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SYNTHESIS OF AN ARRAY OF POTENTIAL MATRIX METALLOPROTEINASE INHIBITORS USING A SEQUENCE OF POLYMER-SUPPORTED REAGENTS

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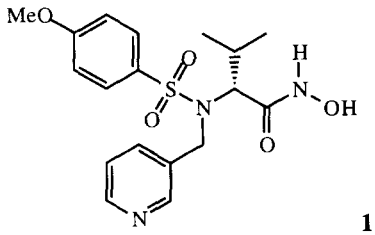
Abstract: Polymer-supported reagents and sequestering agents may be used to generate an array of variously substituted hydroxamic acid derivatives as potential inhibitors of matrix metalloproteinases without any chromatographic purification step.

Keywords: Amino acids and derivatives; enzyme inhibitors; hydroxamic acids; solid phase synthesis

Introduction: Hydroxamic acid derivatives exhibit a variety of pharmaceutical properties, of which their inhibitory effect on the matrix metalloproteinase (MMP) class of enzymes is probably the most important. These enzymes are mediators for the breakdown of structural proteins of the extracellular matrix. Their proposed pathogenic role includes the destruction of cartilage and bone in rheumatoid and osteoarthritis as well as tissue breakdown, metastasis and tumour angiogenesis. During the past years extensive synthesis programmes have focussed on the development of synthetic MMP inhibitors. Screening libraries revealed non-peptidic inhibitors of stromelysin-1 (MMP-3) leading to the development of compound **1** (Figure 1) which shows its best results in the inhibition of gelatinase B (MMP-9).[1]



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K_i (MMP-1) = 33 nM
K_i (MMP-2) = 20 nM
K_i (MMP-3) = 43 nM
K_i (MMP-9) = 8 nM

Figure 1. The known MMP inhibitor CGS-27023A.

Based on this structural knowledge we set out to synthesise analogous molecules using a combinatorial approach by application of polymer-supported reagents. Polymer-supported reagents and sequestering agents[2] offer the advantage of classical solution phase chemistry (*e.g.* monitoring the reactions with LC-MS, TLC or NMR techniques) and benefit from the possibility of using a large excess of the reagents without the need for additional purification steps. Recent work in our group has established the principles for the development of orchestrated multi-step reactions for the generation of chemical compound libraries utilising polymer-supported reagents.[3] In this communication we wish to report the fast and flexible generation of an array of hydroxamic acids as potential matrix metalloproteinase inhibitors.

