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Microwave assisted solid phase synthesis of highly functionalized *N*-alkylated oligobenzamide α-helix mimetics

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ABSTRACT

Protein–protein interactions (PPIs) mediate cellular pathways and are implicated in numerous aberrant conditions. α-Helix mimetics—small molecules that reproduce the spatial projection of key residues from an α-helix involved in a PPI—are attractive generic templates for development of screening libraries, however library syntheses of α-helix mimetics with diverse functionality are less established. This manuscript describes the automated, microwave assisted solid phase synthesis based on one such scaffold; an *N*-alkylated oligobenzamide.

1. Introduction

Oligomers that adopt preferential conformations are named foldamers;[1–3] their stable and predictable folding into well-defined structures have been exploited in various areas of research. Their relative synthetic accessibility from monomer building blocks also confers adaptability, versatility, and the possibility to modify their inherent properties. These features make them attractive utensils to modulate biological processes.[3] Previously, we reported the manual solid phase synthesis (SPS) of an *N*-alkylated aromatic oligoamide scaffold (Fig. 1) and demonstrated that it was suitable for α-helix mimicry through identification of low μM inhibitors of the helix mediated p53/*h*DM2 interaction.[4] In its extended all *trans* conformation, substituents appended to the nitrogen atoms are displayed in such a manner as to match the spatial presentation of side chains located at the *i*, *i* + 4 and *i* + 7 positions of an α-helix. This subset of residues located along one helical face has been shown to be a recurrent pattern in α-helix mediated protein-protein interactions (PPIs),[5–7] where they account for most of the binding energy and are referred to as 'hot-spot' residues.[8,9] PPIs possess features that largely differentiate them from more conventional enzyme-substrate interactions that are traditionally targeted by medicinal chemistry efforts.[10] Such interactions include the gp41 fusion protein, responsible for the fusion process enabling HIV infection;[11] the interaction between p53—a tumor suppressor involved in 50% of all human cancers—and its negative regulators *h*DM2 and *h*DMX;[12–15] and the Bcl-2 family of interactions[16–18] involved in the regulation of apoptosis, a form a programmed cell death that is crucial during the development of multicellular organisms and in avoiding tumourigenesis. Although small molecule inhibitors[19–24] and constrained helical peptides[25–27] or oligomers retaining the helical conformation[28–30] have been used to target these and related PPIs, designing scaffolds that allow mimicry of key interfacial residues on an α-helix involved at a PPI interface offers considerable potential for the elaboration of generic approaches.[5] With this in mind, several such *proteomimetic*[31] scaffolds have been designed over the last decade; Hamilton's terphenyl scaffold was the first true helix mimetic, displaying IC_{50}'s in the micromolar range against several important PPI targets.[20,31–33] Subsequently several further scaffolds were described that were synthetically more accessible and presented drug-like properties including the terephthalamide,[34] the 4,4-dicarboxamide,[35] and the oligo-benzoylurea[36] templates amongst others.[37–40] Aromatic oligoamides[41] represent an attractive class of foldamers,[35,42–47] as their constitutive units can be easily prepared and then assembled into functional structures using modular syntheses. As they are somewhat similar to natural peptides in that they are made of amino acid subunits linked to one another by amide bonds, they are investigated as structural peptide mimetics. Although methods are already well-established for natural peptide synthesis, the assembly of aromatic oligomers (using solid phase synthesis)[48,49] has proven rather troublesome due to the reduced reactivity of the monomers as compared to natural amino acids, making assembly of screening libraries challenging.[44,50] In the present manuscript, we report an automated methodology for the preparation of *N*-alkylated aromatic oligoamides using a state of the art microwave assisted peptide synthesizer. This method provides enhanced

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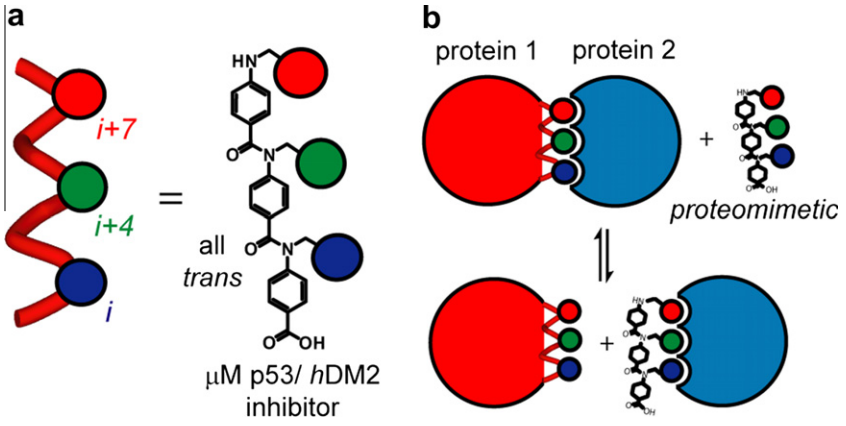


Figure 1. (a) Mimicry of the spatial presentation of residues *i*, *i* + 4, *i* + 7 (coloured spheres) in an α-helix by our *N*-alkylated proteomimetic scaffold; (b) cartoon representing the exploitation of α-helix mimicry in achieving competitive inhibition.

yields and purities as well as reduced handling and coupling times. The tolerance of our coupling method towards functionalities encountered in proteinogenic amino acids is demonstrated, along with some more tailored, unnatural side chains.

