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Design and synthesis by click triazole formation of paclitaxel mimics with simplified core and side-chain structures

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ABSTRACT

A library of paclitaxel (taxol) mimics was obtained by a straightforward strategy involving rational design and an efficient synthesis of a simplified taxane core substitute, together with a click-chemistry combinatorial search for phenylisoserine side-chain surrogates.

The tubulin/microtubule system plays a key role during mitosis and disturbing its dynamic equilibrium can prevent cell division and induce apoptosis. Up to now, most of the known microtubule-stabilizing antitubulin agents, such as paclitaxel (taxol), discodermolide, or epothilones, are characterized by a very complex structure, and are therefore difficult to synthesize, especially on a large scale. The structure–activity relationship for taxoids has been extensively studied and the importance of the C-13 side-chain and the ester group at C-2 have been highlighted.[1,2] Moreover, studies have been carried out in order to determine the bioactive conformation of the taxoids, namely the conformation they adopt when binding to and stabilizing microtubules.[3–5] Using the 3.7 Å structure of the α,β-tubulin–taxol complex obtained by electron crystallography of zinc-induced sheets[3] and electron crystallographic density, a 'T-shaped' taxol was proposed as the bioactive conformation on β-tubulin.[5] Numerous analogues of taxol have been synthesized which possess the complex taxane skeleton. Until now, a few structures exhibiting a simpler core have been elaborated,[6] some of which show interesting biological activity.[6c] In these attempts, the constructs have, however, retained the phenylisoserine structure (or close analogues) of the side-chain at C-13 as an important recognition unit, without (structures **B**–**E**) or with (structures **F**–**I**) a mimic of the benzoate at C-2 (Fig. 1). Using geometrical parameters from the tetracyclic taxane skeleton and molecular modeling, we propose here the synthesis of a small library of taxoid analogues with a simplified core structure supposedly mimicking the taxane skeleton. Moreover, we show that click-chemistry can efficiently be used to rapidly introduce simple potential side-chain surrogates.

In order to properly define the relative orientation of the two exit vectors corresponding to the anchoring of the phenylisoserine and the benzoate side-chains onto the taxane core, we measured the interatomic distance between C-13 and C-2 carbons, the distance between the two corresponding oxygens O-13 and O-2, as well as the dihedral angle between the C-13–O-13 and the C-2–O-2 bonds (Fig. 2) for T-shaped taxol,[5,7] 1JFF taxol,[4] and docetaxel (taxotere)[8] in the crystal. These values showed a very good consensus on the relative orientation of these two vectors. Searching for simple structures that could present similar geometrical orientations, we found that bicyclic β-L-glucurono-γ-lactone **J** could be a good mimic for the taxane core in this respect.[9,10] Molecular modeling using MacroModel [MM3*, GB/SA water, Systematic Pseudo Monte Carlo (SPMC) torsional sampling] showed a good correspondence for these three parameters with the previously determined taxane data (Table 1 and Fig. 2b), hence the synthesis of such derivatives was selected. With further structural simplifications in mind, we chose to conserve the benzoate group, which has been shown to be essential for activity,[1,2] and to replace the taxol side-chain by diverse aromatic motifs introduced by click triazole formation (Scheme 2). We decided to focus on side-chain surrogates bearing aromatic groups, which bring attractive interaction with the corresponding hydrophobic pocket since the taxol side-chain is known to make such hydrophobic interactions. Both aryl

