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Synthesis and binding ability of 1,2,3-triazole-based triterpenoid receptors for recognition of Hg^{2+} ion

Jun Hu [a], Meng Zhang [a], Li B. Yu [a], Yong Ju [a,b,*]

[a] Key Laboratory of Bioorganic Phosphorus Chemistry and Chemical Biology, Ministry of Education, Department of Chemistry, Tsinghua University, Beijing 100084, China
[b] State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China

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ABSTRACT

A novel type of receptors based on 1,2,3-triazole glycyrrhetinic acid derived from natural triterpenoid molecules has been synthesized via click chemistry and they showed high selectivity and affinity for Hg^{2+} ion by both the 1,2,3-triazole rings and aldehyde groups.

Glycyrrhetinic acid (**1**) is a facile pentacyclic triterpenoid presenting in the form of aglycone or glycosides from medicinal plants.[1–3] It is mainly used for anti-inflammation, anti-virus and anti-tumor.[4–8] Although many reports based on steroidal units have appeared in recognition and binding ability,[9–22] there are few reports about triterpenoid scaffolds,[23] which are the biogenic homologue with steroids and possess the similar structures, such as chiral rigid skeleton, relative low-toxicity, biocompatibility and so on. To design the triterpenoid scaffold as ion receptor should open a new venue for molecular sensor development and maybe lead to potential applications.

The mercury environmental pollution, which is caused by the continuous release of mercury in the environment through natural and industrial processes, has always been a matter of concern.[24–26] The oxidized Hg^{2+} ion can be accumulated in plants, soil and water, and mercury could also be converted into methylmercury, a highly potent neurotoxin, by microorganisms.[27,28] The exposure to mercury even at low concentration leads to various health problems, especially neurological disorders. Therefore, there are considerable interest in the development of receptors that can show high selectivity and sensitivity for Hg^{2+} ion.[29–38]

Recently, the role of 1,2,3-triazole in the formation of stable metal complexes has also been realized by providing coordination site and accordingly some triazole-based receptors and dendrimers for the recognition of metals have been reported.[39–52] The click reaction,[53] which supplies a straightforward molecular linking strategy, has attracted much attention in the areas of polymers, materials, organic, biological and medicinal chemistry.[54–59]

In this Letter, we report the synthesis of a novel type of receptors based on 1,2,3-triazole glycyrrhetinic acid derived from natural triterpenoid and their binding properties toward various metal ions for the first time.

1,2,3-Triazole-based triterpenoid receptors **11** and **12** were synthesized through eight steps (Scheme 1). Glycyrrhetinic acid (**1**) was first methylated to methyl ester **2** by methyl iodide, followed by treatment with *p*-toluenesulfonyl chloride to give compound **3**. After refluxing in DMF with lithium carbonate and lithium bromide, 2,11-diene-glycyrrhetinic acid methyl ester **4** was synthesized, which subsequently reacted with *m*-chloroperoxybenzoic acid at rt to give compound **5**. Compound **5** was hydrolysed to afford 2,3-dihydroxyl-glycyrrhetinic acid methyl ester **6**. In order to confirm the configuration of 2,3-dihydroxyl of **6**, the crystal structure was determined by X-ray diffraction analysis (see Supplementary data). After reacting with bromoacetyl bromide at rt to obtain **7** and then refluxing with sodium azide in DMF, 2,3-diazido-glycyrrhetinic acid methyl ester **8** was synthesized. Further treatment with salicylaldehyde and 2-hydroxy-1-naphthaldehyde based terminal alkynes **9** and **10** in the presence of $CuSO_4{\cdot}5H_2O$ and ascorbate acid sodium salt (click reaction) gave target molecules **11** and **12**, respectively.

UV–vis spectroscopy was used to investigate the affinity of compound **11** and **12** towards Hg^{2+} ion by monitoring the absorbance changes. When $Hg(ClO_4)_2$ (0–3 equiv) was added to the solution of compound **11** (2.9×10^{-5} M) in CH_2Cl_2–CH_3OH (7:3, v/v), the absorbance bands at 253 and 317 nm decreased and a new band around 279 nm was observed with two clear isosbestic points

* Corresponding author. Fax: +86 10 62781695.
E-mail address: juyong@tsinghua.edu.cn (Y. Ju).

