]$^+$: 960.3657; found 960.3654.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(6-cyanonicotin-amido)-benz-amido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxybenz-amido)benzoate (S16):** Following the general procedure II acid **43** (35.5 mg, 133 µmol, 2.5 eq) and amine **31** (38.0 mg, 53.2 µmol, 1.0 eq) provided compound **S16** as a beige amorphous solid (34.4 mg, 35.7 µmol, 67%). Preparative HPLC (RP-18; run time 100 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 55 min). $[\alpha]_D^{23}$ = +30.5° (*c* 3.3, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.9 (1H, s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 9.24 (1H, d, *J* = 1.9 Hz, Ar*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.55 (1H, dd, *J* = 1.9, 8.0 Hz, Ar*H*), 8.48 (1H, d, *J* = 8.2 Hz, N*H*CH), 8.25 (1H, d, *J* = 8.0 Hz, Ar*H*), 7.94 – 7.88 (8H, m, Ar*H*), 7.84 (2H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.61 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.54 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.52 (2H, d, *J* = 39.5 Hz, CONH_2), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, dd, *J* = 1.6, 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.21 (1H, dd, *J* = 1.5, 10.5 Hz, C$H_{allyl\text{-}cis}$), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.69 (2H, d, *J* = 5.5 Hz, OCH_2allyl), 4.28 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.10 (1H, d, *J* = 8.0 Hz, C*H*OMe), 3.32 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 168.2 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 164.3 (q, *C*ONH), 163.0 (q, *C*ONH), 150.3 (q, C-Ar), 150.2 (t, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 143.9 (q, C-Ar), 142.8 (q, C-Ar), 141.5 (q, C-Ar), 138.9 (q, C-Ar), 137.3 (t, C-Ar), 134.5 (q, C-Ar), 133.6 (q, C-Ar), 133.5 (t, *C*Hallyl), 133.4 (q, C-Ar), 132.9 (q, C-Ar), 130.1 (2C, t, C-Ar), 129.2 (q, C-Ar), 128.8 (t, C-Ar), 128.3 (2C, t, C-Ar), 126.3 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.9 (t, C-Ar), 122.8 (t, C-Ar$_{Triazol}$), 120.9 (t, C-Ar), 119.8 (2C, t, C-Ar), 119.6 (2C, t, C-Ar), 118.9 (2C, t, C-Ar), 118.0 (s, CH_2allyl), 117.1 (q, CN), 80.4 (q, *C*(CH$_3$)$_3$), 80.0 (t, *C*HOMe), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OCH_2allyl), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 27.8 (3C, p, C(CH$_3$)$_3$), 21.8 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{51}H_{51}N_{10}O_{10}$ [M + H]$^+$: 963.3790; found 963.3795.

***tert*-Butyl-4-(2-(allyloxy)-4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(3-(4-cyanophenyl)-propan-amido)benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-3-isopropoxybenzamido)benzoate (S17):** Following the general procedure II acid **44** (39.0 mg, 133 µmol, 2.5 eq) and amine **31** (38.0 mg, 53.2 µmol, 1.0 eq) provided phenol **S19** as a yellow amorphous solid (10.1 mg, 11.0 µmol, 56%). Preparative HPLC (RP-18; run time 100 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 80 min; t_r = 57 min). $[\alpha]_D^{25}$ = +23.2° (*c* 2.7, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 10.2 (1H, s, N*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.41 (1H, d, *J* = 8.0 Hz, N*H*CH), 7.94 – 7.91 (4H, m, Ar*H*), 7.86 – 7.75 (8H, m, Ar*H*), 7.68 (2H, m, Ar*H*), 7.61 (1H, d, *J* = 8.3 Hz, Ar*H*), 7.57 – 7.53 (2H, m, Ar*H*, CONH_2), 7.49 – 7.47 (3H, m, Ar*H*, CONH_2), 6.07 – 5.97 (1H, m, CH_{allyl}), 5.38 (1H, d, *J* = 17.2 Hz, C$H_{allyl\text{-}trans}$), 5.21 (1H, d, *J* = 10.4 Hz, C$H_{allyl\text{-}cis}$), 4.89 (1H, t, *J* = 8.0 Hz, C*H*NH), 4.69 (2H, d, *J* = 5.1 Hz, OCH_2allyl), 4.28 (1H, hept, *J* = 6.0 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.0 Hz, C*H*OMe), 3.30 (3H, s, OCH_3), 3.01 (2H, t, *J* = 7.4 Hz, ArCH_2CH$_2$), 2.71 (2H, t, *J* = 7.4 Hz, ArCH$_2$CH_2), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.0 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 170.4 (q, *C*ONH), 168.2 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 164.3 (q, *C*ONH), 150.3 (q, C-Ar), 147.3 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 143.9 (q, C-Ar), 142.8 (q, C-Ar), 142.1 (q, C-Ar), 138.9 (q, C-Ar), 133.6 (q, C-Ar), 133.5 (t, *C*Hallyl), 133.0 (q, C-Ar), 132.3 (2C, t, C-Ar), 130.2 (2C, t, C-Ar), 129.5 (2C, t, C-Ar), 128.4 (2C, t, C-Ar), 128.0 (q, C-Ar), 126.3 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.9 (t, C-Ar), 122.8 (t, C-Ar$_{Triazol}$), 120.9 (t, C-Ar), 119.8 (2C, t, C-Ar), 119.0 (q, CN), 118.9 (2C, t, C-Ar), 118.2 (s, CH_2allyl), 118.0 (2C, t, C-Ar), 108.9 (q, C-Ar), 80.4 (q, *C*(CH$_3$)$_3$), 80.0 (t, *C*HOMe), 76.8 (t, *C*H(CH$_3$)$_2$), 74.6 (s, OCH_2allyl), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 37.1 (s, ArCH$_2$CH_2), 30.6 (s, ArCH_2CH$_2$), 27.9 (3C, p, C(CH_3)$_3$), 21.9 (2C, p, CH(CH_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{54}H_{56}N_9O_{10}$ [M + H]$^+$: 990.4150; found 990.4148.

