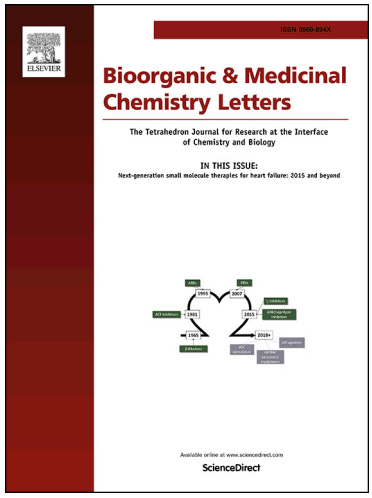
# Accepted Manuscript




Synthesis and evaluation of the HIF-1α inhibitory activities of novel ursolic acid tetrazole derivatives

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# Synthesis and evaluation of the HIF-1α inhibitory activities of novel ursolic acid tetrazole derivatives

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## Abstract

The hypoxia-inducible factor-1α (HIF-1α) pathway has been implicated in tumor angiogenesis, growth, and metastasis. Therefore, the inhibition of this pathway is an important therapeutic target for the treatment of various types of cancers. Here, we designed and synthesized 31 ursolic acid (UA) derivatives containing a tetrazole moiety and evaluated them for their potential anti-tumor activities as HIF-1α transcriptional inhibitors. Of these, compound **14d** ($IC_{50}$ 0.8 ± 0.2 μM) displayed the most potent activity and compounds **14a** ($IC_{50}$ 4.7 ± 0.2 μM) exhibited the most promising biological profile. Analysis of the structure–activity relationships of these compounds with HIF-1α suggested that the presence of a tetrazole group located at C-28 of the UA derivatives was critical for their inhibitory activities.

***Keywords:*** Ursolic acid; Tetrazole; HIF-1α inhibitor; Cytotoxicity

Hypoxia-inducible factor 1α (HIF-1α) has been implicated in a variety of diseases, including cancer,[1,2] infections,[3,4] inflammatory diseases,[5,6] and Parkinson's disease.[7] HIF-1α expression levels are controlled by cellular oxygen concentrations. It is abundantly expressed in solid tumor cells and plays a key role in tumor cell adaptation to hypoxic environments created by rapid tumor growth.[8] HIF-1α is a known regulator of tumor cell proliferation, migration, and angiogenesis,[9] and the presence of a high concentration of HIF-1α is positively correlated with cancer severity.[10] In addition, the recurrence of cancer after resection is related to HIF-1α overexpression.[11] Therefore, HIF-1α has become an attractive target for the development of new anti-cancer drugs.[12-14]

Several recent reports have investigated various structural modifications to develop the bioactive properties of the pentacyclic triterpenoid ursolic acid (UA), with an aim to generate potent novel anti-cancer agents. Indeed, structural modifications of the UA C-28 carboxylic acid group or C-3 hydroxy group have been shown to significantly enhance its anticancer activity.[15-21] Wu *et al* reported that the oxidation of the UA C-3 hydroxyl group to a carbonyl group greatly enhanced its antitumor properties,[19] while Bai *et al* showed that acetylation of the UA C-3 hydroxy group and amidation of the UA C-28 carboxyl group also resulted in an enhancement of its anticancer activity.[16] However, studies by Gu *et al* indicated that substitutions of large functional groups at the C-3 and C-28 positions are likely to decrease its anticancer activity.[17,22] In our previous work, we observed that the introduction of a triazolone moiety to the C-28 position of UA increased HIF-1α inhibition with low cytotoxic effects (Fig. 1, compound A).[23] Recently, we reported the design, synthesis, and screening of a series of compounds containing an aminoguanidine moiety. We revealed that compound B (Fig. 1, compound B) displayed the most potent inhibitory effect on HIF-1α activity. However, some of these derivatives showed significant cytotoxicity against a Hep3B cell line.[24] As a result, we attempted to replace the triazolone moiety with other azoles at the C-28 position of UA and to shorten the distance between UA and the azole ring. In addition, we simultaneously introduced small changes at the C-3 position by acetylation and oxidation to identify further potent novel HIF-1α inhibitors with low

cytotoxicity.