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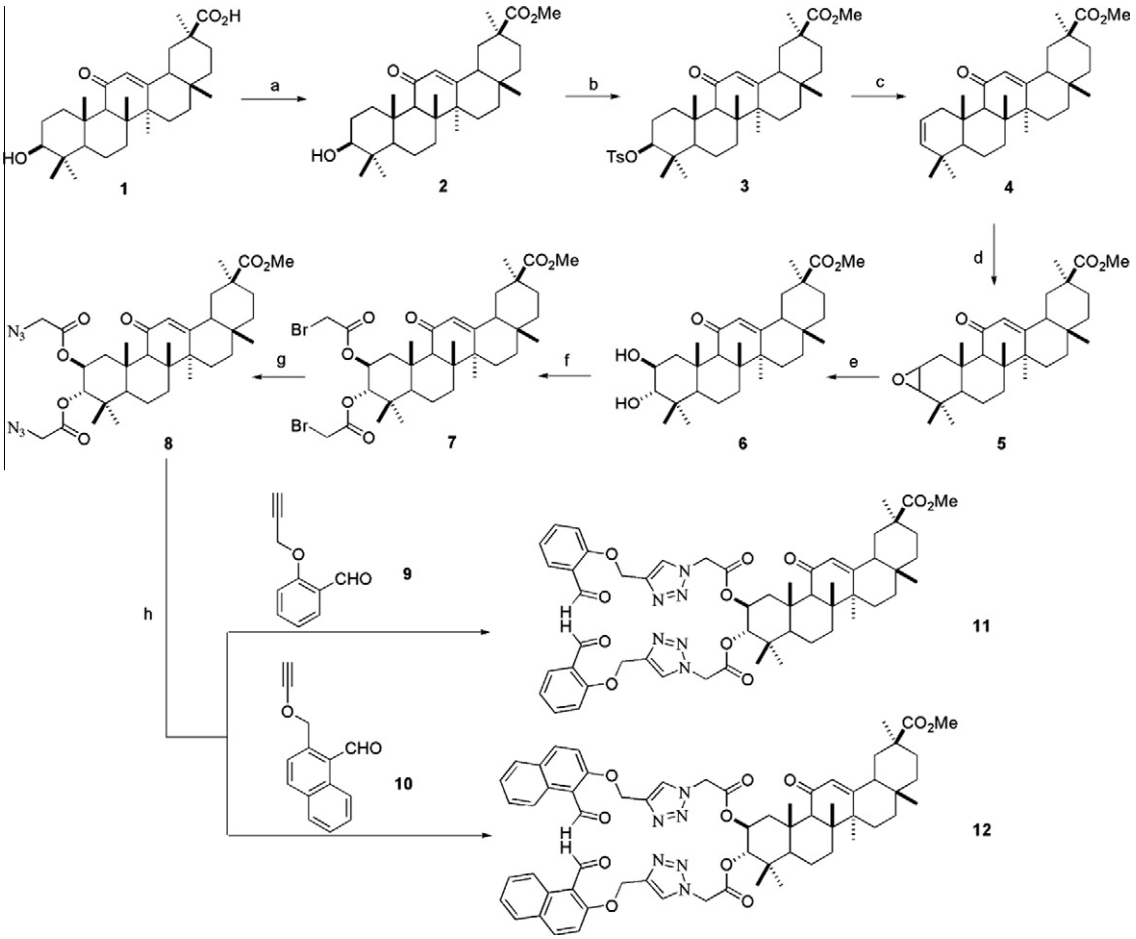

Scheme 1. Reagents and conditions: (a) CH_3I, K_2CO_3, THF, reflux; (b) *p*-TsCl, pyridine, rt; (c) LiBr, Li_2CO_3, DMF, reflux; (d) *m*-CPBA, K_2CO_3, CH_2Cl_2, rt; (e) $HClO_4$, 1,4-dioxane, H_2O, rt; (f) $BrCOCH_2Br$, K_2CO_3, CH_2Cl_2, rt; (g) NaN_3, DMF, 70 °C and (h) $CuSO_4{\cdot}5H_2O$, ascorbate acid sodium salt, *t*-BuOH, 50 °C.

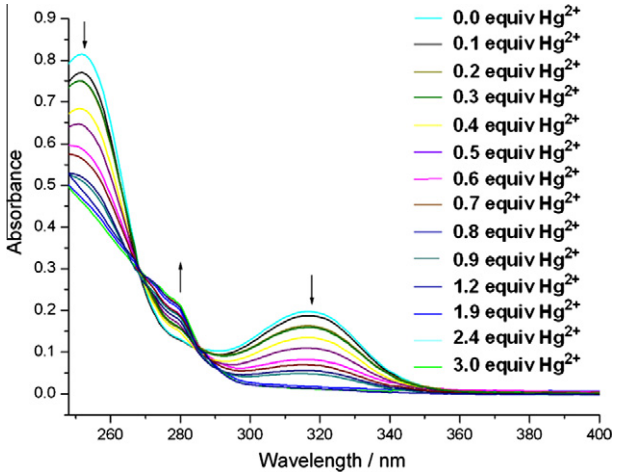

Figure 1. Absorbance spectra of compound **11** (2.9×10^{-5} M) in CH_2Cl_2–CH_3OH (7:3, v/v) in the presence of Hg^{2+} (0–3 equiv).

