Bioorganic & Medicinal Chemistry 17 (2009) 1307–1324

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Solid-phase parallel synthesis and SAR of 4-amidofuran-3-one inhibitors of cathepsin S: Effect of sulfonamides P3 substituents on potency and selectivity

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ARTICLE INFO

Article history:
Received 14 August 2008
Revised 3 December 2008
Accepted 8 December 2008
Available online 24 December 2008

Keywords:
Serin protease
Inhibitors
Cathepsin K
Cathepsin S
Reversible covalent inhibition

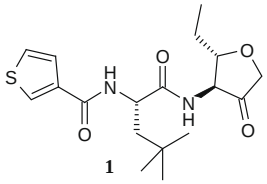
ABSTRACT

Highly potent and selective 4-amidofuran-3-one inhibitors of cathepsin S are described. The synthesis and structure–activity relationship of a series of inhibitors with a sulfonamide moiety in the P3 position is presented. Several members of the series show sub-nanomolar inhibition of the target enzyme as well as an excellent selectivity profile and good cellular potency. Molecular modeling of the most interesting inhibitors describes interactions in the extended S3 pocket and explains the observed selectivity towards cathepsin K.

1. Introduction

Cathepsin S (Cath S) is a cysteine protease of the papain superfamily,[1] being mainly expressed within cells of lymphoid origin and in particular in antigen presenting cells (APCs) such as dendritic cells, B-lymphocytes, and macrophages. The best characterized function of Cath S within APCs relates to its pivotal role in major histocompatibility class II (MHC-II) restricted antigen presentation to CD4+ T-lymphocytes. Cathepsin S it mediates the final proteolytic cleavage of the invariant chain (Ii) chaperone molecule[2] thereby facilitating the subsequent presentation of MHC-II associated peptides to CD4+ T-cells; a crucial step in the initiation of a CD4+ T-cell-mediated immune response. Therefore, selective inhibition of Cath S will block the degradation of the intermediate p10 invariant chain proteolytic fragment (Ii p10), reducing MHC-II associated antigen presentation and thereby acting as an immunosuppressive agent. Thus, inhibition of the proteolytic activity of Cath S is an attractive target for drug development with such inhibitors having potential for modulation and regulation of autoimmune diseases such as multiple sclerosis (MS) and rheumatoid arthritis (RA), and allergic disorders, such as asthma.[3]

The high sequence homology between Cath S, L, and K offers considerable challenges in designing selective Cath S inhibitors. We have previously reported on novel 4-amidofuran-3-ones as potent Cath S inhibitors,[4] represented by compound **1**, with a K_i value of 31 nM. Importantly, analogs of this series are equipotent against mouse and rat Cath S, allowing proof-of-principle studies to be carried out in rodent models of human disease, such as multiple sclerosis and rheumatoid arthritis.



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Using the numbering from the PDB entry 1MS6 (Cath S) the distal region of the S3 subsite of Cath S is defined by backbone Gly62 and the side chains of Lys64 and Phe70. Modelling studies of the binding of inhibitor **1** to the site of Cath S suggested that there were unused interaction possibilities in the S3 subpocket, and it seemed that the carbonyls of Gly62 and Asn67 were prime candidates for potential hydrogen bond acceptors. Lys64 was suggested as a possible hydrogen bond donor, but with less certainty due to the flexibility of the side chain.

The use of rational and structure based drug design led us to compound **11** with methyl cyclopentyl alanine as the preferred

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doi:10.1016/j.bmc.2008.12.020

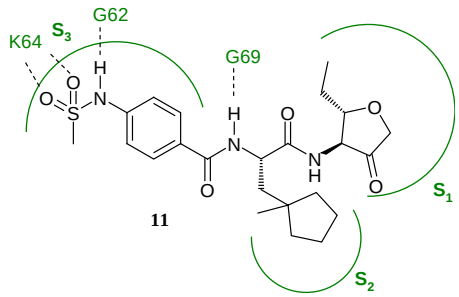


Figure 1. Schematic representation of the predicted binding mode of inhibitor **11** within the active site of human Cath S. The sulfonamide moiety is assumed to bind in the S3 pocket, the cyclopentyl group within the hydrophobic S2 binding pocket and the C5-ethyl furanone in the S1 site.

P2 side chain and a sulfonamide moiety as an extended P3 motif (Fig. 1). The compound showed good inhibitory activity against Cath S (K_i = 2.6 nM), with a 10-fold increase in potency compared to compound **1**, and with moderate selectivity towards Cath K and good selectivity versus Cath L (see Table 5). The encouraging properties of compound **11** supported a more detailed exploration of this class of inhibitors focusing in particular on the S3 pocket of Cath S.

Some recent studies have indicated that structural differences observed in the S3 pockets of Cath S, K, and L give different preferences for the P3 substituents.[5a,b] The reduced size of the S3 pocket in Cath S has previously been recognized from the crystal structures of Cath S inhibitor complexes,[6] and the preference for a larger P3 substituent in S3 of Cath K has also been established.[7] However, in other experimental endeavors,[5c–e] receptor optimization calculations revealed that a unique Lys64 residue residing in the Cath S S3 pocket can re-orient its side chain to accommodate an extended P3 moiety of the inhibitor. This feature provides new opportunities for targeting selectivity when considered in combination with the selectivity requirements of the S2 pocket, which, in Cath S, accepts significantly larger groups compared to the S2 pocket in Cath K.

In this report we detail our investigations to explore the scope of the sulfonamide moiety at the P3 residue of the C5-ethyl furanones, while keeping the P2 and P1 residues constant (Fig. 2) in order to ascertain how it affects the potency and the selectivity profile.

2. Results and discussion

2.1. Chemistry

The solid-phase parallel synthesis of dihydro-2(3*H*)-5-ethyl furanones **11**–**56** containing sulfonamide moieties as P3 motifs (see structures in Tables 1–4) is depicted in Scheme 1.

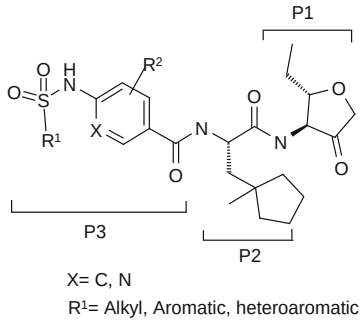


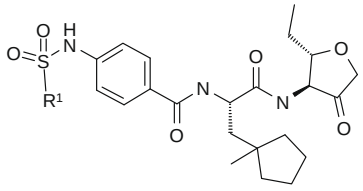
Figure 2. Schematic representation of the intended P3 variations on the Cat S C5-ethyl furanones inhibitors.

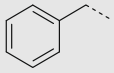
Table 1
Results on inhibitory activity

Compound	P3 acid	R^1	K_i (nM) Cath S
1			31
11	**6g**		2.6
12	**6f**		12
13	**6j**		110
14	**6e**		140
15	**6h**		190

Dihydro-(4*S*-amino-[*N*-Fmoc])-5*S*-ethyl-3(2*H*)-furanone (**2**) synthesized as previously reported,[4] was treated with the Webb's linker acid[8] in MeOH. The resulting semicarbazone acid linker was obtained in 85% yield. This linkage not only temporarily blocks the reactive carbonyl functionality but also serves as an anchor for the construction of the inhibitor via parallel synthesis. To utilize this anchor, treatment of the linker with the aminomethyl functionalized polymer support[9] (0.24 mmol/g) in the presence of *N*-[(1*H*-benzotriazole-1-yl)-(dimethylamino)methylene]-*N*-methylm ethanaminium hexafluorophosphate *N*-oxide (HBTU), 1-hydroxybenzotriazole (HOBt), and *N*-methyl morpholine (NMM) in DMF afforded the P1 bound

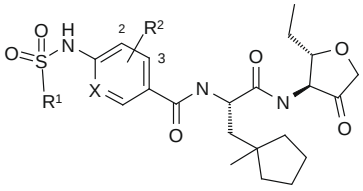
Table 2
Effect of R^1 substituent on inhibitory activity



Compound	P3 acid	R1	*K*i (nM) Cath S
16	**7v**	Et	1.9
17	**7w**	*n*-But	3.4
18[a]	—		8.3
19	**7b**		2.9
20	**7f**		2.4
21	**6a**		180
22	**6i**		5.3
23	**6b**		0.8
24	**6c**		31

[a] The compound was synthesized following the procedure described in Scheme 1, step f. See also experimental part.

Table 3
Effect of variations at the central ring on inhibitory activity



Compound	P3 acid	R^1	R^2	X	K_i (nM) Cath S
25	**7a**	Me	2-OMe	C	26
26	**7e**	Me	3-OMe	C	330
27	**6k**	Me	2-Me	C	4.9
28	**7c**	Me	3-Me	C	30
29	**7d**	Me	2-Cl	C	5.6
30	**7g**	Me	2-F	C	16
31	**7h**	Me	2-COMe	C	57
32	**7n**	Ph	2-Me	C	4
33	**7o**	Ph	2-Cl	C	12
34	**7r**	Ph	H	N	56
35	**7s**	Me	H	N	63

resin **3**. Deprotection of resin **3** with 20% piperidine in DMF followed by standard amino acid coupling of Fmoc protected methyl cyclopentane alanine amino acid[10] **4** employing HBTU, HOBt, and NMM in DMF provided P2–P1 resin **5**. After standard removal of the Fmoc group, the P3 acids **6**–**9** (Figs. 3–6) were coupled using the same coupling conditions as described above furnishing P3–P2–P1 resins **10**. A slightly different procedure was employed for target furanones **18** (Table 2) and **43–45** (Table 4) where the coupling of the P3 acid residue was performed in two steps: attachment of 4-amino benzoic acid onto de-protected P2–P1 resin **5** under standard amino acid coupling conditions (HBTU, HOBt, NMM) and subsequent acylation with the corresponding sulfonyl chloride using DMAP and pyridine in DCM. Final acidic hydrolysis with 95% aqueous TFA cleaved the target ketones **11–56** (Tables 1–4) from the Webb linker bound resin in 75–80% yields. Catalytic hydrogenation using H_2 in the presence of Pd/C was required to provide target **40** (Table 4).

The structures of the commercially available P3 acids **6** utilized for the synthesis of target compounds **11**–**15**, **21**–**24**, **27**, and **51** are shown in Figure 3.

Schemes 2–4 depict the synthesis of the non-commercially available P3 acids **7–9** (Figs. 4–6). A general procedure for the synthesis of the P3 acids **7** (Fig. 4) utilized for the synthesis of target compounds **16**–**17**, **19**–**20**, **25**–**26**, **28**–**42**, **50**, and **52** is described in Scheme 2 where a 4-amino benzoic acid methyl ester derivative is acylated by a sulfonyl chloride derivative using pyridine and a catalytic amount of DMAP in DCM providing the P3 capping group methyl esters. Basic hydrolysis of the methyl ester function furnished the required P3 acids **7a–w** in 3–98% overall yields.

An alternative approach[11a] was used for the synthesis of the P3 acids **8** (Fig. 5) utilized for target compounds **46–49** (Table 4) and is depicted in Scheme 3.

Trifluoromethane sulfonic acid anhydride was reacted with polymer supported triphenylphosphine oxide[11b] in DCM followed by addition of cold pyridinium salt of the corresponding pyridine sulfonic acid and subsequent addition of the corresponding 4-amino benzoic acid derivative to afford the P3 capping group methyl esters. Basic hydrolysis with lithium hydroxide as previously described furnished the P3 acids **8a–d** in 13–25% overall yields.

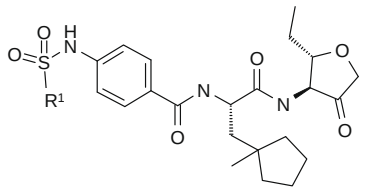
The P3 thiazole sulfonic acids **9** (Fig. 6) required for the synthesis of target compounds **53**–**56** (Table 4) were synthesized following the synthetic procedure depicted in Scheme 4. Thiazoles (utilized for the synthesis of **9b–d**) were treated with the Grignard reagent isopropylmagnesium chloride in methyl *tert*-butylether at 0 °C followed by subsequent treatment with sulfur dioxide in dimethoxyether at 40 °C and addition of chlorosuccinimide at 0 °C to afford the corresponding thiazole-2-sulfonyl chlorides in 59–91% yield.[12a] These sulfonyl chlorides and commercially available 2,4-dimethyl-thiazole-5-sulfonyl chloride (for the synthesis of compound **9a**) were reacted (as shown in Scheme 2) with 4-amino benzoic acid methyl ester and the methyl ester group subsequently hydrolyzed under basic conditions to give P3 acids **9a–d** in 13–62% overall yields 4-Isopropyl thiazole needed for the synthesis of **9d** was synthesized according to literature procedures in 70% yield[12b] and further treated as described above for the commercially available thiazoles.

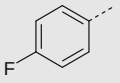
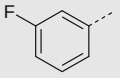
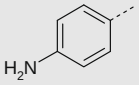
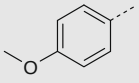
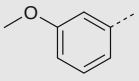
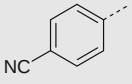
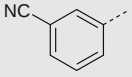
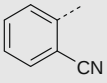
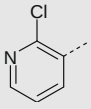
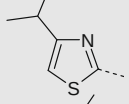
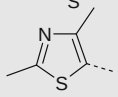
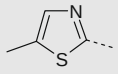
2.2. Biological data and structure–activity relationships

The target compounds, summarized in Tables 1–4, were screened for inhibitory activity against human Cath S, K, and L to determine K_i values.

Table 1 shows the SAR around the initial lead compound **11**. Compound **12**, with the methyl sulfonamide moiety placed at the *meta* position in the phenyl ring, afforded a four times reduction in Cath S inhibitory activity (K_i = 12 nM), indicating the preference for the substitution at the *para* position. Methylation of the nitrogen of the sulfonamide **13** was detrimental for enzyme activity, with a 50-fold reduction in activity, as was also the case for com-

Table 4
Effect of aromatic substituents and heteroaromatic ring P3 capping group R^1 substituent on inhibitory activity



Compound	P3 acid	R^1	K_i (nM) Cath S
36	**7j**		2.0
37	**7i**		3.4
38	**7m**		3.8
39	**7l**		3.9
40	**7t**		1.3
41	**7q**		3.3
42	**7p**		1.0
43[a]	–		1.1
44[a]	–		0.6
45[a]	–		0.8
46	**8c**		2.7
47	**8a**		2.1
48	**8b**		2.3
49	**8d**		0.9
50	**7u**		5.9
51	**6d**		2.3
52	**7k**		4.5
53	**9b**		13
54	**9d**		5.7
55	**9a**		0.7
56	**9c**		8.6

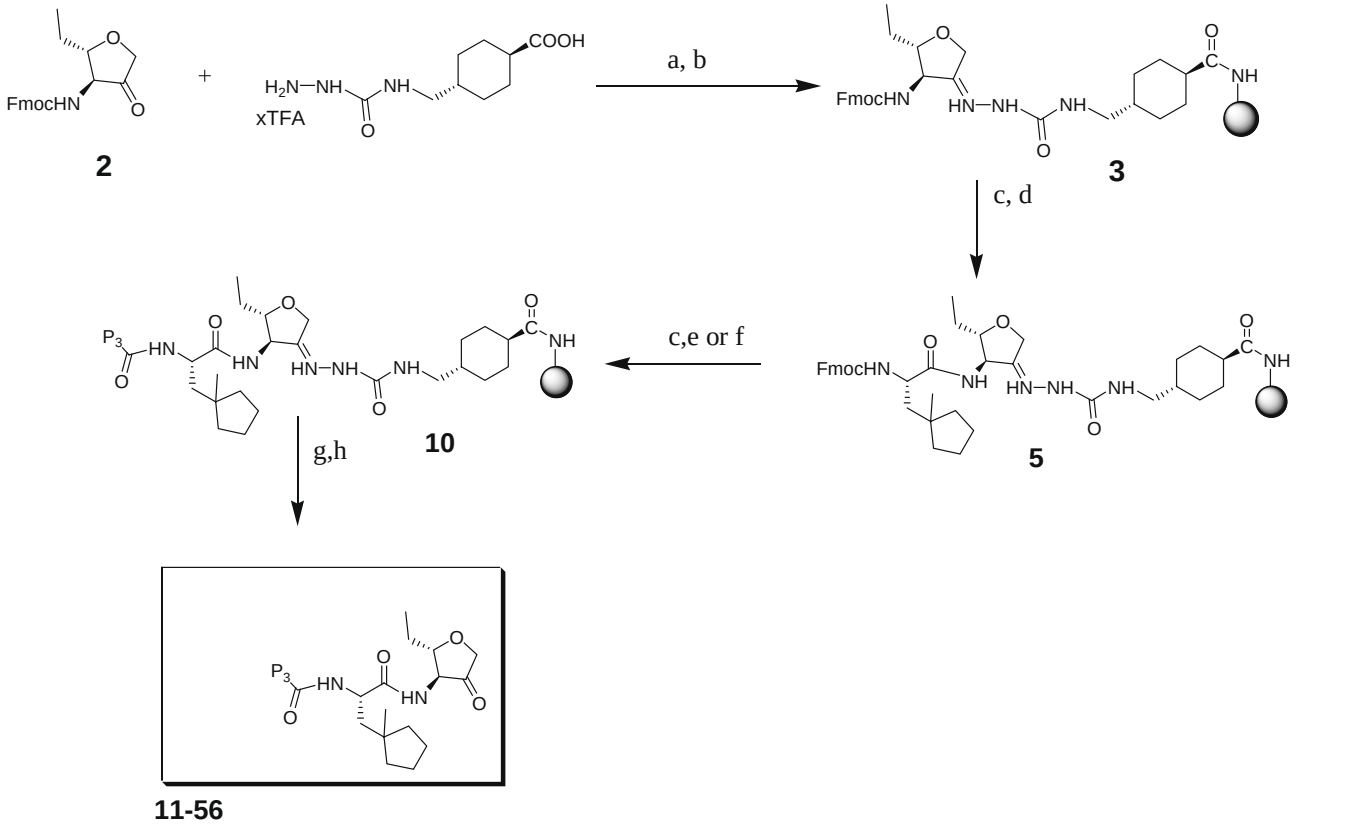
[a] The compounds were synthesized according to Scheme 1, step f. See also experimental part.

pounds **14** and **15** with reversed sulfonamides. These results highlight the importance of the NH and the phenyl substitution pattern for interactions in the S3 pocket.

