Fast and Effective Preparation of Highly Cytotoxic Hybrid Molecules of Schweinfurthin E and OSW-1

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Herein, we present the first synthesis of hybrid molecules combining the pharmacophores of two natural compounds, schweinfurthin E (SW-E) and the glycosidic moiety of OSW-1. These hybrids were designed leveraging the complementary binding of SW-E and OSW-1 to their biological target. The synthetic process highlights, in particular, one-pot functionalization and glycosylation of an L-arabinose unit using a D-xyloside donor and a CuAAC click reaction involving a polyfunctionalized prenylated stilbene derived from SW-E. The cytotoxicity of the four SW-E and OSW-1 hybrids is also reported, two of them being much more cytotoxic than SW-E on a glioblastoma cancer cell line. Finally, a molecular modeling study is conducted to rationalize the biological results obtained.

For over a century, natural products have significantly advanced pharmacotherapy, especially in the field of infectious diseases and cancer, thanks to their scaffold originality, which endows them with specific pharmacological properties.[1,2] The National Cancer Institute (NCI) has developed the COMPARE algorithm to enhance drug screening and identify high-potential molecules for further investigation.[3] This algorithm analyzed the molecular activity of approximately 40,000 compounds against 60 human cancer cell lines, classifying them based on similarities: molecules with identical activity profiles likely follow similar mechanistic pathways.[4] Using COMPARE, various families of natural products, including OSW-1 **1** and schweinfurthins (SWs) like SW-G **2** or SW-E **3** revealed commonalities in their mode of action, which differs from that of all the chemotherapies already in clinical use (**Figure 1**). This group of small molecules showed high efficacy in inhibiting the growth of human cancer cell lines with half-maximal inhibitory concentrations (GI50) in the nanomolar range. Further investigations have established that, despite their major structural differences, these compounds share the same biological target, *i.e.* oxysterol-binding protein (OSBP) and were named ORPphilins. [5] OSBP is a key player in cholesterol homeostasis and allows the transport of cholesterol **4**, within its ORD domain, from the endoplasmic reticulum (ER) to the trans- Golgi network (TGN) in exchange for phosphatidylinositol 4-phosphate (PI(4)P).[6,7]

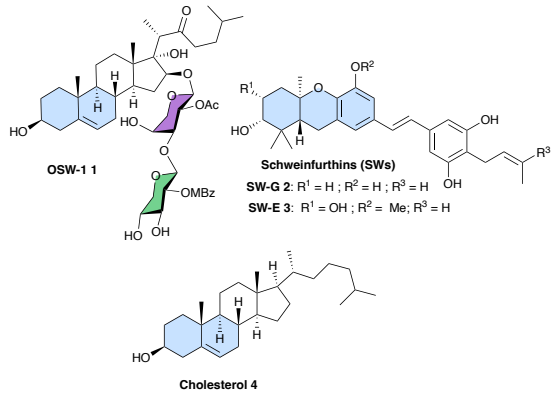


Fig. 1. Natural ORPPhilins OSW-1 **1,** SW-G **2** and SW-E **3** that bind within the OSBP-ORD domain in the place of cholesterol **4**, (MBz = *para*-methoxy benzoyl).

OSW-1 **1**, the most cytotoxic and studied ORPphilin, is a glycosylated saponin first extracted from the bulbs of *Ornithogalum saundersiae*. Its structure consists of an aglycone steroid linked to a disaccharide unit: (*O*-4-methoxybenzoyl)-β-D-xylopyranosyl)-(1→3)-2-*O*-acetyl-α-L-arabinopyranoside. Extensive research has been conducted to understand its structure and function, synthesizing numerous analogs and enabling detailed structure-activity relationship (SAR) studies.[8] These studies have revealed that the integrity of the disaccharide moiety is necessary to retain the compound's potent cytotoxic properties, as any modifications can significantly impact the activity.[9,10,11] This disaccharide fragment could play a significant role in forming an hydrophobic cluster.[12]

