**Synthesis and cytotoxic evaluation of novel triterpenoid-AZT conjugates**

TuyetAnhDang Thi,a Nguyen Thi Kim Tuyet,aChinhPham The,a Ha ThanhNguyen,a Cham Ba Thi,a Tien Doan Duy,a Matthias D’hooghe,bTuyenVan Nguyena,\*

aInstitute of Chemistry, Vietnam Academy of Science and Technology, 18-Hoang Quoc Viet, CauGiay, Hanoi, Vietnam

bSynBioC Research Group, Department of Sustainable Organic Chemistry and Technology, Faculty of Bioscience Engineering, Ghent University, Coupure Links 653, B-9000 Ghent, Belgium

**Abstract**

Betulinic acid and analogous naturally occurring triterpenoids were transformed into the corresponding propargyl esters and subsequently deployed as substrates for a click chemistry-mediated coupling with azidothymidine (AZT) *en route* to novel 1,2,3-triazole-tethered triterpenoid-AZT conjugates. Twelve new hybrids were thus prepared and assessed in terms of their cytotoxic activity, revealing an interesting anticancer activity of five triterpenoid-AZT hybrids on KB and Hep-G2 tumor cell lines.

Pharmacophore hybridization, in which two bioactive moieties are covalently linked and available as a single hybrid entity, has emerged as a privileged strategy in drug discovery for the development of new molecules with pronounced biological activities.[[1]](#endnote-2) Many relevant “privileged” scaffolds can be selected as eligible pharmacophores for molecular hybridization,but it is evident that a broad activity spectrum of the monomeric scaffolds is favorable in the pursuit of potential new hit compounds.For example, the pentacycliclupanetriterpenoidbetulinic acid, isolated from the bark of several plant species, has attracted considerable attention in recent years because of its association with diverse biological activities. In particular, betulinic acid and its derivatives (such as oleanoic acid, ursolic acid and other triterpenoids) have been reported to be effective against a variety of cancer cell lines,[[2]](#endnote-3) rendering this class of natural products suitable candidates for pharmacophore hybridization. Another privileged scaffold concerns azidothymidine (AZT, zidovudine), a nucleoside reverse transcriptase inhibitorused for the treatment of HIV infections. Recently, AZT has also been reported to displaypronounced anticancer activity, especially in combination with other antitumor agents such as 5-fluorouracil, cisplatin and paclitaxel.[[3]](#endnote-4)

Despite their high biological potential, the combination oftriterpenoids and AZT into single hybrid molecules has been studied to a rather limited extent up to now.A tangible example concerns atriterpenoid-AZT conjugate which has been shown to possess potent anti-HIV activity.[[4]](#endnote-5)Other notable literature examples deal with the synthesis of 1,2,3-triazole-substituted betulinic, oleanoic and ursonic acid derivatives and their assessment as anticancer agents.[[5]](#endnote-6)Considering the documented anticancer activity of triterpenoids and AZT,it is reasonable to suggest that the construction of novel triterpenoid-AZT conjugates might result in the identification of useful anticancer hits for further elaboration. Thus, in the present work, new triazole-tethered triterpenoid-AZT hybrids are targeted as potential cytotoxic agents by means of click chemistry-mediated fusion between AZT on the one hand and betulinic acid, ursolic acid, oleanoic acid or one oftheir derivatives on the other hand. In light of the known biological properties of functionalized triazoles,[[6]](#endnote-7) the introduction of a triazole linker in the premised triterpenoid-AZT conjugates might contribute to the overall activity of these hybrid systems as well.

A powerful synthetic methodology for the fusion of two chemical entities involves the Cu(I)-catalyzed azide alkyne Huisgen cycloaddition, which has gained major interest due to its high efficiency and selectivity.[[7]](#endnote-8)In that respect, a synthetic approach toward novel triazole-tethered triterpenoid-AZT hybrids was devised based on a CuI-catalyzed 1,3-cycloaddition between propargyl-substituted triterpenoid derivatives and the azide-containing AZT.

