Pharm. Pharmacol. Commun. 1999, 5: 151–157

Solid-phase Organic Synthesis of Unnatural Polyamine Analogues Bearing a Dansyl or Acridine Moiety

S. CARRINGTON, J. RENAULT*, S. TOMASI*, S. SINBANDHIT†, I. S. BLAGBROUGH AND P. URIAC*

*Department of Pharmacy and Pharmacology, University of Bath, BA2 7AY, UK, *Pharmacochimie des Molécules de Synthèse et des Produits Naturels, Faculté de Pharmacie, 2 Avenue du Professeur Léon Bernard, 35043 Rennes Cedex, and †CRMPO, Université de Rennes I, Campus de Beaulieu, 35042 Rennes Cedex, France*

Abstract

The synthesis of unnatural polyamines and polyamine conjugates from a protected triamine anchored to Wang resin is described. The use of solid-phase organic synthesis for such hydrophilic compounds is of interest because it removes the need for often awkward chromatographic purification of intermediates and is easily applied to the synthesis of compound libraries. Chain elongation was achieved by reductive amination and the resulting resin bound tetraamine was functionalized with dansyl and acridine moieties. The conjugates were cleaved from the resin and these studies should lead to the rapid synthesis of libraries for biological evaluation.

Polyamines are common, low molecular weight polycationic molecules, essential for cell growth and replication (Tabor & Tabor 1964, 1984). The specific biological roles played by these compounds have led to interest in their synthesis and that of analogues as potential mimics or biosynthetic enzyme inhibitors. The discovery that depletion of cellular polyamines leads to the cessation of cell growth has led to the design of polyamino-derived conjugates with potential as antitumour and antiparasitic agents (Marton & Pegg 1995; Blagbrough et al 1997; Tye et al 1998). Other biological targets of interest include NMDA and ion-channel receptors which are blocked by polyamine amides isolated from the venoms of certain spiders and wasps (Blagbrough et al 1997).

We previously reported the solid-phase organic synthesis of putrescine and spermine derivatives and initial biological evaluation of antitumour activity (Tomasi et al 1998). Two major advantages of solid-phase organic synthesis are the simplification of purification procedures which can often be difficult with such hydrophilic compounds, and the possibility of readily introducing molecular diversity by coupling various groups with the polyamine (e.g. amides, sulphonamides, amines, ureas, amino acids). However, one limiting factor is the choice of the polyamine which is first attached to the resin (Dixit & Leznoff 1977, 1978; Hiroshige et al 1995; Marsh et al 1996; Nash et al 1996; Kellam et al 1997; Byk et al 1997; Page et al 1998). A key area of interest associated with the structure–activity of polyamines and their analogues is the spacing between the amino groups along the polyamine chain. The use of solid-phase organic synthesis for polyamine synthesis would be greatly enhanced by the development of a method of regiospecfically constructing chains containing 3, 4, 5 or more amino groups, masked by orthogonally removable protecting groups, allowing for regiospecific conjugation to other moieties.

We report here preliminary attempts at the elaboration of polyamines on a solid support. To extend the polyamine chain we have carried out reductive amination of a tri-amine, tethered to a solid support with an azidoketone, followed by reduction of the azido group (Benalil 1991) using triphenylphosphine and water to generate a new amine. The dansyl group (Chao et al 1997; Seiler et al 1998) and the acridine group (Blagbrough et al 1998) were then coupled with the terminal amine to give, after resin cleavage, novel polyamine conjugates.

Correspondence: P. Uriac, Pharmacochimie des Molécules de Synthèse et des Produits Naturels, Faculté de Pharmacie, 2 Avenue du Professeur Léon Bernard, 35043 Rennes Cedex, France.

Materials and Methods

IR spectra were recorded on a 16 PC FTIR Perkin-Elmer Spectrometer. Solids were examined with a diffuse reflectance accessory. ^{1}H NMR spectra were recorded on a Bruker DMX spectrometer at 500 MHz. Chemical shifts were expressed in ppm downfield from tetramethylsilane.

*Preparation of polymer **3***

A solution of the monoprotected triamine **2** (1·90 g, 8·1 mmol) in anhydrous CH_2Cl_2 (5 mL) was added dropwise to a suspension of the polymer **1** (2·5 g, 1·62 mmol) in anhydrous dichloromethane (CH_2Cl_2, 8 mL). After agitation for 18 h at room temperature, the suspension was washed successively with CH_2Cl_2 (2 × 10 mL), THF (2 × 10 mL), water–THF (1 : 1, 10 mL), water (2 × 10 mL), THF (2 × 10 mL), Et_2O (2 × 10 mL) (general washing procedure) and then dried under reduced pressure.

