Supporting Information

Silylated peptides as building blocks for material synthesis using sol-gel polymerization

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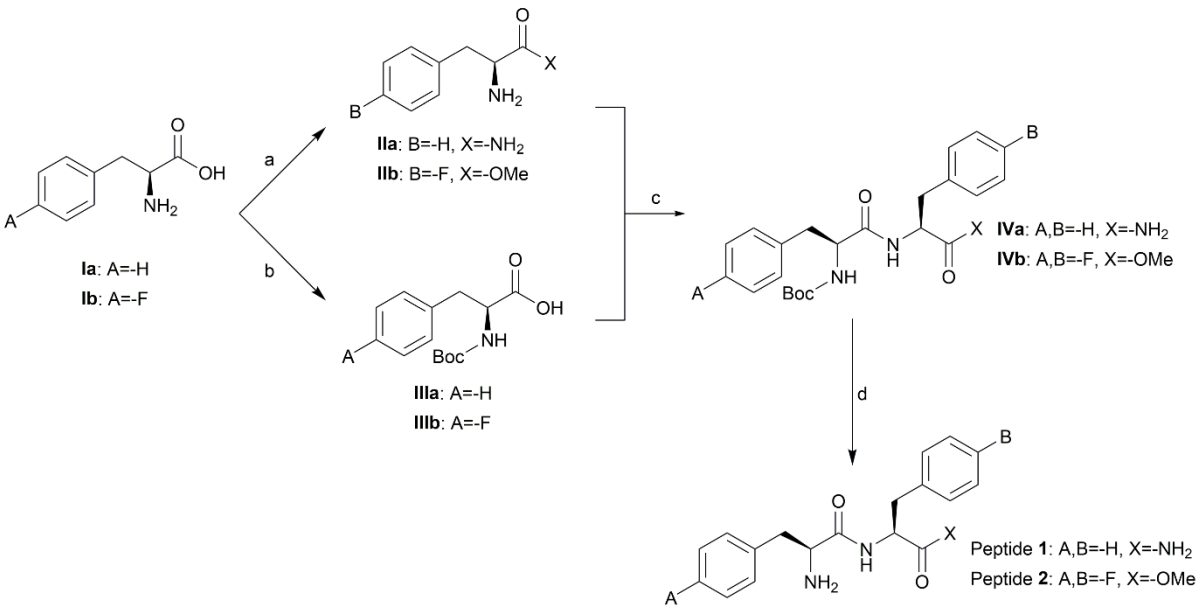

Scheme S1. Chemical route to synthesis of peptide **1** H-Phe-Phe-NH_2 or peptide **2** H-Phe(4-F)-Phe(4-F)-OMe. Reagents and conditions: a) $SOCl_2$, MeOH, 0 °C for 15 min then rt overnight; b) Boc_2O, Dioxane, Water, 0 °C for 15 min then rt for 1h; c) Ethyl chloroformate, N-methylmorpholine, THF, -15 °C for 30 min then rt for 1h; d) Trifluoracetic acid, DCM, 0 °C for 15 min then rt for 2h.

1. Abbreviations

LPPS, liquid phase peptide synthesis; eq, equivalent; DMF, N-N'-dimethylformamide; DCM, dichloromethane; TFA, trifluoroacetic acid; THF, tetrahydrofuran; TDW, triple distilled water; ACN, acetonitrile; HPLC, high performance liquid chromatography; TLC, thin layer chromatography;

2. Materials

All solvents and reagents were used as supplied. Solvents used for HPLC were HPLC grade. DMF, ACN, TFA, THF, piperidine, methanol, dioxane, ethyl acetate, and diethyl ether were purchased from Bio-Lab (Jerusalem, Israel). TDW was obtained through a Milli-Q water filtering system (Millipore). All amino acids were purchased from GL Biochem (Shanghai, China).

