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SOLID PHASE SYNTHESIS OF BENZYLAMINE-DERIVED SULFONAMIDE LIBRARY

Sang Woong Kim,* Chang Yong Hong, Koo Lee, Eun Ju Lee+ and Jong Sung Koh

Biotech Research Institute, LG Chemical Ltd./Research Park
Science Town, Taejon 305-380, KOREA

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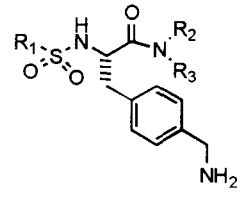
Abstract: Using solid phase synthesis, a library has been constructed of benzylamine-derived sulfonamides which have strong inhibitory activity against the blood coagulant thrombin. The library compounds were obtained in good yield and high purity; four of these thrombin inhibitors showed nanomolar potency (Ki 600-10 nM).

Thrombin is a trypsin-like serine protease that catalyses the formation of fibrin from fibrinogen and thus performs a central function in the blood coagulation cascade.[1] The thrombin enzyme has assumed importance in studies which aim to develop novel antithrombotic therapeutics because of the prominent role it plays as a central mediator in thrombosis and hemostasis.

As part of our program to discover novel thrombin inhibitors, we are interested in the preparation of benzylamine containing sulfonamide derivatives employing combinatorial organic synthesis in the solid phase because this technology is now a hot area in organic chemistry and medicinal chemistry for the rapidly discovery of important biologically active compounds with potential therapeutic value.[2] Recently, this chemistry has been focused on the generation of small molecules instead of peptides or oligonucleotides.[3] Although the solid phase synthesis of formamidines[4] and benzamidines[5] has been described that utilizes linking groups between the target compounds and the resin during preparation, to our knowledge, no report has appeared concerning derivatives of sulfonamide-containing benzylamine residues which have been synthesized in the solid phase without employing such linking groups. Therefore, here we report an efficient solid phase synthesis of benzylamine-containing sulfonamide derivatives **1** as potentially potent thrombin inhibitors in which the compounds are attached directly to the resin during their preparation.



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The synthetic routes towards the 4-nitrophenylcarbonate intermediates **4** or **6** required in the preparation of the benzylamine-containing sulfonamides are outlined in Scheme 1. The coupling reaction of **2** with Wang resin[6] **3** in 2.0 eq. N-methylmorpholine and CH_2Cl_2 was quantitative (>97 %) (loading capacity was 0.82 mmol/g compared to the initial value of 0.85 mmol/g). Reaction of 2-(trimethylsilyl)ethanol **5** with 4-nitrophenyl chloroformate **2** furnished the carbonate **6**. In order to generate the library of benzamidine-derived sulfonamides, two general approaches were adopted, the first of which is shown in Scheme 2 (see top part of Table 1) and the other is shown in Scheme 3 (see bottom part of Table 1). In Scheme 2, the sulfonamide function remains fixed while the amide group is varied, whereas in Scheme 3, the sulfonamide residue is diversified and the amide group is fixed. Boc-protected 4-cyano phenylalanine[7] **7** was treated with K_2CO_3 and methyl iodide in DMF followed by 50% TFA in CH_2Cl_2 to give free amine. The intermediate **6** and free amine were reacted with 4.0 eq. triethylamine and 1.0 eq. DMAP in CH_3CN to give a protected amine