2. Results and discussion

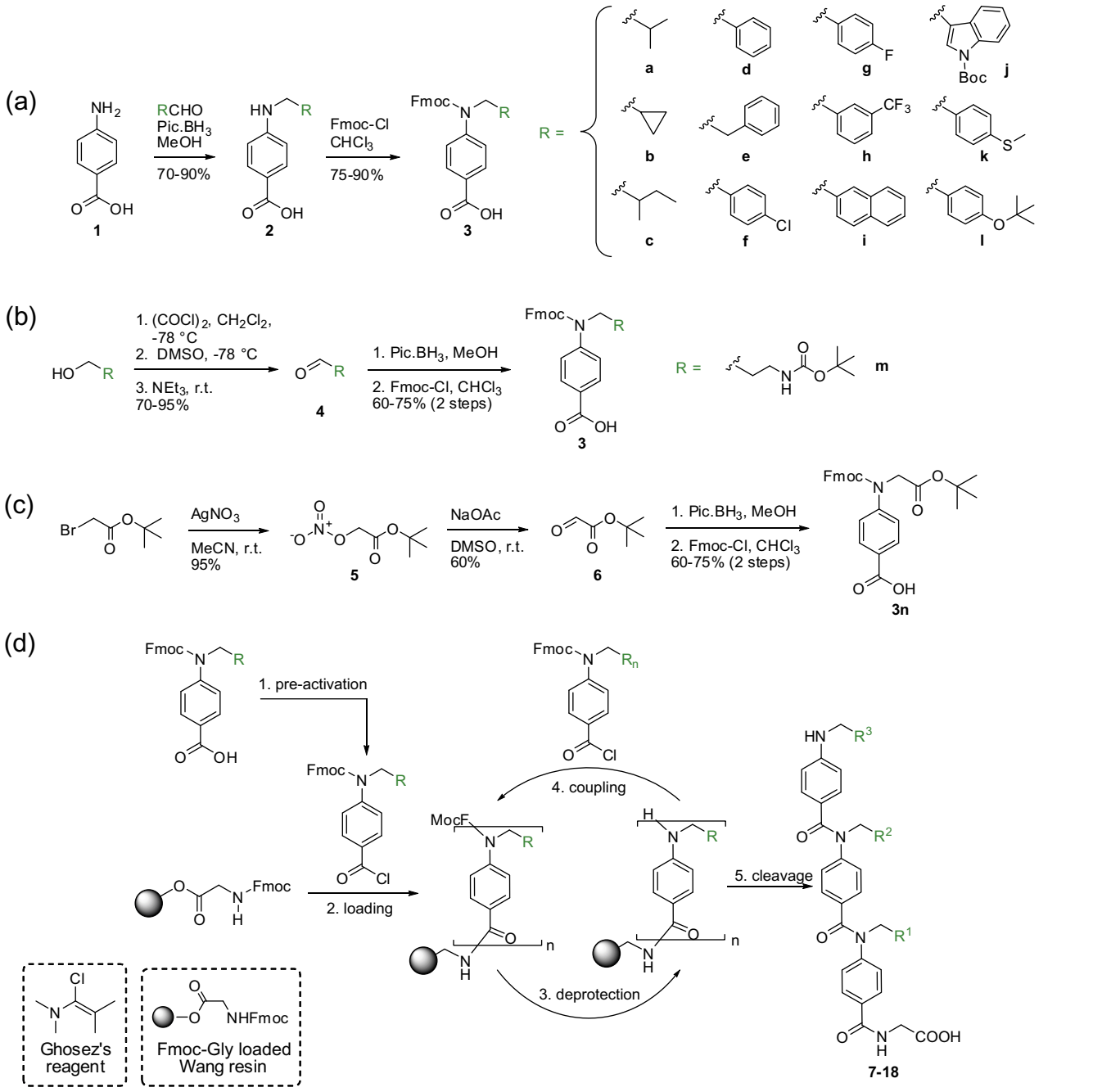
Our strategy for automated solid phase peptide synthesis (SPPS) of *N*-alkylated oligobenzamides centres on use of a microwave assisted peptide synthesizer and the well established Fmoc strategy,[51] providing orthogonality with side chain protecting groups. One of the key features of this oligoamide backbone is its synthetic accessibility. The scaffold is based on trimers of *N*-alkylated *p*-aminobenzoic acid units linked by sequentially installed amide bonds. The preferred *cis* geometry of the amide bond in these molecules[52] has been shown to facilitate the cyclisation of such trimers.[53]

2.1. Monomer synthesis

In order to develop a method amenable to the generation of a library of diversely functionalized tribenzamides, a range of monomers was prepared following the previously reported route (Scheme 1a).[4] Although our prior study confirmed that hydrophobic side chains are privileged for the design of inhibitors of the p53/*h*DM2 interaction (and a considerable number of others),[6] we sought to incorporate a broad range of functionalities encountered in natural amino acids into the monomer set so as to scope the functional group tolerance of our method. In the case of amine containing side chains where the starting aldehydes were not commercially available, Swern oxidation[54] was performed on the parent alcohol (Scheme 1b), whilst one further side chain, containing an acidic functionality, was prepared using a different route (Scheme 1c).

