Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron Letters
Tetrahedron Letters 48 (2007) 4719–4722

Design and synthesis of triazole-based peptide dendrimers

V. Haridas,* Kashmiri Lal and Yogesh K. Sharma

Department of Chemistry, Indian Institute of Technology, New Delhi 110 016, India

Received 14 March 2007; revised 25 April 2007; accepted 2 May 2007
Available online 10 May 2007

Abstract—A series of novel designer dendrimers (**8**, **9**, **11**, **13** and **16**) was synthesized by employing click chemistry. The dendritic structures reported here include symmetrical, unsymmetrical and cationic dendrimers with a variety of cores such as triazole, cystine and Lys-Asp dipeptide.
© 2007 Elsevier Ltd. All rights reserved.

Dendrimers are structurally well-defined large molecules with tree-like architecture having low polydispersity values. These macromolecules find use as gene and drug delivery vehicles,[1] in tissue engineering,[2] photodynamic therapy[3] and in synthetic vaccines development.[4] Dendrimers with a large number of functional groups at the surface can be functionalized with suitable binding entities towards a particular biological receptor. This will lead to a synergistic increase in binding affinity through multivalent interactions called cluster effect.[5] Amphiphilic dendrimers are another class of dendrimers finding applications in diverse areas, for example, as unimolecular micelles[6] and as slow drug delivery agents.[7] The synthesis of large dendrimers is still a challenge[8] which we address here by generating various dendritic structures via an elegant synthetic protocol.

Dendrimers (**8**, **9**, **11**, **13** and **16**) were synthesized by employing a Huisgen 1,3-dipolar cycloaddition reaction commonly called a click reaction.[9] Click reactions have been used extensively in chemical biology,[10] polymer chemistry[11] and in dendrimer syntheses.[12]

In order to make a dual surface dendrimer, we set out to synthesize an aspartic-based dendron with an azido group at the N-terminal and a lysine-based dendron with an alkyne at the C-terminal. Aspartic-based dendron **4** was synthesized from Nα protected aspartic acid **1** and Cα-protected Asp·diOMe. The N-terminal benzyloxycarbonyl group (*Z*) of **2** was deprotected using H_2 and 10% Pd/C and coupled to azidoacetyl chloride[13] to generate dendron **4** ready to couple with the alkyne counterpart (Scheme 1).

A lysine-based dendron terminated with an alkyne moiety $(Lys)_2$Lys-alkyne **7** was synthesized from BocLys(Boc)-OH **5**. The alkyne unit was incorporated as the C-terminal part of BocLys(Boc) by coupling with propargylamine using *N*-hydroxysuccinimide/DCC. Compound **6** thus obtained was deprotected with TFA and then reacted with Boc-Lys(Boc)-OH to produce dendron **7** in 78% yield (Scheme 2).

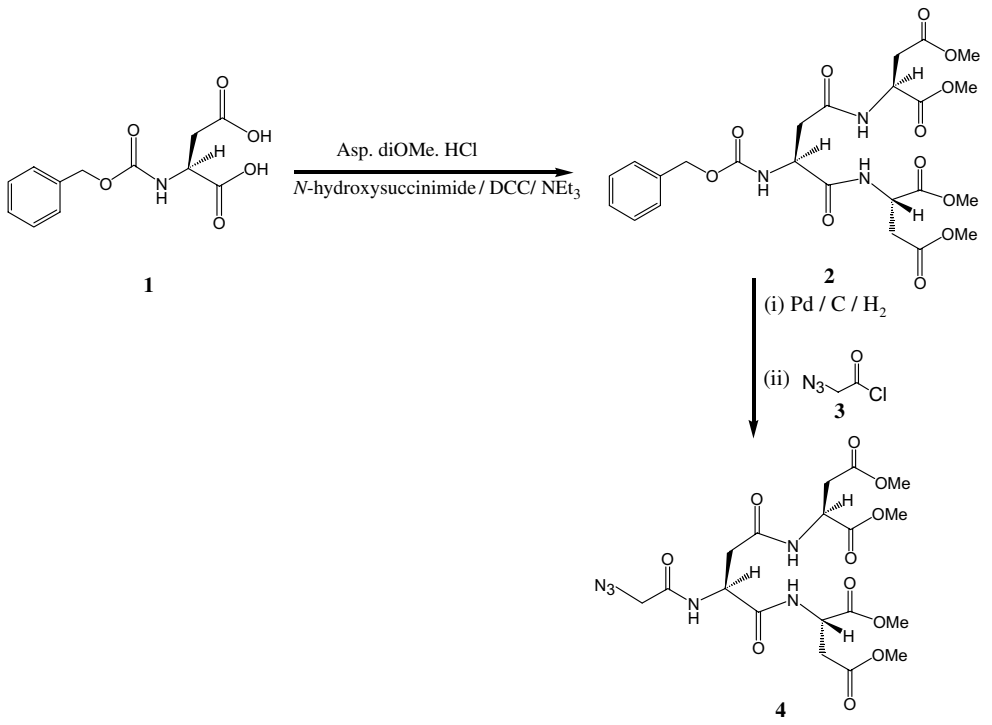
Reaction of **4** and **7** in a Cu(I)-catalyzed 1,3-dipolar cycloaddition reaction gave only 1,4-substituted triazole-based dendrimer **8** in ~68% yield with four Boc protected amines and four carbomethoxy units. The Boc groups were deprotected to generate cationic dendrimer **9** in quantitative yield (Scheme 2).[14]