***tert*-Butyl 4-(4-(4-(4-((2*S*,3*R*)-4-amino-3-methoxy-2-(4-(4-nitrobenzamido)-benzamido)-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)-benzoate (S18):** Following the general procedure VI compound **S10** (20.0 mg, 20.4 µmol, 1.0 eq) was used. Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 53 min) provided Phenol **S18** as a yellow amorphous solid (8.5 mg, 9.03 µmol, 44%). $[\alpha]_D^{24}$ = +42.9° (*c* 0.9, DMSO); ^{1}H-NMR (600 MHz, DMSO-d$_6$): δ = 12.2 (1H, br. s, O*H*), 11.1 (1H, br. s, N*H*), 10.8 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.92 (1H, s, C$H_{Triazol}$), 8.44 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.39 (2H, m, Ar*H*), 8.21 (2H, m, Ar*H*), 7.95 – 7.87 (11H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 46.5 Hz, CONH_2), 7.30 (1H, d, *J* = 8.0 Hz, Ar*H*), 4.93 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.28 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OCH_3), 1.56 (9H, s, C(CH_3)$_3$), 1.02 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 168.2 (q, *C*ONH), 167.4 (q, *C*ONH), 165.4 (q, *C*ONH), 164.5 (q, CO_2*t*Bu), 164.2 (q, *C*ONH), 151.5 (q, C-Ar), 149.3 (q, C-Ar), 146.2 (q, C-Ar$_{Triazol}$), 142.1 (q, C-Ar), 141.7 (q, C-Ar), 140.3 (q, C-Ar), 138.9 (q, C-Ar), 138.9 (q, C-Ar), 134.3 (q, C-Ar), 130.0 (2C, t, C-Ar), 129.3 (2C, t, C-Ar), 129.1 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.8 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (t, C-Ar), 124.9 (q, C-Ar), 123.6 (2C, t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.5 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.4 (q, C-Ar), 114.1 (t, C-Ar), 80.5 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 75.4 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 27.9 (3C, p, C(CH$_3$)$_3$), 21.8 (2C, p, CH(CH$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{48}H_{47}N_9O_{12}Na$ [M + Na]$^+$: 964.3242; found 964.3229.

***tert*-Butyl-4-(4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)-benzoate (S19):** Following the general procedure VI compound **S11** (19.0 mg, 20.4 µmol, 1.0 eq) provided phenol **S19** as a yellow amorphous solid (10.1 mg, 11.0 µmol, 56%). Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 52 min). $[\alpha]_D^{23}$ = +49.6° (*c* 1.0, DMSO); ^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 12.2 (1H, br. s, O*H*), 11.0 (1H, br. s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.90 (1H, s, C$H_{Triazol}$), 8.44 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.13 (2H, m, Ar*H*), 8.05 (2H, m, Ar*H*), 7.96 – 7.87 (11H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 37.9 Hz, CONH_2), 7.32 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.27 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OCH_3), 1.56 (9H, s, C(CH_3)$_3$), 1.02 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH_2), 168.2 (q, *C*ONH), 167.4 (q, *C*ONH), 165.4 (q, *C*ONH), 164.5 (q, CO_2*t*Bu), 164.5 (q, *C*ONH), 155.0 (q, C-Ar), 146.2 (q, C-Ar$_{Triazol}$), 142.0 (q, C-Ar), 141.8 (q, C-Ar), 138.9 (q, C-Ar), 138.8 (q, C-Ar), 138.7 (q, C-Ar), 134.3 (q, C-Ar), 132.5 (2C, t, C-Ar), 130.0 (2C, t, C-Ar), 129.0 (q, C-Ar), 128.6 (2C, t, C-Ar), 128.3 (2C, t, C-Ar), 126.9 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.6 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.5 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.6 (2C, t, C-Ar), 118.4 (q, C-Ar), 118.3 (q, CN), 114.4 (q, C-Ar), 114.1 (t, C-Ar), 80.5 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 75.5 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH_3), 55.7 (t, *C*HNH), 27.8 (3C, p, C(CH_3)$_3$), 21.8 (2C, p, CH(CH_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{49}H_{48}N_9O_{10}$ [M + H]$^+$: 922.3524; found 922.3529.

***tert*-Butyl-4-(4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-fluorobenzamido)benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)-benzoate (S20):** Following the general procedure VI compound **S12** (33.9 mg, 35.5 µmol, 1.0 eq) provided Phenol **S20** as a yellow amorphous solid (20.1 mg, 22.0 µmol, 62%). Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 51 min). $[\alpha]_D^{24}$ = +29.2° (*c* 1.8, MeOH); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.2 (1H, br. s, O*H*), 11.4 (1H, s, N*H*), 10.5 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.91 (1H, s, C$H_{Triazol}$), 8.42 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.08 – 8.05 (2H, m, Ar*H*), 7.95 – 7.86 (11H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 30.8 Hz, CONH_2), 7.39 (2H, m, Ar*H*), 7.25 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.93 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.32 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.10 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OCH_3), 1.55 (9H, s, C(CH_3)$_3$), 1.01 (6H, d, *J* = 6.1 Hz, CH(CH_3)$_2$) ppm; ^{13}C-NMR (100