2.2. Solid phase peptide synthesis

The trimeric oligoamides are built from sequential coupling of *N*-alkylated *p*-aminobenzoic acid monomers via SPS using the well established Fmoc strategy, widely employed in natural peptide synthesis. The previously reported SPS on this scaffold[4] was adapted for a CEM Liberty® automated microwave assisted peptide synthesizer. Our experiments focused on the use of Wang resin preloaded with Gly as the solid support, although it should be noted that we also performed a limited number of experiments using unfunctionalized Wang resin. The same protection strategy as for α-amino acid coupling was sought for our scaffold so as to avoid the development of an entirely new permanent and semi-permanent protecting group strategy, hence the prime synthetic objective was to optimize amide bond formation; however the deactivated secondary aniline is significantly less nucleophilic than a primary amine. Coupling agents that are classically used in peptide synthesis (HCTU, PyBOP, TFFH, EDCI, etc.) proved inefficient when applied to our scaffold under microwave heating (as had been the case in our earlier manual SPS study).[4] Different coupling conditions were thus necessary and have been carefully optimized. Previous studies on the solution phase synthesis of our trimers revealed that the monomers required activation as acyl chlorides in order for the coupling reaction to take place. Acyl chlorides of our monomers could be obtained by reaction with dichlorotriphenylphosphorane[55] (Cl_2PPh_3) at elevated temperatures and with Ghosez's reagent[56] at room temperature. We thus investigated both reagents under microwave heating conditions. As the activation using the phosphorane required heating, both the monomer and the coupling agent had to be dissolved in the desired solvent and placed on the synthesizer's manifold; the acyl chloride was then obtained *in situ* within the reaction vessel. Because Ghosez's reagent could generate the reactive species at room temperature, the acyl chloride could either be generated *in situ*, or obtained by pre-activation. Due to the water sensitivity of these coupling agents and the low reactivity of the aniline towards acyl chlorides at room temperature, significant care was required to exclude water from the pre-activation step and coupling reaction. At first, coupling was optimized for the formation of dimers using dichlorotriphenylphosphorane, as it is easier to handle than Ghosez's reagent. Standard coupling conditions were set to allow the study of each parameter (base, solvent, temperature and coupling time) independently. Temperature and coupling time were set to 60 °C and 30 min respectively, and 4 equiv of monomer were used per coupling. Different solvents were tested, with the pre-requisite that all reagents should be soluble in the considered solvent. Single couplings in dioxane, tetrahydrofuran or dichloromethane provided no or low conversion to dimer, whereas conversions from 55% to 60% were obtained in chloroform or DMF. In DMF, conversion could be somewhat enhanced by raising the coupling temperature to 90 °C. Further optimization was carried out in parallel for both solvents. Prolonging the coupling time to 45 min or 1 h did not improve the conversion, but reducing the coupling time to 20 min was not detrimental either. Finally, switching to a double coupling improved conversion to the dimer from 60% with a single coupling, to quantitative. Despite these encouraging preliminary results, dichlorotriphenylphosphorane proved to be unreliable from batch to batch and in subsequent studies on the functional group tolerance of the method. Further studies on Ghosez's α-chloroenamine were then performed in chloroform; couplings proved



Scheme 1. (a) Synthesis of Fmoc protected *N*-alkylated *p*-aminobenzoic acid monomers; (b) preliminary Swern oxidation of basic side chain; (c) synthetic route for the preparation of the aldehyde precursor of the acidic monomer and (d) outline of procedure used for solid phase synthesis of *N*-alkylated aromatic oligoamide α-helix mimetics. 1. Pre-activation: monomer (5 equiv to resin, 0.5 mmol) in anhydrous $CHCl_3$ (5.5 mL), pre-activated with Ghosez's reagent (0.95 equiv to the monomer, 0.48 mmol) for a minimum of 1 h; 2. Loading: resin (0.1 mmol, 127 mg) swelled in 5 mL DMF, monomer loaded using a double coupling method (2 × 20 min, 60 °C); 3. Coupling: same method as for the loading; 4. Deprotection: standard microwave method used (two cycles, 75 °C, 3 min, cf. experimental section); 5. Manual cleavage: DCM-TFA (1–1, 0.7 mL), 2 × 20 min, r.t.

to be much more reproducible than with dichlorotriphenylphosphorane and it was therefore established as the reagent of choice for these monomers. Further optimization of the coupling time, temperature, number of equivalents of monomer to the resin and solvent led to complete conversion to trimers in good yields (Scheme 1d). Because double couplings are required, using 4 equiv of monomer per coupling means that a large amount of monomer is consumed. After further optimization, the minimum number of equivalents of monomer to the resin was identified as 2.5, and the coupling time was maintained at 20 min. Standard microwave assisted deprotection was used and didn't require any optimization. Including the wash cycles, this new method therefore yields trimers in 4 h, which is a dramatic improvement on the 4 days previously required using our manual SPS method.[4] Although cleavage from the resin can be performed on the synthesizer, this would require additional and extensive washes of the reactor. We therefore chose to carry out the cleavages manually (cf. Experimental section), which also allows to optimize the productivity of the synthesizer.

