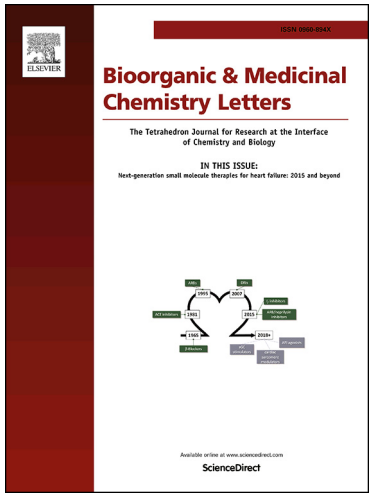
Accepted Manuscript



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

Ming-Jiang Wu, Dong-Mei Wu, Jing-Bo Chen, Jing-Feng Zhao, Liang Gong, Ya-Xiao Gong, Yan Li, Xiao-Dong Yang, Hongbin Zhang

PII: S0960-894X(18)30439-6
DOI: https://doi.org/10.1016/j.bmcl.2018.05.038
Reference: BMCL 25855

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 19 April 2018
Revised Date: 16 May 2018
Accepted Date: 17 May 2018

Please cite this article as: Wu, M-J., Wu, D-M., Chen, J-B., Zhao, J-F., Gong, L., Gong, Y-X., Li, Y., Yang, X-D., Zhang, H., Synthesis and anti-proliferative activity of allogibberic acid derivatives containing 1,2,3-triazole pharmacophore, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.05.038

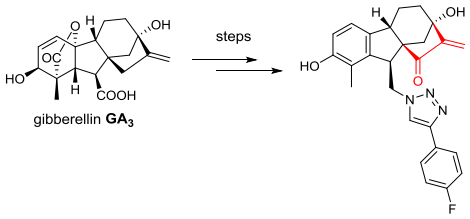
Graphical Abstract

*To create your abstract, type over the instructions in the template box below.
Fonts or abstract dimensions should not be changed or altered.

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

Leave this area blank for abstract info.

Ming-Jiang Wu, Dong-Mei Wu, Jing-Bo Chen, Jing-Feng Zhao, Liang Gong, Ya-Xiao Gong, Yan Li,* Xiao-Dong Yang* and Hongbin Zhang*



C45

tumor cell lines	IC_{50}, μM
HL-60	0.66
SMMC-7721	0.85
A549	0.94
MCF-7	1.72
SW480	0.25

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

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

Ming-Jiang Wu,[a] Dong-Mei Wu,[a,b] Jing-Bo Chen,[a] Jing-Feng Zhao,[a] Liang Gong,[b] Ya-Xiao Gong,[b] Yan Li,[b,*] Xiao-Dong Yang[a,*] and Hongbin Zhang[a,*]

[a] *Key Laboratory of Medicinal Chemistry for Natural Resource, Ministry of Education and Yunnan Province, School of Chemical Science and Technology, Yunnan University, Kunming, 650091, P. R. China.*

[b] *State Key Laboratory for Phytochemistry and Plant Resources in West China, Kunming Institute of Botany, Chinese Academy of Science, Kunming, 650204, P. R. China.*

ARTICLE INFO

Article history:
Received 00th April 2018
Revised 00th April 2018
Accepted 00th April 2018
Available online 00th April 2018

Keywords:
Allogibberic acid
1,2,3-triazole
Cytotoxic activity
Cell cycle
Apoptosis

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**, Figure 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 cycotoxic activity against a panel of human cancer cell lines and inhibited completely the topoisomerase I activity.[7a-7c]

* Corresponding author.
E-mail addresses: liyanb@mail.kib.ac.cn (Y. Li), xdyang@ynu.edu.cn (X.D. Yang), zhanghb@ynu.edu.cn (H. Zhang).

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]

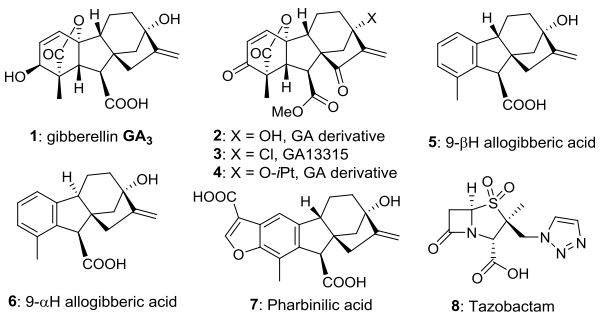


Figure 1. Bioactive gibberellin derivatives and 1,2,3-triazole containing drug.