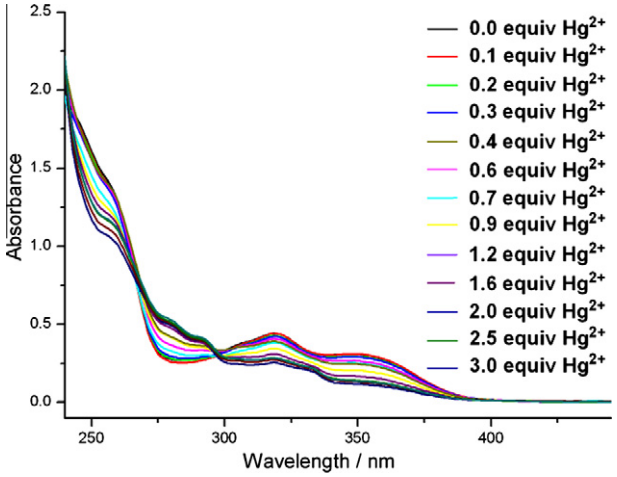

Figure 2. Absorbance spectra of compound **12** (2.8×10^{-5} M) in CH_2Cl_2–CH_3OH (7:3, v/v) in the presence of Hg^{2+} (0–3equiv).

at 268 and 286 nm (Fig. 1). Compound **12** (2.8×10^{-5} M) also showed similar type of behavior with Hg^{2+} ion (Fig. 2) that the absorbance bands at 258 and 320 nm decreased and a new band around 282 nm appeared with two sharp isosbestic points at 272 and 295 nm. Job's plots indicated the 1:1 complex formation in both cases and the binding constants for receptors **11** and **12** were found to be 3.0×10^4 and 2.7×10^4 M^{-1} (Figs. 3 and 4) using Hildebrand–Benesi equation[60], respectively.

The binding behavior of **11** and **12** were also examined with other metal ions such as Cu^{2+}, Zn^{2+}, Cd^{2+} and Mg^{2+}. In all cases, their perchlorate salts were used for the UV–vis titration. Among the above metal ions, only Cu^{2+}, which is always used to dipolar cycloaddition reaction and fluorescent chemosensor recently[61–63],

