AN OVERVIEW ON HETEROCYCLIC PODOPHYLLOTOXIN DERIVATIVES

DOI: http://dx.medra.org/10.17374/targets.2016.19.28

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Abstract. *Due to the antitumor activity of podophyllotoxin, there has been an enormous interest in its derivatization with heterocycles. Introduction of heteroatoms on its structure, attaching heterocycles to it or appending heterocycles at several points, are the main strategies carried out. This overview will treat the different approaches to these compounds and mention the biological activities obtained.*

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1. Introduction

Podophyllotoxin (Figure 1) is a naturally occurring cyclolignan isolated mainly from roots and rhizomes of *Podophyllum* species, but also from many other genera and species.[1] It is biosynthesized through the shikimate pathway and formed by the union of two phenylpropanoid units giving rise to a structure with four almost planar fused rings, labelled A, B, C and D rings, and an additionally pendant trimethoxyphenyl ring, labelled as E ring.

Revising literature concerning podophyllotoxin related compounds, different numbering systems has been used since its characterization in the 50's. In this chapter, we are following the IUPAC recommendations for the lignan family[2] which is based on the two phenylpropanoid subunits that formed the natural product, that is, the one with the phenyl included in the tetracyclic moiety is numbered from 1 to 9 and the other from 1' to 9' as stated in Figure 1.

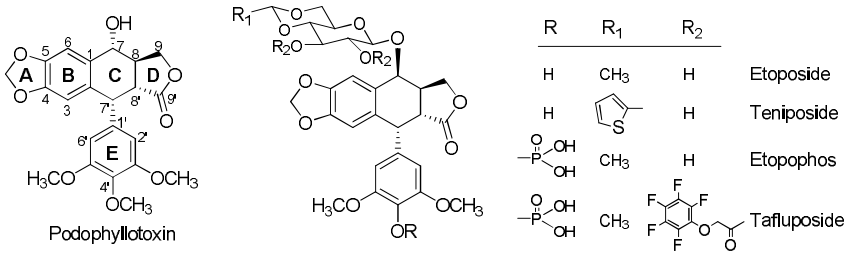


Figure 1. Structure of podophyllotoxin and several derivatives in clinical use.

Plants containing podophyllotoxin have been used in the traditional medicine for centuries as cathartic or antihelmintic.[3] Other biological activities described for podophyllotoxin are antiviral, cytotoxic, antirheumatic or insecticidal. In fact, it is in clinical use as antiviral for the treatment of venereal warts caused by *Papilloma* virus. Nevertheless, the main bioactivity that attracted the attention of the scientific community was its cytotoxicity described by the middle of the 20th century. However, the development of podophyllotoxin as an anticancer agent was limited by its gastrointestinal toxicity and other side effects. As a result, podophyllotoxin became an attractive lead compound for anticancer drug design and nowadays, several semisynthetic derivatives are in clinical use for the treatment of a variety of malignancies. Among those derivatives are etoposide, teniposide, etopophos and more recently tafluposide, which have a common glycosidic moiety at C-7 and are demethylated at C-4' (Figure 1). Surprisingly, these semisynthetic derivatives and the parent compound podophyllotoxin showed different mechanisms of action.[3]

Podophyllotoxin inhibits tubulin polymerization, preventing the formation of the achromatic spindle and arresting cell division in metaphase, while etoposide and its analogues inhibit DNA topoisomerase II, preventing relegation of the double-stranded breaks, and tafluposide is a dual topoisomerases I and II inhibitor. Additionally, the interaction between cyclolignans and biomolecules would imply the existence of another, hitherto unreported, mechanism for antineoplastic cyclolignans, because some lignan derivatives were as cytotoxic as podophyllotoxin and etoposide, but they scarcely inhibit tubulin polymerization and are only weak inhibitors of topoisomerase II.[4,5]

Because of its important biological activities, podophyllotoxin has been the objective of many research groups aiming to get more potent, less toxic and more selective analogues. There are many excellent reviews dealing with different aspect of the history,[6-8] pharmacology,[9,10] total synthesis or semisynthesis[11-13] of podophyllotoxin derivatives. This chapter is focused on heterocyclic derivatives of podophyllotoxin, in which not only the heterocycle is a substituent on different positions of the skeleton, but also those derivatives in which any carbon of the cyclolignan moiety is substituted by a heteroatom and even those derivatives that bore a heterocycle fused to any ring of the cyclolignan.

2. Heterocycles attached to different positions of the podophyllotoxin skeleton

2.1. Heterocycles directly attached to position C-7

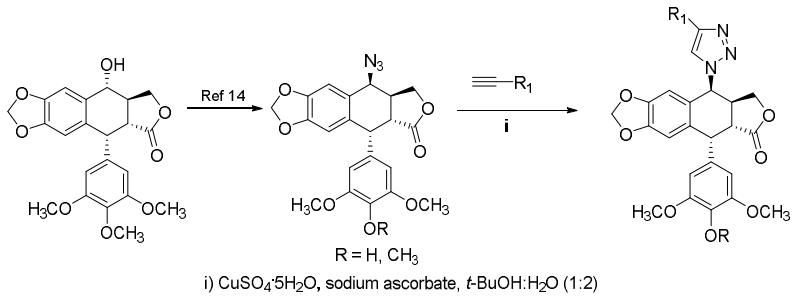
This section deals with those podophyllotoxin derivatives in which the cyclolignan can be considered as a substituent of the heterocycle because the corresponding heterocycle is attached directly to the position C-7 without any linker. Several derivatives with three, five or six membered rings attached to C-7 are considered. The heterocycle could be formed at the last reaction step by click chemistry or can be introduced directly. Only those analogues in which the natural product podophyllotoxin is the starting material will be considered.

2.1.1. Obtained by reaction with azide derivatives

A large number of podophyllotoxin derivatives with a 1,2,3-triazole attached at position 7β have been synthetized by copper-catalysed [3+2] cycloaddition reaction between an azide and a terminal alkyne group, that is, using a click chemistry strategy. In most of cases, the azide function is present in the cyclolignan because podophyllotoxin is easily converted to 7β-azido-7-deoxypodophyllotoxin and 7β-azido-7-deoxy-4'-demethylpodophyllotoxin through its 7β-iodine derivative and further reaction with sodium azide[14]. The terminal alkynes can bear a great variety of substituents, which allow the synthesis of a series of regioselective 7β-[(4-substituted)-1,2,3-triazol-1-yl]podophyllotoxin derivatives (Scheme 1).

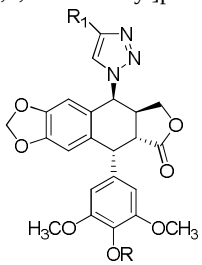
Hu, Jiang *et al.* [15-17] used several glycosides with a propargyl group either directly attached or joined through an oligoethylene glycol linker to obtain more than fifty podophyllotoxin derivatives (Table 1). They used sugars as D-glucose, D-galactose, D-mannose and D-xylose, or peracetylated or perbutyrylated mainly with α configuration at the anomeric carbon. Those analogues were evaluated for their cytotoxicity against several human cancer cell lines. Those authors found that the most potent analogues had an α-D-galactosyl residue directly linked to the triazole ring (IC_{50} 2.85-7.28 μM),[15] a perbutyrylated α-D-galactosyl residue also directly linked to the triazole ring (IC_{50} 0.49-6.70 μM)[17] and a perbutyrylated α-D-glucosyl residue with

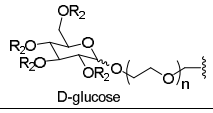
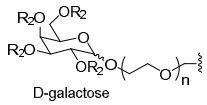
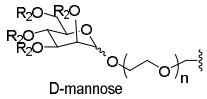
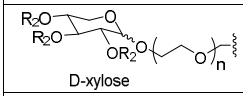
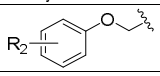
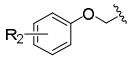
three ethylene glycol units (IC_{50} 0.59-2.90 μM).[16] All of them had a 4'-OH group on the E ring of the cyclolignan skeleton. Similar results were found by Reddy *et al.* with several β-anomeric isomers.[18]

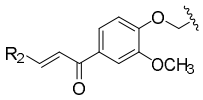
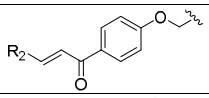
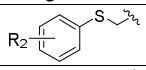
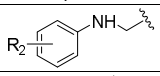
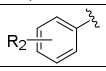


Scheme 1. Synthesis of triazolylpodophyllotoxin derivatives by click chemistry strategy.

Table 1. 7β-[(4-substituted)-1,2,3-triazol-1-yl]podophyllotoxin derivatives.

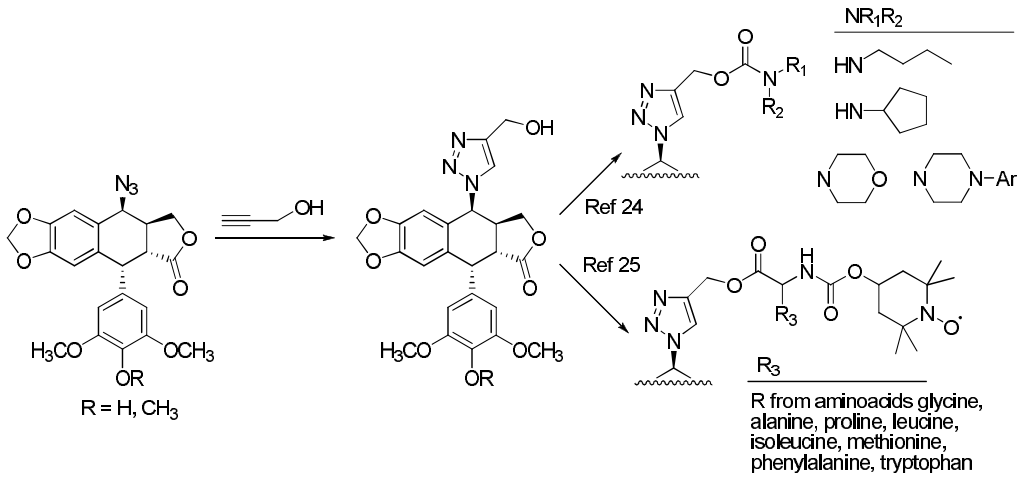


R_1	R	R_2	IC_{50}	References
 D-glucose	H, CH_3	H, CH_3CO, C_3H_7CO n = 0, 3, 6	5/6 tumoral cell lines 0.59->40 μM 0.93-556 μM	 Ref 16 Ref 18
 D-galactose	H, CH_3	H, CH_3CO, C_3H_7CO n = 0, 3, 6	5/6 tumoral cell lines 2.85->40 μM 0.49->40 μM 1.00-316μM	 Ref 15 Ref 17 Ref 18
 D-mannose	H, CH_3	H, CH_3CO, C_3H_7CO n = 0, 3, 6	5/6 tumoral cell lines >40 μM 6.85->40 μM 2.51-237μM	 Ref 15 Ref 17 Ref 18
 D-xylose	H, CH_3	H, CH_3CO, C_3H_7CO n = 0, 3, 6	5 tumoral cell lines 10.29->40 μM 14.94->40 μM	 Ref 15 Ref 17
	H, CH_3	H, 2-CH_3, 3-CH_3, 4-CH_3, 2-Cl, 4-Cl, 4-NO_2	7 tumoral cell lines 0.31-29.6 μM	Ref 20
	CH_3	4-NO_2, 3-NO_2, 4-OCH_3, 4-Alkyl, 4-Ph, -O-CH_2-O-, -CH=CH-CO-O-	4 tumoral cell lines 0.18-66.6 μM	Ref 21