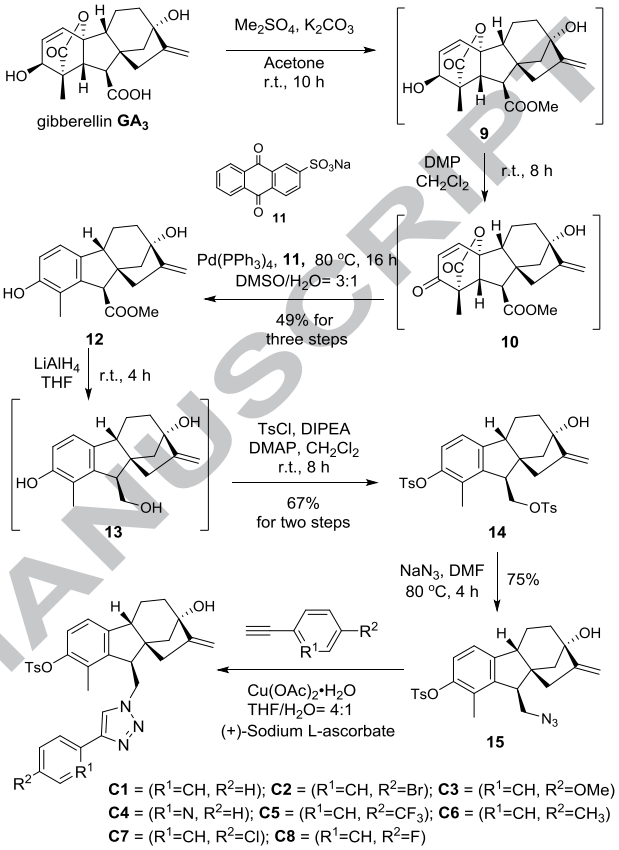
For the last five years, our research group has been interested in the design, synthesis and biological evaluation of a series of new hetercyclic hybrid derivatives.[13] We are curious to know if a suitable *N*-heterocycle could be incorporated into the allogibberic acid system to produce hybrid compounds. 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*-hetercycle 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, anti-fungal, antimalarial, immunosuppressive, anti-allergic, anti-HIV, anti-tubercular, antimicrobial and anti-inflammatory activities.[14] This moiety has also been present in antibacterial drug Tazobactam (**8**, Figure 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 investigate the antitumor activity of the allogibberic structure based hybrids, with the final goal of finding novel antitumor agents.

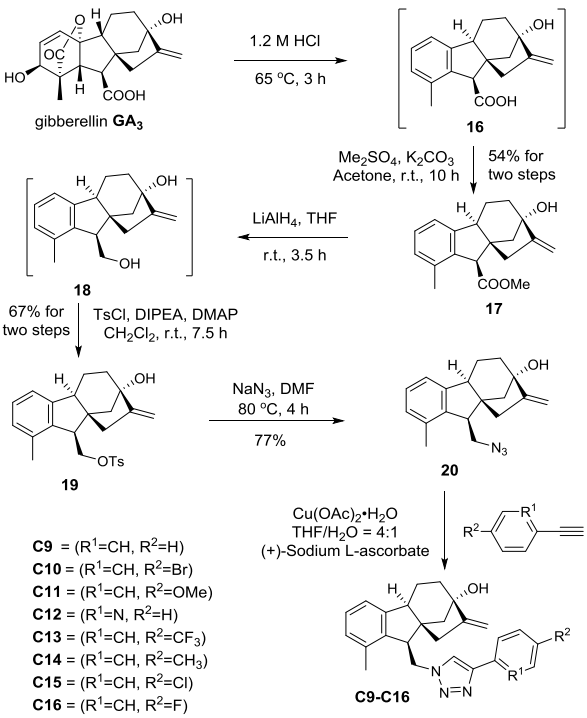
The 1,2,3-triazole hybrids (**C1-C8**) were prepared from commercially available gibberellin GA_3 (**1**) via sequential esterification, oxidation and aromatization to give the allogibberic acid methyl ester (Scheme 1, **12**).[12] After reduction, tosylation and azide formation to yield allogibberic 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 ºC 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 ºC.[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 reaction, the hybrids (**C9-C16**) were obtained.

The 1,2,3-triazole-allogibberic hybrids (**C17-C31**) were prepared from phenol **12** as outlined in Scheme 3. Treatment of compound **12** with *tert*-butyldimethylsilyl chloride (TBSCl) followed by reduction with LAH and tosylation with *p*-toluenesulfonyl chloride provided compound **23**. Removal of the *tert*-butyldimethylsilyl group with tetrabutylammonium fluoride (TBAF), followed by azidation with NaN_3, provided azide **25** in 39% yield over 5 steps. Next, the hybrids (**C17-C24**) were synthesized using Huisgen reaction.

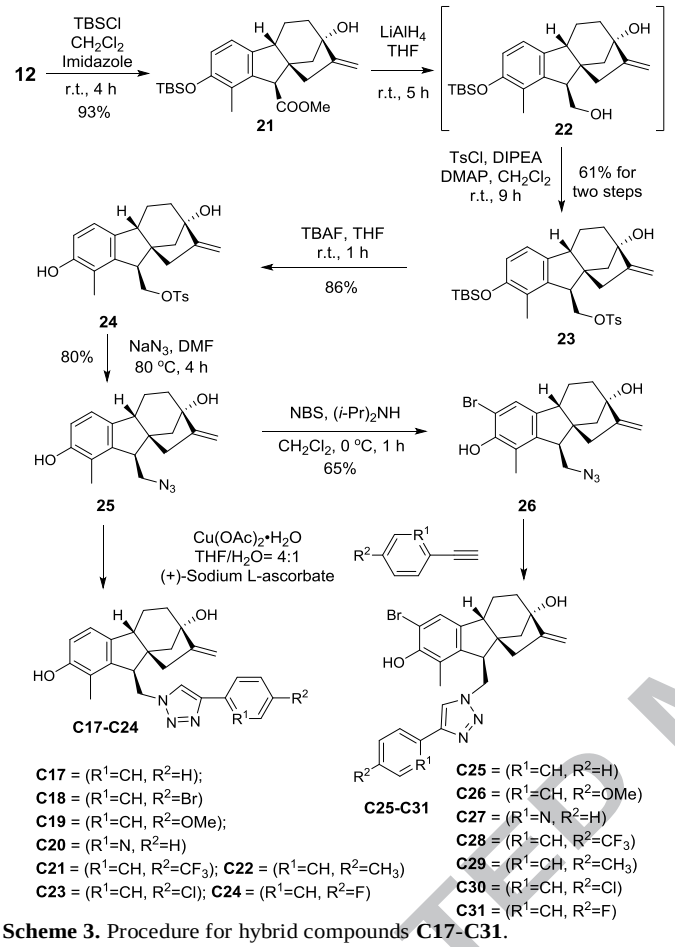


Scheme 1. Synthesis of hybrid compounds **C1**-**C8**.