For side chains containing a reactive functionality that needs to be protected during the coupling, our strategy was to use acid-labile protecting groups. These protecting groups would thus

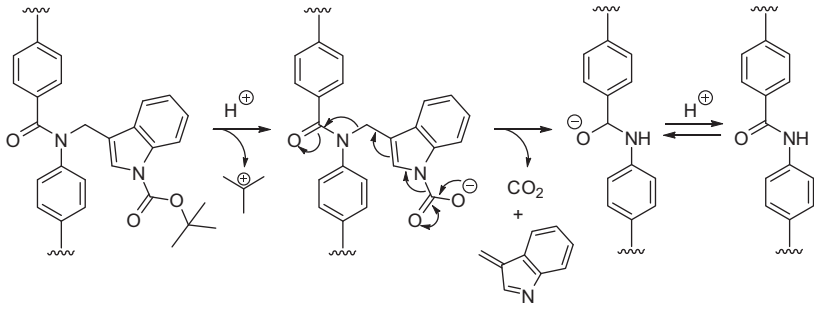
remain untouched during the basic Fmoc deprotection step, but would be removed during acidic cleavage from the resin. During coupling however, one equivalent of hydrochloric acid is generated that can potentially deprotect the side chains. To quench this acidity, a base needed to be present during coupling and the base tolerance of our method was thus assessed. Firstly, *N*-methyl imidazole was tested, but this base presented the inconvenience of being highly hygroscopic, thus requiring distillation and storage under strictly anhydrous conditions prior to use; the reagent was therefore considered incompatible with the microwave synthesizer. For this reason, a solid inorganic base seemed more reasonable and we tested couplings in the presence of sodium bicarbonate, which was introduced in excess at the same time as the resin. Using a solid base presents the additional advantage that it is retained in the reaction vessel after each round of filtered washes following couplings and is therefore introduced only once, again minimizing entry points for water. The bicarbonate is readily removed by rinsing the resin with water prior to the cleavage from the resin.

We then sought to test thoroughly the functional group tolerance of the method by assembly of a small library. These studies were carried out in chloroform, as it is much less hygroscopic than DMF. The present library was designed to assess the ability of our monomers to be coupled to another monomer already attached to the resin to form a dimer, as well as the ability of these dimers to couple to another activated monomer to provide trimers. To obtain consistent data, we performed the majority of experiments using the same monomers at the *N*- and *C*-termini for each trimer, respectively the benzyl and isobutyl monomers. The optimized coupling conditions afforded the desired trimers with good conversion and yield (Table 1) and the crude material was in most cases more than 90% pure as observed on the LC–MS spectrum. When the purity of the crude material was judged unsatisfactory, purification was performed. Several methods were used including column chromatography, preparative TLC, preparative HPLC, mass directed preparative HPLC or precipitation, which improved purity but considerably affected the isolated yields of pure compounds. In the range of monomers that were submitted to coupling, the indole containing monomer was problematic, in agreement with previous observations.[4] LC–MS analysis of the product indicated that the coupling occurs, but that the indole functionality is lost, presumably due to acid catalyzed elimination of the Boc-protecting group during the TFA-cleavage step, followed by cascade elimination of the indole ring (Scheme 2). This issue was addressed by using milder conditions for the cleavage step. The cleaving cocktail was diluted from a 1–1 mixture of dichloromethane-TFA down to a 10% TFA in dichloromethane solution. For side chains containing a functional group that is prone to elimination, it might be necessary to adjust cleaving mixture and cleaving time to achieve neat cleavage from the resin as well as complete deprotection whilst preserving the side chain. The small library demonstrates the tolerance of our method towards: aliphatic chains and hence analogues

Table 1
Library of *N*-alkylated tribenzamides with the side chains sequence

Trimer number	R3	R2	R1	Purity	Yield
7	**d**	**b**	**a**	90%	85%
8	**d**	**d**	**a**	95%	100%
9	**d**	**e**	**a**	~85%	~95%
10	**d**	**i**	**a**	90%	~90%
11	**d**	**h**	**a**	95%	100%
12	**d**	**f**	**a**	95%[a] (crude 80%)	7%[a]
13	**d**	**k**	**a**	80%	~85%
14	**d**	**l**	**a**	95%[b] (crude 75%)	22%[b]
15	**f**	**j**	**a**	95%[c]	10%
16	**a**	**m**	**a**	90%[a] (crude 80%)	~6%[a]
17	**d**	**n**	**a**	95%	100%
18	**h**	**h**	**c**	95%	100%

Unless otherwise specified, the reported purity and yield correspond to crude compounds.
[a] Purified by precipitation.
[b] Purified by MS-directed preparative HPLC.
[c] Purified by column chromatography.



Scheme 2. Cascade elimination of the indole functionality during acidic cleavage from the resin.

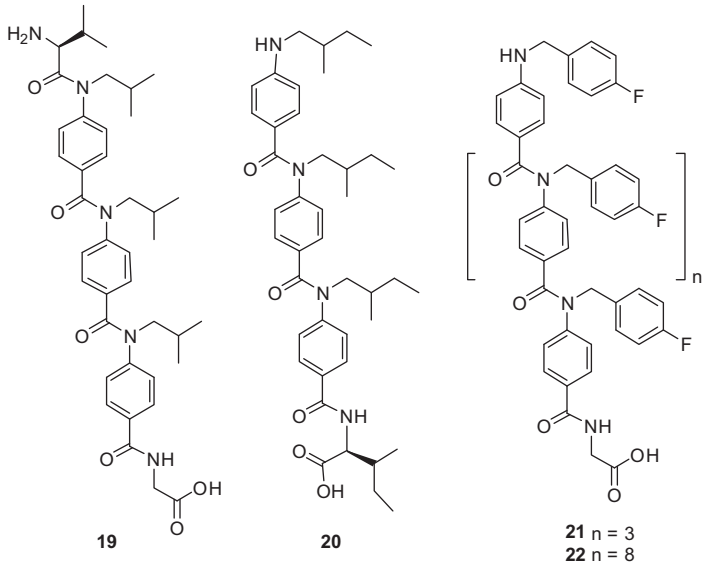


Figure 2. Compatibility of the method with natural amino acids both at the *N*- and *C*-terminus (compounds **19** and **20**) and extension of the method to the synthesis of longer oligomers (**21** and **22**).