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MHz, DMSO-d_6): δ = 171.0 (q, $CONH_2$), 168.2 (q, *C*ONH), 167.4 (q, *C*ONH), 165.0 (q, *C*ONH), 164.7 (q, CO_2*t*Bu), 164.6 (q, *C*ONH), 164.2 (d, *J* = 249.2 Hz, *C*-F), 156.0 (q, C-Ar), 146.1 (q, C-$Ar_{Triazol}$), 142.2 (q, C-Ar), 142.1 (q, C-Ar), 139.0 (q, C-Ar), 138.8 (q, C-Ar), 134.2 (q, C-Ar), 131.1 (d, *J* = 2.9 Hz, C-Ar), 130.5 (2C, d, *J* = 9.2 Hz, C-Ar), 130.0 (2C, t, C-Ar), 128.6 (q, C-Ar), 128.2 (2C, t, C-Ar), 126.7 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.5 (q, C-Ar), 123.6 (t, C-Ar), 122.6 (t, C-$Ar_{Triazol}$), 120.3 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.5 (2C, t, C-Ar), 118.4 (q, C-Ar), 115.4 (2C, d, *J* = 21.8 Hz, C-Ar), 113.5 (t, C-Ar), 80.5 (q, *C*(CH_3)$_3$), 80.1 (t, *C*HOMe), 75.1 (t, *C*H(CH_3)$_2$), 57.7 (p, O*C*H_3), 55.6 (t, *C*HNH), 27.8 (3C, p, C(*C*H_3)$_3$), 21.8 (2C, p, CH(*C*H_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{48}H_{47}N_8O_{10}FNa$ [M + Na]$^+$: 937.3297; found 937.3273.

***tert*-Butyl-4-(4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(5-cyanopicolinamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxy-benzamido)benzoate (S21):** Following the general procedure VI compound **S13** (23.0 mg, 23.9 µmol, 1.0 eq) provided phenol **S21** as a yellow amorphous solid (21.8 mg, 23.6 µmol, 99%). Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 51 min). $[\alpha]_D^{24}$ = +15.4° (*c* 1.1, MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.2 (1H, br. s, O*H*), 11.0 (1H, s, N*H*), 10.4 (1H, s, N*H*), 9.22 (1H, br. s, Ar*H*), 8.87 (1H, s, C*H*$_{Triazol}$), 8.60 (1H, dd, *J* = 2.0, 8.1 Hz, Ar*H*), 8.44 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.31 (1H, d, *J* = 8.1 Hz, Ar*H*), 8.06 (2H, m, Ar*H*), 7.92 – 7.85 (9H, m, Ar*H*), 7.78 (2H, m, Ar*H*), 7.50 (2H, d, *J* = 31.1 Hz, CONH_2), 7.08 (1H, br. s, Ar*H*), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.40 (1H, br. s, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, O*C*H_3), 1.55 (9H, s, C(*C*H_3)$_3$), 1.00 (6H, d, *J* = 6.1 Hz, CH(*C*H_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 171.0 (q, $CONH_2$), 168.1 (q, *C*ONH), 167.3 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 163.0 (q, C-Ar), 161.7 (q, *C*ONH), 152.3 (q, C-Ar), 151.5 (t, C-Ar), 146.0 (q, C-$Ar_{Triazol}$), 142.7 (q, C-Ar), 142.3 (t, C-Ar), 141.0 (q, C-Ar), 139.5 (q, C-Ar), 138.8 (q, C-Ar), 134.0 (q, C-Ar), 130.0 (2C, t, C-Ar), 129.3 (q, C-Ar), 128.2 (2C, t, C-Ar), 126.2 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.6 (q, C-Ar), 123.7 (t, C-Ar), 122.6 (t, C-Ar), 122.6 (t, C-$Ar_{Triazol}$), 120.0 (2C, t, C-Ar), 119.9 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 118.5 (q, C-Ar), 116.6 (q, CN), 111.8 (q, C-Ar), 80.4 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 74.4 (t, *C*H(CH$_3$)$_2$), 57.7 (p, O*C*H_3), 55.7 (t, *C*HNH), 27.9 (3C, p, C(*C*H_3)$_3$), 21.9 (2C, p, CH(*C*H_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{48}H_{46}N_{10}O_{10}Na$ [M + Na]$^+$: 945.3296; found 945.3298.

***tert*-Butyl-4-(4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(4-cyano-3-fluorobenzamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxy-benzamido)benzoate (S22):** Following to the **general procedure VI** compound **S14** (56.2 mg, 57.4 µmol, 1.0 eq) provided phenol **S22** as a colourless amorphous solid (22.4 mg, 23.8 µmol, 42%). Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 50 min). $[\alpha]_D^{23}$ = +21.8° (*c* 1.1, MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.2 (1H, br. s, O*H*), 11.0 (1H, s, N*H*), 10.8 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.92 (1H, s, C*H*$_{Triazol}$), 8.45 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.16 – 8.13 (1H, m, Ar*H*), 8.09 – 8.06 (1H, m, Ar*H*), 7.99 – 7.86 (12H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 30.5 Hz, CONH_2), 7.32 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.93 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.28 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.10 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, O*C*H_3), 1.55 (9H, s, C(*C*H_3)$_3$), 1.02 (6H, d, *J* = 6.1 Hz, CH(*C*H_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 171.0 (q, $CONH_2$), 168.2 (q, *C*ONH), 167.4 (q, *C*ONH), 165.4 (q, *C*ONH), 164.5 (q, CO_2*t*Bu), 163.5 (q, *C*ONH), 162.1 (d, *J* = 223.6 Hz, *C*-F), 155.2 (q, C-Ar), 146.2 (q, C-$Ar_{Triazol}$), 142.0 (q, C-Ar), 141.5 (q, C-Ar), 141.5 (d, *J* = 7.2 Hz, *C*CONH), 141.5 (q, C-Ar), 138.9 (q, C-Ar), 138.8 (q, C-Ar), 134.3 (d, *J* = 7.0 Hz, *C*HCCN), 130.0 (2C, t, C-Ar), 129.2 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.9 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 124.7 (d, *J* = 3.5 Hz, CH*C*HCCONH), 123.6 (t, C-Ar), 122.6 (t, C-$Ar_{Triazol}$), 120.5 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.3 (q, CN), 115.8 (d, *J* = 21.3 Hz, *C*HCF), 114.2 (t, C-Ar), 113.6 (q, C-Ar), 102.9 (d, *J* = 15.3 Hz, *C*CN), 80.5 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 75.5 (t, *C*H(CH$_3$)$_2$), 57.7 (p, O*C*H$_3$), 55.7 (t, *C*HNH), 27.8 (3C, p, C(*C*H_3)$_3$), 21.8 (2C, p, CH(*C*H_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{49}H_{46}N_9O_{10}FNa$ [M + Na]$^+$: 962.3249; found 962.3253.