The effect of the R^1 substituent on the sulfonamide moiety was also investigated, as shown in Table 2. Analysis of the data indicated a preference for the phenyl group (**23**), with an increase in inhibitory activity (K_i = 0.8 nM). Small unbranched alkyl chains (**16**, **17**) and small branched alkyl chains and rings (**19**, **20**) were well tolerated; however, larger rings (**21**) had a detrimental effect. A slight loss in potency was observed for other groups (**18**, **22**). Elongation of the phenyl substituent (**24**) led to a considerable drop in activity compared to compound **23**. From these data, it can be concluded that the phenyl substituent at R^1 is most preferred (**23**) affording a modest improvement in the Cath S K_i value compared to the parent compound **11**.

Table 3 shows the SAR around the variations at the central phenyl ring. Diverse R^2 substituents at the 2- and 3-positions of the ring and the exchange of the phenyl for a pyridine ring were explored. A loss of inhibitory activity was observed for all these compounds, with substitutions at the 2-position of the phenyl ring better tolerated than at the 3-position (**25** vs **26**, **27** vs **28**). Small substituents such as a methyl group in targets **27** and **32** with K_i values of 4.9 nM and 4 nM, respectively, were better tolerated than larger groups (**25**, K_i = 26 nM and **31**, K_i = 57 nM). Despite the fact that substitutions at the 2-position were best tolerated in terms of potency, in general, decorations of the central phenyl ring by the introduction of R^2 substituents did not improve activity, compared to the corresponding unsubstituted compounds **11** (Table 1) and **23** (Table 2) both of which have highly favorable K_i values of 2.7 nM and 0.8 nM, respectively. Pyridine analogs of the phenyl compounds **11** and **23**, namely compounds **34** and **35**, respectively, were considerably less potent (with K_i values of 56 nM and 63 nM, respectively).

The encouraging results obtained for compound **23** (Table 2) prompted us to further explore the SAR around this new lead. Table 4 shows the variations explored at the distal phenyl ring of the sulfonamide. Substitutions at different positions on the phenyl ring with electron withdrawing groups (**36**–**38**, **43**–**45**), electron donating groups (**39**, **41**–**42**), and amino groups (**40**) were explored. Replacement of the distal phenyl ring with heterocycles such as pyridine



Scheme 1. Solid-phase synthesis of dihydro-2(3*H*)-5-ethyl furanone inhibitors. Reagents and conditions: (a) MeOH, 70 °C 2 h, then rt 2 h, 85%; (b) amino resin,[9] HBTU, HOBt, NMM, DMF, 16 h; (c) 20% piperidine in DMF, 1 h; (d) Fmoc-(methylcyclopentyl)-alanine-OH (**4**),[10] HBTU, HOBt, NMM, DMF, 16 h; (e) P3 acid (**6**–**9**),* HBTU, HOBt, NMM, DMF; (f) for compounds **18**, **43**–**45**; 4-amino benzoic acid, HBTU, HOBt, NMM, DMF, 16 h; then, R^1SO_2Cl, DMAP, Py, DCM, 16 h; (g) 95%TFA/H_2O, 1 h; (h) additional step for compound **36**: H_2, Pd/C, MeOH, 2h, 91%. * For non-commercially available P3 acids **7**–**9**, see Schemes 2–4.

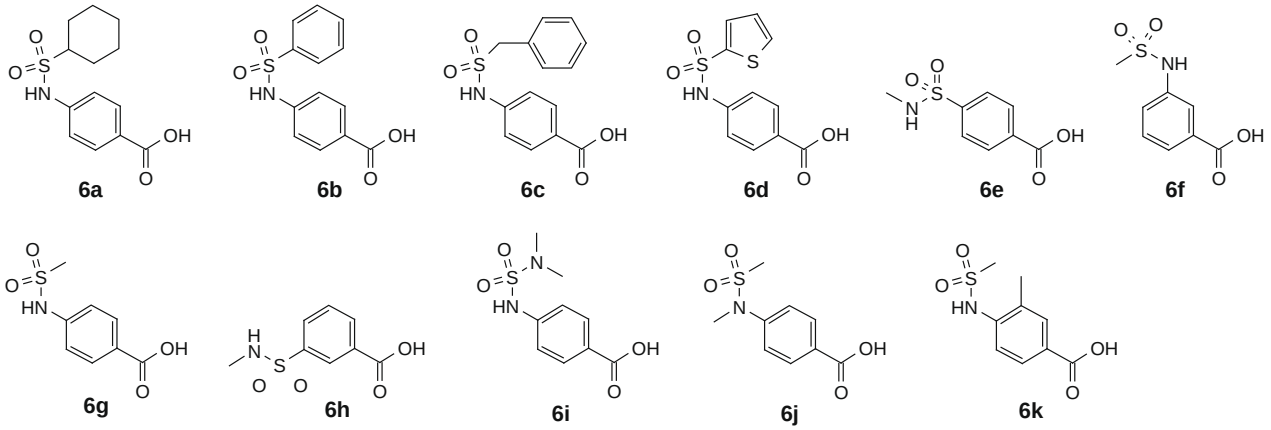


Figure 3. Commercially available P3 acids **6**.

(**46**–**50**), thiophene (**51**), imidazole (**52**) and thiazoles (**53**–**56**) were also investigated. The majority of these inhibitors show good affinity for Cath S, broadly comparable to that of the parent lead compound **23** where some of the most potent compounds have K_i values of 0.7 nM, representing a further increase in potency compared to initial compound **11** (Table 1). Pyridine rings were also well tolerated (**46**–**50**), (K_i values of 0.9–5.9 nM). However, chloro substituted pyridine **50** led to reduced activity (K_i = 5.9 nM) and methyl substituted pyridine **49** was the preferred substituent amongst the set (K_i = 0.9 nM). It was observed that the replacement of the distal phenyl ring for a thiophene (**51**) provided a compound with good inhibitory activity against Cath S (K_i = 2.3 nM), while other heteroaromatic rings such as imidazole (**52**), and 2,5-thiazoles (**53**, **54**, **56**) led to a 5–10-fold reduction in activity compared to compound **23**. Surprisingly, the 2,4-thiazole **55** proved to be a highly potent compound, with a K_i value of 0.7 nM.

All compounds were assayed in a selectivity assay, measuring the K_i values for the related human Cath K and L. As shown in Table 5, all compounds were highly selective against Cath L (>1000×) and affinity for Cath K varies from 98 nM to >20000 nM. The lead compound **11** has a 100-fold selectivity over Cath K, this being a 10-fold improvement in Cath K selectivity compared to the original lead compound **1**. No selectivity between Cath S and K was found for some of the target compounds (**13**, **14**) and loss of selectivity (<100-fold) was observed for a number of targets (**21**, **22**, **24**, **25**–**28**, **30**–**31**, and **34**–**35**). How-

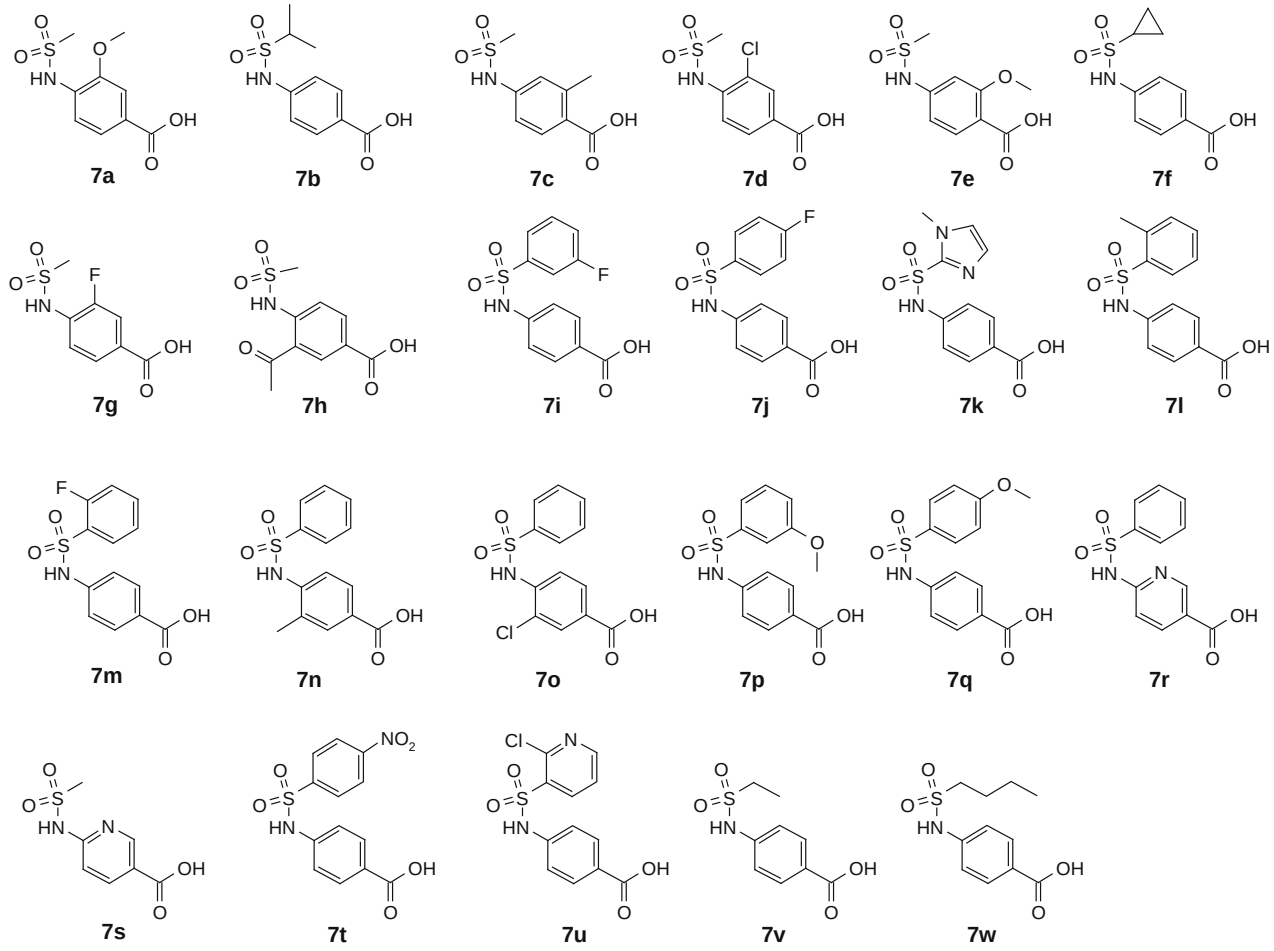


Figure 4. Structures of P3 acids **7**.

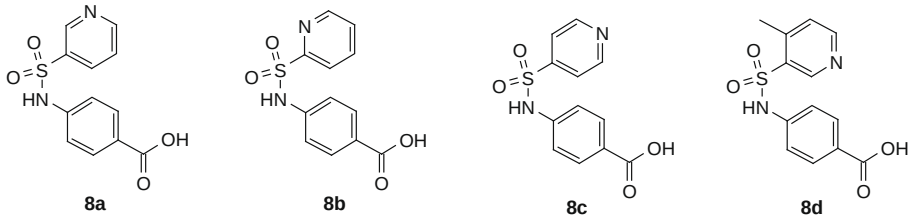


Figure 5. Structures of P3 acid **8**.

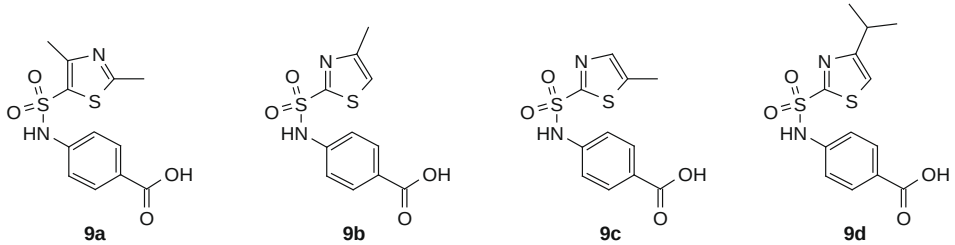
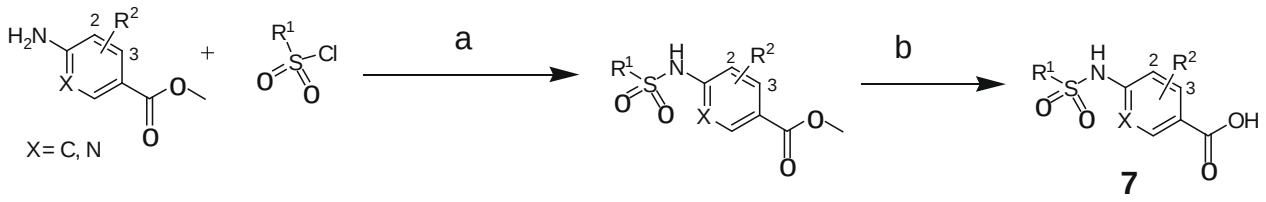
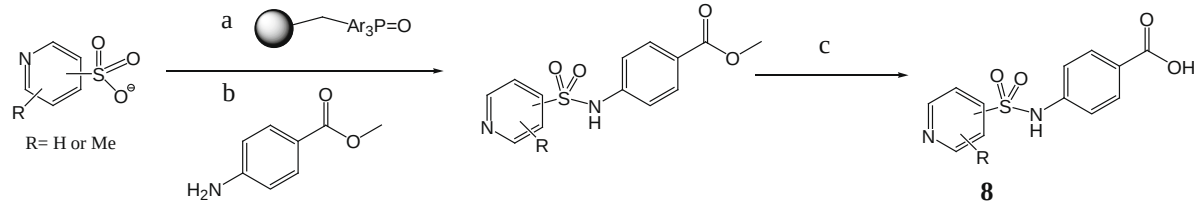


Figure 6. Structure of P3 acids **9**.

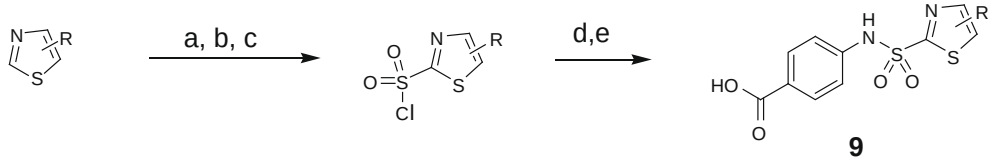
ever, a very interesting finding was made in that the improved Cath S inhibitory activity obtained for compound **23** was complemented by an increase in selectivity towards Cath K (>500-fold), representing a 5-fold increase in selectivity compared to initial compound **11**. The same trend was found for compounds **44**, **45**, and **55**, where the affinity for Cath S (K_i values of 0.6 nM, 0.8 nM, and 0.7 nM, respectively) was similar to compound **23**, but selectivity towards Cath K increased to >1000-fold for compounds **44**, **45** and >2600-fold for compound **55**. These analogs have therefore provided a significant improvement in Cath K



Scheme 2. General procedure for the synthesis of P3 acids **7** (Fig. 4). Reagents and conditions: (a) Py, DMAP, DCM; (b) LiOH (2.5 M), THF/MeOH 2:1, microwave 110 °C, 30 min.



Scheme 3. Synthesis of P3 acids **8** (Fig. 5). Reagents and conditions: (a) $(CF_3SO_2)_2O$, DCM, 1 h; (b) 16 h; (c) LiOH (2.5 M), THF/MeOH 2:1, microwave 110 °C, 30 min.



Scheme 4. Synthesis of P3 acids **9** (Fig. 6). Reagents and conditions: (a) *i*PrMgCl, *t*-BuOMe, 0 °C; (b) SO_2/DME, 0 °C > rt, 40 °C for 1 h; (c) *N*-chlorosuccinimide, 0 °C, 1 h; (d) 4-amino benzoic acid methyl ester, Py, DMAP, DCM; (e) LiOH (2.5 M), THF/MeOH 2:1, microwave 110 °C, 30 min.

selectivity compared to the original lead compound **11,** where a 24-fold improvement was seen and to compound **1**, where a 240-fold increase in selectivity is observed.