This methodology was extended to synthesize homomeric dendrimers on a cystine core. The cystine-based cores **10** and **12** were synthesized from N^{α}-Boc protected cystine and cystine dimethyl ester by coupling propargylamine and azidoacetyl chloride, respectively. The azide terminated dendron **4** was coupled to alkyne-terminated cystine **10** to generate homoaspartic acid dendrimer **11** in 65% yield (Scheme 3). Similarly, lysine-based dendron **7** was coupled with **12** to give dendrimer **13**. These compounds gave satisfactory ^{1}H NMR and ESI-MS spectra.

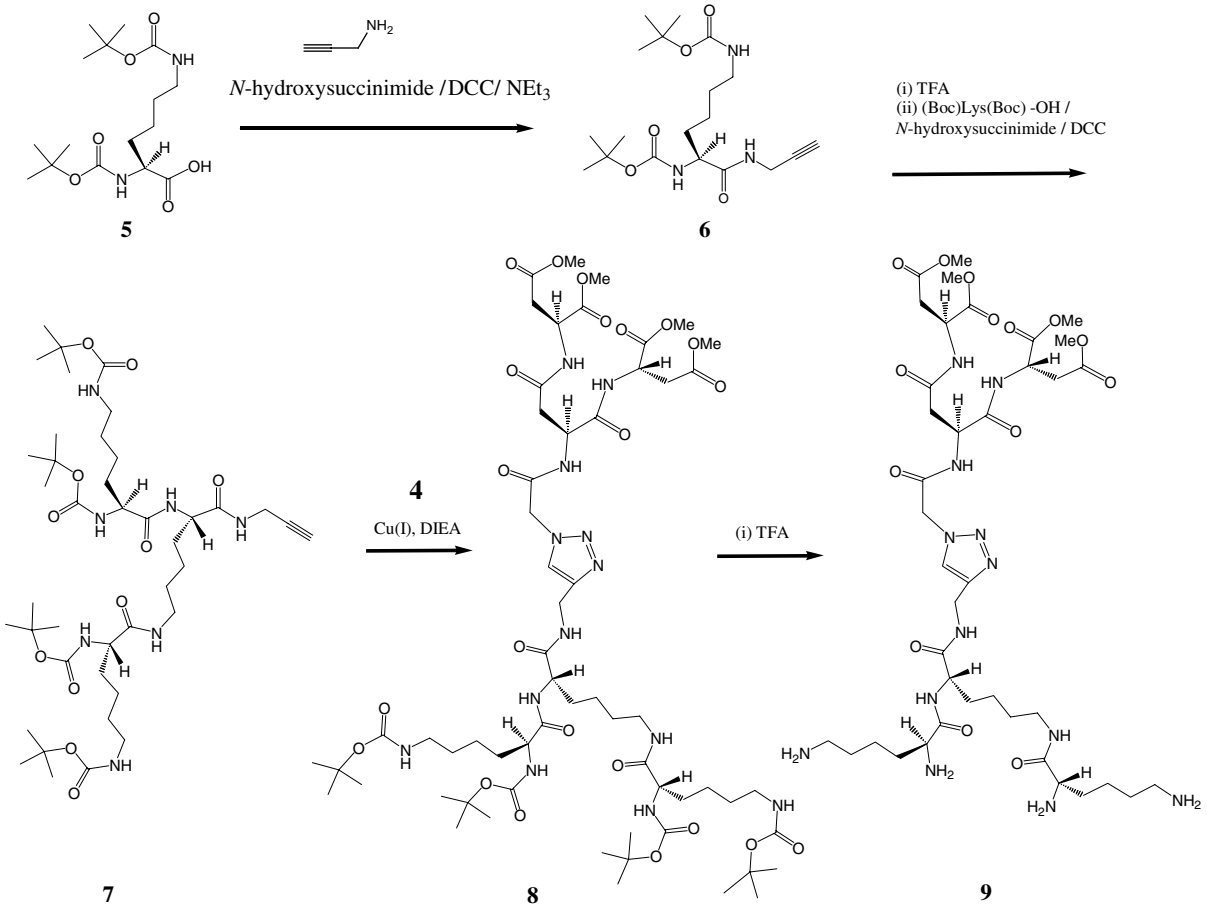
As an extension, and to prove the versatility of this strategy, we used a Lys-Asp as the central core unit. Asp-$(Asp)_2$ dendron **4** was attached by click chemistry to Lys-Asp scaffold **15** to give compound **16** in 70% yield