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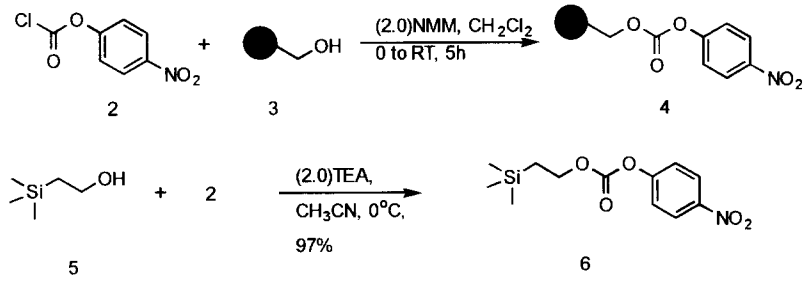
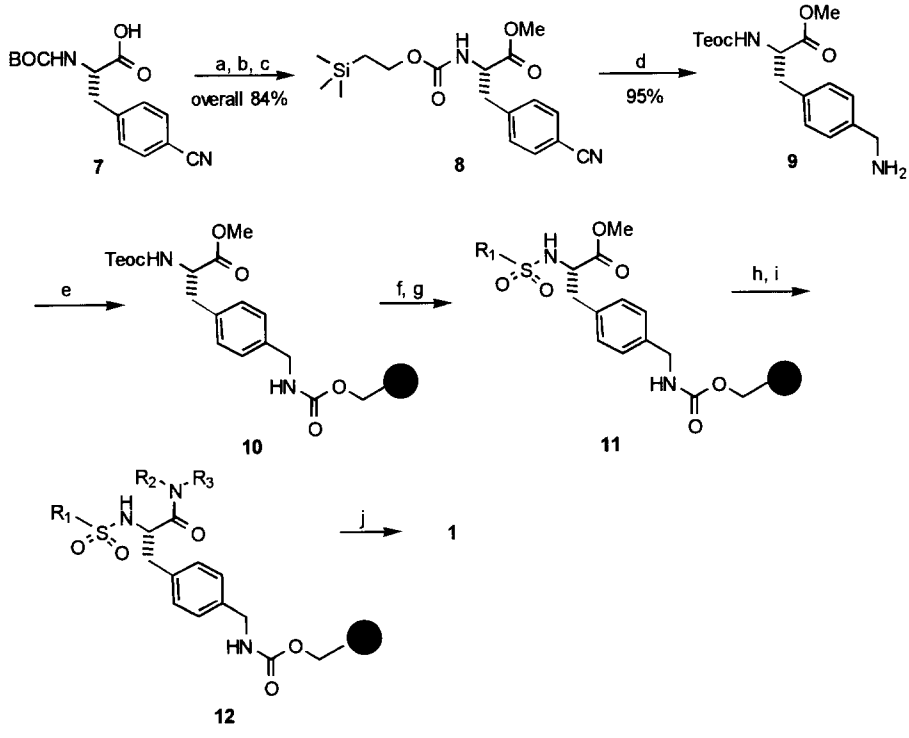
Scheme 1



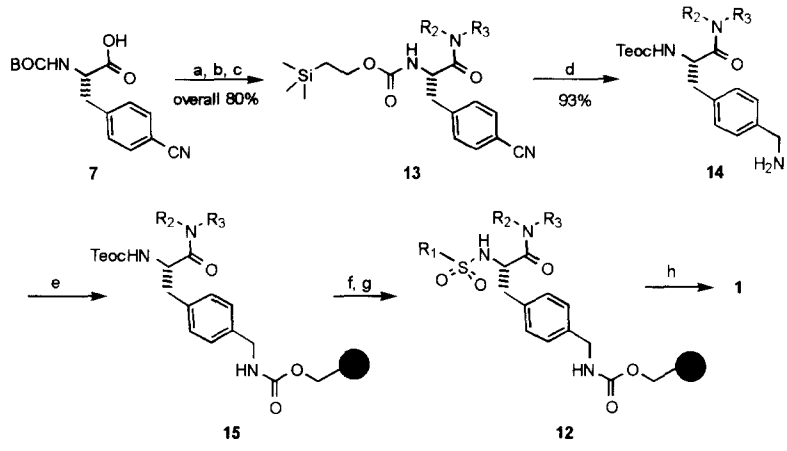
methyl ester **8**. It was found that DMAP was essential for this conversion. To convert the nitrile **8** to the benzylamine, the material was treated with 10% Pd/C and c-HCl in MeOH.[8] To generate the target library using the solid phase, carbonate **4** and compound **9** was treated with 3.5 eq. HOBt, 5.0 eq. DIEA in DMF/CH_2Cl_2. The protective silane group(Teoc) of **10** was removed by treatment with 5.0 eq. n-Bu_4NF in

