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SOLID PHASE SYNTHESIS OF 1,4-BENZOTHIAZEPIN-5-ONE DERIVATIVES

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Abstract: The solid phase synthesis of 1,4-benzothiazepin-5-one derivatives, resulting from the reaction of resin-bound protected cysteine with 2-fluoro-5-nitro-benzoic acid followed by a reductive alkylation and an intra molecular cyclization, is described.

Over the past five years, there have been an ever increasing number of reports describing solid phase organic chemistry (SPOC).[1] This technique, like solid phase peptide synthesis from which it has its origin,[2] is becoming a fundamental tool for the generation of organic compound libraries. Benzothiazepines have been shown to have activity as angiotensin converting enzyme inhibitors,[3] endogenous natriuretic factors,[4] and calcium channel blockers[5] A number of 1,4-benzothiazepines display interesting anticancer properties.[6] As a part of our ongoing efforts toward the design and development of synthetic approaches for the solid phase synthesis of individual and combinatorial libraries of small molecules and heterocyclic compounds from amino acids and modified peptides,[7] we report here the design and solid phase synthesis of 1,4-benzothiazepin-5-one compounds derived from a resin-bound protected cysteine.

N-α-Fmoc-S-trityl-L-Cysteine was coupled to p-methylbenzhydrylamine (MBHA) resin in the presence of diisopropylcarbodiimide (DIPCDI) and hydroxybenzotriazole (HOBt). Following cleavage of the trityl (Trt) group with 10% trifluoroacetic acid (TFA) in dichloromethane (DCM) in the presence of 5% of tBu_3SiH, 2-fluoro-5-nitro-benzoic acid was added to the resin-bound Fmoc-cysteine. The Fmoc group was cleaved and the resulting free amine reductively alkylated with a variety of aldehydes in the presence of sodium cyanoborohydride. The resulting resin-bound intermediate **3** was treated with *O*-benzotriazolyl-N,N,N',N'-tetramethykuronium hexafluorophosphate (HBTU) in anhydrous DCM, which underwent an intramolecular amide bond formation to afford the resin-bound nitro-benzothiazepine **4**. The nitro group was reduced with $SnCl_2$, followed by N-acylation, and following cleavage of the solid support yielded the desired product **6** in good purity. We initially optimized the strategy by testing three different aldehydes and four different carboxylic acids. Using the parallel synthesis approach commonly referred to as the "tea-bag" method,[9] 12 individual benzothiazepines were synthesized (Table 1).

All compounds were analyzed by ^{1}H-NMR and LC-MS. Figure 1 shows a typical LC-MS of the disubstituted benzothiazepine obtained from benzaldehyde and acetic acid, which is representative of the purities obtained for all cases.

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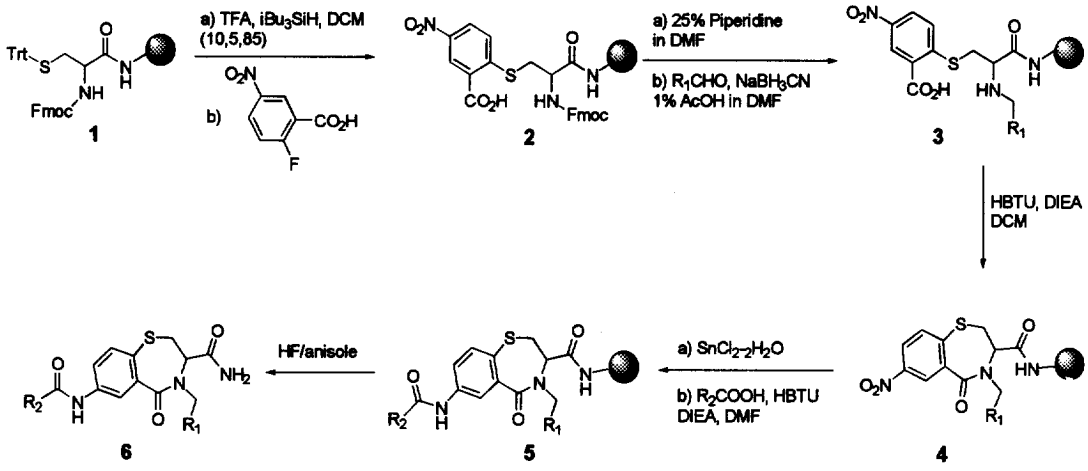
We expanded our optimization by testing 48 aldehydes and 95 carboxylic acids. Using the process illustrated in Scheme 1 and in combination with the divide-couple-recombine (DCR) resin method, [10] a mixture-based library of 95 mixtures of 48 benzothiazepines was produced. The specific library synthesis and results from its screening for the identification of active compounds will be reported elsewhere.