* Corresponding author. Tel.: +91 011 26591380; e-mail: haridasv@chemistry.iitd.ernet.in

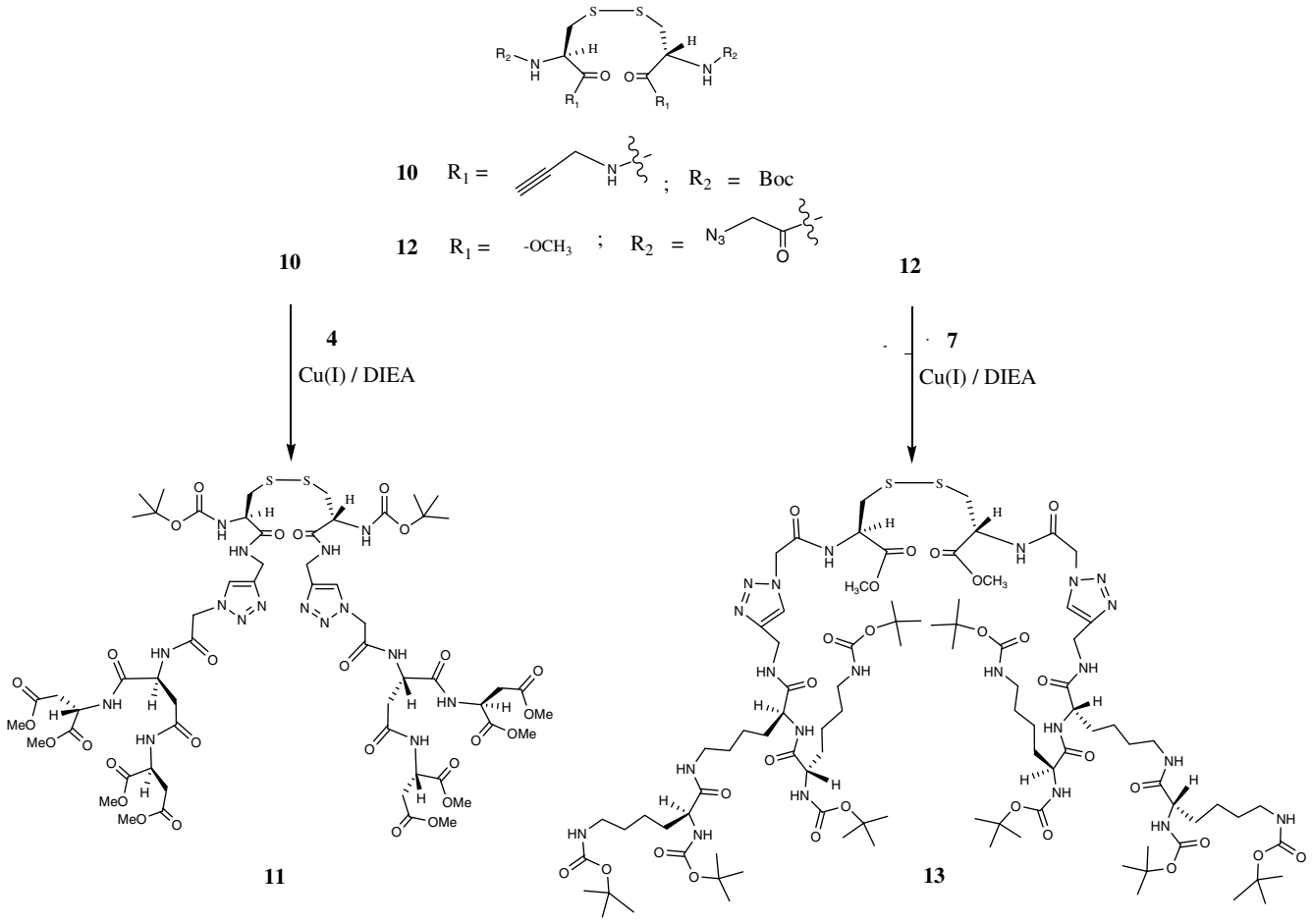
0040-4039/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2007.05.023