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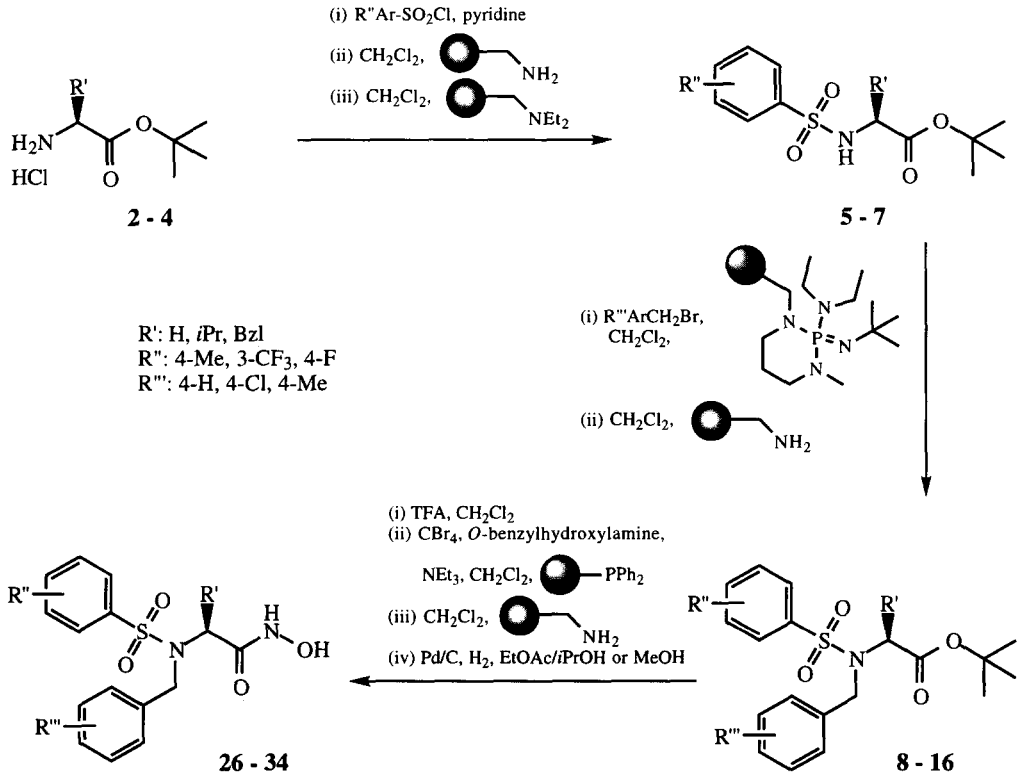
Synthetic Chemistry: Starting from commercially available L-amino acid *tert*-butyl ester hydrochlorides (glycine *tert*-butyl ester **2**, valine *tert*-butyl ester **3** and phenylalanine *tert*-butyl ester **4**) we prepared a set of compounds exhibiting the opposite stereocenter compared with the reported active compound **1**, which we chose to prove the concept of the method, since the *tert*-butyl esters of the D-amino acids are not widely available, but can easily be prepared by literature methods.[4] The first step involved the sulfonamidation of the amino function (Scheme 1), which can be carried out either using our published method applying polymer-supported dimethylaminopyridine[3c,e] or by a classical approach with one equivalent of the sulfonyl chloride in pyridine and work-up of the reaction mixture first with aminomethyl polystyrene (AMPS) and then with Amberlyst A-21 to desalt the solution by binding hydrogen chloride. This reaction furnished the products **5a-c**, **6a-c** and **7a-c** in a nearly quantitative yield and high purity. The isolated sulfonamides **5a-c**, **6a-c** and **7a-c** can then be reacted in dichloromethane with a set of benzyl bromides in the presence of a polymer-supported phosphazene base (BEMP-PS).[5] For the reaction three equivalents of the benzyl bromides (prepared as described earlier[3f]) and 1.1 equivalents of the base have been applied to result in a nearly quantitative reaction. The excess of the benzyl bromides was sequestered with aminomethyl polystyrene in the usual way leaving the clean products **8a-c**, **9a-c**, **10a-c**, **11a-c**, **12a-c**, **13a-c**, **14a-c**, **15a-c** and **16a-c** in solution. Cleavage of the *tert*-butyl group with trifluoroacetic acid (TFA) afforded the free acids. The coupling with *O*-benzyl hydroxylamine was first attempted using commercial polymer-supported cyclohexyl carbodiimide[6] which gave only very poor conversion to the hydroxamic acid esters.



Scheme 1. Reaction sequence using polymer supported reagents and sequestering agents.

Table 1. Summary of polymer-supported reactions. Yields are given for the reaction from the precursor compound. Mass ions are generally [M+H], [M+NH_4] or [M+Na] and obtained in positive mode.

