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Synthesis and cytotoxic evaluation of novel indenoisoquinoline-substituted triazole hybrids

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ABSTRACT

The synthesis of various substituted triazole–indenoisoquinoline hybrids was performed based on a CuI-catalyzed 1,3-cycloaddition between propargyl-substituted derivatives and the azide-containing indenoisoquinoline. Besides, a variety of *N*-(alkyl)propargylindenoisoquinolines was used as substrates for the construction of triazole–indenoisoquinoline–AZT conjugated via a click chemistry-mediated coupling with 3′-azido-3′-deoxythymidine (AZT). Thus, twenty three new indenoisoquinoline-substituted triazole hybrids were successfully prepared and evaluated as cytotoxic agents, revealing an interesting anticancer activity of four triazole linker–indenoisoquinoline–AZT hybrids in KB and HepG2 cancer cell lines.

Pharmacophore hybridization, in which two or more bioactive entities are linked into a single hybrid molecule, has been known as an efficient and comfortable method to give new compounds with anticancer properties. Molecular hybridization can deliver a synthetic advantage through selective chemical modification of the more reactive entity within hybrid systems. Moreover, when bioactive agents are combined, new hybrid structures might display both a biological and a synthetic benefit. In the pursuit of potential new compounds, the selection of molecules with high biological activities for hybridization is occupying an important role.

Thus, indenoisoquinolines are one of the key structural units, which have been attracting considerable interest because of their various biological activities, particularly cytotoxicity against human cancer cell lines.[1] The lead compound of this class is NCS 314622 (**1**) (Fig. 1), which was at first prepared in 1978 and was found to be a mammalian topoisomerase I (Top1) inhibitor.[1b,2] Its cytotoxicity profile revealed a strong resemblance with camptothecin derivatives by stabilizing its covalent complex with DNA, the Top1-DNA cleavage complex (Top1cc), preventing further DNA religation and thus leading to the accumulation of DNA breaks.[3] During the past decade considerable effort has been made to improve the potencies and pharmacokinetics properties of these indenoisoquinolinediones through the contributions of the indenone ring, isoquinoline ring and lactam side chain.[1f,1g,4–6] It was demonstrated that the introduction of heterocycles, which possess a heteroatom capable of serving as a hydrogen-bond acceptor at physiological pH (e.g., hydroxyl, imidazole), in the *N*-functionalized lactam chains significantly enhances the biological activity.[5a,5c,5d,7–14] Well-known examples are anticancer topoisomerase I (Top1) inhibitors indotecan (LMP400, **2**) and indimitecan (LMP776, **5**), which were ultimately promoted to clinical study at the National Cancer Institute.[1i,15] Recently, hydroxylated analogus of the indotecan and indimitecan **4**–**11**, which contain various functionalized at A and D rings and the imidazole or morpholine group in *N*-lactam side chain, have been prepared and found to be very potent Top1 inhibitor and antiproliferative agents.[9] All of them, unlike camptothecin, appear to be stable and are powerful, cytotoxic Top1 poisons that induce long-lasting DNA breaks and overcome the drug resistance issues associated with the camptothecins.[1i,15,16] In addition, in our previous work, a novel of indenoisoquinoline-propan-2-ols **12**–**15** with high cytotoxicity against KB and HepG2 was designed by incorporating an *N*-functionalized three-carbon side chain,

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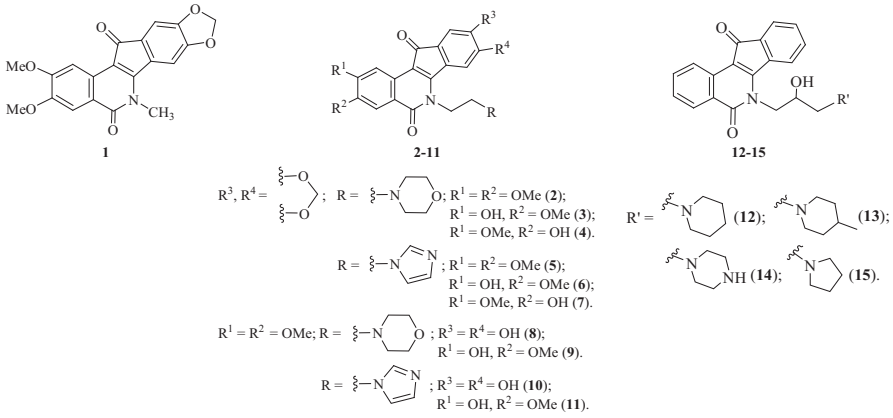


Figure 1. Chemical structure of several bioactive indenoisoquinoline derivatives.

possessing a 2′-hydroxyl group, combined with pyrrolidinyl, piperazine and piperidine units.[7]