***tert*-Butyl-4-(4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(isonicotinamido)benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)-benzoate (S23):** Following to the general procedure VI compound **S15** (26.7 mg, 28.4 µmol, 1.0 eq) provided phenol **S23** as a yellow amorphous solid (16.5 mg, 18.4 µmol, 65%).. Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 45 min). $[\alpha]_D^{23}$ = +22.1° (*c* 0.9, MeOH); ^{1}H-NMR (600 MHz, DMSO-d_6): δ = 12.2 (1H, br. s, O*H*), 10.8 (1H, s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.82 (2H, m, Ar*H*), 8.45 (1H, d, *J* = 8.1 Hz, N*H*CH), 7.97 – 7.87 (13H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 49.8 Hz, CONH_2), 7.36 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.93 (1H, t, *J* = 8.0 Hz, C*H*NH), 4.25 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.10 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, O*C*H_3), 1.56 (9H, s, C(*C*H_3)$_3$), 1.02 (6H, d, *J* = 6.1 Hz, CH(*C*H_3)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d_6): δ = 171.0 (q, $CONH_2$), 168.2 (q, *C*ONH), 167.4 (q, *C*ONH), 165.4 (q, *C*ONH), 164.5 (q, CO_2*t*Bu), 163.0 (q, *C*ONH), 154.6 (q, C-Ar), 150.4 (2C, t, C-Ar), 146.3 (q, C-$Ar_{Triazol}$), 141.9 (q, C-Ar), 141.6 (q, C-Ar), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 134.4 (q, C-Ar), 131.5 (q, C-Ar), 130.0 (2C, t, C-Ar), 129.1 (q, C-Ar), 128.8 (2C, t, C-Ar), 127.0 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.6 (t, C-Ar), 122.6 (t, C-$Ar_{Triazol}$), 121.8 (2C, t, C-Ar), 120.6 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.4 (q, C-Ar), 114.7 (t, C-Ar), 80.5 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 76.7 (t, *C*H(CH$_3$)$_2$), 57.7 (p, O*C*H$_3$), 55.7 (t, *C*HNH), 27.8 (3C, p, C(*C*H_3)$_3$), 21.8 (2C, p, CH(*C*H_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{47}H_{48}N_9O_{10}$ [M + H]$^+$: 898.3524; found 898.3525.

***tert*-Butyl-4-(4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(6-cyanonicotinamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxy-benzamido)benzoate (S24):** Following to the general procedure VI compound **S16** (26.7 mg, 27.7 µmol, 1.0 eq) provided phenol **S24** as a yellow amorphous solid (24.4 mg, 26.5 µmol, 95%). Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 47 min). $[\alpha]_D^{23}$ = +19.5° (*c* 1.2, MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.2 (1H, br. s, O*H*), 11.4 (1H, br. s, N*H*), 10.9 (1H, s, N*H*), 10.4 (1H, s, N*H*), 9.24 (1H, d, *J* = 2.0 Hz, Ar*H*), 8.90 (1H, s, C*H*$_{Triazol}$), 8.55 (1H, dd, *J* = 2.0, 8.1 Hz, Ar*H*), 8.46 (1H, d, *J* = 8.2 Hz, N*H*CH), 8.25 (1H, d, *J* = 8.1 Hz, Ar*H*), 7.94 – 7.86 (11H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 31.3 Hz, CONH_2), 7.25 (1H, d, *J* = 8.5 Hz, Ar*H*), 4.93 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.31 (1H, hept, *J* = 6.0 Hz, C*H*Me$_2$), 4.10 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, O*C*H_3), 1.55 (9H, s, C(*C*H_3)$_3$), 1.02 (6H, d, *J* = 6.0 Hz, CH(*C*H_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 171.0 (q, $CONH_2$), 168.1 (q, *C*ONH), 167.4 (q, *C*ONH), 165.4 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 163.0 (q, *C*ONH), 155.9 (q, C-Ar), 150.2 (t, C-Ar), 146.1 (q, C-$Ar_{Triazol}$), 142.2 (q, C-Ar), 141.5 (q, C-Ar), 139.0 (q, C-Ar), 138.8 (q, C-Ar), 137.3 (t, C-Ar), 134.5 (q, C-Ar), 134.2 (q, C-Ar), 133.4 (q, C-Ar), 130.0 (2C, t, C-Ar), 129.2 (q, C-Ar), 128.8 (t, C-Ar), 128.3 (2C, t, C-Ar), 126.7 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.5 (q, C-Ar), 123.6 (t, C-Ar), 122.6 (t, C-$Ar_{Triazol}$), 120.4 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.6 (2C, t, C-Ar), 118.4 (q, C-Ar), 117.1 (q, CN), 113.5 (t, C-Ar), 80.5 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 75.2 (t, *C*H(CH$_3$)$_2$), 57.7 (p, O*C*H$_3$), 55.7 (t, *C*HNH), 27.9 (3C, p, C(*C*H_3)$_3$), 21.8 (2C, p, CH(*C*H_3)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{48}H_{47}N_{10}O_{10}$ [M + H]$^+$: 923.3477; found 923.3469.

