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Synthesis and anti-proliferative activity of allogibberic acid derivatives containing 1,2,3-triazole pharmacophore

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ABSTRACT

Sixty novel allogibberic acid derivatives containing 1,2,3-triazole pharmacophore were designed and synthesized. The key chemical processes include aromatization of the A ring in gibberellins, formation of allogibberic azides and its copper mediated Huisgen 1,3-dipolar cycloaddition with alkynes. A number of hybrids containing α,β-unsaturated ketone moiety exhibited excellent *in vitro* cytotoxic activities. Some of the hybrids were more selective to MCF-7 and SW480 cell lines with IC_{50} values at least 8-fold more cytotoxic than cisplatin (DDP). The most potent compounds **C43** and **C45** are more cytotoxic than cisplatin (DDP) against all tested five tumor cell lines, with IC_{50} values of 0.25–1.72 μM. Mechanism of action studies indicated that allogibberic-triazole derivative **C45** could induce the S phase cell cycle arrest and apoptosis in SMMC-7721 cell lines.

The biologically validated natural products are important resource for lead generation and development of new pharmaceuticals. These structurally complex natural molecules are historically a significant inspiration for the design and synthesis of bioactive compounds in medicinal chemistry.[1,2] The gibberellins (**GAs**) area family of tetracyclic *ent*-kaurenoid diterpenes presented widely in the plant kingdom, and some of them are used agriculturally as regulators to promote plant germination and growth.[3] Gibberellic acid (**1**, Fig. 1) is nowadays produced commercially in tonne quantities by fermentation of the fungus *Gibberella fujikuroi*.[4,5] We initiated the studies towards anti-tumor activities of gibberellin derivatives on 2003 and a number of anti-cancer gibberellin derivatives were designed and synthesized in the next decade.[6] We found that some gibberellins bearing α,β-unsaturated ketone units (for example, compound **3** IC_{50} = 2.9 μM against HT29, compound **4** IC_{50} = 0.21 μM against MKN28) possessed potent cytotoxic activity against a panel of human cancer cell lines and inhibited completely the topoisomerase I activity.[7a–c]

We also found that compound **3** (GA-13315) blocked angiogenesis by inhibiting VEGF receptor signaling.[7b] In 2009, Koehler discovered that gibberellic acid (**1**) and 9α-H allogibberic acid (**6**) could modulate the NF-κB signaling pathway,[8] a transcription pathway associated with various cancer diseases.[9] Recently, pharbinilic acid (**7**), an allogibberic acid derivative possessing anti-cancer activity, was isolated[10] and pharbinilic acid and a number of allogibberic acid derivatives were synthesized.[11,12] Schindler's research indicated that pharbinilic acid was not active in an NF-κB reporter gene assay, however, conversion of pharbinilic acid to its methyl ester substantially enhanced activity against NF-κB factor.[12]

For the last five years, our research group has been interested in the design, synthesis and biological evaluation of a series of new heterocyclic hybrid derivatives.[13] We are curious to know if a suitable *N*-heterocycle could be incorporated into the allogibberic acid system to produce hybrid compounds. We also wish to determine whether the hybrid molecules combining *N*-heterocycle and allogibberic unit might also have cytotoxic properties when used in anti-tumor screens.

In order to synthesize hybrid molecules containing both *N*-heterocycle moiety and allogibberic acid derivatives, we need to choose a suitable *N*-heterocycle moiety, 1,2,3-triazole thus comes up to our mind. 1,2,3-Triazole is an important building block in drug discovery, and it has gained considerable interests because of its broad range of biological and pharmacological activity, including anticancer, antifungal, antimalarial, immunosuppressive, anti-allergic, anti-HIV, antitubercular, antimicrobial and anti-inflammatory activities.[14] This moiety has also been present in antibacterial drug Tazobactam (**8**, Fig. 1).[14b] It is of our interests to combine allogibberic acid derivatives and the pharmacophore 1,2,3-triazoletogether. In this paper, we report the synthesis and cytotoxic evaluation of a series of allogibberic acid derivatives containing 1,2,3-triazoles. The purpose of this study was to