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

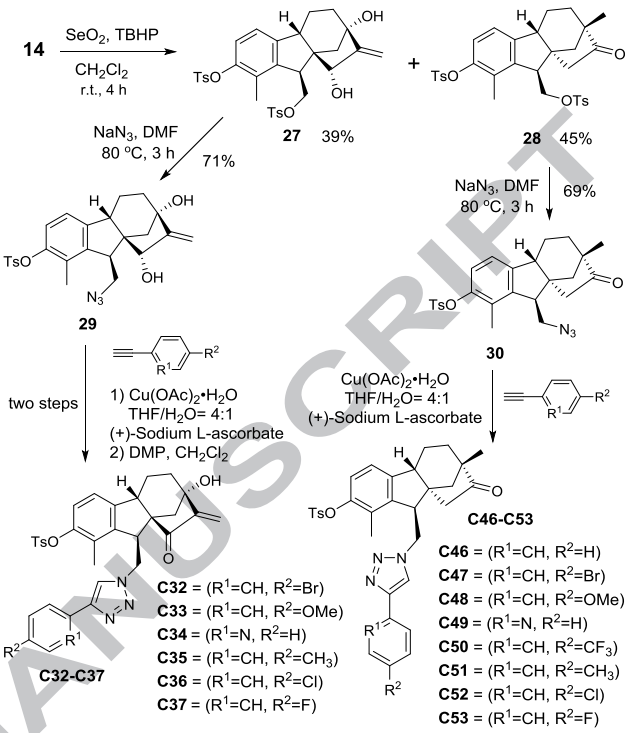
To see the electronic effect on the benzene ring of the allogibberic system, the 1,2,3-triazoles hybrids (**C25-C31**) were also synthesized from azide **25** (Scheme 3) by bromination of azide **25** with *N*-bromosuccinimide (NBS) in dichloromethane and copper mediated Huisgen cyclization.



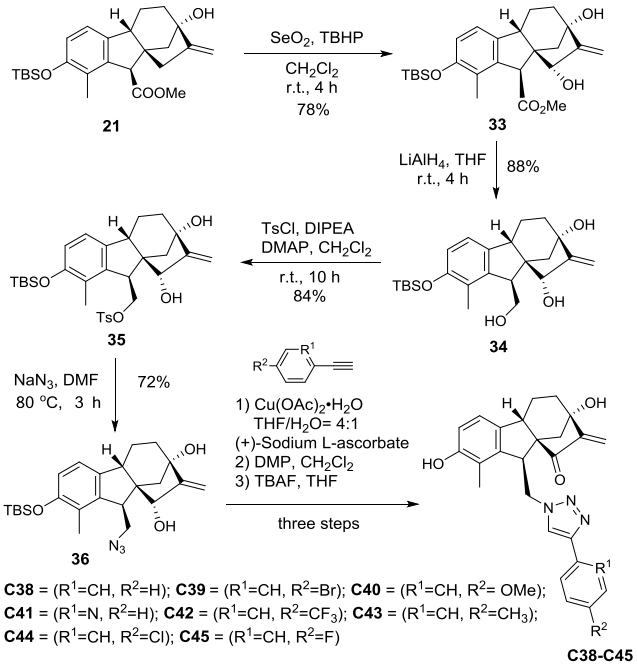
Scheme 3. Procedure for hybrid compounds **C17**-**C31**.

In our previous studies, we found that α,β-unsaturated ketone functionality presented in the gibberellins ring system is the key factor for anti-tumor activities,[6,7] therefore we decided to prepare hybrids with this moiety (**C32-C37**, Scheme 4). Starting from tosylate **14**, allylic oxidation with selenium dioxide (SeO_2) and *tert*-butyl hydroperoxide (TBHP) afforded the desire alcohol **27**. To our surprise, ketone product **28** was also obtained in 45% yield, and this is obviously produced by a Wagner–Meerwein rearrangement of allylic alcohol **14**.[16] Treatment of compound **27** with sodium azide followed by Huisgen reaction provided corresponding triazoles in good yields. After oxidation with DMP, hybrid compounds **C32-C37** bearing α,β-unsaturated ketone unit in the D ring of allogibberic system were obtained. It is noteworthy that the formation of α,β-unsaturated ketone unit must be conducted right after the Huisgen's 1,3-dipolar cyclization. To increase the structure diversity, a number of hybrids (**C46-C53**) bearing a rearranged D ring system were also synthesized with similar transformations.

Next, a number of hybrid compounds containing α,β-unsaturated ketone moiety (**C38-C45**) were also synthesized from compound **21** (Scheme 5). Allylic oxidation of **21** with SeO_2 afforded alcohol **33** in 78% yield. With similar transformation, hybrids (**C38-C45**) were obtained in good yields.