***tert*-Butyl-4-(4-(4-(4-((2*S*,3*R*)-4-amino-2-(4-(3-(4-cyanophenyl)-propan-amido)-benz-amido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)benzoate (S25):** Following to the general procedure VI compound **S17** (29.5 mg, 29.8 µmol, 1.0 eq) provided Phenol **S25** as a yellow amorphous solid (19.8 mg, 20.9 µmol, 70%). Preparative HPLC (RP-18; run time 80 min; H_2O/MeCN = 70 : 30 → 0 : 100 in 70 min; t_r = 49 min). $[\alpha]_D^{22}$ = +14.9° (*c* 1.0, MeOH); ^{1}H-NMR (400 MHz, DMSO-d_6): δ = 12.2 (1H, br. s, O*H*), 11.2 (1H, s, N*H*), 10.4 (1H, s, N*H*), 10.2 (1H, s, N*H*), 8.92 (1H, s, C*H*$_{Triazol}$), 8.37 (1H, d, *J* = 8.0 Hz, N*H*CH), 7.95 – 7.87 (7H, m, Ar*H*), 7.83 – 7.75 (6H, m, Ar*H*), 7.68 (2H, m, Ar*H*), 7.54 – 7.46 (4H, m, Ar*H*, CONH_2), 7.29 (1H, d, *J* = 8.5 Hz, Ar*H*), 4.90 (1H, t, *J* = 8.0 Hz, C*H*NH), 4.29 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.08 (1H, d, *J* = 8.0 Hz, C*H*OMe), 3.31 (3H, s, O*C*H_3), 3.01 (2H, t, *J* = 7.4 Hz, ArCH_2CH$_2$), 2.71 (2H, t, *J* = 7.5 Hz, ArCH$_2$CH_2), 1.55 (9H, s, C(*C*H_3)$_3$), 1.02 (6H, d, *J* = 6.1 Hz, CH(*C*H_3)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d_6): δ = 171.1 (q, $CONH_2$), 170.5 (q, *C*ONH), 168.2 (q, *C*ONH), 167.4 (q, *C*ONH), 165.5 (q, *C*ONH), 164.6 (q, CO_2*t*Bu), 147.3 (q, C-Ar), 146.2 (q, C-$Ar_{Triazol}$), 142.1 (q, C-Ar), 139.0 (q, C-Ar), 138.9 (q, C-Ar), 134.3 (q, C-Ar), 132.3 (2C, t, C-Ar), 130.0 (2C, t, C-Ar), 129.5 (2C, t, C-Ar), 128.4 (2C, t, C-Ar), 128.1 (q, C-Ar), 126.9 (q, C-Ar), 125.9 (2C, t, C-Ar), 125.5 (q, C-Ar), 123.6 (t, C-Ar), 122.6 (t, C-$Ar_{Triazol}$), 120.5 (2C, t, C-Ar), 119.9 (2C, t, C-Ar), 119.0 (q, C-Ar), 118.5 (q, CN), 118.3 (2C, t, C-Ar), 108.9 (q, C-Ar), 80.6 (q, *C*(CH$_3$)$_3$), 80.1 (t, *C*HOMe), 75.4 (t, *C*H(CH$_3$)$_2$), 57.8 (p, O*C*H$_3$), 55.7 (t, *C*HNH), 37.2 (s, ArCH$_2$CH$_2$), 30.6 (s, ArCH$_2$CH$_2$), 27.9 (3C, p, C(*C*H_3)$_3$), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{51}H_{51}N_9O_{10}Na$ [M + Na]$^+$: 972.3657; found 972.3661.

4-(4-(4-(4-((2*S*,3*R*)-4-Amino-3-methoxy-2-(4-(4-nitrobenzamido)benzamido)-4-oxo-butanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxy-benzamido)-benzoic acid (45): Following to the general procedure V Phenol **S18** (8.5 mg, 9.03 µmol, 1.0 eq) was stirred for 6 h. Acid **45** was obtained as a colourless amorphous solid (6.2 mg, 7.00 µmol, 78%). $[\alpha]_D^{24}$ = +37.1° (*c* 0.1, DMSO); ^{1}H-NMR (500 MHz, DMSO-d_6): δ = 12.9 (1H, br. s, CO_2*H*), 12.2 (1H, br. s, O*H*), 10.8 (1H, br. s, N*H*), 10.8 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.44 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.39 (2H, m, Ar*H*), 8.21 (2H, m, Ar*H*), 8.00 – 7.87 (11H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.50 (2H, d, *J* = 39.2 Hz, CONH_2), 7.37 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.24 (1H, hept,

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J = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OC*H*$_3$), 1.02 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH$_2$), 168.2 (q, *C*ONH), 167.5 (q, *C*ONH), 166.9 (q, *C*O$_2$H), 165.4 (q, *C*ONH), 164.2 (q, *C*ONH), 154.5 (q, C-Ar), 149.3 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 141.9 (q, C-Ar), 141.7 (q, C-Ar), 140.3 (q, C-Ar), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 134.4 (q, C-Ar), 130.7 (2C, t, C-Ar), 130.3 (q, C-Ar), 129.4 (2C, t, C-Ar), 128.7 (2C, t, C-Ar), 128.3 (q, C-Ar), 126.5 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (t, C-Ar), 123.6 (2C, t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.6 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.4 (q, C-Ar), 114.8 (t, C-Ar), 80.1 (t, *C*HOMe), 75.7 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.7 (t, *C*HNH), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for C$_{44}$H$_{40}$N$_9$O$_{12}$ [M + H]$^+$: 886.2796; found 886.2798.