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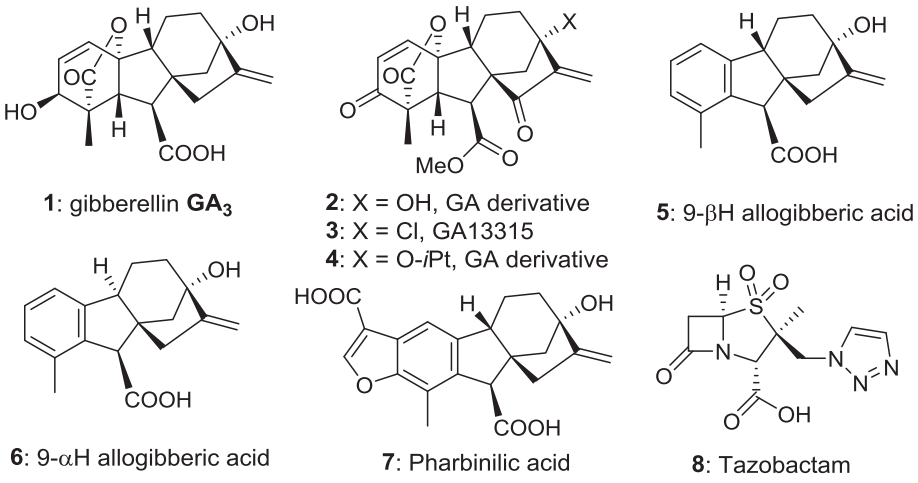
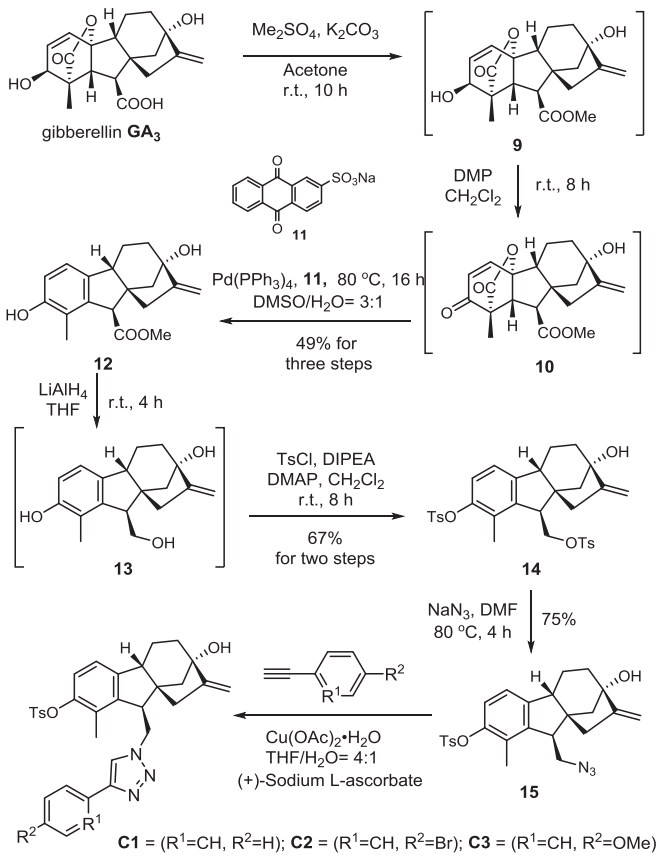


Fig. 1. Bioactive gibberellin derivatives and 1,2,3-triazole containing drug.

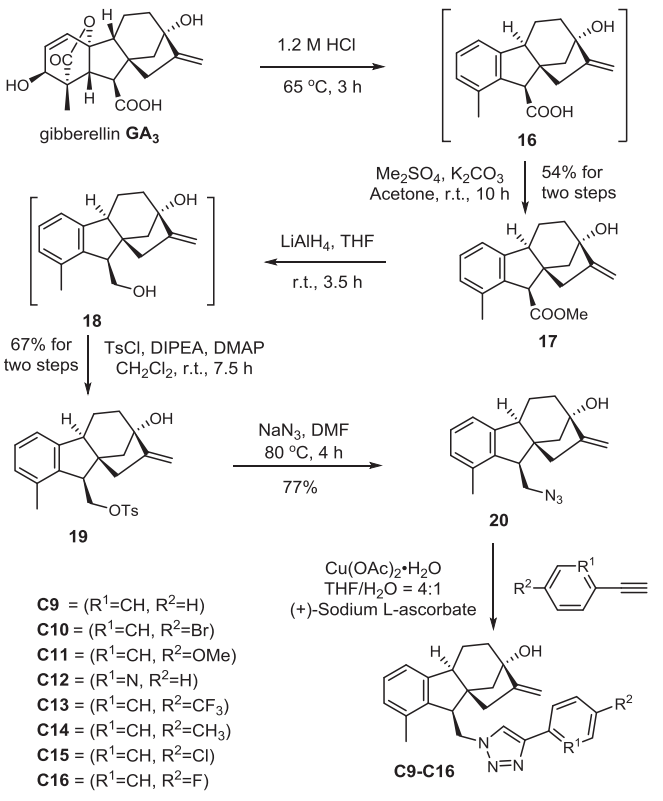
investigate the antitumor activity of the allogibberic structure based hybrids, with the final goal of finding novel antitumor agents.

The 1,2,3-triazole hybrids (**C1—C8**) were prepared from commercially available gibberellin GA_3 (**1**) via sequential esterification, oxidation and aromatization to give the allogibberic acid methyl ester (Scheme 1, **12**).[12] After reduction, tosylation and azide formation to yield allogibberic azides,[11b] the copper catalyzed Huisgen 1,3-dipolar cyclization (click chemistry)[15] of the resulting allogibberic azides with alkynes provided the title compounds (Scheme 1, **C1–C8**). In particular, the gibberellin GA_3 was treated with dimethylsulfate and potassium carbonate to yield the methyl ester **9**. After oxidation with Dess-Martin periodinane (DMP), enone **10** was obtained in high yields. Aromatization of enone **10** using $Pd(PPh_3)_4$ in DMSO/H_2O solution[12] at 80 °C provided phenol **12** in 49% yield over three steps. Treatment of phenol **12** with lithium aluminum hydride ($LiAlH_4$) followed by *p*-toluenesulfonyl chloride afforded tosylate **14** (67%, two steps). Azidation of compound **14** with sodium azide (NaN_3)[11b] provided azide **15** in 75% yield. Treatment of the azide with a number of terminal alkynes in the presence of copper acetate [$Cu(OAc)_2$][15] afforded a variety of 1,2,3-triazoles hybrids (**C1—C8**) in good to excellent yields.

The allogibberic-triazole hybrids (**C9—C16**) were obtained similarly from gibberellin GA_3 (Scheme 2). Aromatization of the A ring in gibberellin GA_3 was achieved by reacting GA_3 with hydrochloric acid at 65 °C.[11a,16] After reduction of ester **17** with $LiAlH_4$, tosylation with *p*-toluenesulfonyl chloride and azidation with NaN_3, azide **20** was obtained in 28% yield over 5 steps. After cyclization with Huisgen



Scheme 1. Synthesis of hybrid compounds **C1–C8**.



Scheme 2. Preparation of hybrid compounds **C9–C16**.