Schweinfurthins (SWs) are a family of natural prenylated stilbene featuring a hexahydroxanthene (HHX) moiety essential for their biological properties.[13,14,15] The first derivative of this family was isolated from the leaves of *Macaranga vedeliana* in 1992.[16] A few years ago, we showed that natural SW-G **2**, like OSW-1 **1**, binds within the

ORD domain of OSBP and inhibits the OSBP-catalyzed lipid exchange cycle, affecting post-Golgi trafficking, membrane cholesterol levels, and PI(4)P turnover.[17] We have also recently demonstrated an excellent correlation between K*i* for OSBP and cytotoxicity on the U-87 MG glioblastoma cell line on a large panel of SW derivatives.[18] As confirmed by a crystal structure,[19] the hydroxyl of cholesterol **4** forms a network of hydrogen bonds at the bottom of the OSBP-ORD domain, while the hydrocarbon chain and tetracyclic core point toward the top. Owing to the steroidal moiety of OSW-1 **1** and the presence of a hydroxyl function on the HHX of SWs, these compounds bind probably similarly in the ORD, their hydroxyls being buried at the bottom of the pocket. Anyway, given the structural divergences between OSW-1 **1** and SWs, it is likely that their binding sites only partially overlap. As the disaccharide unit is necessary for the high affinity of OSW-1 **1** for ORD, the steroid part alone being ineffective,[8] we wondered whether hybrids of SW-E **3** with the glycosidic part of OSW-1 **1** would be more potent than SW-E **3** alone.

The targeted hybrid compound **5** could be synthesized by a Copper-catalysed Azide–Alkyne Cycloaddition (CuAAc)[20,21] between 1-azido sugar **6** and a propargylated derivative **7** (**Figure 2**). The latter would derive from SW-E **3**, which can be isolated at a gram scale from *Macaranga tanarius*.[22,23] The benefits of the CuAAc reactions are no longer demonstrated, involving highly chemo- and regioselective reactions, under mild reaction conditions, with efficient performance over a wide range of solvents and compatibility with diverse functionalities. This has enabled the creation of remarkable compounds with diverse applications, notably in the field of carbohydrate chemistry.[24,25] In addition, we intended to follow a new strategy to develop the disaccharide unit of OSW-1, to simplify the synthesis process and reduce the number of purifications. Previous synthetic approaches, all relying on commercially available D-xylose and L-arabinose as starting materials, often involved many steps (ranging from 13 to 19) and resulted in relatively low overall yields.[26,27,28,29,30,31,32,33] Our method, using a switchable boronic ester as both a protecting and activating group, should enable a streamlined one-pot synthesis and stereoselective glycosylation of the L-arabinoside derivative **8**, leading to the fast formation of the desired disaccharide adduct (**Figure 2**).[34]