4-(4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(4-cyanobenzamido)benzamido)-3-methoxy-4-oxo-butanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)-benzoic acid (46): Following the general procedure V Phenol **S19** (10.1 mg, 11.0 µmol, 1.0 eq) was stirred for 3 h. Acid **46** was obtained as a beige amorphous solid (7.4 mg, 8.55 µmol, 78%). [α]$_D^{25}$ = +55.9° (*c* 0.2, DMSO); ^{1}H-NMR (600 MHz, DMSO-d$_6$): δ = 12.8 (1H, br. s, CO$_2$*H*), 12.2 (1H, br. s, O*H*), 10.8 (1H, br. s, N*H*), 10.7 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.43 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.13 (2H, m, Ar*H*), 8.05 (2H, m, Ar*H*), 7.99 – 7.87 (11H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.50 (2H, d, *J* = 45.0 Hz, CONH$_2$), 7.34 (1H, d, *J* = 7.0 Hz, Ar*H*), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.26 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OC*H*$_3$), 1.02 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH$_2$), 168.2 (q, *C*ONH), 167.4 (q, *C*ONH), 166.8 (q, *C*O$_2$H), 165.4 (q, *C*ONH), 164.5 (q, *C*ONH), 154.7 (q, C-Ar), 146.2 (q, C-Ar$_{Triazol}$), 141.9 (q, C-Ar), 141.7 (q, C-Ar), 138.9 (q, C-Ar), 138.8 (q, C-Ar), 138.7 (q, C-Ar), 134.3 (q, C-Ar), 132.5 (2C, t, C-Ar), 130.3 (2C, t, C-Ar), 129.0 (q, C-Ar), 128.6 (2C, t, C-Ar), 128.3 (2C, t, C-Ar), 126.4 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.5 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.6 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.6 (2C, t, C-Ar), 118.4 (q, C-Ar), 118.3 (q, CN), 114.6 (q, C-Ar), 114.0 (t, C-Ar), 80.1 (t, *C*HOMe), 75.6 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.6 (t, *C*HNH), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for C$_{45}$H$_{40}$N$_9$O$_{10}$ [M + H]$^+$: 866.2898; found 866.2897.

4-(4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(4-fluorobenzamido)benzamido)-3-methoxy-4-oxo-butanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)-benzoic acid (47): Following the general procedure V phenol **S20** (20.1 mg, 22.0 µmol, 1.0 eq) was stirred for 3.5 h. Acid **47** was obtained as an orange amorphous solid (19.1 mg, 19.6 µmol, 89%). **[α]$_D^{24}$** = +27.6° (*c* 0.9, DMSO); **^{1}H-NMR** (600 MHz, DMSO-d$_6$): δ = 12.2 (1H, br. s, O*H*), 10.8 (1H, s, N*H*), 10.5 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.41 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.07 – 8.05 (2H, m, Ar*H*), 8.00 – 7.87 (11H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.50 (2H, d, *J* = 47.2 Hz, CONH$_2$), 7.40 – 7.36 (3H, m, Ar*H*), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.25 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OC*H*$_3$), 1.03 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; **^{13}C-NMR** (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH$_2$), 168.2 (q, *C*ONH), 167.5 (q, *C*ONH), 166.9 (q, *C*O$_2$H), 165.0 (q, *C*ONH), 164.7 (q, *C*ONH), 164.4 (d, *J* = 311.0 Hz, *C*-F), 158.2 (TFA), 154.5 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 142.1 (q, C-Ar), 141.9 (q, C-Ar), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 134.4 (q, C-Ar), 131.1 (d, *J* = 2.8 Hz, C-Ar), 130.5 (2C, d, *J* = 9.1 Hz, C-Ar), 130.3 (2C, t, C-Ar), 129.8 (TFA), 128.6 (q, C-Ar), 128.2 (2C, t, C-Ar), 126.5 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.5 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.6 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.5 (2C, t, C-Ar), 118.4 (q, C-Ar), 115.4 (2C, d, *J* = 21.8 Hz, C-Ar), 114.8 (t, C-Ar), 80.1 (t, *C*HOMe), 75.7 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.6 (t, *C*HNH), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for C$_{44}$H$_{40}$N$_8$O$_{10}$F [M + H]$^+$: 859.2851; found 859.2851.

4-(4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(5-cyanopicolinamido)benzamido)-3-methoxy-4-oxo-butanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)benzoic acid (48): Following the general procedure V phenol **S21** (21.8 mg, 23.6 µmol, 1.0 eq) was stirred for 6 h. Acid **48** was obtained as a yellow amorphous solid (8.2 mg, 9.47 µmol, 40%). [α]$_D^{24}$ = +27.2° (*c* 0.8, DMSO); ^{1}H-NMR (600 MHz, DMSO-d$_6$): δ = 12.9 (1H, br. s, CO$_2$*H*), 12.2 (1H, br. s, O*H*), 11.0 (1H, s, N*H*), 10.8 (1H, s, N*H*), 10.4 (1H, s, N*H*), 9.22 (1H, dd, *J* = 0.7, 2.0 Hz, Ar*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.61 (1H, dd, *J* = 2.0, 8.2 Hz, Ar*H*), 8.43 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.31 (1H, dd, *J* = 0.7, 8.2 Hz, Ar*H*), 8.06 (2H, m, Ar*H*), 7.99 – 7.87 (9H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.50 (2H, d, *J* = 43.0 Hz, CONH$_2$), 7.37 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.91 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.24 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OC*H*$_3$), 1.02 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH$_2$), 168.2 (q, *C*ONH), 167.5 (q, *C*ONH), 166.8 (q, *C*O$_2$H), 165.4 (q, *C*ONH), 161.7 (q, *C*ONH), 154.5 (q, C-Ar), 152.3 (q, C-Ar), 151.5 (t, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 142.3 (t, C-Ar), 141.9 (q, C-Ar), 141.0 (q, C-Ar), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 134.4 (q, C-Ar), 130.3 (2C, t, C-Ar), 129.3 (q, C-Ar), 128.2 (2C, t, C-Ar), 126.5 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.5 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.6 (2C, t, C-Ar), 119.9 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 118.4 (q, C-Ar), 116.7 (q, CN), 114.8 (t, C-Ar), 111.8 (q, C-Ar), 80.1 (t, *C*HOMe), 75.7 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.6 (t, *C*HNH), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for C$_{44}$H$_{39}$N$_{10}$O$_{10}$ [M + H]$^+$: 867.2851; found 867.2857.