of Ala, Val, Leu, Ile residues (trimers **7** and **18**, Table 1), aromatic analogues of Phe and halogenated aromatics (**8**–**12**), sulfur containing side chains (**13**), tyrosine analogues (**14**), tryptophan analogues (**15**), basic and acidic chains analogues of Lys, Asp and Glu (**16** and **17**). We also investigated the incorporation of an aliphatic sulfur containing side chain (i.e. a true Met analogue), but the synthesis and purification of the corresponding monomer was problematic, and its limited solubility contributed to inefficient coupling. In the case of an imidazole bearing monomer (i.e. a His analogue), two protecting groups were considered, (Boc and Trt), but in both cases the Fmoc protection step proved cumbersome and fully protected monomer was not successfully isolated. Functional tolerance towards a few other remaining proteinogenic functionalities still remains to be demonstrated; notably proline, cysteine, arginine and asparagine/glutamine, however the method we have developed is sufficiently powerful for exploration of SAR space. In addition, we have shown that amino acids can be coupled to the *N*-terminus of the oligobenzamide; Val has been coupled to the *N*-terminus (i.e. **19**) rendering the approach entirely compatible with standard oligopeptide synthesis (noting that amino acid loaded resins demonstrate this feature for the *C*-terminus Gly for **7**–**18** and Ile for **20**, Fig. 2).

We have also investigated the robustness of our method towards synthesizing longer oligomers, which might allow the mimicry of longer helical domains. The optimized coupling conditions described in Scheme 1d have been applied in this study, using up to ten rounds of deprotection-coupling cycles. Test cleavages on small aliquots of resin were performed at different stages. To date, pentamers for example **21** have been made with purity confirmed by NMR as well as HRMS (cf. Supplementary data) and we have been able to extend the synthesis as far as the decamer (Fig. 2, compound **22**).

3. Conclusions

We have established a robust automated SPS methodology for the synthesis of *N*-alkylated oligobenzamides using a microwave assisted peptide synthesizer, allowing facile library generation of diversely functionalized compounds. A wide range of monomers has been prepared and incorporated into trimers to demonstrate the reproducibility and functional tolerance of our method. Side chains compatible with this method cover the whole range of hydrophobic side chains, which are the most commonly involved in PPI interfaces. Combinations of side chains give access to a wide variety of oligomers, and thus allow mimicry of numerous potential helix surfaces. We have also reported the synthesis of oligomers up to the decamer, which broadens the range of possible applications for both this method and the present scaffold. Our

ongoing efforts are directed towards the synthesis of a library and its screening against a diverse range of α-helix mediated PPIs.

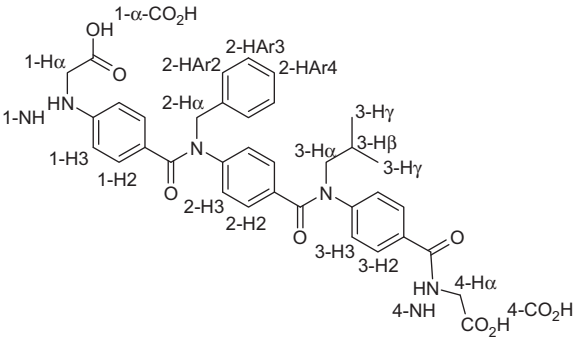
4. Experimental section

4.1. General considerations

All reagents were obtained from Aldrich, Alfa Aesar, Acros or Fluka and used without further purification. All solvents used were HPLC grade. Analytical TLC was performed using 0.2 mm silica gel 60 F254 pre-coated aluminium sheets (Merck) and visualised using UV irradiation or, in the case of amine intermediates, by staining with a ninhydrin solution. Flash column chromatography was carried out on silica gel 60 (35–70 micron particles, FluoroChem). Solvent ratios are described where appropriate. Solvents were removed under reduced pressure using a Büchi rotary evaporator at diaphragm pump pressure. Samples were freed of remaining traces of solvents under high vacuum. ^{1}H and ^{13}C NMR spectra were measured on a Bruker DPX300 or a Bruker Avance 500 spectrometer using an internal deuterium lock. Chemical shifts are reported in parts per million (ppm) downfield from TMS in δ units and coupling constants are given in hertz (Hz). Coupling constants are reported to the nearest 0.1 Hz. TMS is defined as 0 ppm for ^{1}H NMR spectra and the centre line of the triplet of $CDCl_3$ was defined as 77.10 ppm for ^{13}C NMR spectra. When describing ^{1}H NMR data the following abbreviations are used; s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet. Melting points were determined using a Griffin D5 variable temperature apparatus and are uncorrected. Microanalyses were obtained on a Carlo Erba Elemental Analyser MOD 1106 instrument, found composition is reported to the nearest 0.05%. Infrared spectra were recorded on a Perkin–Elmer FTIR spectrometer and samples analysed as solids (unless stated). Mass spectra (HRMS) were recorded in house using a Micromass GCT Premier, using electron impact ionisation (EI) or a Bruker Daltonics micrOTOF, using electron spray ionisation (ES). LC–MS experiments were run on a Waters Micromass ZQ spectrometer, samples ionised by electrospray and analysed by a time-of-flight mass spectrometer, or a Bruker Daltronics HCT UltraTM series spectrometer, samples ionised by electrospray. All experiments were run through a C18 column on an acetonitrile–water gradient (typically 0–95% acetonitrile over 3 min). A representative example of each synthetic procedure is provided with all examples described in the ESI.