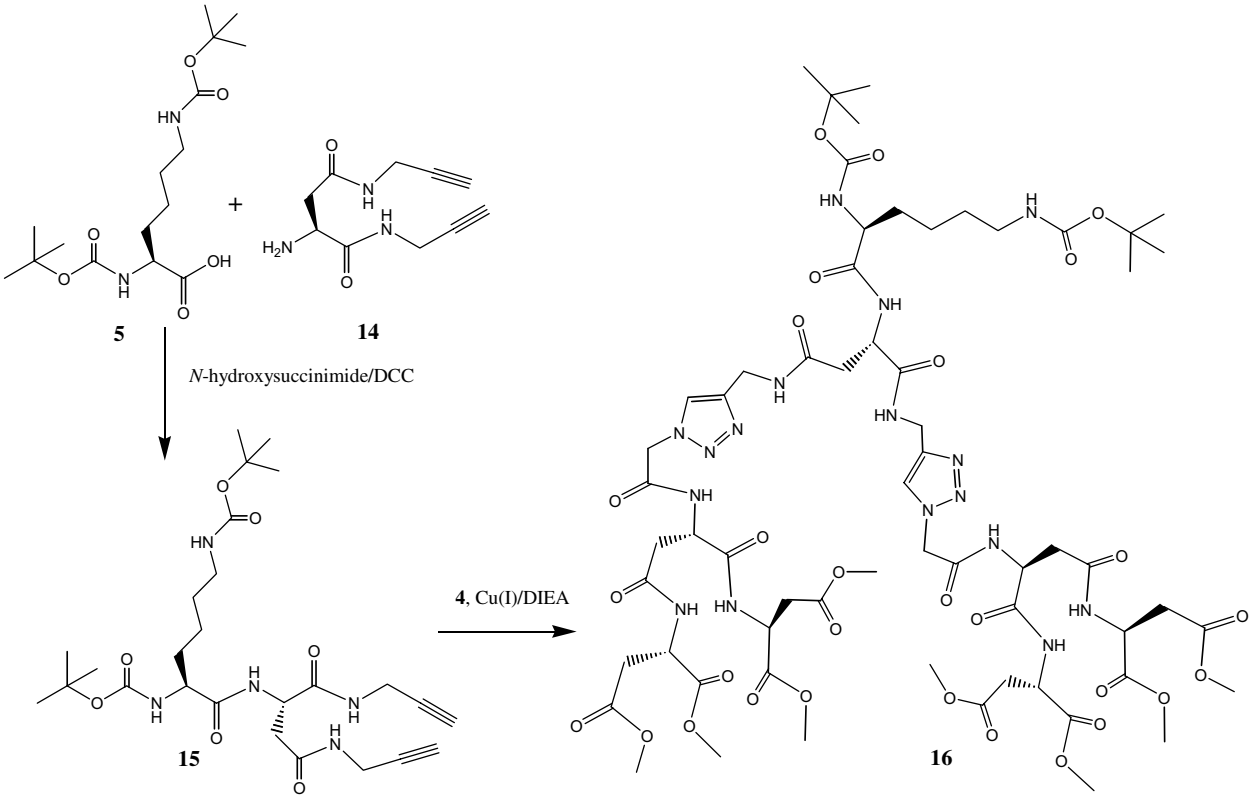
Scheme 1.