To that end, the conversion of betulinic acid **1** into its propargyl ester **2a** was realized upon treatment with 2.0 equiv of propargyl bromide in DMF/THF (1:1) at room temperature in the presence of Cs2CO3 (Scheme 1). Subsequent reaction of alkyne**2a** with 0.8 equivof AZT in the presence of CuI (0.2 equiv) in *t*-BuOH at 70oC for 12hresulted in the formation of triazole-tethered AZT-betulinic acid conjugate**3a** in 59% yield. Alternatively,propargylation of betulinic acid **1** was followed by esterification of the freehydroxyl group by employing 4.0 equiv of succinic anhydride,glutaric anhydride or 3-metylglutaric anhydride in pyridine at 120oC for 12h to give compounds **2b-d**, which were converted into new AZT conjugates **3b-d** in acceptable yieldsby means of click chemistry with AZT (Scheme 1).



Scheme 1. Synthesis of betulinic acid-derivedtriterpenoid-AZT hybrids**3**

In order to provide a small library of novel triterpenoid-AZT conjugates, the same procedure as explained above was also applied to triterpenoidanalogs of betulinic acid **1**. In a first approach, ursolic acid **4a** and oleanoic acid **4b** were deployed as pharmacophoric templates *en route* to novel chimeras, and propargylation of these triterpenoids**4**to the corresponding propargyl esters **5**followed by CuI-mediated click reaction with AZT furnished hybrid products **6a**and **6b** in 53% and 90% yield, respectively (Scheme 2).



Scheme 2. Synthesis of ursolic acid- and oleanoic acid-derived AZT-conjugates **6**  
Reagents and conditions: (a) 2.0 equivpropargyl bromide, 2.0 equiv Cs2CO3, DMF:THF (1:1), rt, 4-6h; (b) 0.8 equivAZT, 0.2 equiv. CuI, *t*-BuOH, 70°C, 12h

Furthermore, dicarboxylic acids**7a,b**, isolated from *Scheffleraoctophylla* (Ivy tree),[[8]](#endnote-9)werealso evaluated as templates for derivatization. Initial Jones oxidation (CrO3) of β-hydroxy acids**7**using H2SO4 in acetone resulted in the corresponding β-oxo acid intermediates, which underwent decarboxylation to provide ketones**8**. Next, the corresponding propargyl esters **9** were prepared and subjected to a click reaction protocol with AZT to result in the novel AZT conjugates **10a,b** in good yields (Scheme 3).



Scheme 3. Synthesis of triterpenoid-AZT conjugates **10**

Furthermore, stereoselectivecarbonyl reduction with NaBH4 in MeOH/THF and subsequent propargylationin DMF/THF transformed oxo acid **8a** into hydroxy ester **11** in 56% yield,[[9]](#endnote-10) which served as a substrate for further esterification at the hydroxyl group with succinic anhydride or glutaric anhydride in pyridine to give compounds **12a,b** in good yields. Cu(I)-catalyzed Huisgen cycloaddition between alkynes **12** and AZT finally produced the desired new hybrids **13a** and **13b** in 50% en 48% yield, respectively. Alcohol **11** was also employed as a substrate for a click reaction with AZT, affording conjugate **13c** in 56% yield (Scheme 4).



Scheme 4.Synthesis of triterpenoid-AZT hybrids**13**  
Reagentsandconditions: (a) 4.0 equiv NaBH4, MeOH, THF, rt,10h; (b)2.0 equivpropargyl bromide, 2.0 equiv Cs2CO3, DMF:THF (1:1), rt, 4-6h; (c) 4.0equiv anhydride, pyridine, 120°C, 12h; (d) 0.8 equiv AZT, 0.2 equivCuI, *t*-BuOH, 70°C, 12h

Finally, hydroxy acid**14**, isolated from *Acanthopanaxtrifoliatus*,[[10]](#endnote-11)wasinvestigated as an eligible substrate for molecular hybridization. Thus, this compoundwas esterified using propargyl bromide in DMF/THF (1:1) to furnish the corresponding ester**15**, followed by conjugation with AZT following the above-described click chemistry methodology. This approach resulted in novel triterpenoid-AZT hybrid**16** in a good yield (Scheme 5).



Scheme 5. Synthesis of triterpenoid-AZT conjugate**16**  
Reagents and conditions: (a) 2.0 equivpropargyl bromide, 2.0 equiv Cs2CO3, DMF:THF (1:1), rt, 4-6h; (b) 0.8 equiv. AZT, 0.2 equivCuI, *t*-BuOH, 70°C, 12h

In summary, 1,3-cycloaddition has been applied successfully as a tool for the construction of 12 novel triazole-tethered triterpenoid-AZT conjugates as potentially useful entities for biological screening. The molecular identity of all new products was confirmed by detailed 1H NMR, 13C NMR, IR and MS analysis.