Scheme 1. Solid-phase synthesis of 1,4-benzothiazepin-5-ones

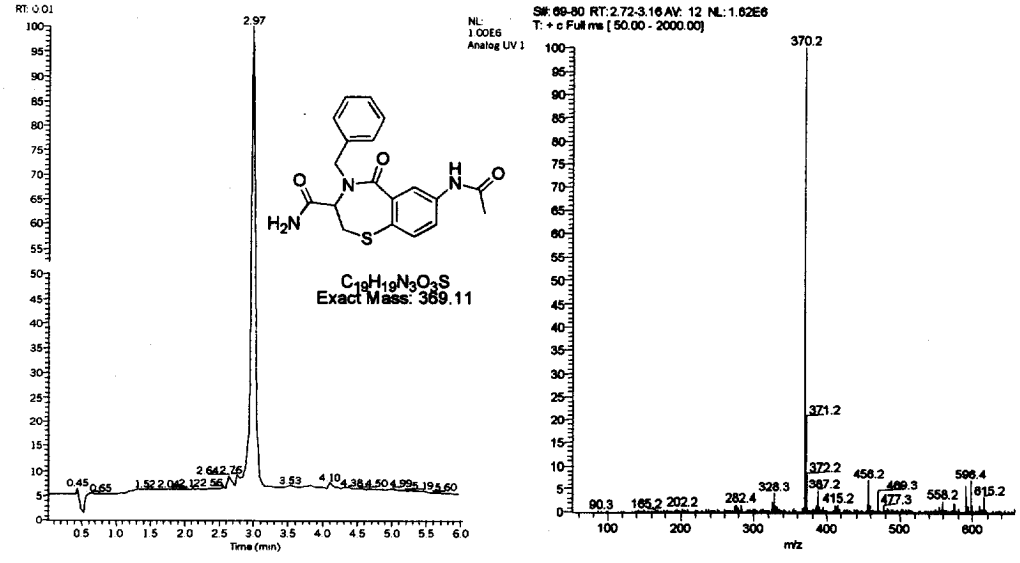
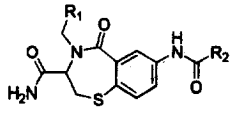


Figure 1. LC-MS spectra of compound **6h.**

Table 1. Individual benzothiazepines



Compound #	R_1	R_2	HPLC purity, %	MW (expected)	MW (found)
6a	—		>95%	361.15	362.30 (MH+)
6b	—		>95%	355.10	356.3 (MH+)
6c	—		>95%	355.10	356.30 (MH+)
6d	—	Me—	>95%	279.09	280.10 (MH+)
6e			92%	451.19	452.60 (MH+)
6f			91%	445.15	446.3 (MH+)
6g			93%	445.15	446.3 (MH+)
6h		Me—	>95%	369.11	370.20 (MH+)
6i	MeO—		87%	481.20	483.60 (MH+)
6j	MeO—		90%	475.16	476.60 (MH+)
6k	MeO—		88%	475.16	476.60 (MH+)
6l	MeO—	Me—	92%	399.13	400.20 (MH+)

The products were run on a Vydac column, gradient 5 to 95% of 0.05% TFA in ACN in 7 min. The purity was estimated on analytical traces at 214 nm. The yields (crude products) obtained in all cases are higher then 90% relative to the initial loading of the resin.

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8. Typical procedure for the synthesis of individual benzothiazepine **6f**: 100 mg MBHA resin was contained within a polypropylene mesh packet. The resin was neutralized with 5% DIEA in DCM. Fmoc-Cys(Trt)-OH was coupled for 60 min in the presence of DIPCDI (5eq) and HOBt (5eq) in anhydrous DCM. The Trt group was cleaved with a solution of TFA/tBu_3SiH/DCM (10:5:85) for 30 min and the resin was treated overnight with a 10-fold excess of 2-fluoro-5-nitro-benzoic acid. Following displacement of the fluoro group, the Fmoc group was cleaved with a solution of 25%piperidine in DMF and the amine reductively alkylated using benzaldehyde (5eq, 0.1 M) and sodium cyanoborohydride (5eq) in a solution of 1% AcOH in DMF anhydrous for 60 min. An intramolecular amidation occurred following overnight treatment of the resin-bound compound **3** with HBTU (3eq) in the presence of DIEA (3eq) in anhydrous DMF. The nitro group was reduced using a 2M solution of $SnCl_2.2H_2O$ in anhydrous DMF overnight. The generated amine was then acylated with phenylacetic acid (15 eq) in DMF anhydrous in the presence of HBTU (15 eq) and DIEA (3eq) overnight. Following washes with DMF and DCM, the resin was dried and cleaved with HF/anisole (95:5) to afford, following extraction and lyophilization, the desired product.

   ^{1}H NMR (500 MHZ, DMSO-d_6): δ 10.49 (s, 1H), 7.25-8.00 (m, 13 H), 4,77(m, 2H), 4.30(m, 1H), 3.64(m, 3H), 2.90(m, 1H). ^{13}C NMR (125 MHZ, DMSO-d_6): 36.17, 43.44, 59.50, 120.30, 120.88, 122.04, 126.63, 127.00, 127.89, 128.05, 128.35, 129.06, 133.65, 135.74, 138.21, 139.77, 141.74, 168.9, 169.35, 169.38.
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