Tetrazole derivatives have been reported to possess a broad spectrum of therapeutic activities including anti-microbial,[25,26] anti-bacterial,[27,28] antioxidant,[29,30] anti-HIV,[31] anti-leishmanial,[32] and anti-cancer activities.[26,33] Tetrazole is also a mimetic of carboxylic acid.[34] Several tetrazole-containing drugs have been developed for clinical use, including cefazolin,[35] valsartan,[36] and pentetrazole,[37] some of which possess a tetrazolium group as a terminal moiety (Fig. 1). Therefore, we hypothesized that the introduction of a terminal tetrazole functional group to the C-28 of UA is likely to enhance its biological potency. In this study, we designed and synthesized eight novel series of UA derivatives containing a tetrazole moiety (31 compounds in total) and evaluated their ability to inhibit hypoxia-induced HIF-1α transcriptional activity.

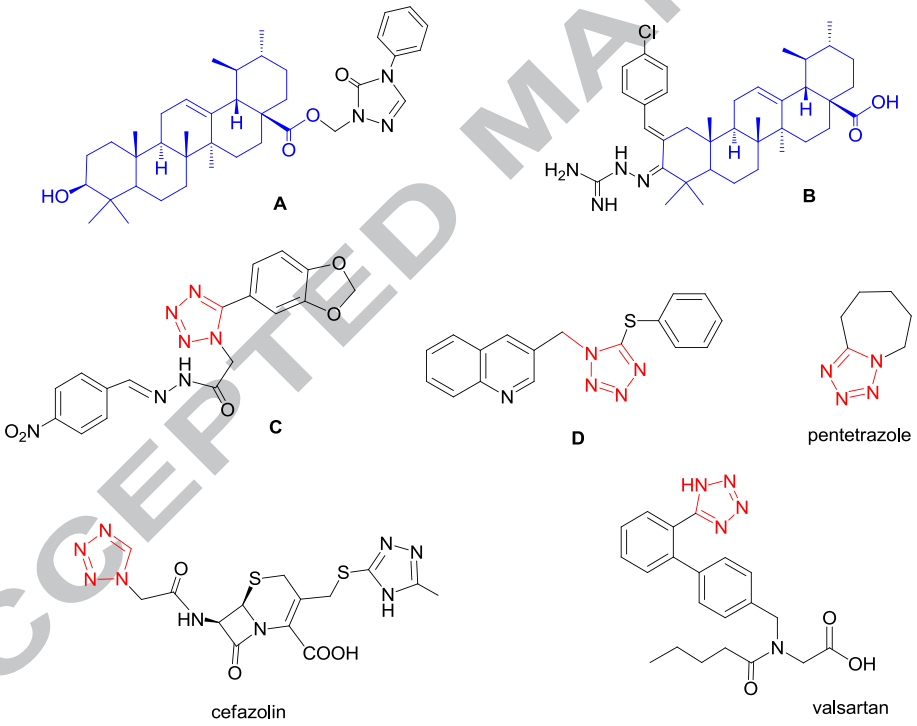
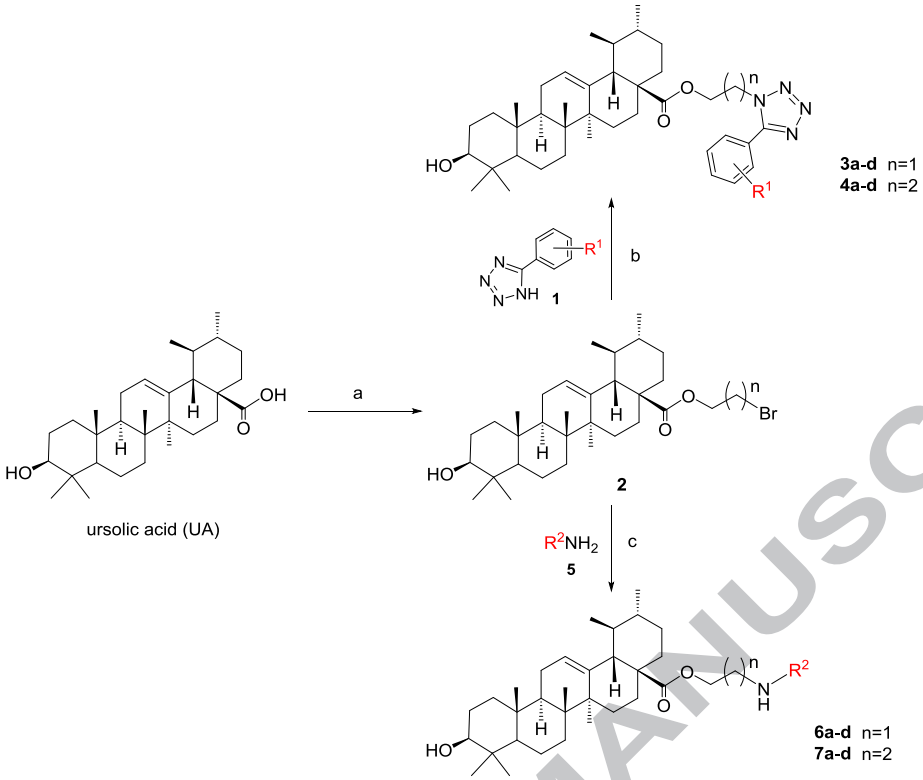