	CH_3	2-OCH_3-Ph, 2,4,5-$(OCH_3)_2$-Ph, 3,4-$(OCH_3)_2$-Ph, 3,4,5-$(OCH_3)_3$-Ph, 4-F-Ph, 4-CF_3-Ph, 2-Thienyl, 4-Pyridyl, 4-$(CH_3)_2N$-Ph	4 tumoral cell lines 0.53->80 μM	Ref 21
	H, CH_3	Ph, 2-F-Ph, 3-F-Ph, 4-F-Ph, 3-CH_3-Ph, 4-OCH_3-Ph	6 tumoral cell lines 0.35-3.0 μM	Ref 22
	H, CH_3	H, 4-CH_3, 4-Cl,	7 tumoral cell lines 0.37-50.0 μM	Ref 20
	H, CH_3	H, 2-CH_3, 4-CH_3, 2-Cl, 3-Cl, 3-NO_2,	7 tumoral cell lines 0.14-9.14 μM	Ref 19
	H, CH_3	CH_2-$N(CH_3)_2$, $COOCH_3$, CH_2OH, CH_2-COOH	3 tumoral cell lines 0.62-3.90 μM	Ref 23
CH_2-$N(CH_3)_2$, $COOCH_3$, CH_2OH, CH_2-COOH	H, CH_3		3 tumoral cell lines 0.62-3.90 μM	Ref 23

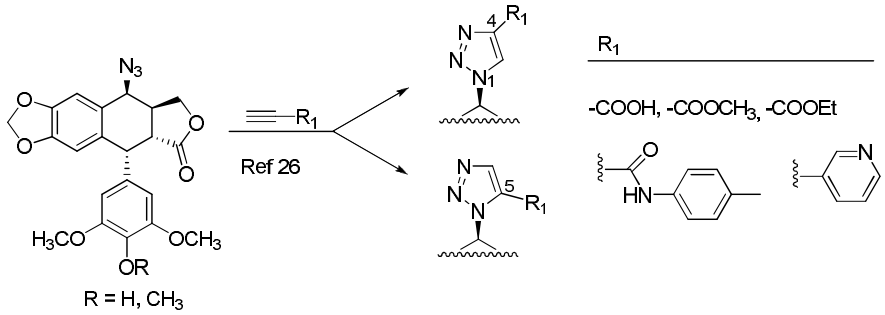
Other alkynes used for the click chemistry reaction are also shown in Table 1 and they included *O*-aryl, *S*-aryl and *N*-aryl propargyl derivatives with a great variety of substituent at the aryl ring, including aromatic or heteroaromatic rings such as chalcones, thiophene or pyridine.[19-23] All of them were evaluated as cytotoxic against a number of tumoral cell lines and the results obtained were at the micromolar range, improving in many cases the cytotoxicity found for etoposide.

In other cases, the triazole system is constructed with the propargyl alcohol to give the corresponding 4-hydroxymethyltriazolylpodophyllotoxin derivative (Scheme 2). The hydroxyl group was further derived as a carbamate[24] or as an ester[25] that can bear other heterocycles such as piperazine, morpholine or nitroxyl free radicals that contributed to the bioactivity of these podophyllotoxin analogues. Those with the nitroxyl free radicals were weak cytotoxics but those with the carbamate group showed IC_{50} values under micromolar.



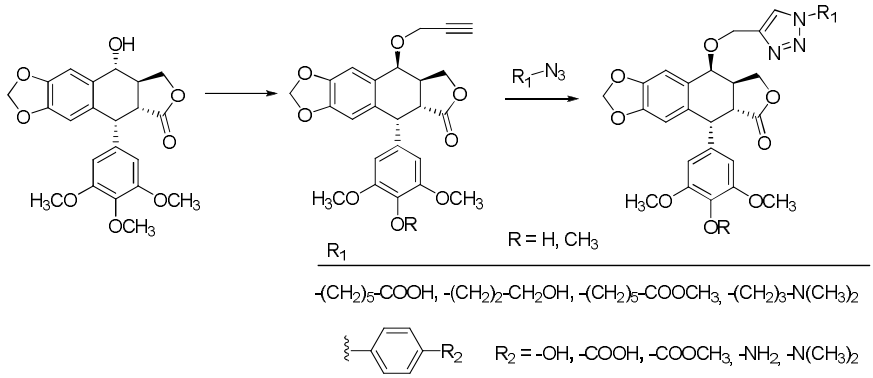
Scheme 2. Other triazole podophyllotoxin derivatives at C-7.

In all the examples described in Schemes 1 and 2, always the triazoles substituted at position 4 were obtained regioselectively, and only when no catalyst was added or it changed from sodium ascorbate to 2,6-lutidine or pyridine, the regioisomers 1,5-disubstituted triazoles were formed,[26] which showed even better cytotoxicity than the corresponding 1,4-disubstituted triazoles (Scheme 3).



Scheme 3. Click chemistry for the synthesis of triazole derivatives in different reaction conditions.

Usually in the reactions described above, the azide function is attached to the cyclolignan skeleton, but Austin, Rodriguez *et al.*[23] prepared few examples in which the cyclolignan had the alkyne, thus the podophyllotoxin residue is now the substituent at the 4 position of the triazole formed, all of them kept the cytotoxicity (Scheme 4).

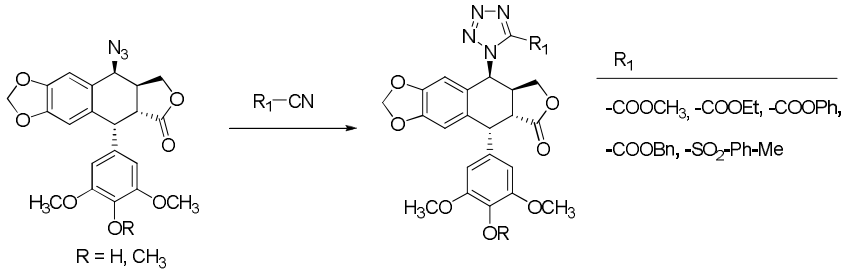


Scheme 4. Other derivatives obtained by click chemistry with the alkyne attached to the lignan.

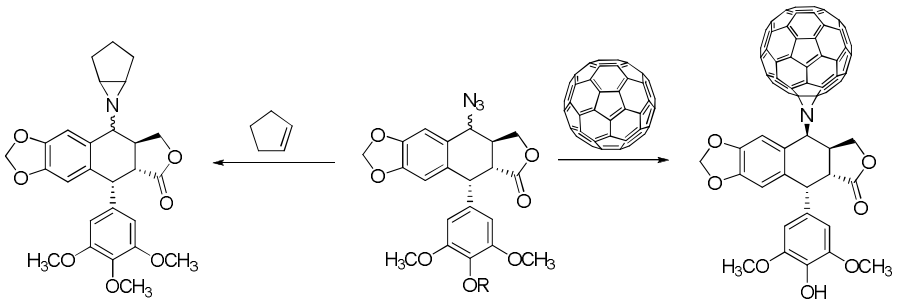
Not only alkynes have been used to perform click chemistry with azidoepipodophyllotoxin derivative. Kumar *et al.*[27] used several cyano compounds without any other additive or in the presence of zinc bromide to give the corresponding tetrazoles (Scheme 5). Their IC_{50} values against a panel of four cancer cell lines were in the range of 2.4-29.1 μM and they were inhibitors of tubulin polymerization.

Some thermally induced reactions have also been done with azidoepipodophyllotoxin and olefins to give triazenes, which after photochemical cleavage gave aziridine derivatives. When the olefin was

cyclopentene, the aziridine was obtained, however when cyclohexene was used, the expansion of the C ring to an azepine was done.[28] Similar aziridine derivative was obtained with fullerene[29] (Scheme 6).



Scheme 5. Synthesis of tetrazole derivatives.



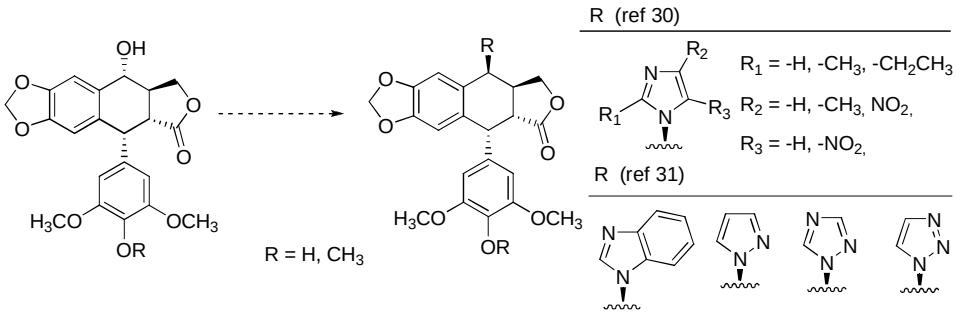
Scheme 6. Synthesis of aziridine podophyllotoxin derivatives.

2.1.2. Obtained by direct reaction with heterocycles

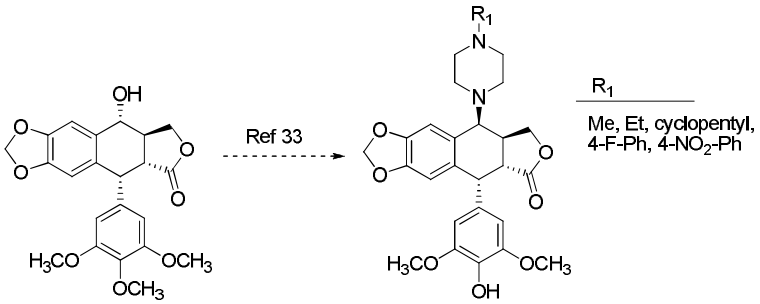
Several five or six membered heterocyclic rings, with one or more heteroatoms, were introduced at position C-7 by reaction of either podophyllotoxin or 7β-halopodophyllotoxin derivatives with the corresponding heterocycles.

Imidazole rings at 7β position were introduced through the direct coupling of podophyllotoxin or 4'-demethylpodophyllotoxin with electron-withdrawing substituted imidazoles in the presence of $FeCl_3$. However, derivatization of the 7-OH as a mesylate was necessary before the nucleophilic substitution with imidazoles bearing electron donating groups.[30] These analogues were less cytotoxic than the parent compound. Different five membered *N*-heterocycles were also introduced through the chloro-derivative at C-7, obtained from reaction of podophyllotoxin with $SOCl_2$ and further nucleophilic substitution with the corresponding heterocycle[31] (Scheme 7).

Wang *et al.*[32] performed this reaction with *N*-substituted imidazoles to give imidazolium salts as precursors of palladium *N*-heterocyclic carbene ligands, that were used as catalysts in allylic alkylation reactions.[32] Several saturated heterocycles, such as piperazines, have also been introduced at C-7 position through the 7β-iodo-7-deoxypodophyllotoxin intermediate, which gave easily the nucleophilic substitution by the corresponding amines[33] (Scheme 8).

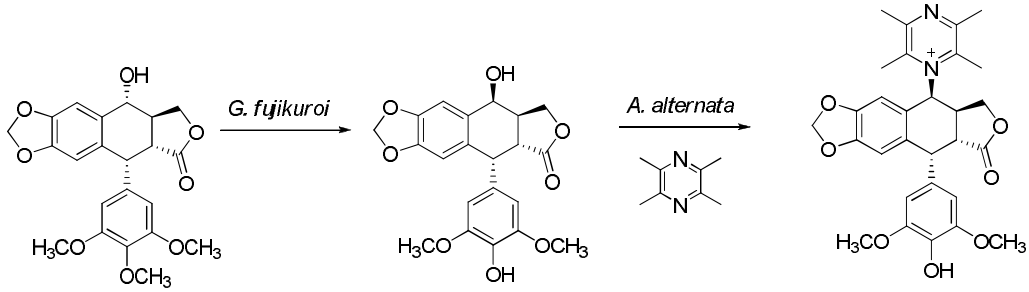


Scheme 7. Imidazole**,** pyrazole, triazole and benzimidazole derivatives.