IR: *v* NH 3400 cm^{-1}, *v* CO 1685 cm^{-1}; ^{13}C NMR (gel phase in $CDCl_3$): 3 × CH_3 (28·40), C-2, C-6 (31·6, 32·40), C-1 (39·35), C-7 (40·45), C-3, C-5 (43·90), $C(CH_3)_3$ (79·75), CO (155·85).

*Preparation of polymer **4***

A solution of 4-methylmorpholine (0·70 g, 0·65 mmol) in CH_2Cl_2 (1 mL) and a solution of dansyl chloride (0·17 g, 0·65 mmol) in CH_2Cl_2 (2 mL) were added successively to a suspension of polymer **3** (0·5 g, 0·32 mmol). The suspension was stirred for 18 h and washed according to the general procedure. The polymer was reacted and washed a second time under the same conditions to ensure the reaction went to completion.

IR: *v* NH 3350 cm^{-1}, *v* CO 1685 cm^{-1}.

*Cleavage of compound **5***

Polymer **4** (0·5 g, 0·32 mmol) was stirred in a mixture of TFA–CH_2Cl_2 1 : 1 (1 mL) for 2 h at room temperature. The polymer was removed by filtration. The filtrate was concentrated to dryness under reduced pressure, dissolved in a minimal amount of water (2 mL), basified with 10% aqueous NaOH and then extracted with CH_2Cl_2 (3 × 20 mL). The organic layer was dried over K_2CO_3 and the solvent removed under reduced pressure. The crude residue was dissolved in EtOH (2 mL) and a 1·5 M ethanolic solution of hydrochloric acid (1·2 equiv.) was added at 0°C. After 30 min of stirring, the EtOH was evaporated and the residue was triturated with Et_2O to yield **5** as a solid (0·05 g, 33%). ^{1}H NMR (D_2O) H-3 (m: 1·85, 2H), H-7 (m: 2·10, 2H), H-2, 4, 6, 8 (m: 3·10, 8H), 2 × CH_3 (s: 3·45, 6H), Ar-H (m: 7·90, 2H), Ar-H (d: 8·05, 1H), Ar-H (d: 8·35, 1H), Ar-H (d: 8·50, 1H), Ar-H (d: 8·75, 1H).

*Preparation of polymer **6***

Acridine-9-carboxylic acid hydrate (1·1 g, 5·6 mmol) was suspended in anhydrous DMF (20 mL) then DCC (1·43 g, 6·86 mmol) in anhydrous DMF (5 mL) and HOBt (0·68 g, 5·03 mmol) in anhydrous DMF (5 mL) were added to the suspension. The reaction was stirred for 18 h at 60°C and then cooled and filtered. The filtrate was mixed with 0·4 g (0·26 mmol) polymer **3** in DMF (3·5 mL) and then the reactor was flushed with N_2, sealed and agitated for 16 h. The resin was washed with anhydrous DMF (5 × 5 mL) and the procedure was repeated with the same quantity of reagent, agitating for 3 h. The resin was washed according to the general procedure and dried under reduced pressure.

IR: *v* NH 3310 cm^{-1}, *v* CO 1870 cm^{-1}, 1800 cm^{-1}

*Cleavage of compound **7***

Polymer **6** (0·9 g, 0·58 mmol) was treated with a mixture of TFA–CH_2Cl_2 (1 : 1, 2 mL) for 1 h at 0°C. The residue was concentrated under reduced pressure, purified by flash column chromatography on silica gel eluting with CH_2Cl_2–CH_3OH–concentrated aqueous NH_3 (8 : 5 : 1) and converted into the hydrochloride salt as described for compound **5** to yield the product as a pale yellow glass (0·08 g, 40%).

^{1}H NMR (D_2O) $-CH_2-$ (m: 2·18, 2H), $-CH_2-$ (m: 2·27, 2H), $-CH_2N-$ (m: 3·15, 3·27, 3·31, 6H), CH_2NCO- (m: 3·80, 2H), Ar-H (t: 7·82, 2H, J = 7), Ar-H (t: 8·09, 2H, J = 7), Ar-H (d: 8·14, 2H, J = 8), Ar-H (d: 8·26, 2H, J = 8).

*Preparation of 5-azidopentan-2-one **8***

To a solution of 5-chloropentan-2-one (6 g, 50 mmol) in methyl sulphoxide (DMSO, 100 mL) in the presence of a catalytic amount of sodium iodide (0·25 g), sodium azide (4·85 g, 75 mmol) was added. The suspension was stirred at 50°C for 18 h and the mixture was then diluted with water (150 mL) and extracted with Et_2O (4 × 50 mL). The combined organic layers were washed with brine (2 × 50 mL), dried over magnesium sulphate and evaporated to dryness at 30°C under reduced pressure to yield **8** as a pale yellow oil (5·60 g, 90%).

