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Liquid phase parallel synthesis of iminodiacetic acid derivatives

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Abstract

Liquid phase parallel synthesis has been developed to synthesize a novel series of iminodiacetic acid derivatives targeting the integrin receptors. This library was synthesized using a four-step reaction sequence. In each step of the sequence, the PEG-bound products were precipitated selectively and the excess reagents and the by-products were removed by simple filtration. The most notable result was that the library members were obtained in high purities (>90% pure).

In an effort to develop methodology for the rapid parallel synthesis of chemical libraries, we have been exploring 'liquid phase parallel synthesis'[1] for the synthesis of chemical libraries. We wish to report here the synthesis of iminodiacetic acid derivatives[2] targeting the integrin receptors.[3] Integrins are the major family of cell surface receptors that mediate attachment to the extracellular matrix. There have been considerable efforts aimed at the design of RGD (Arg-Gly-Asp) containing peptides and RGD mimetics as integrins antagonists.[4]

'Liquid phase parallel synthesis' uses a supporting polymer (PEG) that is soluble in many organic solvents but can be precipitated selectively for isolation and purification purposes.[5] Excess reagents (3 equiv. or 4 equiv.) were used to drive the reaction to completion and were removed by simple filtration. This library was synthesized using a four-step reaction sequence (Scheme 1). In each step of the sequence, the PEG-bound products were precipitated selectively and the excess reagents and the by-products were removed by simple filtration. The PEG-bound products are readily detectable by TLC so it was used to confirm the complete removal of the reagent in excess and the soluble by-products. The PEG-bound intermediates were analyzed by NMR spectroscopy to confirm the structure. Fig. 1 shows the targeted compounds for the present study. The considerations that led to the design were: (1) the iminodiacetic acid template functions as a central scaffold; and (2) the added pendant groups provide the required pharmacophores and molecular diversity.

The Boc-protected iminodiacetic acid template was attached to the hydroxyl end groups of polyethylene glycol monomethyl ether (MeO-PEG) by reacting MeO-PEG (average M.W. 5000) with excess

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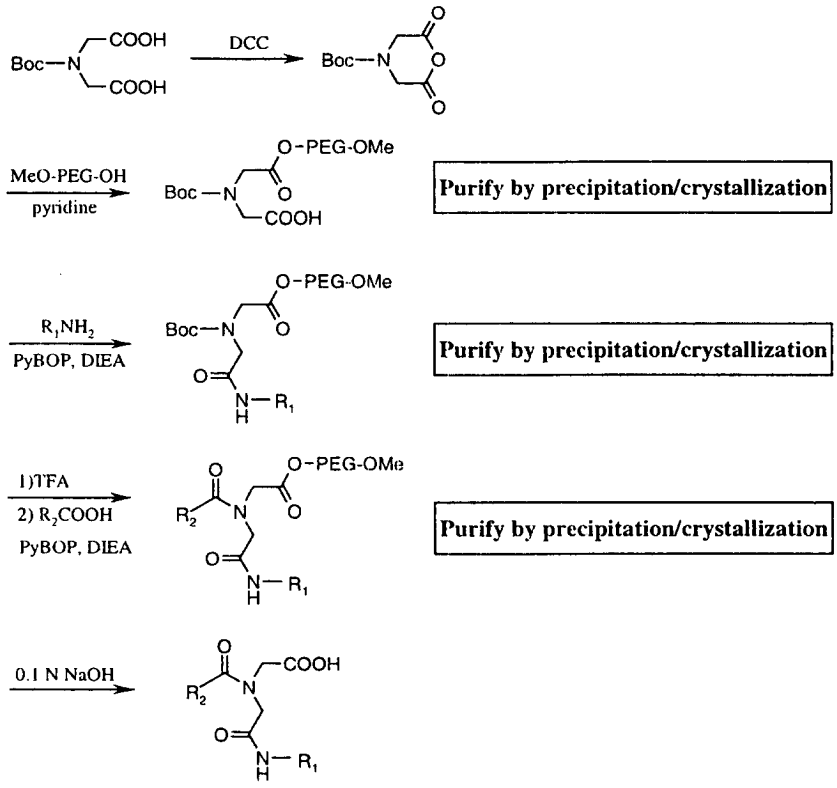

Scheme 1.