Selected compounds were tested for cellular potency, using a comparable assay to that described by Thurmond et al.[13] that quantifies the accumulation of the Ii p10 substrate of Cath S in the presence of inhibitor (Table 6). Most of the compounds showed greatly improved cellular potencies as compared to compound **11** (IC_{50} value of 1.7 μM) with IC_{50} values in the range of 0.31–0.062 μM. Despite the good enzymatic activity obtained for compound **44** we did not observe a corresponding increase in cellular potency, as was also the case for the pyridine analog **49** for which cellular activity was abolished. The reasons for the decreased cellular potency of **44** relative to compound **23** and the low cellular potency of **49** are not readily apparent, however factors that could influence this parameter include overall cell permeability, access to sub-cellular compartments containing Cath S and protein binding. Notably, compound **42** with a Cath S K_i value of 1.0 nM conferred the best cellular potency with an IC_{50} value of 62 nM, a 27-fold increase with respect to compound **11**.

2.3. Molecular modeling

Modeling was used to rationalize the SAR observed for the various P3 extensions, and to explain some of the selectivity towards Cath K. The model of Compound **11** (Fig. 7), built in the active site of Cath S of an in-house crystal structure, was used as a starting point.

The movement of the sulfonamide to the *meta* position as in compound **12** (Table 1) leads to a moderate reduction of the activity compared to compound **11**. This relatively small difference is due to a possibility for the sulfonamide NH to make a hydrogen bond to the back bone carbonyl of Asn67, instead of Gly62 as in compound **11**, while keeping the interaction with Lys64. The methylation of the sulfonamide nitrogen as in compound **13** removes the possibility to form this important hydrogen bond, thus leading to reduced potency.

The phenyl R^1 substituent on the sulfonamide gave the most potent inhibitor (compound **23**, Table 2). This increased potency is due to aromatic stacking of Phe70 with both the central and the distal phenyl groups in P3, whilst maintaining the hydrogen bonds to Gly62 and Lys64. The model of compound **23** (Fig. 8) shows the aromatic stacking with Phe70. The loss of potency for compound **21** having a cyclohexyl R^1 substituent and **24** having a benzyl substituent can be explained by the lack of aromatic stacking with Phe70. The smaller R^1 substituents (**16**–**20** and **22**) all have close contact interactions with Phe70, without altering the hydrogen bonds to Gly62 and Lys64, however none have the same advantageous aromatic stacking pattern as compound **23**.

The whole series is less active towards Cath K than Cath S. The selectivity for Cath S is approximately 100 times for compound **11** and increases to approximately 2600 times for compound **55** (Table 5). The structural explanation for this is mainly due to the lack of specific interactions with the sulfonamide in the S3 subsite of Cath K. Neither of the hydrogen bonds to Gly62 or Lys64 in Cath S are replaced by the corresponding Glu59 and Asp61, respectively, in Cath K. Even more interesting is the increased selectivity of the inhibitors with an aromatic substituent on the sulfonamide. This selectivity is due both to increased activity in Cath S and decreased activity in Cath K. The decreased Cath K activity of these inhibitors is due to the lack of hydrogen bond interactions with the sulfonamide and to a less defined aromatic stacking in the S3 subsite. A comparison of the active sites of Cath K and S is shown in Fig. 9, where a model of compound **55** is shown in the active site of Cath S.

Table 5
Selectivity assay: comparison of inhibitory activity of the compounds **11**–**56** in human Cath S, K and L enzymes

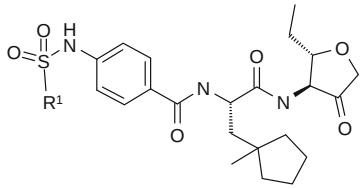
Compound	Cath S K_i (nM)	Cath K K_i (nM)	Cath L K_i (nM)	Cath K/Cath S
1	31	318	10,000	10
11	2.6	290	12,000	110
12	12	1500	2500	120
13	110	98	11,000	1
14	140	420	27,000	3
15	190	23,000	15,000	120
16	1.9	470	17,000	250
17	3.4	1500	21,000	440
18	8.3	1200	15,000	140
19	2.9	500	15,000	170
20	2.4	440	12,000	180
21	180	950	64,000	5
22	5.3	300	16,000	60
23	0.8	430	11,000	520
24	31	1700	15,000	50
25	26	560	7200	20
26	330	5000	29,000	10
27	4.9	240	2000	50
28	30	1900	23,000	60
29	5.6	840	970	150
30	16	700	7800	40
31	57	750	9500	10
32	4.0	730	2300	180
33	12	1600	1100	130
34	56	2200	31,000	40
35	63	1200	14,000	20
36	2.0	370	5900	180
37	3.4	520	7800	150
38	3.8	980	11,000	260
39	3.9	550	8400	140
40	1.3	950	9100	730
41	3.3	500	11,000	150
42	1.0	270	14,000	270
43	1.1	950	7900	860
44	0.6	730	6800	1140
45	0.8	820	8500	1040
46	2.7	1100	13,000	400
47	2.1	570	14,000	270
48	2.3	450	13,000	190
49	0.9	260	8700	280
50	5.9	800	23,000	130
51	2.3	1000	13,000	430
52	4.5	640	24,000	140
53	13	3000	27,000	230
54	5.7	1700	9100	300
55	0.7	1800	16,000	2610
56	8.6	2300	17,000	270

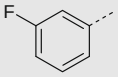
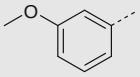
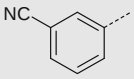
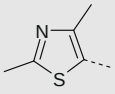
3. Conclusion

The solid-phase parallel synthesis and structure–activity relationship of a series of inhibitors with a sulfonamide moiety in the P3 position has resulted in the discovery of highly potent and selective 4-amidofurane-3-one inhibitors of Cath S.

This study demonstrates that it is possible to improve the inhibitory enzyme and cellular activities of the 4-amidofurane-3-ones class of compounds for Cath S cysteine protease through modification of the interactions in the S3 sub-site. Although the main selectivity determinant between Cath S and Cath K resides in the S2 pocket, we have shown in this report that through favorable interactions between the inhibitor and the S3 pocket of Cath S, further enhanced selectivity can be achieved (Table 5). Despite the existence of previous reports describing the smaller S3 pocket of Cath S in comparison to the S3 pocket of Cath K, the extended P3 sulfonamides reported herein show that inhibitors with large P3 groups can be accommodated in the S3 pocket of Cath S.

Table 6
Effect of R^1 substituent on the Ii p10 cell assay



Compound	R^1	K_i (nM) Cath S	Ii p10 IC_{50} (μM)
11	Me	2.6	1.7
23		0.8	0.12
37		3.4	0.15
42		1.0	0.062
44		0.6	1.4
49		0.9	>20
55		0.7	0.31

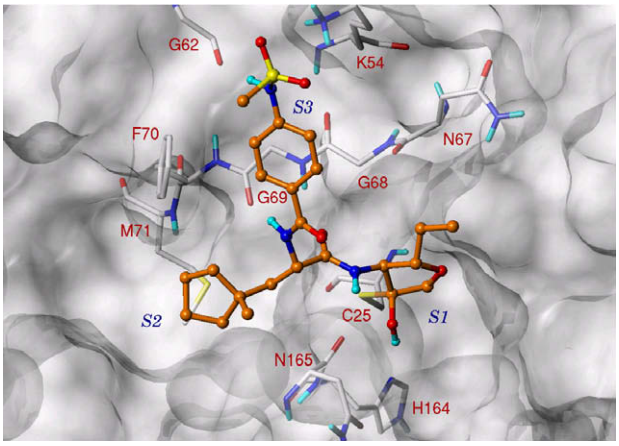


Figure 7. Compound **11** modeled in the active site of Cath S. Notably, the binding mode of the sulfonamide gives this series increased potency in Cath S. The subsites are denoted with S1 for subsite 1 etc.

The Cath S potency of these inhibitors can be attributed to the hydrogen bond network between the sulfonamide and two residues in the distal region of the S3 pocket. The incorporation of aromatic substituents on the sulfonamide moiety proved to be useful for improving the inhibitory enzyme and cellular potencies against Cath S and enzyme selectivity over Cath K.

After a detailed SAR analysis, we identified several highly potent inhibitors of Cath S, namely **23**, **42**, **44**, **45**, and **55** with an improved enzyme activity respect to compound **11** and 48 times with respect to compound **1** and with improved cellular potencies. Such

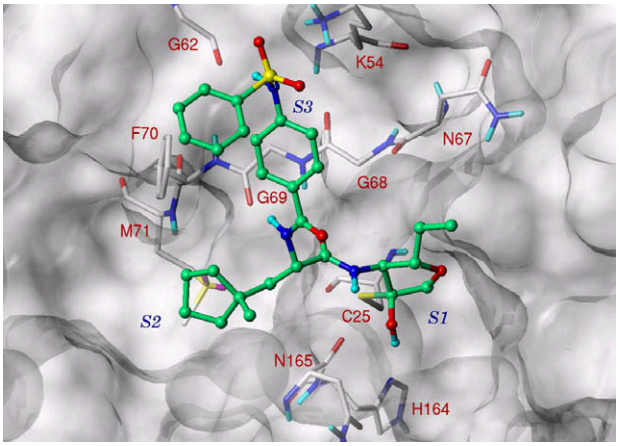


Figure 8. A model of compound **23** in the active site of Cath S. The additional aromatic stacking with Phe70, while maintaining the optimal interactions with the sulfonamide, increases the activity of compound **23** compared to compound **11**.

compounds were also highly selective towards the related proteases Cath K and L. Notably, the P3 thiazole sulfonamide compound **55** is of particular interest with an improvement in selectivity over Cath K of 24-fold and 5-fold improvement in selectivity over Cath L compared to compound **11**. In addition, compound **42** delivered an IC_{50} value of 62 nM, a 27-fold increase in cellular potency compared to initial compound **11**.

Whilst these compounds showed excellent potency and selectivity profiles the P3 sulfonamide moieties did not confer favorable in vitro drug metabolism and permeability properties, with compounds in general suffering from high metabolic liability and low predicted permeability in the CaCo-2 assay. Such properties did not support further development of this series of compounds.

4. Experimental

4.1. Biological assays

4.1.1. Enzyme assays

Cathepsins S and K were recombinant human enzymes expressed in *Baculovirus*, purified and activated in-house. Purified human cathepsin L was obtained form Calbiochem.

For cathepsin S the substrate was boc-Val-Leu-Lys-AMC, for cathepsin K the substrate was H-D-Ala-Leu-Lys-AMC and for cathepsin L the substrate was H-D-Val-Leu-Lys-AMC, all from Bachem. For cathepsin S the buffer was 100 mM sodium phosphate, 100 mM NaCl, 1 mM DTT, 0.1% PEG 4000, pH 6.5. For cathepsin K the buffer was 100 mM sodium phosphate, 5 mM EDTA, 1 mM DTT, 0.1% PEG 4000, pH 6.5. For cathepsin L the buffer was 100 mM sodium acetate, 1 mM EDTA, 1 mM DTT, 0.1% PEG 4000, pH 5.5.

Substrate and inhibitor dilutions were made in buffer and combined (10 μL of each) in orthogonal directions on a white 384 well plate (Corning). The assay was initiated by the addition of 30 μL of enzyme in buffer (final concentrations of 2 nM cathepsin S, 0.5 nM cathepsin K, or 5 nM cathepsin L). Plates were read in a Fluoroskan Ascent (Thermo Labsystems, Helsinki) in kinetic mode, with excitation and emission filters of 390 nm and 460 nm, respectively. Rates were determined by linear regression of the fluorescence/time data in Excel (Microsoft). Rates were fitted by non-linear regression to the competitive inhibition equation using SigmaPlot 2000 (SPSS Inc.) to obtain K_M, V, and K_i. A control inhibitor was included in all assays, allowing estimation of the error of the K_i values to be approximately 10%.

4.1.2. Cellular assay. Cath S Ii p10 accumulation assay

Human EVB B-lymphocytes were cultured in RPMI 1640 (PAA), supplemented with 10% fetal calf serum, 100 U/mL penicillin, 100 μg/mL streptomycin, 100 μM non-essential amino acids, and 1 mM sodium-pyruvate (all from Gibco/Invitrogen). Cells were grown at a density of one million cells per mL over-night, then seeded on a 48-well plate at 625,000 cells/well. The test compounds were either two or fourfold serially diluted in DMSO to 500 times the final concentration, and added to the wells with an end concentration of DMSO below 1%.

The cells were incubated with compound at 37 °C, 5% CO_2, for 4 h. The plates were then centrifuged, medium removed and cells lysed. Cell lysate proteins were separated by SDS–PAGE, and the amount of accumulated Ii p10 fragment was quantified on a ChemiDoc XRS (Bio-Rad) by Western blotting using an anti-CD74/invariant chain antibody (Stressgen).

The IC_{50} values were calculated using GraphPad Prism 5, and represents the concentration of compound that increases the Ii p10 accumulation to 50% of the maximum response. 50 nM of the irreversible Cath S inhibitor leucine homo-phenylalanine vinyl sulfone (LHVS), was used for normalization of the data.

4.2. Modelling

All modeling have been made using Sybyl 7.3 (Tripos Inc. 1699 South Hanley Rd., St. Louis, Missouri, 63144, USA). Compounds **11, 23**, and **55** were modeled in the active site of in-house crystal structures of Cath S, and thereafter minimized using the MMFF94s force field. The Cath K surface shown is also from an in-house crystal structure.

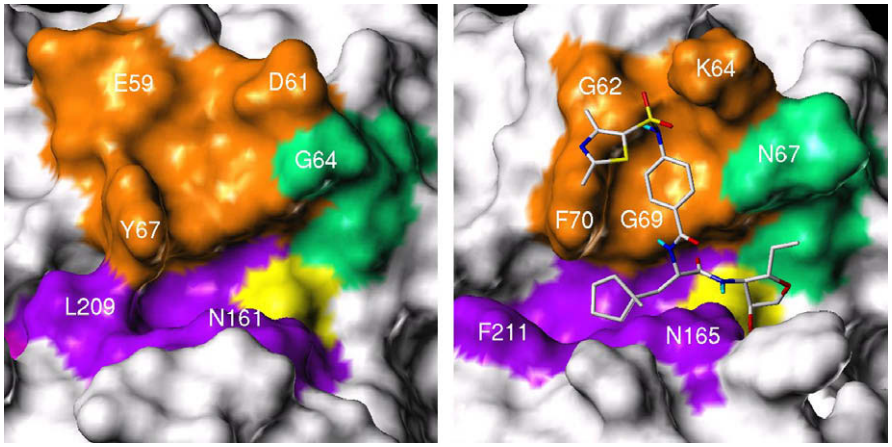


Figure 9. A comparison of the active site of Cath K to the left and Cath S to the right. A model of compound **55** is shown in the active site of Cath S. The different shapes of primarily S2 (purple) and S3 (orange) are visible. The most important interactions of this series that are lost in Cath K is the hydrogen bonds with the sulfonamide.

4.3. General methods

Unless stated otherwise, all the materials were obtained from commercial suppliers and used without further purification. Solid supported reactions were performed in 4 and 8 mL Wheaton vials with screw caps. Agitation was performed using IKA KS 260 basic shaker. Washing and rinsing of the resins between steps was performed using the VacMaster from IST using single fritted columns of 15 or 6 mL from IST. Concentrations were performed under reduced pressure at <40 °C (bath temperature) or at the vacuum centrifuge HT-4 from Genevac Technologies. The efficiency of the coupling reactions to the solid support was measured by quantitative UV measurement of Fmoc chromophore release[4] and/or from the mass balance of purified recovered product obtained after cleavage from the solid support by acidic hydrolysis with 95% aqueous TFA. A Water-Micromass instrument, using Waters 2790 Alliance, Waters 996 photodiode array detector and Micromass ZMD (API ES pos. and neg.) mass detector were used for recording LC–MS. Synergi MAX-RP 50 × 4.6 mm 80 A, 4u from Phenomenex was used as reverse phase column for the LC–MS analysis, and acetonitrile/water 0.1% HCOOH was used as mobile phase. The preparative RP-LC–MS was performed on a Water-Micromass instrument, using Waters 2700 auto injector, Waters 996 photodiode array detector, waters 600 controller, waters fraction collector II and Micromass ZMD (API ES positive ionization) mass detector. Synergi MAX-RP 60 × 21 mm 80A, 4u from Phenomenex was used as reverse phase prep column, and acetonitrile/water 0.1% HCOOH was used as mobile phase. Thin layer chromatography was performed using Silica Gel 60 F-254 plates with detection by UV, and charring with ninhydrine or $KMnO_4$. Silica gel (0.040–0.063 mm) or commercial Flash silica columns from Isolute were used for column chromatography. NMR-spectra were recorded on a Varian 400 or 500 MHz instruments using $CDCl_3$ or CD_3OD as solvents. TMS was used as reference.

