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# Construction of triazolyl bidentate glycoligands (TBGs) by grafting of 3-azidocoumarin to epimeric pyranoglycosides via a fluorogenic dual click reaction

Jia-Lu Xue [a], Xiao-Peng He [a,*], Jin-Wei Yang [a], De-Tai Shi [a], Chao-Ying Cheng [a], Juan Xie [b], Guo-Rong Chen [a,*], Kaixian Chen [a,c]

[a] Key Laboratory for Advanced Materials & Institute of Fine Chemicals, East China University of Science and Technology, Shanghai 200237, PR China
[b] PPSM, Institut d'Alembert, ENS Cachan, av du Pt Wilson, F-94235 Cachan, France
[c] State Key Laboratory of Drug Research, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, PR China

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ABSTRACT

Glycoligands, which feature a glycoside as the central template incorporating Lewis bases as metal chelation sites and various fluorophores as the chemical reporter, represent a range of interesting scaffolds for development of chemosensors. Here, new types of triazolyl bidentate glycoligands (TBGs) based on the grafting of 3-azidocoumarin to the C2,3- or C4,6-positions of three epimeric pyranoglycosides including a glucoside, a galactoside, and a mannoside were efficiently synthesized via a fluorogenic dual click reaction assisted by microwave irradiation. The desired TBGs were afforded in high conversion rates (>90%) and reasonable yields (~70%). Moreover, a preliminary optical study of two hydroxyl-free glucoside-based TBGs indicates that these compounds are strongly fluorescent in pure water, implying their potential for ion detections in aqueous media.



There grows increasing interest in the employment of sugars that are among the most ample raw materials provided by nature as the central scaffold for the development of functional compounds due to their well-defined stereoinformation, benign water solubility, and especially, high biocompatibility. Sugar-based chemosensors are a class of recently identified small-molecule probes that consist of sugar moieties as a core template in conjunction with Lewis bases as metal chelation sites and diverse fluorophores as the chemical reporter.[1–10] Of the various chemical entities disclosed, triazolyl bidentate glycoligands (we christen them as TBGs) have more recently emerged to be of particular interest in the selective detection of ions.[11–15]

The construction of these compounds is succinct considering that it simply requires the pre-introduction of an azide or an alkyne functionality to the selected sugar or fluorophore skeletons via readily accessible methods to obtain the intermediates, and a subsequent $Cu^{I}$-catalyzed azide-alkyne 1,3-dipolar cycloaddition click reaction (CuAAC),[16–19] which has fulfilled the preparation of countless functional glyco-molecules,[20–36] efficiently forms the desired triazolyl fluorescent glycoligands. Notably, the triazole rings generated in these glycoligands not only may serve as a linker, but can also function as an ion coordination site.[11,12] However, former studies mainly stressed on the synthesis of TBGs by using furanoglycosides as the sugar template (Fig. 1), whereas correlative examples based on the six-membered ring pyranoses such as glucose, galactose, and mannose, which are abundant natural materials and are also structurally more diverse compared to the five-membered ring furanoses, are rare.

Therefore, we sought to use the pyranoglycosides as the template for the diversification of TBGs (Fig. 1). We have reported in previous studies that C3,4-disubstituted triazolyl glucosides and galactosides may perform as selective cation or anion probes in aqueous media.[13–15] In this study, three natural epimeric pyranoglycosides, that is, a glucoside, a galactoside, and a mannoside that differ in their C4- or C2-configuration were used as the sugar template, whereon the fluorescently deactivated 3-azidocoumarin was introduced efficiently via a fluorogenic CuAAC to their C2,3- or C4,6-positions.

*Synthesis*: Coumarins are prevalent fluorophores and have been used extensively as the substrate of fluorogenic click chemistry in many biochemical studies due to their small size and high biocompatibility.[37] Furthermore, some triazole-connected coumarin–sugar conjugates have been synthesized recently.[38–41]

We therefore chose 3-azidocoumarin **a** (Scheme 1), a fluorogen with quenched fluorescence because of the presence of an electron-rich α-nitrogen atom on its 3-position,[37] for the construction

* Corresponding authors. Tel./fax: +86 21 64253016.
*E-mail addresses:* xphe@ecust.edu.cn (X.-P. He), mrs_guorongchen@ecust.edu.cn (G.-R. Chen).