Scheme 8. Piperazine podophyllotoxin derivatives at C-7.

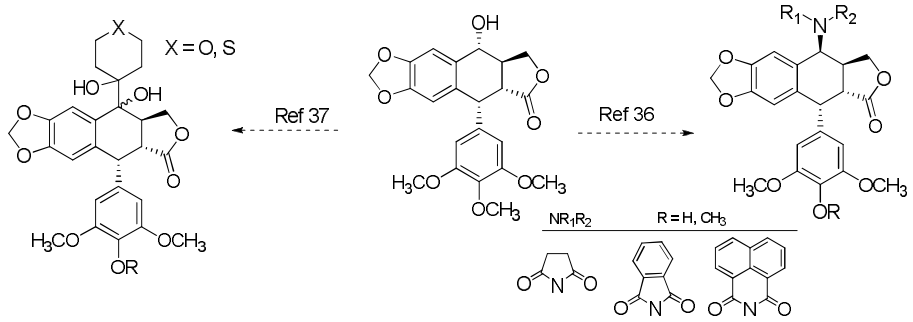
Another very interesting podophyllotoxin derivative has a tetramethylpyrazine ring at position C-7, which was obtained from podophyllotoxin by a tandem biotransformation process using two microorganisms: *Gibberella fujikuroi* for demethylation at C-4' and epimerization at C-7 and *Alternaria alternata* for oxidation and transamination reactions. The pyrazine derivative showed significative enhanced anti-tumor activity[34,35] (Scheme 9).



Scheme 9. Synthesis of pyrazine derivatives by biotransformation process.

Several 7β-imido substituted podophyllotoxin analogues have been obtained from podophyllotoxin by coupling imides as succinimide, phthalimide and naphthalimide with the 7β-bromo-7-deoxypodophyllotoxin intermediate.[36] The compounds obtained were good cytotoxic with IC_{50} values in the range 0.004-0.50 μM.

Tetrahydropyran and tetrahydrothiopyran attached to the position C-7 were obtained by López-Pérez, Díaz *et al.* through McMurry type condensation of podophyllotoxone with symmetric heterocyclic ketones to give the corresponding pinacols. These analogues retained the initial hydroxyl group of podophyllotoxin at 7α or 7β configuration and also the cytotoxicity and the mechanism of action of the parent compound.[37] (Scheme 10).



Scheme 10. Imides, pyrans and thiopyrans derivatives.

2.2. Heterocycles attached to podophyllotoxin skeleton through different linkers

In this section, we are considering those podophyllotoxin analogues that bear any heterocycle as substituent at different positions of the podophyllotoxin skeleton but attached through a variety of linkers. Position C-7 is the main point for attached these heterocyclic substituents, although C-9, C-9' or C-4' are also good points. In many cases the linker is only one heteroatom such as nitrogen, in other cases are other functional groups such as ester or amide and the heterocycle can be near to the cyclolignan skeleton or at the end of a longer substituent.

2.2.1. Heterocycles at C-7

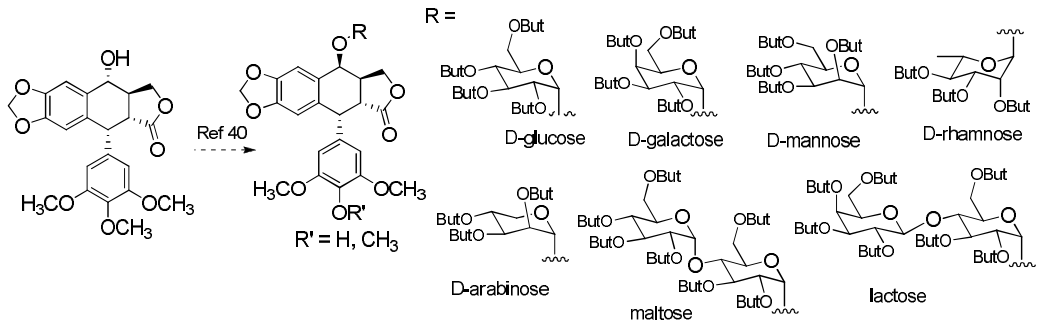
2.2.1.1. Heterocycles at C-7 joined by an ether group

In this section, the glycosides derivatives can be included. The semisynthetic podophyllotoxin derivatives in clinical use such as etoposide, etopophos or tafluposide (Figure 1) are β-D-glucopyranosides. Thus, they are very well known and are the subject of several reviews,[38,39] however other podophyllotoxin glycosides are much less studied and only recently Jiang and Hu[40] have described the synthesis and antitumor activity of perbutyrylated glycosides of podophyllotoxin using sugars as D-galactose, D-mannose, D-rhamnose, D-arabinose, maltose and lactose, apart from D-glucose (Scheme 11). Some of the glycosides obtained were more potent than the control drugs etoposide and cisplatin.

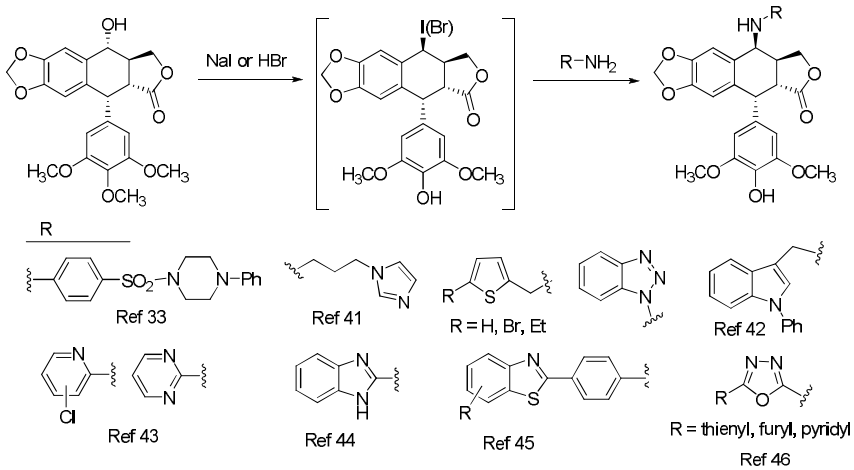
2.2.1.2. Heterocycles at C-7 joined by an amine group

As mentioned above, podophyllotoxin derivatives with a halogen atom at C-7, either bromine or iodine, have been frequently used as intermediates for the introduction of different nucleophilic moieties at C-7. In this sense, many aliphatic and aromatic amines have been used to introduce a great variety of substituents at that position obtaining analogues with very interesting cytotoxic properties.[33,41-46] Some of

them are inhibitors of DNA-topoisomerase II and other act as podophyllotoxin, that is, by inhibiting tubulin polymerization. Most representative heterocyclic substituents are showed in Scheme 12.



Scheme 11. Glycosides podophyllotoxin derivatives.



Scheme 12. Heterocycles attached through an amino group at C-7.

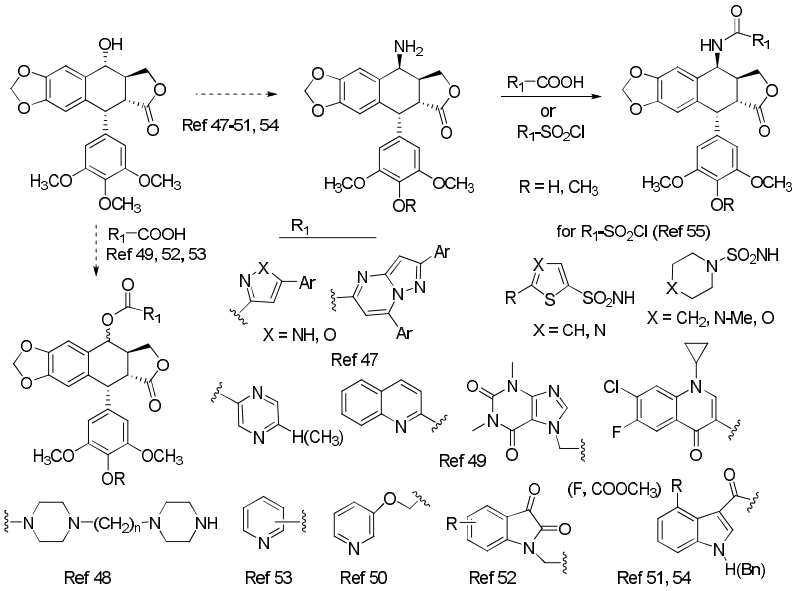
2.2.1.3. Heterocycles at C-7 joined by ester or amide groups

Functions as esters or amides are frequently used in medicinal chemistry to obtain prodrugs because they can modulate aqueous solubility or enhance absorption. In this sense, podophyllotoxin has also been the subject of these structural modifications and a huge number of derivatives were obtained. Those functions can be easily introduced on hydroxyl or amino functionalities of the parent drug molecule. In Scheme 13 there are shown those that bore a heterocyclic ring, which showed significant antiproliferative activity and some of them were able even to induce apoptosis.[47-55]

2.2.2. Heterocycles at C-9

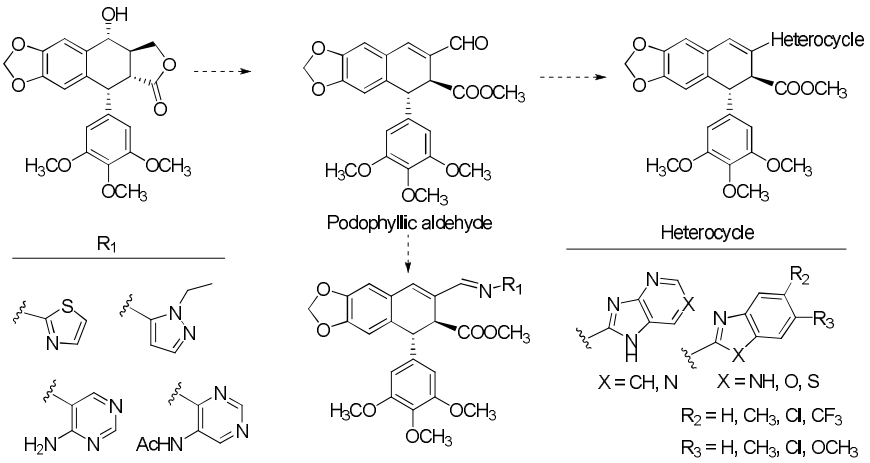
The γ-lactone ring, ring D, is considered essential for the cytotoxicity of cyclolignans; Castro *et al.* prepared several analogues, lacking the lactone ring, with very interesting cytotoxicity and selectivity[56-58]

and even proposed that cyclolignanolides might work as alkylating agents, through the C-9 methylene, rather than as acylating agents as proposed early.[56]



Scheme 13. Extended structures with heterocycles.

Additionally, our group also described, by the first time, *in vitro* and *in vivo* immunosuppressive activity for cyclolignans (Scheme 14).[59,60] These results were the subject of two international patents.[61,62]

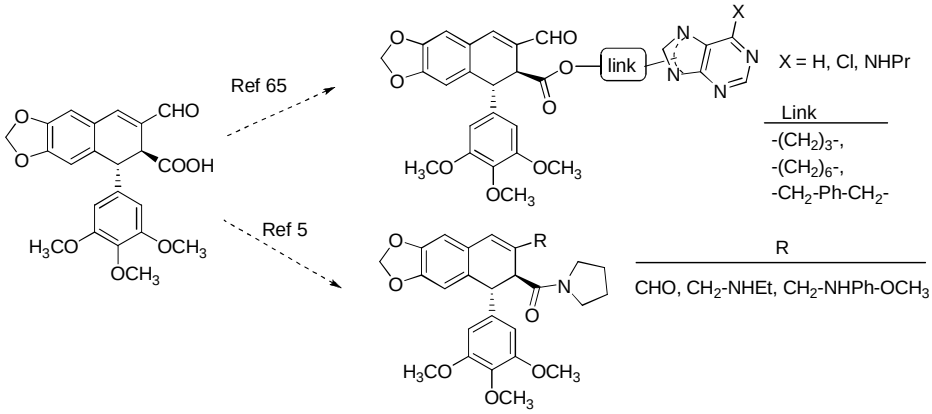


Scheme 14. Heterocycles attached to C-9.