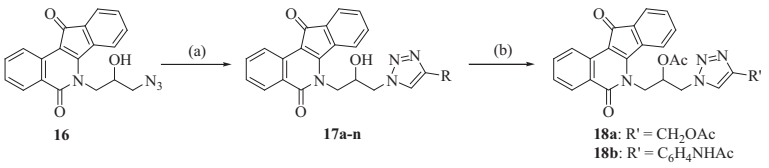
Another nitrogen-containing heterocycle 1,2,3-triazole has been known as a part of biologically active agent. Triazole has a high aromatic stabilization and high dipole moment, which might participate actively in hydrogen bond formation and in dipole–dipole and π stacking interactions.[17] Triazole is relatively resistant to metabolic degradation,[18] stable to acid and basic hydrolysis as well as reductive and oxidative conditions. Planar heteroaromatic triazole might lead to a more facile interaction with DNA, proteins, or cells.[19] Besides, triazole is easy synthesized by 'click' chemistry and exhibits a broad-spectrum of anticancer activities[20] and antiproliferative properties.[21] Therefore the combining 1,2,3-triazole with other pharmacophores becomes one of the most importance medicinal chemistry strategies. By this way a number of compounds with potent antitumor activity have been synthesized and are now available in the market such as tazobactam,[22] cefatrizine[23] and carboxyamidotriazole.[24]

From the multitude of contributions in the scientific literature, it is clear that indenoisoquinolines and triazoles can be considered as valuable compounds, both from a medicinal and a synthetic point of view. Moreover, consideration for the chemical structure of indimitecan, the addition of one more nitrogen atom to the imidazole ring could give more interesting bioactivities. All together, these findings have led to the hypothesis that the introduction of triazole group into *N*-functionalized three-carbon side chain of indenoisoquinoline, especially indenoisoquinoline-propan-2-ols, could give the promising potent biological compounds. However, the combination of these two bioactive moieties into hybrid molecules has not been reported in the literature so far. Having been inspired by the biological importance of 1,2,3-triazoles and indenoisoquinoline-propan-2-ols as anticancer agents and in continuation of our interest in pharmacophore hybridization we herein reported the synthesis of novel triazole–indenoisoquinolines hybrids. The anticancer activity evaluation results revealed that the 1,2,3-triazole–indenoisoquinoline hybrids exhibited potent anticancer activity.

The strategies for the formation of five-membered heterocyclic ring systems contain 1,3-dipolar cycloaddition reactions, which have gained major interest for several decades in view of the large numbers of potential dipoles and dipolarophiles.[25] As one such possibility, Cu(I)-catalyzed azide–alkyne cycloaddition is a widely utilized, reliable and powerful way to form 1,4-disubstituted 1,2,3-triazole.[26] In that respect, a synthetic approach toward novel triazole–indenoisoquinoline hybrids was devised based on a CuI-catalyzed 1,3-cycloaddition between propargyl-substituted derivatives and the azide-containing indenoisoquinoline.

In this way, the key starting material, 6-(3-azido-2-hydroxypropyl)indenoisoquinoline **16**, or shortly azidoindenoisoquinoline **16**, was prepared by four-step methodology in our previous report.[7] Azidoindenoisoquinoline **16** exhibits an excellent precursor for the efficient generation of triazole–indenoisoquinoline hybrids **17a**–**n** in high yields (60–80%) upon treatment with the appropriate 1-propargyl derivative, as illustrated in Scheme 1.[27] This reaction was carried out in refluxing tetrahydrofuran in the presence of *N*,*N*-diisopropylethylamine (DIPEA) and CuI. The chemical structures of the obtained indenoisoquinolines **17a**–**n** were confirmed by means of spectral data (^{1}H NMR, ^{13}C NMR, IR and MS). In the previous work, it was shown that the hydroxy group in the *N*-lactam side chain of indenoisoquinoline-propan-2-ols increases antiproliferative activity.[7] In order to persuade this hypothesis, the hydroxy group in side chain was acylated by treatment with acetic anhydride to obtain esters **18a**,**b**, respectively (Scheme 1).

As a part of our ongoing work, the introduction of bioactive moieties into *N*-lactam side chain of indenoisoquinolines is also studied in this Letter. 3′-Azido-3′-deoxythymidine (AZT, zidovudine) has known as a nucleoside reverse transcriptase inhibitor used for the treatment of HIV infections. AZT has also been exhibited pronounced anticancer activity, especially in combination with other antitumor agents, for example, such as 5-fluorouracil, cisplatin, paclitaxel[28] and triterpenoids.[29,30] Thus, considering the documented anticancer activity of indenoisoquinolines, AZT and functionalized triazole, it is reasonable to suggest that the



Scheme 1. Synthesis of triazole–indenoisoquinoline hybrids **17a**–**n** and **18a**,**b**. Reagents and conditions: (a) 1.1 equiv ethynyl derivatives, 0.2 equiv DIPEA, 0.1 equiv CuI, THF, reflux, 24 h; (b) 3 equiv Ac_2O, 2 equiv Et_3N, DMF, rt, 24 h.