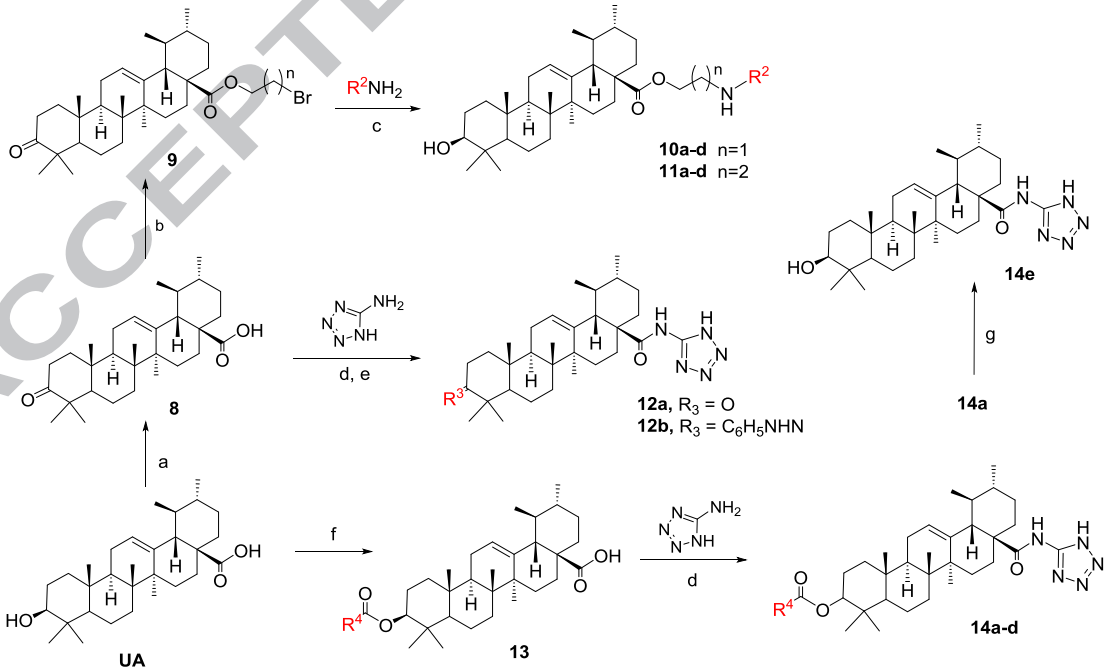

**Figure 1**. Structures of previously reported compounds as anticancer agents and clinical medicines containing tetrazole moiety.

The synthetic pathway of the target compounds **3a–d**, **4a–d**, **6a–d**, and **7a–d** is presented in Scheme 1. The intermediate **1** was synthesized according to a reported method.[2] The intermediate **2** was prepared by mixing UA with an equimolar concentration of $K_2CO_3$, a catalytic amount of KI, and more than two equivalents of 1,2-dibromoethane or 1,3-dibromopropane in DMF and stirring at 50 °C for 6h. The