IR: *v* N_3 2090 cm^{-1}, *v* CO 1710 cm^{-1}; ^{1}H NMR ($CDCl_3$): H-4 (m: 1·85, 2H), H-1 (s: 2·15, 2H), H-3 (t: 2·55, 2H), H-5 (t: 3·30, 2H).

*Preparation of polymer **9***

Method a. Polymer **3** (1 g, 0·65 mmol) was suspended in trimethyl orthoformate (10 mL) for

30 min under nitrogen flush. 5-Azidopentan-2-one **8** (1·15 g, 13 mmol), was added. The suspension was agitated for 18 h at room temperature under nitrogen atmosphere then washed successively with THF (2 × 20 mL), EtOH (5 × 20 mL), CH_2Cl_2 (2 × 20 mL), Et_2O (2 × 20 mL) and then dried under reduced pressure. A second procedure was carried out under the same conditions and the polymer obtained was suspended in trimethyl orthoformate (10 mL), stirred for 48 h at room temperature in the presence of sodium cyanoborohydride (0·80 g, 13 mmol), washed successively with EtOH (2 × 20 mL), a mixture of water and EtOH (20 mL), water (3 × 20 mL), EtOH (3 × 20 mL), CH_2Cl_2 (2 × 20 mL), Et_2O (2 × 20 mL) and dried under reduced pressure.

Method b. Polymer **3** (2 g, 1·30 mmol) was suspended in a mixture of dimethylformamide (DMF) and EtOH (3 : 1, 10 mL). The azidoketone **8** (1·15 g, 13 mmol) and borane–pyridine complex (13 mmol) were added successively to the polymer under argon atmosphere. The polymer was stirred at room temperature for 48 h and washed according to the general procedure.

IR: ν NH 3350 cm^{-1}, ν N_3 2095 cm^{-1}, ν CO 1685 cm^{-1}.

*Cleavage of compound **10***

Polymer **9** (0·1 g, 0·065 mmol) was treated with a mixture of TFA–CH_2Cl_2 (1 : 1, 0·5 mL) for 2 h at room temperature. The residue was concentrated under reduced pressure to yield a pale solid.

^{1}H NMR (D_2O): CH_3 (d: 1·35, 3H), H-2, 3, 7, 11 (m: 3·10, 8H), H-4, 6, 8, 10, 12 (m: 3·20, 9H), H-1 (m: 3·30, 2H).

*Preparation of polymer **11***

Polymer **9** (1 g, 0·65 mmol, prepared according to Method b) was treated with 4-methylmorpholine (1·4 g, 1·30 mmol) and dansyl chloride (0·35 g, 1·30 mmol) under the conditions described for the polymer **4**.

IR: ν NH 3330 cm^{-1}, ν N_3 2090 cm^{-1}, ν CO 1680 cm^{-1}.

*Cleavage of compound **12***

Polymer **11** (0·1 g, 0·065 mmol) was treated with a mixture of TFA–CH_2Cl_2 (1 : 1, 0·5 mL) under the conditions described for the compound **10**, to yield a white solid.

^{1}H NMR (D_2O): CH_3 (d: 1·35, 3H), H-2, 3, 7, 11 (m: 2·10, 8H), H-4, 6, 8, 10, 12 (m: 3·20, 9H), H-1 (m: 3·30, 2H), 2 × CH_3 (s, 3·40, 6H), Ar-H (m: 7·85, 2H), Ar-H (m: 7·95, 1H), Ar-H (m:8·45, 2H), Ar-H (m: 8·65, 1H).

*Preparation of polymer **13***

Polymer **11** (0·9 g, 0·58 mmol) was suspended in THF (5 mL) in the presence of water (0·1 mL) and triphenylphosphine (0·30 g, 1·16 mmol) and stirred for 18 h at room temperature. The polymer was washed according to the general procedure and treated again under the same conditions.

IR: ν NH 3340 cm^{-1}, ν CO 1700 cm^{-1}.

*Preparation of polymer **14***

Polymer **13** (0·9 g, 0·58 mmol) was treated with 4-methylmorpholine (1·20 g, 1·16 mmol) and dansyl chloride (0·31 g, 1·16 mmol) under the conditions described for the polymer **4**.

IR: ν NH 3340 cm^{-1}, ν CO 1685 cm^{-1}.

*Cleavage of compound **15***

Polymer **14** (0·8 g, 0·52 mmol) was treated with a mixture of TFA–CH_2Cl_2 (1 : 1, 2 mL) under the conditions described for the compound **5** to yield a white solid. (0·15 g, 35%).