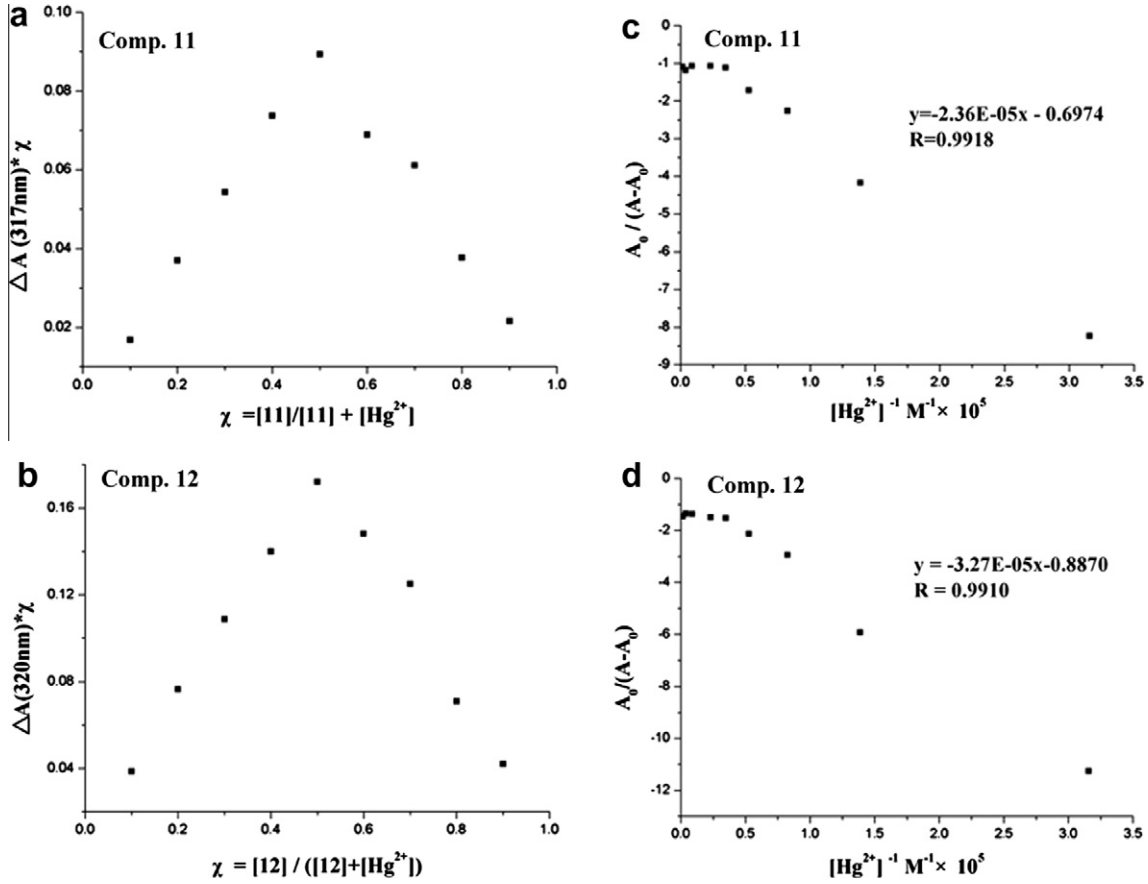

Figure 3. Job's plot showing 1:1 complex formation for (a) receptor **11** and (b) receptor **12**; Hildebrand–Benesi plot based on the 1:1 for (c) receptor **11** with Ka = 3.0×10^4 M^{-1} and (d) receptor **12** with Ka = 2.7×10^4 M^{-1}.

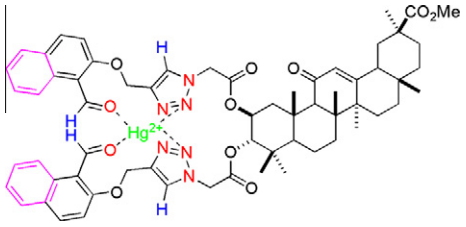

Figure 4. The 1:1 complex formation for compounds **11** and **12** with Hg^{2+} ion

showed appreciable binding towards these receptors and the binding constants for receptor **11** (4.4×10^{-5} M) and **12** (3.7×10^{-5} M) were 1.6×10^3 M^{-1} and 5.0×10^3 M^{-1} (absorbance spectra and job's plot see Supplementary data), respectively. The other metal ions did not show any binding affinity for the receptors. These results clearly indicated that receptors **11** and **12** were selective to bind with Hg^{2+} ion.

The mode of binding of Hg^{2+} ion with compounds **11** and **12** was ascertained by ^{1}H NMR spectroscopy. After addition of Hg^{2+} ion (3 equiv) to the solution of compound **11** (5 mM) and **12** (5 mM) in $CDCl_3$–CD_3OD (7:3, v/v), respectively, the protons of 1,2,3-triazole rings were downfield shifted to δ 0.58 and 0.56 ppm, and the protons of aldehyde group attached to phenyl rings were upfield shifted to δ 0.37 and 0.25 ppm (Figs. 5 and 6). The change of chemical shift indicated that both 1,2,3-triazole rings and aldehyde groups of compounds **11** and **12** should bind with Hg^{2+} ion.

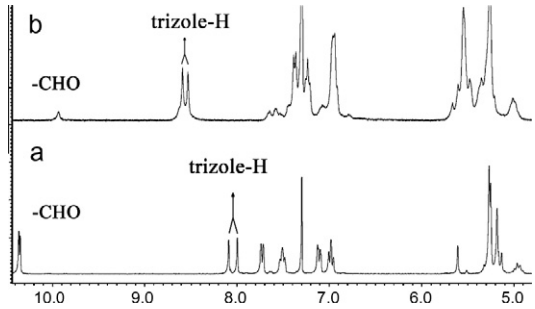

Figure 5. Partial ^{1}H NMR spectra of (a) compound **11** and (b) compound **11** + 3 equiv $Hg(ClO_4)_2$.

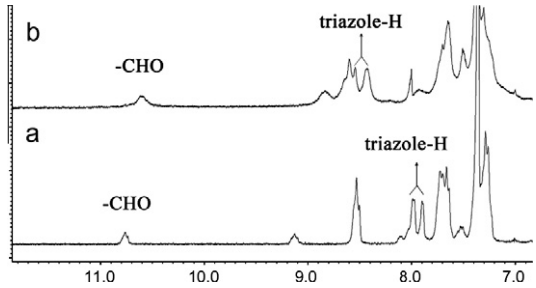

Figure 6. Partial ^{1}H NMR spectra of (a) compound **12** and (b) compound **12** + 3 equiv $Hg(ClO_4)_2$.

In conclusion, a novel type of receptors based on 1,2,3-triazole glycyrrhetinic acid derived from natural triterpenoid molecules were developed and the receptors showed remarkable selectivity and affinity for Hg^{2+} ion by the 1,2,3-triazole rings and aldehyde groups simultaneously. It might lead to the potential applications in managing environmental pollution and used as a potential antidote for mercury.

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Supplementary data

Synthesis and spectra data of compounds **2**–**12**; ORTEP drawing of compound **6**; UV–vis titrations and calculation of binding constants of Cu^{2+}. Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2010.06.079.

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