Scheme 2.



Scheme 3.



Scheme 4.

(Scheme 4). The unused Lys Nα and Nε amino handle will allow other dendrons to be attached. Moreover, these Nα and Nε amino groups could, in principle also be reacted with molecules of biological significance.

Triazole unit has already been illustrated as an amide bond surrogate in the peptide design.[15] The large dipole of triazole and the presence of two nitrogens as hydrogen bond acceptors, makes the triazole an excellent peptide bond surrogate.[16] Triazole unit may impart rigidity, lipophilicity, enhanced absorption and protease stability. Thus the incorporation of the triazole unit in the dendrimer structure is an added advantage.

In conclusion, we have demonstrated a simple and elegant method to synthesize peptide-dendrimers based on click chemistry. This synthesis will enable us to generate various peptide or hybrid dendrimers which may find applications in drug delivery, gene therapy, tissue engineering etc. Further work on the functional properties of these novel dendrimers is in progress and will be reported in due course.

Acknowledgements

Financial assistance from CSIR and DST, New Delhi, is gratefully acknowledged.

References and notes

1. Kano, K.; Liu, M.; Frechet, J. M. *Bioconjugate Chem.* **1999**, *10*, 1115–1121.
2. Grinstaff, M. W. *Chem. Eur. J.* **2002**, *8*, 2838–2846.
3. Morosini, V.; Frochot, C.; Barberi-Heyob, M.; Schneider, R. *Tetrahedron Lett.* **2006**, *47*, 8745–8749.
4. Tam, J. P. *Proc. Natl. Acad. Sci. U.S.A.* **1988**, *85*, 5409–5413.
5. Mammen, M.; Cho, S.-K.; Whitesides, G. M. *Angew. Chem., Int. Ed.* **1998**, *37*, 2754–2794.
6. Newkome, G. R.; Moorefield, C. N.; Baker, G. R.; Saunders, M. J.; Grossman, S. H. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1178–1180.
7. Boas, U.; Heegaard, P. M. H. *Chem. Soc. Rev.* **2004**, *33*, 43–63; Tomalia, D. A.; Naylor, A. M.; Goddard, W. A., III. *Angew. Chem., Int. Ed. Engl.* **1990**, *29*, 138–175; Frechet, J. M. *Science* **1994**, *263*, 1710–1715.
8. Sadler, K.; Tam, J. P. *Rev. Mol. Biotechnol.* **2002**, *90*, 195–229; Twyman, L. J.; Beezer, A. E.; Mitchell, J. C. *Tetrahedron Lett.* **1994**, *35*, 4423–4424.
9. Rostovtsevi, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596–2599.
10. Lewis, W. G.; Green, L. G.; Grynszpan, F.; Radic, Z.; Carlier, P. R.; Taylor, P.; Fin, M. G.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 1053–1056; Chin, J. W.; Santoro, S. W.; Martin, A. B.; King, D. S.; Wang, L.; Schultz, P. G. *J. Am. Chem. Soc.* **2002**, *124*, 9026–9027.
11. Opsteen, J. A.; Hest, J. C. M. V. *Chem. Commun.* **2005**, 57–59.
12. Wu, P.; Feldman, A. K.; Nugent, A. K.; Hawker, C. J.; Scheel, A.; Voit, B.; Pyun, J.; Frechet, M. J.; Sharpless, K. B.; Fokin, V. V. *Angew. Chem., Int. Ed.* **2004**, *43*, 3928–3932.
13. Taggi, A. E.; Hafez, A. M.; Wack, H.; Young, B.; Ferraris, D.; Lectka, T. *J. Am. Chem. Soc.* **2002**, *124*, 6626–6635.