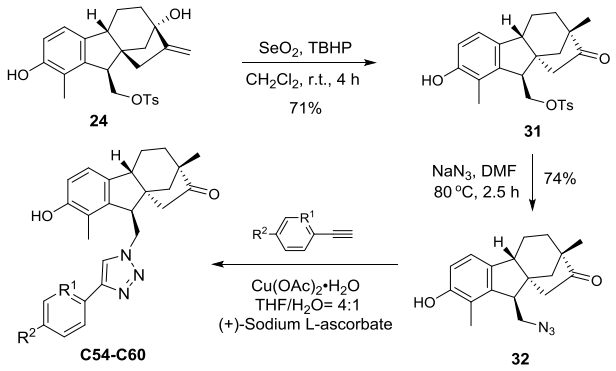
Scheme 4. Synthesis of hybrids **C32**-**C37** and **C46**-**C53**.



Scheme 5. Synthesis of allogibberic hybrids **C38**-**C45**.

Although the structure of compound **24** is similar to intermediate **14** (Scheme 1), it behaved differently when subjected to oxidative condition with SeO_2 and TBHP. The Wagner–Meerwein rearrangement product **31** was obtained as the major product (Scheme 6). In order to investigate the biological activities of more D-ring rearranged hybrids, we also

synthesized 1,2,3-triazoles (**C54-C60**) based on intermediate **31**.



C54 = (R^1=CH, R^2=H);
C55 = (R^1=CH, R^2=OMe); **C56** = (R^1=N, R^2=H); **C57** = (R^1=CH, R^2=CF_3);
C58 = (R^1=CH, R^2=CH_3); **C59** = (R^1=CH, R^2=Cl); **C60** = (R^1=CH, R^2=F)

Scheme 6. Preparation of hybrid compounds **C54-C60**.

The cytotoxic potential of all hybrid allogibberic triazole derivatives were evaluated *in vitro* against a panel of human tumor cell lines according to procedures described in the literature.[17, 18] The panel comprised human myeloid leukaemia (HL-60), human lung carcinoma (A549), human liver carcinoma (SMMC-7721), human colon carcinoma (SW480) and human breast carcinoma (MCF-7) cell lines. Taxol and Cisplatin (DDP) were used as the reference drugs. The results were indicated in Table 1 and Table 2.

Table 1

Cytotoxic activities of hybrid compounds **C1-C31** *in vitro*[b] (IC_{50}, mean ± SD, μM[a]).

Compd	HL-60	SMMC-7721	A-549	MCF-7	SW480
C1	>20	>20	>20	>20	>20
C2	>20	>20	>20	>20	>20
C3	>20	>20	>20	>20	>20
C4	>20	>20	>20	>20	>20
C5	>20	>20	>20	>20	>20
C6	>20	>20	>20	>20	>20
C7	>20	>20	>20	>20	>20
C8	>20	>20	>20	>20	>20
C9	>20	>20	>20	>20	>20
C10	>20	>20	>20	>20	>20
C11	>20	>20	>20	>20	>20
C12	>20	>20	>20	>20	>20
C13	>20	>20	>20	>20	>20
C14	>20	>20	>20	>20	>20
C15	>20	>20	>20	>20	>20
C16	>20	>20	>20	>20	>20
C17	>20	>20	>20	>20	>20
C18	>20	>20	>20	>20	>20
C19	>20	>20	>20	>20	>20
C20	>20	>20	>20	>20	>20
C21	8.95±0.48	>20	10.37±1.44	12.41±2.13	>20
C22	>20	>20	>20	>20	>20
C23	>20	>20	>20	>20	>20
C24	>20	>20	>20	>20	>20
C25	>20	>20	>20	>20	>20
C26	>20	>20	>20	>20	>20
C27	>20	>20	>20	>20	>20
C28	7.38±0.71	12.81±0.90	9.28±0.60	8.10±0.83	15.21±1.97
C29	>20	>20	>20	>20	>20
C30	5.59±0.34	19.14±0.79	10.52±0.40	10.18±0.53	17.99±2.17
C31	6.60±0.95	>20	17.92±0.88	19.22±4.05	>20
DDP	2.52±0.16	12.33±0.64	9.68±0.81	11.52±2.01	5.91±1.06
Taxol	<0.008	<0.008	<0.008	<0.008	<0.008

[a] Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay.
[b] Data represent the mean values of three independent determinations.

Table 2

Cytotoxic activities of hybrid compounds **C32-C60** *in vitro*[b] (IC_{50}, mean ± SD, μM[a]).

Compd	HL-60	SMMC-7721	A-549	MCF-7	SW480
C32	1.02±0.02	4.32±0.60	1.63±0.18	0.25±0.06	1.59±0.09
C33	1.02±0.12	1.72±0.14	1.47±0.06	0.31±0.03	1.64±0.38
C34	1.81±0.07	2.83±0.09	2.31±0.06	0.32±0.06	1.97±0.26
C35	1.11±0.09	4.41±0.92	1.83±0.24	0.32±0.04	1.46±0.10
C36	1.26±0.07	6.18±0.41	1.87±0.17	1.44±0.46	2.39±1.08
C37	1.29±0.11	4.28±0.07	1.95±0.04	0.33±0.07	1.63±0.26
C38	0.75±0.10	1.32±0.08	1.16±0.03	1.74±0.44	0.26±0.01
C39	0.56±0.04	1.30±0.05	1.14±0.01	0.27±0.02	0.31±0.01
C40	1.15±0.26	0.86±0.03	1.25±0.17	1.71±0.39	0.22±0.05
C41	1.97±0.32	1.27±0.13	1.57±0.19	2.24±0.76	0.41±0.15
C42	0.72±0.15	1.44±0.06	1.11±0.04	1.84±0.11	0.37±0.03
C43	0.83±0.19	0.92±0.05	1.26±0.06	0.37±0.08	0.33±0.05
C44	0.69±0.06	0.67±0.01	0.64±0.08	2.47±0.15	0.28±0.05
C45	0.66±0.04	0.85±0.05	0.94±0.05	1.70±0.26	0.25±0.03
C46	>20	>20	>20	>20	>20
C47	>20	>20	>20	>20	>20
C48	>20	>20	>20	>20	>20
C49	>20	>20	>20	>20	>20
C50	>20	>20	>20	>20	>20
C51	>20	>20	>20	>20	>20
C52	>20	>20	>20	>20	>20
C53	>20	>20	>20	>20	>20