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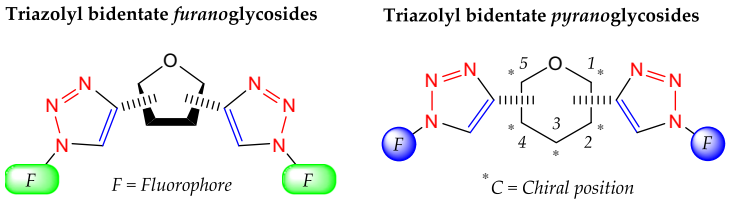
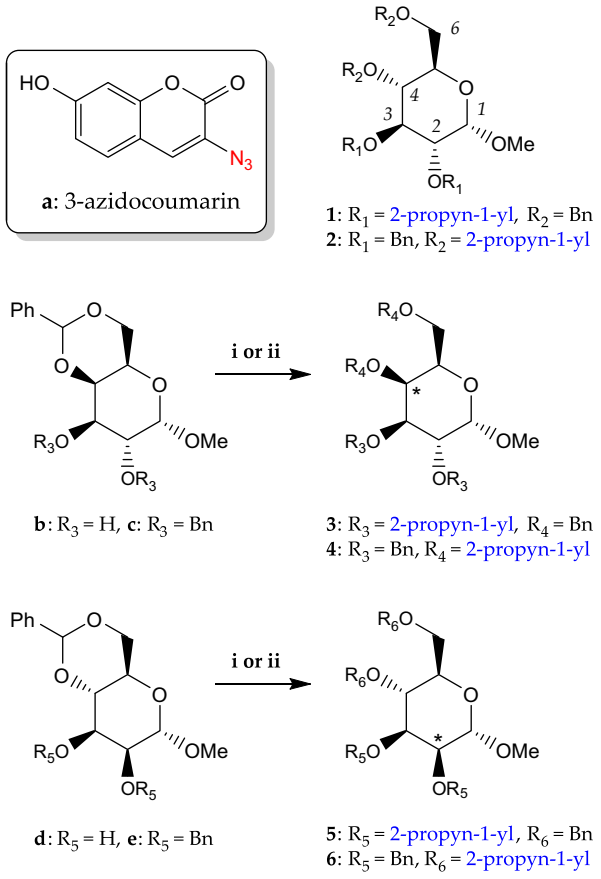



**Figure 1.** Triazolyl bidentate glycoligands (TBGs).




**Scheme 1.** Reagents: (i) (a) NaH, propargyl bromide, DMF, then (b) *p*-TsOH, MeOH, then (c) NaH, BnBr, DMF; (ii) (a) *p*-TsOH, MeOH, then (c) NaH, propargyl bromide, DMF.

of the TBGs. The fluorogenic coumarin was envisaged to be introduced simultaneously to the epimeric position and a neighboring position of the side chain of glucose, galactose, and mannose, three readily available natural sugar epimers. As shown in Scheme 1, the commercially available methyl α-*O*-glycosides of these monosaccharides were used to undergo facile and regioselective protection–deprotection reactions for preparing the di-propargyloxy glycosyl templates.

The C2,3- and C4,6-di-propargyloxy methyl α-*O*-glucosides **1** and **2** were synthesized via previous methods.[42] The known C4,6-benzylidene methyl α-*O*-galactoside and mannoside **b**[43] and **c**[44] were first propargylated via Williamson method in the presence of NaH and propargyl bromide. Subsequent removal of the benzylidene group by *p*-TsOH, followed by a benzylation in the presence of NaH and BnBr led to C2,3-di-propargyloxy methyl *O*-α-galactoside **3** and mannoside **4** in 56.4% and 50.6% yields (three-step), respectively. Likewise, the C4,6-di-propargyloxy methyl α-*O*-galactoside **4** and mannoside **6** were obtained in 78.2% and 75.1% yields, respectively, through a successive two-step sequence involving deprotection of benzylidene of the known **c**[43] and **e**,[45] followed by an O-alkylation in the presence of NaH and propargyl bromide.