4.2. Naming and numbering of *N*-alkylated aromatic oligoamides

To simplify the numbering and NMR assignment of our trimers, we have devised a sequential nomenclature (based upon conventional peptide naming), where each monomer building block is considered separately. The monomers are numbered from 1 upwards starting from the *N*-terminus, (and for the current series glycine is numbered 4). Within each monomer, the numbering is the same: carbons from the aminobenzoic acid are numbered using the standard system (the aromatic carbon bearing the carboxylic acid is C1, the one bearing the amine is C4). Then, the lateral chain is numbered: the carbon attached to the nitrogen is the Cα, and the numbering of the aliphatic part of the side chain continues with Cβ, etc. In the case of aromatic side chains, the aromatic carbons are numbered CAr1, CAr2, etc. The numbering of the protons is based on the carbon numbering. To differentiate each individual carbon/proton, the monomer number is added as a prefix to the carbon/proton number. The same nomenclature is applied to the Fmoc-protected monomers, and the protons corresponding to the Fmoc system are differentiated by the prefix F. The protons from the CH_2 group are numbered FHα, the neighbouring CH is FHβ, and the aromatic protons are FH2 to FH5.



4.3. General procedure for reductive amination

To a stirred solution of primary aniline (1 equiv, 36.4 mmol) and aldehyde (1.05 equiv, 38.2 mmol) in methanol (120 mL) under an atmosphere of nitrogen, was added borane–picoline[57] (1.2 equiv, 43.7 mmol). The reaction mixture was stirred at room temperature for 4–36 h, until TLC indicated reaction completion. Concentration and either direct purification by column chromatography or precipitation gave the target material which was dried under vacuum.

4.4. Solid phase synthesis experimental

127 mg of Fmoc-Gly-Wang resin (0.79 mmol g^{-1}, 100–200 mesh; carrier: polystyrene, crosslinked with 1% DVB) from Novabiochem, was used throughout. All solvents used were HPLC grade. 1-Chloro-*N*,*N*,2-trimethyl-1-propenylamine (Ghosez's reagent) was purchased from Sigma–Aldrich. The reagent was stored at −20 °C and the bottle was used under a nitrogen atmosphere to prevent degradation. For each coupling reaction, 5 equiv (to the resin, spread over two couplings) of fully protected monomer and 0.95 equiv of Ghosez's reagent to the monomer were used. The resin was swelled in DMF for at least 15 min prior to coupling. The reactions were all carried out on a CEM Liberty® microwave assisted automated peptide synthesiser. The software interface allows the creation of personalised loading, deprotection and coupling cycles (order, number and volumes of additions of monomer, DMF and CH_2Cl_2 washes), as well as the setting of parameters for the microwave method (temperature, temperature gradient, heating time, power, etc.). Up to 12 methods can be run in daisy-chain on the synthesizer with no external intervention.

4.5. General coupling

For each coupling, the volume of pre-activated monomer solution added to the microwave reactor was set to 2.5 mL. Each fully protected monomer was thus dissolved in anhydrous chloroform (~5.5 mL), in VWR® tubes that fit on the CEM® synthesizer and Ghosez's reagent added. This mixture was then allowed to incubate at room temperature for at least 1 h to allow acyl chloride formation. Each coupling cycle was carried out at 60 °C for 20 min.

4.6. General Fmoc deprotection

After each coupling reaction, the contents of the microwave reactor were automatically drained and the resin washed three times with CH_2Cl_2 and three times with DMF (7 mL each).

Following the final DMF wash, 6 mL of 25% piperidine in DMF was added to the reaction vessel and two deprotection cycles were carried out (microwave heating to 75 °C for 3 min). The reactor was then drained and the resin washed with neat DMF three times (5 mL each). Finally, the deprotected resin was washed twice with CH_2Cl_2 (5 mL each).

4.7. Cleavage

The cleavage steps were carried out manually in 1.5 mL 'Extract-Clean' polypropylene reservoirs fitted with 20 mm polyethylene frits, both available from Alltech and a 1–1 mixture of TFA-dichloromethane was used, unless otherwise stated.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmc.2012.09.053.