C54	>20	>20	>20	>20	>20
C55	>20	>20	>20	>20	>20
C56	>20	>20	>20	>20	>20
C57	>20	>20	>20	>20	>20
C58	>20	>20	>20	>20	>20
C59	>20	>20	>20	>20	>20
C60	>20	>20	>20	>20	>20
DDP	1.77±0.22	3.62±0.60	5.40±0.97	11.52±2.01	8.22±1.62
Taxol	<0.008	<0.008	<0.008	<0.008	<0.008

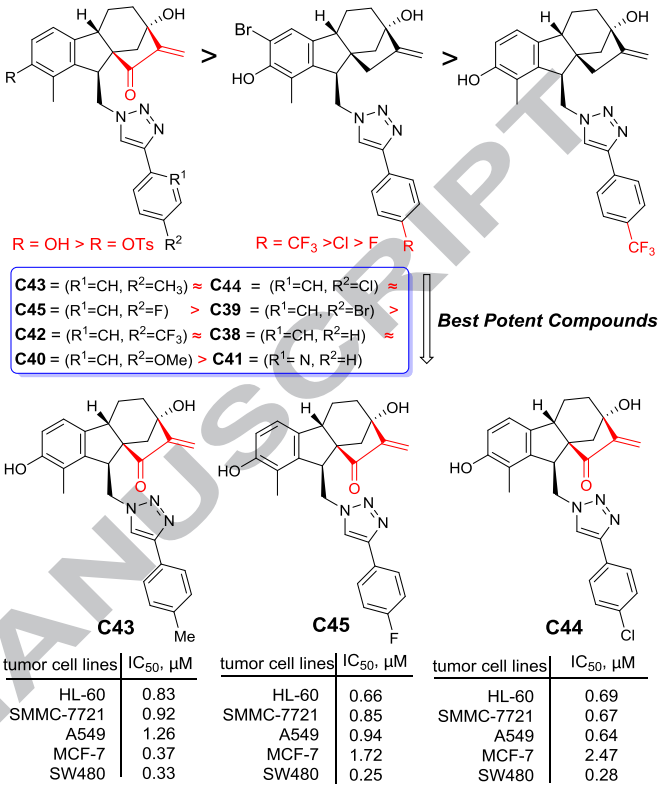
[a] Cytotoxicity as IC_{50} for each cell line, is the concentration of compound which reduced by 50% the optical density of treated cells with respect to untreated cells using the MTT assay.

[b] Data represent the mean values of three independent determinations.

As displayed in Table 1 and Table 2, the allogibberic triazoles **C1-C20**, **C22-C27**, **C29** and **C46-C60** were inactive against all five human cancer cell lines at concentrations lower than 20 μM. The hybrid compounds **C21**, **C28**, **C30**, **C31** showed weak activities, however, the hybrid compounds **C32-C45** containing α,β-unsaturated ketone moiety exhibited excellent activities against all five human tumor cell lines. The *p*-toluenesulfonate hybrids (**C32-C37**) exhibited potent cytotoxic activities against A-549, MCF-7 and SW480 cell lines with IC_{50} value of 0.25-2.31 μM. Specifically, the allogibberic *p*-toluenesulfonate derivatives (**C32-C37**) were more selective to MCF-7 cell lines with IC_{50} values 46-fold, 37-fold, 36-fold, 36-fold, 8-fold and 35-foldbetter than DDP, respectively. To our delight, the phenolic hybrids **C38-C45** also displayed excellent inhibitory activities against HL-60, SMMC-7721, A549, MCF-7 and SW480 cell lines as compared with standard drug Cisplatin (DDP). Interestingly, the allogibberic phenol derivatives (**C38-C45**) were more sensitive to SW480 cell lines with IC_{50} values 31-fold, 26-fold, 29-fold, 20-fold, 22-fold, 25-fold, 29-fold and 33-fold better than DDP, respectively.

Among hybrid compounds without α,β-unsaturated ketone system, only four compounds, namely **C21**, **C28**, **C30**, **C31**, bearing electron withdrawing groups in the 4-phenyl-1,2,3-triazole units showed weak activities against cancer cell lines. These results suggested that electron withdrawing groups presented on the phenyl ring of the 4-phenyl-1,2,3-triazole system might play some role.