The CuAAC ligation of the azide with the six alkynyl sugar templates was then performed (Scheme 2). It has been well-noted that the microwave irradiation can powerfully enhance the efficiency of CuAAC,[46,47] especially of those involving polyvalent alkynyl scaffolds as the substrate with large steric hindrance that hampers the reactivity.[14,42]

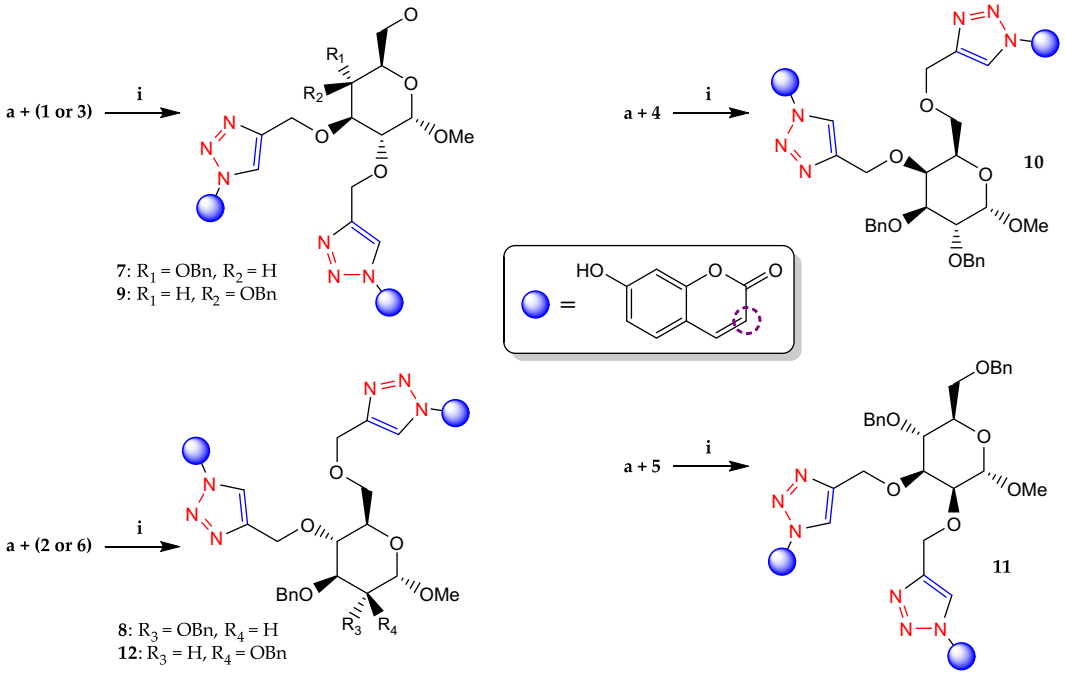
As a consequence, CuAACs of 3-azidocoumarin (2.2 equiv) **a** with different di-propargyloxy glycosides **1**–**6** (1 equiv) were performed under microwave irradiation (60 °C, Yalian-YL8023B1 microwave oven) by using $[Cu(CH_3CN_4)]PF_6$[48] as the catalyst in a solvent system of *t*BuOH/$H_2O$/$CH_2Cl_2$ (1:1:1, V/V/V).[49] The *Huisgen* [3+2] cycloaddition of **a** with **1** was proceeded as a model reaction, from which we first noticed that relatively low catalyst loadings ranging from 0.1 to 1.0 equiv resulted in the generation of only trace amounts of new products as monitored by TLC, even by stirring for 12 h. While the catalyst loading was increased to more than 2.0 equiv, the consumption of the starting materials tended to become greater. However, limited reaction times from 30 min to 2 h led generally to the partial formation of three main products with gradually increased polarities, which are deduced to be the C2- or C3-mono-triazole-linked coumarin–sugar conjugate and the title bis-triazolyl compound.[14,50]

Eventually, the optimal condition was determined to be the addition of 4.0 equiv of $[Cu(CH_3CN_4)]PF_6$ to the reaction system together with a reaction time of 4 h, which led to the formation of the desired C2,3-bis-triazolyl coumarin–glucoside conjugate **7** (confirmed by NMR and MS) in an excellent conversion rate of 94% and a reasonable isolated yield of 71% (Table 1). To test the superiority of the microwave technique employed, the same reaction was performed conventionally by stirring at 60 °C in the presence of 4.0 equiv of the catalyst.