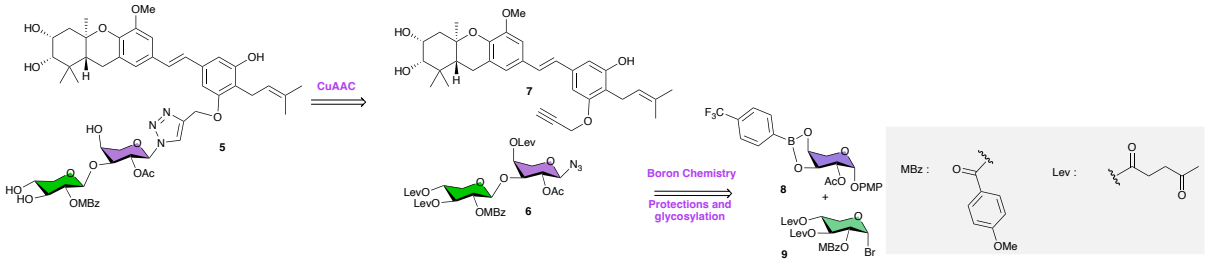
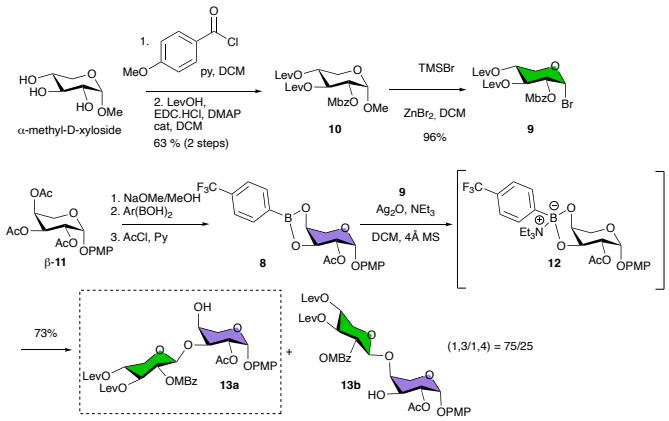
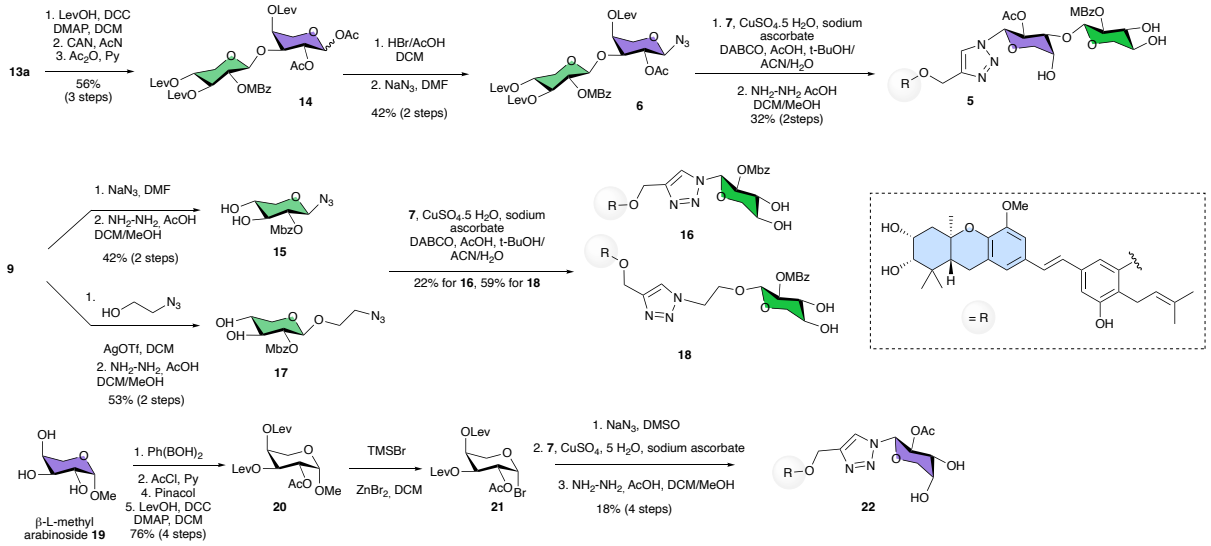


Fig. 2. Retrosynthetic pathway toward SWE-OSW1 hybrid analog **5**.