iminodiacetic acid anhydride in the presence of pyridine. The iminodiacetic acid anhydride was prepared by reacting iminodiacetic acid with DCC in methylene chloride and insoluble DCU was removed prior to coupling. After the attachment, the PEG-bound monoacid was precipitated selectively by adding ether to the reaction media and purified by recrystallization from EtOH. The PEG-bound monoacid was then partitioned into three portions. Each of the three equal portions was treated with a different R_1NH_2 (3 equiv.) (Fig. 1), PyBOP (3 equiv.), and diisopropylethylamine (6 equiv.) in CH_2Cl_2:DMF (1:2). The mixtures were stirred at 25°C for 20 h to afford three monoamides which were effectively purified by precipitation and recrystallization from EtOH.[6] Following the first functionalization, *N*-Boc deprotections were carried out using 50% (v/v) TFA in CH_2Cl_2. The three amines were each partitioned into 12 portions. Reaction of the 12 equal portions of each amine with a different R_2COOH (4 equiv.) (Fig. 1) in the presence of PyBOP (4 equiv.) and diisopropylethylamine (7 equiv.) provided 36 PEG-bound diamides.[7] The diamides were cleaved from the MeO-PEG by hydrolysis (0.1N NaOH:dioxane, 1:1)[8] which concurrently saponified the amino acid methyl esters to the corresponding carboxylic acids. Each library member was obtained as an individual entity in 14 mg to 74 mg quantities in overall yields ranging from 13% to 73%. The most notable result was that each library member was obtained in high purities (>90% pure).[9]

In conclusion, we have developed liquid phase methodologies for the efficient synthesis of novel iminodiacetic acid derivatives. In each step of the sequence, the PEG-bound intermediates were purified by precipitation followed by simple filtration. The structural properties of these derivatives may provide important leads as integrin antagonists. These compounds are in the process of being assayed against a number of integrin receptors.

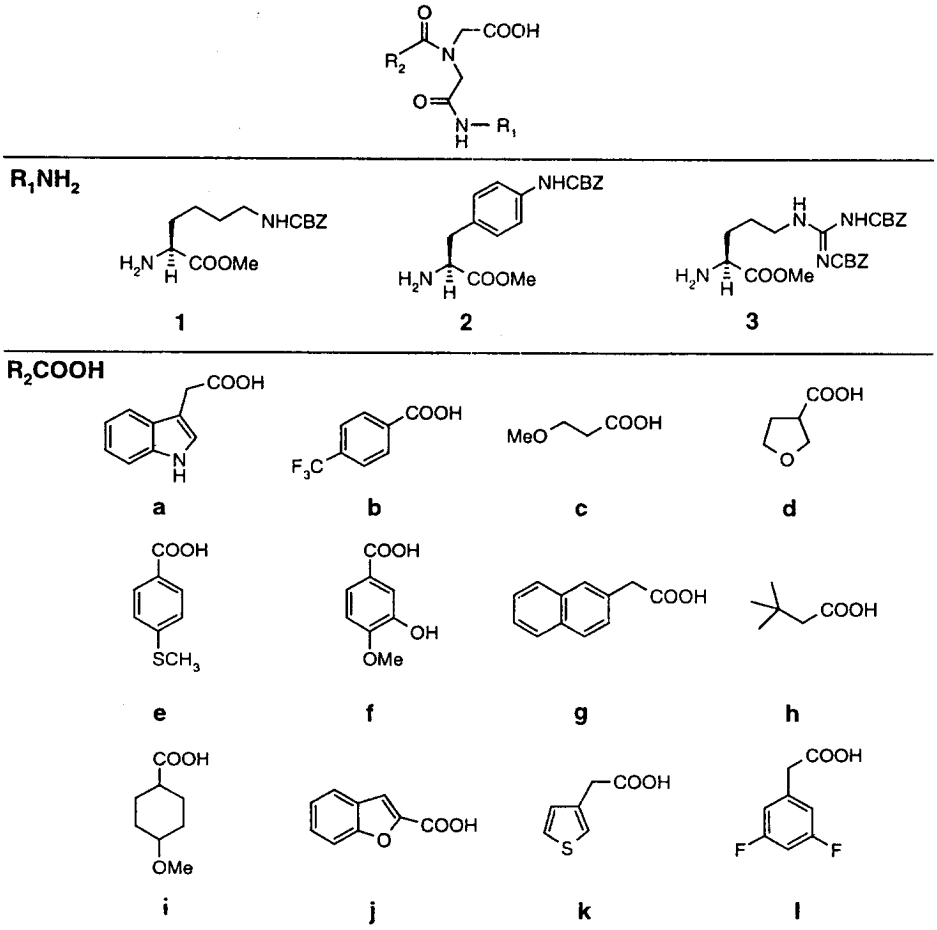

Figure 1.

