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Solid phase synthesis of 3-(5′-carboxypentyl)-5-substituted tetrahydro-2*H*-1,3,5-thiadiazin-2-thione derivatives

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Abstract

The solid phase synthesis of 3-(5′-carboxypentyl)-5-substituted tetrahydro-2*H*-1,3,5-thiadiazin-2-thione derivatives **5** is described. 6-Amino-*n*-hexanoic acid was attached via its C-terminal to hydroxymethyl polystyrene using a 'SASRIN' linker. The bound amino acid was converted to the corresponding dithiocarbamate **3** followed by cyclization in the presence of formaldehyde and the corresponding free amino acids to afford 3-(5′-carboxypentyl)-5-substituted tetrahydro-2*H*-1,3,5-thiadiazin-2-thiones **4**. The final products were cleaved from the resin and obtained in moderate yields.

Keywords: solid-phase synthesis; thiadiazin-2-thiones; resins amino acids.

The development of solid phase synthetic methods is an important aspect of today's drugs design process.[1–4] There has been growing interest in such methodology over the last five years, opening new horizons in the search of suitable drug candidates. As a contribution toward this goal, we report here the first solid phase synthesis of 3-(5′-carboxypentyl)-5-(substituted)-tetrahydro-2*H*-1,3,5-thiadiazine-2-thione from readily available starting materials.

Numerous studies have been published on the antibacterial,[5,6] antifungal[7,8] and antihelmintic[9] activity of tetrahydro-2*H*-1,3,5-thiadiazine-2-thione derivatives (TTT) **1** as prodrugs (see Fig. 1). We previously demonstrated the feasibility of the synthesis of thiadiazine-2-thiones in solution with amino acidic residues attached to its central core (R and R′).[10] The great variety of amino acid building blocks and the presence of two points of diversity at nitrogen N3 and N5 of the heterocycle ring encouraged us to develop the solid phase synthesis of new TTT derivatives as a first approach to design a thiadiazine-like library.

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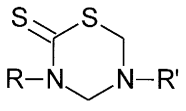

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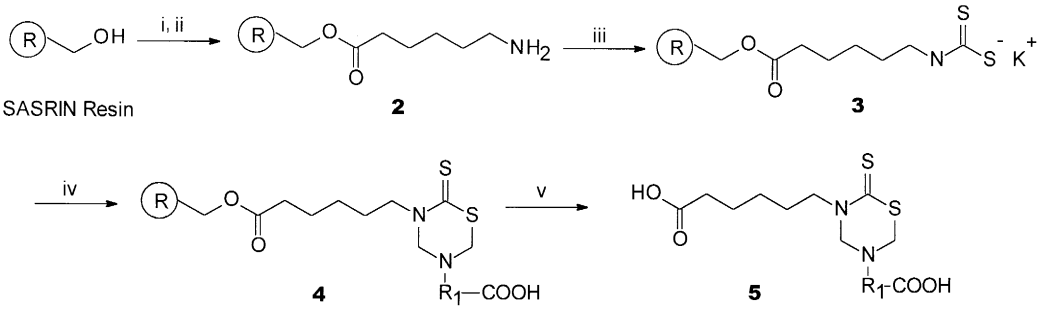
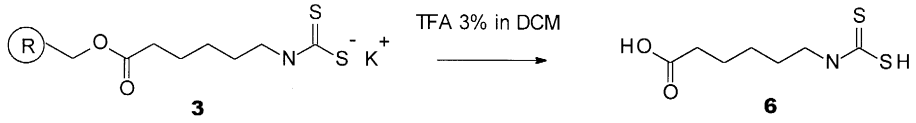
Fig. 1.

Although in our first attempt to synthesize **5** we used Wang resin as solid support, the extremely acid conditions for the cleavage of the final product provoked the hydrolysis of the thiadiazine ring. Therefore in our second approach, we chose the SASRIN resin, which can be cleaved under milder conditions. Thus, as illustrated in Scheme 1, the resin bound amino acid **2** was prepared from SASRIN resin (0.89 mmol/g), the corresponding Fmoc-amino acid, 1,3-diisopropyl carbodiimide (DIC) and 4-dimethylaminopyridin (DMAP) (0.01 equiv.) using the standard coupling conditions.[11] The loading of the amino acid-containing resin was determined by photometric quantitation method based on Fmoc content, being the average loading of 0.7 mmol/g. The remaining free hydroxyl groups were acetylated (Ac_2O, DIEA) to avoid the presence of by-products. The Fmoc cleaved was performed with 20% piperidine in DMF, and **2** was subsequently allowed to react with carbon disulfide (CS_2) (10 equiv.), KOH (10 equiv.) in 1,4-dioxan, at room temperature for 12 h, to afforded the desired resin bound dithiocarbamate intermediate **3**. The resin was collected by filtration and washed thoroughly with 1,4-dioxan, water, methanol, and DCM to remove excess reagents.[12] To confirm the presence of the dithiocarbamate a sample of **3** was treated with a solution of TFA/DCM (3%) (see Scheme 2). The crude solution containing **6** was analyzed by HPLC and NMR.[13]



Scheme 1. (i) Fmoc-Ahx-OH, DIC, DMAP, DMF; (ii) piperidine 20% in DMF; (iii) CS_2, KOH/H_2O 20%, 1,4-dioxan; (iv) HCOH, H_2N-R_1-COOH, DIEA, 1,4-dioxan; (v) TFA 3% in DCM



Scheme 2.