4-(4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(4-cyano-3-fluorobenzamido)benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)-benzoic acid (49): Following the general procedure V phenol **S22** (22.4 mg, 23.8 µmol, 1.0 eq) was stirred for 2 h. Acid **49** was obtained as a beige amorphous solid (21.0 mg, 23.8 µmol, quant.). [α]$_D^{24}$ = +39.5° (*c* 1.3, DMSO); ^{1}H-NMR (600 MHz, DMSO-d$_6$): δ = 12.8 (1H, br. s, CO$_2$*H*), 12.2 (1H, br. s, O*H*), 10.8 (1H, s, N*H*), 10.8 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.45 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.16 – 8.13 (1H, m, Ar*H*), 8.09 – 8.07 (1H, m, Ar*H*), 8.00 – 7.96 (4H, m, Ar*H*), 7.93 – 7.87 (8H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.51 (2H, d, *J* = 47.9 Hz, CONH$_2$), 7.37 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.25 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OC*H*$_3$), 1.03 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH$_2$), 168.2 (q, *C*ONH), 167.5 (q, *C*ONH), 166.9 (q, *C*O$_2$H), 165.4 (q, *C*ONH), 163.2 (q, *C*ONH), 162.2 (d, *J* = 256.3 Hz, *C*-F), 154.5 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 141.9 (q, C-Ar), 141.5 (d, *J* = 6.1 Hz, *C*CONH), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 134.4 (d, *J* = 7.0 Hz, *C*HCCN), 130.7 (q, C-Ar), 130.3 (2C, t, C-Ar), 129.2 (q, C-Ar), 128.8 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.5 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 124.7 (d, *J* = 3.4 Hz, CH*C*HCCONH), 123.5 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.6 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.4 (q, CN), 115.8 (d, *J* = 21.3 Hz, *C*HCF), 114.8 (t, C-Ar), 113.6 (q, C-Ar), 102.9 (d, *J* = 15.3 Hz, *C*CN), 80.1 (t, *C*HOMe), 75.7 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.7 (t, *C*HNH), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for C$_{45}$H$_{39}$N$_9$O$_{10}$F [M + H]$^+$: 884.2804; found 884.2808.

4-(4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(isonicotinamido)benzamido)-3-methoxy-4-oxo-butanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)-benzoic acid (50): Following the general procedure V phenol **S23** (16.5 mg, 18.4 µmol, 1.0 eq) was stirred for 4 h. Acid **50** was obtained as a yellow amorphous solid (13.7 mg, 16.3 µmol, 89%). [α]$_D^{24}$ = +22.6° (*c* 1.4, DMSO); ^{1}H-NMR (500 MHz, DMSO-d$_6$): δ = 12.2 (1H, br. s, O*H*), 10.8 (1H, s, N*H*), 10.8 (1H, s, N*H*), 10.4 (1H, s, N*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.85 (2H, m, Ar*H*), 8.44 (1H, d, *J* = 8.0 Hz, N*H*CH), 8.13 – 7.87 (13H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.50 (2H, d, *J* = 31.9 Hz, CONH$_2$), 7.37 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.92 (1H, t, *J* = 8.0 Hz, C*H*NH), 4.25 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.0 Hz, C*H*OMe), 3.32 (3H, s, OC*H*$_3$), 1.03 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH$_2$), 168.2 (q, *C*ONH), 167.5 (q, *C*ONH), 166.9 (q, *C*O$_2$H), 165.4 (q, *C*ONH), 164.1 (q, *C*ONH), 154.5 (q, C-Ar), 149.8 (2C, t, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 141.9 (q, C-Ar), 141.5 (q, C-Ar), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 134.4 (q, C-Ar), 130.3 (2C, t, C-Ar), 129.2 (q, C-Ar), 128.3 (2C, t, C-Ar), 126.5 (q, C-Ar), 125.9 (q, C-Ar),125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.5 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 122.0 (2C, t, C-Ar), 120.6 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.7 (2C, t, C-Ar), 118.4 (q, C-Ar), 114.8 (t, C-Ar), 80.1 (t, *C*HOMe), 75.7 (t, *C*H(CH$_3$)$_2$), 57.7 (p, OCH$_3$), 55.7 (t, *C*HNH), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for C$_{43}$H$_{40}$N$_9$O$_{10}$ [M + H]$^+$: 842.2898; found 842.2903.

4-(4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(6-cyanonicotinamido)benzamido)-3-methoxy-4-oxo-butanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxybenzamido)benzoic acid (51): Following the general procedure V phenol **S24** (24.4 mg, 26.5 µmol, 1.0 eq) was stirred for 5 h. Acid **51** was obtained as a beige amorphous solid (15.6 mg, 18.0 µmol, 68%). [α]$_D^{22}$ = +25.1° (*c* 1.5, DMSO); ^{1}H-NMR (600 MHz, DMSO-d$_6$): δ = 12.8 (1H, br. s, CO$_2$*H*), 12.2 (1H, br. s, O*H*), 10.9 (1H, br. s, N*H*), 10.8 (1H, s, N*H*), 10.4 (1H, s, N*H*), 9.24 – 9.23 (1H, m, Ar*H*), 8.93 (1H, s, C*H*$_{Triazol}$), 8.55 – 8.53 (1H, m, Ar*H*), 8.45 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.26 – 8.25 (1H, m, Ar*H*), 8.00 – 7.87 (11H, m, Ar*H*), 7.79 (2H, m, Ar*H*), 7.50 (2H, d, *J* = 46.3 Hz, CONH$_2$), 7.37 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.92 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.25 (1H, hept, *J* = 6.0 Hz, C*H*Me$_2$), 4.09 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.32 (3H, s, OC*H*$_3$), 1.03 (6H, d, *J* = 6.0 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (125 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH$_2$), 168.2 (q, *C*ONH), 167.5 (q, *C*ONH), 166.8 (q, *C*O$_2$H), 165.3 (q, *C*ONH), 163.0 (q, *C*ONH), 154.5 (q, C-Ar), 150.2 (t, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 141.9 (q, C-Ar), 141.5 (q, C-Ar), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 137.3 (t, C-Ar), 134.5 (q, C-Ar), 134.4 (q, C-Ar), 133.4 (q, C-Ar), 130.3 (2C, t, C-Ar), 129.2 (q, C-Ar), 128.8 (t, C-Ar), 128.3 (2C, t, C-Ar), 126.5 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.5 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.6 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.6 (2C, t, C-Ar), 118.4 (q, C-Ar), 117.1 (q, CN), 114.8 (t, C-Ar), 80.0 (t, *C*HOMe), 75.7 (t, *C*H(CH$_3$)$_2$),

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57.7 (p, O*C*H$_3$), 55.6 (t, *C*HNH), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{44}H_{39}N_{10}O_{10}$ [M + H]$^+$: 867.2851; found 867.2858.