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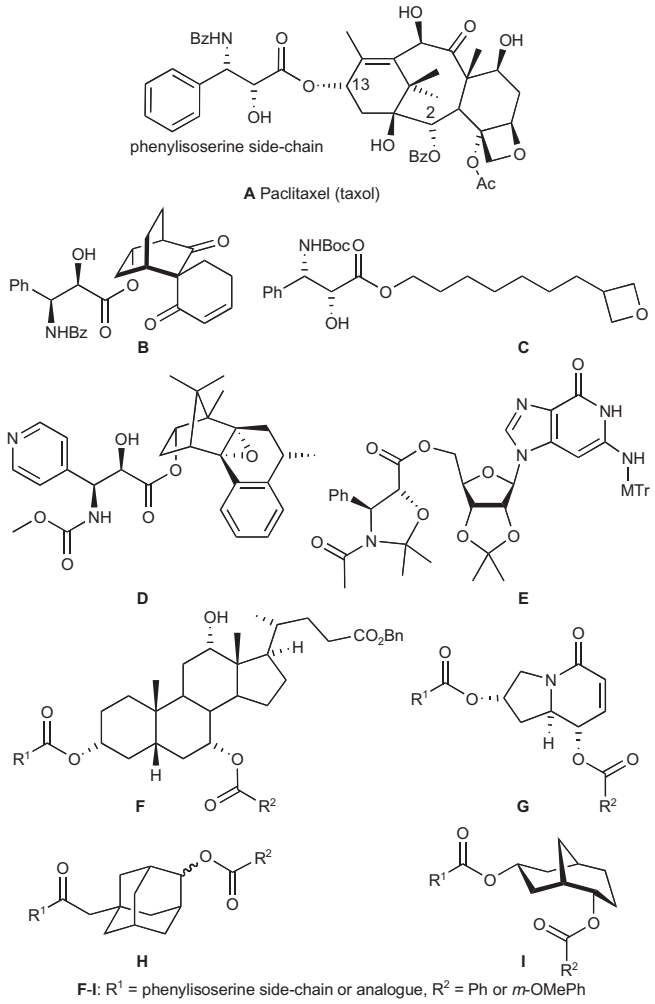


Figure 1. The structure of paclitaxel (taxol) **A**, as well as some literature examples of taxoid mimics with simpler structures replacing the taxane core.

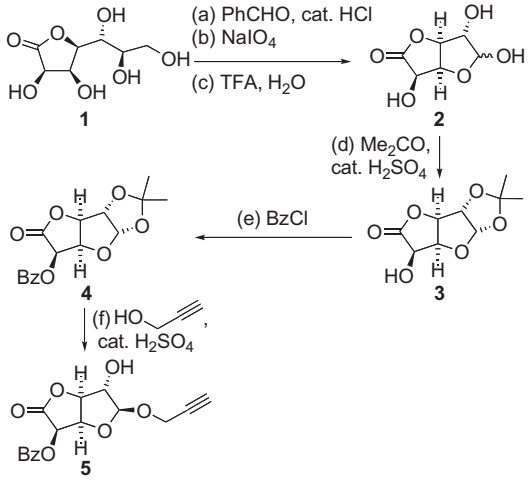
Table 1
Selected geometrical parameters for T-taxol, 1JFF taxol, taxotere, and β-L-glucurono-γ-lactone **J**

	C_{13}–C_2 (tax.)/ C_1–C_5 (lact.) (Å)	O_{13}–O_2 (tax.)/ O_1–O_5 (lact.) (Å)	Dihedral angle[a] (deg.)
T-taxol	3.70	4.86	−47.75
1JFF taxol	3.74	4.89	−44.07
Taxotere	3.68	4.93	−45.94
Lactone **J** (aver.)[b]	3.62	4.89	−51.59
Lactone **J** (min.)[c]	3.63	4.92	−52.91

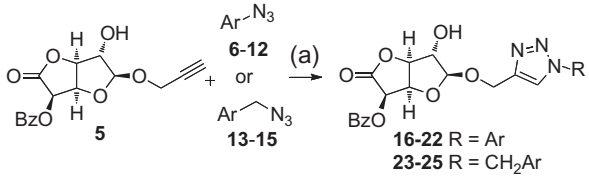
[a] C_{13}–O_{13}/C_2–O_2 dihedral angle for taxoids, C_1–O_1/C_5–O_5 for lactone **J**.
[b] Average values over the 20 conformations obtained by SPMC (all within 5.0 kcal mol^{-1} above global minimum).
[c] Values for the lowest energy conformation obtained by SPMC and used in Fig. 2b.

and benzyl groups were selected to probe the influence of side-chain flexibility.