In general, the bioassay results of compounds **C1-C60** indicated that presence of α,β-unsaturated ketone moiety in the allogibberic units is vital for anti-tumor activities. For the 4-aryl-1,2,3-triazole system, 4-phenyl-1,2,3-triazoles are better than 4-pyridyl substituent compounds. Although the electronic effects, based on hybrids **C32-C45**, are not obvious, the electron withdrawing 4-chlorophenyl-1,2,3-triazole and 4-fluorophenyl-1,2,3-triazole hybrid compounds are more cytotoxic than electron donating 4-methoxyphenyl substituent compounds. Compound **C43-C45** have broad spectrum of anticancer activity and can be used for further studies. The structure-activity relationship (SAR) results were summarized in Scheme 7.



tumor cell lines	IC_{50}, μM
HL-60	0.83
SMMC-7721	0.92
A549	1.26
MCF-7	0.37
SW480	0.33

tumor cell lines	IC_{50}, μM
HL-60	0.66
SMMC-7721	0.85
A549	0.94
MCF-7	1.72
SW480	0.25

tumor cell lines	IC_{50}, μM
HL-60	0.69
SMMC-7721	0.67
A549	0.64
MCF-7	2.47
SW480	0.28

Scheme 7. Structure-activity relationship of allogibberic 1,2,3-triazole hybrids.

We also conducted experiments on apoptosis and the cell cycle distribution of SMMC-7721 cell lines with hybrid compound **C45**. The SMMC-7721 cell lines were exposed to increasing concentrations of compound **C45** and cell apoptosis was determined with Annexin V-FITC/PI double-labeled cell cytometry. As displayed in Figure 2, after treatment of cells with compound **C45** at 0.425, 0.85, 1.7 and 3.4 μM for 48 h, the apoptotic cell rate was 15.90±0.16%, 18.63±0.13%, 55.20±0.85% and 97.81±0.01%, respectively, which were statistically different from the control (0.035±0.0007%).

To determine whether the high inhibitory effect of hybrid compound **C45** was caused by cell cycle accumulation at a certain phase, a cell-cycle cytotoxicity assay was performed by treating SMMC-7721 cells at different concentrations of compound **C45** (0, 0.425, 0.85, 1.7, 3.4 μM). The results of cell-cycle cytotoxicity assay on SMMC-7721 cell lines treated with compound **C45** were indicated in Figure 3. Compared with the control cells, the proportion of cells in the S phase was increased in the cells incubated with compound **C45** in a dose dependent manner. Meanwhile, the percentage of cells in the G0/G1 and G2/M phases decreased slightly. The data suggest that compound **C45** may induce S phase arrest in the cell cycle.

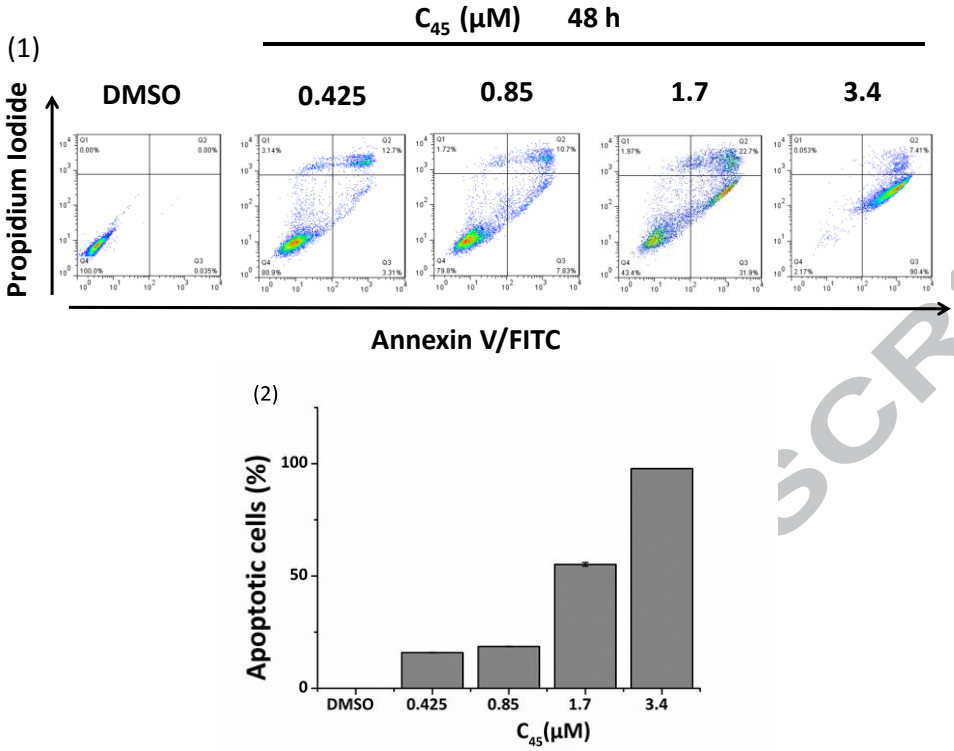
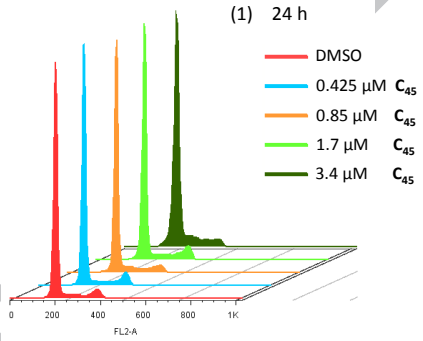


Figure 2. Compound **C45** caused significant apoptosis of SMMC-7721 cell lines. (1) Cells were treated with 0.425, 0.85, 1.7 and 3.4 μM compound **C45** for 48 h. Cell apoptosis was determined by Annexin V-FITC/PI double-staining assay. (2) The quantification of cell apoptosis. Data represents the mean ± S.D. of three independent experiments.