In those studies, the podophyllic aldehyde synthesized from podophyllotoxin, was the lead compound for further chemical modifications, including the introduction of several heterocycles joined to position C-9 by a nitrogen atom,[63] and formation of new derivatives in which the carbon C-9 was part of the new formed heterocyclic ring.[64] Those derivatives are shown in the Scheme 14.

2.2.3. Heterocycles at C-9'

Position C-9' is another important point to introduce substituents of any type as stated before. For long time the lactone ring was considered essential for the cytotoxicity, however, several derivatives lacking the lactone ring showed very interesting cytotoxicity and selectivity.[56-58,64] Among them, it is worth to mention a new family of podophyllotoxin hybrids, named lignopurines, which combined a purine ring with the selective cytotoxic podophyllic aldehyde, obtained from podophyllotoxin. In these hybrids the purine moiety is attached to the cyclolignan skeleton through position C-9' by an ester function.[65] Both fragments, cyclolignan and purine, were linked through aliphatic or aromatic spacers to give conjugates that kept the selectivity of the podophyllic aldehyde, they are able to interfere with tubulin polymerization and to arrest cells at the G2/M phase, as the precursors, podophyllotoxin and podophyllic aldehyde, do. Castro *et al.* also prepared some amide derivatives at that position, although they were less cytotoxic than podophyllotoxin[5] (Scheme 15).



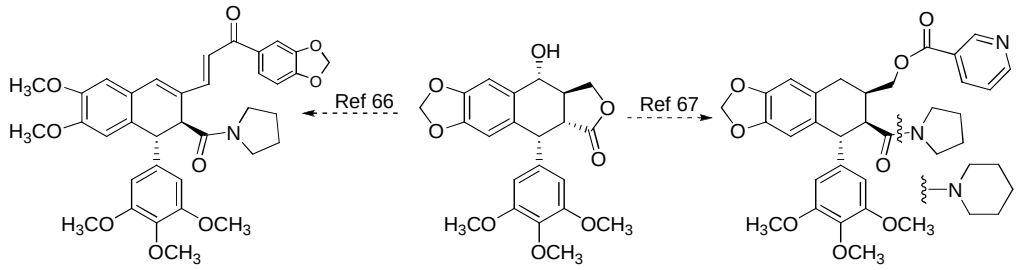
Scheme 15. Heterocycles derivatives at C-9' from podophyllic aldehyde.

Similar amides at C-9' with pyrrolidine and piperidine moieties were prepared as analogues of deoxypodophyllotoxin, not only with antitumor activity,[66] but also with insecticidal activity.[67] Some of them also have an additional heterocycle attached to C-9 (Scheme 16).

2.2.4. Heterocycles at C-4'

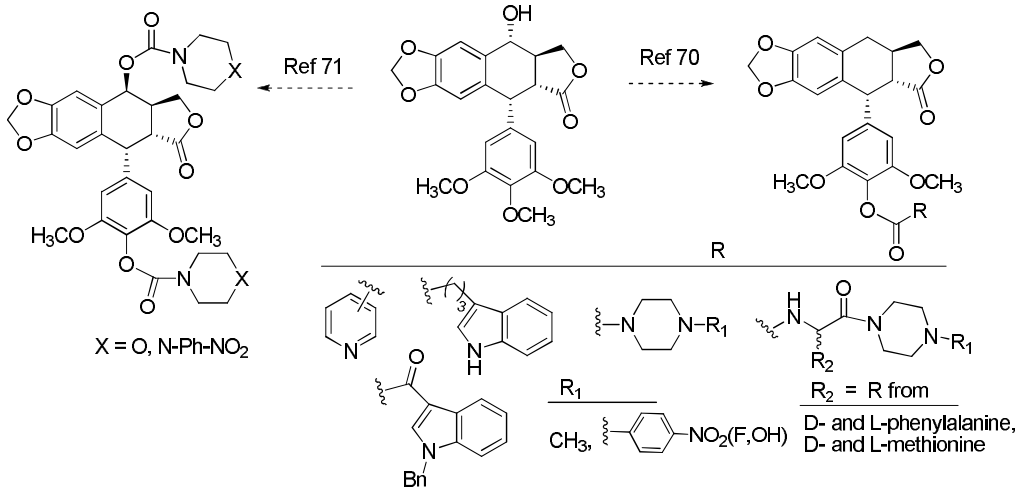
The phenol group present in 4'-demethylpodophyllotoxin is easily obtained from podophyllotoxin and used to be considered an interaction point with the enzyme DNA-topoisomerase II. It is an interesting point to perform structural modifications towards agents with better pharmacokinetics, in fact etopophos is a more

soluble prodrug of etoposide, which has the 4'-hydroxy as a phosphate. This OH group has been derived as ester, carbamate, etc with many substituents, including some conjugates with other antitumor or antiviral agents.



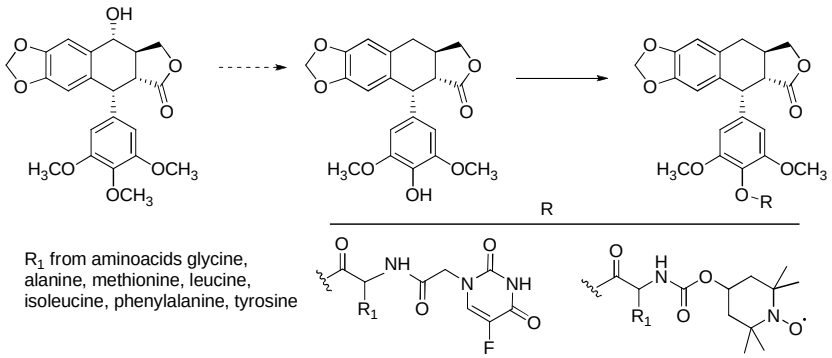
Scheme 16. Other amides derivatives.

Xu, Yao *et al.* prepared some ester derivatives bearing a pyridyl or indolyl groups with pronounced insecticidal activity.[68,69] Hui, Cheng *et al.* have synthesized some examples of carbamates at that position, either derived from deoxypodophyllotoxin or from epipodophyllotoxin,[70,71] the later bore the heterocycles at both positions 7 and 4' (Scheme 17).



Scheme 17. Heterocycles appended at 4'-OH.

Some substituents with the same type of heterocycles than those described before at C-7 have been prepared an evaluated as cytotoxics. Chen *et al.* [72,73] synthesized 4'-demethyl-4-deoxypodophyllotoxin by subsequent hydrogenolysis to remove the 7-OH, followed by 4'-demethylation. Several examples with 5-fluorouracil[73] or spin-labelled derivatives[72,74] are shown at the Scheme 18 and most of them enhanced cytotoxic or antitumor activity compared with the parent compound. Those with the oxyltetramethylpiperidinyl moiety showed also antifeedant activity.[74]



Scheme 18. Heterocycles appended at C4'-OH of deoxypodophyllotoxin.

2.2.5 Conjugates or hybrids of podophyllotoxin with other biologically active heterocyclic compounds

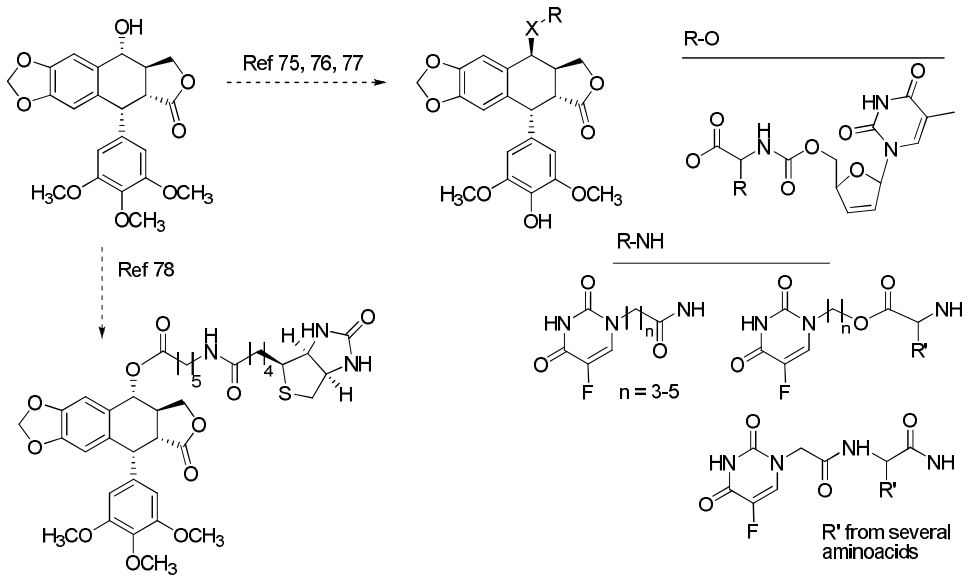
Hybridization is a classic strategy in drug design consisting in combining different bioactive fragments to get what are called "hybrids" or "conjugates". Sometimes they are able to improve the precursors' properties, to overcome resistance associated to individual fragments or to show different activities or even different mechanisms of action to that of their precursors. This strategy is based in Nature because many natural products are hybrid structures themselves and the scientists used it to generate new drugs; this is particularly interesting in chemotherapy, where natural products play an important role in the development of new therapeutical agents. In this sense, podophyllotoxin derivatives have been conjugate with different endogenous metabolites or with other cytotoxic agents in an attempt to improve either the transport towards the biological target or to find compounds that could act on different biological targets simultaneously. As this chapter deals with heterocyclic podophyllotoxin analogues, we only showed here those conjugates with fragments bearing any heteroatom as part of a heterocyclic system, either from natural or synthetic origin.

Tian *et al.* have synthetized several conjugates of podophyllotoxin with pyrimidine nucleoside analogues such as 5-fluorouracil[75,76] and stavudine.[77] The pyrimidine nucleoside is attached to the position C-7 by amine[75], amide[76] or ester[77] functions using different spacers such as aminoacids or alkyl chains (Scheme 19). Most compounds showed better water solubility and more effective cytotoxicity than etoposide. Another natural metabolite connected to C-7 of podophyllotoxin is the biotin moiety. In this case, podophyllotoxin is directly esterified with biotinylaminocaproic acid, keeping the 7α configuration[78] (Scheme 19).

In this section, it could also be considered etoposide and analogues as hybrids of cyclolignans and sugars, and also some derivatives shown in previous schemes such as the lignopurines described in Scheme 15, which are conjugates of podophyllotoxin and purines and others shown in Scheme 13.

Other bioactive compounds conjugated with podophyllotoxin through the position C-7 are acridine,[79] campthotecin,[80,81] vinblastine derivatives[82] and podophyllotoxin itself,[48] obtaining very interesting cytotoxicity. Lu *et al.* synthesized for the first time the succinic acid 12α-deoxoartemisinyl ester 4'-*O*-demethyl-7β-(4''-nitroanilino)-7-desoxypodophyllotoxin[83] and very recently Zhang, Wang *et al.* have made the conjugate of podophyllotoxin and artesunate[84] and evaluated for its cytotoxicity against human cancer

cell lines by CCK-8 assay. The conjugate exhibited good cytotoxicity and found to disrupt the microtubule network and induce G2/M cell cycle arrest in multidrug resistance K562/ADR cells.



Scheme 19. Some hybrids of podophyllotoxin.