	R'	R"	R'''	Yield	LC-Purity	ES-MS		R'	R"	R'''	Yield	LC-Purity	ES-MS
5a	H	4-Me	–	97%	>98%	303.26	**20a**	*i*Pr	4-Me	4-H	82%	>95%	467.37
5b	H	3-CF_3	–	92%	>98%	362.27	**20b**	*i*Pr	3-CF_3	4-H	69%	>98%	521.34
5c	H	4-F	–	93%	>95%	312.19	**20c**	*i*Pr	4-F	4-H	65%	>98%	471.34
6a	*i*Pr	4-Me	–	91%	>98%	349.34	**21a**	*i*Pr	4-Me	4-Cl	39%	>95%	501.28
6b	*i*Pr	3-CF_3	–	quant	>95%	399.35	**21b**	*i*Pr	3-CF_3	4-Cl	69%	>98%	555.18
6c	*i*Pr	4-F	–	91%	>98%	345.36	**21c**	*i*Pr	4-F	4-Cl	61%	>95%	505.23
7a	Bzl	4-Me	–	quant	>98%	393.37	**22a**	*i*Pr	4-Me	4-Me	52%	>98%	481.35
7b	Bzl	3-CF_3	–	quant	>98%	428.01	**22b**	*i*Pr	3-CF_3	4-Me	72%	>98%	535.30
7c	Bzl	4-F	–	95%	>98%	397.34	**22c**	*i*Pr	4-F	4-Me	63%	>92%	485.35
8a	H	4-Me	4-H	89%	>95%	376.31	**23a**	Bzl	4-Me	4-H	64%	>92%	515.27
8b	H	3-CF_3	4-H	94%	>95%	447.31	**23b**	Bzl	3-CF_3	4-H	64%	>98%	569.22
8c	H	4-F	4-H	96%	>95%	397.28	**23c**	Bzl	4-F	4-H	69%	>95%	519.23
9a	H	4-Me	4-Cl	quant	>95%	427.92	**24a**	Bzl	4-Me	4-Cl	90%	>98%	549.18
9b	H	3-CF_3	4-Cl	quant	>95%	481.21	**24b**	Bzl	3-CF_3	4-Cl	82%	>98%	603.13
9c	H	4-F	4-Cl	quant	>98%	431.18	**24c**	Bzl	4-F	4-Cl	88%	>98%	553.15
10a	H	4-Me	4-Me	97%	>98%	390.21	**25a**	Bzl	4-Me	4-Me	51%	>95%	529.35
10b	H	3-CF_3	4-Me	quant	>98%	461.24	**25b**	Bzl	3-CF_3	4-Me	72%	>98%	583.28
10c	H	4-F	4-Me	95%	>98%	411.19	**25c**	Bzl	4-F	4-Me	64%	>95%	533.33
11a	*i*Pr	4-Me	4-H	quant	>98%	362.33	**26a**	H	4-Me	4-H	69%	>92%	335.19
11b	*i*Pr	3-CF_3	4-H	96%	>98%	489.48	**26b**	H	3-CF_3	4-H	66%	>95%	389.18
11c	*i*Pr	4-F	4-H	quant	>98%	439.39	**26c**	H	4-F	4-H	75%	>92%	339.11
12a	*i*Pr	4-Me	4-Cl	98%	>92%	469.26	**27a**	H	4-Me	4-Cl	61%	>95%	369.21
12b	*i*Pr	3-CF_3	4-Cl	quant	>92%	523.21	**27b**	H	3-CF_3	4-Cl	60%	>90%	423.17
12c	*i*Pr	4-F	4-Cl	quant	>92%	473.26	**27c**	H	4-F	4-Cl	78%	>90%	373.21
13a	*i*Pr	4-Me	4-Me	98%	>95%	449.30	**28a**	H	4-Me	4-Me	90%	>90%	349.19
13b	*i*Pr	3-CF_3	4-Me	quant	>98%	503.29	**28b**	H	3-CF_3	4-Me	91%	>95%	402.94
13c	*i*Pr	4-F	4-Me	quant	>98%	453.30	**28c**	H	4-F	4-Me	92%	>90%	353.08
14a	Bzl	4-Me	4-H	96%	>98%	483.42	**29a**	*i*Pr	4-Me	4-H	62%	>98%	377.20
14b	Bzl	3-CF_3	4-H	quant	>95%	537.33	**29b**	*i*Pr	3-CF_3	4-H	77%	>98%	431.33
14c	Bzl	4-F	4-H	quant	>98%	487.39	**29c**	*i*Pr	4-F	4-H	97%	>98%	381.18
15a	Bzl	4-Me	4-Cl	quant	>98%	517.27	**30a**	*i*Pr	4-Me	4-Cl	65%	>98%	411.20
15b	Bzl	3-CF_3	4-Cl	quant	>95%	571.23	**30b**	*i*Pr	3-CF_3	4-Cl	69%	>98%	465.30
15c	Bzl	4-F	4-Cl	quant	>98%	521.30	**30c**	*i*Pr	4-F	4-Cl	77%	>98%	415.27
16a	Bzl	4-Me	4-Me	99%	>98%	497.30	**31a**	*i*Pr	4-Me	4-Me	59%	>95%	390.18
16b	Bzl	3-CF_3	4-Me	quant	>98%	551.22	**31b**	*i*Pr	3-CF_3	4-Me	quant	>98%	445.14
16c	Bzl	4-F	4-Me	quant	>98%	501.38	**31c**	*i*Pr	4-F	4-Me	71%	>90%	395.22
17a	H	4-Me	4-H	44%	>98%	425.22	**32a**	Bzl	4-Me	4-H	91%	>90%	425.19
17b	H	3-CF_3	4-H	59%	>98%	479.24	**32b**	Bzl	3-CF_3	4-H	93%	>95%	479.20
17c	H	4-F	4-H	58%	>95%	429.18	**32c**	Bzl	4-F	4-H	94%	>95%	429.14
18a	H	4-Me	4-Cl	59%	>90%	459.15	**33a**	Bzl	4-Me	4-Cl	89%	>90%	459.19
18b	H	3-CF_3	4-Cl	39%	>95%	513.13	**33b**	Bzl	3-CF_3	4-Cl	quant	>95%	513.19
18c	H	4-F	4-Cl	51%	>90%	463.12	**33c**	Bzl	4-F	4-Cl	quant	>90%	463.16
19a	H	4-Me	4-Me	72%	>92%	439.27	**34a**	Bzl	4-Me	4-Me	75%	>98%	439.25
19b	H	3-CF_3	4-Me	63%	>95%	493.31	**34b**	Bzl	3-CF_3	4-Me	82%	>98%	493.19
19c	H	4-F	4-Me	64%	>95%	443.24	**34c**	Bzl	4-F	4-Me	82%	>98%	443.24