LC–MS accurate mass measurements were performed using a HDMS Synapt instrument from Waters (UK) equipped with a lockspray interface, connected to a Waters Aquity system. The acquisition range was m/z 100 to 1000 with an acquisition time of 0.15 s (+ESI). Leucine enkephalin was used as lock mass. The reversed phase column was an YMC-UltraHT Pro C_{18}, 2.1 × 50 mm, 2 μm, 120 A from YMC (USA) and the mobile phases were based on water/acetonitrile containing 0.2% formic acid.

LC–MS purity measurements were performed on the analytical RP-HPLC system consisted of Waters 2695 Alliance separation module, Waters 996 photodiode array detector, and Micromass ZQ2000 mass detector (+ESI). Chromatography system A: ACE C_8, 50 × 3 mm, 3 μm, 100 A column, with 5 mM ammonium acetate in water/acetonitrile as mobile phases. Chromatography system B: Phenomenex Gemini C_{18}, 50 × 3 mm, 3 μm, 110 A column, with 0.1% formic acid in water/acetonitrile as mobile phases. Generic gradients from 20% to 99% acetonitrile for 5 min at a flow rate 0.8 mL/min were used.

4.4. Synthetic experimentals

4.4.1. Synthesis of 3: preparation of P1 resin

Solid-phase synthesis was carried out using the methodology described in WO00/69055. Fmoc-protected 5-ethyl furanone **2**[4] (1 g, 2.85 mmol) was suspended in MeOH (30 mL) followed by the addition of Webb's linker[8] as trifluoroacetic acid salt (937 mg, 2.85 mmol) as a solid. The suspension was stirred at room temperature for 3.5 h. The white precipitate formed was filtered, washed with MeOH and dried at a vacuum to afford the semicarbazone linker in 85%. This linker (1.22 g, 2.22 mmol) was then coupled to an aminomethyl functionalized polymer support[9] (5.7 g, 0.24 mmol/g loading, 1.37 mmol) previously suspended in DMF (55 mL), by using HBTU (896 mg, 6.66 mmol), HOBt (360 mg, 6.66 mmol) and NMM (500 μL, 14.4 mmol) as coupling reagents. The suspension was agitated for 16 h, the resin filter of, washed with DMF (3 × 40 mL), DCM (3 × 40 mL), MeOH (3 × 40 mL), DCM (3 × 40 mL), MeOH (3 × 40 mL) and finally with *tert*-butyl methyl ether (3 × 40 mL), and then dried at a vacuum to afford resin **3** (6.24 g, 0.17 mmol/g loading, 77% loading efficiency).

4.4.2. Synthesis of 4: 2-[1-(9*H*-fluoren-9-yl)-ethoxycarbonylamino]-3-(1-methyl-cyclopentyl)-propionic acid

2-*tert*-Butoxycarbonylamino-3-(1-methyl-cyclopentyl)-propionic acid methyl ester[10] (3.1 g, 10.86 mmol) was dissolved in a solution of TFA/DCM/MeOH 1:1:0.05 (8 mL) and stirred for 3 h. The solution was concentrated, co-evaporated with toluene and freeze-dried. The resulting trifluoroacetic acid amine salt was dissolved in 37% HCl (15 mL) and heated at 110 °C in a microwave oven for 1 h. After concentration and lyophilization, the resulting ammonium salt was dissolved in saturated aqueous solution of sodium hydrogen carbonate (60 mL). Dioxane (50 mL) was added and the solution cooled down to 0 °C. 9-Fluorenylmethyl chloroformate (2.1 g, 10.8 mmol) was added portionwise as a solid and the solution was allowed to reach room temperature and left over night. After potassium carbonate (1.49 g, 10.8 mmol) was added, the solution was washed with *tert*-butyl methyl ether (2 × 50 mL). The aqueous layer was acidified with 1 N HCl and then extracted with EtOAc (2 × 50 mL). The organic layer was separated and dried over anhydrous sodium sulfate, and concentrated at a vacuum to afford the product in 79% yield. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.35–1.45 (m, 4H), 1.54–1.66 (m, 5H), 1.96 (dd, 1H), 4.20–4.23 (m, 1H), 4.35–4.45 (m, 3H), 5.11 (d, NH), 7.25–7.31 (m, 2H), 7.36–7.40 (m, 2H), 7.55–7.59 (m, 2H), 7.73–7.77 (m, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 23.5, 23.6, 24.9, 39.7, 39.9, 41.9, 44.2, 47.2, 52.2, 67.0, 119.9, 125.0, 127.0, 127.7, 141.3, 143.6, 143.9, 155.9. MS for (MH^+) $C_{24}H_{27}NO_4$: 394.3.

4.4.3. Synthesis of 5: Preparation of P2–P1 resin

Resin **3** (6.24 g, 0.17 mmol/g loading, 1.06 mmol) was treated twice with a solution of 20% piperidine in DMF (50 mL) for 30 min, filtered, and washed several times as indicated for resin **3**. The resin was then suspended in DMF (60 mL) and to the suspension were added HBTU (1.2 g, 3 mmol), HOBt (489 mg, 3 mmol), Fmoc-(methyl cyclopentyl)-alanine-OH (P2 Fmoc acid) (1.35 g, 3 mmol), and NMM (710 μL, 6.1 mmol). The suspension was agitated for 16 h, the resin filtered and washed as described for resin **3** to afford resin **5** (6.1 g, 0.15 mmol/g loading, 86% loading efficiency).

4.4.4. Synthesis of 7

The required sulfonyl chloride (6.62 mmol) was added to a solution of the methyl 4-aminobenzoate (1 g), a catalytic amount of DMAP and pyridine (0.5 mL) in DCM (15 mL) at 0 °C under N_2 atmosphere. The reaction was allowed to warm up to room temperature and kept for 1–72 h. One of the following work-up methods was used:

Work-up method A: Addition of DCM and 1 M HCl was followed by separation of the two layers. The organic layer was washed with 1 M HCl, water and brine, dried over Na_2SO_4 and concentrated to dryness.

Work-up method B: Reaction mixture was concentrated to near dryness and the product crystallized from added ethanol.

After work-up the ester was hydrolyzed in 2.5 M LiOH (5 mL), THF (14 mL), and MeOH (7 mL) in a microwave oven at 110 °C for 30 min. After cooling, the solution was acidified with 1 M HCl and extracted with ethyl acetate, dried over Na_2SO_4 and concentrated to dryness to afford compound **7**.

Compound **7a**: *4-Methanesulfonylamino-3-methoxy-benzoic acid:* Synthesized as described above using methanesulfonyl chloride and methyl 4-amino-3-methoxy-benzoate. Work-up method B was used. Yield: 77% ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.05 (s, 3H), 3.86 (s, 3H), 7.40–7.55 (m, 3H). MS for (M−H) $C_9H_{11}NO_5S$: 244.1.

Compound **7b**: *4-(Propane-2-sulfonylamino)-benzoic acid:* Synthesized as described above using commercially available propane-2-sulfonyl chloride. Work-up method B was used followed by flash chromatography on silica with DCM/MeOH (95:5) as eluent. Yield: 3%.^{1}H NMR (500 MHz, CD_3OD) δ 1.36 (d, 6H), 3.37 (m, H), 3.88 (s, 3H), 7.30 (d, 2H), 7.94 (d, 2H) (NMR for the methyl ester).

Compound **7c**: *4-Methanesulfonylamino-2-methyl-benzoic acid:* Synthesized as described above using methanesulfonyl chloride and methyl 4-amino-2-methyl-benzoate. Work-up method B was used. Yield: 46% ^{1}H NMR (500 MHz, DMSO-d_6) δ 2.48 (s, 3H), 3.05 (s, 3H), 7.05–7.09 (m, 2H), 7.81 (d, 1H). MS for (M−H) $C_9H_{11}NO_4S$: 228.1.

Compound **7d**: *3-Chloro-4-methanesulfonylamino-benzoic acid:* Synthesized as described above using methanesulfonyl chloride and methyl 4-amino-3-chloro-benzoate. Work-up method B was used. Yield: 64% ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.05 (s, 3H), 7.58–7.94 (m, 3H). MS for (M−H) $C_8H_8Cl\ NO_4S$: 248.0.

Compound **7e**: *4-Methanesulfonylamino-2-methoxy-benzoic acid:* Synthesized as described above using methanesulfonyl chloride and 4-amino-2-methoxy-benzoic acid. Work-up method B was used. Yield: 61%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.06 (s, 3H), 3.89 (s, 3H), 6.86 (dd, H), 6.97 (d, H), 7.85 (d, H). MS for (MH^+) $C_9H_{11}NO_5S$: 246.1

Compound **7f**: *4-Cyclopropanesulfonylamino-benzoic acid:* Synthesized as described above using cyclopropanesulfonyl chloride and work-up method B. Yield: 13% ^{1}H NMR (500 MHz, CD_3OD) δ 0.99 (m, 2H), 1.12 (m, 2H), 2.68 (m, H), 7.36 (d, 2H), 7.98 (d, 2H). MS for (MH^+) $C_{11}H_{13}NO_4S$: 256.1 (MS for the methyl ester).

Compound **7g**: *3-Fluoro-4-methanesulfonylamino-benzoic acid:* Synthesized as described above using methanesulfonyl chloride and methyl 4-amino-3-fluoro-benzoate. Work-up method B was used. Yield: 57% ^{1}H NMR (500 MHz, DMSO-d_6) δ 3.11 (s, 3H), 7.53 (t, 1H), 7.68–7.76 (m, 2H). ^{13}C NMR (125.68 MHz, DMSO-d_6) δ 42.2, 118.8, 121.7, 123.6, 126.5, 132.7, 153.5, 167.8.

Compound **7h**: *3-Acetyl-4-methanesulfonylamino-benzoic acid:* 5-Amino-furan-2-carboxylic acid methyl ester (0.42 g, 3.0 mmol) and methyl vinyl ketone (10 mL) in benzene were heated to reflux for 1 h. Concentration to dryness was followed by flash column chromatography on silica using DCM/MeOH (95:5) as eluent to yield 44% (278 mg. 1.31 mmol) of *5-Acetyl-4-amino-1-hydroxy-cyclohexa-2,4-dienecarboxylic acid methyl ester*. The product was mixed with $BF_3 \cdot OEt_2$ (284 mg, 2.0 mmol) in benzene (15 mL) and heated to reflux for 0.5 h. The reaction mixture was quenched with $NaHCO_3$ (aq, sat) and extracted with DCM (20 mL). Upon standing a precipitation was formed in the organic layer. The precipitate was collected and confirmed to be the product by characterization with LC–MS and ^{1}H NMR. Yield: 127 mg (50%). Yield: 35% ^{1}H NMR (500 MHz, CD_3OD) δ 2.73 (s, 3H), 3.18 (s, 3H), 7.79 (d, H), 8.22 (dd, H), 8.71 (d, H).

Compound **7i**: *4-(3-Fluoro-benzenesulfonylamino)-benzoic acid:* Synthesized as described above using 3-fluoro-benzenesulfonyl chloride and work-up method B. Yield: 33%. ^{1}H NMR (500 MHz, CD_3OD) δ 7.21 (d, 2H), 7.24 (t, 2H), 7.89 (d, 2H), 7.90 (m, 2H). MS for (MH^+) $C_{14}H_{12}FNO_4S$: 310.2 (MS for the methyl ester).

Compound **7j**: *4-(4-Fluoro-benzenesulfonylamino)-benzoic acid:* Synthesized as described above using 4-fluoro-benzenesulfonyl chloride and work-up method B. Yield: 66%. ^{1}H NMR (500 MHz, CD_3OD) δ 7.21 (d, 2H), 7.34 (m, H), 7.52 (d, 2H), 7.53 (m, H), 7.64 (d, H), 7.90 (d, 2H). MS for (MH^+) $C_{14}H_{12}FNO_4S$: 310.2 (MS for the methyl ester).

Compound **7k**: *4-(1-Methyl-1H-imidazole-2-sulfonylamino)-benzoic acid:* Synthesized as described above using 1-methyl-1*H*-imidazole-2-sulfonyl chloride and work-up method B. Yield: 32%. MS for (MH^+) $C_{11}H_{11}N_3O_4S$: 282.3.

Compound **7l**: *4-(Toluene-2-sulfonylamino)-benzoic acid:* Synthesized as described above using 2-methyl-benzenesulfonyl chloride and work-up method B. Yield: 65%. ^{1}H NMR (500 MHz, CD_3OD) δ 2.65 (s, 3H), 7.24 (d, 2H), 7.32 (d, H), 7.33 (t, H), 7.47 (t, H), 7.84 (d, 2H), 8.02 (d, H). (MH^+) $C_{14}H_{13}NO_4S$: 292.3.

Compound **7m**: *4-(2-Fluoro-benzenesulfonylamino)-benzoic acid:* Synthesized as described above using 2-fluoro-benzenesulfonyl chloride and work-up method B. Yield: 74%. ^{1}H NMR (500 MHz, CD_3OD) δ 7.21 (d, 2H), 7.24 (t, H), 7.32 (t, H), 7.62 (m, H), 7.84 (d, 2H), 7.93 (m, H). MS for (MH^+) $C_{13}H_{10}FNO_4S$: 296.3.

Compound **7n**: *4-Benzenesulfonylamino-3-methyl-benzoic acid:* Synthesized as described above using benzenesulfonyl chloride and 4-amino-2-methyl-benzoic acid. Work-up method A was used. Yield: 31%. MS for (MH^+) $C_{14}H_{13}NO_4S$: 292.3.

Compound **7o**: *4-Benzenesulfonylamino-3-chloro-benzoic acid:* Synthesized as described above using benzenesulfonyl chloride and 4-amino-3-chloro-benzoic acid. Both work-up methods A and B were used. Yield: 6%. MS for (M−H) $C_{13}H_{10}ClNO_4S$: 326.2.

Compound **7p**: *4-(3-Methoxy-benzenesulfonylamino)-benzoic acid:* Synthesis as described above using 3-benzenesulfonyl chloride and work-up method B. Yield: 98%. MS for (MH^+) $C_{14}H_{13}NO_5S$: 308.3.

Compound **7q**: *4-(4-Methoxy-benzenesulfonylamino)-benzoic acid:* Synthesis as described above using 4-benzenesulfonyl chloride and work-up method B. Yield: 79%. MS for (MH^+) $C_{14}H_{13}NO_5S$: 308.3.

Compound **7r**: *6-Benzenesulfonylamino-nicotinic acid:* 6-Aminonicotinic acid (600 mg, 4.34 mmol) was treated with concentrated HCl in MeOH for 10 min at room temperature followed by 12 min in a microwave oven at 110 °C. 6-Aminonicotinic acid methyl ester hydrochloric salt was obtained after concentration as a white solid (86% yield) which was used in next step following the general procedure for **7** using benzenesulfonyl chloride and work-up method B. Yield: 20%. ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.25 (br d, 1H), 7.51–7.54 (m, 2H), 7.58–7.61 (m, 1H), 7.98 (d, 2H), 8.17 (d, 1H), 8.62 (s, 1H). ^{13}C NMR (125.68 MHz, DMSO-d_6) δ 110.0, 112.3, 126.8, 128.6, 132.6, 140.0, 140.9, 146.9, 155.2, 165.9. MS for (MH^+) $C_{12}H_{10}N_2O_4S$: 279.2.

Compound **7s**: *6-Methanesulfonylamino-nicotinic acid:* 6-Aminonicotinic acid (600 mg, 4.34 mmol) was treated with concentrated HCl in MeOH for 10 min at room temperature followed by 12 min in a microwave oven at 110 °C. 6-Aminonicotinic acid methylester hydrochloric salt was obtained after concentration as a white solid (86% yield) which was used in next step following the general procedure for **7** using methanesulfonyl chloride and work-up method B. Yield: 44%. MS for (MH^+) $C_7H_8N_2O_4S$: 217.2.

Compound **7t**: *4-(4-Nitro-benzenesulfonylamino)-benzoic acid:* Synthesized as described above using 4-nitro-benzenesulfonyl chloride and work-up method B. Yield: 74%. MS for (M−H) $C_{11}H_{10}N_2O_4S_2$: 321.2.

Compound **7u**: *4-(2-Chloro-pyridine-3-sulfonylamino)-benzoic acid:* Synthesized as described above using 2-chloropyridine-3-sulfonyl chloride and work-up method B. Yield: 42%. MS for (MH^+) $C_{12}H_9ClN_2O_4S$: 313.3.

Compound **7v**: *4-Ethanesulfonylamino-benzoic acid:* Synthesized as described above using ethanesulfonyl chloride and work-up method B. Yield: 75%. MS for (MH^+) $C_9H_{11}NO_4S$: 230.2.

1*Compound* **7w**: *4-(Butane-1-sulfonylamino)-benzoic acid*: Synthesized as described above using butane-1-sulfonyl chloride and work-up methods A and B. Yield: 54%. (M−H) $C_{11}H_{15}NO_4S$: 256.3.