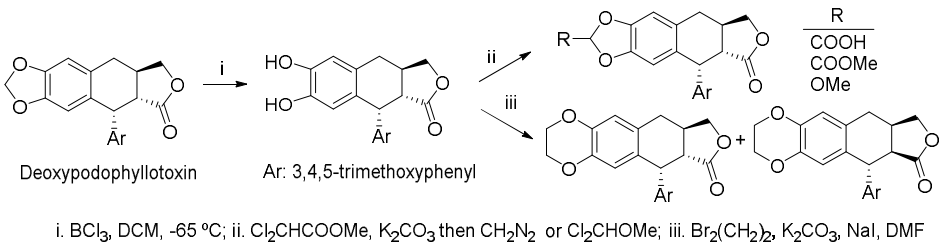
3. Heterocycles being part of the podophyllotoxin skeleton

Those podophyllotoxin derivatives in which any ring of the skeleton is substituted by a heterocycle are considered in this heading. In contrast with the previous one, where the parent natural product is the starting material for all the transformations, the analogues presented here are obtained mainly by total synthesis thus, they are obtained in racemic form when no starting from the natural product or a chiral compound. In many cases, they are simplified analogues of podophyllotoxin that might be less potent than the parent compound but contribute to SAR studies and structure optimization. Medarde *et al*. published in 1999 an exhaustive review covering every aspect on heterolignans.[11] This section do not try to be so exhaustive and cover literature dealing with those analogues that remember most to podophyllotoxin and, for instance, the arylnaphtalene derivatives, in which the ring C is aromatized or those in which a carbon of any propanoid unit is missing were not considered. The information presented here is organized according the cyclolignan ring that is modified with heteroatoms, although there are several heteroanalogues that could be considered in more than one section. The way of labelling the rings is shown in Figure 1.

3.1. Heteroatoms on ring A

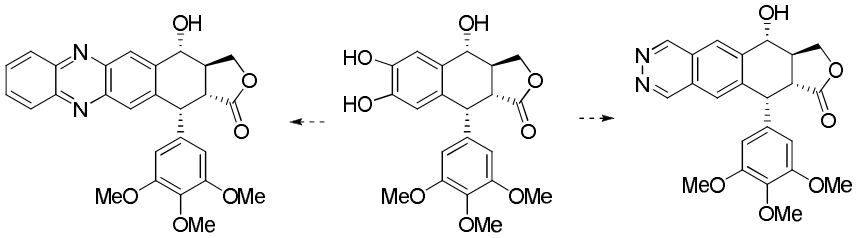
One of the most usual variations in this ring is to change the methylendioxy for an ethylendioxy, feature that can be observed in the review of Malhotra *et al.*[85] Castro *et al.* deprotected the methylendioxy group of podophyllotoxin and made several derivatives (Scheme 20).[86] They applied this methodology not

only to podophyllotoxin but also to other heterocyclic derivatives obtained by them with an additional isoxazole ring fused to the skeleton.



Scheme 20. Castro *et al.* modifications of ring A.

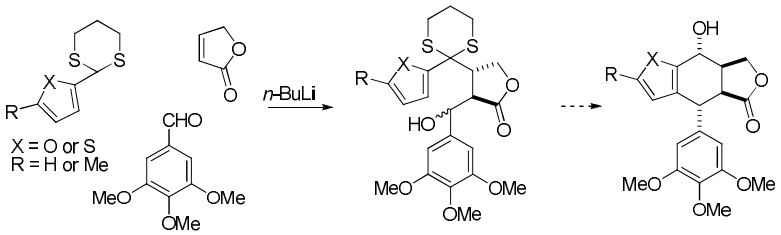
More interesting is the modification carried out for Monneret group[87] that changed ring A into a pyridazine. Deprotection of the methylendioxy, transformation of the hydroxy groups into their triflates and Still coupling led to the corresponding diolefin that were cleavaged into the aldehydes and treated with hydrazine to obtain the corresponding pyridazine, as shown in Scheme 21. With a different strategy consisting in oxidation of A ring and condensation with phenylenediamines, Lee *et al.* obtained the corresponding phenazines.[4]



Scheme 21. Synthesis of phenazine and pyridazine derivatives on ring A.

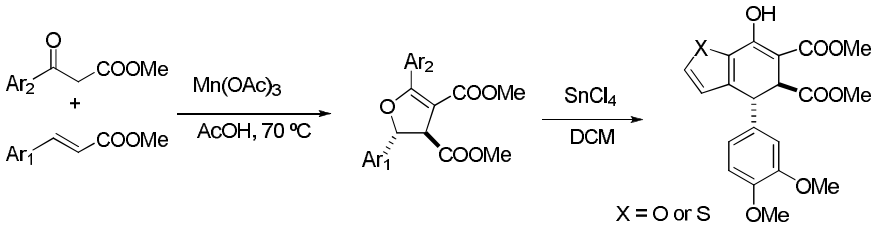
3.2. Heteroatoms on ring B

Medarde *et al.* using a Michael addition to furan-2(5*H)*-one were able to substitute rings A and B with a thiophene or furan as shown in Scheme 22.[88]



Scheme 22. Medarde *et al.* synthesis of thiophene podophyllotoxin derivatives.

A very different approach was carried out by Bruns's group.[89] Condensation between cinnamic derivatives and β-ketoesters give 2,5-disubstituted-2,3-dihydrofurans, which yield several heterolignans by rearrangement mediated by $SnCl_4$, as shown in Scheme 23.



Scheme 23. Synthesis of furan and thiophene derivatives by Brun *et al*.

3.3. Heteroatoms on ring C

The aim of changing one or more carbon atoms by heteroatoms in ring C is to avoid the stereochemical instability at C-8' position and to increase the biological activity of the parent compounds. The epimerization at C-8' leads to inactive compounds and can be reduced by introducing a nitrogen atom at that position or in another nearby or even structures with additionally heteroatoms at C-7. Here will be described the synthesis and properties of these compounds grouped according the position of the heteroatom in the podophyllotoxin skeleton as stated in Figure 2.

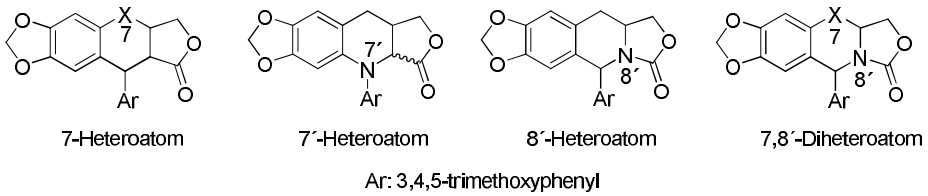


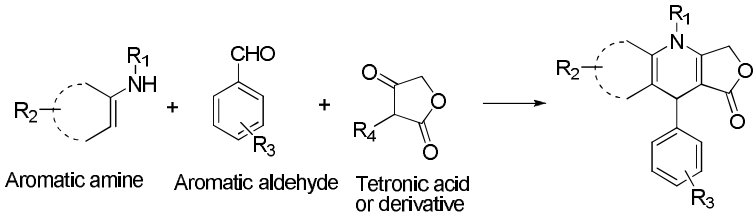
Figure 2. Heteroatom substitution on ring C.

3.3.1. 7-Heteropodophyllotoxin analogues

3.3.1.1. 7-Azapodophyllotoxin derivatives

There has been a great interest in the synthesis of this kind of podophyllotoxin analogues as they retain cytotoxicity as well as inhibition of tubulin polymerisation. There has been two important reviews in this subject, the one of Alegria and Malhotra in 2011[85] and the one of van Otterlo *et al.*[13] in 2014 that refer to the synthesis of these compounds by multicomponent reactions (MCRs). In this chapter we include the new work done until date together with some background about it. First of all, in 2000, Husson, Giorgi-Renault *et al.* described the straightforward synthesis of 7-azapodophyllotoxin derivatives via a 3-component reaction, which involves the condensation of a tetronic acid derivative with variously substituted anilines and aldehydes (Scheme 24).[90] Due to the facility of this approach many groups have done 7-azapodophyllotoxin derivatives or analogues. To this respect, Giorgi-Renault *et al.* described the synthesis of several quinoline

lactones that can be considered as rigid analogues of 7-aza-8,8'-didehydropodophyllotoxins and many other different compounds with antitumoral or vascular-disrupting activities.[91-94]



Scheme 24. Synthesis of 7-azapodophyllotoxin derivatives by MCRs.

There has been many contributions made with this strategy for the synthesis of insecticidal 7-azapodophyllotoxin derivatives, Ji *et al.* use microwave methodology and the authors say that this increases the yield, lower the cost and reduces the environmental impact.[95] Yao *et al.* using a thia-tetronic acid derivative, 3,4-(methylenedioxy)aniline and differently substituted aromatic aldehydes,[96] and Kamal, Vishnuvardhan *et al.* using tetronic acid, heteroaromatic amines and substituted terphenyl aldehydes,[97] obtained several derivatives that exhibited promising anticancer activity at micromolar concentration. Also Kamal *et al.* used tetronic acid, 1,10-phenantrolin-5-amine and different substituted aromatic aldehydes,[98] to obtain new compounds that exhibited remarkable antiproliferative activities on different cancer cell lines, comparable to that of podophyllotoxin and etoposide. Kumar, Malhotra and Fattorusso using tetronic acid, *N*-hydroxyethyl aromatic amines and different substituted aromatic aldehydes,[99,100] synthesized 7-azapodohyllotoxin derivatives that were more active in cancer cell lines less responsive to paclitaxel and in particular compound NSC756093, Figure 3, was able to modulate the GBP1:PIM1 interaction, reporting this inhibition for the first time. Alegria *et al.* used the same kind of *N*-hydroxyethyl aromatic amines for the synthesis of 7-aza-8,8'-didehydropodophyllotoxin derivatives with potential antitumor activity.[101,102] As can be deduced in some of these syntheses if the aromatic aldehyde is a heterocycle, the derivatives could also be considered in the section dealing with heteroatoms on ring E, although they have been included here due to the importance of ring C.

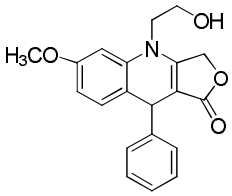


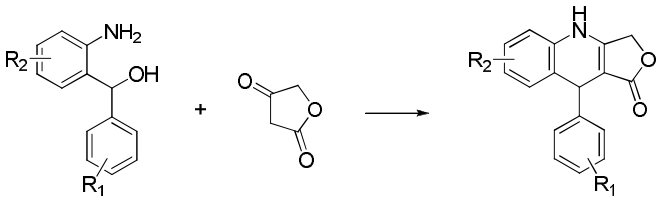
Figure 3. NSC756093.