^{1}H NMR (D_2O): CH_3 (d: 1·15, 3H), H-2, 3, 7, 11 (m: 2·10, 8H), H-1,4, 6, 8, 10, 12 (m: 3·10, 11H), 2 × CH_3 (s: 3·35, 6H), 2 × CH_3 (s: 3·45, 6H), Ar-H (m: 7·85, 4H), Ar-H (m: 7·95, 1H), Ar-H (m: 8·15, 1H), Ar-H (m: 8·30, 1H), Ar-H (m: 8·45, 1H), Ar-H (m: 8·50, 2H), Ar-H (m: 8·55, 1H), Ar-H (m: 8·70, 1H).

*Preparation of polymer **16***

Polymer **9** (1 g, 0·65 mmol) was suspended in CH_2Cl_2 (8 mL) and a solution of di-*tert*-butyl dicarbonate (0·70 g, 3·25 mmol) in CH_2Cl_2 was added. The suspension was stirred at room temperature for 18 h, washed and treated again under the same conditions to drive the reaction to completion.

IR: ν NH 3330 cm^{-1}, ν N_3 2090 cm^{-1}, ν CO 1690 cm^{-1}.

*Preparation of polymer **17***

Polymer **16** (0·9 g, 0·58 mmol) was treated with water (0·1 mL) and triphenylphosphine (0·30 g, 1·16 mmol) under the conditions described for the preparation of **13**.

IR: ν NH 3400 cm^{-1}, ν CO 1690 cm^{-1}.

*Preparation of polymer **18***

Polymer **17** (0·9 g, 0·58 mmol) was treated with 4-methylmorpholine (1·20 g, 1·16 mmol) and dansyl chloride (0·31 g, 1·16 mmol) under the conditions described for the polymer **4**.

IR: ν NH 3400 cm^{-1}, ν CO 1690 cm^{-1}.

*Cleavage of compound **19***

Polymer **18** (0·8 g, 0·52 mmol) was treated with a mixture of TFA–CH_2Cl_2 (1 : 1, 2 mL) under the

conditions described for compound **5** to yield a white solid. (0·02 g, 10%).

^{1}H NMR (D_2O): CH_3 (d: 1·15, 3H), H-2, 3, 7, 11 (m: 2·10, 8H), H-1, 4, 6, 8, 10, 12 (m: 3·20, 11H), 2 × CH_3 (s: 3·45, 6H), Ar-H (m: 7·85, 2H), Ar-H (d: 8·05, 1H), Ar-H (d: 8·35, 1H), Ar-H (d: 8·45, 1H), Ar-H (d: 8·80, 1H).

*Preparation of polymer **20***

Polymer **17** (0·9 g, 0·58 mmol) was mixed with the solution of HOBt-activated acridine (1·3 mmol) in DMF (7 mL) under the conditions described for polymer **6**.

IR: *v* NH 3310 cm^{-1}, *v* CO 1870 cm^{-1}, 1800 cm^{-1}.

*Cleavage of compound **21***

Polymer **20** (0·9 g, 0·58 mmol) was treated with a mixture of TFA–CH_2Cl_2 (1 : 1, 2 mL) for 1 h at 0°C. The residue was concentrated under reduced pressure, purified by flash column chromatography on silica gel eluting with CH_2Cl_2–CH_3OH–concentrated aqueous NH_3 (8 : 5 : 1) and converted to the hydrochloride salt as described for compound **5**, to yield the product as a pale yellow glass (0·009 g).

^{1}H NMR (D_2O) CH_3 (s, 1·42, 3H) $-CH_2-$ (m: 2·15–2·21, 8H), $-CH_2N-$ (m: 3·04–3·32, 8H), $CHCH_3$ (m: 3·42–3·53, 1H), CH_2NHCO- (t: 379, 2H), Ar-H (t: 7·98, 2H, J = 7), Ar-H (m: 8·31, 4H), Ar-H (d: 8·48, 2H, J = 8).

Results and Discussion

The starting compounds, 5-(*tert*-butoxycarbonyl)-1,5,9-triazanonane **2** (O'Sullivan & Dalrymple 1995; Blagbrough & Geall 1998) and 5-azidopentan-2-one **8** (Benalil 1991) were readily prepared in sufficient quantities. The solid support used in this work was Wang resin linked to monoprotected triamine **2** through a carbamate anchor (Dixit & Leznoff 1977, 1978) for the synthesis of unsymmetrical diamines. The Wang resin was activated with 4-nitrophenylchloroformate then the carbonate **1** was reacted with protected triamine **2** according to a previously reported procedure (Tomasi et al 1998) (Figure 1). This reaction was found to be almost quantitative using gel phase ^{13}C NMR. Carbon signals corresponding to the Boc group, methylene groups and carbonyl groups in **3** were apparent, and there was no sign of a carbonyl resonance corresponding to a carbonate. Carbamate formation was also assessed by the *v* CO vibration appearing at approximately 1685 cm^{-1}. After this step, two small portions of the polymer were conjugated to chromophores. Dansylation was performed using dansyl chloride in the presence of 4-methylmorpholine leading to 1-dansyl-1,5,9-triazanonane **5** in a 33% yield after cleavage by TFA–CH_2Cl_2. A second fraction of **3** was reacted with the activated amide formed between acridine-9-carboxylic acid and *N*-hydroxybenzotriazole and was then cleaved and treated with ethanolic HCl to yield **7** (40%).