4.4.5. Synthesis of 8

A general procedure as follows: trifluoromethane sulfonic anhydride (2.1 mmol, 354 μL) was added to a polymer supported triphenylphosphine oxide (2.8 mmol, 0.93 g) in DCM (15 mL). After 1 h the mixture was cooled to 0 °C and a solution of the corresponding pyridine sulfonic acid (2.1 mmol) as pyridine salt in DCM (4 mL) was added. After 30 min 4-amino-benzoic acid methyl ester (1.96 mmol, 296 mg) in DCM (4 mL) was added. The mixture was agitated at 25 °C for 16 h. The resin was filtered off and the filtrate concentrated to dryness. The crude was purified by silica gel column chromatography (0.1–1.0% MeOH/DCM). The desired products **8** were obtained by hydrolysis of the methyl ester in 2.5 M LiOH (5 mL), THF (14 mL), MeOH (7 mL) in a microwave oven at 110 °C for 30 min. After cooling, the solution was acidified with aq HCl and extracted with ethyl acetate, dried with Na_2SO_4 and concentrated to dryness to afford compounds **8** in 13–25% overall yields.

Compound **8a**: *4-(Pyridine-3-sulfonylamino)-benzoic acid:* Synthesized as described above using 3-pyridine sulfonic acid. Yield: 25%. MS for (MH^+) $C_{12}H_{10}N_2O_4S$: 279.2.

Compound **8b**: *4-(Pyridine-2-sulfonylamino)-benzoic acid:* Synthesized as described above using 2-pyridine sulfonic acid. Yield: 15%. MS for (MH^+) $C_{12}H_{10}N_2O_4S$: 279.2.

Compound **8c**: *4-(Pyridine-4-sulfonylamino)-benzoic acid:* Synthesized as described above with the additional steps: 4-mercaptopyridine (500 mg) was dissolved in glacial acetic acid (18 mL), followed by the addition of 35% hydrogen peroxide (6 mL). The solution was warmed at 80 °C for 90 min and then concentrated to dryness. The product was re-crystallized from methanol–water, dried in a vacuum to afford 4-pyridine sulfonic acid (ES^+: 160.3 (MH^+), 201.3 (MNa^+). Yield: 21%. ^1H NMR (500 MHz, DMSO-d_6) δ 7.19 (d, 2H), 7.72 (d, 2H), 7.81 (d, 2H), 8.82 (d, 2H), 11.09 (br s, NH, 1H), 12.75 (br s, OH, 1H). ^{13}C NMR (125.68 MHz, DMSO-d_6) δ 167.0, 151.8, 148.1, 142.0, 131.3, 127.1, 120.4, 119.3. MS for (MH^+) $C_{12}H_{10}N_2O_4S$: 279.2.

Compound **8d**: *4-(4-Methyl-pyridine-3-sulfonylamino)-benzoic acid:* Synthesized as described above using 4-methyl-3-pyridine sulfonic acid commercially available. Yield: 13%. MS for (MH^+) $C_{13}H_{12}N_2O_4S$: 293.2.

4.4.6. Synthesis of 9

A general procedure as follows:

Step 1: A thiazole (20.2 mmol) was dissolved in methyl-*t*-butylether (46 mL) and the solution was cooled to 0 °C. After dropwise addition of isopropyl magnesium chloride (10.1 mL, 2.0 M) at 0 °C the mixture was heated to 40 °C and sulfur dioxide in dimethoxymethane (4.2 mL, 6.0 M) was added dropwise. The reaction was then left at 40 °C for 1 h. After cooling to 0 °C, *N*-chlorosuccinimide (4.05 g, 30.3 mmol) was added. After 45 min HCl (0.2 M, aq, 50 mL) was added followed by leaving the reaction to warm up to ambient temperature for 2 h. Methyl-*t*-butyl ether was added and the organic layer was washed with of HCl (0.2 M, aq), water and brine. The organic layer was then dried over Na_2SO_4, filtered, and concentrated to yield thiazolesulfonyl chlorides in 59–91% yield.

Step 2: Methyl-aminobenzoate was dissolved in DCM (15 mL) together with a catalytic amount of DMAP and pyridine (0.5 mL). The reaction mixture was cooled to 0 °C and the thiazolesulfonyl chloride (6.62 mmol) was added. The reaction was heated to ambient temperature and stirred overnight. Concentration was followed by the addition of DCM (50 mL). The organic layer was washed with HCl (aq, 1 M) (3 × 20 mL), brine (2 × 20 mL), dried over Na_2SO_4, filtered, and concentrated. Re-crystallization from EtOH (20 mL) produced of 4-(thiazole-2-sulfonylamino)-benzoic acid methyl esters in 46–75% yield.

Step 3: The product from the previous step was dissolved in THF/MeOH (2:1) (15 mL). LiOH was added (15 mL) and the solution heated in a microwave cavity at 110 °C for 1 h. The reaction solution was acidified with HCl (aq, 1 M) to pH 3 and extracted with EtOAc (3 × 15 mL). The organic layer was washed with HCl (aq, 1 M) (20 mL), water (2 × 20 mL), brine (2 × 20 mL) and dried over Na_2SO_4, filtered, and concentrated. Re-crystallization from EtOH (10 mL) produced compounds **9** in 36–88% yield.

Compound **9a:** *4-(2,4-Dimethyl-thiazole-5-sulfonylamino)-benzoic acid:* Synthesized as described above using 2,4-dimethyl-thiazole-5-sulfonyl chloride. Yield: 62% (starting from step 2). MS for (MH^+) $C_{12}H_{12}N_2O_4S_2$: 313.21.

Compound **9b**: *4-(4-Methyl-thiazole-2-sulfonylamino)-benzoic acid:* Synthesized as described above using 4-Methyl-thiazole. Yield: 24%. MS for (MH^+) $C_{11}H_{10}N_2O_4S_2$: 299.22.

Compound **9c**: *4-(5-Methyl-thiazole-2-sulfonylamino)-benzoic acid:* Synthesized as described above using 5-methyl-thiazole. Yield: 15%. MS for (MH^+) $C_{11}H_{10}N_2O_4S_2$: 299.23.

Compound **9d**: *4-(4-Isopropyl-thiazole-2-sulfonylamino)-benzoic acid:* Synthesis followed the general procedure for **9** using 4-isopropyl-1,3-thiazole, synthesized as follows: 1-Bromo-3-methyl-butan-2-one (1.15 g, 6.95 mmol) and thioformamide (0.43 g, 6.95 mmol) were dissolved in dioxane (10 mL) and heated in a microwave cavity at 110 °C for 15 min. DCM and $NaHCO_3$ was added and after separation the organic layer was washed with NaOH (aq, 1 M) and water. Back-extracted water layer with DCM. The combined organic layers were washed with water and brine, dried over Na_2SO_4, filtered, and evaporated to yield 0.82g (70%) of 4-isopropyl-1,3-thiazole. Yield: 13%. MS for (MH^+) $C_{13}H_{14}N_2O_4S_2$: 327.22.

4.4.7. Synthesis of 10. Preparation of P3–P2–P1 resins

Method A: After standard Fmoc removal from resin **5**, the P3 acids (**6–9**) were introduced using standard coupling conditions as follows: The corresponding P3 acid capping group (**6**–**9**) (0.13 mmol), HOBt (19 mg, 0.12 mmol), HBTU (45 mg, 0.12 mmol), and NMM (25 μL, 0.24 mmol) were added to the Fmoc de-protected P1–P2 resin **5** (170 mg, 0.025 mmol) in DMF (6 mL). The reaction was agitated for 16–72 h, filtered and then washed with DMF (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL) and DCM (3 × 15 mL) to furnish the corresponding P3–P2–P1 resin **10**.

Method B: After standard Fmoc removal from resin **5**, 4-amino benzoic acid was coupled to the resin using standard coupling conditions as follows: 4-amino benzoic acid (16.5 mg, 0.12 mmol), HOBt (16 mg, 0.12 mmol), HBTU (45 mg, 0.12 mmol), and NMM (25 μL, 0.24 mmol) were added to the Fmoc de-protected P1–P2 resin **5** (200 mg, 0.15 mmol/g loading, 0.03 mmol) in DMF (6 mL). The reaction was agitated for 16 h, filtered and then washed with DMF (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL) and DCM (3 × 15 mL). Coupling of the corresponding sulfonyl chloride was done subsequently as follows: The corresponding sulfonyl chloride (0.12 mmol), pyridine (0.38 mmol), and DMAP (0.01 mmol) were added to the resin in DCM (6 mL). The reaction was agitated for 16–72 h, filtered and then washed with DMF (2 × 10 mL), DCM (2 × 10 mL), MeOH (2 × 10 mL) and DCM (3 × 15 mL) to furnish the corresponding P3–P2–P1 resin **10**.

4.4.8. Synthesis of compounds 11–56

Targeted compounds **11**–**56** were obtained after cleavage of the corresponding P3–P2–P1 resin **10** with a solution of 95% aqueous TFA. After concentration the products were purified on preparative LC–MS and lyophilized in yields 19–96%. The products were characterized by LC–MS (see chromatography systems A and B under General methods) with a purity > 95 % in all the cases in both systems, HRMS and NMR.

Compound **11**: *N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-methanesulfonylamino-benzamide*: The corresponding resin **10** was synthesized according

to Method A using P3 acid **6g**. Subsequent treatment of **10** as above. Yield: 49%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, 3H), 1.01 (s, 3H), 1.36–1.48 (m, 8H), 1.58–1.68 (m, 2H), 1.74–1.80 (m, 1H), 1.88–1.99 (m, 1H), 3.07 (s, 3H), 3.79–3.83 (m, 1H), 4.04–4.07 (m, 1H), 4.07–4.18 (dd, J = 2H), 4.79–4.84 (m, 1H), 7.16–7.18 (m, 2H), 7.52 (br s, NH, 1H), 7.65–7.68 (m, 2H), 7.84 (br s, NH, 1H), 8.55 (br s, NH, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 23.51, 24.1, 25.2, 26.8, 39.7, 40.0, 40.0, 41.9, 43.5, 51.9, 59.9, 71.0, 80.3, 118.6, 128.3, 128.8, 140.9, 166.6, 173.9, 211.9. HRMS (ES+): *m/z* calcd for $C_{23}H_{33}N_3O_6S$: 480.2095; found: 480.2173 $[H+M]^+$. LC–MS System A: t_R = 3.45 min, System B: t_R = 3.70 min.

Compound **12**: *N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-3-methanesulfonylamino-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **6f**. Subsequent treatment of **10** as above. Yield: 69%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (t, J = 7.4 Hz, 3H), 1.05 (s, 3H), 1.40–1.48 (m, 4H), 1.63–1.65 (m, 4H), 1.73–2.00 (m, 4H), 3.02 (s, 3H), 3.92–3.96 (m, 1H), 4.06–4.11 (m, 1H), 4.10–4.22 (dd, overlapped, 2H, J = 17.3 Hz), 5.02–5.05 (m, 1H), 7.37–7.48 (m, NH, 2H), 7.56 (d, J = 8.2 Hz, NH), 7.68 (d, J = 8.2 Hz, 1H), 8.10 (s, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.5, 23.7, 24.4, 25.4, 27.0, 39.4, 40.0, 40.2, 42.1, 44.9, 51.6, 59.9, 71.2, 80.8, 121.0, 122.1, 123.2, 130.1, 134.0, 138.9, 166.3, 173.6, 211.6. HRMS (ES+): *m/z* calcd for $C_{23}H_{33}N_3O_6S$: 480.2095; found: 480.2178 $[H+M]^+$. LC–MS System A: t_R = 3.48 min, System B: t_R = 3.74 min.

Compound **13**: *N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(methanesulfonyl-methyl-amino)-benzamide*: The corresponding resin 10 was synthesized according to Method A using P3 acid **6j**. Subsequent treatment of 10 as above. Yield: 49%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02 (s, 3H), 1.03 (t, 7.3 Hz, 3H), 1.44 (m, 4H), 1.62–1.84 (m, 7H), 2.12–2.16 (dd, J = 4.6 Hz, 14.3 Hz, 1H), 2.88 (s, 3H), 3.37 (s, 3H), 3.84–3.88 (m, 1H), 3.97–4.01 (m, 1H), 4.06–4.22 (dd, J = 17.1 Hz, 2H), 4.73–4.77 (m, J = 4.6 Hz, 8.2 Hz, 1H), 6.73 (d, J = 8.2 Hz, NH), 7.05 (s, J = 7.6 Hz NH), 7.46 (d, J = 8.8 Hz, 2H), 7.79 (d, J = 8.8 Hz, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.4, 25.4, 26.9, 36.0, 37.9, 40.1, 40.3, 41.9, 43.3, 51.8, 60.1, 71.2, 81.1, 125.5, 128.4, 131.9, 144.9, 166.8, 172.8, 211.7. HRMS (ES+): *m/z* calcd for $C_{24}H_{35}N_3O_6S$: 494.2247; found: 494.2325 $[H+M]^+$. LC–MS System A: t_R = 3.70 min, System B: t_R = 3.97 min.

Compound **14**: *N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-methylsulfamoyl-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **6e**. Subsequent treatment of **10** as above. Yield: 64%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.40–0.42 (m, 3H), 0.9 (s, 3H), 1.32–1.49 (m, 4H), 1.50–1.71 (m, 4H), 1.72–1.81 (m, 1H), 1.83–1.90 (m, 1H), 2.04–2.13 (m, 1H), 2.54 (s, 3H), 3.88–3.93 (m, 1H), 3.99–4.05 (m, 1H), 4.07–4.15 (m, 2H), 4.98–5.02 (m, 1H), 7.44 (d, J = 8.6 Hz, 2H), 7.72 (d, J = 8.6 Hz, 2H), 8.12 (br d, NH), 9.96 (br s, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 11.9, 24.2, 26.3, 27.9, 29.3, 40.3, 43.0, 43.6, 51.4, 60.1, 71.2, 80.7, 126.2, 129.5, 138.8, 141.1, 167.1, 173.1, 221.7. HRMS (ES+): *m/z* calcd for $C_{23}H_{33}N_3O_6S$: 480.2076; found: 480.2155 $[H+M]^+$. LC–MS System A: t_R = 3.56 min, System B: t_R = 3.82 min.

Compound **15**: *N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-3-methylsulfamoyl-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **6h**. Subsequent treatment of **10** as above. Yield: 77% ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.05 (t, 3H), 1.37–1.45 (m, 4H), 1.60–1.65 (m, 4H), 1.74–1.88 (m, 3H), 2.15 (dd, J = 4.5, 14.7 Hz, 1H), 2.65 (s, 3H), 3.90–3.93 (m, 1H), 4.07–4.21 (m, 3H), 4.76–4.80 (m, 1H), 5.67 (br d, J = 5.9 Hz, NH, 1H), 7.41 (br d, J = 7.7 Hz, NH, 1H), 7.51 (t, J = 7.7 Hz, 1H), 7.58 (br d, J = 8.7 Hz, NH, 1H), 7.88–7.92 (m, 2H), 8.24 (s, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.43, 23.7, 24.4, 25.4, 26.9, 29.5, 39.9, 40.2, 41.7, 41.9, 43.3, 52.1, 60.2, 71.2, 80.8, 125.9, 129.6, 130.6, 131.4, 134.7, 139.8, 166.2, 172.9, 212.8. HRMS (ES+): *m/z* calcd for $C_{23}H_{33}N_3O_6S$: 480.2092; found: 480.2170 $[H+M]^+$. LC–MS System A: t_R = 3.59 min, System B: t_R = 3.86 min.

Compound **16**: *4-Ethanesulfonylamino-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7v**. Subsequent treatment of **10** as above. Yield: 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98–1.03 (m, 6H), 1.25–1.87 (m, 12H), 1.99–2.06 (m, 1H), 2.17–2.24 (m, 2H), 3.17–3.21 (m, 2H), 3.86 (m, 1H), 3.96 (m, 1H), 4.05–4.22 (q, J = 17.1 Hz, 2H), 4.70 (m, 1H), 6.37 (d, J = 8.3 Hz, NH), 6.62 (br s, NH), 6.44 (d, J = 7.3 Hz, NH), 7.26 (d, 2H), 7.75 (d, J = 8.8 Hz, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 8.7, 9.3, 25.2, 29.5, 40.3, 40.4, 43.7, 47.0, 51.6, 60.2, 70.2, 81.4, 119.4, 128.6, 129.3, 141.1, 166.7, 175.5, 211.5. HRMS (ES+): *m/z* calcd for $C_{24}H_{36}N_3O_6S$: 494.2325; found: 494.2336 $[H+M]^+$. LC–MS System A: t_R = 3.61 min, System B: t_R = 3.87 min.

Compound **17**: *4-(Butane-1-sulfonylamino)-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7w**. Subsequent treatment of **10** as above. Yield: 34%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89–0.93 (m, 3H), 0.94–1.03 (m, 6H), 1.40–1.47 (m, 4H), 1.59–1.69 (m, 8H), 1.70–1.85 (m, 4H), 2.08–2.12 (m, 1H), 3.15–3.18 (m, 2H), 3.84–3.87 (m, 1H), 4.00–4.03 (m, 1H), 4.08–4.21 (dd, 2H), 6.81 (br s, 1H) 7.19–7.21 (d, 2H), 7.27 (s, 1H), 7.69–7.71 (d, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 13.5, 21.4, 23.5, 24.2, 25.2, 25.4, 26.7, 39.9, 40.0, 41.0, 41.7, 51.6, 52.2, 59.9, 71.0, 80.7, 118.4, 128.8, 140.9, 166.6, 173.0. HRMS (ES+): *m/z* calcd for $C_{26}H_{39}N_3O_6S$: 522.2558; found: 522.2637 $[H+M]^+$. LC–MS System A: t_R = 4.09 min, System B: t_R = 4.38 min.