Finally Raju *et al.* made use of tetronic acid, different substituted aromatic aldehydes and heteroaromatic amines as indole, indazole, pyridine, pyrazole and oxazole amines to obtain the required 7-

azapodophyllotoxin derivatives and molecular docking simulations were carried out against topoisomerase II.[103]

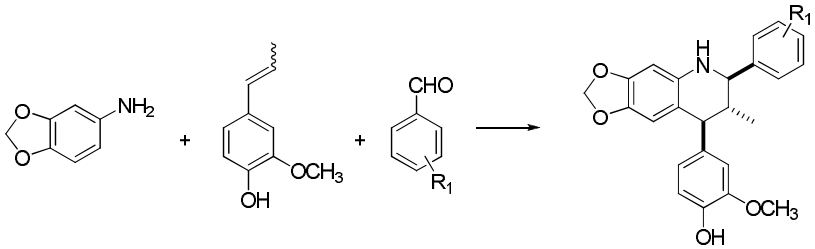
Other groups have employed the same approach but using different starting materials. To this respect, it can be signalled the Wu group that changed the tetronic acid by 2-hydroxy-1,4-naphtoquinone, and made it to react with 3,4-methylendioxyaniline and different aromatic aldehydes to obtain the corresponding 7-azapodophyllotoxin analogues.[104] Moreover, the cytotoxic activities of these compounds were evaluated *in vitro* on two different cancer cell lines and the results show that some compounds exhibited excellent antitumor activities against HepG2 and Hela. Kornienko *et al.* made an oversimplification of the podophyllotoxin skeleton and used aminopyrazoles together with other heterocyclic aldehydes to give structural analogues of 7-azapodophyllotoxin.[105] Very recently, Roche *et al.* used this strategy to obtain many 7-azapodophyllotoxin derivatives and found that many of them had antileukaemic activity.[106,107]

Pélinski *et al.* used, instead of an aromatic amine and an aromatic aldehyde, aromatic aminoalcohols, that made to react with tetronic acid, 2-hydroxy-1,4-naphtoquinone, 1,3-cyclohexanediones or even cyclohexanone, being depicted in Scheme 25 the use of tetronic acid to obtain the desired analogues.[108]



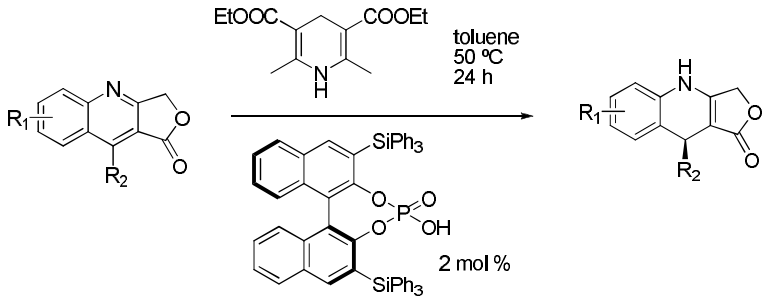
Scheme 25. Pélinski *et al.* approach to the synthesis of 7-azapodophyllotoxin derivatives.

A different multicomponent reaction has been carried out by Kouznetsov *et al.*[109] that using borontrifluoride etherate, were able to produce a three component imino Diels-Alder reaction using isoeugenol, 3,4-methylendioxyaniline and aromatic aldehydes[11] as shown in Scheme 26.



Scheme 26. Kouztnetsov *et al.* synthesis of 7-azapodophyllotoxin derivatives.

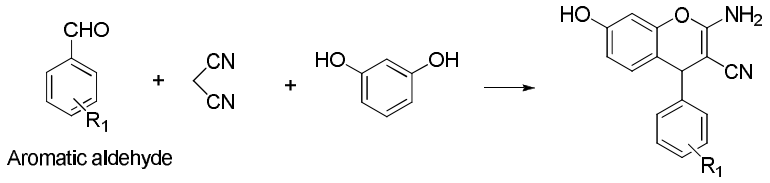
All the reactions described above produce racemic compounds. In order to obtain chiral compounds, the Pélinski group made use of an enantioselective organocatalytic partial transfer hydrogenation of the intermediates lactone-fused quinolines obtained by MCRs methodology as described in Scheme 27.[110]



Scheme 27. Pélinski *et al.* chiral synthesis of 7-azapodophyllotoxin derivatives.

3.3.1.2. 7-Oxapodophyllotoxin derivatives

Semenov group has made important contribution to the synthesis and biological activity not only of 7-azapodophyllotoxin but also 7-oxapodophyllotoxin derivatives. They observed that the 7-oxapodophyllotoxin derivatives are potent microtubule destabilizing agents exhibiting significant cytotoxicity and more stable towards oxidation as compared to the respective aza-derivatives.[111,112] They have reported the synthesis of 4-aryl-4*H*-chromenes, considered 7-oxapodophyllotoxin derivatives by the authors, as shown in Scheme 28. These authors, after testing several 4-aryl-4*H*-chromenes in cellular and phenotypic sea urchin embryo assays for antimitotic microtubule destabilizing activity, conclude that neither methylendioxy nor lactone functionalities were essential for antimitotic microtubule destabilizing activity and could be replaced by 2-amino, 3-carbonitrile and 7-hydroxy groups.

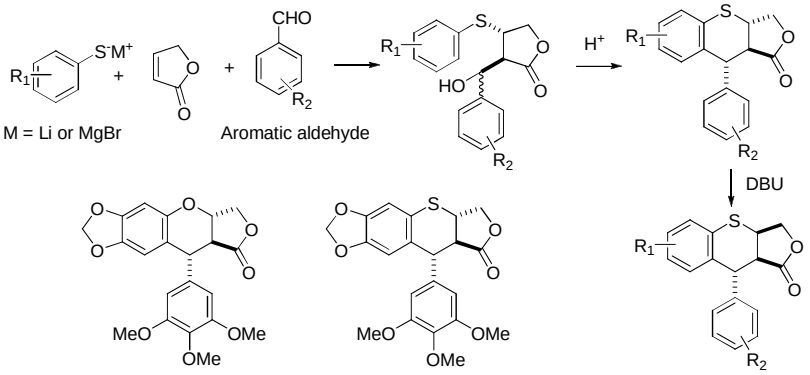


Scheme 28. Semenov *et al.* 7-oxapodophyllotoxinderivatives.

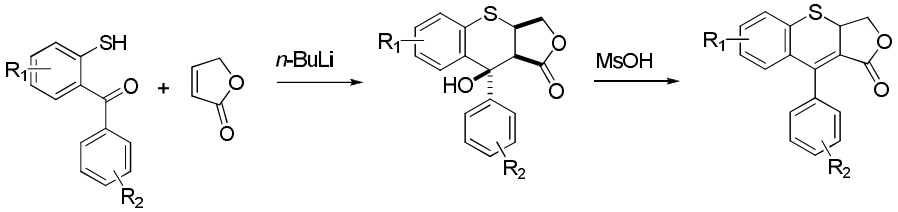
3.3.1.3. 7-Thiapodophyllotoxin derivatives

McCombie *et al.* made 7-thiapodophyllotoxin derivatives using the classical Michael addition of three components obtaining the required compounds that by treatment with acid give the tricyclic all *trans* compounds, which by treatment with DBU isomerise to the *cis* lactones (Scheme 29).[113] In this manner, the authors were able to obtain the 7-thiapodophyllotoxin analogues and the 7-oxa, although the latter in very low yield. In order to synthesize compounds at a higher oxidation level, the same authors made use of a two components Michael addition as showed in Scheme 29.

Reaction of 2-mercaptobenzophenones (lithium salt) with furan-2(5*H*)-one gave the tricyclic compound with the stereochemistry shown in Scheme 30, which by treatment in acidic conditions gave the unsaturated 7-thiapodophyllotoxin analogues.[113]



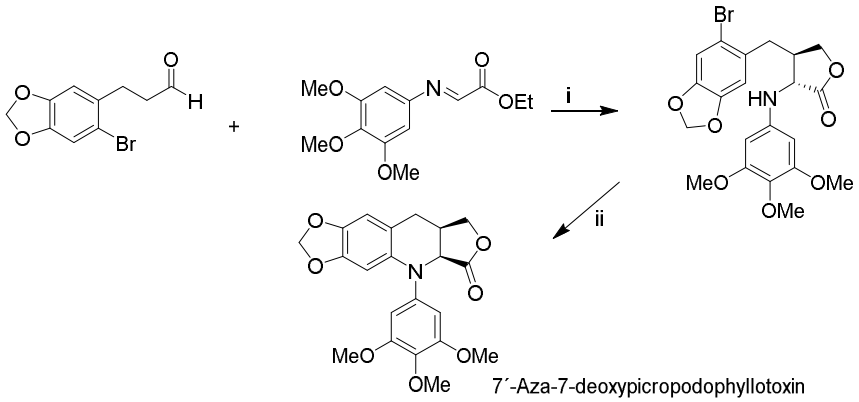
Scheme 29. Michael addition approach for the synthesis of 7-thiapodophyllotoxin derivatives.



Scheme 30. 7-Thiapodophyllotoxin derivatives.

3.3.2. 7'-Azapodophyllotoxin analogues

The synthesis of this kind of compounds was reported by De Borggraeve *et al.*[114] In their report, the 7'-aza-7-deoxypicropodophyllotoxin was synthesized through a direct asymmetric Mannich reaction by using D-proline in the key step for introduction of the chiral centres (Scheme 31).

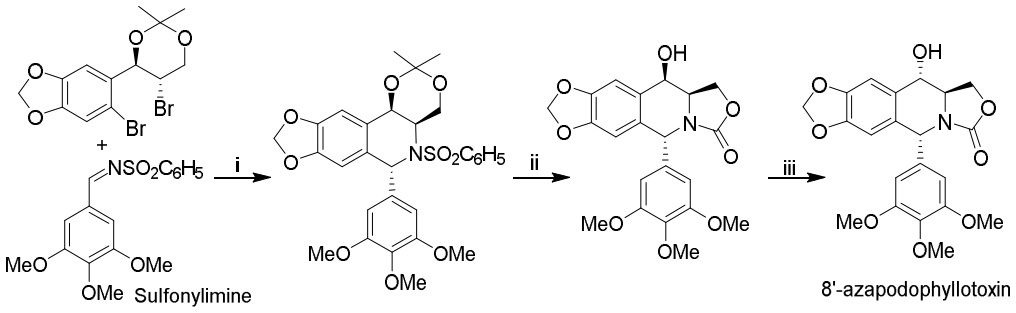


i: D-proline (30 mol %), THF, 4 ºC; $NaBH_4$, 0 ºC; $ZnCl_2$; ii: $Pd_2(dba)_3$,Sphos,Cs_2CO_3, toluene, 80 ºC.

Scheme 31. Synthesis of 7'-aza-7-deoxypicropodophyllotoxin by de Borggraeve *et al.*

3.3.3. 8'-Azapodophyllotoxin analogues

There are a large number of proposed routes to achieve a podophyllotoxin derivative containing a nitrogen atom at C-8' following different strategies and starting materials. The first approach to these structures was proposed by Pearce *et al.*[115] based on a stereocontrolled synthesis of the 8'-azaepipodophyllotoxin from appropriated sulfonylimine followed by intramolecular ring closure and finally changing the stereochemistry to obtain 8'-azapodophyllotoxin (Scheme 32).



i. (a) *n*-BuLi, THF at -75 ºC for 10 min then sulfonylimine; (b) sodium hydride in DMF at 0 ºC; ii. (a) sodium napthalenide/DME in THF at -75 ºC for 10 min and hydrolysis with 2 N HCl; (b) phosgene/Py in DCM at 0 ºC for 4 h; iii. (a) PCC in DCM at 23 ºC for 4 h; (b) lithium tri-*t*-butyloxyaluminium hydride in THF.