(2)

Treatment	SMMC 7721 (%)		
	G0/G1	S	G2/M
DMSO	77.85±1.90	13.71±0.62	5.72±0.59
0.425 μM **C45**	78.27±0.07	13.92±0.06	6.24±0.82
0.85 μM **C45**	74.23±0.69	17.38±1.74	7.70±5.30
1.70 μM **C45**	70.87±0.30	19.35±1.92	6.05±1.70
3.40 μM **C45**	71.54±0.17	22.73±0.63	0.89±0.01

Figure 3. Cell-cycle cytotoxicity assay in SMMC-7721 cell lines. (1) Cells were treated with 0.425, 0.85, 1.7 and 3.4 μM of compound **C45** for 24 h. Cell cycle was determined by PI staining and cell cytometry. (2) The percentages of cells in different phases were quantified. At least three independent experiments were performed and data of one representative experiment is displayed.

A series of novel alligibberic 1,2,3-triazole hybrids were designed and synthesized. Their biological activities were evaluated *in vitro* against five human tumor cell lines. The results indicated that the presence of α,β-unsaturated ketone moiety in the allogibberic units had remarkable effects for anti-tumor cytotoxicity. The hybrid compounds **C21**, **C28**, **C30**, **C31** showed only weak activities against five human tumor cell lines. However, the hybrids **C32-C45** bearing α,β-unsaturated ketone moiety exhibited excellent *in vitro* cytotoxicity. Compounds **C32-C37** were more sensitive to MCF-7 cell lines while the hybrids **C38-C45** were more selective to SW480 cell lines, with IC_{50} values at least 8 to 20-fold more cytotoxic than Cisplatin (DDP). Compounds **C43-C45** have broad spectrum of anticancer activities. The best potent compounds were **C43** and **C45**, with IC_{50} values of 0.33–1.26 μM and IC_{50} values of 0.25–1.72 μM against all five tested tumor cell lines respectively. Mechanism of action studies indicated that compound **C45** can cause the S phase cell cycle arrest and apoptosis in SMMC-7721 cell lines. In summary, compounds **C43**, **C44** and **C45** were promising hybrids of allogibberic derivatives and 1,2,3-

triazoles. This kind of hybrid structure could serve as a new starting point to explore better lead compounds for the development of new anti-breast and colon cancer agents.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

This work was supported by grants from the Program for Changjiang Scholars and Innovative Research Team in University (IRT17R94), Natural Science Foundation of China (U1702286, 21572197,U1402227 and 21662043), Yunling scholar of Yunnan Provinceand the Program for Innovative Research Team (in Science and Technology) in University of Yunnan Province. Prof. Yang acknowledges support from the Donglu scholar and excellent young talents program of Yunnan University.

A. Supplementary data

Details of experimental procedure, spectral data and copies of all novel compounds. See DOI: 10.1039/x0xx00000x.

Notes and references

1 Harvey AL. *Drug Discovery Today*.2008; 13: 894.

2 Newman DJ, Cragg GM. *J. Nat. Prod.* 2012; 75: 311.

3 (a) Mander LN. *Chem. Rev*. 1992; 92: 573; (b) Mander LN. *Nat. Prod. Rep*. 2003; 20: 49.

4 Curtis PJ, Cross BE. *Chemistry & Industry*. 1954; 35: 1066.

5 Rodrigues C, Vandenberghe LPD, Oliveira J de, Soccol CR. *Crit Rev Biotechnol*, 2012; 32: 263.

6 Zhang H, Chen J, Liu J, Qing C. Chin. Patent, CN156004A, 2005; ZL200410021939.2: 2007.

7 (a) Chen J, Sun Z, Zhang Y, Zeng X, Qing C, Liu J, Li L, Zhang H. *Bioorg. Med. Chem. Lett*. 2009; 19: 5496; (b) Zhang Y, Zhang H, Chen J, Zhao H, Zeng X, Zhang H, Qing C. *Invest New Drugs* 2012; 30: 8; (c) Chen J, Sun Z, Zhang Y, Chen J, Li P, Zeng X, Yin B, Xie Y, Qing C, Zhang H. *Chin. J. Org. Chem.* 2014; 34: 788.

8 Koehler KN. Methods for modulating NF-kB using gibberellins, U.S. Patent, WO2010/62372.

9 (a) Balkwill F, Mantovani A. *Lancet*. 2001; 357: 539; (b) Coussens LM,Werb Z. *Nature*. 2002; 420: 860.

10 Kim KH, Choi SU, Son MW, Choi SZ, Clardy J, Lee KR. *J. Nat. Prod*. 2013; 76: 1376.

11 (a) Huigens Ⅲ RW, Morrison KC, Hicklin RW, Flood Jr TA, Richter MF, Hergenrother PJ. *Nat. Chem.* 2013; 5: 195; (b) Richter MF, Drown BS, Riley AP, Garcia A, Shirai T, Svec RL, Hergenrother PJ. *Nature*. 2017; 545: 299.