target compounds **3a–d**, **4a–d**, **6a–d**, and **7a–d** were prepared by reacting intermediate **2** with 5-substituted-phenyl-1*H*-tetrazoles (**1**) or amines (**5**), respectively, in the presence of $KI/K_2CO_3$ in refluxing acetone. The synthetic pathway of the target compounds **10a–d**, **11a–d**, **12a–b**, and **14a–e** is presented in Scheme 2. Jones reagent was used to prepare intermediate **8** with UA, which was subsequently alkylated to yield intermediate **9**. The series **10** and **11** compounds were synthesized using the same method described above to generate series **6** and **7**. The intermediate **8** was reacted with sulfoxide chloride for 4h in refluxing dichloromethane (DCM) to obtain acyl chloride, which was dissolved in anhydrous DCM and added to a mixture of DMF/DCM (1:1), trimethylamine, and 5-aminotetrazole in an ice bath. Following a 1h reaction, the mixture was stirred for another 2 days at room temperature to yield compound **12a**. Compound **12b** was synthesized by reacting **12a** with phenyl hydrazine hydrochloride with a few drops of acetic acid in refluxing ethanol. Intermediate **13** was prepared by mixing UA with corresponding anhydrides in the presence of DMAP and trimethylamine in an ice bath, followed by stirring overnight at room temperature. Compounds **14a-d** were synthesized by reacting **13** with sulfoxide chloride in refluxing dichloromethane (DCM). Compound **14e** was prepared by hydrolyzing compound **14a** with 10%NaOH. The structures of all derivatives were characterized by $^{1}H$ and $^{13}C$ NMR spectroscopy and high-resolution mass spectrometry.




**Scheme 1.** Synthetic scheme for the synthesis of compounds **3a-d**, **4a-d**, **6a-d and 7a-d**. Reagents and conditions: (a) 1,2-dibromoethane or 1,3-dibromopropane, $K_2CO_3$, KI, DMF, 50 °C, 6h; (b) $K_2CO_3$, KI, acetone, reflux, 8h; (c) $K_2CO_3$, KI, acetone, reflux, 10h.




**Scheme 2.** Synthetic scheme for the synthesis of compounds **10a-d**, **11a-d**, **12a-b and 14a-f**. Reagents and conditions: (a) Jones' reagent, acetone, 0 °C, 5 h, 90%; (b) 1,2-dibromoethane or 1,3-dibromopropane, $K_2CO_3$, KI, DMF, 50 °C, 6h; (c) $K_2CO_3$,

KI, acetone, reflux, 10h; (d) $SOCl_2$, DMF/DCM (1:1), trimethylamine; (e) Phenyl hydrazine hydrochloride, acetic acid, ethanol, reflux,8h; (f) anhydride, DMAP, DCM, trimethylamine, r.t., overnight; (g) 10%NaOH, 4N HCl, 50% methanol in water.

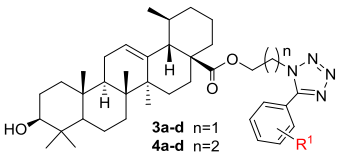
The *in vitro* activities of the UA derivatives are summarized in Table 1 and Table 2. To examine the effect of the UA derivatives on hypoxia-induced HIF-1α transcriptional activity, Hep3B cells were transfected with a luciferase reporter construct containing six hypoxia-response elements, and then exposed to hypoxia (1% $O_2$) for 24h. Luciferase activity in the cell culture supernatants was subsequently measured.[2] The cytotoxicity of each of the derivatives against Hep3B cells was evaluated using the MTT assay. UA and compounds A and B were used as positive controls.

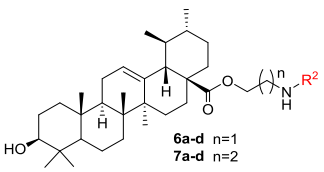
We found the majority of the synthesized compounds inhibited HIF-1α transcriptional activity. While six of the eight series **3** and **4** compounds exhibited moderate to good inhibitory activities, compound **4b** exhibited a potent inhibitory activity ($IC_{50}$ 7.5 ± 0.2 μM). The substituents on the benzene ring attached to the tetrazole moiety were found to affect potency in an arbitrary manner, which meant that a meaningful structure–activity relationship could not be determined from the data. Similarly, we did not observe any significant correlation between inhibitory potency and the relative distance between UA and the tetrazole moiety. Most of the series **6** and **7** compounds containing a terminal free tetrazole moiety showed moderate inhibitory activities in the following order: *meta* position > *para* position > *ortho* position. Compounds with two carbon linkages between UA and the tetrazole moiety exhibited higher inhibitory activities compared with compounds with three carbon linkages. A comparison of the activities of compounds **6a** or **7a** with compounds containing a benzene group connected to the tetrazole ring suggested that HIF-1α inhibitory activity was enhanced in the absence of a benzene ring. Next, we compared the inhibitory activities of the compounds in series **10** and **11** to their series **6** and **7** counterparts. The only difference between these compounds is that the hydroxy group at the C-3 position in the series **6** and **7** compounds was oxidized by Jones' reagent to create the series **10** and **11** compounds. All other substituents were equivalent. We concluded that the series **10** and **11** compounds were slightly less

potent than their series **6** and **7** counterparts. Furthermore, the structure–activity relationships of the series **10** and **11** compounds were comparable to the compounds from series **6** and **7**.