Scheme 32. Synthesis of 8'-azapodophyllotoxin derivatives by Pearce *et al.*

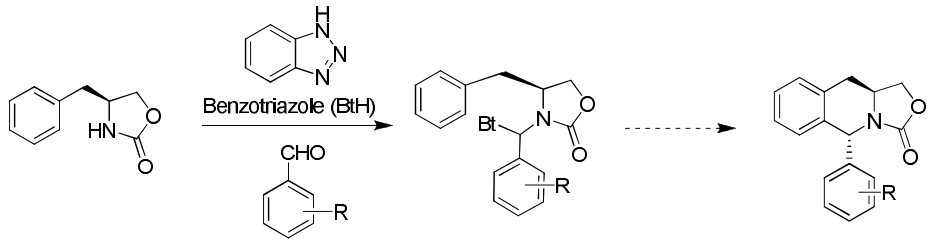
Other strategies make use of the Bischler-Napieralski reaction. Vandewalle *et al.* through the construction of a tetrahydroisoquinoline, synthesized the 7-deoxy-8'-azapodophyllotoxin,[116,117] Bosmans *et al.* synthesized 8'-azapodophyllotoxins using piperonal as starting material to form the corresponding β-arylethylamide[118] and Husson *et al.* reached the 8'-azapodophyllotoxin structure using a cyano-oxazolopiperidine derivative to form the appropriated amino-alcohol with the right configuration of the hydroxyl group.[119,120] All these approaches are included in the review of Kumar-Alegria-Malhotra.[85]

Another strategy made use of the Pictet-Spengler reaction, in this manner Tomioka, Koga *et al.* synthesized 8'-azapodophyllotoxin derivatives[121] and observed that racemic compounds exhibited promising growth inhibition of KB cell (ED_{50} between ~0.3 and 4.55 μg/mL) and *in vivo* activity against P-388 mouse (T/C 145 and 170). These authors observed that cytotoxicity of azadeoxypodophyllotoxin relies mostly on the absolute configuration at the C-7' position, not that at the C-8' position. Using the same strategy Medarde *et al.* reported analogues of these azalignans carrying an imidazole ring and employing histidinol as starting material.[122] These strategies are collected in Kumar-Alegria-Malhotra review.[85]

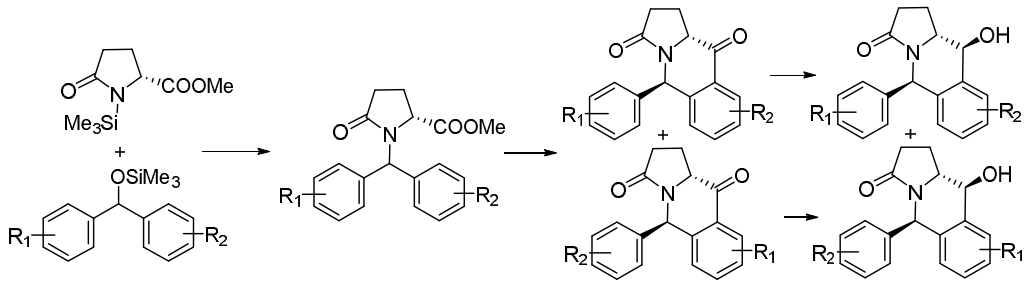
Katritzky *et al.* implement the synthesis of tetrahydroisoquinolines with this strategy using 5(*S*)-benzyl-1,3-oxazolan-2-one by benzotriazole methodology[123] (Scheme 33). Other authors as Petrini *et al.* apply this methodology for the same kind of chiral compounds.[124]

Finally, it is important to say that Friedel-Crafts reaction has been used for the synthesis of 8'-azapodophyllotoxin derivatives by the group of Rigo.[125,126] Starting with a pyroglutamic derivative, which is made to react with a dibenzylcarbinol or benzylnaphtylcarbinol differently substituted, the corresponding

esters were obtained, and further Friedel-Crafts cyclization of the acids gave the 8'-azapodophyllotoxin analogues (Scheme 34).

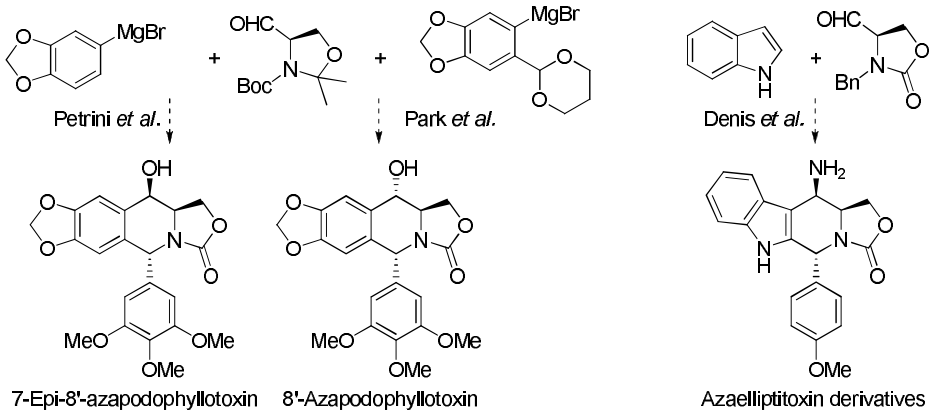


Scheme 33. Katrizky synthesis of 8'-azapododophyllotoxin analogues.



Scheme 34. Rigo's approach to 8'-azapodophyllotoxin analogues

There have been recent reports that employ Garner aldehydes to build the lignan structure. Petrini *et al.* propose an approach to the synthesis of some useful intermediates for the preparation of aza-analogues of podophyllotoxin using L-DOPA and (*R*)-Garner aldehyde synthesizing 7-epi-8'-azapodophyllotoxin derivatives (Scheme 35).[127]

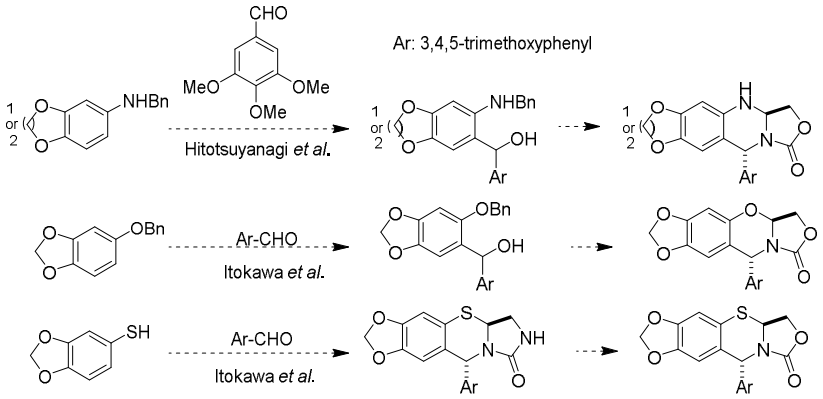


Scheme 35. Petrini, Denis and Park approaches to 8'-azapodophyllotoxin derivatives.

Denis *et al.* starting from (*S*)-glycidol obtain a Garner aldehyde that it is used with indole for an eight-step sequence for the preparation of enantiopure 11-(pivaloylamino) analogue of azaelliptitoxin.[128] Park *et al.* developed an efficient synthetic route for enantiopure tetrahydroisoquinolines, which are used for the total synthesis of the 8'-azapodophyllotoxin.[129] All these compounds were tested for biological activity especially for inhibition of tubulin polymerization and antitumor activity but none had interesting properties.

3.3.4. 8'-Aza-7-X-podophyllotoxin analogues

In this case, podophyllotoxin derivatives containing another heteroatom apart from the nitrogen in position 8' are considered. C-7 has been substituted by N, O or S atoms. The synthesis begins with the appropriated aromatic derivative containing the desired heteroatom and introducing the aza function in C-8' with different strategies as described by the groups of Hitotsuyanagi and Itokawa.[130-133] The biological activities show that the diaza analogues are the more promising ones showing good activity against P388/VCR and potent activity against B16 melanoma, the aza-thia analogue it is not especially active and the aza-oxa analogue showed significant activity (IC_{50}= 0.031 μg/mL) against adriamycin-resistant P-388 leukaemia cells (Scheme 36).



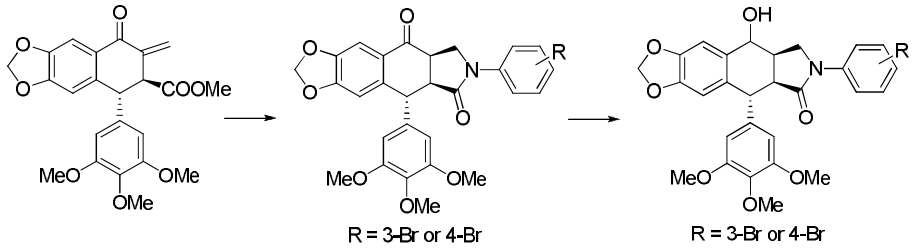
Scheme 36. Synthetic approaches for 8'-aza-7-X-podophyllotoxin derivatives.

3.4. Heteroatoms on ring D

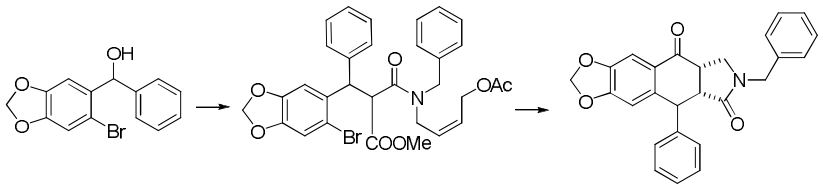
Bertounesque *et al.* made the homologation of the lactone ring to obtain δ-lactone-containing picropodophyllotoxin, podophyllotoxin and 4'-demethyl-epipodophyllotoxin derivatives.[134] Florent and Bertounesque *et al.* proposed an interesting transformation of ring D into a lactam. Starting with podophyllotoxin, they transformed it into thuriferic acid methyl ester and then, by a tandem aza-Michael addition/$InCl_3$-catalysed cyclization, the corresponding *N*-aryl picropodophyllone γ-lactams were obtained, as shown in Scheme 37.[135] The authors were able to obtain compounds that were further derivatized by reduction of the ketone and Suzuki coupling on the aromatic bromide function.

Poli and Gamblastiani[136] make a different approach synthesizing rings A/B and E in an early stage via a cationic benzhydrilation process. Then a palladium-catalysed pseudo-domino intramolecular process

generates rings C/D in a clever synthetic step (Scheme 38). Madec, Poli *et al.* used similar strategy using a copper mediated Ullmann type intramolecular cyclization from *N*-substituted tetronamides.[137]

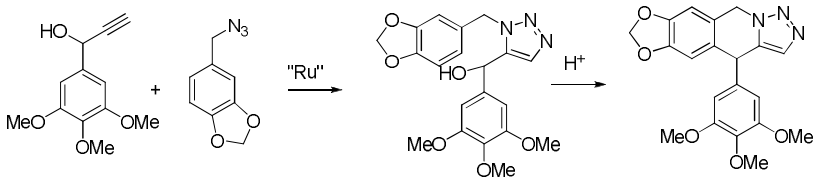


Scheme 37. Florent and Bertounesque synthesis of ring D variations.



Scheme 38. Poli and Gamblastiani's modification of ring D.

Tron *et al.* made a different approach to this ring D heterocyclic modification.[138] By click chemistry, they obtain the corresponding triazole that by the usual Friedel-Crafts reaction gives the required compound as can be seen in Scheme 39.

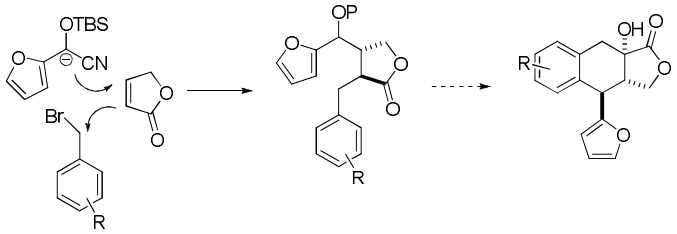


Scheme 39. Click chemistry for the synthesis of triazole derivatives of podophyllotoxin.