In order to chain extend the resin bound polyamine two methods of reductive amination were investigated. The most frequently used method uses the reducing agent $NaBH_3CN$ in trimethyl orthoformate (Look et al 1995) and, in an alternative method, reduction is performed using a borane–pyridine complex in THF under argon (Khan et al 1996, Bilodeau & Cunningham 1998). In our study, the best results for condensation of **8** to **3** were obtained with the borane–pyridine complex. The formation of **9** was monitored through the appearance of the *v* N_3 vibration clearly located at approximately 2090 cm^{-1}. A small scale cleavage (100 mg resin) was performed giving compound **10**, which was clearly characterized by ^{1}H NMR and mass spectroscopy.

The polymer-supported polyamine precursor **9** has two functional groups, a secondary amine and an azido group acting as a masked primary amine. Thus, two strategies for functionalizing this polyamine were proposed. In the first (Figure 2), dansylation of the secondary amine was carried out with dansyl chloride then a small scale cleavage was performed producing compound **12**. The azido group was reduced to a primary amine using triphenylphosphine and water. Complete transformation of **11** into **13** was monitored by the disappearance of the N_3 vibration at approximately 2090 cm^{-1} in the IR spectrum.

The primary amine was also dansylated leading to **14** which was subjected to cleavage by TFA–CH_2Cl_2. The bis-dansylated compound **15** was obtained in a 35% yield after conversion to the hydrochloride.

In the second strategy (Figure 3), the azido group was transformed to a primary amine using triphenylphosphine and water as previously described after Boc-protection of the secondary amine **16**. The polymer-bound polyamine **17** was divided into two portions. Dansylation and cleavage under the conditions described for the compound **15** produced **19** in 10% yield. The second portion of the polymer **17** was treated with HOBt-activated acridine and was cleaved as described for the preparation of **7**. The acridine derivative **21** was thus isolated in a low yield (5%).

In these preliminary studies, we have shown that the synthesis of an aminoazide by condensation of