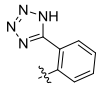
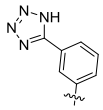
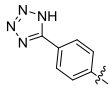
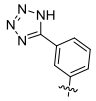
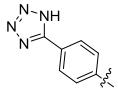
Almost all of the series **12** and **14** compounds exhibited higher activities compared with the compounds in the other series. In these series, the tetrazole group was directly linked to a nitrogen atom of the amide group at the C-28 position, and the C-3 hydroxy group was either unmodified, oxidized, esterified, or changed to hydrazine. The unique feature of this series of compounds was that the tetrazole moiety was directly introduced to the C-28 position by means of an amide bond without any additional linkages. Compound **14d** showed the most potent inhibition of HIF-1α transcriptional activity with an $IC_{50}$ value of 0.8 ± 0.2 μM. However, it did exert a moderate cytotoxic effect ($IC_{50}$ 18.5 ± 0.2 μM). In contrast, we recorded a reasonable inhibitory activity without an enhancement of cytotoxicity when the C-3 hydroxy group was oxidized to a ketone, as shown for compound **12a** ($IC_{50}$ 18.1 ± 0.2 μM)**.** However, further modification of the C-3 hydroxy group to a phenylhydrazine derivative (**12b**) resulted in increases in both the HIF-1α transcriptional inhibitory activity ($IC_{50}$ 2.2 ± 0.1 μM) and cytotoxicity ($IC_{50}$ 11.9 ± 0.2 μM). The results obtained for compounds **14a**–**e** ($IC_{50}$ 4.7 ± 0.2 μM**,** 1.6 ± 0.2 μM, 1.4 ± 0.2 μM, 0.8 ± 0.2 μM, and 13.3 ± 0.2 μM respectively**)** strongly suggested that the esterification of the **14e** C-3 hydroxy group could not only increase the HIF-1α inhibitory activity but also enhanced the cytotoxicity except for **14a**, indicating that the presence of a larger group in this position is detrimental for the development of a suitable HIF-1α inhibitor.

**Table 1.** *In vitro* inhibition of HIF-1α transcriptional activity and cytotoxicity of the series **3**, **4**, **6** and **7** compounds.



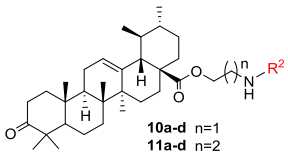

| Compound | n | $R^1$ | $R^2$ | $IC_{50}$(μM) | |
|---|---|---|---|---|---|
| | | | | HRE [a] | Cytotoxicity [b] |

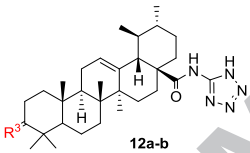
| | | | | | |
|---|---|---|---|---|---|
| UA | – | – | – | >100 | 23.8 ± 0.2 |
| 3a | 1 | H | – | 18.1 ± 0.2 | >100 |
| 3b | 1 | 4-Cl | – | 76.4 ± 0.2 | >100 |
| 3c | 1 | 4-$CH_3O$ | – | >100 | >100 |
| 3d | 1 | 3,4-($OCH_2O$) | – | >100 | >100 |
| 4a | 2 | H | – | 40.0 ± 0.2 | >100 |
| 4b | 2 | 4-Cl | – | 7.5 ± 0.2 | >100 |
| 4c | 2 | 4-$CH_3O$ | – | 27.4 ± 0.2 | >100 |
| 4d | 2 | 3,4-($OCH_2O$) | – | 83.0 ± 0.2 | >100 |
| 6a | 1 | – |  | >100 | >100 |
| 6b | 1 | – |  | 8.9 ± 0.2 | >100 |
| 6c | 1 | – |  | 26.2 ± 0.2 | >100 |
| 6d | 1 | – |  | 8.5 ± 0.2 | >100 |
| 7a | 2 | – |  | >100 | >100 |
| 7b | 2 | – |  | 13.2 ± 0.2 | >100 |
| 7c | 2 | – |  | >100 | >100 |