Compound **18**: *N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-trifluoromethanesulfonylamino-benzamide*: The corresponding resin **10** was synthesized according to Method B using 2,2,2-trifluoromethane sulfonyl chloride. Subsequent treatment of **10** as above. Yield: 45% (2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.89–1.02 (m, 6H), 1.42–1.83 (m, 11H), 2.06–2.08 (m, 1H), 3.78–3.89 (m, 3H), 4.02–4.06 (m, 1H), 4.14 (dd, J = 17.2 Hz, 2H), 4.72–4.76 (m, 1H), 6.88 (br s, NH, 1H), 7.17–7.31 (m, 2H), 7.18 (br s, overlapped, NH, 1H), 7.67–7.70 (m, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 23.5, 24.1, 25.2, 26.7, 39.8, 40.0, 41.7, 43.3, 51.7, 57.5, 60.0, 70.9, 80.5, 119.6, 119.7, 128.7, 128.8, 130.5, 138.3, 166.5, 190.1, 218.6. HRMS (ES+): *m/z* calcd for $C_{24}H_{32}F_3N_3O_6S$: 548.1968; found: 548.2047 $[H+M]^+$. LC–MS Purity System A: t_R = 3.83 min, System B: t_R = 4.29 min.

Compound **19**: *N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(propane-2-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7b**. Subsequent treatment of **10** as above. Yield: 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95 (t, J = 7.3 Hz, 3H), 1.01 (s, 3H), 1.39–1.49 (m, 6H), 1.59–1.65 (m, 4H), 1.67–1.79 (m, 6H), 1.88–1.93 (m, 1H), 2.00–2.02 (m, 1H), 3.34–3.90 (m, 1H), 3.87–3.90 (m, 1H), 4.00–4.05 (m, 1H), 4.14 (dd, J = 17.3 Hz, 2H), 4.83–4.87 (m, 1H), 7.17–7.19 (m, 2H), 7.31–7.32 (m, NH, 1H), 7.67–7.69 (m, 2H), 7.77–7.80 (m, NH, 1H), 8.63 (br s, NH, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 16.6, 16.8, 23.7, 24.3, 25.4, 26.9, 39.9, 40.2, 42.0, 43.7, 52.1, 53.9, 59.9, 71.2, 80.6, 118.3, 118.4, 127.9, 128.8, 128.9, 141.9, 166.8, 174.1, 211.9. HRMS (ES+): *m/z* calcd for $C_{25}H_{37}N_3O_6S$: 508.2412; found: 508.249 $[H+M]^+$. LC–MS System A: t_R = 3.79 min, System B: t_R = 4.05 min.

Compound **20**: *4-Cyclopropanesulfonylamino-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7f**. Subsequent treatment of **10** as above. Yield: 62%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.97 (t, J = 7.3 Hz, 3H), 1.00 (s, 3H), 1.01 (s, 3H), 1.24 (m, 2H), 1.40–1.48 (m, 4H), 1.60–1.66 (m, 4H), 1.69–1.81 (m, 2H), 1.87–1.91 (m, 1H), 2.02–2.04 (m, 1H), 2.59–2.62 (m, 1H), 3.85–3.90 (m, 1H), 4.02–

4.05 (m, 1H), 4.09–4.20 (dd, 2H, *J* = 16.8 Hz), 4.82–4.87 (m, 1H), 7.21 (d, *J* = 8.4 Hz, 2H), 7.29 (m, NH), 7.68 (d, *J* = 8.4 Hz, 2H), 7.71 (m, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 5.8, 6.2, 9.4, 23.8, 24.3, 25.4, 27.0, 30.9, 40.0, 40.2, 42.0, 43.8, 52.0, 60.0, 71.2, 80.7, 119.5, 128.6, 128.8, 141.4, 166.8, 173.9, 211.8. HRMS (ES+): *m/z* calcd for $C_{25}H_{35}N_3O_6S$: 506.2242; found: 506.232 $[H+M]^+$. LC–MS Purity A: t_R = 3.69 min, System B: t_R = 3.96 min.

Compound **21***: 4-Cyclohexanesulfonylamino-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **6a**. Subsequent treatment of **10** as above. Yield: 71%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.40 (t, *J* = 7.6 Hz, 3H), 0.92 (s, 3H), 0.96–1.75 (m, 15H), 1.90–2.19 (m, 4H), 3.07 (br m, 2H), 3.89–4.17 (m, 4H), 4.56 (m, 1H), 4.72 (m, 1H,), 4.99 (m, 1H), 7.28 (s, 1H), 7.51 (d, *J* = 8.6 Hz, 2H), 7.71 (d, *J* = 8.6 Hz, 2H), 8.27 (d, *J* = 8.6 Hz, NH), 9.89 (d, *J* = 6.8 Hz, NH) ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.5, 24.4, 25.4, 27.0, 39.4, 40.0, 40.2, 42.1, 44.9, 51.6, 59.9, 71.2, 80.8, 121.0, 122.1, 123.2, 130.1, 134.0, 138.9, 166.3, 173.6, 211.6. HRMS (ES+): *m/z* calcd for $C_{28}H_{41}N_3O_6S$: 548.2727; found: 548.2805 $[H+M]^+$. LC–MS System A: t_R = 4.42 min, System B: t_R = 4.75 min.

Compound **22**: *4-(N-Dimethylamino)-sulfonylamino-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **6i**. Subsequent treatment of **10** as above. Yield: 67%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.93 (t, *J* = 7.4 Hz, 3H), 1.00 (s, 3H), 1.38–1.48 (m, 4H), 1.60–1.65 (m, 4H), 1.67–1.79 (m, 2H), 1.89–2.04 (m, 2H), 2.90 (s, 3H), 3.90–3.94 (m, 1H), 3.98–4.03 (m, 1H), 4.09–4.16 (dd, *J* = 16.9 Hz, 2H), 4.85–4.88 (m, 1H), 7.10 (d, *J* = 8.8 Hz, 2H), 7.26–7.28 (br d, NH), 7.66 (d, *J* = 8.8 Hz, 1H), 7.75 (br d, NH), 8.61 (s, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.3, 25.4, 27.0, 38.4, 40.0, 40.2, 42.0, 43.8, 52.1, 59.9, 71.2, 80.7, 118.1, 127.6, 128.7, 141.9, 166.7, 174.1, 211.6. HRMS (ES+): *m/z* calcd for $C_{24}H_{36}N_4O_6S$: 509.2352; found: 509.243 $[H+M]^+$. LC–MS System A: t_R = 3.73 min, System B: t_R = 4.14 min.

Compound **23**: *4-Benzenesulfonylamino-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **6b**. Subsequent treatment of **10** as above. Yield: 66%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.90–0.96 (m, 3H), 1.00 (br s, 3H), 1.37–1.45 (m, 4H), 1.58–1.64 (m, 4H), 1.46–1.77 (m, 2H), 1.85–2.05 (m, 2H), 3.77–3.82 (m, 1H), 4.01–4.05 (m, 1H), 4.07–4.18 (dd, 2H), 4.86–4.90 (m, 1H), 7.03–7.04 (m, 2H), 7.14 (br s, NH), 7.46–7.57 (m, 5H), 7.82 (br s, NH), 7.88.7.91 (m, 2H), 9.10 (br s, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.41, 23.77, 24.31, 25.43, 26.999, 40.01, 40.16, 42.02, 44.03, 51.97, 60.01, 71.24, 80.52, 119.12, 127.44, 128.44, 128.61, 129.43, 133.45, 139.57, 140.97, 166.80, 173.91, 211.87. HRMS (ES+): *m/z* calcd for $C_{28}H_{35}N_3O_6S$: 542.2244; found: 542.2322 $[H+M]^+$. LC–MS System A: t_R = 4.04 min, System B: t_R = 4.34 min.

Compound **24***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-phenylmethanesulfonylamino-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **6c**. Subsequent treatment of **10** as above. Yield: 38%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94–1.05 (m, 6H), 1.43–1.47 (m, 4H), 1.63–1.69 (m, 4H), 1.70–1.73 (m, 1H), 1.74–1.84 (m, 2H), 1.84–2.06 (m, 1H), 3.78–3.81 (m, 1H), 3.95–4.16 (m, 3H), 4.73–4.77 (m, 1H), 6.97 (br s NH, 1H), 7.07–7.08 (m, 2H), 7.25–7.28 (m, 2H), 7.31–7.36 (m, 3H), 7.43 (br s, NH, 1H), 7.64–7.66 (m, 2H), 7.90 (br s, NH, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.4, 25.4, 26.9, 40.1, 40.2, 41.9, 43.5, 51.9, 58.6, 60.1, 71.2, 80.7, 118.5, 118.6, 128.4, 128.5, 128.6, 128.9, 129.1, 129.2, 129.3, 131.1, 141.3, 166.8, 173.6, 211.9. HRMS (ES+): *m/z* calcd for $C_{29}H_{37}N_3O_6S$: 556.2415; found: 556.2493 $[H+M]^+$. LC–MS System A: t_R = 4.13 min, System B: t_R = 4.43 min.

Compound **25***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-methanesulfonylamino-3-methoxy-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7a**. Subsequent treatment of **10** as above. Yield: 48%. ^{1}H NMR/^{13}C NMR δ 1.02 (s, 3H), 1.03 (t, *J* = 7.4 Hz, 3H), 1.42–1.45 (m, 4H), 1.62–1.85 (m, 7H), 2.17 (dd, *J* = 4.5, 14.5 Hz, 1H), 3.04 (s, 3H), 3.85–3.88 (m, 1H), 3.95–3.99 (m, 1H), 3.96 (s, overlapped, 3H), 4.14 (dd, *J* = 17.2 Hz, 2H), 4.71–4.75 (m, 1H), 6.62 (br d, *J* = 8.3 Hz, NH, 1H), 6.94 (br d, *J* = 8.3 Hz, NH, 1H), 7.30 (dd, *J* = 1.9, 8.3 Hz, 1H), 7.45 (d, *J* = 1.9 Hz, 1H), 7.58 (d, *J* = 8.3 Hz, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.4, 25.4, 26.9, 39.9, 40.1, 40.3, 41.7, 41.8, 43.3, 51.7, 56.3, 60.1, 71.1, 81.2, 110.4, 118.3, 119.8, 130.0, 130.1, 130.2, 148.8, 166.9, 172.8, 211.7. HRMS (ES+): *m/z* calcd for $C_{24}H_{35}N_3O_7S$: 510.2214; found: 510.2293 $[H+M]^+$. LC–MS System A: t_R = 3.64 min, System B: t_R = 3.90 min.

Compound **26***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-methanesulfonylamino-2-methoxy-benzamide*: The corresponding resin **10** was synthesized according to method A using P3 acid capping group **76**. Subsequent treatment of **10** as above. Yield: 62%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99 (s, 3H), 1.01 (t, *J* = 7.6 Hz, 3H), 1.43–1.50 (m, 4H), 1.62–1.69 (m, 4H), 1.72–1.86 (m, 3H), 2.02–2.10 (m, 1H), 3.06 (s, 3H), 3.82–3.85 (m, 1H), 3.97 (s, 3H), 4.06–4.11 (m, 1H), 4.14–4.20 (dd, *J* = 17.1 Hz, 2H), 6.77 (d, *J* = 7.7 Hz, 1H), 7.07 (s, 1H), 7.45–7.60 (br d, NH), 7.98 (d, *J* = 8.2 Hz, 1H), 8.25 (d, *J* = 8.2 Hz, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.4, 25.4, 27.0, 39.9, 40.1, 40.3, 42.0, 43.7, 51.8, 56.4, 60.0, 71.2, 80.8, 102.1, 112.0, 116.3, 133.7, 142.7, 159.1, 165.3, 173.5, 212.1. HRMS (ES+): *m/z* calcd for $C_{24}H_{35}N_3O_7S$: 510.2193; found: 510.2271 $[H+M]^+$. LC–MS System A: t_R = 3.64 min, System B: t_R = 3.89 min.

Compound **27***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2-(1-methyl-cyclopentyl)-ethyl]-4-methanesulfonylamino-3-methyl-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **6k**. Subsequent treatment of **10** as above. Yield: 48%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (t, *J* = 7.2 Hz, 3H), 1.01 (s, overlapped, 3H), 1.43–1.45 (m, 4H), 1.62–1.69 (m, 4H), 1.70–1.83 (m, 3H), 2.14 (dd, *J* = 4.4, 14.6 Hz, 1H), 2.32 (s, 3H), 3.08 (s, 3H), 3.83–3.86 (m, 1H), 3.97–4.01 (m, 1H), 4.13 (dd, *J* = 17.3 Hz, 2H), 4.74–4.78 (m, 1H), 6.74 (br d, *J* = 8.7 Hz, NH, 1H), 7.12 (br d, *J* = 7.1 Hz, NH, 1H), 7.52 (d, *J* = 8.7 Hz, 1H), 7.61 (br dd, *J* = 2.0, 8.6 Hz, 1H), 7.66 (d, *J* = 2.0, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 18.1, 23.7, 24.4, 25.4, 26.9, 40.1, 40.2, 40.5, 41.9, 43.4, 51.7, 60.1, 71.1, 81.1, 120.4, 126.4, 128.9, 130.1, 130.5, 138.7, 172.9, 211.7. HRMS (ES+): *m/z* calcd for $C_{24}H_{35}N_3O_6S$: 494.2263; found: 494.2342 $[H+M]^+$. LC–MS System A: t_R = 3.56 min, System B: t_R = 3.81 min.

Compound **28***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-methanesulfonylamino-2-methyl-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7c**. Subsequent treatment of **10** as above. Yield: 56%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.02–1.06 (m, 6H), 1.45–1.46 (m, 4H), 1.64–1.83 (m, 7H), 2.10 (dd, *J* = 5.3, 14.6 Hz, 1H), 2.39 (s, 3H), 3.65 (s, 3H), 3.79–3.82 (m, 1H), 4.01–4.06 (m, 1H), 4.13 (dd, *J* = 16.9 Hz, 2H), 4.72–4.76 (m, 1H), 6.51 (br d, *J* = 9.1 Hz, NH, 1H), 7.03–7.05 (m, 2H), 7.26 (br d, *J* = 8.3 Hz, NH, 1H), 7.33 (d, *J* = 8.2 Hz, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.5, 20.2, 23.9, 24.4, 25.6, 27.0, 39.9, 40.0, 40.1, 41.8, 43.3, 51.5, 60.1, 71.2, 80.9, 116.9, 122.1, 128.6, 131.7, 138.9, 139.1, 169.8, 172.8, 211.6. HRMS (ES+): *m/z* calcd for $C_{24}H_{35}N_3O_6S$: 494.2254; found: 494.2332 $[H+M]^+$. LC–MS System A: t_R = 3.54 min, System B: t_R = 3.77 min.

Compound **29***: 3-Chloro-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-methanesulfonylamino-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7d**. Subsequent

treatment of **10** as above. Yield: 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01–1.03 (m, 6H), 1.41–1.45 (m, 4H), 1.62–1.69 (m, 4H), 1.72–1.86 (m, 3H), 2.11 (dd, J = 4.7, 14.7 Hz, 1H), 3.10 (s, 3H), 3.84–3.88 (m, 1H), 3.98–4.02 (m, 1H), 4.14 (dd, J = 17.4 Hz, 2H), 4.72–4.76 (m, 1H), 6.93 (br d, J = 8.0 Hz, NH, 1H), 7.13 (br d, J = 7.5 Hz, NH, 1H), 7.66–7.70 (m, 2H), 7.89 (s, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.4, 25.4, 26.9, 40.1, 40.2, 40.7, 41.9, 43.6, 51.9, 60.1, 71.1, 81.0, 120.1, 124.3, 126.9, 129.4, 130.6, 137.1, 165.5, 172.9, 204.6. HRMS (ES+): *m/z* calcd for $C_{23}H_{32}ClN_3O_6S$: 514.1713; found: 514.1791 $[H+M]^+$. LC–MS System A: t_R = 3.63 min, System B: t_R = 4.02 min.