After stirring over night, only 60% of the sugar alkyne **1** has been consumed and **7** was isolated with a poor yield of 12.8% along with the generation of the monotriazolyl byproducts. This demonstrates that despite the relatively long reaction time (4 h), the microwave irradiation is helpful for obtaining the title product with an acceptable efficiency. We then performed the CuAAC of **a** with the rest of the alkynes **2**–**6** under the optimized condition, and the results are shown in Table 1. To our delight, all title bis-triazolyl products **8**–**12** were similarly obtained in high conversion rates (~90%) and reasonable yields (~70%).

*Optical study*: Glucoside-based benzyl TBGs **7** and **8** were selected for a preliminary optical study, which were first subject to a hydrogenolysis in the presence of $H_2/PdCl_2$,[47,51] giving the hydroxyl-free TBGs **13** (94%) and **14** (96%) in excellent yields (Scheme 3). The UV absorbance and fluorescence intensity of **13** and **14** were then recorded in pure water.

As shown in Figure 2, both compounds display a single peak centered at 345 nm in their UV spectra (left), while by excitation at 345 nm, they exhibit strong fluorescence and interpret a broad emission band ranging from 400 to 550 nm akin to that of coumarin. This indicates that the fluorescence of coumarin has been successfully restored upon the sugar template. Moreover,




**Scheme 2.** Reagents and conditions: (i) $[Cu(CH_3CN_4)]PF_6$, *t*BuOH/$H_2O$/$CH_2Cl_2$, microwave irradiation.

**Table 1**
Microwave-assisted CuAAC of azide **a** with alkynes **1**–**6**

| Azide | Alkyne | Product | Conversion rate (%) | Yield (%) |
|---|---|---|---|---|
| **a** | 1 | 7 | 94 | 71.4 |
| | 2 | 8 | 94 | 70.2 |
| | 3 | 9 | 92 | 66.5 |
| | 4 | 10 | 95 | 72.6 |
| | 5 | 11 | 90 | 64.8 |
| | 6 | 12 | 91 | 66.8 |

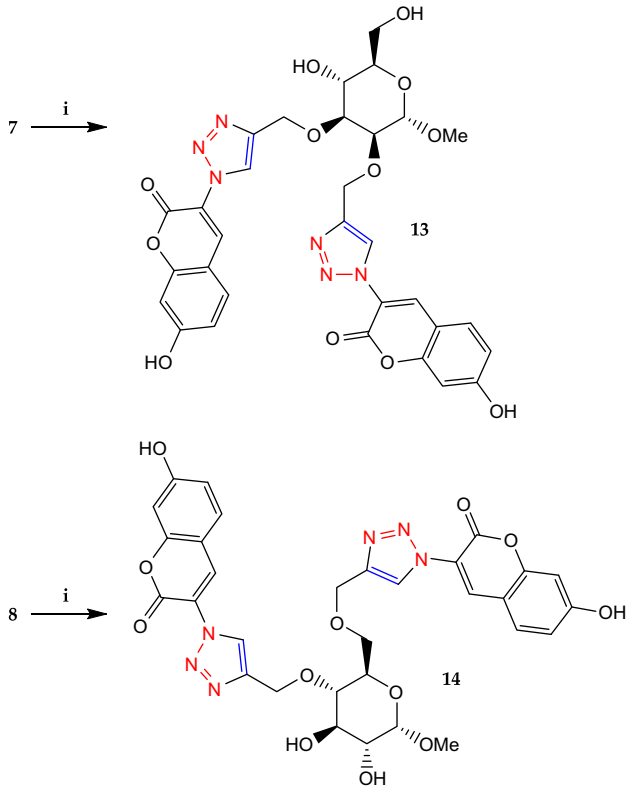
the C4,6-modified TBG **14** shows much stronger florescence intensity than its C2,3-modified counterpart **13**, suggesting that the optical property of the TBGs can be tuned by grafting the fluorogenic precursor to different substitution sites of a sugar moiety.