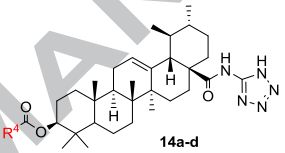
| | | | | | |
|---|---|---|---|---|---|
| 7d | 2 | – |  | 10.3 ± 0.2 | >100 |
| Comp. A | – | – | – | 36.9 ± 0.3 | >100 |
| Comp. B | – | – | – | 4.0 ± 0.2 | >100 |

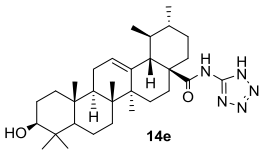
[a] The inhibitory effects of all the derivatives on HIF-1α transcriptional activity were tested by HRE luciferase reporter assay after 24 h treatment of Hep3B cells under hypoxic conditions. Values were shown as mean ± SE, n=3.
[b] The cytotoxic activity was evaluated by MTT assay after 24 h treatment of compounds under normoxic conditions. Values were shown as mean ± SE, n=3.

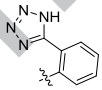
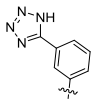
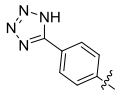
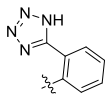
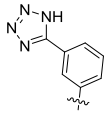
**Table 2.** *In vitro* inhibition of HIF-1α transcriptional activity and cytotoxicity of the series **10**, **11**, **12** and **14** compounds.

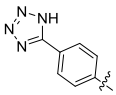
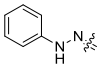
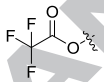
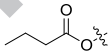
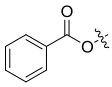









| Compound | n | $R^2$ | $R^3$ | $R^4$ | $IC_{50}$(μM) | |
|---|---|---|---|---|---|---|
| | | | | | HRE [a] | Cytotoxicity [b] |
| 10a | 1 |  | – | – | >100 | >100 |
| 10b | 1 |  | – | – | >100 | >100 |
| 10c | 1 |  | – | – | 18.1 ± 0.2 | >100 |
| 10d | 1 |  | – | – | 14.2 ± 0.2 | >100 |
| 11a | 2 |  | – | – | >100 | >100 |
| 11b | 2 |  | – | – | >100 | >100 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 11c | 2 |  | – | – | >100 | >100 |
| 11d | 2 |  | – | – | 16.7 ± 0.2 | >100 |
| 12a | – | – |  | – | 18.1 ± 0.2 | >100 |
| 12b | – | – |  | – | 2.2 ± 0.1 | 11.9 ± 0.2 |
| 14a | – | – | – |  | 4.7 ± 0.2 | >100 |
| 14b | – | – | – |  | 1.6 ± 0.2 | 6.4 ± 0.2 |
| 14c | – | – | – |  | 1.4 ± 0.2 | 4.7 ± 0.2 |
| 14d | – | – | – |  | 0.8 ± 0.2 | 18.5 ± 0.2 |
| 14e | – | – | – | – | 13.3 ± 0.2 | >100 |

[a] The inhibitory effects of all the derivatives on HIF-1α transcriptional activity were tested by HRE luciferase reporter assay after 24 h treatment of Hep3B cells under hypoxic conditions. Values were shown as mean ± SE, n=3.
[b] The cytotoxic activity was evaluated by MTT assay after 24 h treatment of compounds under normoxic conditions. Values were shown as mean ± SE, n=3.

Compound **14a** with the most desirable inhibitory activity against HIF-1α out of all the derivatives tested, was selected for further biological evaluation. As shown in Fig. 2, compound **14a** dose-dependently inhibited the luciferase activity in Hep3B cells (Figs. 2A) and concentration up to 30 μM did not adversely affect cell viability (Fig. 2B).