3. General synthesis of peptide **1** *H-Phe-Phe-NH_2* and peptide **2** *H-Phe(4-F)-Phe(4-F)-OMe*

Peptide **1** *H-Phe-Phe-NH_2* and peptide **2** *H-Phe(4-F)-Phe(4-F)-OMe* were synthesized according to Scheme S1 starting from H-Phe-OH (**Ia**) and H-Phe(4-F)-OH (**Ib**), respectively. For the synthesis of peptide **2** *H-Phe(4-F)-Phe(4-F)-OMe, H-Phe(4-F)-OH* **Ib** was transformed into *H-Phe(4-F)-OMe* **IIb**. *H-Phe(4-F)-OH* **Ib** was suspended in methanol (100 mL) at a concentration of 50 mM and cooled to 0 °C in an ice bath followed by a very slow addition of thionyl chloride over 15 min. The reaction mixture was then stirred at room temperature for 15 min and heated in an oil bath to reflux for 2h. After completion of the reaction as indicated by TLC, the reaction mixture was concentrated to its 1/3 volume under vacuum and *HCl.NH_2-Phe(4-F)-OMe* was precipitated by cold diethyl ether (200 mL). The white precipitate was collected by filtration, washed with cold diethyl ether (50 mL), and dried under vacuum to constant weight to yield *H-Phe(4-F)-OMe* **IIb** (88.4% yield). On the other hand, *H-Phe-NH_2* **IIa** was commercially available.

In parallel, *H-Phe-OH* **Ia** and *H-Phe(4-F)-OH* **Ib** were protected with a Boc group to obtain *Boc-Phe-OH* **IIIa** and *Boc-Phe(4-F)-OH* **IIIb**. Briefly, a suspension of *H-Phe-OH* **Ia** or *H-Phe(4-F)-OH* **Ib** (50 mM) in a water dioxane mixture (1:1 v/v, 50 mL) was cooled over an ice bath for 15 min. Precooled aqueous NaOH solution (2 M, 27.5 mL) was added followed by a slow addition of Boc_2O (12 g, 55 mM) dissolved in dioxane (27.5 mL). The reaction mixture was stirred for an additional 1h at room temperature. After completion of the reaction, the mixture was concentrated under vacuum to 60 mL volume, cooled over an ice bath, covered with a layer of ethyl acetate (100 mL), and acidified to pH 2-3 by slow addition of 15% aq. $NaHSO_4$ (50 mL). The aqueous phase was extracted with ethyl acetate (2 x 75 mL) and the organic phases were combined, washed with water (2 x 75 mL), dried over anhydrous Na_2SO_4, and evaporated to a constant weight to yield *Boc-Phe-OH* **IIIa** (95% yield) or *Boc-Phe(4-F)-OH* (94.2% yield) **IIIb** as white solids.

For the coupling, ethyl chloroformate (2.3 g, 21.3 mM) was slowly added to a stirred solution of *Boc-Phe-OH* **IIIa** or *Boc-Phe(4-F)-OH* **IIIb** (17.65 mM) in tetrahydrofuran (90 mL) at -15 °C in an ice-salt bath. N-methyl morpholine (2.91 mL, 26.48 mM) was added and the reaction mixture was stirred for 30 mins. After maintaining the reaction at -15 °C for 30 mins, *H-Phe-NH_2* **IIa** or *H-Phe(4-F)-OMe* **IIb** (19.41 mM) and N-methyl morpholine (2.91 mL, 26.48 mM) was added. The reaction mixture was allowed to warm up to room temperature for 1h and further stirred at room temperature for an additional 1h. After completion, the volatiles were removed under vacuum and the residue was dissolved in ethyl acetate (100 mL), washed with

water (2 x 75 mL), 5% aq. $NaHCO_3$ (100 mL), 10% aq. $NaHSO_4$ and finally with brine (50 mL). The ethyl acetate layer was dried over anhydrous sodium sulfate, filtered, and evaporated to constant weight and yielded *Boc-Phe-Phe-NH_2* **IVa** (97.96% yield) or *Boc-Phe(4-F)-Phe(4-F)-OMe* **IVb** (95.1% yield) as white powders.