We initiated our investigation by glycosylating β-L-*p*-methoxyphenyl arabinoside β-**11** with xyloside bromide **9** (**Scheme 1**). The latter was synthesized through the regioselective esterification of the triol using *p*-methoxy benzoyl chloride, as described by Pakulski and Cmoch.[31] Subsequently, the alcohols at positions 3 and 4 were esterified with levulinic acid employing EDC.HCl and a catalytic amount of DMAP in DCM. This process yielded compound **10** in 63% over two steps. The resulting methyl glycoside was then directly converted into glycoside bromide **9** using trimethylsilyl bromide in combination with zinc bromide,[35] achieving an excellent yield of 96%. Regarding the arabinoside moiety, we prepared compound β-**11**, which features a *p*-methoxyphenyl group at the anomeric position.[33] We then followed the acylation/glycosylation protocol described by Taylor and coll.[34] After deacetylation (MeONa in MeOH), the *cis*-diol protection was achieved through a reaction with the electron-deficient 4-(trifluoromethyl)phenylboronic acid. The resulting compound was subsequently acetylated at position 2 to lead compound **8**. Utilizing a Lewis base (NEt_3), the behavior of the boronic ester can then be switched to an activating group forming the tetracoordinated boronate **12**. This facilitates the glycosylation step with glycosyl bromide **9** under Koenigs-Knorr conditions, using Ag_2O as the promoter in DCM leading to the expected adducts in 73% overall yield. In this case, the importance of adding an excess of the crude glycosyl bromide **9** (1.8 equiv.) in 8 portions over 6 hours to obtain maximum yield should be noted. The glycosylation reaction was highly stereoselective (100% β), with no evidence for the formation of α-configured by-products. However, the reaction lacked complete regioselectivity, resulting in a mixture of β-1,3- and β-1,4-linked products **13a** and **13b** in a 75/25 ratio. Typically, selectivity for activating the equatorial OH group in *cis*-1,2-diol motifs is observed through tetracoordinate boron adducts. In our case, the deactivating effect of the neighboring acetyl protective group may have influenced this selectivity.[36] Despite this unexpected outcome, this 4-step sequence (deprotection, protection, acetylation, and glycosylation) remains operationally simple and does not necessitate any purification of the intermediates. This results in a fast process leading to the desired β-1,3 glycosylated product **13a** with a yield of 55% from β-**11**.



Scheme 1. Preparation of the disaccharides **13** by sequential functionalizations of **11** enabled by a boronic ester as a switchable protective/activating group.



Scheme 2. Preparation of hybrids **5**, **16**, **18** and **22**.

Having **13a** in hand, the hydroxyl at position 4 of the arabinose moiety underwent esterification with levulinic acid in the presence of DCC and DMAP. The resulting compound was then subjected to CAN oxidation, allowing deprotection of the PMP. This was followed by acetylation (using Ac_2O and pyridine) of the anomeric position, giving compound **14** in an overall yield of 56% over the three steps. After treatment with HBr/AcOH in DCM at 0 °C, the obtained glycosyl bromide was reacted in the presence of sodium azide in DMF providing the corresponding 1-azido sugar **6**. This one was then engaged in a CuAAC reaction with the propargylated schweinfurthin E **7** using the protocol of Chandak.[37] Indeed, the $CuSO_4$-ascorbate/DABCO/acetic acid combination has demonstrated the ability to accelerate the copper(I)-catalyzed cycloaddition of azides and alkynes in water. Its efficacy has been particularly advantageous in facilitating the reaction involving SWs.[38] After the reaction was completed, the crude mixture was treated with hydrazine acetate, which selectively deprotected the levulinate esters, yielding the expected hybrid **5** in 32% yield over the two steps following reverse phase purification.

We also explored the synthesis of other hybrids featuring a monosaccharide moiety derived from L-arabinose or D-xylose. Starting with xylosyl bromide **9**, we synthesized the 1-azido derivative **15** by reacting it with NaN_3 in DMF, followed by deprotection using hydrazine acetate. We also obtained compound **17** by glycosylating 1-azido ethanol with silver triflate in DCM and subsequently deprotecting the levulinate esters. Both compounds were subjected to the CuAAC reaction, yielding the expected compounds **16** and **18** in 22% and 59% yields, respectively. The higher yield in the latter case can be attributed to the greater stability of the azide compound. To complete the synthesis of a hybrid containing L-arabinose, we began with commercially available β-L-methyl arabinoside **19**. This starting material was subjected to a four-step sequence involving protection with phenylboronic acid, acetylation at position 2, deprotection of the boronic ester using pinacol and esterification of the resulting diol with levulinic acid. This efficient sequence provided compound **20** with a good overall yield and one final purification. Next, compound **20**

was converted into the anomeric bromide **21** using TMSBr/$ZnBr_2$ in DCM. Following the protocol by Kumar *et al.*, we performed a one-pot formation of the 1-azido compound in DMSO, which then reacted sequentially with alkyne compound **7** and $CuSO_4 \cdot 5H_2O$. Finally, the obtained compound was treated with hydrazine acetate, resulting in the hybrid **22** with an 18% yield over the four steps.