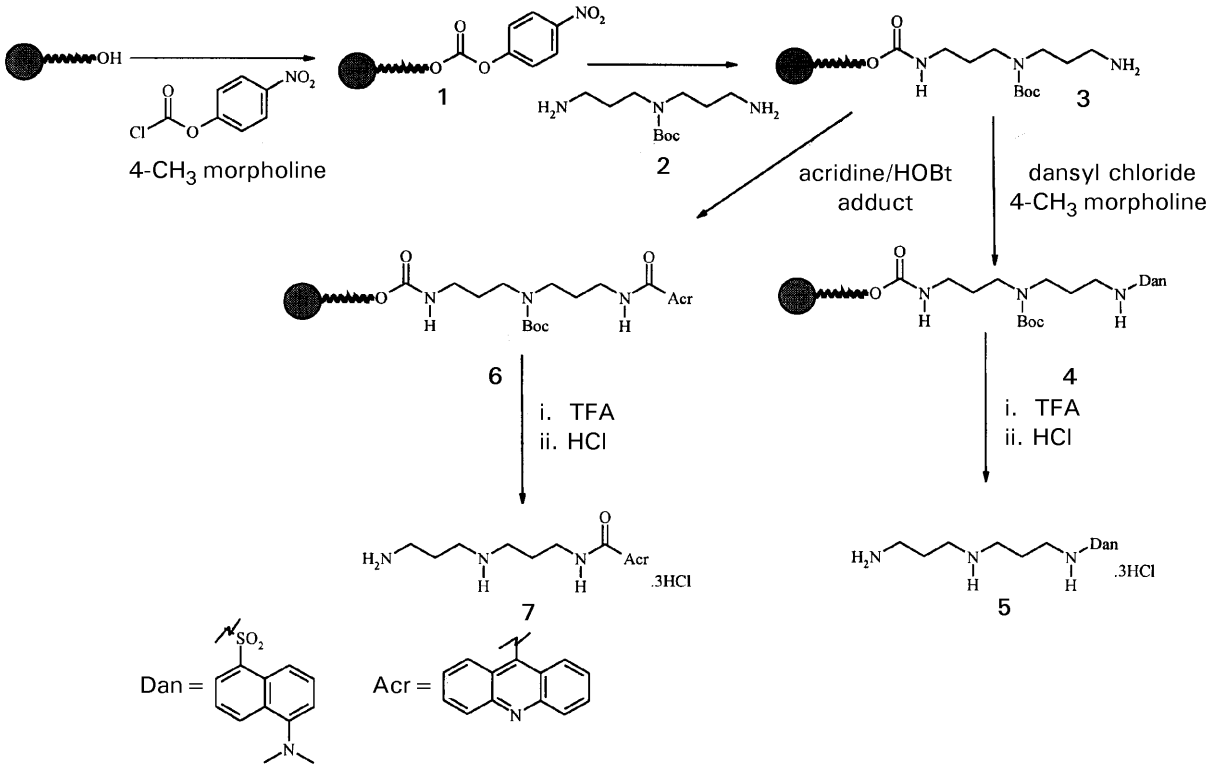

Figure 1. Loading the resin with protected triamine and acylation.

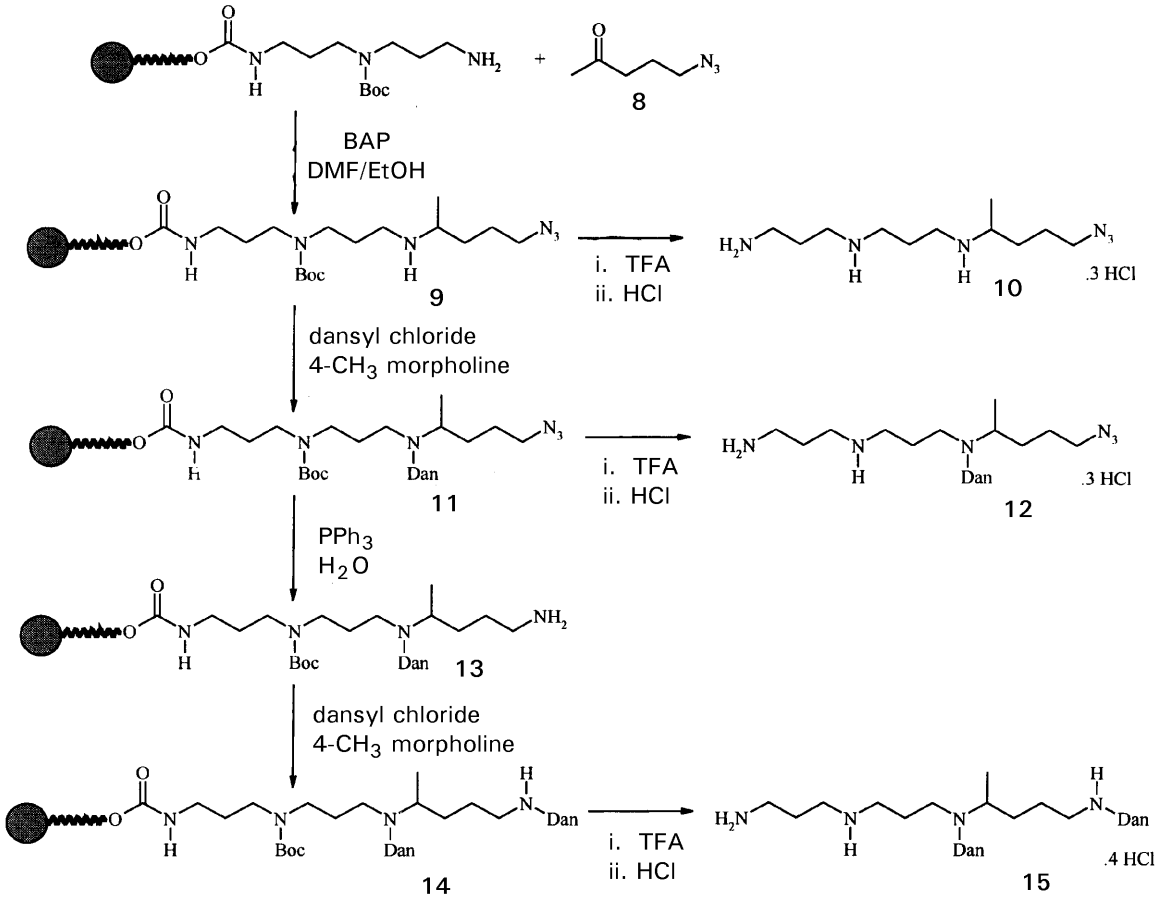

Figure 2. Reductive amination, azide reduction and acylation.