References and notes

1. Gellman, S. H. *Acc. Chem. Res.* **1998**, *31*, 173.
2. Seebach, D.; Beck, A. K.; Bierbaum, D. J. *Chem. Biodivers.* **2004**, *1*, 1111.
3. Goodman, C. M.; Choi, S.; Shandler, S.; DeGrado, W. F. *Nat. Chem. Biol.* **2007**, *3*, 252.
4. Campbell, F.; Plante, J. P.; Edwards, T. A.; Warriner, S. L.; Wilson, A. J. *Org. Biomol. Chem.* **2010**, *8*, 2344.
5. Davis, J. M.; Tsou, L. K.; Hamilton, A. D. *Chem. Soc. Rev.* **2007**, *36*, 326.
6. Bullock, B. N.; Jochim, A. L.; Arora, P. S. *J. Am. Chem. Soc.* **2011**, *133*, 14220.
7. Edwards, T.; Wilson, A. *Amino Acids* **2011**, *41*, 743.
8. Clackson, T.; Wells, J. A. *Science* **1995**, *267*, 383.
9. Stites, W. E. *Chem. Rev.* **1997**, *97*, 1233.
10. Wilson, A. J. *Chem. Soc. Rev.* **2009**, *38*, 3289.
11. Chan, D. C.; Chutkowski, C. T.; Kim, P. S. *Proc. Natl. Acad. Sci. U.S.A.* **1998**, *95*, 15613.
12. Kussie, P. H.; Gorina, S.; Marechal, V.; Elenbaas, B.; Moreau, J.; Levine, A. J.; Pavletich, N. P. *Science* **1996**, *274*, 948.
13. Chene, P. *Nat. Rev. Cancer* **2003**, *3*, 102.
14. Murray, J. K.; Gellman, S. H. *Pept. Sci.* **2007**, *88*, 657.
15. Patel, S.; Player, M. R. Expert Opin. Investig *Drugs* **1865**, *2008*, 17.
16. Sattler, M.; Liang, H.; Nettesheim, D.; Meadows, R. P.; Harlan, J. E.; Eberstadt, M.; Yoon, H. S.; Shuker, S. B.; Chang, B. S.; Minn, A. J.; Thompson, C. B.; Fesik, S. W. *Science* **1997**, *275*, 983.
17. Cory, S.; Adams, J. M. *Nat. Rev. Cancer* **2002**, *2*, 647.
18. Lessene, G.; Czabotar, P. E.; Colman, P. M. *Nat. Rev. Drug Discov.* **2008**, *7*, 989.
19. Wells, J. A.; McLendon, C. L. *Nature* **2007**, *1001*, 450.
20. Ernst, J. T.; Kutzki, O.; Debnath, A. K.; Jiang, S.; Lu, H.; Hamilton, A. D. *Angew. Chem., -Int. Ed.* **2002**, *41*, 278.
21. Vassilev, L. T.; Vu, B. T.; Graves, B.; Carvajal, D.; Podlaski, F.; Filipovic, Z.; Kong, N.; Kammlott, U.; Lukacs, C.; Klein, C.; Fotouhi, N.; Liu, E. A. *Science* **2004**, *303*, 844.
22. Oltersdorf, T.; Elmore, S. W.; Shoemaker, A. R.; Armstrong, R. C.; Augeri, D. J.; Belli, B. A.; Bruncko, M.; Deckwerth, T. L.; Dinges, J.; Hajduk, P. J.; Joseph, M. K.; Kitada, S.; Korsmeyer, S. J.; Kunzer, A. R.; Letai, A.; Li, C.; Mitten, M. J.; Nettesheim, D. G.; Ng, S.-C.; Nimmer, P. M.; O'Connor, J. M.; Oleksijew, A.; Petros, A. M.; Reed, J. C.; Shen, W.; Tahir, S. K.; Thompson, C. B.; Tomaselli, K. J.; Wang, B.; Wendt, M. D.; Zhang, H.; Fesik, S. W.; Rosenberg, S. H. *Nature* **2005**, *435*, 677.
23. Shangary, S.; Qin, D.; McEachern, D.; Liu, M.; Miller, R. S.; Qiu, S.; Nikolovska-Coleska, Z.; Ding, K.; Wang, G.; Chen, J.; Bernard, D.; Zhang, J.; Lu, Y.; Gu, Q.; Shah, R. B.; Pienta, K. J.; Ling, X.; Kang, S.; Guo, M.; Sun, Y.; Yang, D.; Wang, S. *Proc. Natl. Acad. Sci. U.S.A.* **2008**, *105*, 3933.
24. Zhou, H.; Chen, J.; Meagher, J. L.; Yang, C.-Y.; Aguilar, A.; Liu, L.; Bai, L.; Cong, X.; Cai, Q.; Fang, X.; Stuckey, J. A.; Wang, S. *J. Med. Chem.* **2012**, *55*, 4664.
25. Moellering, R. E.; Cornejo, M.; Davis, T. N.; Bianco, C. D.; Aster, J. C.; Blacklow, S. C.; Kung, A. L.; Gilliland, D. G.; Verdine, G. L.; Bradner, J. E. *Nature* **2009**, *462*, 182.
26. Walensky, L. D.; Pitter, K.; Morash, J.; Oh, K. J.; Barbuto, S.; Fisher, J.; Smith, E.; Verdine, G. L.; Korsmeyer, S. J. *Mol. Cell* **2006**, *24*, 199.
27. Patgiri, A.; Yadav, K. K.; Arora, P. S.; Bar-Sagi, D. *Nat. Chem. Biol.* **2011**, *7*, 585.
28. Johnson, L. M.; Mortenson, D. E.; Yun, H. G.; Horne, W. S.; Ketas, T. J.; Lu, M.; Moore, J. P.; Gellman, S. H. *J. Am. Chem. Soc.* **2012**, *134*, 7317.