Lastly, the Boc group of *Boc-Phe-Phe-NH_2* **IVa** or *Boc-Phe(4-F)-Phe(4-F)-OMe* **IVb** was deprotected to yield the peptide **1** *H-Phe-Phe-NH_2* or peptide **2** *H-Phe(4-F)-Phe(4-F)-OMe*. Simply, a solution of *Boc-Phe-Phe-NH_2* **IVa** or *Boc-Phe(4-F)-Phe(4-F)-OMe* **IVb** (8.65 mM) in 40 mL of DCM was cooled to 0 °C in an ice bath for 5 min with stirring under N_2 and TFA (10 mL, 130 mM) was added dropwise over 5 min. The mixture was stirred for 15 min at 0 °C and additional 2h at room temperature under nitrogen. After complete deprotection as indicated by TLC, the solvent was evaporated under vacuum to its 1/10 volume, and the TFA salt of the dipeptides was precipitated by adding diethyl ether (80 mL). The precipitate was allowed to cool in a refrigerator for 2h to maximize the salt precipitation in diethyl ether. The precipitate was filtered, washed with cold diethyl ether (50 mL), and dried in a desiccator under vacuum to a constant weight to get peptide **1** *H-Phe-Phe-NH_2* (88% yield) or peptide **2** *H-Phe(4-F)-Phe(4-F)-OMe* (95.3% yield) as a white powder.

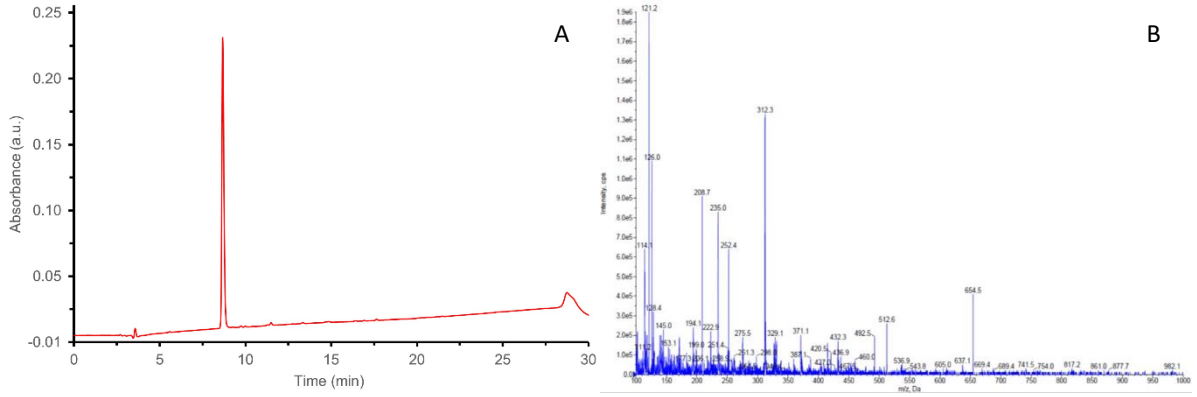

Figure S1. A) Analytical HPLC chromatogram (λ=254) of peptide **1** H-Phe-Phe-NH_2 (purity 99.3%) B) ESI-MS data of purified peptide **1** H-Phe-Phe-NH_2. Calculated mass 311.16 Da, observed mass 312.3 Da for $(M+H)^+$.