The resin bound dithiocarbamate **3** was suspended in a solution of formaldehyde (20 equiv.) in 1,4-dioxan. The mixture was stirred for 3 h, then DIEA (1 equiv.) and the appropriate free amino acid were added and stirring was continued for another 6 h. The resin bound thiadiazine **4** was then washed several times with 1,4-dioxan, K_2CO_3 5%, water, methanol and DCM. The desired products **5** were cleaved from the resin using TFA 3% in DCM. The products were obtained in 30–80% yield and 70–95% of purity as shown in Table 1. The impurities of the cleaved products could not be identifiable. One and two-dimensional NMR experiments confirmed the formation of the thiadiazine ring,[14] over the dithiocarbamate intermediary **3**. We assumed that the main cause of the low yields of some of these

Table 1
3,5-Disubstituted-tetrahydro-2*H*-1,3,5-thiadiazin-2-thione

Compound	R_1-COOH	Yield (%)[a]	Purity (%)[b]
5a	-CH(CH_2-$CONH_2$)-COOH	80	70
5b	-CH(CH_2-CH_2-$CONH_2$)-COOH	81	72
5c	-CH(CH_2-COOH)-COOH	32	72
5d	-CH(CH_2-CH_2-COOH)-COOH	30	72
5e	-$(CH_2)_5$-COOH	31	91
5f	-CH_2-CH_2-COOH	42	95

[a] Yields based on the calculated loading after coupling of Fmoc 6-amino-*n*-hexanoic acid to SASRIN
[b] Purity of the compounds were based on the integration area on HPLC @ 226 nm

reactions is low solubility of the corresponding free amino acids in 1,4 dioxan. Attempts to increase the time reactions did not improve the overall yield.

In summary, we have demonstrated that 3-(5′-carboxypentyl)-5-(substituted)-tetrahydro-2*H*-1,3,5-thiadiazine-2-thione **5** can be prepared from SASRIN resin. The thiadiazin-2-thiones were prepared in five steps and 30–80% overall yields. Further modifications of the methodology reported here will be published in due course along with the biological activity of the molecules.

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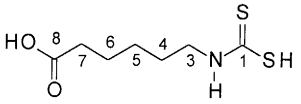
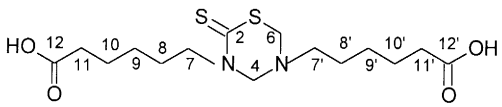
11. SASRIN: A review of its manifold applications including many useful procedures. Copyright 1995 by BACHEM.
12. The resin bound dithiocarbamic intermediate **3** has to be washed out thoroughly to remove the excess of CS_2 and base before the next step of the synthesis in order to improve the yields and the purity of the final product.
13. NMR data for compound **6**.



^{1}H NMR (DMSO-d_6, 300 MHz): δ 9.86 (1H, s, SH), 8.27 (1H, s, NH), 3.63 (2H, t, [CH_2]-3), 2.22 (2H, t, [CH_2]-7), 1.56 (2H, m, [CH_2]-6), 1.48 (2H, m, [CH_2]-4) and 1.32 (2H, m, [CH_2]-5); ^{13}C NMR (DMSO-d_6, 75.47 MHz): δ 190.2 (C1), 174.4 (C8), 40.5 (C3), 33.5 (C7), 25.7 (C4), 25.5 (C5) and 24.1 (C6).

14. Data for compound **5e**.



^{1}H NMR (DMSO-d_6, 300 MHz): δ 11.96 (s, 2H, OH), 4.47 (s, 2H, [CH_2]-6), 4.45 (s, 2H, [CH_2]-4), 3.8 (t, 2H, [CH_2]-7), 2,6 (t, 2H, [CH_2]-7′), 2.19 (t, 4H, [CH_2]-11 and [CH_2]-11′), 1.28 (m, 4H, [CH_2]-9 and [CH_2]-9′), 1.5 (m, 8H, [CH_2]-8, [CH_2]-10, [CH_2]-8′ and [CH_2]-10′); ^{13}C NMR (DMSO-d_6, 75.47 MHz): δ 189.9 (C2), 175.4 (COOH), 69.1 (C4), 57.2 (C6), 50.7 (C7), 48.8 (C7′), 36.5, 33.6 (C11, C11′) and 26.4, 26.0, 25.6, 24.3, 24.2, 24.0, 23.7 (C8, C9, C10, C8′, C9′, C10′); *m/z*: 362 (M^+, 1%), 156 (20), 155 (18), 142 (13), 128 (15), 111 (14), 98 (14), 86 (10) and 76 (100). Anal. calcd for $C_{15}H_{26}N_2O_4S_2$ (362.50) C, 49.70; H, 7.23; N, 7.73. Found: C, 49.82; H, 7.35; N, 7.81.