Scheme 2



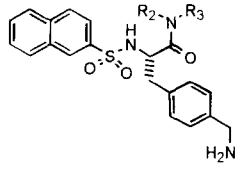
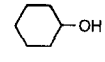
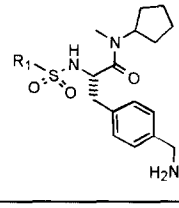
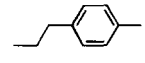
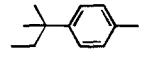
Conditions: a) (2.0)K_2CO_3, (1.2)CH_3I, DMF b) 50% TFA in CH_2Cl_2 c) **6**, (4.0)TEA, (1.0)DMAP, CH_3CN, reflux d) (10%)Pd/C, HCl (3 drops), MeOH, 50 psi e) **4**, (3.0)HOBt, (5.0)DIEA, DMF/CH_2Cl_2, RT, 12h f) (5.0)n-Bu_4NF, THF, 50 °C, 5h g) (3.5)R_1SO_2Cl, (3.0)TEA, CH_2Cl_2 h) (5.0)LiOH, THF/H_2O(5:1 v/v) i) (3.5)R_1R_2NH, (3.5)EDC, (3.5)HOBt, (3.5)TEA, DMF, 12h. j) 50% TFA in CH_2Cl_2, 30 min.

Scheme 3



Conditions: a) (3.5)N-Methylcyclopentylamine, (3.5)EDC, (3.5)HOBt, (3.5)TEA, DMF, 12h. b) 50% TFA in CH_2Cl_2 c) **6**, (4.0)TEA, (1.0)DMAP, CH_3CN, reflux d) (10%)Pd/C, HCl (3 drops), MeOH, 50 psi e) **4**, (3.0)HOBt, (5.0)DIEA, DMF/CH_2Cl_2, RT, 12h f) (5.0)n-Bu_4NF, THF, 50 °C, 5h g) (3.5)R_1SO_2Cl, (3.0)TEA, CH_2Cl_2 h) 50% TFA in CH_2Cl_2, 30 min.

Table 1. Representative members of the benzylamine-derived sulfonamide libraries.

Compounds	R_1, R_2, or R_3	Yield[a]	Purity[b]	K_i(μM)[c]
	a) R_2=CH_3 R_3= 	73%	85%	0.05
	b) R_2=H R_3= 	76%	84%	31.7
	c) R_2, R_3= 	68%	87%	0.2
	d) R_2, R_3= 	70%	82%	15.6
	e) R_2=H R_3= 	79%	80%	97.2
	f) R_2=CH_3 R_3= CH_3	78%	90%	3.06
	g) R_2=CH_3 R_3= 	80%	83%	0.6
	h) R_1= 	75%	88%	0.01
	i) R_1= 	80%	84%	ND[d]

[a] All crude yields (%) based on the support-bound carbonate **4** for the six steps in Scheme 2 and the four steps in Scheme 3; [b]Determined by reverse phase HPLC; [c]Inhibition constant; [d]No data was observed.

THF at 50 °C for 5 hours and then sulfonamide formation was performed with 3.5 eq. of an aromatic sulfonyl chloride and 3.5 eq. triethylamine in CH_2Cl_2 to give a sulfonamide methyl ester **11**. The free acid was obtained by treatment with LiOH in THF/H_2O (5:1 v/v) at room temperature for 1h. Then a coupling reaction was accomplished by treatment of the acid with 3.5 eq. R_1R_2NH, 3.5 eq. EDC, 3.5 eq. HOBt, and 3.5 eq. TEA in DMF at room temperature for 12 hours. Finally, treatment with 50% TFA in CH_2Cl_2 for 30 minutes gave the desired products (Scheme 2). Scheme 3 consists of a similar procedure to Scheme 2 except that the amide bond formation follows the sulfonamide coupling. Table 1 displays the yield, purity and potency of thrombin inhibitor of some members of the synthesized benzylamine-derived sulfonamide libraries.

In summary, we have constructed 200 libraries (10 sulfonyl chloride x 20 amines) of benzylamine-containing sulfonamides by means of an efficient route using solid phase synthesis. The obtained libraries have good yields (average 77%) and high purity (average 86%) as well as high thrombin potency.

References and Notes

[+]Korea Advanced Institute of Science and Technology, Science Town, Taejon 306-701, Korea

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