29. Lee, E. F.; Smith, B. J.; Horne, W. S.; Mayer, K. N.; Evangelista, M.; Colman, P. M.; Gellman, S. H.; Fairlie, W. D. *ChemBioChem* **2011**, *12*, 2025.
30. Bautista, A. D.; Appelbaum, J. S.; Craig, C. J.; Michel, J.; Schepartz, A. *J. Am. Chem. Soc.* **2010**, *132*, 2904.
31. Orner, B. P.; Ernst, J. T.; Hamilton, A. D. *J. Am. Chem. Soc.* **2001**, *123*, 5382.
32. Yin, H.; Lee, G.-I.; Park, H. S.; Payne, G. A.; Rodriguez, J. M.; Sebti, S. M.; Hamilton, A. D. *Angew. Chem., -Int. Ed.* **2005**, *44*, 2704.
33. Kazi, A.; Sun, J.; Doi, K.; Sung, S.-S.; Takahashi, Y.; Yin, H.; Rodriguez, J. M.; Becerril, J.; Berndt, N.; Hamilton, A. D.; Wang, H.-G.; Sebti, S. D. M. *J. Biol. Chem.* **2011**, *286*, 9382.
34. Yin, H.; Lee, G. I.; Sedey, K. A.; Rodriguez, J. M.; Wang, H. G.; Sebti, S. M.; Hamilton, A. D. *J. Am. Chem. Soc.* **2005**, *127*, 5463.
35. Rodriguez, J. M.; Nevola, L.; Ross, N. T.; Lee, G.-I.; Hamilton, A. D. *ChemBioChem* **2009**, *10*, 829.
36. Rodriguez, J. M.; Ross, N. T.; Katt, W. P.; Dhar, D.; Lee, G.-I.; Hamilton, A. D. *ChemMedChem* **2009**, *4*, 649.
37. Adler, M. J.; Hamilton, A. D. *J. Org. Chem.* **2011**, *76*, 7040.
38. Ehlers, I.; Maity, P.; Aubé, J.; König, B. *Eur. J. Org. Chem.* **2011**, *2011*, 2474.
39. Biros, S. M.; Moisan, L.; Mann, E.; Carella, A.; Zhai, D.; Reed, J. C.; Rebek, J. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 4641.
40. Lee, J. H.; Zhang, Q.; Jo, S.; Chai, S. C.; Oh, M.; Im, W.; Lu, H.; Lim, H.-S. *J. Am. Chem. Soc.* **2010**, *133*, 676.
41. Huc, I. *Eur. J. Org. Chem.* **2004**, 17.
42. Ernst, J. T.; Becerril, J.; Park, H. S.; Yin, H.; Hamilton, A. D. *Angew. Chem., -Int. Ed.* **2003**, *42*, 535.
43. Ahn, J. M.; Han, S. Y. *Tetrahedron Lett.* **2007**, *48*, 3543.
44. Shaginian, A.; Whitby, L. R.; Hong, S.; Hwang, I.; Farooqi, B.; Searcey, M.; Chen, J.; Vogt, P. T.; Boger, D. L. *J. Am. Chem. Soc.* **2009**, *131*, 5564.
45. Plante, J. P.; Burnley, T.; Malkova, B.; Webb, M. E.; Warriner, S. L.; Edwards, T. A.; Wilson, A. J. *Chem. Commun.* **2009**, 5091.
46. Azzarito, V.; Prabhakaran, P.; Bartlett, A. I.; Murphy, N. S.; Hardie, M.; Kilner, C.; Edwards, T. A.; Warriner, S.; Wilson, A. *Org. Biomol. Chem.* **2012**, *10*, 6469.
47. Yap, J. L.; Cao, X.; Vanommeslaeghe, K.; Jung, K.-Y.; Peddaboina, C.; Wilder, P. T.; Nan, A.; MacKerell, A. D.; Smythe, W. R.; Fletcher, S. *Org. Biomol. Chem.* **2012**, *10*, 2928.
48. Baptiste, B.; Douat-Casassus, C.; Laxmi-Reddy, K.; Godde, F.; Huc, I. *J. Org. Chem.* **2010**, *75*, 7175.
49. Konig, H. M.; Abbel, R.; Schollmeyer, D.; Kilbinger, A. F. M. *Org. Lett.* **1819**, *2006*, 8.
50. Lu, F.; Chi, S.-W.; Kim, D.-H.; Han, K.-H.; Kuntz, I. D.; Guy, R. K. *J. Comb. Chem.* **2006**, *8*, 315.
51. Blankemeyer-Menge, B.; Nimtz, M.; Frank, R. *Tetrahedron Lett.* **1990**, *31*, 1701.
52. Saito, S.; Toriumi, Y.; Tomioka, N.; Itai, A. *J. Org. Chem.* **1995**, *60*, 4715.
53. Campbell, F.; Plante, J.; Carruthers, C.; Hardie, M. J.; Prior, T. J.; Wilson, A. J. *Chem. Commun.* **2007**, 2240.
54. Mancuso, A. J.; Brownfain, D. S.; Swern, D. *J. Org. Chem.* **1979**, *44*, 4148.
55. Azumaya, I.; Okamoto, T.; Imabeppu, F.; Takayanai, H. *Tetrahedron* **2003**, *59*, 2325.
56. Devos, A.; Remion, J.; Frisque-Hesbain, A. M.; Colens, A.; Ghosez, L. *J. Chem. Soc., Chem. Commun.* **1979**, 1180.
57. Sato, S.; Sakamoto, T.; Miyazawa, E.; Kikugawa, Y. *Tetrahedron* **2004**, *60*, 7899.