We assessed the cytotoxicity of compounds **5**, **16**, **18**, and **22** compared to that of SW-E **3** on the U-87 MG glioblastoma cancer cell line, highly sensitive to SWs (**Figure 3A**). All the derivatives demonstrated significant potency, with some outperforming the parent compound SW-E **3**. The most remarkable result is that the cytotoxicity of all the compounds depends on the nature of the sugar appended to SW-E **3**. Thus, hybrid **22** which solely features a L-arabinose moiety attached to the triazole had similar activity to SW-E **3**. On the other hand, hybrids **16** and **18**, carrying a D-xylose instead of a L-arabinose, exhibited a much better cytotoxicity. Particularly hybrid **16**, whose D-xylose moiety is directly attached to the triazole, was 10 times more cytotoxic than **3** and **22** which only differs by the nature of the sugar. In contrast, hybrid **5** containing the whole disaccharide moiety of OSW-1 exhibited a lower activity. These results indicate at first sight that triazole is an advantageous replacement for L-arabinopyranose and allows D-xylose to interact selectively with the protein. To gain a better insight into the bioactivity results, we next performed a molecular docking simulation of hybrids **5**, **16**, **18** and **22** into the OSBP-ORD domain (PDB ID: 7v62)[19] using AutoDock Vina and compared their binding mode with that of OSW-1 **1** and SW-E **3** (**Figure 3B**). Except hybrid **5**, which we were unable to dock properly, the terpene moiety of hybrids **16**, **18** and **22** superimposed perfectly with that of SW-E **3** *i.e.* in a relatively similar way to that of the aglycone of OSW-1 **1**. The hydroxyls of the hexahydroxanthene moiety of all these compounds pointed toward the bottom of the ORD domain.