Since the core we selected is a derivative of non-natural L-glucose, we had to elaborate this structure from another synthetic precursor. The propargylic derivative **5** was therefore prepared from commercially available D-glucoheptonolactone **1** in six steps (Scheme 1). The first three steps provided L-glucurone **2** in a 60%



Scheme 1. Reagents and conditions: (a) PhCHO, cat. HCl, 20 °C, 2 h; (b) $NaIO_4$, THF/H_2O, 40 °C, 1 h; (c) TFA, H_2O, 20–45 °C, 1 h (88%, three steps); (d) acetone, cat. H_2SO_4, 20 °C, 3 h (80%); (e) BzCl, DMAP, CH_2Cl_2, 20 °C, 3 h (80%); (f) propargyl alcohol, cat. H_2SO_4, 80 °C, 1 h (70%).



Scheme 2. Reagents and conditions: (a) $CuSO_4$ (0.05 equiv), sodium ascorbate (0.1 equiv), H_2O/CH_2Cl_2 (1:1), 20 °C overnight, (57–92%).

overall yield, using the large-scale optimization recently published by Fleet[11,12] from a strategy initially described by Sowa.[13] Subsequent protection of the two contiguous *hydroxy* groups in the form of an isopropylidene (**3**, 70%), followed by benzoylation of the remaining *hydroxy* readily led to intermediate **4** (80%). Sulfuric acid-catalyzed glycosylation of **4** in propargyl alcohol gave the desired propargyl glycoside **5**.[14]

Product **5** crystallized from ethyl acetate/cyclohexane, and the stereoselectivity of this last glycosylation step, hence the required β-configuration of the resulting product, was unambiguously assessed by X-ray crystallographic studies (Fig. 3).[15]

Compound **5** was then engaged into copper-accelerated azide-alkyne cycloadditions (CuAAC)[16] with a series of substituted aryl (**6**–**12**)[17] or benzyl (**13**–**15**)[18] azides which were prepared according to literature procedures.[19,20] The ten desired triazoles (**16**–**25**, Fig. 4) were obtained using Soo-Kim reaction conditions,[21] using a biphasic dichoromethane/water system (Scheme 2) in yields ranging from 57% to 92%.[22]

None of these triazoles showed an appreciable antitubulin activity (tubulin depolymerization assay), although nitro phenol derivative **19** moderately inhibited the tubulin depolymerization (IC_{50} of 90 μM).[23]

In summary, we have developed a very simple and efficient synthetic route to possible taxol substitutes by a stereoselective β-glycosylation of L-glucurono-γ-lactone followed by a click cycloaddition of aromatic structures, providing fast access to a small library of compounds. The molecules obtained in this work will be further studied for their biological activity, including potential inhibition of tubulin depolymerization and possible cytotoxic properties. This oversimplified taxoid core mimic certainly does not contain some of the key taxoid–tubulin interactions for