In conclusion, we have realized in this study the efficient construction of new types of pyranoglycosyl TBGs by grafting 3-azidocoumarin to the C2,3- or C4,6-positions of three epimeric monosaccharides via a microwave-assisted fluorogenic CuAAC ligation in high conversion rates and reasonable yields. A preliminary optical study of two hydroxyl-free glucoside-based TBGs shows that these compounds are strongly fluorescent in pure water, implying their potential for ion detections in aqueous media. Detailed optical studies as well as tests of their biological activities are currently underway and will be reported in due course.

## 1. Experimental section

### 1.1. General information

Solvents were purified by standard procedures. Petroleum ether (PE) used refers to the fraction boiling in the range of 60–90 °C. The organic extracts were dried over $MgSO_4$. $^1H$ and $^{13}C$ NMR spectra were recorded on a Bruker AM-400 spectrometer in $CDCl_3$ or DMSO-$d_6$ solutions using TMS as the internal standard (chemical shifts in parts per million). Standard abbreviations are used to describe the signal multiplicity. All reactions were monitored by TLC. Optical rotations were measured using a Perkin–Elmer 241 polarimeter at room temperature in a 10-cm, 1-mL cell. High and low resolution mass spectra (HRMS and LRMS) were recorded on a Waters LCT Premier XE spectrometer using standard conditions (ESI, 70 eV). Analytical HPLC was measured using Agilent 1100 series equipment. All UV–vis absorption spectra were measured on a Varian Cary 500 UV–vis spectrophotometer and fluorescence




**Scheme 3.** Reagents: (i) $PdCl_2$, $H_2$, MeOH.

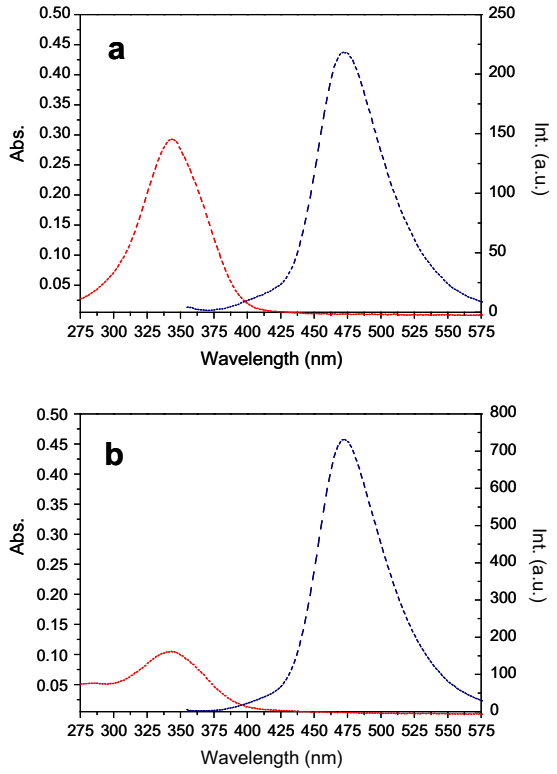



**Figure 2.** Stacked UV–vis (red) and fluorescence (blue) spectra (excited at 345 nm) of $10^{-4}$ M of (a) TBG **7** and (b) TBG **8** in deionized water. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

spectra measured on a Varian Cary Eclipse Fluorescence spectrophotometer.

### 1.2. General procedure for the microwave-assisted CuAAC

To a solution of the sugar alkyne (1.0 equiv) and 3-azidocoumarin (2.2 equiv) in *t*BuOH/$H_2O$/$CH_2Cl_2$ (5 mL/5 mL/5 mL) was added [$Cu(CH_3CN_4)$]$PF_6$ (4.0 equiv). This mixture was then transferred to a Yalian (YL8023B1) microwave oven and stirred at 60 °C with a ramp time of 6 min and a hold time of 4 h. Solvent was then removed in vacuum and the resulting residue was diluted with $CH_2Cl_2$ and washed successively with water and brine. The combined organic layer was dried over $MgSO_4$, filtered, and then concentrated in vacuum to give a crude product which was purified by column chromatography.