4-(4-(4-(4-((2*S*,3*R*)-4-Amino-2-(4-(3-(4-cyanophenyl)-propanamido)-benzamido)-3-methoxy-4-oxobutanamido)phenyl)-1H-1,2,3-triazol-1-yl)-2-hydroxy-3-isopropoxy-benzamido)benzoic acid (52): Following the general procedure V phenol **S25** (19.8 mg, 20.9 µmol, 1.0 eq) was stirred for 4.5 h. Acid **52** was obtained as a grey amorphous solid (18.6 mg, 20.9 µmol, quant.). $[\alpha]_D^{24}$ = +20.8° (*c* 1.9, DMSO); ^{1}H-NMR (400 MHz, DMSO-d$_6$): δ = 12.8 (1H, br. s, CO$_2$*H*), 12.2 (1H, br. s, O*H*), 10.8 (1H, s, N*H*), 10.3 (1H, s, N*H*), 10.2 (1H, s, N*H*), 8.92 (1H, s, C*H*$_{Triazol}$), 8.35 (1H, d, *J* = 8.1 Hz, N*H*CH), 8.00 – 7.95 (3H, m, Ar*H*), 7.93 – 7.87 (4H, m, Ar*H*), 7.82 – 7.75 (6H, m, Ar*H*), 7.67 (2H, m, Ar*H*), 7.53 – 7.45 (4H, m, Ar*H*, CONH$_2$), 7.37 (1H, d, *J* = 8.6 Hz, Ar*H*), 4.90 (1H, t, *J* = 8.1 Hz, C*H*NH), 4.25 (1H, hept, *J* = 6.1 Hz, C*H*Me$_2$), 4.07 (1H, d, *J* = 8.1 Hz, C*H*OMe), 3.31 (3H, s, OC*H*$_3$), 3.01 (2H, t, *J* = 7.5 Hz, ArC*H*$_2$CH$_2$), 2.71 (2H, t, *J* = 7.5 Hz, ArCH$_2$C*H*$_2$), 1.02 (6H, d, *J* = 6.1 Hz, CH(C*H*$_3$)$_2$) ppm; ^{13}C-NMR (100 MHz, DMSO-d$_6$): δ = 171.0 (q, CONH$_2$), 170.4 (q, *C*ONH), 168.2 (q, *C*ONH), 167.5 (q, *C*ONH), 166.8 (q, *C*O$_2$H), 165.4 (q, *C*ONH), 154.5 (q, C-Ar), 147.3 (q, C-Ar), 146.3 (q, C-Ar$_{Triazol}$), 142.1 (q, C-Ar), 141.9 (q, C-Ar), 138.9 (q, C-Ar), 138.7 (q, C-Ar), 134.4 (q, C-Ar), 132.2 (2C, t, C-Ar), 130.3 (2C, t, C-Ar), 129.5 (2C, t, C-Ar), 128.3 (2C, t, C-Ar), 128.0 (q, C-Ar), 126.5 (q, C-Ar), 125.8 (2C, t, C-Ar), 125.4 (q, C-Ar), 123.5 (t, C-Ar), 122.6 (t, C-Ar$_{Triazol}$), 120.6 (2C, t, C-Ar), 119.8 (2C, t, C-Ar), 119.0 (q, C-Ar), 118.4 (q, CN), 118.2 (2C, t, C-Ar), 114.8 (t, C-Ar), 108.9 (q, C-Ar), 80.1 (t, *C*HOMe), 75.7 (t, *C*H(CH$_3$)$_2$), 57.7 (p, O*C*H$_3$), 55.6 (t, *C*HNH), 37.1 (s, ArCH$_2$*C*H$_2$), 30.6 (s, Ar*C*H$_2$CH$_2$), 21.8 (2C, p, CH(*C*H$_3$)$_2$) ppm; HRMS (ESI): *m/z* calc. for $C_{47}H_{43}N_9O_{10}$ [M + H]$^+$: 916.3031; found 916.3029.

Biological Activity

Minimal inhibitory concentrations (MIC). MIC values were determined in standard microbroth dilution assays as described elsewhere[1,2].

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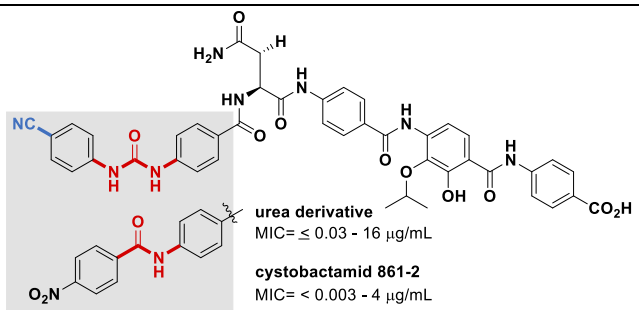
Entry for the Table of Contents

FULL PAPER

Fighting Gram-negative and Gram-positive bacteria: Thirteen new cystobactamids, that derive from cystobactamid 861-2 are prepared by chemical synthesis. Main modifications are exchange of the amide group by the chemically more stable urea group and the triazole ring as well as located in ring A. Antibiotic activities against Gram-negative and -positive bacteria including a multidrug-resistant strain can be preserved, when the urea function is located between rings A and B and the triazole is positioned beween rings C and D.



Antibiotics

*T. Planke, K. Cirnski, J. Herrmann, R. Müller, A. Kirschning**

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Synthetic and Biologic Studies on New Urea and Triazole Containing Cystobactamid Derivatives