Compound **30***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-3-fluoro-4-methanesulfonylamino-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7g**. Subsequent treatment of **10** as above. Yield: 58%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00 (s, 3H), 1.01 (t, J = 7.3 Hz, 3H), 1.39–1.47 (m, 4H), 1.61–1.66 (m, 4H), 1.73–1.89 (m, 3H), 2.00–2.03 (m, 1H), 3.12 (s, 3H), 3.83–3.87 (m, 1H), 4.00–4.03 (m, 1H), 4.07–4.21 (dd, J = 17.2 Hz, 2H), 4.76–4.80 (m, 1H), 7.41 (br d, J = 8.9 Hz, NH), 7.53–7.57 (m, 4H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.4, 25.5, 26.9, 40.0, 40.2, 40.7, 42.1, 43.4, 52.2, 60.1, 70.5, 71.2, 80.8, 115.4 + 115.6 (d), 121.5, 123.9, 128.7 + 128.8 (d), 130.8, 152.1, 154.1, 165.6, 176.5, 211.6. HRMS (ES+): *m/z* calcd for $C_{23}H_{32}FN_3O_6S$: 498.1998; found: 498.2077 $[H+M]^+$. LC–MS System A: t_R = 3.49 min, System B: t_R = 3.83 min.

Compound **31***: 3-Acetyl-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-methanesulfonylamino-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7h**. Subsequent treatment of **10** as above. Yield: 31%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.01 (s, 3H), 1.05 (t, J = 7.5, 7.5 Hz, 3H), 1.44–1.46 (m, 4H), 1.64–1.71 (m, 5H), 1.75–1.87 (m, 3H), 2.14–2.18 (m, 1H), 2.74 (s, 3H), 3.15 (s, 3H), 3.85–3.88 (dd, J = 8.1, 9.4 Hz, 1H), 4.00–4.07 (m, 1H), 4.10–4.24 (dd, J = 17.1 Hz, 2H), 4.72–4.77 (m, 1H), 6.79 (d, J = 8.4 Hz, NH), 6.87 (d, J = 6.4 Hz, NH), 7.78 (d, J = 8.8 Hz, 1H), 7.87 (d, J = 1.6, 8.8 Hz, 1H), 8.46 (s, 1H), 11.59 (s, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.5, 23.7, 24.4, 25.4, 27.0, 28.6, 40.1, 40.3, 41.0, 41.9, 43.4, 51.9, 60.2, 71.2, 81.1, 117.4, 121.3, 127.2, 132.7, 133.0, 143.7, 165.9, 172.8, 202.5, 211.8. HRMS (ES+): *m/z* calcd for $C_{25}H_{35}N_3O_7S$: 522.2205; found: 522.2283 $[H+M]^+$. LC–MS System A: t_R = 3.90 min, System B: t_R = 4.20 min.

Compound **32***: 4-Benzenesulfonylamino-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-3-methyl-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7n**. Subsequent treatment of **10** as above. Yield: 45%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98(t, J = 7.4Hz, 3H), 1.01 (s, 3H), 1.41–1.44 (m, 4H), 1.62–1.83 (m, 7H), 2.05 (s, 3H), 2.13–2.16 (dd, J = 5.0, 14.5 Hz, 1H), 3.82–3.86 (m, 1H), 3.96 (m, 1H), 4.05–4.21 (q, J = 17.2 Hz, 2H), 4.72–4.76 (m, 1H), 6.61 (d, J = 8.4 Hz, NH), 7.08 (d, J = 7.4 Hz, NH), 7.43–7.52 (m, 5H), 7.59 (m, 1H), 7.78 (d, J = 8.7 Hz, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 17.8, 23.7, 24.4, 25.4, 26.9, 40.1, 40.2, 41.9, 43.4, 51.6, 60.0, 62.5, 71.2, 81.1, 122.4, 126.0, 127.3, 129.5, 130.2, 130.4, 133.6, 138.4, 139.5, 167.1, 172.9, 212.1. HRMS (ES+): *m/z* calcd for $C_{29}H_{37}N_3O_6S$: 556.2401; found: 556.2479 $[H+M]^+$. LC–MS System A: t_R = 4.17 min, System B: t_R = 4.50 min.

Compound **33***: 4-Benzenesulfonylamino-3-chloro-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7o**. Subsequent treatment of **10** as above. Yield: 81%. ^{1}H NMR/^{13}C NMR δ 0.97 (s, 3H), 0.98 (t, J = 7.4 Hz, 3H), 1.38–1.42 (m, 4H), 1.59–1.66 (m, 4H), 1.68–1.81 (m, 3H), 2.03–2.07 (dd, J = 4.5, 14.8 Hz, 1H), 3.81–3.85 (m, 1H), 3.95–3.99 (m, 1H), 4.04–4.19 (dd, J = 17.4 Hz, 2H) 4.70–4.74 (m, 1H,), 6.97 (d, J = 8.9 Hz, NH), 7.33 (br s, NH), 7.34 (br d, NH), 7.48–7.51 (m, 2H), 7.57–7.61 (m, 2H), 7.67 (d, J = 8.4 Hz, 1H), 7.69 (s, 1H), 7.84 (d, J = 8.5 Hz, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.4, 25.4, 26.9, 40.0, 40.2, 41.9, 43.7, 51.9, 60.0, 71.2, 80.9, 120.6, 124.5, 126.7, 127.5, 129.1, 129.6, 130.4, 134.0, 136.9, 138.8, 165.6, 173.0, 211.7. HRMS (ES+): *m/z* calcd for $C_{28}H_{34}ClN_3O_6S$: 576.1882; found: 576.196 $[H+M]^+$. LC–MS System A: t_R = 4.11 min, System B: t_R = 4.69 min.

Compound **34***: 6-Benzenesulfonylamino-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-nicotinamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7r**. Subsequent treatment of **10** as above. Yield: 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.87–0.93 (m, 6H), 1.19–1.23 (m, 2H), 1.31–1.43 (m, 2H), 1.52–1.85 (m, 8H), 3.85–3.90 (m, 2H), 4.02 (dd, overlapped, J = 17.2 Hz, 2H), 4.51–4.55 (m, 1H), 7.12 (d, J = 9.0 Hz, 1H), 7.53–7.60 (m, 3H), 7.89–7.91 (m, 2H), 8.08–8.09 (m, 1H), 8.27–8.28 (m, NH, 1H), 8.51 (br d, J = 8.2 Hz, NH, 1H), 8.52–8.56 (m, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.8, 23.8, 24.5, 25.7, 26.9, 39.5, 42.3, 43.5, 51.6, 59.2, 70.5, 71.1, 80.7, 118.5, 118.6, 127.4, 128.4, 128.5, 128.9, 129.1, 129.3, 129.6, 132.8, 141.3, 166.8, 173.0, 212.6. HRMS (ES+): *m/z* calcd for $C_{27}H_{34}N_4O_6S$: 543.2195; found: 543.2274 $[H+M]^+$. LC–MS System A: t_R = 3.53 min, System B: t_R = 3.96 min.

Compound **35***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-6-methanesulfonylamino-nicotinamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid **7s**. Subsequent treatment of **10** as above. Yield: 30%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.00–1.06 (m, 6H), 1.39–1.58 (m, 4H), 1.62–1.75 (m, 5H), 1.75–1.90 (m, 3H), 2.02–2.06 (m, 1H), 3.66 (s, 3H), 3.97–4.03 (m, 2H), 4.17–4.21 (d, 2H), 4.71–4.73 (m, 1H), 7.07–7.09 (m, 1H), 8.14–8.16 (m, 4H), 8.70 (br s, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 8.4, 8.8, 23.4, 24.0, 24.5, 26.5, 39.5, 40.7, 41.9, 43.5, 52.0, 58.6, 59.3, 70.3, 70.7, 80.9, 111.7, 138.0, 174.0, 211.8. HRMS (ES+): *m/z* calcd for $C_{22}H_{32}N_4O_6S$: 481.2044; found: 481.2123 $[H+M]^+$. LC–MS System A: t_R = 2.96 min, System B: t_R = 3.30 min.

Compound **36***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(4-fluoro-benzenesulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **7j**. Subsequent treatment of **10** as above. Yield: 30%. ^{1}H NMR/^{13}C NMR δ 0.97–1.03 (m, 6H), 1.42–1.46 (m, 4H), 1.59–1.67 (m, 4H), 1.69–1.82 (m, 3H), 2.08–2.12 (dd, J = 4.9, 14.5 Hz, 1H), 3.80–3.84 (dd, J = 8.4, 9.4 Hz 1H), 4.01–4.05 (m, 1H), 4.08–4.22 (dd, J = 17.5 Hz 2H), 4.76–4.80 (m, 1H), 6.80 (br s, NH), 7.06–7.08 (m, 2H), 7.27–7.29 (m, 3H), 7.98–7.67 (m, 4H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 24.4, 25.4, 27.0, 40.1, 40.2, 41.9, 43.7, 51.9, 60.1, 71.6, 80.8, the rest is not resolved due to low s/n, HRMS (ES+): *m/z* calcd for $C_{28}H_{35}N_3O_6SF$: 560.2231; found: 560.2230 $[H+M]^+$. LC–MS System A: t_R = 4.14 min, System B: t_R = 4.44 min.

Compound **37***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(3-fluoro-benzenesulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **7i**. Subsequent treatment of **10** as above. Yield: 43%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91–1.00 (m, 6H), 1.38–1.45 (m, 4H), 1.58–1.65 (m, 4H), 1.65–1.83 (m, 3H), 2.00–2.08 (m, 1H), 3.78–3.81 (m, 1H), 3.99–4.04 (m, 1H), 4.05–4.21 (m, 2H), 4.79–4.84 (m, 1H), 6.97–7.01 (br d, NH, 1H), 7.02–7.06 (m, 2H), 7.12–7.18 (m, 2H), 7.48–7.54 (m, 2H), 7.60–7.63 (m, NH, 1H), 7.84–7.95 (m, 2H), 7.70–7.75 (br s, NH, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 23.5, 24.1, 25.2, 25.4, 26.7, 39.8, 39.9, 41.7, 43.6, 51.6, 59.8, 71.0, 80.3, 116.4, 116.6, 119.2 (d), 128.4, 128.7, 129.9, 130.0, 135.2, 140.4, 166.6, 173.4, 211.7. HRMS (ES+): *m/z* calcd for $C_{28}H_{34}FN_3O_6S$: 560.2159; found: 560.2238 $[H+M]^+$. LC–MS System A: t_R = 4.13 min, System B: t_R = 4.46 min.

Compound **38***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(2-fluoro-benzenesulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **7m**. Subsequent treatment of **10** as above. Yield: 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91–1.00 (m, 6H), 1.37–1.44 (m, 4H), 1.55–1.65 (m, 4H), 1.65–2.00 (m, 4H), 3.80–3.84 (m, 1H), 3.98–4.03 (m, 1H), 4.06–4.18 (m, 2H), 4.79-4-85 (m, 1H), 7.09–7.17 (m, 2H), 7.24–7.28 (m, 1H), 7.53–7.64 (m, 3H), 7.70 (br s, NH), 7.92–7.93 (m, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 23.7, 24.3, 25.4, 26.9, 40.0, 40.1, 42.0, 43.9, 52.0, 60.0, 71.2, 80.7, 117.2, 117.4, 119.2, 124.9, 127.1, 127.2 (d), 128.7, 130.0 (d), 136.0 (d), 140.3, 166.8, 173.8, 212.0. HRMS (ES+): *m/z* calcd for $C_{28}H_{34}FN_3O_6S$: 560.2155; found: 560.2234 $[H+M]^+$. LC–MS System A: t_R = 4.03 min, System B: t_R = 4.36 min.

Compound **39***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(toluene-2-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **7l**. Subsequent treatment of **10** as above. Yield: 89%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98 (br s, 6H), 1.36–1.44 (m, 4H), 1.57–1.64 (m, 4H), 1.65–2.02 (m, 4H), 2.69 (s, 3H), 3.81–3.85 (m, 1H), 3.99–4.05 (m, 1H), 4.05–4.16 (m, 2H), 4.83–4.87 (m, 1H), 6.99–7.07 (m, 2H), 7.25 (br s, NH), 7.28–7.33 (m, 2H), 7.44–7.46 (m, 1H), 7.54–7.60 (m, 2H), 7.92 (br s, NH), 8.05–8.07 (m, 1H), 9.36 (br s, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 20.5, 23.7, 23.7, 24.3, 25.4, 27.0, 40.0, 40.1, 42.0, 44.0, 52.1, 59.9, 71.2, 80.5, 118.0, 118.0, 126.6, 127.8, 128.7, 130.1, 133.0, 133.6, 137.6, 137.7, 141.1, 167.0, 174.1. HRMS (ES+): *m/z* calcd for $C_{29}H_{37}N_3O_6S$: 556.2405; found: 556.2483 $[H+M]^+$. LC–MS System A: t_R = 4.20 min, System B: t_R = 4.50 min.

Compound **40**: 4-(4-Amino-benzenesulfonylamino)-*N*-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide. The corresponding resin 10 was synthesized according to Method A using P3 acid capping group 7t. Yield: 68%. Subsequent treatment of 10 as above was followed by catalytic hydrogenation with 10 % Pd/C in methanol. Yield: 91%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99–1.01 (m, 6H), 1.20–1.30 (m, 4H), 1.50–1.60 (m, 4H), 1.60–1.84 (m, 3H), 2.15–2.19 (m, 1H), 3.83–3.86 (m, 1H), 3.93–3.97 (m, 1H), 4.04–4.21 (dd, 2H), 4.64–4.69 (m, 1H), 6.31–6.32 (d, NH), 6.60–6.61 (m, 2H), 6.68 (br s, NH), 6.76 (br s, NH), 7.11–7.13 (m, 2H), 7.58–7.64 (m, 4H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 24.4, 25.8, 27.3, 40.2, 43.1, 42.2, 51.8, 60.0, 71.5, 81.3, 119.6, 128.2, 129.9, 137.1, 167.3, 173.3, 210.7. HRMS (ES+): *m/z* calcd for $C_{28}H_{36}N_4O_6S$: 557.2357; found: 557.2435 $[H+M]^+$. LC–MS System A: t_R = 3.69 min, System B: t_R = 3.95 min.

Compound **41***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(4-methoxy-benzenesulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **7q**. Subsequent treatment of **10** as above. Yield: 62%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.95–1.04 (m, 6H), 1.36–1.56 (m, 4H), 1.64–1.73 (m, 2H), 1.75–2.02 (m, 2H), 3.83 (s, 3H), 3.94–4.19 (m, 3H), 4.67–4.68 (m, 1H), 6.99–7.01 (m, 2H), 7.18–7.22 (m, 2H), 7.69–7.77 (m, 4H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 8.40, 8.79, 23.98, 24.50, 25.98, 39.4543.46, 52.04, 80.96, 84.71, 114.08, 118.95, 128.52, 128.61, 129.27, 131.19, 141.68, 163.55, 167.89, 174.18, 211.85. HRMS (ES+): *m/z* calcd for $C_{29}H_{37}N_3O_7S$: 572.2369; found: 572.2448 $[H+M]^+$. LC–MS System A: t_R = 4.09 min, System B: t_R = 4.39 min.

Compound **42***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(3-methoxy-benzenesulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **7p**. Subsequent treatment of **10** as above. Yield: 54%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.91–1.00 (m, 6H), 1.37–1.45 (m, 4H), 1.58–1.79 (m, 6H), 1.85–2.05 (m, 2H), 3.80 (s, 3H), 4.00–4.06 (m, 2H), 4.08–4.18 (d, 2H), 4.85–4.89 (m, 1H), 7.01–7.03 (m, 2H), 7.07–7.09 (m, 2H), 7.14–7.15 (br d, NH), 7.40 (s, 1H) 7.37–7.49 (m, 3H), 7.81 (br s, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.5, 23.8, 24.3, 25.4, 25.4, 27.0, 40.0, 42.0, 44.0, 52.0, 5.9, 60.1, 71.3, 80.5, 112.5, 119.0, 119.5, 119.6, 128.3, 128.6, 130.5, 140.7, 141.0, 160.1, 166.8, 173.9. HRMS (ES+): *m/z* calcd for $C_{29}H_{37}N_3O_7S$: 572.2352; found: 572.243 $[H+M]^+$. LC–MS System A: t_R = 4.12 min, System B: t_R = 4.45 min.

Compound **43***: 4-(4-Cyano-benzenesulfonylamino)-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method B using 4-cyano sulfonyl chloride. Subsequent treatment of **10** as above. Cleavage from the corresponding P3–P2–P1 resin **10** with 95% TFA (aq, 6 mL) and agitation for 0.5 h. Toluene (3 mL) was added after filtration from resin, followed by evaporation and purification as in general method. Yield: 17% (2 steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.84–0.88 (m, 3H), 0.99 (s, 3H), 1.21–1.33 (m, 4H), 1.54–1.69 (m, 4H), 2.08 (dd, 1H), 3.76–3.85 (m, 1H), 3.98–4.21 (m, 3H), 4.72–4.75 (m, 1H), 6.74 (br s, NH, 1H), 7.05 (m, 2H), 7.13 (br s, NH, 1H), 7.54–7.56 (m, 2H), 7.78–7.81 (m, 2H), 7.94–7.96 (m, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 22.7, 23.5, 24.1, 25.2, 26.8, 39.9, 40.0, 41.7, 43.4, 51.6, 60.0, 71.0, 80.5, 117.1, 119.7, 127.8, 127.9, 128.6, 129.9, 133.0, 139.7, 166.5, 179.1, 211.6. HRMS (ES+): *m/z* calcd for $C_{29}H_{35}N_4O_6S$: 567.2277; found: 567.2276 $[H+M]^+$. LC–MS System A: t_R = 4.03 min, System B: t_R = 4.36 min.