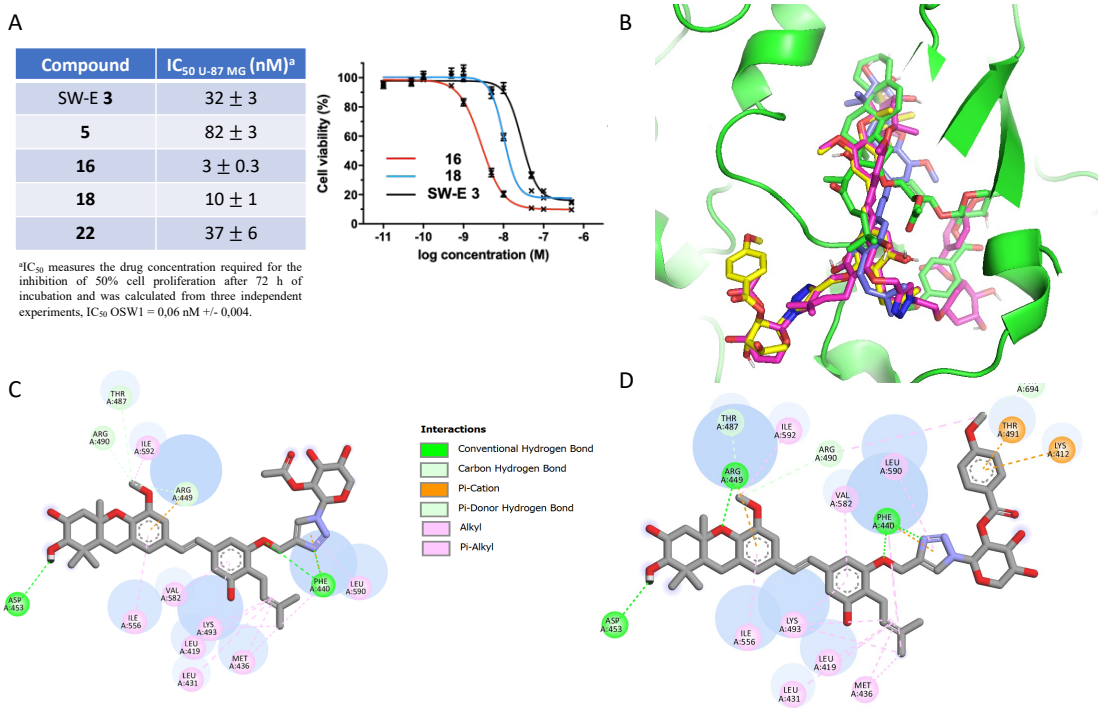


Fig. 3. A- Evaluation of the cytotoxic activity of the hybrid compounds **5**, **16**, **18** and **22** on U-87 MG glioblastoma cell line compared with that of SW-E **3** and OSW1 **1**; **B**- Superimposition of OSW-1 **1** (green), SW-E **3** (violet) and hybrids **16** (yellow), **18** (magenta) and **22** (fushia pink) in OSBP ORD domain (PDB ID: 7v62); **C**- 2D interaction map of hybrid **22** with the amino acids of the ORD domain of OSBP; **D**- 2D interaction map of hybrid **16** with the amino acids of the ORD domain of OSBP.

Anyway, contrary to our assumption, only the triazole-sugar chain of hybrid **18** superimposed with the disaccharide unit of OSW-1 **1**, those of hybrids **16** and **22** were located in another pocket near the lid of the ORD domain (**Figure 3B**). Furthermore, although the side chain of hybrid **18** occupied the same pocket as that of OSW-1, its orientation differed: it descended towards the bottom of the ORD domain and adopted a pincer-like conformation, the phenyl of the benzoate group making a stabilizing π–π interaction with the aromatic of the HHX motif (see SI, **Figure 1S**). In contrast, the sugar moiety of OSW1 **1** pointed towards the top of the domain. The 2D visualization of the interaction between hybrid **22** (**Figure 3C**) and **16** (**Figure 3D**) and the residues of the ORD domain of OSBP showed a crucial hydrogen bond between the hydroxyl of their HHX motifs and Asp 453 as well as another hydrogen bond and a π-cation interaction between their triazole and a phenylalanine (Phe 440). In addition, the benzoate of hybrid **16**, the most cytotoxic, developed two additional π-cation interactions with a theronine (Thr 491) and a lysine (Lys 412) and the ether of its HHX, a further hydrogen bond with Arg 449. The 2D visualization of hybrid **18** suggested H bonds

between the xylopyranosyl and three amino acids of the ORD domain, among which Ser 432 et Asn 496 similarly to OSW-1 **1** (see SI, **Figure 1S**). It also showed numerous π interactions between various amino acids and the stilbene, the benzoate or the triazole motif. However, unlike hybrids **16** and **22** and OSW-1 **1**, no hydrogen bonds appear to be formed between the alcohol of the HHX motif and Asp 453. This discrepancy in the interactions of the different hybrids with the amino acids of the OSBP-ORD domain could explain the differences in biological activity observed. These docking results remain speculative but are consistent with the difference of cytotoxicity of the hybrids, considering that we have previously demonstrated on a large panel of SWs that there is a very good parallel between cytotoxicity on U-87 MG cell line and Ki for OSBP.[18]

In conclusion, we have successfully synthesized the first hybrid molecules of SW-E **3** and OSW-1 **1** by combining the pharmacophores of each partner. This was achieved through a CuAAC click reaction involving a polyfunctionalized alkyne derived from **3** and various azido sugars. Additionally, we developed a novel and efficient method for preparing the disaccharide of OSW-1 **1** through sequential functionalizations of L-arabinose, facilitated by a boronic ester as a switchable protective/activating group. This study allowed us to improve the existing synthesis routes of OSW-1 **1** disaccharide by reducing the number of steps and purifications, thereby saving time and simplifying manipulation.

The evaluation of the hybrid derivatives, particularly **16**, demonstrated promising results against the U-87 MG glioblastoma cancer cell line. We are currently synthesizing additional compounds to enhance these outcomes, particularly focusing on direct glycosylation reactions of one of the phenols of SW-E **3**.

Conflicts of interest

There are no conflicts to declare.

Data availability

The data supporting this article have been included as part of the ESI

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