Therefore, we decided to activate the acid *via* a phosphonium salt method. Earlier literature recommended the reaction of the acid with carbon tetrachloride and polymer-supported triphenylphosphine for the preparation of acyl chlorides.[7] In the course of our investigations it was found, that better results (faster and cleaner reaction) could be obtained by an *in situ* activation of the acids to the acyl bromides using 1.1 equivalent of carbon tetrabromide in the presence of three equivalents of polymer-supported triphenylphosphine[8] and three equivalents of triethylamine using dichloromethane as solvent. The acyl bromides generated react smoothly with the 0.95 equivalents of *O*-benzyl hydroxylamine hydrochloride applied in the reaction to give the corresponding hydroxamic acid esters (**17a-c**, **18a-c**, **19a-c**, **20a-c**, **21a-c**, **22a-c**, **23a-c**, **24a-c** and **25a-c**), but with variable yields. An observed side reaction of this process is the formation of a small amount of the corresponding acid anhydride, which itself can react with the amino function. The reaction mixture is worked up by addition of aminomethyl polystyrene, which captures remaining acid anhydride, eventually remaining acyl bromide as well as the free acid, to leave a clean product in solution which was filtered through a pad of silica. The final step is the hydrogenation of the benzyl ester, which is carried out either in a mixture of ethyl acetate and propan-2-ol or in methanol using palladium on charcoal in a hydrogen atmosphere.[9] After the hydrogenation, the solution was filtered through a pad of Celite 521 to remove the catalyst, furnishing the clean product compounds (**26a-c**, **27a-c**, **28a-c**, **29a-c**, **30a-c**, **31a-c**, **32a-c**, **33a-c** and **34a-c**).

Results and discussion: In conclusion we have prepared an array of 27 hydroxamic acid derivatives (**26a-c**, **27a-c**, **28a-c**, **29a-c**, **30a-c**, **31a-c**, **32a-c**, **33a-c** and **34a-c**) without any chromatographic purification step which is an additional example for the great versatility of the application of polymer-supported reagents in combinatorial chemistry. Further analogues can be easily generated by this route. Since all reactions furnished essentially clean products, as shown by LC-MS and NMR-spectroscopy, the intermediates could be isolated and used in other synthesis programmes. Yields and purities of the various compounds are given in table 1.

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5 BEMP on polystyrene was 2.3 mmol g^{-1} and purchased from Fluka.

6 Used as supplied by Novabiochem, Order No. 01-64-0211.

7 Hodge, P.; Richardson, G. *J. Chem. Soc., Chem. Commun.* **1975**, 622.

8 Triphenylphosphine on polystyrene was 3 mmol g^{-1} and purchased from Fluka.

9 It is essential to use ethyl acetate/propan-2-ol (20:1) for the hydrogenation of compounds **18a-c**, **21a-c** and **24a-c** in order to prevent dechlorination which readily occurs in methanol.