Compound **44***: 4-(3-Cyano-benzenesulfonylamino)-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method B using using 3-cyano sulfonyl chloride. Subsequent treatment of **10** as above. Cleavage from the corresponding P3–P2–P1 resin **10** was with 95% TFA (aq, 6 mL) and agitation for 0.5 h. Toluene (3 mL) was added after filtration from resin, followed by evaporation and purification as in general method.Yield: 16% (2 steps). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 14.3, 24.7, 27.2, 28.0, 40.3, 40.7, 43.7, 52.0, 59.9, 70.8, 80.7, 114.6, 117.4, 120.1, 128.4, 130.4, 131.3, 131.4, 133.6, 135.0, 136.8, 140.7, 166.9, 171.9, 211.9. ^{1}H-NMR/^{13}C-NMR, HRMS (ES+): *m/z* calcd for $C_{29}H_{35}N_4O_6S$: 567.2277; found: 567.2298 $[H+M]^+$. LC–MS System A: t_R = 3.98 min, System B: t_R = 4.34 min.

Compound **45**: *4-(2-Cyano-benzenesulfonylamino)-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method B using using 2-cyano sulfonyl chloride. Subsequent treatment of **10** as above. Cleavage from the corresponding P3–P2–P1 resin **10** with 95% TFA (aq, 6 mL) and agitation for 0.5 h. After filtration from resin, toluene (3 mL) was added, followed by evaporation and purification as in general method. Yield: 19% (2 steps). ^{1}H NMR (500 MHz, CD_3OD) δ 0.97 (t, 3H), 1.00 (s, 3H), 1.26 (m, 2H), 1.40 (m, 2H), 1.59–1.82 (m, 7H), 2.10 (m, 1H), 3.80–3.83 (m, 1H), 3.93–3.96 (m, 1H), 4.04–4.20 (dd, J = 17.1 Hz, 63.9 Hz, 2H), 4.64–4.69 (m, 1H), 6.45 (d, J = 7.8 Hz, NH), 6.83 (d, J = 7.3 Hz, NH), 7.18 (d, J = 8.8 Hz, 2H), 7.61 (d, J = 8.8 Hz, 2H), 7.68 (m, 2H), 7.82 (d, J = 7.8 Hz, 1H), 7.90 (br s, NH), 8.15 (d, J = 7.8 Hz,1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.1, 23.5, 24.2, 25.2, 26.7, 39.9, 40.0, 41.6, 43.0, 43.5, 51.4, 59.8, 70.9, 80.9, 109.9, 119.7, 128.6, 130.7, 133.3, 133.6, 134.2, 135.1, 166.5, 172.5, 211.3. HRMS (ES+): *m/z* calcd for $C_{29}H_{35}N_4O_6S$: 567.2277; found: 567.2277 $[H+M]^+$. LC–MS System A: t_R = 3.81 min, System B: t_R = 4.27 min.

Compound **46***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(pyridine-4-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized

according to Method A using P3 acid capping group **8c**. Subsequent treatment of **10** as above. Yield: 66%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94–0.97 (m, 6H), 1.35–1.39 (m, 4H), 1.56–1.62 (m, 4H), 1.65–1.96 (m, 4H), 3.77–3.79 (m, 1H), 3.92–3.96 (m, 1H), 4.01–4.16 (m, 2H), 4.65–4.68 (m, 1H), 7.11–7.13 (m, 2H), 7.61–7.66 (m, 4H), 8.69–8.70 (m, 2H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.27, 23.66, 24.30, 25.11, 26.82, 39.82, 40.16, 41.82, 43.98, 49.13, 51.40, 59.67, 70.47, 71.13, 80.90, 119.95, 120.70, 128.90, 129.70, 140.38, 148.12, 150.97, 166.96, 173.58, 212.21. HRMS (ES+): *m/z* calcd for $C_{27}H_{34}N_4O_6S$: 543.2194; found: 543.2272 $[H+M]^+$. LC–MS System A: t_R = 3.41 min, System B: t_R = 3.86 min.

Compound **47***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(pyridine-3-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **8a**. Subsequent treatment of **10** as above. Yield: 79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.88–0.91 (m, 6H), 1.28–1.34 (m, 4H), 1.51–1.62 (m, 4H), 1.63–1.69 (m, 4H), 1.88–1.90 (m, 2H), 3.75–4.10 (m, 4H), 4.57–4.60 (dd, 1H), 7.10–7.12 (m, 2H), 7.34–7.37 (m, 1H), 7.58–7.61 (m, 3H), 8.02–8.04 (m, 2H), 8.61–8.62 (m, 1H) 8.90 (br s, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.1, 23.6, 24.2, 25.0, 26.7, 39.7, 40.1, 41.7, 44.0, 51.5, 59.5, 71.0, 81.0, 119.7, 119.7, 124.2, 128.8, 129.7, 135.4, 136.7, 140.5, 147.7, 153.1, 167.0, 173.6, 212.1. HRMS (ES+): *m/z* calcd for $C_{27}H_{34}N_4O_6S$: 543.2188; found: 543.2267 $[H+M]^+$. LC–MS System A: t_R = 3.50 min, System B: t_R = 4.87 min.

Compound **48***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(pyridine-2-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **8b**. Subsequent treatment of **10** as above. Yield: 79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.94–1.00 (m, 6H), 1.38–1.41 (m, 4H), 1.58–1.79 (m, 7H), 2.07–2.10 (dd, 1H), 3.81–3.84 (dd, 1H), 3.95–3.99 (m, 1H), 4.04–4.18 (dd, 2H), 4.70–4.75 (m, 1H), 6.72 (br s, NH, 1H), 7.17–7.23 (m, 3H), 7.48–7.49 (m, 1H), 7.55–7.57 (m, 2H), 7.87–7.88 (m, 1H), 7.98–8.00 (m, 1H) 8.37 (br s, 1H) 8.66 (s, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 23.5, 24.1, 25.2, 26.7, 39.8, 40.0, 41.7, 43.3, 51.6, 59.8, 70.9, 80.7, 120.2, 123.0, 127.3, 128.4, 129.4, 138.3, 140.1, 150.2, 156.2, 166.7, 172.9, 211.6. HRMS (ES+): *m/z* calcd for $C_{27}H_{34}N_4O_6S$: 543.2214; found: 543.2292 $[H+M]^+$. LC–MS System A: t_R = 3.65 min, System B: t_R = 3.96 min.

Compound **49***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(4-methyl-pyridine-3-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **8d**. Subsequent treatment of **10** as above. Yield: 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ *0.93 (t, J* = 7.3 Hz, 3H), 0.97 (s, 3H), 1.36–1.41 (m, 4H), 1.58–1.77 (m, 6H), 1.85–2.00 (m, 2H), 2.69 (s, 3H), 3.75 (m, 1H), 4.00–4.04 (m, 1H), 4.06–4.17 (d, *J* = 17.1 Hz, 1H), 4.76–4.80 (m, 1H), 6.99 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 7.8 Hz, 1H), 7.47–7.56 (br d, NH), 7.55–7.56 (d, *J* = 7.3 Hz, 1H), 7.76 (br d, NH), 8.62 (d, *J* = 4.9 Hz, 1H), 9.07 (d, 1H), 9.42–9.58 (br d, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 20.0, 23.5, 24.1, 25.2, 26.8, 39.7, 40.0, 41.8, 43.4, 51.9, 59.9, 71.0, 80.3, 118.3, 119.4, 127.3, 128.7, 129.0, 134.6, 140.1, 147.4, 149.5, 153.3, 166.4, 188.3, 220.1. HRMS (ES+): *m/z* calcd for $C_{28}H_{36}N_4O_6S$: 557.2372; found: 557.245 $[H+M]^+$. LC–MS System A: t_R = 3.56 min, System B: t_R = 3.91 min.

Compound **50***: 4-(2-Chloro-pyridine-3-sulfonylamino)-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **7u**. Subsequent treatment of **10** as above. Yield: 19%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.83–0.92 (m, 3H), 0.94–1.02 (m, 3H), 1.14–1.48 (m, 4H), 1.50–1.82 (m, 5H), 1.99–2.01 (m, 1H), 2.18 (dd, *J* = 4.5, 14.5 Hz, 1H), 3.81–3.84 (m, 1H), 3.93–3.96 (m, 1H), 4.12 (dd, *J* = 17.2 Hz, 2H), 4.65–4.67 (m, 1H), 6.36 (br d, *J* = 8.3 Hz, NH, 1H), 7.04 (br d, *J* = 8.3 Hz, NH, 1H), 7.20 (d, *J* = 8.8 Hz, 2H), 7.37–7.39 (m, 1H), 7.62–7.64 (d, *J* = 8.3 Hz, 2H), 8.34 (d, *J* = 8.2 Hz, 1H), 8.52–8.53 (m, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 14.4, 24.7, 20.1, 27.4, 37.6, 39.2, 43.6, 51.9, 60.2, 71.2, 81.4, 120.9, 123.8, 129.2, 130.9, 134.1, 139.1, 141.1, 147.9, 153.7, 167.1, 172.6, 211.6. HRMS (ES+): *m/z* calcd for $C_{27}H_{34}ClN_4O_6S$: 577.1888; found: 577.1893 $[H+M]^+$. LC–MS System A: t_R = 3.83 min, System B: t_R = 4.14 min.

Compound **51***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(thiophene-2-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **6d**. Subsequent treatment of **10** as above. Yield: 38%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96–1.04 (m, 6H), 1.44–1.46 (m, 4H), 1.61–1.85 (m, 7H), 2.07–2.09 (m, 1H), 3.80–3.83 (m, 1H), 4.03–4.21 (m, 3H), 4.79–4.83 (m, 3H), 6.93 (m, NH, 1H), 7.03–7.04 (m, 1H), 7.13–7.14 (br s, NH, 1H), 7.47–7.66 (m, 4H), 8.6 (br s, NH, 1H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.4, 23.7, 24.3, 25.4, 26.9, 40.2, 40.3, 41.9, 43.8, 51.9, 60.1, 71.3, 80.7, 119.6, 119.7, 127.7, 128.6, 128.7, 129.1, 129.2, 132.9, 133.3, 139.8, 166.8, 173.6, 211.9. HRMS (ES+): *m/z* calcd for $C_{26}H_{33}N_3O_6S_2$: 548.1812; found: 548.189 $[H+M]^+$. LC–MS System A: t_R = 3.95 min, System B: t_R = 4.30 min.

Compound **52***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(1-methyl-1H-imidazole-2-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **7k**. Subsequent treatment of **10** as above. Yield: 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.99–1.03 (m, 6H), 1.37–1.52 (m, 4H), 1.64–1.73 (m, 4H), 1.73–1.87 (m, 3H), 1.98–2.00 (dd, 1H), 3.55–3.61 (m, 1H), 3.72 (s, 3H), 3.79–4.19 (m, 3H), 4.69–4.70 (m, 1H), 7.23–7.27 (m, 2H), 7.68–7.76 (m, 4H). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 8.4, 23.3, 23.4, 24.0, 26.5, 33.1, 39.4, 39.7, 41.8, 43.5, 52.0, 59.2, 70.3, 80.9, 118.4, 118.5, 126.0, 126.1, 128.4, 128.5, 128.9, 138.6, 140.0, 167.8, 174.2, 211.8. HRMS (ES+): *m/z* calcd for $C_{26}H_{35}N_5O_6S$: 546.2312; found: 546.239 $[H+M]^+$. LC–MS System A: t_R = 3.34 min, System B: t_R = 3.53 min.

Compound **53***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(4-methyl-thiazole-2-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **9b**. Subsequent treatment of **10** as above. Yield: 31%. ^{1}H NMR (500 MHz, CD_3OD) δ 1.00 (t, *J* = 7.1 Hz, 3H), 1.03 (s, 3H), 1.38–1.54 (m, 4H), 1.64–1.87 (m, 6H), 1.99–2.02 (dd, *J* = 3.7, 14.4 Hz, 2H), 2.43 (s, 3H), 3.95–4.02 (m, 2H), 4.00–4.19 (dd, overlapping, *J* = 16.5 Hz, 2H), 4.69 (dd, *J* = 3.8, 9.6 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 2H), 7.46 (s, 1H), 7.76 (d, *J* = 8.8 Hz, 2H), 8.44 (d, *J* = 8.8 Hz, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 8.4, 15.7, 23.4, 24.0, 24.5, 24.5, 26.0, 39.4, 39.7, 41.9, 43.5, 52.1, 59.2, 70.7, 80.9, 119.7, 120.7, 128.5, 128.6, 130.1, 140.5, 155.2, 165.3, 174.2, 211.9. HRMS (ES+): *m/z* calcd for $C_{26}H_{34}N_4O_6S_2$: 563.1921; found: 563.1999 $[H+M]^+$. LC–MS System A: t_R = 3.47 min, System B: t_R = 4.24 min.

Compound **54***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(4-isopropyl-thiazole-2-sulfonylamino)-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **9d**. Subsequent treatment of **10** as above. Yield: 47%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, overlapping, 3H), 0.98 (s, 3H), 1.25 (m, 8H), 1.41 (m, 5H), 1.59–1.81 (m, 9H), 2.09 (m, 2H), 3.07–3.10 (m, 1H), 3.82 (m, 1H), 4.00 (m, 1H), 4.06–4.20 (dd, *J* = 17.1 Hz, 50.8 Hz, 2H), 4.73 (m, 1H), 6.82 (br d, NH), 7.14 (s, 1H), 7.21 (d, *J* = 7.8 Hz, 2H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.65 (br d, NH), 8.71 (s, NH) ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 22.1, 23.5, 24.1, 25.2, 26.7, 31.0, 40.0, 40.9, 41.7, 43.3, 51.6, 59.9, 71.0, 80.7, 117.9, 120.6, 128.3, 139.5, 162.7, 166.0, 166.1, 166.6, 213.5. HRMS (ES+): *m/z* calcd for $C_{28}H_{38}N_4O_6S_2$: 591.2241; found: 591.2319 $[H+M]^+$. LC–MS System A: t_R = 4.00 min, System B: t_R = 4.72 min.

Compound **55***: 4-(2,4-Dimethyl-thiazole-5-sulfonylamino)-N-[1-(2S-ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-benzamide*: The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **9a**. Subsequent treatment of **10** as above. Yield: 84%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.96 (t, J = 7.3 Hz, 3H), 1.00 (s, 3H), 1.42 (m, 4H), 1.62 (m, 4H), 1.66–1.88 (m, 4H), 2.02 (m, 1H), 2.54 (s, 3H), 2.63 (s, 3H), 3.87 (m, 1H), 4.04–4.18 (m, 3H), 4.80 (m, 1H), 7.03 (d, J = 7.8 Hz, 1H), 7.15 (br d, NH), 7.53 (d, J = 7.8 Hz, 2H), 7.69 (br d, NH), 9.29 (s, NH) ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 16.3, 19.4, 23.5, 24.1, 25.2, 26.8, 39.8, 39.9, 41.8, 43.6, 51.9, 60.0, 71.0, 80.2, 119.1, 128.5, 128.6, 140.1, 156.9, 166.6, 169.5, 212.5. HRMS (ES+): *m/z* calcd for $C_{27}H_{36}N_4O_6S_2$: 577.2074; found: 577.2152 $[H+M]^+$. LC–MS System A: t_R = 3.71 min, System B: t_R = 4.14 min.

Compound **56***: N-[1-(2S-Ethyl-4-oxo-tetrahydro-furan-3S-ylcarbamoyl)-2S-(1-methyl-cyclopentyl)-ethyl]-4-(5-methyl-thiazole-2-sulfonylamino)-benzamide*. The corresponding resin **10** was synthesized according to Method A using P3 acid capping group **9c**. Subsequent treatment of **10** as above. Yield: 34%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.98–1.04 (m, 6H), 1.36–1.45 (m, 4H), 1.59–1.67 (m, 4H), 1.68–1.85 (m, 3H), 2.04–2.09 (m, 1H), 2.53 (s, 3H), 3.85 (br s, 1H), 4.02 (br s, 1H), 4.07–4.20 (dd, 2H), 4.73 (m, 1H), 6.94 (br s, NH), 7.13 (br s, 2H), 7.50 (br s, 2H), 7.59 (s, 1H), 9.04 (s, NH). ^{13}C NMR (125.68 MHz, $CDCl_3$) δ 9.2, 12.2, 23.6, 24.1, 25.2, 26.7, 39.8, 40.9, 41.7, 43.4, 51.8, 59.9, 71.0, 80.4, 119.7, 128.4, 129.3, 139.7, 141.5, 142.4, 166.7, 173.4. HRMS (ES+): *m/z* calcd for $C_{26}H_{34}N_4O_6S_2$: 563.1927; found: 563.2006 $[H+M]^+$. LC–MS System A: t_R = 3.56 min, System B: t_R = 4.28 min.

Acknowledgments

The authors are grateful to Dr. Dean Derbyshire for supplying the protein crystal structures on which much of this work is based. Also, we thank Dr. Kevin Parkes and Dr. Urszula Grabowska for their valuable comments and helpful discussions.

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