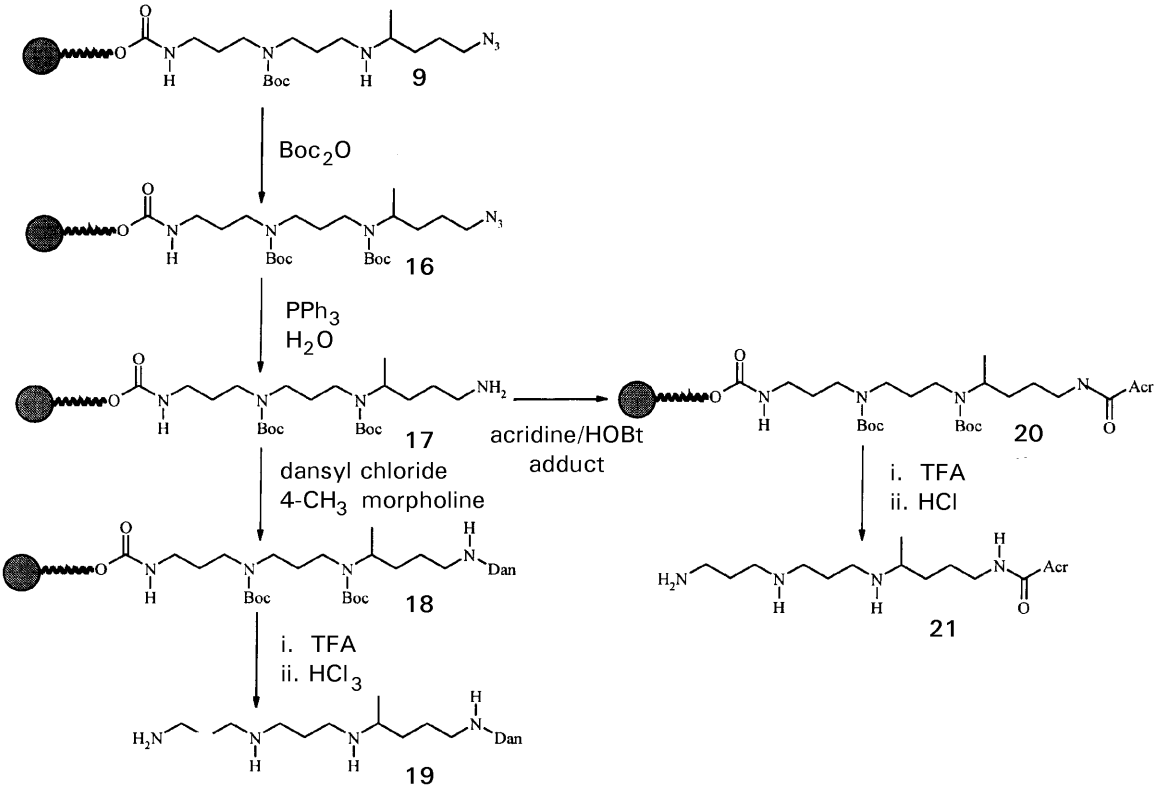

Figure 3. Boc protection, azide reduction and acylation.

an azidocarbonyl compound to a resin-bound polyamine is useful for the preparation of unnatural polyamines and polyamine conjugates. A first source of diversity originates from the anchored polyamine which can be either a diamine, a monoprotected triamine or a diprotected tetramine. The azidocarbonyl allows us to introduce further diversity and the potential to build libraries of polyamines with variable (controlled, unsymmetrical) methylene spacings.

It is also possible to make selected nitrogen functionalities react without a convoluted protection–deprotection sequence. As a consequence, we can attach pharmacologically interesting moieties which form a third source of diversity. These results must be compared with those obtained by traditional synthetic methods. Equivalent solution phase synthesis would have required the careful introduction of protecting groups regiospecifically to the polyamine and potentially difficult chromatographic separation of the desired product after each step. Yields are often less than quantitative due to reactions at amines other than the desired one. In this solid-phase study, low yielding reductive aminations or acylations have led to low recovery of products. Nevertheless, improvement of the overall yield (particularly for solid-phase reductive amination) is in progress. Once conditions have been optimized there will exist the potential for the rapid synthesis of unnatural polyamines and polyamine amides for biological evaluation.

Acknowledgements

We are grateful to the GP2A, the ARC (Association pour la Recherche sur le Cancer) and to the Ligue Nationale contre le Cancer (Comités d'Ille-et-Vilaine et des Côtes d'Armor) for financial support and to J. -C. Corbel, M. Le Roch and A. J. Geall for their input into this work.

References

Benalil, A. (1991) Synthese d'aminoazides. Etude de leur réactivité. Application à la synthèse de polyamines et d'hétérocycles. PhD Thesis, l'Université de Rennes.