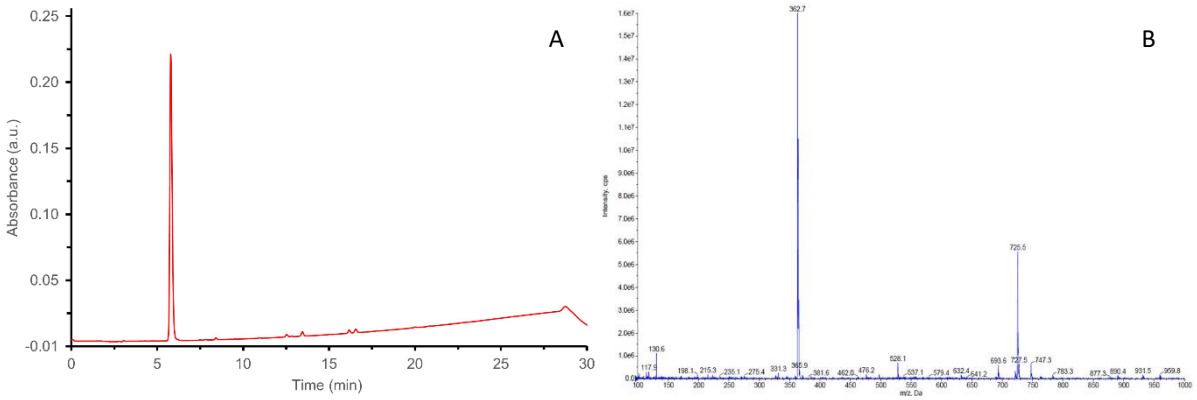

Figure S2. A) Analytical HPLC chromatogram (λ=254) of peptide **2** H-Phe(4-F)-Phe(4-F)-OMe (purity 96%) B) ESI-MS data of purified peptide **2** H-Phe(4-F)-Phe(4-F)-OMe. Calculated mass 362.14 Da, observed mass 362.7 Da for $(M+H)^+$ and 725.5 Da for $(2M+H)^+$.

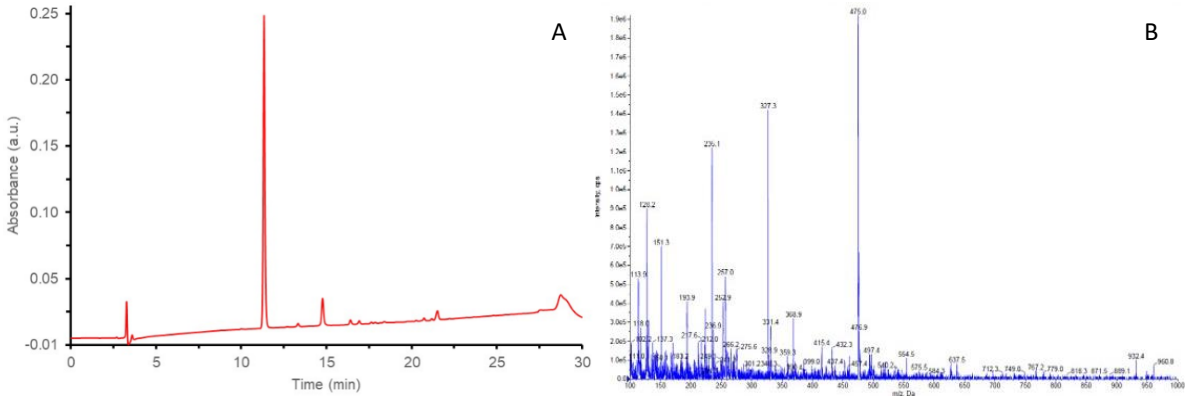

Figure S3. A) Analytical HPLC chromatogram (λ=254) of compound **3** (purity 90%) B) ESI-MS data of purified compound **3**. Calculated mass 474.19 Da for the hydrolyzed compound, observed mass 475 Da for $(M+H)^+$.