12 Annand JR, Bruno PA, Mapp AK, Schindler CS. *Chem. Commun*. 2015; 51: 8990.

13 (a) Liu LX, Wang XQ, Yan JM, Li Y, Sun CJ, Chen W, Zhou B, Zhang HB, Yang XD. *Eur. J. Med. Chem.* 2013; 66: 423; (b) Wang XQ, Liu LX, Li Y, Sun CJ, Chen W, Li L, Zhang HB, Yang XD. *Eur. J. Med. Chem.* 2013; 62: 111; (c) Chen W, Zeng XH, Deng XY, Li Y, Yang LJ, Wan WC, Wang XQ, Zhang HB, Yang XD. *Bioorg. Med. Chem. Lett.* 2013; 23: 4297; (d) Sun C, Chen W, Li Y, Liu L, Wang X, Li L, Zhang H, Yang X. *RSC Adv*. 2014; 4: 16312; (e) Xu X, Wang J, Yu C, Chen W, Li Y, Zhang H, Yang X. *Bioorg. Med. Chem. Lett.* 2014; 24: 4926; (f) Liu L, Wang X, Zhou B, Yang L, Li Y, Zhang H, Yang X. *Sci. Rep*. 2015; 5: 13101; (g) Wang X, Li Y, Yang X, Zhang H. *Chin. J. Org. Chem.* 2015; 35: 1276; (h) Liu J, Wang M, Zhou Y, Yan J, Yang L, Li Y, Zhang H, Yang X. *RSC Adv*. 2015; 5: 63936; (i) Xu X, Yu C, Chen W, Li Y, Yang L, Li Y, Zhang H, Yang X. *Org. Biomol. Chem.* 2015; 13: 1550; (j) Zhou B, Liu Z, Deng G, Chen W, Li M, Yang L, Li Y, Yang X, Zhang H. *Org. Biomol. Chem.* 2016; 14: 9423; (k) Liu ZF, Zhang CB, Duan SZ, Li Y, Chen W, Li Y, Zhang HB, Yang XD. *Chin. J. Org. Chem.* 2017; 37: 1506; (k) Zhang CB, Liu Y, Liu ZF, Duan SZ, Li MY, Chen W, Li Y, Zhang HB, Yang XD. *Bioorg. Med. Chem. Lett.* 2017; 27: 1808.

14 For selected reviews and research articles, see: (a) Thirumurugan P, Matosiuk D, Jozwiak K. *Chem. Rev*. 2013; 113: 4905; (b) Zhang S, Xu Z, Gao C, Ren QC, Chang L, Lv ZS, Feng L. *Eur. J. Med. Chem.* 2017; 138: 501; (c) Simone R De, Chini MG, Bruno I, Riccio R, Mueller D, Werz O, Bifulco G, *J. Med. Chem.* 2011; 54: 1565; (d) Patpi RS, Pulipati L, Yogeeswari P, Sriram D, Jain N, Sridhar B, Murthy R, Devi TA, Kalivendi SV, Kantevari S. *J. Med. Chem.* 2012; 55: 3911; (e) Duan Y, Zheng Y, Li X, Wang M, Ye X, Guan Y, Liu G, Zheng J, Liu H. *Eur. J. Med. Chem.* 2013; 64: 99; (f) Xu J, Zhang E, Shi X, Wang Y, Yu B, Jiao W, Guo Y, Liu H. *Eur. J. Med. Chem.* 2014; 80: 593; (g) He Y, Dong C, Zhao J, Ma L, Li Y, Aisa HA, *Eur. J. Med. Chem.* 2014; 76: 245; (h) Senwar KR, Sharma P, Reddy TS, Jeengar MK, Nayak VL, Naidu VGM, Kamal A, Shankaraiah N. *Eur. J. Med. Chem.* 2015; 102: 413; (i) Pribut N, Veale CGL, Basson AE, van Otterlo WAL, Pelly SC. *Bioorg. Med. Chem. Lett.* 2016; 26: 3700; (j) Mohammed I, Kummetha IR, Singh G, Sharova N, Lichinchi G, Dang J, Stevenson M, Rana TM, *J. Med. Chem.* 2016; 59: 7677; (k) Ali AA, Gogoi D, Chaliha AK, Buragohain AK, Trivedi P, Saikia PJ, Gehlot PS, Kumar A, Chaturvedi V, Sarma D. *Bioorg. Med. Chem. Lett.* 2017; 27: 3698; (l) Song P, Cui F, Li N, Xin J, Ma Q, Meng X, Wang C, Cao Q, Gu Y, Ke Y, Zhang Q, Liu H. *Chin. J. Chem.*, 2017; 35: 1633; (m) Wang B, Zhao B, Chen Z, Pang L, Zhao Y, Guo Q, Zhang X, Liu Y, Liu G, Zhang H, Zhang X, Ma L, Liu H. *Eur. J. Med. Chem.* 2018; 143: 1535.

15 (a) Rostovtsev VV, Green LG, Fokin VV, Sharpless KB. *Angew. Chem. Int. Ed*.2002; 41: 2596. (b) Kolb HC, Finn MG, Sharpless KB. *Angew. Chem. Int. Ed*. 2001; 40: 2004.

16 (a) Cross BE. *J. Chem. Soc.* 1954; 4670. (b) Cross BE, Grove JF, Morrison A, *J. Chem. Soc.*, 1961, 2498.

17 Kim DK, Ryu DH, Lee JY, Lee N, Kim YW, Kim JS, K. Chang, Im GJ, Kim TK, Choi WS. *J. Med. Chem.* 2001; 44: 1594.

18 Cao R, Chen Q, Hou X, Chen H, Guan H, Ma Y, Peng W, Xu A. *Bioorg. Med. Chem.* 2004; 12: 4613.

Highlights

► Novel allogibberic acid derivatives containing 1,2,3-triazole were prepared.

► Their anti-proliferative activity were evaluated.

► Hybrids containing α,β-unsaturated ketone exhibited excellent cytotoxic activity.

► Hybrids **C43** and **C45** were found to be the most potent derivatives.

► **C45** can induce the S phase cell cycle arrest and apoptosis in SMMC-7721 cells.