### 1.3. General procedure for the debenzylation

To a solution of the benzyl glycoside (1.0 equiv) in MeOH was added $PdCl_2$ (0.6 equiv), and the mixture was stirred under hydrogen atmosphere for 30 min at rt. Then the solvent was removed in vacuum and the residue was directly filtered to afford the desired products.

#### 1.3.1. 3,3′-(4,4′-((((2*S*,3*S*,4*S*,5*R*,6*R*)-5-Hydroxy-6-(hydroxymethyl)-2-methoxytetrahydro-2*H*-pyran-3,4-diyl)bis(oxy))bis(methylene))bis(1*H*-1,2,3-triazole-4,1-diyl))bis(7-hydroxy-2*H*-chromen-2-one) (13)

From **7** (60 mg, 0.07 mmol), afforded **13** as a light yellow solid (47.4 mg, 94.2%). $R_f$ = 0.25 ($CH_2Cl_2$/MeOH, 10:1). $[\alpha]_D^{25}$ +25.0 (*c* 0.1, MeOH). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.75 (br s, 1H), 8.59–8.47 (m, 2H), 7.97 (s, 4H), 7.70 (d, *J* = 7.6 Hz, 1H), 6.91 (d, *J* = 6.0 Hz, 1H), 6.84 (s, 1H), 6.51 (br s, 6H), 4.92 (s, 1H), 4.81 (d, *J* = 9.5 Hz, 2H), 3.67–3.58 (m, 2H), 3.52–3.34 (m, 4H), 3.30–3.28 (m, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 162.5, 162.3, 156.2, 154.5, 136.1, 130.8, 127.3, 124.7, 124.4, 119.1, 114.2, 113.8, 110.1, 102.0, 96.9, 81.3, 78.8, 72.5, 69.8, 65.5, 62.9, 60.5, 54.2; HRMS (ESI): *m*/*z* calcd for $C_{31}H_{28}N_6O_{12}$-H: 675.1687; found: 675.1711. Analytical HPLC: $t_R$ = 4.6 min (solvent: MeOH, 0.5 mL/min over 8.9 min, purity 98.8%).

#### 1.3.2. 3-(4-((((2*R*,3*S*,4*R*,5*R*,6*S*)-4,5-Dihydroxy-2-(((1-(7-hydroxy-2-oxo-2*H*-chromen-3-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)methyl)-6-methoxytetrahydro-2*H*-pyran-3-yl)oxy)methyl)-1*H*-1,2,3-triazol-1-yl)-7-hydroxy-2*H*-chromen-2-one (14)

From **8** (60 mg, 0.07 mmol), afforded **14** as a light yellow solid (47.4 mg, 96.3%). $R_f$ = 0.27 ($CH_2Cl_2$/MeOH, 10:1). $[\alpha]_D^{25}$ +22.0 (*c* 0.1, MeOH). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.49 (d, *J* = 12.0 Hz, 2H), 8.46 (d, *J* = 12.0 Hz, 2H), 7.68 (d, *J* = 8.1 Hz, 2H), 6.91 (t, *J* = 6.2 Hz, 2H), 6.85 (s, 2H), 4.96 (d, *J* = 11.8 Hz, 1H), 4.69-4.60 (m, 4H), 3.61 (br s, 2H), 3.58 (d, *J* = 8.7 Hz, 1H), 3.51 (d, *J* = 9.5 Hz, 1H), 3.31–3.26 (m, 2H), 3.26 (s, 3H); $^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 162.5, 162.4, 156.2, 154.5, 144.5, 143.9, 136.1, 130.8, 127.3, 124.8, 124.6, 119.1, 114.3, 110.1, 102.1, 99.6, 77.8, 73.5, 71.9, 69.4, 68.7, 64.8, 63.3, 54.5; HRMS (ESI): *m*/*z* calcd for $C_{31}H_{28}N_6O_{12}$+H: 677.1843; found: 677.1845. Analytical HPLC: $t_R$ = 4.7 min (solvent: MeOH, 0.5 mL/min over 9.1 min, purity 98.0%).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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.carres.2012.10.001.

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