In the next part of this work, the newly prepared compounds were subjected to cytotoxic evaluation in order to assess their biological relevance. Thus, triterpenoid derivatives **2a-d**, **5a,b**, **9a,b, 12a,b**, **15** and AZT-triazole-triterpenoidhybrids**3a-d, 6a,b, 10a,b, 13a-c, 16**were evaluated *in vitro* for their cytotoxic activity against two human tumor cell lines (KB, Hep-G2), and the results are summarized in Table 1.These results indicate that most of these derivatives possess moderate cytotoxic activity, and some AZT conjugates even display a promising activity profile. In particular, three hybrid AZT-triazoletriterpenoids (**3a**, **6b** and **13a**) show good cytotoxicity against KB, and five AZT-triazoleconjugates (**3a**, **6b**, **13a**, **13c** and **16**) exhibit considerable cytotoxicity against Hep-G2 cancer cell lines, pointing to the potential interest in this new class of hybrid molecules in the field of cancer research.

In addition, also AZT and the parenttriterpenoid acids **1**, **4a**, **4b**, **7a**, **7b**, **8a** and **14**were subjected to cytotoxic analyses (Table 1).It is important to note that these separate pharmacophores display considerably less potent cytotoxic activities (IC50-values ranging from 24 to >400 µM) as compared to the most promising conjugates **3a**, **6b**, **13a**, **13c** and **16** (IC50-values between 5.9 and 8.5 µM), withtriterpenoid acid **8a**as the only exception showing a reasonable activity against both cancer cells. These biological results clearly indicate the added value of merging AZT and triterpenoids into single hybrid compounds in terms of their anticancer properties.

Table 1. Cytotoxicity evaluation

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Entry | Compound | IC50 (µM) KB | IC50 (µM) Hep-G2 | Entry | Compound | IC50 (µM) KB | IC50 (µM) Hep-G2 |
| 1 | **AZT** | >479 | >479 | 17 | **7a** | 110.1 | 222.9 |
| 2 | **1** | 27.5 | 23.9 | 18 | **7b** | >255 | >255 |
| 3 | **2a** | >258.7 | 113.9 | 19 | **8a** | 7.7 | 11.2 |
| 4 | **2b** | 22.2 | 49.9 | 20 | **9a** | >267 | >267 |
| 5 | **2c** | 28.7 | 19.9 | 21 | **9b** | 63.9 | 59.5 |
| 6 | **2d** | 12.5 | 129.2 | 22 | **10a** | >172 | >172 |
| 7 | **3a** | 5.9 | 7.0 | 23 | **10b** | >168 | >168 |
| 8 | **3b** | 24.7 | 20.6 | 24 | **11** | 40.0 | 133.1 |
| 9 | **3c** | 20.4 | 18.3 | 25 | **12a** | 10.6 | 11.4 |
| 10 | **3d** | 111.4 | 35.2 | 26 | **12b** | 9.9 | 27.3 |
| 11 | **4a** | 31.5 | 42.9 | 27 | **13a** | 7.3 | 7.8 |
| 12 | **4b** | >280 | >280 | 28 | **13b** | >148 | >148 |
| 13 | **5a** | 38.0 | 36.5 | 29 | **13c** | 34.0 | 7.3 |
| 14 | **5b** | 38.4 | >259 | 30 | **14** | 46.8 | 58.0 |
| 15 | **6a** | 28.5 | 34.0 | 31 | **15** | 21.9 | 39.6 |
| 16 | **6b** | 6.3 | 7.4 | 32 | **16** | 136.5 | 8.5 |
|  |  |  |  | 33 | **Ellipticine** | 4.9 | 5.0 |

In conclusion, different triterpenoid acids were transformed into the corresponding propargyl esters and subsequently used as substrates for a CuI-catalyzed 1,3-cycloaddition with AZT to produce a set of novel 1,2,3-triazole-tethered triterpenoid-AZT conjugates. Cytotoxic analysis of these hybrids and their triterpenoid precursors revealed moderate to good cytotoxic activities against two human tumor cell lines (KB, Hep-G2), and five representatives of the newly prepared class of triterpenoid-AZT conjugates displayed a promising potential for further elaboration toward novel anticancer agents.

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