14. *Selected data*: Preparation of dendron **4**: *Z*-Asp-(Asp·di-OMe)Asp·diOMe **2** (221 mg, 0.4 mmol) was deprotected in 20 ml methanol with 10% Pd/charcoal/H_2 (peptide/catalyst 1:0.5 w/w). The methanol was evaporated; the residue obtained was dissolved in dry dichloromethane. The solution was cooled in an ice-bath and triethylamine (0.056 ml, 0.4 mmol) added, followed by the slow addition of azidoacetyl chloride (48 mg, 0.4 mmol) over a period of 0.5 h, and the mixture stirred at room temperature for 12 h. The solvents were removed in vacuo, and the residue was dissolved in ethyl acetate (~50 ml) and washed, with 2 N H_2SO_4, water and 5% aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4, evaporated and purified by silica gel column chromatography using EtOAc/hexane to give dendron **4**. Yield 72%; mp 135–136 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.60–3.20 (m, 6H), 3.70 (s, 6H), 3.75 (s, 3H), 3.76 (s, 3H), 4.02 (s, 2H), 4.82 (m, 3H), 6.85 (d, 1H, $J = 7.4$ Hz), 7.65 (d, 1H, $J = 7.5$ Hz), 7.87 (d, 1H, $J = 7.0$ Hz); IR (KBr) 3309, 2111, 1741, 1666, 1643, 1535 cm^{-1}; ESI-MS: calcd ($MH^+ = C_{18}H_{27}N_6O_{11}^+$), 503.2 Da; found ($MH^+$), *m*/*z* 503.3.
Preparation of dendrimer **8**: Dendrimer **8** was synthesized by using standard click reaction conditions.[15] Dendron terminated with an alkyne **7** (151 mg, 0.18 mmol) was dissolved in 20 ml dry acetonitrile, cooled in an ice-bath and N_2 bubbled for 15 min. To this solution was added diisopropylethylamine (0.031 ml, 0.18 mmol), cuprous iodide (4 mg, 0.018 mmol) and the mixture stirred for 5 min. Dendron **4** terminated with an azide (90 mg, 0.18 mmol) in 15 ml acetonitrile was then added and the reaction mixture was stirred for 17 h under nitrogen. The reaction mixture was evaporated, dissolved in ethyl acetate and filtered. The residue was washed with 2 N H_2SO_4, water, 9:1 NH_4Cl/NH_4OH solution and finally with water. The solid thus obtained was dried and crystallized from a mixture of chloroform and methanol to give dendrimer **8**. Yield 68%; mp 158–160 °C; ^{1}H NMR (300 MHz, DMSO-d_6) δ 1.36 (s+m, 54H), 2.71–3.20 (m, 12H), 3.60 (s, 12H), 3.81 (br s, 2H), 4.31 (m, 3H), 4.62 (m, 3H), 5.09 (br s, 2H), 6.74 (m, 2H), 6.90 (d, 1H, $J = 7.8$ Hz), 7.74 (br s, 2H), 7.80 (s, 1H), 8.44 (m, 3H), 8.58 (d, 2H, $J = 7.8$ Hz); IR (KBr): 3438, 2932, 1753, 1643, 1533, 1448 cm^{-1}; ESI-MS: calcd ($MH^+ = C_{59}H_{100}N_{13}O_{22}^+$), 1342.7 Da; found ($MH^+$), *m*/*z* 1342.8.
15. van Maarseveen, J. H.; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7*, 4503–4506; Horne, W. S.; Stout, C. D.; Ghadiri, M. R. *J. Am. Chem. Soc.* **2003**, *125*, 9372–9376.
16. Brik, A.; Alexandratos, J.; Lin, Y.-C.; Elder, J. H.; Olson, A. J.; Wlodawer, A.; Goodsell, D. S.; Wong, C.-H. *ChemBioChem* **2005**, *6*, 1167–1169.