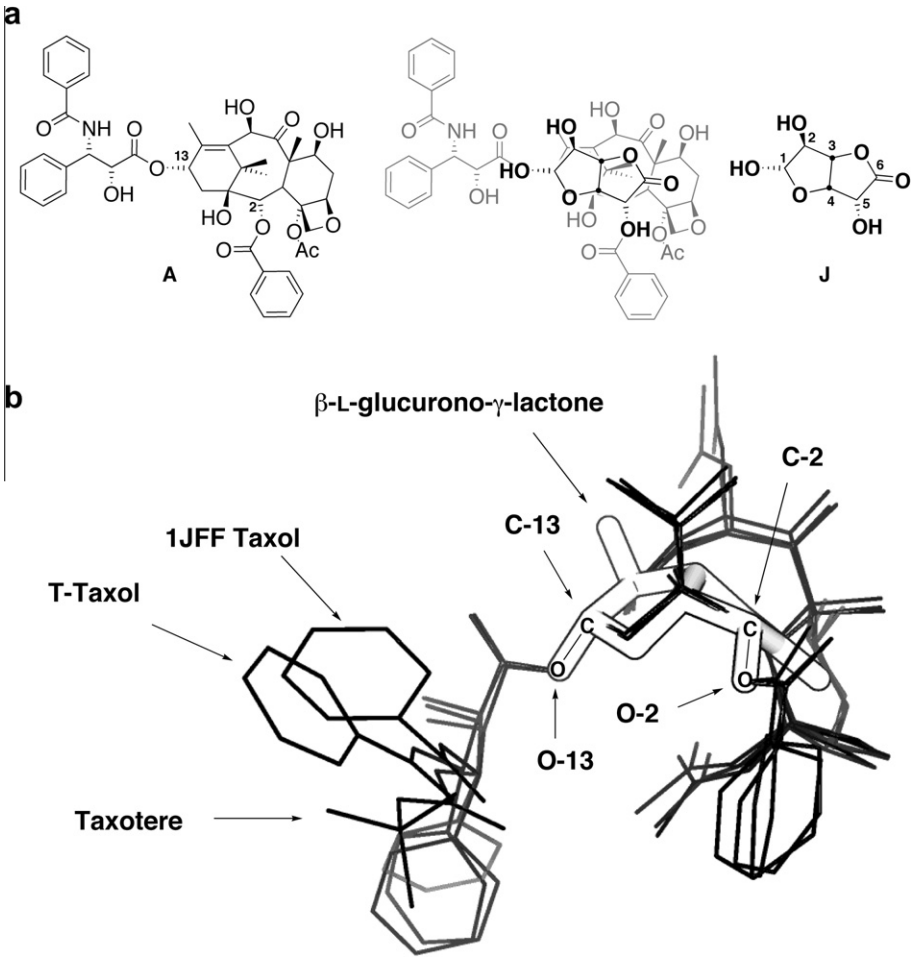


Figure 2. (a) Schematic representation of the overlay of β-L-glucurono-γ-lactone **J** with the taxane core of taxol **A**. (b) Overlay of the MM3* conformation of **J** (white sticks) with T-taxol, 1JFF-taxol, and taxotere (dark lines). Hydrogens have been omitted for clarity.

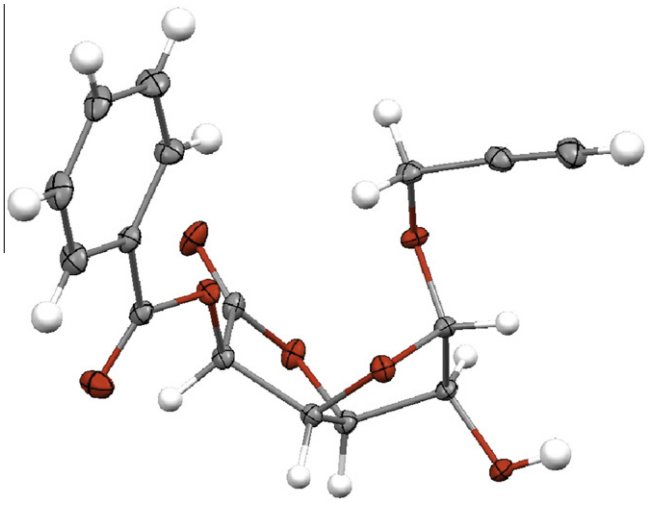


Figure 3. X-ray structure of glycoside **5**, confirming anomeric configuration.

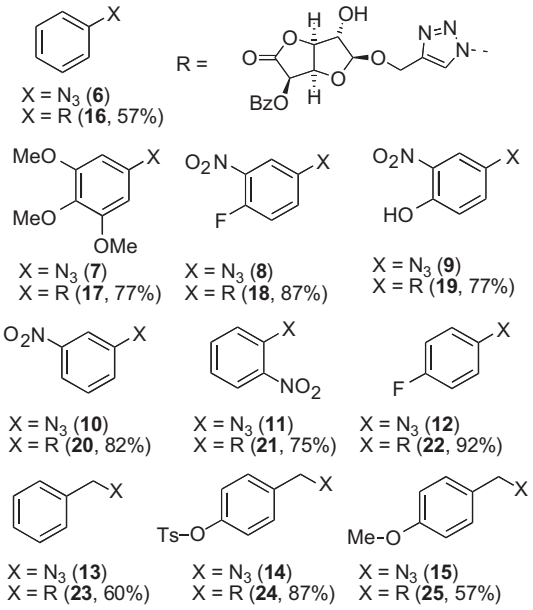


Figure 4. Structure of azido precursors **6**–**15** and triazole derivatives **16**–**25** with yields for the cycloaddition reaction.

efficient tubulin binding activity (e.g., C and D rings). In future work, the elaboration of closer mimics carrying the phenylisoserine side-chain of taxol as β-glycosyl esters of the L-glucurono-γ-lactone scaffold will notably be elaborated and the results of these studies will be reported in due course.