3.5. Heteroatoms on ring E

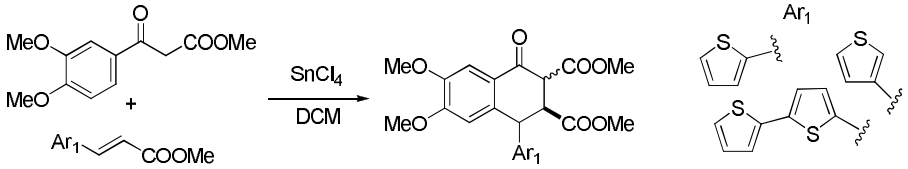
In order to obtain heterocyclic variation of ring E, two different strategies can be found, one that synthesized the compounds by employing the reactions already seen above changing the 3,4,5-trimethoxyphenyl for an adequate heterocycle derivative and the other making use of the very activated ring to oxidise it into a quinone and derivatise it. Among the first strategy can be cited Ohmizu, Iwasaki *et al.* that made an interesting entry into these compounds by Michael addition of a furan derivative into furan-2(5*H)*-one and capture of the produced anion with a benzyl bromide as shown in Scheme 40.[139] After the condensation and capture of the enolate, the condensation compound was obtained and was transformed by hydroxylation and Friedel-Crafts intramolecular condensation into the final product. Similarly Husson *et al.*,

already mentioned in the synthesis of 8'-azapodophyllotoxin derivatives, made the analogues with a thiophene or furan ring instead of the trimethoxyphenyl group.[119]



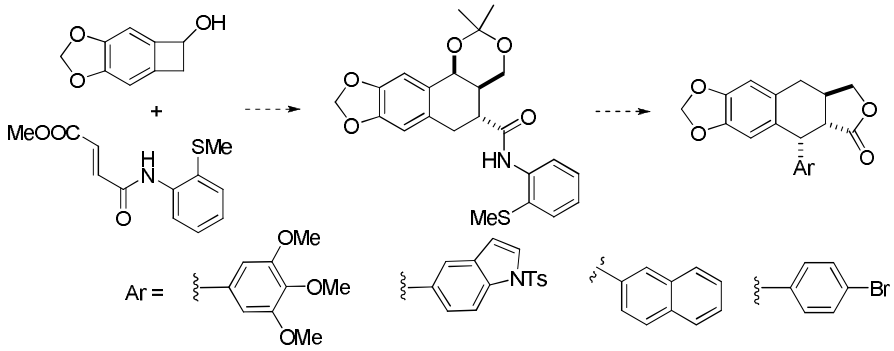
Scheme 40. Ohmizu and Iwasaki approach to ring E furan variation.

Following the strategy as before but changing the substituent for the 2,5-disubstituted-2,3-dihydrofuran, Brun *et al.* obtained differently thiophene substituent for ring E (Scheme 41).[140]



Scheme 41. Thienyl derivatives of ring E by Braun *et al*.

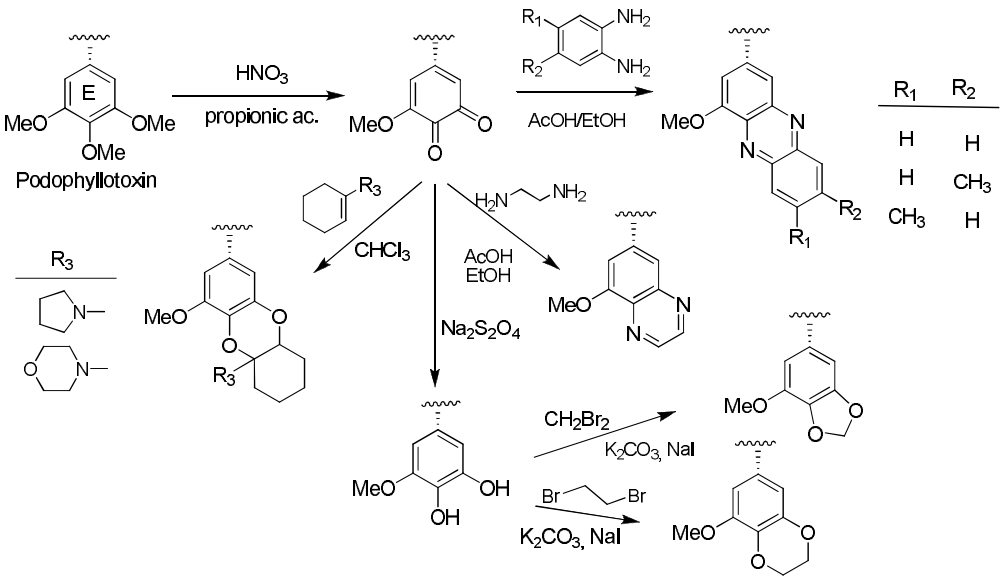
Recently Maimone and Ting described a total synthesis of podophyllotoxin by a C-H bond arylation that permits the access to ring E heterocyclic derivatives as shown in Scheme 42.[141]



Scheme 42. C-H bond arylation in the synthesis of aryltetralin lignans.

For the second strategy, that is oxidation of E ring to an ortho quinone and functionalization, Castro *et al.* described the synthesis of several heterocycles as shown in Scheme 43.[1,64,142] These compounds were prepared and evaluated for their cytotoxicity on four neoplastic cell lines (P-388, A-549, HT-29 and MEL-28) and for their antiherpetic activity against Herpes simplex virus type II. Using the same strategy the group

of Xu has obtained a large variety of phenazines and made variations for using them as insecticidal compounds.[143-146]

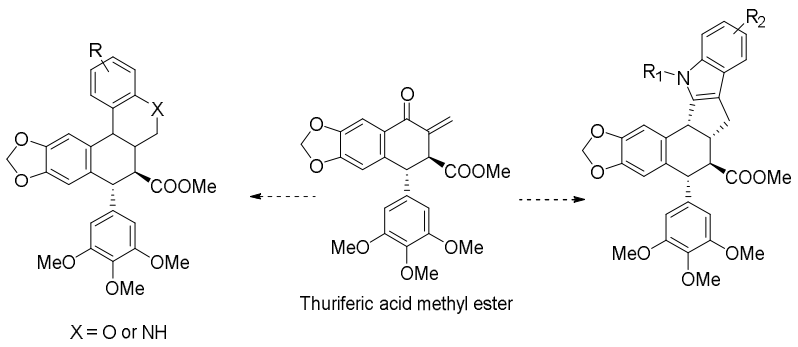


Scheme 43. Ring E heterocyclic variations, by Castro *et al*.

3.6. Additional heterocycles fused to the cyclolignan skeleton

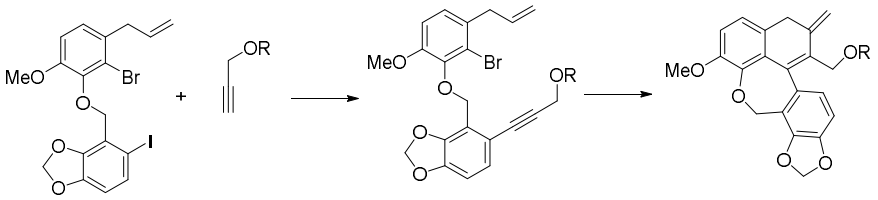
In this section, series of variations that imply the formation of an extra heterocycle fused to the podophyllotoxin structure will be shown.

Florent, Bertounesque *et al.* made a magnific work starting with thuriferic acid methyl ester and, by Michael addition of the required nucleophile and ulterior $InCl_3$-catalyzed Friedel-Crafts-type cyclization, are able to obtain indole and pyran or piperidine podophyllotoxin derivatives as shown in Scheme 44.[135]



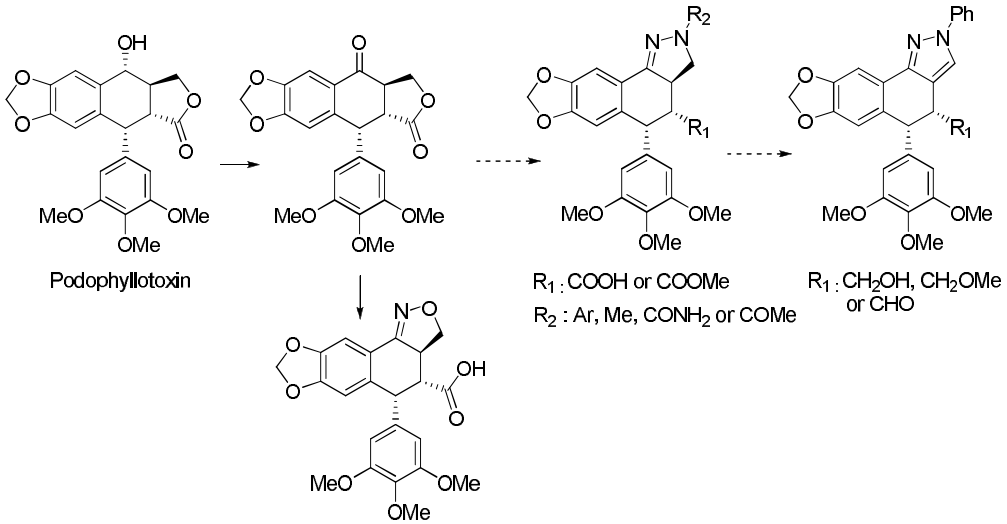
Scheme 44. Indole and pyran and piperidine derivatives of podophyllotoxin.

Using extensive Pd chemistry, Tietze *et al.* obtained compounds with an oxa-membered ring as shown in Scheme 45.[147]



Scheme 45. Tietze approximation to an extra heterocyclic system.

Gordaliza, Miguel del Corral *et al.* have obtained oxaheterocycles by an intramolecular cyclization between C-7 and C-9' positions to give neoanhydropodophyllols.[148,149] They also made several pyrazolignans and isoxazolignans, which were evaluated for their cytotoxic activities in cell cultures of P-388 murine leukaemia, A-549 lung carcinoma and HT-29 colon carcinoma. They made those heterocycles by podophyllotoxin oxidation into the C-7 ketone and condensation with different reagents as hydroxylamines or hydrazines to obtain isoxazolines or pyrazolines that were transformed into pyrazoles fused to the podophyllotoxin structure (Scheme 46).[56,150]



Scheme 46. Isoxazole and pyrazole podophyllotoxin derivatives by Gordaliza, Miguel del Corral *et al*.

Despite the lack of the lactone moiety, these pyrazolignans showed IC_{50} values at μM levels.[56] The authors made an isoxazoline-fused cyclolignan with a carboxylic acid group (isoxazopodophyllic acid) that was transformed into its methyl ester, alcohol and aldehyde derivatives and evaluated for their biological activity, against cell cultures of P-388 murine leukaemia, A-549 human lung carcinoma and MEL-28 human melanoma.[150] The results showed that the tested compounds were two or three orders of magnitude less

potent than those of podophyllotoxin confirming that the presence of the lactone moiety is a prominent factor for displaying high cytotoxic activity. By contrary the isoxazoline with acid function at C-8', among other compounds, was tested for immunosuppressive activity and found that was the most potent with respect to the suppression of activated splenocytes.[59,60] These authors have made combinations of this isoxazoline heterocyclic derivative with other heterocycles at ring E[142] and ring A.[86]

Similar pyrazoles, showing very good activity against bacteria and fungi, were obtained by Basavaraju *et al.* by cyclization reaction of cyclopropyl ketones in presence of stannyl chloride.[151,152] They obtained tetralones that, after formylation, were transformed into the corresponding unprotected pyrazoles by treatment with hydrazine. Recently, Xu *et al.* have obtained isoxazopodophyllic acid and transformed the acid function into esters, amides and hydrazones and tested for their insecticidal activity.[153,154]

4. Conclusions

The substitution of any carbon for heteroatoms on the podophyllotoxin structure, the introduction of different heterocycles as substituents and the formation of hybrids between heterocycles and podophyllotoxin have been considered. The biological activities described for these compounds showed that the bioactivity is increased in many cases with different mode of action and even other biological activities are described. Due to the importance of podophyllotoxin and its analogues, the synthesis and evaluation of these kinds of compounds continue being in expansion.

Acknowledgments

APH acknowledges the support of the Junta de Castilla y León-FSE for financial support. The authors acknowledge financial support from MINECO (CTQ2015-68175-R), Consejería de Sanidad de la J. C. y L.-FSE (Project BIO/SA59/15) and University of Salamanca for financial support.

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