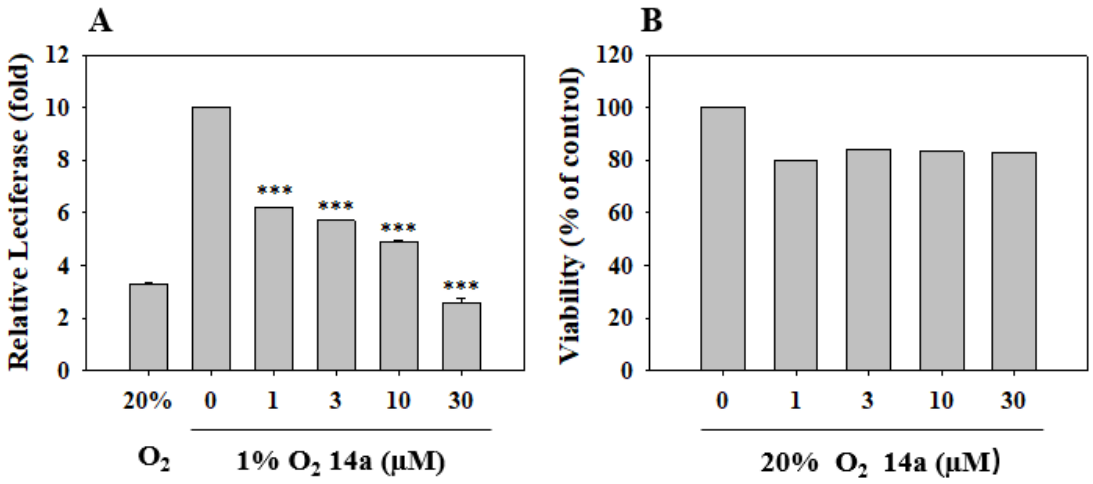



**Figure 2.** Effect of compound **14a** on HRE-mediated reporter gene expression. (A) Hep3B cells were transiently co-transfected with a pGL3-HRE-Luciferase and pRL-CMV vectors. Following 24 h incubation, the cells were incubated under hypoxia in the absence or presence of the indicated concentrations of compound **14a**. Luciferase activities were determined as described in "Materials and Methods". Data are represented as the mean ± standard deviation of three independent experiments. $*p < 0.05$, $**p < 0.01$, $***p < 0.001$, significant with respect to the control. (B) Hep3B cells were treated with the indicated concentrations of compound **14a**. After 24 h incubation, cell viability was determined by MTT assays.

In summary, several series of ursolic acid tetrazole derivatives were designed, synthesized, and evaluated for their HIF-1α inhibitory activities. Of the compounds tested, compound **14a** showed the most promising HIF-1α inhibitory activity with an $IC_{50}$ of 4.7 ± 0.2 μM and did not show any significant cytotoxicity at a concentration of 30μM against a Hep3B cell line. Furthermore, its inhibitory activity was comparable to compound B and eight times more potent than compound A. Analysis of the structure–activity relationships of the compounds inhibiting HIF-1α suggested that introduction of the tetrazole moiety at the C-28 position of UA is critical for increasing the HIF-1α inhibitory activity and a larger group at the C-3 position is detrimental for the development of a suitable HIF-1α inhibitor.

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Graphical abstract

# Synthesis and evaluation of the HIF-1α inhibitory activities of novel ursolic acid tetrazole derivatives

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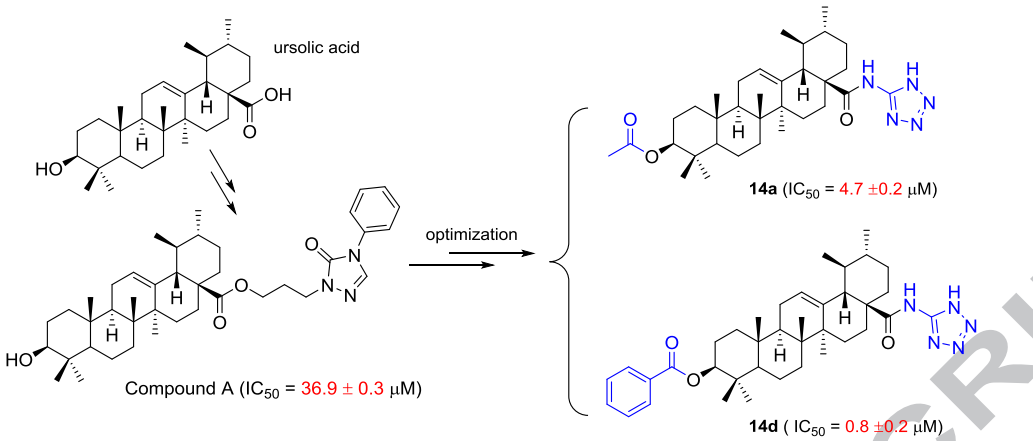

**Highlights:**

- Eight series of ursolic acid-tetrazole derivatives were designed and synthesized.
- The inhibitory activity on HIF-1α pathway and cytotoxicity of these compounds were evaluated.
- Compound **14a** is a promising lead for searching effective HIF-1α inhibitors**.**
- The investigation of dose-dependently inhibiting the luciferase activity in Hep3B cells of compound **14a** was performed.