Bilodeau, M. T., Cunningham, A. M. (1998) Solid-supported synthesis of imidazoles: a strategy for direct resin-attachment to the imidazole core. J. Org. Chem. 63: 2800–2801

Blagbrough, I. S., Geall, A. G. (1998) Practical synthesis of unsymmetrical polyamine amides. Tetrahedron Lett. 39: 439–442

Blagbrough, I. S., Carrington, S., Geall, A. J. (1997) Polyamines and polyamine amides as potent selective receptor probes, novel therapeutic lead compounds and synthetic vectors in gene therapy. Pharm. Sci. 3: 223–233

Blagbrough, I. S., Taylor, S., Carpenter, M. L., Novoselskiy, V., Shamma, T., Haworth, I. S. (1998) Asymetric intercalation of N^1-(acridin-9-ylcarbonyl)spermine at homopurine sites of duplex DNA. Chem. Comm. 929–930

Byk, G., Fredceric, M., Scherman, D. (1997) One pot synthesis of unsymmetrically functionalised polyamines by a solid phase strategy starting from their symmetrical polyamine-counterparts. Tetrahedron Lett. 38: 3219–3222

Chao, J., Seiler, N., Renault, J., Kashiwagi, K., Masuko, T., Higarashi, K., Williams, K. (1997) N^1-Dansylspermine and N^1-(*n*-octanesulfonyl)-spermine, novel glutamate receptors antagonists: block and permeation of *N*-methyl- *D*-aspartate receptors. Mol. Pharmacol. 51: 861–871

Dixit, D. M., Leznoff, C. C. (1977) Insoluble polymer supports as monoblocking agents of symmetrical diamines. Chem. Comm. 798–799

Dixit, D. M., Leznoff, C. C. (1978) The synthesis of unsymetrical diamides and monoamide monotosylamides from symetrical diamines. Isr. J. Chem. 17: 248–252

Hiroshige M., Hauske, J. R., Zhou, P. (1995) Palladium-mediated macrocyclisations on solid support and its applications to combinatorial synthesis. J. Am. Chem. Soc. 117: 11590–11591

Kellam, B., Bycroft, B. W., Chhabra, S. R. (1997) Solid phase applications of Dde and the analogue Nde: synthesis of trypanothione disulphide. Tetrahedron Lett. 38: 4849–4852

Khan, N. M., Vijayalakshmi, A., Balasubramanian, S. (1996) Solid phase reductive alkylation of secondary amines. Tetrahedron Lett. 37: 4819–4822

Look, G. C., Murphy, M. M., Campbell, D. A., Gallop, M. A. (1995) Trimethylorthoformate: a mild effective dehydrating reagent for solution and solid phase imine formation. Tetrahedron Lett. 36: 2937–2940

Marsh, I., Smith, H., Bradley, M. (1996) Solid phase polyamine linkers – their utility in synthesis and the preparation of directed libraries against trypanothione reductase. Chem. Comm. 941–942

Marton, L. J., Pegg, A. E. (1995) Polyamines as targets for therapeutic intervention. Annu. Rev. Toxicol. 35: 55–91

Nash, I. A., Bycroft, B. W., Chan, W. C. (1996) Dde-A selective primary amine protecting group: a facile solid phase synthetic approach to polyamine conjugates. Tetrahedron Lett. 37: 2625–2628

O'Sullivan, M. C., Dalrymple, D. M. (1995) A one-step procedure for the selective trifluoroacetylation of primary amino groups of polyamines. Tetrahedron Lett. 36: 3451–3452

Page, P., Burrage, S., Baldock, L., Bradley, M. (1998) The synthesis of symmetrical spermine conjugates using solid-phase chemistry. Bioorg. Med. Chem. Lett. 8: 1751–1756

Seiler, N., Douaud, F., Renault, J., Delcros, J. G., Havouis, R., Uriac P., Moulinoux, J. P. (1998) Polyamine sulfonamides with NMDA antagonist properties are potent calmodulin antagonists and cytotoxic agents. Int. J. Biochem. Cell. Biol. 30: 393–406

Tabor, H., Tabor, C. W. (1964) Spermidine, spermine and related amines. Pharmacol. Rev. 16: 245–300

Tabor, C. W., Tabor, H. (1984) Polyamines. Ann. Rev. Biochem. 53: 749–790

Tomasi, S., Le Roch, M., Renault, J., Corbel, J. C., Uriac, P., Carboni, B., Moncoq, D., Martin, B., Delcros, J. G. (1998) Solid phase organic synthesis of polyamine derivatives and initial biological evaluation of their antitumoral activity. Bioorg. Med. Chem. Lett. 8: 635–640

Tye, C. K., Kasinathan, G., Barrett, M. P., Brun, R., Doyle, V. E., Fairlamb, A. H., Weaver, R., Gilbert, I. H. (1998) An approach to use an unusual adenosine transporter to selectively deliver polyamine analogues to trypanosomes. Bioorg. Med. Chem. Lett. 8: 811–816