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6. General procedure: MeO-PEG ester of *N*-(benzyloxycarbonyl)-*N'*-(Lys(CBZ) methyl ester)-iminodiacetic acid amide: MeO-PEG ester of *N*-(benzyloxycarbonyl)-iminodiacetic acid (12.0 g, 2.4 mmol) and Lys(CBZ)–OMe (5.4 mmol) were stirred together in DCM/DMF (36/64 mL) until the solids dissolved. Diisopropylethylamine (DIEA) (3.7 mL, 21.6 mmol) was added followed by PyBOP (3.8 g, 7.2 mmol) and the mixture stirred for 16 h at room temperature. Diethyl ether (300 mL) was added to precipitate out the material. The white solid was collected on a filter and washed with diethyl ether (3×30 mL). The material was then re-dissolved in dry EtOH at 40°C and allowed to crystallize overnight while cooling. The next day, the material was collected on a filter, washed with diethyl ether (3×30 mL) and dried overnight in vacuo to

yield the MeO-PEG ester of *N*-(benzyloxycarbonyl)-*N'*-(Lys(CBZ) methyl ester)-iminodiacetic acid amide (11.5 g, 95% recovery).

7. General procedure: MeO-PEG ester of *N*-(alkyl or aryl carbonyl)-*N'*-(Lys(CBZ) methyl ester)-iminodiacetic acid amide: MeO-PEG ester of *N'*-(Lys(CBZ) methyl ester)-iminodiacetic acid amide, TFA salt (9.45 g) was then dissolved in DCM/DMF (20/52 mL) and DIEA (3.44 mL) was added and mixed. Twelve portions (7 mL) were removed and each put into a vial containing one of the carboxylic acids (R_2COOH) (4.0 equiv.). PyBOP (0.380 g, 4.0 equiv.) was then added to each vial and the mixtures were allowed to stir overnight at room temperature. The next day, the materials were precipitated out with diethyl ether and recrystallized from dry EtOH as previously described and dried overnight in vacuo to yield 12 products of the MeO-PEG ester of *N*-(alkyl or aryl carbonyl)-*N'*-(Lys(CBZ) methyl ester)-iminodiacetic acid amide (average recovery=66%).
8. General procedure: Compounds **1a–l**: Each of the PEG-bound products was treated with a solution of 0.1 M NaOH:dioxane 1:1 (3 mL). The resulting clear solutions were stirred for 90 min at room temperature. Each mixture was then acidified to pH 2–3 with 10% HCl (v/v) (10 mL) and extracted with EtOAc (2×25 mL). EtOAc extracts were combined and washed with brine (25 mL). The organic solutions were then dried over Na_2SO_4, filtered, evaporated to dryness and dried further overnight in vacuo to yield compounds **1a–l** (average yield=52%, 11/12 products were 95% pure by LC/MS).
9. Selected NMR and LC/MS data: Compound **1l**: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.57 (brs, 5H), 7.15–7.06 (m, 3H), 5.30 (s, 2H), 4.66–4.60 (m, 1H), 4.60–4.30 (m, 4H), 3.36 (m, 2H), 2.14–1.64 (m, 6H); $C_{26}H_{29}N_3O_8F_2$=549.5. MS: $[M+H]^+$=550.5, 95% pure. Compound **2l**: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.62–7.58 (m, 7H total), 7.42 (t, J=9.0 Hz, 2H), 7.10–6.98 (m, 3H), 5.38 (s, 2H), 4.99 (m, 1H), 4.37 and 4.30 (two s, 4H total), 3.72 (d, J=4.5 Hz, 2H); $C_{29}H_{27}N_3O_8F_2$=583.5. MS: $[M+H]^+$=584.5, 96% pure. Compound **3l**: ^{1}H NMR (CD_3OD, 300 MHz) δ 7.45–7.38 (m, 10H), 6.95–6.80 (m, 3H), 5.31 (s, 4H), 4.47–4.38 (m, 1H), 4.35–4.20 (m, 4H), 3.80 (s, 2H), 2.03–1.69 (m, 4H); $C_{34}H_{35}N_5O_{10}F_2$=711.6. MS: $[M+H]^+$–CBZ=578.2, 92% pure.