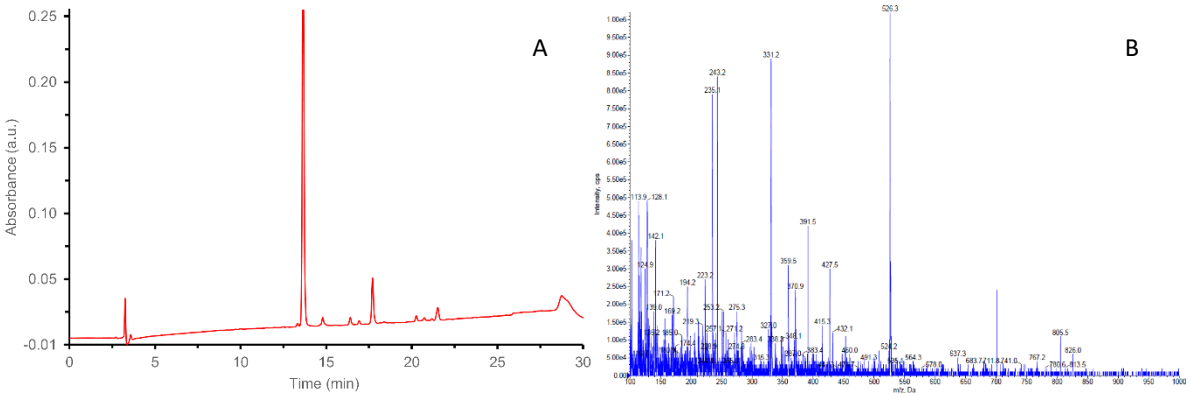

Figure S4. A) Analytical HPLC chromatogram (λ=254) of compound **4** (purity 86%) B) ESI-MS data of purified compound **4**. Calculated mass 525.17 Da for the hydrolyzed compound, observed mass 526.3 Da for $(M+H)^+$.

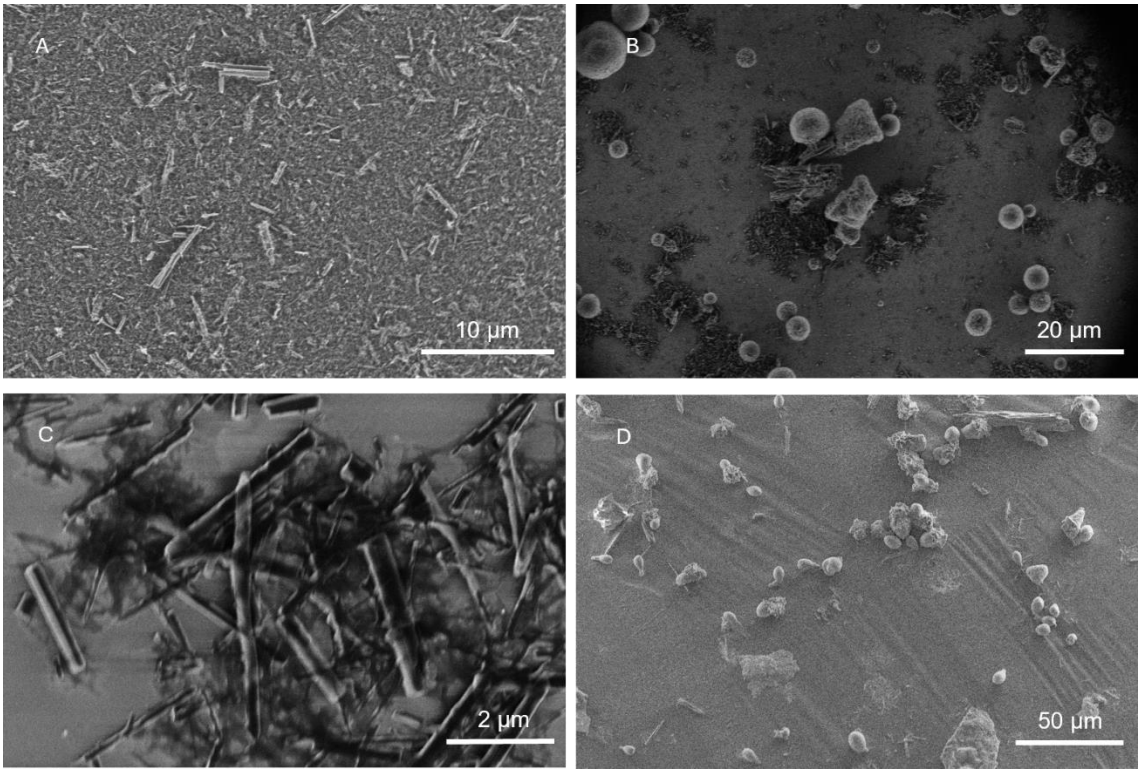

Figure S5. SEM images of the materials formed by A) **N3H** B) **N4H** C) **N3L** and D) **N4L**