Acknowledgment

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14. 1,2-*O*-Isopropylidene-α-L-glucurono-3,6-lactone (500 mg) **3** was dissolved in 23 mL of freshly distilled methylene chloride (DCM). *N*,*N*-Dimethylaminopyridine (535 mg) was added, followed by 377 μL of benzoyl chloride, at 0 °C. After stirring 5 min, the temperature was allowed to reach room temperature. After 3 h stirring, control by thin layer chromatography showed no trace of starting compound, and the reaction was quenched by addition of saturated aqueous $NaHCO_3$. The organic layer was then washed with brine, dried over Na_2SO_4, and concentrated in vacuo. Filtration on silica gel (DCM/MeOH 95:5) gave 590 mg (80%) of **4** as a colorless syrup. H_2SO_4 (57 μL) was added dropwise to a solution of **4** (133 mg) in 1.7 mL of propargyl alcohol. The solution was stirred at 80 °C for 1 h. The mixture was neutralized with saturated aqueous $NaHCO_3$. After dilution with DCM, the organic layer was washed with $NaHCO_3$ and brine, dried over Na_2SO_4 and concentrated in vacuo. Flash chromatography on silica gel (DCM/MeOH 45:1) gave 91.4 mg (69%) of **5** as a brown syrup. Selected analytical data for **5**: mp: 129–130 °C (AcOEt/Cy); $[\alpha]_D^{25} = -14.0$ (*c* 1, $CHCl_3$); ^{1}H NMR (360 MHz, $CDCl_3$), δ (ppm): 8.11 (dd, 2H; $J_{o\text{-}m} = 7.9$, $^4J_{o\text{-}p} = 1.4$; 2H-o (Bz)); 7.61 (tt, 1H; $J_{p\text{-}m} = 7.5$; $^4J_{p\text{-}o} = 1.4$; H-p (Bz)); 7.47 (ddt, 2H; $J_{o\text{-}m} = 7.9$, $J_{m\text{-}p} = 7.5$, $^4J_{m\text{-}m} = 1.4$; 2 H-m (Bz)); 5.44 (d, 1H; $J_{4\text{-}5} = 6.9$; H-5); 5.33 (dd, 1H; $J_{3\text{-}4} = 4.9$, $J_{4\text{-}5} = 6.9$; H-4); 5.30 (s, 1H; H-1); 4.99 (d, 1H; $J_{3\text{-}4} = 4.9$; H-3); 4.51 (s, 1H; H-2); 4.27 (dd, 1H; $J_{gem} = 15.7$, $^4J = 2.3$; OC*H*aHb); 4.20 (dd, 1H; $J_{gem} = 15.7$, $^4J = 2.3$; OCH_aH_b); 2.40 (t, 1H; $^4J = 2.3$; C*CH*); 2.27 (br s, 1H, O*H*). ^{13}C NMR (90 MHz, $CDCl_3$), δ (ppm): 170.4 C-6; 165.4 CO (Bz); 134.2 C-p (Bz); 130.3 2C-o (Bz); 128.9 2 C-m (Bz); 128.5 C-q (Bz); 106.4 C-1; 83.9 C-3; 78.3 *CCH*; 78.1 C-2; 76.3 C-4; 75.5 *CCH*; 69.9 C-5; 54.7 OCH_2. MS (ESI^+): $m/z = 341.1$ M+Na$^+$; HRMS (ESI^+): calcd for $C_{16}H_{14}O_7Na$: 341.0632, found: 341.0644.
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22. Representative procedure for the synthesis of **22** using click-chemistry. Lactone **5** (32 mg, 0.10 mmol, 1.0 equiv) and 4-fluorophenyl azide (15 mg, 0.11 mmol, 1.1 equiv) were dissolved in methylene chloride (300 μL) and water (210 μL). Solutions of sodium ascorbate (40 μL, 0.25 M in water, 2.0 mg, 0.01 mmol, 0.1 equiv) and $CuSO_4{\cdot}5H_2O$ (50 μL, 0.10 M in water, 1.2 mg, 0.005 mmol, 0.05 equiv) were added, and the mixture was stirred overnight at room temperature. After dilution with methylene chloride, the organic layer was washed with water, dried over sodium sulfate, and concentrated in vacuo. After chromatography on silica gel (cyclohexane/ethyl acetate 1:1), the pure desired products was obtained (42 mg, 92%). Selected analytical data for **22**: ^{1}H NMR (300 MHz, $CDCl_3$), δ (ppm): 8.04 (s, 1H; H-triazole); 7.95 (dd, 2H; $J_{o\text{-}m} = 8.1$, $^4J_{o\text{-}p} = 1.4$; 2H-o (Bz)); 7.66 (dd, 2H; $J_{o\text{-}m} = 9.1$, $^4J_{o\text{-}F} = 4.6$; 2 H-o (Ar)); 7.52 (tt, 1H; $J_{p\text{-}m} = 7.4$, $^4J_{p\text{-}o} = 1.2$; H-p (Bz)); 7.36 (dd, 2H; $J_{m\text{-}o} = 8.1$, $J_{m\text{-}p} = 7.4$; 2H-m (Bz)); 7.14 (dd, 2H; $J_{m\text{-}o} = 9.1$, $^3J_{m\text{-}F} = 8.0$; 2H-m (Ar)); 5.58 (d, 1H; $J_{4\text{-}5} = 6.8$; H-5); 5.36 (dd, 1H; $J_{4\text{-}5} = 6.8$, $J_{3\text{-}4} = 4.9$; H-4); 5.24 (s, 1H; H-1); 5.07 (d, 1H; $J_{3\text{-}4} = 4.9$; H-3); 4.95 (d, 1H; $^2J_{Ha\text{-}Hb} = 12.0$; OC*H*aHb); 4.61 (d, 1H; $^2J_{Ha\text{-}Hb} = 12.0$; OCH*a*H*b*); 4.50 (s, 1H; H-2); ^{13}C NMR (75 MHz, $CDCl_3$), δ (ppm): 171.7 C-6; 165.3 CO (Bz); 162.7 (d, $^1J_{C\text{-}F} = 244$) Cq-F (Ar); 144.8 Cq (triazole); 134.2 CH-p (Bz); 133.2 (d, $^4J_{C\text{-}F} = 3$) Cq (Ar); 130.0 2CH-o (Bz); 128.9 2CH-m (Bz); 128.3 Cq (Bz); 122.7 (d; $^3J_{C\text{-}F} = 9$) 2CH-o (Ar); 122.0 CH (triazole); 116.9 (d; $^2J_{C\text{-}F} = 23$) 2CH-m (Ar); 108.5 CH-1; 84.5 CH-3; 77.6 CH-2; 76.5 CH-4; 70.2 CH-5; 61.3 OCH_2; MS (ESI^+): $m/z = 455.9$ M+H$^+$; 477.9 M+Na$^+$; HRMS (ESI^+): calcd for $C_{22}H_{20}FN_3O_7$: 456.1202; found: 456.1202. Anal. Calcd for $C_{22}H_{18}FN_3O_7$, $2H_2O$: C, 53.77; H, 4.51; N, 8.55. Found: C, 54.03; H, 4.11; N, 8.09.
23. In the standard in vitro tubulin depolymerization assay used, taxol showed an IC_{50} of 0.5 μM under the same conditions (IC_{50} is the concentration that inhibits 50% of the rate of microtubule disassembly). These tests were preformed by Sylviane Thoret at the Institut de Chimie des Substances Naturelles, CNRS.